A Central Partition of Molecular Conformational Space.
IV. Extracting information from the graph of cells.

Jacques Gabarro-Arpa
Ecole Normale Supérieure de Cachan, LBPA,CNRS UMR 8113
61, Avenue du Président Wilson, 94235 Cachan cedex, France
Email: jga@infobiogen.fr

Abstract In previous works it was shown that the $3 \times N$-dimensional conformational space of a molecular system could be divided into a number of cells, and from data sampled from molecular dynamics simulations it was possible to build a structure: the graph of cells, encoding the set of cells in conformational space that the system visits in its thermal wandering. Here we describe a set of procedures for extracting useful information from this huge structure: 1st) interesting regions in the volume occupied by the system in conformational space can be bounded by a polyhedral cone whose faces are determined empirically from a set of relations between the coordinates of the molecule, 2nd) it is also shown that this cone can be split into a hierarchical set of smaller cones, 3rd) extracting sets of inter-atomic distances from the graph of cells is equivalent to finding maximal cliques in a graph.

Keywords Molecular Conformational Space, Hyperplane Arrangement, Face Lattice, Molecular Dynamics
Mathematics Subject Classification: 52B11, 52B40, 65Z05
PACS: 02.70.Ns

I. The basic construction

It was shown in a series of papers [1-4] that the conformational space of a molecule of $N+1$ atoms $\mathbb{R}^{3N}$ (thereafter referred as $CS$) could be described to a fair degree of accuracy by means of the partition generated by a set of hyperplanes passing through the origin that form a Coxeter reflection arrangement denominated $A^N$ [5,6], moreover the reflections form a symmetry group that is isomorphic to the symmetric group.

In our description of $CS$ we have three independent arrangements one for each coordinate ($x, y, z$), i.e. $A^{3N} = A^N \times A^N \times A^N$, that generate three partitions of $\mathbb{R}^{3N}$, each dividing $\mathbb{R}^N$ into a hierarchical set of regions shaped as polyhedral cones denominated cells. The hyperplanes in our partition are defined as

$$\mathcal{H}_{ij} : x_i - x_j = 0 \quad , \quad 1 \leq i < j \leq N+1$$ (1)

$^1$ $N+1$ is because the translation symmetry makes one dimension spurious [1,4].
$^2$ That a reflection through one of the hyperplanes leaves the arrangement unchanged.
each $H_{ij}$ divides $\mathbb{R}^N$ into three regions:

$$x_i < x_j \quad , \quad x_i = x_j \quad \text{and} \quad x_i > x_j$$

(2)

in the first case we say that $x_j$ dominates $x_i$, in the second case neither $x_i$ nor $x_j$ dominates, in the last case $x_i$ dominates $x_j$. As cells are bounded by the hyperplanes (1) a consequence of (2) is that the points inside a given cell (in $x$, $y$ or $z$) have the following property:

$$x_{i_1} \leq x_{i_2} \leq x_{i_3} \leq \ldots \leq x_{i_{N-2}} \leq x_{i_{N-1}} \leq x_{i_N}$$

(3)

where the sequence $(i_1, i_2, i_3, \ldots, i_{N-2}, i_{N-1}, i_N)$ is a permutation of the set $\mathcal{Z}_{N+1} = (1, 2, 3, \ldots, N-1, N, N+1)$, reflecting a point through $H_{ij}$ is equivalent to permute the coordinates $i$ and $j$ [6]. Thus a cell where a strict “less than” relation holds for every pair of coordinates in (3) is encoded by the dominance sequence

$$(i_1)(i_2)(i_3)\ldots(i_{N-2})(i_{N-1})(i_N)$$

(4a)

while for a cell where $x_{ia} = x_{ia+1} = \ldots = x_{ia+r}$, for $r+1$ consecutive indices $(i_\alpha, i_\alpha+1, \ldots, i_\alpha+r)$ in (3) will be encoded by the dominance sequence

$$(i_1)(i_2)(i_3)\ldots(i_\alpha i_{\alpha+1}\ldots i_{\alpha+r})\ldots(i_{N-1})(i_N)(i_{N+1})$$

(4b)

the first (4a) represents an $N$-dimensional cell while (4b) is a $(N-r)$-dimensional cell because it corresponds to the intersection of the hyperplanes $H_{ij}$ with $i, j \in (i_\alpha i_{\alpha+1}\ldots i_{\alpha+r})$.

