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Robust Perron cluster analysis in conformation dynamics ☆

Peter Deuflhard, Marcus Weber *

Konrad-Zuse-Zentrum fuer Informationstechnik, Berlin D-14195, Germany

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Abstract

The key to molecular conformation dynamics is the direct identification of metastable conformations, which are almost invariant sets of molecular dynamical systems. Once some reversible Markov operator has been discretized, a generalized symmetric stochastic matrix arises. This matrix can be treated by Perron cluster analysis, a rather recent method involving a Perron cluster eigenproblem. The paper presents an improved Perron cluster analysis algorithm, which is more robust than earlier suggestions. Numerical examples are included.

AMS classification: 15A51; 65F15; 62H30; 91C20

Keywords: Markov chains; Cluster algorithms; Perron cluster analysis; Conformation dynamics

1. Introduction

In the past few years, Deuflhard and Schütte together with their research group have created the conformation dynamics approach based on concepts of nonlinear dynamics—see [2,7,20] for recent survey papers. The key to the conformation dynamics approach is the direct identification of metastable conformations together

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* Corresponding author.
E-mail address: weber@zib.de (M. Weber).

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with their life times and their transition patterns. This approach, based on first ideas of Deuflhard et al. [3], performs the task of cluster analysis by analyzing a stochastic eigenproblem corresponding to a cluster of eigenvalues around the Perron eigenvalue $\lambda = 1$, therefore named Perron cluster. The whole approach is called *Perron cluster analysis*, its algorithmic realization is abbreviated as PCCA (from **P**erron **C**luster **C**luster **A**nalysis). An alternative discrete approach has been suggested by Froyland et al. [9,10], which tackle more general problems, but in a different context and lower fixed dimensions. The PCCA as derived by Deuflhard et al. [6] has been based on the concept of characteristic functions for almost invariant sets (or aggregates). With more and more computational experience, that algorithm has appeared to be not robust enough. That is why the present paper suggests a new improved variant to be called PCCA+ here.

The present paper is organized as follows. In Section 2, we revisit the stochastic generalized symmetric eigenproblem corresponding to the Perron cluster of eigenvalues, which can be viewed as being generated from a *multiple* Perron eigenvalue by perturbation. Motivated by a perturbation analysis, which is a slight improvement over [6], we derive the concept of our new algorithm introducing *almost characteristic functions* to describe almost invariant sets (or aggregates)—see Section 3. In Section 4, the Perron cluster analysis problem is formulated as a *constrained* maximization problem with *metastability* as the objective function. In Section 5, the problem is reformulated as an *unconstrained* maximization problem, which is the basis for our improved, more robust Perron cluster algorithm PCCA+. A predecessor of this algorithm has originally been suggested by Weber [21,22]; our derivation here, however, differs substantially from the earlier reports and establishes a new frame. Finally, in Section 6, numerical experiments are given to document the improvement by our new algorithm over the former one.

2. Perron cluster eigenproblem

In order to present our new Perron cluster analysis algorithm, we first need to collect some (partly new) results about the Perron cluster eigenproblem. The stochastic matrices treated in this paper are proper discretizations of the self-adjoint transfer operator constructed by Schütte [18,19]. For the theoretical part of this paper we only need to keep in mind that the arising matrices are stochastic and generalized symmetric in a sense to be described below.

Given a stochastic matrix T of dimension N, say. Then the eigenproblem for the *Perron eigenvalue* $\lambda_1 = 1$ has the form

$$\pi^T T = \pi^T, \quad Te = e, \quad \pi^T e = 1. \tag{2.1}$$

In terms of the underlying Markov chain, the left eigenvector $\pi^T = (\pi_1, \ldots, \pi_N)$ can be interpreted as the *discrete invariant measure*, while the right eigenvector $e^T = (1, \ldots, 1)$ represents the characteristic function of the *discrete invariant set*. Given

$u, v \in \mathbb{R}^N$ and the diagonal scaling matrix $\mathscr{D}^2 = \mathrm{diag}(\pi_1, \ldots, \pi_N)$, we may introduce a special inner product and its induced norm by

$$\langle u, v\rangle_\pi = \sum_{l=1}^{N} u_l \pi_l v_l = u^T \mathscr{D}^2 v, \quad \|v\|_\pi = \langle v, v\rangle_\pi^{1/2},$$

to be called π*-product* and π*-norm* further on. The self-adjointness of the underlying transfer operator is inherited by the symmetry of the matrix T with respect to the π-product.

2.1. Uncoupled Markov chains

Let $\mathscr{S} = \{1, 2, \ldots, N\} = \mathscr{S}_1 \oplus \cdots \oplus \mathscr{S}_k$ denote the total index set decomposed into k disjoint index subsets, each of which represents a state subspace wherein a Markov subchain is running over "infinitely long time", i.e. each of which represents an *invariant subset*. Then, after appropriate permutation, the total transition matrix T is strictly *block diagonal* with submatrices $\{T_1, \ldots, T_k\}$—see, e.g., [15]. Each of these submatrices is stochastic and gives rise to a single Perron eigenvalue $\lambda(T_i) = 1$, $i = 1, \ldots, k$. Assume the submatrices to be primitive. Then, due to the Perron-Frobenius theorem, each block T_i possesses a unique right eigenvector having unit entries over the index subset $\mathscr{S}_i$. In terms of the total (N, N)-matrix T, the Perron eigenvalue is k-fold, i.e.

$$\lambda_1 = \cdots = \lambda_k = 1,$$

and the corresponding eigenspace is spanned by the extended vectors

$$\chi_i^T = (0, \ldots, 0, \underbrace{1, \ldots, 1}_{\mathscr{S}_i}, 0, \ldots, 0), \quad i = 1, \ldots, k.$$

Note that these eigenvectors can be interpreted as *characteristic functions* of the discrete invariant subsets—compare Fig. 1, left. To simplify language, we call k the *Perron index*. Any Perron eigenvector basis $X = [X_1, \ldots, X_k]$ can be written as a linear combination of the characteristic functions and vice versa. With $\chi = [\chi_1, \ldots, \chi_k]$ and a non-singular (k, k)-matrix $\mathscr{A}$ we may write

$$\chi = X\mathscr{A}, \quad X = \chi\mathscr{A}^{-1}. \tag{2.2}$$

with $\mathscr{A}^{-1} = (a_{ij})$ we obtain componentwise

$$X_i(l) = \sum_{j=1}^{k} a_{ji}\chi_j(l), \quad i = 1, \ldots, k, \;\; l = 1, \ldots, N, \tag{2.3}$$

which is an overdetermined system of kN equations for the k^2 unknowns a_{ji}. Systems (2.2) or (2.3), respectively, are consistent by construction: The Perron eigenvectors are constant on each index subset $\mathscr{S}_m$—see Fig. 1, right. For this reason we may represent each subset by just one index $l_m \in \mathscr{S}_m$, $m = 1, \ldots, k$ and arrive at the system of k^2 equations

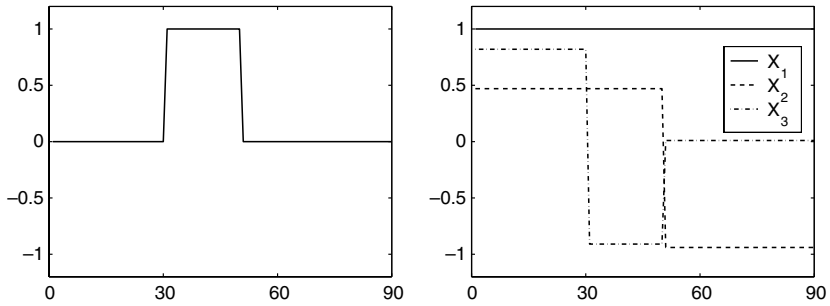

Fig. 1. Uncoupled Markov chain over $k = 3$ disjoint index subsets. The state space $\mathscr{S} = \{s_1, \ldots, s_{90}\}$ divides into the index subsets $\mathscr{S}_1 = \{s_1, \ldots, s_{29}\}$, $\mathscr{S}_2 = \{s_{30}, \ldots, s_{49}\}$, and $\mathscr{S}_3 = \{s_{50}, \ldots, s_{90}\}$. *Left*: characteristic function χ_2. *Right*: eigenbasis $\{X_1, X_2, X_3\}$ corresponding to 3-fold eigenvalue $\lambda = 1$.

$$X_i(l_m) = \sum_{j=1}^{k} a_{ji}\chi_j(l_m), \quad i = 1, \ldots, k, \;\; m = 1, \ldots, k. \tag{2.4}$$

Since $\chi_j(l_m) = \delta_{m,j}$, this system can be directly solved to yield

$$a_{mi} = X_i(l_m), \quad i = 1, \ldots, k, \;\; m = 1, \ldots, k, \tag{2.5}$$

or, in matrix notation

$$\mathscr{A}^{-1} = \begin{pmatrix} X_1(l_1) & \ldots & X_k(l_1) \\ \vdots & & \vdots \\ X_1(l_k) & \ldots & X_k(l_k) \end{pmatrix}. \tag{2.6}$$

