A Central Partition of Molecular Conformational Space.
III. Combinatorial Determination of the Volume Spanned by a Molecular System.

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Abstract— In the first work of this series [1] it was shown that the conformational space of a molecule could be described to a fair degree of accuracy by means of a central hyperplane arrangement. The hyperplanes divide the space into a hierarchical set of cells that can be encoded by the face lattice poset of the arrangement.

The model however, lacked explicit rotational symmetry which made impossible to distinguish rotated structures in conformational space. This problem was solved in a second work [2] by sorting the elementary 3D components of the molecular system into a set of morphological classes that can be properly oriented in a standard 3D reference frame.

This also made possible to find a solution to the problem that is being addressed in the present work: for a molecular system immersed in a heat bath we want to enumerate the subset of cells in conformational space that are visited by the molecule in its thermal wandering.

If each visited cell is a vertex on a graph with edges to the adjacent cells, here it is explained how such graph can be built.

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I. Introduction

Molecular dynamics simulations (MDS) are an essential tool for the modeling of large and very large molecules, it gives us a precise and detailed view of a molecule’s behaviour [3]. However, it has two limitations that hamper many practical applications: it is a random algorithm, as such it does not perform a systematic exploration of molecular conformational space (CS); and that currently, the output from an MDS represents only a very small fraction of the volume spanned by the system in CS.

Here it is presented a complementary approach that locally is less precise but that can encompass a broader view of CS. It consists in dividing the CS into a finite set of cells, so that the only knowledge we seek about the system is whether it can be located in a given cell or not.

As was extensively discussed in ref. [1] the partition is a variant of the $A_N$ partition [4-5]: a

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central arrangement of hyperplanes that divides CS into a set of cells shaped as polyhedral cones, such that for a molecule with $N$ atoms we have $(N!)^3$ cells. The set of hyperplanes is also a Coxeter reflection arrangement: the arrangement is invariant upon reflection on any of the hyperplanes.

This structure has three important properties [1]:

1. Associated with a Coxeter arrangement there is a polytope [5] whose symmetry group is the reflection group of the arrangement. The face lattice poset$^3$ of the polytope is a hierarchical combinatorial structure that enables us to manage the sheer complexity of CS, since with simple codes we can describe from huge regions down to single cells.

2. The information needed to encode any face in the polytope is a sequence of $3 \times N$ integers, which is a generalization of a structure known to combinatorialists as non-crossing partition sequence [5,6].

3. The construction is modular: if we consider the CS of two subsets of atoms from a system, the CS of the union set has an associated polytope that is the cartesian product of the polytopes$^4$ of the two subspaces, and its partition sequence is the ordered union of the two partition sequences [1].

The last one is particularly important since the CS of the whole system can be built from that of the parts, and the CS of a small number of atoms is very much smaller than that of the whole molecule and we can reasonably assume that it can be thoroughly explored by an MDS. Moreover, in merging the CSs corresponding to subsets of atoms the number of cells grows exponentially while the length of coding sequences grows only linearly.

II. The basic construction

Let $(e_1, ..., e_N)$ be the standard basis in $\mathbb{R}^N$, the convex hull of the endpoints of the vectors $\{e_i\}$ is a regular $(N-1)$-simplex: this gives a segment, an equilateral triangle and a tetrahedron in 2, 3 and 4 dimensions respectively.

For each edge of the regular $(N-1)$-simplex there is an hyperplane $H_{ij} : x_i - x_j = 0$, perpendicular to the edge and containing the other vertices, this hyperplane divides $\mathbb{R}^N$ in three regions. A point $x$ can be in one of these:

- $x_i > x_j$ the positive side, where the $i^{th}$ coordinate dominates the $j^{th}$ coordinate,
- $x_i < x_j$ the negative side, with the $j^{th}$ coordinate dominating the $i^{th}$ coordinate,
- $x_i = x_j$ on the plane.

This leads to a sign vector $S$ for every point $x \in \mathbb{R}^N$, where the $\alpha^{th}$ component $X_{\alpha} \in \{+, -, 0\}$ denotes whether $x$ is on the positive side of $H_{\alpha}$, on its negative side or lies on $H_{\alpha}$.

Also notice that the line $x_1 = x_2 = ... = x_{N-1} = x_N$ is contained in every plane $H_{ij}$, if the orthogonal complement to this line is $U : x_1 + x_2 + ... + x_{N-1} + x_N = 0$, we can define a partition

$^2$That pass through the origin.

$^3$The faces in the induced decomposition of the polytope ordered by inclusion.