**Definition 1.** The position of a coordinate $c_i$ in a cell of dimension $N$ is the position of index $i$ in the dominance sequence.

An alternative encoding of cells is by means of an $N \times N$ antisymmetric sign matrix $\mathcal{S}^c$, where $c$ stands for $x$, $y$ or $z$.

For $\mathcal{S}^c$: let $1 \leq i < j \leq N+1$, then for an arbitrary point $p$ the matrix elements for the $c$ coordinates are defined:

$$\mathcal{S}_{ij}^c = - \quad \text{if} \quad p_i^c < p_j^c$$

$$\mathcal{S}_{ij}^c = 0 \quad \text{if} \quad p_i^c = p_j^c$$

$$\mathcal{S}_{ij}^c = + \quad \text{if} \quad p_i^c > p_j^c$$

(5)

It was explained in [1,5] that as a direct consequence of (3) $\mathcal{S}^c$ can be interpreted as the incidence matrix of a digraph with no directed cycles, and that the cell encodings (3) and (5) can be readily interconverted into one another.

**Theorem 1.** Contiguous cells in space have different dimensionalities.

Crossing to a contiguous cell is implies going between two regions in (2), so one element $\mathcal{S}_{ij}^c$ in (5) changes its value, and this change can never be between $+$ and $-$ because this would mean crossing $H_{ij}$ avoiding the region $c_i = c_j$.

**Definition 2.** A contiguous set are all the $n$-dimensional cells contiguous to a $(n-1)$-dimensional separator cell.

This allows to build a hierarchical structure: the cell lattice poset, that results from ordering contiguous cells by dimensionality [1,7].

Consider two arbitrary subpartitions $A_a^{da}$ and $A_b^{db}$ of $A^N$, corresponding to the sets of indices $\chi_a = (i_{a1}, i_{a2}, \ldots, i_{ada+1}) \subset \mathcal{Z}_{N+1}$ and $\chi_b = (i_{b1}, i_{b2}, \ldots, i_{bda+1}) \subset \mathcal{Z}_{N+1}$ respectively, and let $\chi_{a^*b} = \ldots$
\( \chi_a \cap \chi_b \) be the set of indices that are common to both partitions.

**Definition 3.** Two cells \( \zeta_a \in A^d_a \) and \( \zeta_b \in A^d_b \) with sign matrices \( S^a \) and \( S^b \) respectively, are said to be compatible if \( S^a_{ij} = S^b_{ij} \quad \forall \ i, j \in \chi_a \cap \chi_b \).

**Theorem 2.** The cell \( \zeta_a \in A^d_a \) is the projection of all the cells in \( A^N \) whose sign matrix \( S \) is such that \( S_{ij} = S^a_{ij} \quad \forall \ i, j \in \chi_a \).

This is an immediate consequence of (3) and (5).

Let \( \Xi_a \) and \( \Xi_b \) be the set of cells in \( A^N \) that are projected on \( \zeta_a \) and \( \zeta_b \) respectively.

**Theorem 3.** The set \( \Xi_a \cap \Xi_b \) is non empty iff \( \zeta_a \) and \( \zeta_b \) are compatible.

Suppose we have \( \xi \in \Xi_a \) but \( \xi \not\in \Xi_b \), this means that the relative positions of the set of indices \( \chi_{b|a} = \chi_b \setminus \chi_a \) in the dominance sequence (4) is not the same as in \( \zeta_b \), since the reflection group of the arrangement is the symmetric group we only have to apply the reflection that corresponds to the permutation that puts the indices \( \chi_{b|a} \) in the dominance sequence in the same order as in \( \zeta_b \), this generates a cell \( \xi' \in \Xi_a \cap \Xi_b \).

II. The graph of cells

Theorems 2 and 3 suggest a way of building \( A^{k\times N} \) from partitions of lower dimensionality and the lowest dimensionality for the CS of a 3D system is 4, moreover \( A^{3\times 4} \) has two important properties:

1. it has a total of 13824 cells, computations on this structure are within reach,
2. one can reasonably assume that such small CS can be thoroughly scanned by an MDS.

Atoms in MDSs are represented as pointlike structures surrounded by a force field \[8,9\], the convex envelope of a set of 4 points in 3D-space is an irregular polytope called a 4-simplex or simplex, in what follows this denomination will be used to designate 4-atoms/points sets.