2.2. Nearly uncoupled Markov chains

Suppose now we have k nearly uncoupled Markov chains, each of which is running "for a long time" in one of the subsets $\mathscr{S}_i$, which are therefore called *almost invariant subsets*. In this case the transition matrix $\widetilde{T}$ will be *block diagonally dominant* after suitable permutation. As a perturbation of the k-fold Perron root $\lambda = 1$, a *Perron cluster* of eigenvalues

$$\widetilde{\lambda}_1 = 1, \quad \widetilde{\lambda}_2 = 1 - \mathrm{O}(\epsilon), \quad \ldots, \quad \widetilde{\lambda}_k = 1 - \mathrm{O}(\epsilon),$$

will arise, where $\epsilon > 0$ denotes some perturbation parameter, which we here scale as

$$\epsilon = 1 - \widetilde{\lambda}_2. \tag{2.7}$$

Let formal ϵ-expansions be introduced for the stochastic matrix as

$$\widetilde{T}(\epsilon) = T + \epsilon T^{(1)} + \mathrm{O}(\epsilon^2), \tag{2.8}$$

and for the Perron cluster eigenvectors $\widetilde{X} = [\widetilde{X}_1, \ldots, \widetilde{X}_k] \in \mathbb{R}^{N\times k}$ as

$$\widetilde{X}_i(\epsilon) = X_i + \epsilon X_i^{(1)} + \mathrm{O}(\epsilon^2). \tag{2.9}$$

In [6], the result

$$X_i^{(1)} = \underbrace{\sum_{j=1}^{k} b_{ji}\chi_j}_{\text{(I)}} + \underbrace{\sum_{j=k+1}^{N} \frac{1}{1-\lambda_j} \Pi_j T^{(1)} X_i}_{\text{(II)}} \tag{2.10}$$

has been obtained using projections Π_j as defined in the book of Kato [14]. Obviously, the term (I) represents just shifts of the locally constant levels to be associated with the almost invariant sets—see Fig. 1, right. As a slight improvement over [6], we now show that the term (II) vanishes.

Lemma 2.1. *With $B = (b_{ij})$ the expansion* (2.10) *can be simplified to*

$$X_i^{(1)} = \sum_{j=1}^{k} b_{ji}\ \chi_j, \quad i = 1, \ldots, k \quad \textit{or} \quad X^{(1)} = \chi B. \tag{2.11}$$

Proof. First, we additionally expand the perturbed eigenvalues as

$$\widetilde{\lambda}_i(\epsilon) = \lambda_i - \epsilon\ \delta\lambda_i + \mathrm{O}(\epsilon^2) \leqslant 1, \quad i = 1, \ldots, N. \tag{2.12}$$

With the help of the π-product we may write the projections Π_j as

$$\sum_{j=k+1}^{N} \frac{1}{1-\lambda_j} \Pi_j T^{(1)} X_i = \sum_{j=k+1}^{N} \frac{1}{1-\lambda_j} \langle X_j, T^{(1)} X_i \rangle_\pi X_j, \quad i = 1, \ldots, k.$$

For further treatment of these terms we need to find an expression for the first order term $T^{(1)}$. Following the usual procedure, we start from

$$\widetilde{T}(\epsilon)\widetilde{X}_i(\epsilon) = \widetilde{\lambda}_i(\epsilon)\widetilde{X}_i(\epsilon), \quad i = 1, \ldots, N.$$

Upon inserting the above ϵ-expansions, the zero order comparison yields

$$T X_i = X_i \quad \text{for } i = 1, \ldots, k, \tag{2.13}$$

while the first order comparison leads to

$$T^{(1)} X_j = (I - T) X_j^{(1)} - X_j \delta\lambda_j, \quad j = 2, \ldots, N. \tag{2.14}$$

The stochastic matrix $\widetilde{T}(\epsilon)$ is symmetric with respect to the π-product and so are the expansion matrices T and $T^{(1)}$. Hence, for $j = k+1, \ldots, N$ and $i = 2, \ldots, k$, the individual terms in the above sum are

$$\begin{aligned} \langle X_j, T^{(1)} X_i \rangle_\pi &= \langle X_i, T^{(1)} X_j \rangle_\pi = \langle X_i, (I - T) X_j^{(1)} - \delta\lambda_j X_j \rangle_\pi \\ &= \langle (I - T) X_i, X_j^{(1)} \rangle_\pi - \delta\lambda_j \langle X_i, X_j \rangle_\pi = 0. \end{aligned}$$

The first term above vanishes due to (2.13), the second one due to the π-orthogonality of the unperturbed eigenvectors, which verifies (2.11) and thus completes the proof. □

In Fig. 4, left, we show an example of the Perron cluster eigenvectors at a simple illustrative molecule for Perron index $k = 3$.

PCCA approach. The first algorithm for Perron cluster analysis has been the PCCA method, as worked out in detail in [6]; for a rather elementary introduction see also Section 5.5 of the latest edition of the textbook [5].

Least squares formulation. In PCCA, the generally inconsistent overdetermined system (2.2) is replaced by the linear least squares system

$$\|\chi - \widetilde{X}\mathscr{A}\|_\pi = \min . \tag{2.15}$$

The unknowns herein are the k^2 entries of the matrix $\mathscr{A}$.

Sign pattern. Algorithmically speaking, PCCA exploits the fact that, for $\epsilon = 0$, each cluster is clearly associated with the set of signs of the components of the eigenvectors $X_1, \ldots, X_k$—compare Fig. 1, right. It is tacitly assumed that this sign pattern is only slightly changed under perturbation—an assumption which is certainly not unreasonable, since the sign of a component is the leading binary digit. However, as shown in Lemma 2.1, the *signs* of the components of $\widetilde{X}$ are perturbed in $O(\epsilon)$ as opposed to the *constant level* pattern of the eigenvectors, which is perturbed in $O(\epsilon^2)$ only.

We may also look at the sign pattern from a *combinatorial* point of view. In the case $\epsilon = 0$ the eigenbasis X selects k sign patterns out of 2^{k-1} possible ones (note that the positive sign from X_1 is fixed)—or even 3^{k-1} possible ones, if we include the sign function value 0 to be implemented as some "dirty zero" not easy to handle. Perturbations $\epsilon \neq 0$ may give rise to additional possibilities, i.e. to more than k patterns, part of which will not have a correspondence for $\epsilon = 0$.

The generic occurrence of so-called transition sets, where the sign structures differ from the ones in the case $\epsilon = 0$, see Huisinga et al. [12], shows that the "dirty zero" problem is also generic for conformation dynamics.

Summarizing, the PCCA algorithm, even though looking intriguing at first glance, exhibits certain structural discontinuities, which, in turn, induce some lack of robustness. This insight is in agreement with numerical experience in more complex biomolecular computations. As a consequence, we were eventually led to abandon this algorithmic approach, but not the concept of Perron cluster analysis as a whole.

3. Almost characteristic functions

In the new algorithmic approach to be presented here, the inconsistency of the overdetermined system (2.2) for $\epsilon \neq 0$ is treated in a way different from (2.15). Given the perturbed eigenvectors $\widetilde{X} = [\widetilde{X}_1, \ldots, \widetilde{X}_k]$ as input data, the main idea of the new approach is to describe almost invariant sets by *almost characteristic functions* $\widetilde{\chi}(\epsilon) = [\widetilde{\chi}_1, \ldots, \widetilde{\chi}_k]$ such that

$$\widetilde{\chi}(\epsilon) = \widetilde{X}(\epsilon)\widetilde{\mathscr{A}}(\epsilon)$$

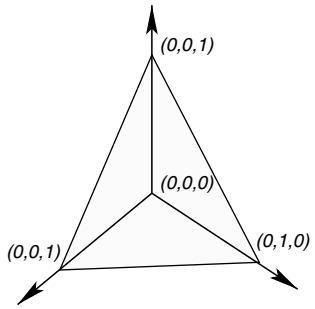

Fig. 2. Simplex σ_2 with vertices $\{(1,0,0),(0,1,0),(0,0,1)\}$.

or componentwise, in terms of the k^2 coefficients $\widetilde{\mathscr{A}} = (\alpha_{ij})$,

$$\widetilde{\chi}_i = \sum_{j=1}^{k} \alpha_{ji} \widetilde{X}_j. \tag{3.1}$$

These almost characteristic functions are assumed to satisfy the *positivity* property

$$\widetilde{\chi}_i(l) \geqslant 0, \quad i = 1, \ldots, k, \;\; l = 1, 2, \ldots, N, \tag{3.2}$$

and the *partition of unity* property

$$\sum_{i=1}^{k} \widetilde{\chi}_i(l) = 1, \quad l = 1, 2, \ldots, N. \tag{3.3}$$

These conditions define a $(k-1)$-simplex, say $\sigma_{k-1} \subset \mathbb{R}^k$. The k vertices of this simplex are the coordinate unit vectors—see Fig. 2.