$^4$If $P \subset \mathbb{R}^p$ and $Q \subset \mathbb{R}^q$ are polytopes the product polytope $P \times Q$ has the set of vertices $(x,y) \in \mathbb{R}^{p+q}$ where $x$ and $y$ are vertices of $P$ and $Q$ respectively.
on \( \mathcal{U} \), known to combinatorialists as \( \mathcal{A}_{N-1} \) [4-5], with the set of hyperplanes \( \mathcal{H}_{ij} = \mathcal{U} \cap H_{ij} \). For reasons that are explained below the points outside \( \mathcal{U} \) are not relevant to our construction.

The set of all points \( x \in \mathcal{U} \) having the same sign vector \( S \) form a cell in the decomposition of \( \mathcal{U} \) induced by \( \mathcal{A}_{N-1} \), associated to this decomposition is the following important structure: the face poset, which is the set of all cells induced by \( \mathcal{A}_{N-1} \) ordered by inclusion. The maximal cells (all \((N-1)\)-dimensional) are called regions and are shaped as polyhedral cones, the coordinates of the points in the interior of a region obey the relation:

\[
x_{i_1} < x_{i_2} < \ldots < x_{i_{N-1}} < x_{i_N} \quad (1)
\]

the dominance relations (1) between the coordinates can be encoded by the sequence

\[(i_1)(i_2) \ldots (i_{N-1})(i_N) \quad (2)\]

thereafter referred as the cell dominance partition sequence (DPS), where the set of indices \( i_{\alpha} \) is a permutation of \((1, 2, \ldots, N-1, N)\). Each index appears enclosed between parenthesis for reasons that will be made clear in the next section.

Reflecting a point in general position on \( \mathcal{H}_{ij} \) gives an image where the coordinates \( i \) and \( j \) are switched and the others are left unchanged. Multiple reflections of a point on the hyperplanes \( \mathcal{H}_{ij} \) generate a set of \( N! \) images which are the permutations of its coordinates. This leads to the fact that the \( \left( \begin{array}{c} N \\end{array} \right) \) hyperplanes form a Coxeter reflection arrangement [7] whose symmetry group is isomorphic to the symmetric group \( S_N \) of permutations of the set \((1, 2, \ldots, N-1, N)\).

The reflection group \( \mathcal{A}_{N-1} \) is also the symmetry group of a polytope: the \( N \)-permutohedron or \( \Pi_{N-1} \) [5], so called because its vertices are obtained by permuting the coordinates of the vector \((1, 2, \ldots, N-1, N)\). The faces of the the permutohedron are polar to the cells of the hyperplane arrangement and the face lattices of both are isomorphic.

For a molecule with \( N \) atoms as the \( x, y \) and \( z \) coordinates are independent of each other [1] we have a \( \mathcal{A}_{N-1} \) partition for each of them, that is \( \mathcal{A}_{N-1}^3 \) for the whole \( CS \). As it has been emphasized in [1-2] the \(-1\) is because of the translation symmetry: the conformations outside the hyperplane \( \mathcal{U} \) correspond clear in the next section.

The radial dimension in \( CS \) is also spurious: multiplying the coordinates of an arbitrary 3D conformation by a positive factor generates a set of points lying on a half-line starting at the origin. The partition \( \mathcal{A}_{N-1} \) is central because that takes into account the scaling symmetry.

\( \mathcal{A}_{N-1}^3 \) on the other hand does not take into account the rotation symmetry [2], the solution of this problem and its consequences will be discussed in sections IV to VII.

### III. The face lattice poset

The combinatorial structure of the \( \mathcal{A}_{N-1} \) face poset is the fundamental concept behind this work, it can be understood by studying a class of objects called tournaments which are directed graphs with \( N \) nodes [8], these are used to investigate the properties of permutations, so useful for characterizing the cells in \( CS \).

A permutation of a set of \( N \) elements can be represented by an acyclic, complete and labelled tournament (see fig. 1 for a description), where:
• The term **acyclic** means that the graph contains no directed cycles.

• A graph is **complete** if there is always an arc between any two nodes, if an arc goes from \( i \) to \( j \) we say that \( i \) **dominates** \( j \). The **score** of a node is the number of nodes it dominates.

• Each node of the graph has a unique **label** which is a number between 1 and \( N \) that distinguishes it from the other nodes.

In what follows the term tournament refers exclusively to tournaments where the above qualifiers apply.

![Figure 1](image-url)

**Figure 1.**

a) A complete acyclic tournament corresponding to the permutation \((3, 6, 1, 4, 2, 5)\) which is the score of each vertex plus 1, the indices in the dominance sequence of vertices \((3)(5)(1)(4)(6)(2)\) correspond to the inverse permutation.

b) The antisymmetric incidence matrix, the rows in the upper triangle form the sign vector.

For a tournament with \( N \) nodes the following statements are true:

I. *In a tournament there is always a node called the sink that is dominated by every other node.*
   Consider the last node of any maximal directed path, if an arc connects it to another node then either the path is not maximal or there is a cycle; if there were another sink it would be connected to the former and either it would dominate or be dominated.

II. *In a tournament there is always a node called the source that dominates every other node.*

III. *Any subgraph of a tournament is also a tournament.*
   Any subgraph from a complete graph is also complete, and it can contain no cycles otherwise they would also be present in the parent graph.

IV. *There is one maximal path that spans the graph.*
   Consider the subtournament obtained by removing the source, then start the path with the arc that goes from the source to the subsource, and repeat the same step with the subgraph.
until you reach the sink. The path obtained goes through every node since there are $N - 1$
steps, and is maximal since skipping a subsource for another node shortens the path since
the node is dominated by the subsource.

V. The sequence of labels of the nodes visited by the maximal path is the dominance partition
sequence.

By the construction procedure the first node, the source, dominates all other nodes, the
second dominates the remaining nodes and so on.

**Theorem 1.** In a tournament the arcs between a set of consecutive nodes in the maximal path
can be arbitrarily reversed and the resulting graph still be a tournament if the subgraph spanning
the consecutive nodes is a tournament.

Since the subgraph and its complement are tournaments they contain no cycles, thus a cycle
must involve nodes between the subgraph and the complement, but this is not possible since by
construction the set of consecutive nodes is dominated by the preceding nodes in the maximal
path and likewise it dominates the following ones.

By $V$ reversing an arc between contiguous nodes is equivalent to a transposition in the $DPS$.

**Theorem 2.** In a tournament encoded by $(i_1)(i_2) ... (i_\alpha) ... (i_{\alpha+n-1}) ... (i_{N-1})(i_N)$ the permutations in the set of $n$ consecutive indices $i_\alpha ... i_{\alpha+n-1}$ give a set of tournaments that encode the vertices of an $n$-permutohedron.

If we restrict ourselves to the $n$-dimensional subspace spanned by the coordinates $(x_{i_\alpha}, ..., x_{i_{\alpha+n-1}})$
the permutations of the indices above corresponds to the permutations of the coordinates of the
vector $(\alpha, \alpha + 1, ..., \alpha + n - 1)$ which are the vertices of a $\Pi_{n-1}$.

**Corollary.** The $n$-permutohedron is a face of $\Pi_{N-1}$.

Obviously since it is contained in the affine hyperplane $x_{i_\alpha} + x_{i_{\alpha+1}} + ... + x_{i_{\alpha+n-1}} = n(\alpha+(n-1)/2)$.
This face is encoded by the $DPS$

$$(i_1)(i_2) ... (i_\alpha ... i_{\alpha+n-1}) ... (i_{N-1})(i_N) \quad (3)$$

that represents the set of $n!$ sequences that are permutations of the indices $i_\alpha$ to $i_{\alpha+n-1}$.

**Corollary.** The sequence $(i_1)(i_2) ... (i_\alpha ... i_{\alpha+n-1}) ... (i_\beta ... i_{\beta+m-1}) ... (i_{N-1})(i_N)$ encodes the
$(n + m - 2)$-face $\Pi_{n-1} \times \Pi_{m-1}$.

This can be seen from the definition given above of the product of polytopes.

Thus the meaning of parenthesis in $DPS$s becomes apparent: each parenthesis enclosing a
sequence of length $n$ encodes an $\Pi_{n-1}$ polytope, and the whole sequence encodes the product of
all these polytopes.

These sequences can be ordered by inclusion to form a face lattice poset, which is isomorph to
the one obtained with the sign vectors, since like $DPS$s they are another encoding scheme for
tournaments [1].