Assume that $\widetilde{\mathscr{A}}$ as defined in (3.1) is non-singular and let $\widetilde{\mathscr{A}}^{-1}(\epsilon) = (a_{ij})$. Then $\widetilde{X} = \widetilde{\chi}.\widetilde{\mathscr{A}}^{-1}$ or, componentwise,

$$\widetilde{X}_i(l) = \sum_{j=1}^{k} a_{ji} \widetilde{\chi}_j(l), \quad i = 1, \ldots, k, \;\; l = 1, \ldots, N. \tag{3.4}$$

Consider the k-simplex having the k vertices of σ_{k-1} plus the origin in $\mathbb{R}^k$ as its $k+1$ vertices (compare Fig. 2 for the special case $k = 3$). By the above linear mapping, this k-simplex transforms into a k-simplex. Whenever a solution of our cluster problem exists, then this simplex should contain all input data $(\widetilde{X}_1(l), \ldots, \widetilde{X}_k(l))$ for $l = 1, \ldots, N$. Since $\widetilde{X}_1(l) = 1$ holds trivially, we may restrict our interest to the $(k-1)$-simplex $\widetilde{\sigma}_{k-1}$, which then should contain the data $(\widetilde{X}_2(l), \ldots, \widetilde{X}_k(l))$.

Example: Butane molecule. In Figs. 3 and 4 we exemplify the geometrical ideas behind our concept. The presented results have been obtained from the algorithm PCCA+ to be described in Section 5. The occurrence of 'dirty zero' data indicates that the previous algorithmic approach PCCA would have required some extra treatment of these data, even though they obviously do not play any extra role.

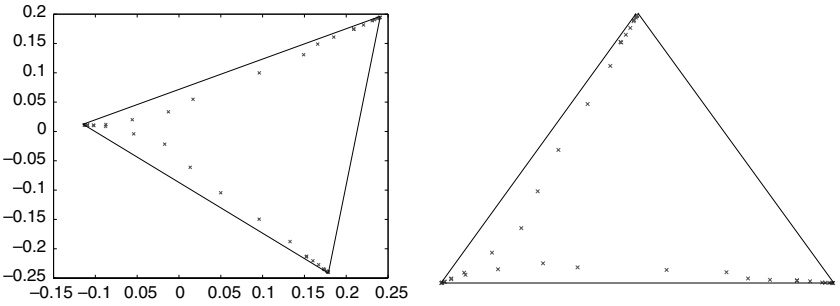

Fig. 3. *Butane molecule* ($k = 3$): *left*: simplex $\widetilde{\sigma}_2$ containing $(\widetilde{X}_2(l), \widetilde{X}_3(l))$, $l = 1, \ldots, N$. Observe the occurrence of 'dirty zero' data in the left corner. *Right*: simplex σ_2 for almost characteristic functions $(\widetilde{\chi}_1, \widetilde{\chi}_2, \widetilde{\chi}_3)$.

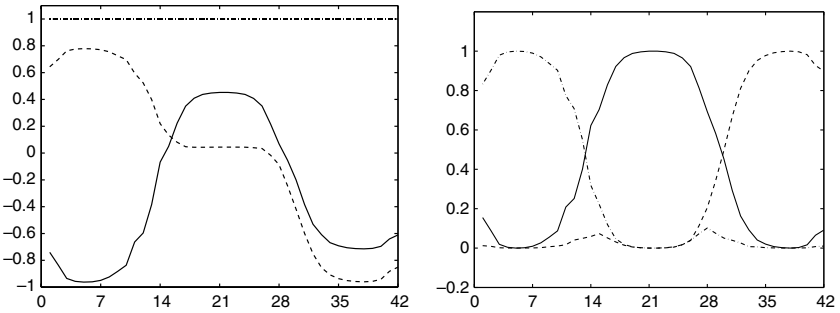

Fig. 4. *Butane molecule* ($k = 3$): *left:* Perron cluster eigenvectors $\widetilde{X}_1 = e, \widetilde{X}_2, \widetilde{X}_3$ to Perron cluster eigenvalues $\widetilde{\lambda} = 1, 0.99, 0.98$. Observe the occurrence of 'dirty zero' data in the range $\{16, \ldots, 26\}$. *Right:* perturbed characteristic functions $\widetilde{\chi}_1, \widetilde{\chi}_2, \widetilde{\chi}_3$.

In the strictly uncoupled case $\epsilon = 0$, we already know that the overdetermined system (3.4) is uniquely solvable by $\widetilde{\chi}(0) = \chi$. Geometrically speaking, this means that all data points lie in the k vertices of the simplex σ_{k-1}. Vice versa, if all data points lie in the vertices, then the underlying Markov chains are uncoupled. In the coupled case $\epsilon \neq 0$, we expect our cluster problem to be solvable, if all *data points*

$$(\widetilde{\chi}_1(l), \ldots, \widetilde{\chi}_k(l)), \quad l = 1, \ldots, N,$$

lie in σ_{k-1} and satisfy (3.4) in addition. This is confirmed by the following theorem.

Theorem 3.1. *Notation as just introduced. For a solution of the cluster problem in terms of almost characteristic functions* $\widetilde{\chi}_1, \ldots, \widetilde{\chi}_k$ *always three out of the following four conditions are satisfiable*:

(i) $\sum_{i=1}^{k} \widetilde{\chi}_i = e$,

(ii) *for all* $i = 1, \ldots, k$ *and* $l = 1, \ldots, N$: $\widetilde{\chi}_i(l) \geqslant 0$,

(iii) $\widetilde{\chi} = \widetilde{X}\widetilde{\mathscr{A}}$ *with* $\widetilde{\mathscr{A}}$ *regular*,
(iv) *for all* $i = 1, \ldots, k$ *there exists* $l \in \{1, \ldots, N\}$ *with* $\widetilde{\chi}_i(l) = 1$.
If all four of the conditions hold, the solution is unique up to permutation of the index set $\{1, \ldots, k\}$.

Proof. We select the condition triples one after the other.

"(i), (ii), (iv)" is trivial: For each $l = 1, \ldots, N$ choose an arbitrary $i = 1, \ldots, k$ with $\widetilde{\chi}_i(l) := 1$ and $\widetilde{\chi}_j(l) := 0$ for $j \neq i$.

"(i), (iii) , (iv)": Choose an index subset $\{l_1, \ldots, l_k\} \subset \{1, \ldots, N\}$ such that

$$\mathscr{B} := \begin{pmatrix} \widetilde{X}_1(l_1) & \ldots & \widetilde{X}_k(l_1) \\ \vdots & & \vdots \\ \widetilde{X}_1(l_k) & \ldots & \widetilde{X}_k(l_k) \end{pmatrix} \tag{3.5}$$

is regular. A solution satisfying (i), (iii) and (iv) is given by $\widetilde{\mathscr{A}} := \mathscr{B}^{-1}$, since by construction $\widetilde{\chi}_i(l_i) = 1$ and therefore (iv) holds. The first column of the equation $\chi\mathscr{B} = \widetilde{X}$ with $\widetilde{X}_1 = e$ and $\mathscr{B}_{1i} = 1$ gives us (i).

"(i), (ii), (iii)": Since $\widetilde{X}_1(l) \equiv 1$, the points $(\widetilde{X}_1(l), \ldots, \widetilde{X}_k(l)) \in \mathbb{R}^k, l = 1, \ldots, N$, are included in a big enough $(k-1)$-simplex spanned by the vertices

$$\big\{(1, b_{12}, \ldots, b_{1k}), \ldots, (1, b_{k2}, \ldots, b_{kk})\big\}.$$

With $b_{1i} := 1$ and $\mathscr{B}_{ij} := b_{ij}$ one defines a regular (k, k)-matrix $\mathscr{B}$ and $\widetilde{\mathscr{A}} := \mathscr{B}^{-1}$. Condition (ii) holds by construction of the simplex. Condition (i) can be proved as above.

"(ii), (iii), (iv)": Take the solution satisfying (i), (ii) and (iii) and scale each χ_i such that (iv) is met.

"Uniqueness": If there exists a solution satisfying (i), (ii) and (iv), then there exists an index subset $\{l_1, \ldots, l_k\} \subset \{1, \ldots, N\}$ such that $\widetilde{\chi}_i(l_j) = \delta_{i,j}$. If, in addition, condition (iii) holds, then the points $(\widetilde{X}_1(l), \ldots, \widetilde{X}_k(l)) \in \mathbb{R}^k, l = 1, \ldots, N$ lie inside a regular $(k-1)$-simplex spanned by the vertices

$$\big\{(1, \widetilde{X}_2(l_1), \ldots, \widetilde{X}_k(l_1)), \ldots, (1, \widetilde{X}_2(l_k), \ldots, \widetilde{X}_k(l_k))\big\}$$

and $\widetilde{\mathscr{A}} = \mathscr{B}^{-1}$ with $\mathscr{B}$ defined in (3.5). As the choice of the vertices among the data points is unique up to index permutation within $\{1, \ldots, k\}$, $\widetilde{\mathscr{A}}$ and therefore the solution is unique. □

Available information. Any algorithm on the described basis will supply k metastable conformations (typically as visual objects) together with

- the probabilities $\widetilde{\pi}_i$ for the system to *be* within state i as

$$\widetilde{\pi}_i = \sum_{l=1}^{N} \pi_l \widetilde{\chi}_i(l) = \langle \widetilde{\chi}_i, e \rangle_\pi, \tag{3.6}$$

- the probabilities w_{ii} for the system to *stay* in state i,

$$w_{ii} = \frac{\langle \widetilde{\chi}_i, \widetilde{T}\widetilde{\chi}_i\rangle_\pi}{\langle \widetilde{\chi}_i, e\rangle_\pi} = \frac{\langle \widetilde{\chi}_i, \widetilde{T}\widetilde{\chi}_i\rangle_\pi}{\widetilde{\pi}_i}, \tag{3.7}$$

- the probabilities w_{ij}, $i \neq j$, for the system to *move* from state i to j,

$$w_{ij} = \frac{\langle \widetilde{\chi}_i, \widetilde{T}\widetilde{\chi}_j\rangle_\pi}{\langle \widetilde{\chi}_i, e\rangle_\pi} = \frac{\langle \widetilde{\chi}_i, \widetilde{T}\widetilde{\chi}_j\rangle_\pi}{\widetilde{\pi}_i}. \tag{3.8}$$

With $\widetilde{D}^2 = \mathrm{diag}(\widetilde{\pi}_1, \ldots, \widetilde{\pi}_k)$ the coupling matrix $\widetilde{W} = (w_{ij})$ reads

$$\widetilde{W} = \widetilde{D}^{-2}\langle \widetilde{\chi}, \widetilde{T}\widetilde{\chi}\rangle_\pi. \tag{3.9}$$

Following a suggestion of Huisinga in his thesis [11], we characterize *metastability* by the term

$$\sum_{i=1}^{k} w_{ii} = \mathrm{tr}(\widetilde{W}).$$

Of course, this definition makes only sense as long as the (stochastic) coupling matrix is diagonally dominant, which means that $w_{ii} > 0.5$, $i = 1, \ldots, k$.

Huisinga and Schmidt [13] have shown an $O(\epsilon)$ lower bound for the measure of metastability in the case of a strict {0,1}-clustering. Further insight into our new framework, where we use almost characteristic functions, can be gained by an perturbation analysis, which provides an $O(\epsilon^2)$ result for the estimation of metastability.

Theorem 3.2. *In terms of the perturbation parameter ϵ, the following approximation results hold*:

$$\widetilde{\chi} = \chi + O(\epsilon^2), \quad \widetilde{\pi} = \pi + O(\epsilon^2). \tag{3.10}$$

Let $\widetilde{\Lambda} = diag(\widetilde{\lambda}_1, \ldots, \widetilde{\lambda}_k)$. Assume that for a feasible set of almost characteristic functions $\widetilde{\chi} = \widetilde{X}\widetilde{\mathscr{A}}$ the inequality

$$\Theta = \|\widetilde{\mathscr{A}}^{-1}\widetilde{\Lambda}\widetilde{\mathscr{A}} - I_k\|_1 < 1 \tag{3.11}$$

is satisfied. Then metastability can be bounded via

$$\sum_{i=1}^{k} \widetilde{\lambda}_i - O(\epsilon^2) \leqslant \sum_{i=1}^{k} w_{ii} < \sum_{i=1}^{k} \widetilde{\lambda}_i. \tag{3.12}$$

Proof. We introduce the formal expansions

$$\widetilde{\chi} = \chi + \epsilon\chi^{(1)} + O(\epsilon^2), \quad \widetilde{\mathscr{A}} = \mathscr{A} + \epsilon A^{(1)} + O(\epsilon^2).$$

Insertion into the defining equation $\widetilde{\chi} = \widetilde{X}\widetilde{\mathscr{A}}$ then yields the zero order result $\chi = X\mathscr{A}$ and the first order result

$$\chi^{(1)} = \chi(\mathscr{A}^{-1}A^{(1)} + B\mathscr{A})$$

with B from Lemma 2.1. As already mentioned, the first order correction $X^{(1)} = \chi B$ represents just a shift of the constant levels within each of the invariant subsets—see Fig. 1, right. In our new frame of almost characteristic functions this means that all data $\widetilde{X}(l)$, $l = 1, \ldots, N$, are still condensed in the k vertices of the simplex $\widetilde{\sigma}_{k-1}$; this is expressed in the transformation result $\widetilde{\mathscr{A}} = \mathscr{B}^{-1}$ given in (3.5). Consequently, the relations

$$A^{(1)} = -\mathscr{A}B\mathscr{A}, \quad \chi^{(1)} = 0$$

must hold. From this, we then see that

$$\widetilde{\pi}_i = \langle \widetilde{\chi}_i, e\rangle_\pi = \langle \chi_i + \mathrm{O}(\epsilon^2), e\rangle_\pi = \pi_i + \mathrm{O}(\epsilon^2),$$

which confirms (3.10) and completes the first part of the proof.

For the second part of the theorem, we return to the representation (3.9) for $\widetilde{W}$. Upon reformulating

$$\langle \widetilde{\chi}, \widetilde{T}\widetilde{\chi}\rangle_\pi = \widetilde{\mathscr{A}}^T \langle \widetilde{X}, \widetilde{T}\widetilde{X}\rangle_\pi \widetilde{\mathscr{A}} = \widetilde{\mathscr{A}}^T \langle \widetilde{X}, \widetilde{X}\widetilde{\Lambda}\rangle_\pi \widetilde{\mathscr{A}} = \widetilde{\mathscr{A}}^T \langle \widetilde{X}, \widetilde{X}\rangle_\pi \widetilde{\Lambda}\widetilde{\mathscr{A}}$$

and using π-orthogonality of the eigenvectors $\widetilde{X}$ we arrive at

$$\widetilde{W} = \widetilde{D}^{-2}\widetilde{\mathscr{A}}^T\widetilde{\Lambda}\widetilde{\mathscr{A}}. \tag{3.13}$$

Moreover, based on the relation

$$\langle \widetilde{\chi}, \widetilde{\chi}\rangle_\pi = \widetilde{\mathscr{A}}^T \langle \widetilde{X}, \widetilde{X}\rangle_\pi \widetilde{\mathscr{A}} = \widetilde{\mathscr{A}}^T \widetilde{\mathscr{A}},$$

we may derive the alternative expression

$$\widetilde{W} = \underbrace{\widetilde{D}^{-2}\langle \widetilde{\chi}, \widetilde{\chi}\rangle_\pi}_{S} \underbrace{\widetilde{\mathscr{A}}^{-1}\widetilde{\Lambda}\widetilde{\mathscr{A}}}_{M}. \tag{3.14}$$

By a short calculation, the above matrix $S = (S_{ij})$ can be shown to be stochastic, which implies that $\sum_{j=1}^k S_{ij} = 1$. The matrix $M = (M_{ij})$ is obviously spectrally similar to the eigenvalue matrix $\widetilde{\Lambda}$. By assumption, M satisfies the condition $\Theta = \|M - I_k\|_1 < 1$, where $\|\cdot\|_1$ denotes the maximum column sum norm; this implies that $M_{ii} > M_{ji}$ for $j \neq i$.

With these properties, the upper bound in (3.12) can be directly verified as follows:

$$\sum_{i=1}^k w_{ii} = \sum_{i=1}^k \sum_{j=1}^k S_{ij}M_{ji} < \sum_{i=1}^k \left(\sum_{j=1}^k S_{ij}\right) M_{ii} = \sum_{i=1}^k M_{ii} = \sum_{i=1}^k \widetilde{\lambda}_i.$$

In order to verify the lower bound in (3.12), let $D^2 = \mathrm{diag}(\pi_1, \ldots, \pi_k)$ and observe that $D^2 = \langle \chi, \chi\rangle_\pi$. With this preparation and the help of the just proven results (3.10), we derive the perturbation pattern of the matrix S as

$$S = \widetilde{D}^{-2}\langle \widetilde{\chi}, \widetilde{\chi}\rangle_\pi = (D^2 + \mathrm{O}(\epsilon^2))^{-1}(\langle \chi, \chi\rangle_\pi + \mathrm{O}(\epsilon^2)) = I_k + \mathrm{O}(\epsilon^2).$$

Insertion into the expression (3.14) then immediately yields

$$\mathrm{tr}(\widetilde{W}) = \mathrm{tr}(SM) = \mathrm{tr}(M) + \mathrm{O}(\epsilon^2) = \mathrm{tr}(\widetilde{\Lambda}) + \mathrm{O}(\epsilon^2).$$

This result applies for both the upper and the lower bound of the metastability and therefore confirms (3.12) in particular, which completes the proof. □

Note that $\widetilde{\Lambda}(\epsilon)|_{\epsilon=0} = I_k$ so that for sufficiently small perturbation parameter the above inequality (3.11) will be satisfied.