This is an important feature because it implies the modularity of the model: the face lattice of
a molecule can be obtained as the product of the face lattices of subsets of atoms.
IV. Enumerating the orientations of a simplex

For a simplex with random morphology we define the set of vectors that run along the edges and their associated central planes (figs. 2a and 2b)

\[ \mathbf{e}_{ij} = \mathbf{v}_i - \mathbf{v}_j, \ 1 \leq i < j \leq 4 \]  
\[ \mathcal{E}_{ij}^0(x) = \{x \in \mathbb{R}^3 : \mathbf{e}_{ij} \cdot x = 0\} \]

Each plane divides 3D space into positive and negative halves

\[ \mathcal{E}_{ij}^+(x) = \{x \in \mathbb{R}^3 : \mathbf{e}_{ij} \cdot x > 0\} \quad \text{and} \quad \mathcal{E}_{ij}^-(x) = \{x \in \mathbb{R}^3 : \mathbf{e}_{ij} \cdot x < 0\} \]

As for the regular tetrahedron described above (5) and (6) generate an \( A_3 \) partition of 3D space in 24 irregular shaped cells, fig. 2b.

This partition has the following interesting property: assume for instance that the \( x \) axis of a central orthogonal reference system in general position lies entirely within the cell encoded by the permutation (3, 1, 4, 2), or equivalently the sign vector (+ + − − +), then the dominance relation \( v_2x < v_4x < v_1x < v_3x \) holds for the \( x \) coordinates of the vertices of the simplex.

This suggests a method for enumerating the cells in \( A_3 \) that correspond to the different orientations of the simplex: it suffices to enumerate the cells with the lowest dimensions, the more numerous (3, 3, 3)-dimensional cells can be easily obtained through the connecting paths in the

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5All along this work the term orientation is used interchangeably with DPS and sign vector.
face lattice.

The 1-dimensional cells in $\mathcal{A}_3$ are determined by the set of vectors perpendicular to the faces of the simplex and to pairs of opposite edges

$$
\begin{align*}
&f_{123} = e_{12} \wedge e_{23}, \quad f_{124} = e_{12} \wedge e_{24}, \quad f_{134} = e_{13} \wedge e_{34}, \quad f_{234} = e_{23} \wedge e_{34}, \\
&f_{12} = e_{12} \wedge e_{23}, \quad f_{13} = e_{13} \wedge e_{24}, \quad f_{14} = e_{14} \wedge e_{23}
\end{align*}
$$

(7)

their corresponding central planes will be designated $F_{ijk}$ and $F_{ij}$.

If we take the sign of the scalar products between the sets of vectors (4) and (7) we obtain a matrix

$$
\begin{array}{ccccccc}
e_{12} & e_{13} & e_{14} & e_{23} & e_{24} & e_{34} & DPS \\
f_{123} & 0 & 0 & + & 0 & + & + & (4)(123) \\
f_{124} & 0 & - & 0 & - & 0 & + & (234)(3) \\
f_{134} & + & 0 & 0 & - & - & 0 & (2)(134) \\
f_{234} & + & + & + & 0 & 0 & 0 & (234)(1) \\
f_{12} & 0 & - & - & - & - & 0 & (12)(34) \\
f_{13} & + & 0 & + & - & 0 & + & (24)(13) \\
f_{14} & - & - & 0 & 0 & + & + & (14)(23)
\end{array}
$$

(8)

that up to a sign reversal is an invariant [4,9], it is the same for any simplex whatever its morphology. The rows are the sign vectors of the 1-dimensional cells with the corresponding dominance partition sequence on the right, these cells can be seen in fig. 2b where the labels $f_{ijk}$ and $f_{ij}$ are on top of the lines intersected by the planes $E_{ij}$, $E_{ik}$, $E_{jk}$ and $E_{il}$ respectively.

We start by enumerating the orientations of a reference system whose $z$ axis is parallel to one of the vectors (7), $f_{123}$ for example, the remaining axis $x$ and $y$ will be on the plane $F_{123}$, the problem is to determine how the $E_{ij}$ (5) divide this plane into 2-dimensional cells. In fig. 3 we can see the four possible 12-sector partitions that can be generated by the vectors $e_{12}$, $e_{13}$ and $e_{23}$ and the perpendicular intersections of the planes $E_{12}$, $E_{13}$ and $E_{23}$. This partition gives us only half of the sign vectors components, to obtain the remaining ones we need to introduce a morphological classification of simplexes.