Remark. We have implicitly assumed that

$$\sum_{i=1}^{k}(1 - \widetilde{\lambda}_i) = \mathrm{O}(\epsilon),$$

which implies, in particular, that the Perron index k must be chosen small enough such that $1 - \widetilde{\lambda}_k = \mathrm{O}(\sqrt{\epsilon})$ does not occur. Otherwise, the $\mathrm{O}(\epsilon^2)$-terms would degenerate to $\mathrm{O}(\epsilon)$-terms that would interfere with the $\mathrm{O}(\epsilon)$-terms in $\widetilde{\Lambda}(\epsilon)$—thus making our analysis meaningless.

Interpretation. Before finishing the section, we want to discuss certain interpretations of the here introduced concept of almost characteristic functions. Recall that the formerly used *exact* characteristic functions χ represented the geometrical objects of almost invariant sets. Consequently, we might interpret *almost* characteristic functions $\widetilde{\chi}$ as characterizing almost invariant 'fuzzy' sets. Such a definition is certainly all but clear. However, in our former conformation analysis in terms of exact characteristic functions, metastable conformations have been naturally visualized (typically in volume rendering or isosurface representation) via the probabilities

$$(\pi_1 \chi_i(1), \ldots, \pi_N \chi_i(N)).$$

Therefore, in our new conformation analysis in terms of almost characteristic functions, we will visualize metastable conformations via the probabilities

$$(\pi_1 \widetilde{\chi}_i(1), \ldots, \pi_N \widetilde{\chi}_i(N)).$$

4. Constrained optimization problems

Throughout this section, we will drop all tildas, which means that we write $\widetilde{X} = X$, $\widetilde{\chi} = \chi$, $\widetilde{\mathscr{A}} = \mathscr{A}$, unless explicitly stated otherwise. From Theorem 3.1 we know that in general the solution of the cluster problem in terms of almost characteristic functions is not unique. Therefore, in order to obtain a solution, we cannot impose all of the four conditions simultaneously. In the earlier papers [21,22], the positivity condition (ii) had been abandoned. Here, however, we stick to the stochastic interpretation of χ, which means that we keep the three conditions (i), (ii), and (iii), but

drop the maximal scaling condition (iv). Instead we make either the metastability or the scaling a possible objective function to be maximized subject to constraints. The k^2 unknown coefficients α_{ij} enter as variables into this optimization problem.

4.1. Feasible set

Let $\mathscr{F}$ denote the feasible set defined by the linear constraints (i)–(iii) of Theorem 3.1. Insertion of (i) into (ii) yields the positivity constraints

$$0 \leqslant \sum_{j=1}^{k} \alpha_{ji} X_j(l) = \alpha_{1i} + \sum_{j=2}^{k} \alpha_{ji} X_j(l), \quad i = 1, \ldots, k, \;\; l = 1, \ldots, N. \tag{4.15}$$

Upon inserting (iii) into (i) we get

$$\sum_{i=1}^{k} \sum_{j=1}^{k} \alpha_{ji} X_j = \sum_{j=1}^{k} \left(\sum_{i=1}^{k} \alpha_{ji} \right) X_j = e. \tag{4.16}$$

As $X_1 = e$ and X is linear independent, we can further reduce this equation to

$$\sum_{i=1}^{k} \alpha_{ji} = \delta_{j1}, \quad j = 1, \ldots, k, \tag{4.17}$$

with the canonical Kronecker δ. Setting $i = 1$ in (4.15) we may proceed as

$$\begin{aligned} 0 &\leqslant \sum_{j=1}^{k} \alpha_{j1} X_j(l) \\ &= \alpha_{11} + \sum_{j=2}^{k} \alpha_{j1} X_j(l) \\ &= \alpha_{11} + \sum_{j=2}^{k} \left(-\sum_{i=2}^{k} \alpha_{ji} \right) X_j(l). \end{aligned}$$

Thus we arrive at the following representation of F:

$$\begin{aligned} &\alpha_{j1} = \delta_{j1} - \sum_{i=2}^{k} \alpha_{ji}, \quad j = 1, \ldots, k, \\ &\alpha_{11} \geqslant \sum_{j=2}^{k} \left(\sum_{i=2}^{k} \alpha_{ji} \right) X_j(l), \quad l = 1, \ldots, N, \\ &\alpha_{1i} \geqslant -\sum_{j=2}^{k} \alpha_{ji} X_j(l), \quad i = 2, \ldots, k, \;\; l = 1, \ldots, N. \end{aligned} \tag{4.18}$$

This set has at least the interior point $\alpha^*_{ji} = \delta_{j1} k^{-1}$ and is therefore not empty.

4.2. Objective functions

There is a variety of objective functions to model the given problem of cluster identification. We select two intuitive options. The first one directly takes the dropped *scaling* condition (iv) as the objective function

$$I_1[\alpha] = \sum_{j=1}^{k} \max_{l=1,\dots,N} \chi_j(l) \leqslant k \tag{4.19}$$

to be *maximized*. The above upper bound arises trivially and is actually reached at a unique solution—compare Theorem 3.1. The second choice of objective function is the *metastability*

$$I_2[\alpha] = \sum_{j=1}^{k} w_{jj} = \sum_{j=1}^{k} \frac{\langle \chi_j, T\chi_j \rangle_\pi}{\langle \chi_j, e \rangle_\pi} < \sum_{i=1}^{k} \lambda_i, \tag{4.20}$$

which also is to be *maximized*; the above upper bound has been shown in Theorem 3.2. Upon inserting the coefficients α_{ij} into $I_{1,2}$ and using (4.17), we obtain

$$I_1[\alpha] = 1 + \sum_{j=1}^{k} \max_{l=1,\dots,N} \sum_{i=2}^{k} \alpha_{ij} X_i(l) \leqslant k \tag{4.21}$$

and

$$I_2[\alpha] = \sum_{j=1}^{k} \sum_{i=1}^{k} \lambda_i \frac{\alpha_{ij}^2}{\alpha_{1j}} = 1 + \sum_{i=2}^{k} \lambda_i \sum_{j=1}^{k} \frac{\alpha_{ij}^2}{\alpha_{1j}} < 1 + \sum_{i=2}^{k} \lambda_i. \tag{4.22}$$

Over the feasible set $\mathscr{F}$, both objective functions are positive, convex, and bounded from above. Therefore, any solution of the associated maximization problem will have to lie on one of the vertices of the feasible set $\mathscr{F}$ (in the non-degenerate case).

4.3. Reduced feasible set

We assume that there are no linear dependencies in (4.18). In this case, $k(k-1)$ out of the kN inequalities in (4.18) must be active. These inequalities represent the fact that each of the k almost characteristic functions is non-negative; equality means that the corresponding data directly lie on one of the k facets of the simplex σ_{k-1}. Under the assumption of linear independence made, we can satisfy a maximum of $k-1$ equalities per facet. As a consequence, each type of inequality in (4.18) will arise at most $(k-1)$ times. There are $\binom{N}{k}$ possibilities to choose these equations. Among them are certainly the following $2k$ necessary conditions for optimality: k conditions for the first column of $\mathscr{A}$,

$$\alpha_{j1} = \delta_{j1} - \sum_{i=2}^{k} \alpha_{ji}, \quad j = 1, \ldots, k, \tag{4.23}$$

and k conditions for the first row of $\mathscr{A}$,

$$\alpha_{1i} = -\min_{l=1,\ldots,N} \sum_{j=2}^{k} \alpha_{ji} X_j(l), \quad i = 1, \ldots, k. \tag{4.24}$$

Obviously, these conditions define a subset $\mathscr{F}'$ of the feasible set $\mathscr{F}$. Note that we have dropped the equation corresponding to the second inequality in (4.18), which may be verified via (4.23) to be identical to (4.24) for $i = 1$. By construction the optimal solution lies in $\mathscr{F}'$. Eqs. (4.23) and (4.24) can be used to reduce the dimension of the objective function from k^2 to $(k-1)^2$ by eliminating the $2k-1$ coefficients α_{ij} with either $i = 1$ or $j = 1$ from the problem. Observe that the case $i = j = 1$ occurs both in (4.23) and in (4.24), which implies the hidden side condition

$$(\alpha_{11} =) \quad 1 - \sum_{i=2}^{k} \alpha_{1i} = -\min_{l=1,\ldots,N} \sum_{j=2}^{k} \alpha_{j1} X_j(l). \tag{4.25}$$

4.4. Solution for $k = 2$

In this special case, the sums in system (4.23) and (4.24) degenerate to just one term yielding

$$\begin{aligned} &\alpha_{11} = 1 - \alpha_{12}, && \alpha_{21} = -\alpha_{22}, \\ &\alpha_{11} = \max_{l=1,\ldots,N} \alpha_{22} X_2(l), && \alpha_{12} = -\min_{1,\ldots,N} \alpha_{22} X_2(l). \end{aligned} \tag{4.26}$$