V. Morphological classification of simplexes

For a given simplex, like the one in fig. 2a for instance, we compute the sign of the scalar products of the vectors (4) and (7) between them, this gives the following two tables

$$
\begin{array}{cccc}
e_{13} & e_{14} & e_{23} & e_{24} & e_{34} & f_{124} & f_{134} & f_{234} & f_{12} & f_{13} & f_{14} \\
e_{12} & + & + & - & - & - & f_{123} & + & + & - & + & + \\
e_{13} & + & + & - & - & - & f_{124} & + & + & + & + \\
e_{14} & + & + & + & + & + & f_{134} & + & + & + & - \\
e_{23} & + & + & + & + & + & f_{234} & - & + & - \\
e_{24} & + & + & + & + & + & f_{12} & + & + & + \\
e_{24} & + & + & + & + & + & f_{13} & + & + & + \\
e_{24} & + & + & + & + & + & f_{13} & + & + & +
\end{array}
$$

(9)

The set of signs (9) refer mostly to angles between adjacent edges and dihedral angles between contiguous faces: $+$, 0 and $-$ are for acute, right and obtuse angles respectively.
Within figs. a to d the vector \( f_{123} \) points in the upward direction, the labels \( e_{12}, e_{13} \) and \( e_{23} \) are over the lines that run along these vectors, and the corresponding perpendicular lines are the intersections with the planes \( E_{12}, E_{13} \) and \( E_{23} \) respectively. The label \( f'_{ijk} \) means that the corresponding line runs along the projection of vector \( f_{ijk} \) on \( F_{123} \). The labels \( f'_{124} \) and \( f'_{12} \) over the intersection of plane \( E_{12} \), for instance, is because \( f_{124} \) and \( f_{12} \) are contained in that plane, and reciprocally \( e_{12} \) is contained in the planes \( F_{124} \) and \( F_{12} \).

All these lines converge at the origin and partition \( F_{123} \) in 12 sectors: between the inner and outer circles are the sign vector components of \( e_{12}, e_{13} \) and \( e_{23} \), for each sector they should be read from inside out in that order; within the inner circle there are the sign vector components of \( f'_{124}, f'_{134} \) and \( f'_{234} \) respectively.

The sectors are numbered from 1 to 12 as indicated in a.

Thus the rough morphological characteristics of a simplex can be encoded in a 36 bit binary\(^6\) sequence: there are a total of 3936 sequences that correspond to geometrically realizable simplexes, these define the set of morphological classes \( A \) of labelled simplexes. We define the volume of a

\(^6\)We exclude sequences harboring 0s as they form a set of null measure.
class as the set of cells it spans in $A_3^3$.

It should be reminded that this classification has a graph structure, since geometrical deformations in a simplex from one class induce a transition to other classes thus establishing a connectivity between them; the precise structure of such a graph is of no utility in the present work, but the concept is important when we will introduce below the dynamical states of a simplex.

The binary sequence (9) is instrumental in finding the partition of the planes perpendicular to 1-dimensional cells, in our example it can be deduced from (9) that the partition of $F_{123}$ is the one of fig. 3c, since it is the only one that satisfies the relation

$$(SIGN(e_{12},e_{13}), SIGN(e_{12},e_{23}), SIGN(e_{13},e_{23})) = (+)$$

There are also the relations concerning vectors $e_{14}$, $e_{24}$ and $e_{34}$

$$(SIGN(e_{14},e_{12}), SIGN(e_{14},e_{13}), SIGN(e_{14},e_{23})) = (+ + +) \quad (10a)$$
$$(SIGN(e_{24},e_{12}), SIGN(e_{24},e_{13}), SIGN(e_{24},e_{23})) = (- - +) \quad (10b)$$
$$(SIGN(e_{34},e_{12}), SIGN(e_{34},e_{13}), SIGN(e_{34},e_{23})) = (- + +) \quad (10c)$$

thus $e_{14}'$, the projection$^7$ of $e_{14}$, must lie in sectors 2 or 3 by (10a); similarly $e_{24}'$ and $e_{34}'$ must be in sectors 6 or 7 by (10b) and (10c). These ambiguities can be resolved by set of relations

$$(SIGN(e_{14},f_{123}), SIGN(e_{24},f_{123}), SIGN(e_{34},f_{123})) = (++) \quad (11a)$$
$$(SIGN(f_{124},f_{123}), SIGN(f_{134},f_{123}), SIGN(f_{234},f_{123})) = (++) \quad (11b)$$
$$(SIGN(f_{12},f_{123}), SIGN(f_{13},f_{123}), SIGN(f_{14},f_{123})) = (- + +) \quad (11c)$$

$e_{14}$ for instance, lies on $F_{124}$ and together with $f_{124}$ stands above $F_{123}$, by (11a) and (11b), this implies that $SIGN(e_{14}',f_{124}) = -$. Repeating this procedure for $f_{134}$ and $f_{234}$, and for each of the vectors $e_{24}$ and $e_{34}$ we end up with

$$(SIGN(e_{14}',f_{124}), SIGN(e_{14}',f_{134}), SIGN(e_{14}',f_{14})) = (--) \quad (12a)$$
$$(SIGN(e_{24}',f_{124}), SIGN(e_{24}',f_{134}), SIGN(e_{24}',f_{234})) = (--) \quad (12b)$$
$$(SIGN(e_{34}',f_{124}), SIGN(e_{34}',f_{134}), SIGN(e_{34}',f_{234})) = (+ -) \quad (12c)$$

(12a), (12b) and (12c) imply that $e_{14}'$, $e_{24}'$ and $e_{34}'$ are to be found in sectors 3, 6 and 7 respectively, thus removing these ambiguities.

There is one ambiguity though that cannot be resolved by the binary sequence (9) : $H_{24}$ runs through sectors 3 and 9 together with $e_{14}'$, and $H_{14}$ runs through sectors 6 and 12 as $e_{24}'$, so we end up with two possible partitions of $F_{123}$ that are shown in fig. 4.

As can be seen from fig. 4 each partition generates 12 2-dimensional cells and the same number in one dimension, by construction the lines along the 1-dimensional cells are never perpendicular to each other, as a consequence for an $(x,y)$ reference system centered at the origin if one of the axis runs along the edge of a sector the other will be located inside a sector: rotating the axis system enables us to scan 12 $(1,2,3)$ and 12 $(2,1,3)$ dimensional cells (see fig. 4).

Thus for any orientation structure associated with a plane $F_{...}$, a reference system with one axis perpendicular to the plane can be in $2 \times 12 \times 6$ cells with dimensions any permutation of the sequence $(3,2,1)$ in $(x,y,z)$. This solves the problem of enumerating the cells with the lowest possible dimensions that correspond to an orientation of the simplex, the $(3,3,3)$-dimensional cells can be found from these through the connecting paths in the $A_3^3$ cell lattice poset.

$^7$The $'$ superscript designates the projection of a vector on $F_{...}$.
Figure 4. The two possible orientation structures of $F_{123}$.

The thick lines are the intersections of $E_{ij}$ with $F_{123}$, the thin ones are lines along the vectors $e_{ij}$ and $e'_{ij}$. The sign vectors of the 2-dimensional cells lie inside the circle, the 1-dimensional ones are outside along the corresponding partition line, they should be read from inside out. An (X,Y) axis system has been superimposed on the first structure as a visual aid to show how the sectors can be scanned.

Thus for any orientation structure associated with a plane $F_{ijk}$, a reference system with one axis perpendicular to the plane can be in $2 \times 12 \times 6$ cells with dimensions any permutation of the sequence (3,2,1) in $(x, y, z)$. This solves the problem of enumerating the cells with the lowest possible dimensions that correspond to an orientation of the simplex, the (3,3,3)-dimensional cells can be found from these through the connecting paths in the $A_3^3$ cell lattice poset.

VI. THE CONFORMATIONAL SPACE OF A SIMPLEX

We have seen that the binary sequences (9) cannot define unambiguous partitions of the planes $F_{ijk}$: for each $F_{ijk}$ there can be between 1 and 3 possible orientation structures, and between 1 and 24 for each $F_{ij}$; in a given class only a fraction of the combinations between the different orientation structures, one from each plane, give geometrically realizable simplexes.

To remove ambiguities we need to define a set $B$ of morphological classes such that for each one the range of geometrical variation only allows one orientation structure per $F_{ijk}$. An empirical Monte Carlo calculation yields a total of 125712 classes of labelled simplexes, a class $A$ has a number of subclasses $B$ that goes from a minimum of 1 up to a maximum of 220. These morphological subclasses have the remarkable property that for a 3D conformation any cell in the volume can be reached through a rotation, which is is an obvious consequence of the one to one correspondence between $F_{ijk}$ planes and orientation structures.

Thus a class $A$ can be decomposed into a set of subclasses $B$, that can be unambiguously oriented in a standard 3D reference frame, and its volume in $CS$ is simply the union of the volumes of its subclasses.
VII. The orientation structures

To achieve a morphological classification of simplexes we need to know how many classes of orientation structures there are, since the classes A decompose into subclasses B and each of these is determined by 7 orientation structures.

A first classification concerns the circular order of the vectors $e'_{ij}$ in the plane $F_\alpha$. This can be deduced from the set of signs (9), for instance: by (4) and (7) the shortest circular path going through $e'_{12}$, $e'_{13}$ and $e'_{23}$ must be less than $\pi$, and it runs counter-clockwise if the sign of $F_{123}$, $F_\alpha$ is +.