This system has exactly 2 solutions for $\alpha_{22} > 0$ and $\alpha_{22} < 0$ each. From the first line of (4.26) we may readily observe that the second solution can be obtained by mere permutation of columns 1 and 2 in $\mathscr{A}$, i.e. by mere index permutation, so that it represents the identical set of almost characteristic functions. Let $\alpha_{22} > 0$ and introduce the convenient notation

$$X_2^+ = \max_{l=1,\ldots,N} X_2(l), \quad X_2^- := -\min_{1,\ldots,N} X_2(l).$$

By orthogonality of X we know that X_2^+, X_2^- are both positive. The above system of equations may now be rewritten as

$$\begin{aligned} &\alpha_{11} = 1 - \alpha_{12}, && \alpha_{21} = -\alpha_{22}, \\ &\alpha_{11} = \alpha_{22} X_2^+, && \alpha_{12} = \alpha_{22} X_2^-. \end{aligned} \tag{4.27}$$

In this special case, the vertex conditions alone already fix the maximal solution for both objective functions as

$$\begin{aligned} &\alpha_{21} = -\frac{1}{X_2^+ + X_2^-}, && \alpha_{11} = \frac{X_2^+}{X_2^+ + X_2^-}, \\ &\alpha_{22} = \frac{1}{X_2^+ + X_2^-}, && \alpha_{12} = \frac{X_2^-}{X_2^+ + X_2^-}. \end{aligned} \tag{4.28}$$

The optimal choice of almost characteristic functions therefore comes out to be

$$\chi_1(l) = \frac{X_2^+ - X_2(l)}{X_2^+ + X_2^-}, \quad \chi_2(l) = \frac{X_2(l) + X_2^-}{X_2^+ + X_2^-}. \tag{4.29}$$

For the scaling objective function we obtain

$$I_1(\alpha_{opt}) = 1 - \alpha_{21} X_2^- + \alpha_{22} X_2^+ = 2, \tag{4.30}$$

which is the upper bound in (4.19). As a consequence, this solution must be unique due to Theorem 3.1. For the metastability we get

$$I_2(\alpha_{\mathrm{opt}}) = 1 + \frac{1}{X_2^+ X_2^-}\lambda_2. \tag{4.31}$$

Upon combining the upper bound in (3.12) and the above special result, we see that $X_2^+ X_2^- > 1$ must hold.

5. Unconstrained optimization

In this section we treat the *constrained* optimization problem for $k > 2$ as derived in Section 4 above and reformulate it as an unconstrained optimization problem. Appropriate splitting of terms in the *scaling* objective function yields

$$I_1[\alpha] = 1 + \max_{l=1,\ldots,N} \sum_{j=2}^{k} \alpha_{j1} X_j(l) + \sum_{i=2}^{k} \max_{l=1,\ldots,N} \sum_{j=2}^{k} \alpha_{ji} X_j(l). \tag{5.32}$$

Next, we apply (3.1) to express the *metastability* objective function by means of the k^2 coefficients α_{ij} so that

$$I_2[\alpha] = 1 + \sum_{i=2}^{k} \lambda_i \left(\frac{\alpha_{i1}^2}{\alpha_{11}} + \sum_{j=2}^{k} \frac{\alpha_{ij}^2}{\alpha_{1j}} \right). \tag{5.33}$$

It is certainly worth mentioning that, in comparison with (3.6), the above denominators can be rewritten as

$$\alpha_{1j} = \langle X_1, \chi_j \rangle_\pi = \langle \chi_j, e \rangle_\pi = \widetilde{\pi}_j,$$

i.e. these coefficients are the probabilities for the system to *be* in metastable conformation j and should be positive—so that the functional I_2 as a whole is well-defined.

For both of the objective functions, the above deliberate splitting of terms indicates that the $2k - 1$ coefficients

$$\alpha_{11}, \ldots, \alpha_{1k}, \alpha_{21}, \ldots, \alpha_{k1}$$

must be inserted from the equality constraints (4.23) and (4.24). With this decoupling we have arrived at an *unconstrained* optimization problem in terms of the reduced set of $(k-1)^2$ coefficients α_{ij} with $i \neq 1$, $j \neq 1$. Indeed, once the optimal reduced

coefficient set has been computed, we may use (4.23) for $j = 2, \ldots, k$ and (4.24) for $i = 1, \ldots, k$.

Thus we are only left with the treatment of the hidden condition (4.25), which means we have to simultaneously satisfy (4.23) for $j = 1$. For this purpose, a small detour is necessary: Careful examination of the analytic form of the two objective functions shows homogeneity of order 1, which means that

$$I_{1,2}[\gamma\alpha] = 1 + \gamma(I_{1,2}[\alpha] - 1), \quad \gamma > 0. \tag{5.34}$$

In view of (4.23) for $j = 1$, we may just evaluate the arising sum for precomputed coefficients $\bar{\alpha}_{ij}$ and rescale them by the factor

$$\bar{\gamma} = \left(\sum_{i=1}^{k} \bar{\alpha}_{1i} \right)^{-1}$$

according to

$$\bar{\alpha}_{ij} \longrightarrow \alpha_{ij} = \bar{\gamma}\bar{\alpha}_{ij} \quad \text{for all } i, j = 1, \ldots, k. \tag{5.35}$$

By insertion of $\bar{\gamma}$ into (5.34) we arrive at an unconstrained optimization problem for the functionals

$$J_{1,2}[\bar{\alpha}] = I_{1,2}[\bar{\gamma}\bar{\alpha}] \tag{5.36}$$

in terms of the $(k-1)^2$ unknowns $\bar{\alpha}_{ij}$.

In order to keep our interpretation of metastable clusters, we will select the functional J_2 for maximization. Once a computational scheme has generated an optimal or suboptimal solution, we may monitor the *defect*

$$\delta = 1 - J_1/k \geqslant 0,$$

which measures the difference of the maxima of the almost characteristic functions from unity. If the defect vanishes, then the solution is *unique*. Otherwise, any positive defect is certainly tolerable within the interpretation of almost characteristic functions as given in (3.6), (3.7), and (3.8).

Note that both of the above functionals $J_{1,2}$ as defined in (5.36) are homogeneous of order 0, i.e.

$$J_{1,2}[\gamma\bar{\alpha}] = J_{1,2}[\bar{\alpha}], \quad \gamma > 0.$$

In passing we mention that for $\bar{\alpha}_{ij} = 0$ with $i, j \neq 1$ the functionals J_1 and J_2 are not defined—a degenerate case which is not relevant, since it would mean that $\chi_1 = e$ and $\chi_i = 0$ for $i \neq 1$, i.e. the only cluster would be the whole invariant set ($k = 1$ only).

Algorithm PCCA+. As derived so far, we achieve a solution of our original *constrained* maximization problem by solving the *unconstrained* maximization problem with respect to J_2, which supplies optimal coefficients $\bar{\alpha}_{ij}$ for $i, j \neq 1$. From these coefficients we then compute the actual coefficients $\alpha_{ij} = \bar{\gamma}\bar{\alpha}_{ij}$ via (5.35).

The above unconstrained optimization problem is continuous, but not differentiable. Therefore any BFGS type algorithm would not be expected to be efficient here. As a first choice, we selected the classical nonlinear simplex method of Nelder and Mead [16], which turned out to require only few iterations in all examples tested so far. Strictly speaking, this algorithm will only find a local maximum close to the starting guess, not a guaranteed global one.

In order to construct a reasonable *starting guess* for this iteration we recur to Theorem 3.1. In the *unperturbed* case, Eq. (2.5) gives us the inverse $\widetilde{\mathscr{A}}^{-1} = \mathscr{A}^{-1} = (a_{ji})$ with

$$a_{ji} = X_i(l_j), \quad i = 1, \ldots, k, \quad j = 1, \ldots, k,$$

for a selection of indices $l_j \in \mathscr{S}_j$. In this case, all data can be transformed into the k vertices of the simplex σ_{k-1}. In the *perturbed* case, the problem is to find a simplex $\widetilde{\sigma}_{k-1}$ which approximates the convex hull of the input data $(\widetilde{X}_2(l), \ldots, \widetilde{X}_k(l)) \in \mathbb{R}^k$ for $l = 1, \ldots, N$—compare also Fig. 3, left. In order to construct this simplex, we start from the barycenter $\overline{X}$ of all data, defined via the π-product as

$$\overline{X} = \frac{1}{N}\langle \widetilde{X}, e\rangle_\pi = \left(\frac{1}{N}, 0, \ldots, 0\right)^T.$$

Therefore the origin $\overline{X}' = (0, \ldots, 0) \in \mathbb{R}^{k-1}$ can be taken as starting point for the construction of $\widetilde{\sigma}_{k-1}$. With this geometry in mind, an algorithm in the spirit of suggestions of [21] can be stated as follows:

A. Subalgorithm for starting simplex $\widetilde{\sigma}_{k-1}$:

I. Determine the input point $\widetilde{X}(l_1)$ as the one that has the maximum distance to $\overline{X}'$, i.e. the one with maximum $\|\widetilde{X}(l)\|_2$. This is an $O(N)$ computational process. Let $\mathscr{X}_1 = \widetilde{X}(l_1)$.