This example leads to the general solution that was discussed in [2]: the 7 vectors (7) define a central partition dual to $A_3$ [9] that divides the 3D space in 32 cells. The sign vector of the cell that contains $F_\alpha$ defines the sense of the shortest circular path that connects the projected vectors in the 7 ordered sets $\{e'_{12}, e'_{13}, e'_{23}\}$, $\{e'_{12}, e'_{14}, e'_{24}\}$, $\{e'_{13}, e'_{14}, e'_{34}\}$, $\{e'_{23}, e'_{24}, e'_{34}\}$, $\{e'_{12}, e'_{34}\}$, $\{e'_{13}, e'_{24}\}$ and $\{e'_{14}, e'_{23}\}$. This generates a set of 7 constraints from which the circular order of the $e'_{ij}$ in $F_\alpha$ can be deduced, making a total of 32 possible circular orientations.

As can be seen in fig. 4 on the plane $F_\alpha$ each $e'_{ij}$ contributes a total of 4 separations between sectors at periodic intervals of 90° each comprising exactly 6 sectors, on the other hand there are two classes of separations: either a line along the vector $e'_{ij}$ or the intersection of a plane $H_{ij}$, in an interval of 90° the possible distributions of the two separators amounts to a total of $2^5$ combinations. This makes 1024 classes of orientation structures like those in fig. 4, among these 48 appear to be not geometrically realizable since they are not found in any class B.

VIII. Determination of the graph of cells

Most often in mesoscopic models of biological macromolecules atoms are represented as point-like structures surrounded by an atomic force field [10,11], thus any four atoms are the vertices of a 3-simplex. Also for a molecular system with $N$ atoms an order relation can be defined by numbering its atoms from 1 to $N$, so that 3-simplexes can be designated as a 4-tuple of ordered integers which are the numbers of its atoms.

Beyond the orientation problem, the classes A and B bring the possibility of analyzing the dynamics of a molecular system in terms of discrete entities, the range of morphological variation for simplexes within a molecule can be explored in molecular dynamics simulations (MDS) and the results can be summarized as follows [2,12]

- 90% of simplexes in a structure evolve within less than 20 classes A.
- The maximum variation observed is somewhat less than 200 classes, about 5% of the total.

This result opens up the possibility of determining the set of geometrically accessible cells in the CS of a molecular system.

The CS of a simplex has a total of 13824 cells and, typically, the volume of a class A is about one third of that number, much less if we exclude structures that can be derived through a rotation. This volume is very small when compared to the huge number of cells spanned by a molecular system, and it can be reasonably assumed that the volume of a simplex can be scanned by a molecular dynamics run. What cannot be scanned by a simulation is the set of structures that arise by combining the local movements.
MDSs can be used to determine the subgraph of classes spanned by every simplex, and the volume of the molecular system in CS can be obtained by progressively merging the CS of individual simplexes. As we were able to determine the different orientations of a simplex this process can be done excluding redundant rotated structures.

Before proceeding further let us show with a simple example the basic operations that are involved in the process of merging CSs. If we have two adjoining simplexes \( S_\alpha \) and \( S_\beta \) represented by the tetrads \{14,33,82,86\} and \{14,82,86,91\} respectively (notice that their common faces correspond to the vertices \((v_1,v_3,v_4)\) and \((v_1,v_2,v_3)\)), if the 3D structure of \( S_\alpha \) is in a cell encoded by the dominance partition sequence

\[
((82)(14)(86)(33), (33)(82)(86)(14), (86)(14)(33)(82))
\]

then the set cells in \( CS_\beta \) geometrically compatible with (13) will be those whose DPS contains the pattern

\[
((82)(14)(86), (82)(86)(14), (86)(14)(82))
\]

Thus a cell in \( CS_\beta \) with DPS

\[
((82)(91)(14)(86), (91)(82)(86)(14), (86)(14)(91)(82))
\]

can be merged with (13) and generates the set of 4 cells in \( CS_\alpha \times CS_\beta \)

\[
((82)(91)(14)(86)(33), (33 91)(82)(86)(14), (86)(14)(33 91)(82))
\]

which corresponds to a square face in the polar polytope.

To calculate the graph of the geometrically accessible cells we begin by picking an arbitrary reference simplex, preferably one with low morphological variation, and arbitrarily choose an orientation among those available, this will be the simplex on level 1, the simplexes adjacent to this one form the level 2, and so on. Since adjacent simplexes in a 3D structure share three vertices the shortest adjacency path between any two of them has at most length 4, so we end up with simplexes in 5 levels.

We need not to include every simplex from the molecule to perform a useful calculation, but there is the minimum requirement that every pair of atoms from a total of \( \binom{N}{2} \) should be present at least once in a 4-tuple, otherwise the DPSs could not be determined.

The calculation can be done through the following procedure:

1. Start at level 1.
2. From any simplex in level \( n \) we select the compatible orientations in the adjoining simplexes in level \( n + 1 \).
3. From any simplex in the level \( n + 1 \) we select compatible orientations on the adjoining simplexes at the same level.
4. If \( n < 5 \) we go to step 2 and continue with level \( n + 1 \).

A link is created between any two compatible orientations in adjacent simplexes. This is done in two steps:

1. If the simplex in the lower level has not yet been visited any orientation compatible with those from the simplex in the upper level is selected.
2. Otherwise any orientation that has not been selected is discarded. And likewise an orientation that fails to form a link with an adjacent simplex is discarded because of geometrical inconsistency.

The implementation of this procedure as an efficient computer algorithm requires that the CS of a class A simplex be quickly searched for orientations compatible with those from the adjoining simplexes, these can be obtained from the set of orientation structures available to each 1-dimensional cell \( \mathcal{F}_- \) (7). This requirement can be fulfilled by building a hash table from where the DPSs like (15) can be retrieved, such table has the following set of entries:

1. the number of the orientation class: from 1 to 976,
2. the connecting face, numbered from 1 to 4,
3. the 1-dimensional \( \mathcal{F}_- \) cell (7) corresponding to the orientation structure, numbered from 1 to 7,
4. the chirality of the simplex: right or left-handed,
5. the pattern (14), of a total of 216 possible patterns.

IX. Conclusion

The aim of the present work has been to bring the sheer complexity of molecular conformational space to tractable dimensions, by building a structure that encodes the set of geometrically accessible 3D-conformations of a thermalized molecule, and putting it in a compact and manageable code. The price to pay to achieve this result is the loss of the absolute precision over the local 3D-conformations of molecular structures [1], but this has no concern with this work since we only seek to obtain a global view of conformational space. From this point of view the present formalism may be a useful complement of molecular dynamics simulations that in the detailed exploration of small regions is unexcelled.

What remains to be done is to explore the graph of cells with a Hamiltonian functional over a force field and perform energy optimizations. It should be emphasized that as a Hamiltonian is a function of distances between atoms the present structure offers the possibility of calculating the energy over entire regions of CS, since the interatomic distances can be enumerated for a set of cells and in this case the energy function is nothing else than an integral over a rational function.

References

[1] J. Gabarro-Arpa, "A central partition of molecular conformational space. I. Basic structures" Comp. Biol. and Chem., 27, 153-159, (2003).

[2] J. Gabarro-Arpa, "A central partition of molecular conformational space. II. Embedding 3D-structures", Proceedings of the 26th Annual International Conference of the IEEE EMBS, San Francisco, 3007-3010 (2004).

[3] M. Karplus and J.A. McCammon, "Molecular dynamics simulations of biomolecules", Nature Struct. Biol. 9, 949-852 (2002).

[4] A. Bjorner, M. las Vergnas, B. Sturmfels, N. White, "Oriented Matroids". Cambridge, UK, Cambridge University Press, sect. 2 (1993).

[5] S. Fomin and N. Reading, "Root systems and generalized associahedra", math.CO/0505518 (2005).
[6] G. Kreweras, "Sur les partitions non croisées d’un cycle", Disc. Math. 1, 333-350 (1972).

[7] H.S.M. Coxeter, "Regular polytopes". Dover Publicaions, Inc., New York (1973).

[8] J. W. Moon, "Topics on Tournaments". Holt, Rinehart and Winston, New York (1968).

[9] J. Folkman, J. Lawrence, "Oriented matroids", J. Combinatorial Theory B 25, 199-236 (1978).

[10] A.D. MacKerell Jr., et al., "All-Atom empirical potential for molecular modeling and dynamics studies of proteins", J. Phys. Chem. B 102, 3586-3616 (1998).

[11] W. Wang, O. Donini, C.M. Reyes, P.A. Kollman, "Biomolecular simulations: recent developments in force fields, simulations of enzyme catalysis, protein-ligand, protein-protein, and protein-nucleic acid noncovalent interactions", Annu. Rev. Biophys. Biomol. Struct. 30, 211-243 (2001).

[12] C. Laboulais, M. Ouali, M. Le Bret, J. Gabarro-Arna, "Hamming distance geometry of a protein conformational space", Proteins: Struct. Funct. Genet. 47, 169-179 (2002).