II. For $i = 2, \ldots, k$ determine an index l_i such that $\|\widetilde{X}(l_i) - \mathscr{X}_{i-1}\|$ is maximal. Again, this is an $O(N)$ computational process. Let the projection plane spanned by the data points selected so far be denoted as $\mathscr{X}_i = \text{span}\{\widetilde{X}(l_1), \ldots, \widetilde{X}(l_i)\}$.

From this algorithm we obtain the k vertices $(\widetilde{X}(l_1), \ldots, \widetilde{X}(l_k))$ of an initial guess for $\widetilde{\sigma}_{k-1}$. In view of (3.5) we can then compute the (k, k)-matrix

$$\overline{\mathscr{A}} = \begin{pmatrix} \widetilde{X}_1(l_1) & \ldots & \widetilde{X}_k(l_1) \\ \vdots & & \vdots \\ \widetilde{X}_1(l_k) & \ldots & \widetilde{X}_k(l_k) \end{pmatrix}^{-1}.$$

Dropping the first row and the first column of $\overline{\mathscr{A}}$ we arrive at some reduced $(k-1, k-1)$-matrix $\overline{\mathscr{A}}' = (\bar{\alpha}_{ij})$.

B. Subalgorithm for computing $\mathscr{A}$:

Given any reduced matrix $\mathscr{A}'$, the matrix $\mathscr{A}$ is computed as follows:

I. For $j = 2, \ldots, k$ set $\bar{\alpha}_{j1} := -\sum_{i=2}^{k} \bar{\alpha}_{ji}$.

For $i = 1, \ldots, k$ set $\bar{\alpha}_{1i} := -\min_{l=1,\ldots,N} \sum_{j=2}^{k} \bar{\alpha}_{ji} X_j(l)$.

II. Compute the sum of the elements of the first row of $\overline{\mathscr{A}}$,

$$\gamma := \sum_{i=1}^{k} \bar{\alpha}_{1i}.$$

The elements of the feasible matrix $\mathscr{A}$ are computed as follows:

$$\alpha_{ji} := \frac{\bar{\alpha}_{ji}}{\gamma}, \quad i, j = 1, \ldots, k.$$

Complete constrained minimization algorithm:

I. Apply subalgorithm A to compute a starting guess for the unconstrained optimization variables, i.e. the elements of $\mathscr{A}'$.

II. Compute all constrained optimization variables via subalgorithm B. Evaluate the functional J_2.

III. **If** convergence is achieved: STOP. **Else** do a Nelder/Mead update of the unconstrained variables and **goto** II.

6. Numerical illustrations

In Figs. 3 and 4 we had already given results for the simple butane molecule; in that case, a unique solution had existed. In the present section we exemplify our new algorithm PCCA+ at two more illustrative examples, where non-uniqueness plays a role.

Generally speaking, in nearly all our molecular examples, the initial guess of the coefficient matrix $\widetilde{\mathscr{A}}$ has turned out to be already rather accurate so that only few Nelder/Mead iterations were required to find an optimal solution. In order to be able to demonstrate a visible difference between initial and final iterate, we start with an artificial example especially constructed for the purpose of illustration.

6.1. Artificial example ($k = 3$)

In Fig. 5 the iterative behavior of PCCA+ in the case of a non-unique solution is shown. For the simplices $\widetilde{\sigma}_2$ and σ_2, we compare the initial guesses, the rescaled initial simplices, and the final iterates, i.e. the computed solutions.

For the functional I_1 as defined in (4.19) together with its upper bound we get

$$I_1[\alpha^*] = 2.57 < 3 \quad \Leftrightarrow \quad \delta = 0.14.$$

Since $\delta \neq 0$, the solution is seen to be not unique. The final functional value I_2 as defined in (4.20) compared with its upper bound is

$$I_2[\alpha^*] = 1.67 < 2.68.$$

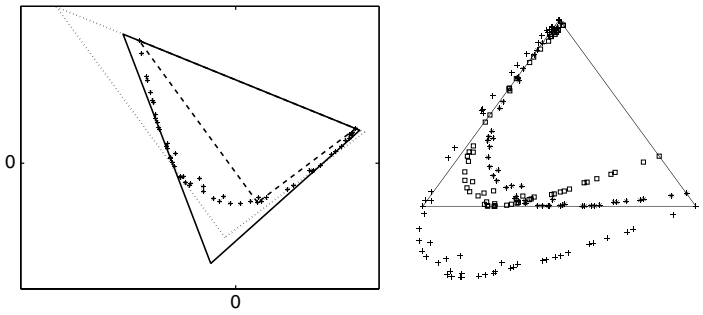

Fig. 5. Artificial example. Left: input data (∗) in simplex $\widetilde{\sigma}_2$. Initial simplex guess (- - -), rescaled initial guess (· · ·), and final iterate (—). *Right: almost characteristic function values in simplex* σ_2. Initial guess (+), rescaled initial guess (□), and final iterate (∗).

6.2. Example: HIV protease inhibitor VX-478

This moderate size molecule is the basis for the anti-AIDS drug Agenerase distributed by Glaxo Wellcome. Generally speaking, the HIV is hard to attack directly by drugs, since it is a so-called retrovirus that mutates faster than any molecular recognition can take place. As a consequence, any HIV pharmaceutical will attack the supporting enzymes. One of them is the HIV protease, which regulates the passage of HIV through the cell membrane. The here selected molecule has been exactly designed (by Vertex) to inhibit this passage. The molecular data were taken from the public domain Protein Data Bank (PDB).

As shown in Cordes et al. [1], the present PCCA+ is a frequently called subroutine in the spatial box discretization of the underlying transfer operator in biomolecules; that discretization device would not have worked with the less robust former version PCCA.

Typically, a hierarchical series of runs for successively decreasing temperature is realized—see, e.g., Fischer et al. [8]. The selected example has been simulated at a temperature of 900 K, where a first separation of different conformations is visible. The conformational changes according to the most relevant dihedral angle have been examined. The corresponding transition matrix has the spectrum

$$\widetilde{\lambda}_1 = 1.0,\ \widetilde{\lambda}_2 = 0.997,\ \widetilde{\lambda}_3 = 0.985,\ \widetilde{\lambda}_4 = 0.815, \ldots$$

with a small gap after the second eigenvalue and a significant gap after the third one; hence, we chose $k = 3$ for the Perron index, but compared it with $k = 2$ and $k = 4$, too, for the purpose of illustration.

6.3. Perron index k = 3

In Fig. 6, the three almost characteristic functions $\widetilde{\chi}_1, \widetilde{\chi}_2, \widetilde{\chi}_3$ are visualized by volume rendering according to their weighted probabilities

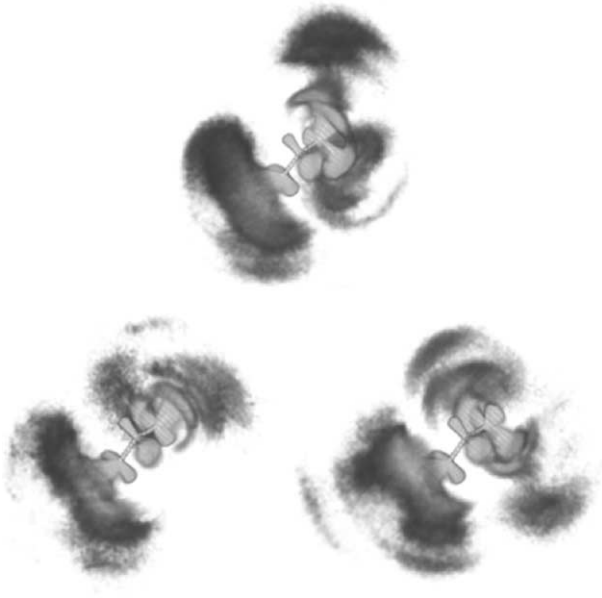

Fig. 6. *HIV protease inhibitor*. *Top:* conformation 1. *Bottom left:* conformation 2. *Bottom right:* conformation 3.

$$\big(\pi_1 \widetilde{\chi}_i(1), \ldots, \pi_N \widetilde{\chi}_i(N)\big).$$

The probabilities (3.6) to *be* in conformation 1, 2, or 3, came out as

$$\widetilde{\pi}_1 = \langle \widetilde{\chi}_1, e\rangle_\pi = 0.51, \quad \widetilde{\pi}_2 = \langle \widetilde{\chi}_2, e\rangle_\pi = 0.37, \quad \widetilde{\pi}_3 = \langle \widetilde{\chi}_3, e\rangle_\pi = 0.12.$$

The coupling matrix $\widetilde{W} = (w_{ij})$, reflecting the probabilities w_{ij} for transitions *between* conformations i and j, is

$$\widetilde{W} = \left(\frac{\langle \widetilde{\chi}_i, \widetilde{T}\widetilde{\chi}_j\rangle_\pi}{\langle \widetilde{\chi}_i, e\rangle_\pi} \right) = \begin{pmatrix} 0.93 & 0.02 & 0.05 \\ 0.03 & 0.95 & 0.02 \\ 0.20 & 0.06 & 0.74 \end{pmatrix}.$$

As for assumption (3.11) in Theorem 3.2, we here obtain $\Theta = 0.0165 < 1$ so that all $O(\epsilon^2)$ results apply. For the sake of illustration of our new method, Fig. 7 shows the simplices for the corresponding eigenvector components and the almost characteristic function values. Again 'dirty zero' data occur, which would have caused extra treatment and, as a consequence, possible non-robustness in the former algorithmic version PCCA.

Finally, the functionals I_1, I_2 were obtained as

$$I_1[\alpha^*] = 2.89 < 3 \quad \Leftrightarrow \quad \delta = 0.04, \quad I_2[\alpha^*] = 2.62 < 2.98.$$

Obviously, since $\delta \neq 0$, the solution is not unique. Nevertheless it is extremely useful for the purpose of cluster analysis. In fact, Fig. 7 gives is a clear indication of three clusters which condense close to the corners of the simplices.

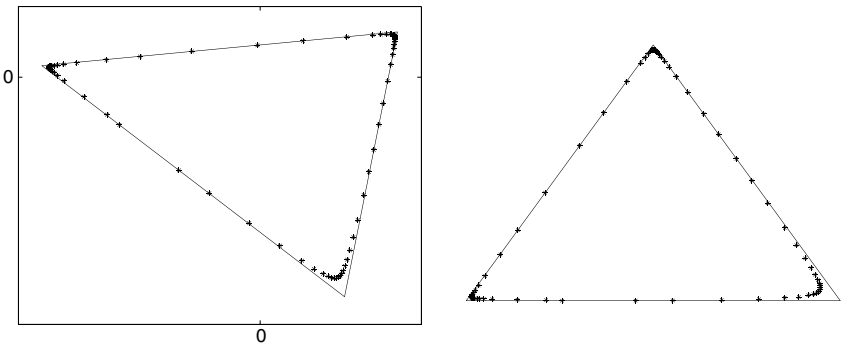

Fig. 7. *HIV protease inhibitor: eigenvectors and almost characteristic function values. Left:* input data and final iterate simplex $\widetilde{\sigma}_2$. Observe the occurrence of 'dirty zero' data. *Right:* almost characteristic function values in simplex σ_2.

Fig. 8. *HIV protease inhibitor:* almost characteristic function values in simplex σ_1.

6.4. Comparison case $k = 2$

From the final paragraph in Section 4 we know that in this case $I_1[\alpha^*] = 2$, $\delta = 0$, which means that a unique solution for the two almost characteristic functions is guaranteed. From (4.31) we obtain

$$I_2[\alpha] = 1.9 < 1.997$$

for the metastability. The coupling matrix arises as

$$\widetilde{W} = \begin{pmatrix} 0.94 & 0.06 \\ 0.04 & 0.96 \end{pmatrix}$$

As for (3.11) , we here obtain $\Theta = 0.0027 < 1$. In Fig. 8, the corresponding data distribution is represented. Note that the intervals $\widetilde{\sigma}_1$ and σ_1 differ only by some shift and some scaling. This representation clearly reveals the fact that the data contain three clusters rather than just two ones.

6.5. Comparison case $k = 4$

In this case we obtain the objective function values

$$I_1[\alpha^*] = 2.99 < 4 \quad \Leftrightarrow \quad \delta = 0.25, \qquad I_2[\alpha^*] = 2.75 < 3.797.$$

For the coupling matrix PCCA+ supplies

$$\widetilde{W} = \begin{pmatrix} 0.84 & 0.03 & 0.06 & 0.07 \\ 0.02 & 0.25 & 0.02 & 0.71 \\ 0.02 & 0.01 & 0.95 & 0.02 \\ 0.02 & 0.25 & 0.02 & 0.71 \end{pmatrix}.$$

Note that the second row is no longer diagonally dominant ($w_{22} = 0.25 < 0.5$) so that the definition of metastability no longer makes any sense. Moreover, we here get $\Theta = 10.776 > 1$, which means that assumption (3.11) in Theorem 3.2 is violated.

7. Conclusion

We have suggested and worked out in detail a new Perron cluster analysis algorithm PCCA+. The main idea behind the new method is to describe almost invariant sets by almost characteristic functions, understood to be generated by perturbation of characteristic functions describing exact invariant sets. On the basis of perturbation theory, the new algorithm can be seen to be clearly more robust than the former version PCCA. This is also confirmed by numerical examples.

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References

[1] F. Cordes, M. Weber, J. Schmidt-Ehrenberg. Metastable conformations via successive Perron-Cluster Cluster Analysis of dihedrals, Technical Report ZIB 02-40, Zuse Institute Berlin, 2002.
[2] P. Deuflhard, From molecular dynamics to conformational dynamics in drug design, in: M. Kirkilionis, S. Krömker, R. Rannacher, F. Tomi (Eds.), Trends in Nonlinear Analysis, Springer, 2003, pp. 269–287.
[3] P. Deuflhard, M. Dellnitz, O. Junge, Ch. Schütte, Computation of essential molecular dynamics by subdivision techniques. In [4], pp. 98–115, 1999.
[4] P. Deuflhard, J. Hermans, B. Leimkuhler, A.E. Mark, S. Reich, R.D. Skeel (Eds.), Computational Molecular Dynamics: Challenges, Methods, Ideas, Lecture Notes in Computational Science and Engineering, Springer-Verlag, vol. 4, 1999.
[5] P. Deuflhard, A. Hohmann, Numerical Analysis in Modern Scientific Computing: An Introduction, in: Texts in Applied Mathematics, Springer, New York, vol. 43, 2003.
[6] P. Deuflhard, W. Huisinga, A. Fischer, Ch. Schütte, Identification of almost invariant aggregates in reversible nearly uncoupled Markov chains, Linear Algebra Appl. 315 (2000) 39–59.
[7] P. Deuflhard, Ch. Schütte. Molecular conformation dynamics and computational drug design, in: J.M. Hill, R. Moore (Eds.), Applied Mathematics Entering the 21st Century, Proc. ICIAM 2003, Sydney, Australia, 2004.
[8] A. Fischer, Ch. Schütte, P. Deuflhard, F. Cordes, Hierarchical uncoupling–coupling of metastable conformations. In [17], pp. 235–259, 2002.
[9] G. Froyland, Statistically optimal almost-invariant sets, Technical Report, BHP Billiton Innovations, GPO Box 86A, Melbourne, Vic. 3121, Australia, 2003.
[10] G. Froyland, M. Dellnitz, Detecting and locating near-optimal almost-invariant sets and cycles, SIAM J. Sci. Comput. 24 (6) (2003) 1839–1863.

[11] W. Huisinga, Metastability of Markovian systems: a transfer operator based approach in application to molecular dynamics, PhD thesis, Free University Berlin, 2001.
[12] W. Huisinga, S. Meyn, Ch. Schütte, Phase transitions and metastability in Markovian and molecular systems, Ann. Appl. Probab. 14 (1) (2004) 419–458.
[13] W. Huisinga, B. Schmidt, Metastability and Dominant Eigenvalues of Transfer Operators, Preprint, Free University Berlin, June 2004.
[14] T. Kato, Perturbation Theory for Linear Operators, Springer, Berlin, 1995. Reprint of the 1980 edition.
[15] C.D. Meyer, Stochastic complementation, uncoupling Markov chains, and the theory of nearly reducible systems, SIAM Rev. 31 (1989) 240–272.
[16] J.A. Nelder, R. Mead, A simplex method for function minimization, Comput. J. 7 (1965) 308–313.
[17] T. Schlick, H.H. Gan (Eds.), Computational Methods for Macromolecules: Challenges and Applications—Proceedings of the 3rd International Workshop on Algorithms for Macromolecular Modelling, Springer, Berlin, Heidelberg, New York, 2000.
[18] Ch. Schütte, Conformational dynamics: modelling, theory, algorithm, and application to biomolecules, Habilitation thesis, Fachbereich Mathematik und Informatik, Freie Universität Berlin, 1999.
[19] C. Schütte, A. Fischer, W. Huisinga, P. Deuflhard, A direct approach to conformational dynamics based on hybrid Monte Carlo, J. Comput. Phys., Special Issue on Computational Biophysics 151 (1999) 146–168.
[20] Ch. Schütte, W. Huisinga, Biomolecular conformations can be identified as metastable sets of molecular dynamics, in: P.G. Ciarlet, C. Le Bris (Eds.), Handbook of Numerical Analysis, Special Volume Computational Chemistry, North-Holland, vol. X, pp. 699–744, 2003.
[21] M. Weber, Improved Perron cluster analysis, Technical Report ZIB 03-04, Zuse Institute Berlin, 2003.
[22] M. Weber, T. Galliat, Characterization of transition states in conformational dynamics using Fuzzy sets, Technical Report 02-12, Konrad–Zuse–Zentrum (ZIB), Berlin, March 2002.