In ref. \[2,3,4\] it was proposed a procedure to build the CS of a molecular system that we outline here

1. a molecular structure is decomposed into simplexes,
2. the morphology of simplexes can be decomposed into 3936 classes,
3. if an orientation in 3D-space has been defined for the molecular structure, there is a procedure that allows to build the CS of each morphological class,
4. for each simplex the set of visited morphological classes is sampled from an MDS.

From the CS of the simplexes we can construct a graph denominated the graph of cells or \( G \) which is defined as follows:

**Definition 4.** Two simplexes are adjacent if they share a face.

**Definition 5.** The nodes of \( G \) are the visited cells of each simplex with edges towards the compatible cells in adjacent simplexes.

This graph embodies all the information contained in the CS of a molecular system since
**Theorem 4.** A cell from $A^3 \times N$ is a subgraph of $G$ where its nodes are exactly one cell from every simplex that has edges towards every cell in adjacent simplexes.

A cell from $A^3 \times N$ is a class in an equivalence relation, since it contains all the 3D-structures that have the same dominance sequence. Thus for each simplex there can be only one cell where the indices have the same relative positions as in the dominance sequence of the mother cell, and from definition 3 the cells in adjacent simplexes must be compatible. In what follows we use the terms cell and 3D-structure interchangeably.

Finally notice that in this structure a node that fails to form an edge with an adjacent simplex cannot exist since it is geometrically inconsistent.

A useful structure derived from $G$ is its compact form $C$ obtained by recursively substituing every contiguous set of $n$-dimensional nodes by their $(n-1)$-dimensional separator cell.

**IV. Determining a conical boundary for the molecular dynamics trajectory**

$G$ is a huge structure and it is useless to explore it in full, rather the approach we take here is how to focus on regions of interest and how to extract useful information. We start with the problem of finding the bounds of interesting regions, with a concrete exemple concerning a 2.1 ns bovine pancreatic trypsin inhibitor (BPTI) [10] MDS that was fully described in [11].

As in [11] we restrict ourselves to study the motion of $C_n^m$ carbons each bearing a number $n$ that reflects the linear order of residues along the polypeptide chain, as our description of $CS$ is strictly modular any conclusion that can be drawn on any subset of atoms is automatically valid for the whole structure.

An information that can be easily extracted from a MDS are the dominance relations matrices $DR^c$, where $c$ stands for either $x$, $y$ or $z$, each element of these matrices defines the equation of a face in a polyhedral cone in $CS$ that is the boundary of the volume spanned by the molecular system. The determination of the $DR^c$s from the MDS [11] takes the following steps:

- First, the simplex corresponding to the residue numbers $S_r = \{6, 36, 40, 47\}$ was selected as the reference simplex because all along the MDS it stays within one morphological class, and because it spans a wide range within the molecule.
- Second, the coordinates of $S_r$ in the 1st MD frame were taken as a reference and the other frames were rotated and translated so that the RMS between $S_r(1)$ and $S_r(f)$ be a minimum [12].
- Third, the quantities $DR^c_{ij}$, $1 \leq i < j \leq N+1$, were determined:
  - $DR^c_{ij} = +$, $DR^c_{ji} = -$ if $c_i > c_j$ for all coordinate frames.
  - $DR^c_{ij} = -$, $DR^c_{ji} = +$ if $c_i < c_j$ for all coordinate frames.
  - $DR^c_{ij} = DR^c_{ji} = 0$ if neither of the above relations holds.

The meaning of the matrix elements is obvious if $DR^c_{ij} = +/-$ means that the trajectory always stays on the positive/negative side of $H^c_{ij}$ (2), $DR^c_{ij} = 0$ means that the trajectory can be on either side. The matrices for $x$, $y$ and $z$ for the MDS [11] are shown in Figure 1, the number of non-zero terms in the matrix is the dimension of the cone.
Antisymmetric dominance relations matrices for the $C_\alpha$ coordinates, only the upper triangle is shown. For sake of clarity row and column amino acid numbers can be read from the annotated axes $r$ and $c$. A matrix element can have three values

+ $x_r > x_c$ for all coordinate frames in the molecular dynamics run.
- $x_r < x_c$ for all coordinate frames in the molecular dynamics run.
0 neither of the above relations holds.
III. The fragmentation of the cone

The dominance relations matrices $DR_c$ encode a lot of information about the structure of the volume occupied by the system in $CS$. They give us the range of positions that a given coordinate can have in the dominance sequence (3)

**Theorem 5.** The minimum position of a coordinate $c_\mu$ is the number of matrix elements $DR_{\mu j}^c = +$ plus 1 , $1 \leq j \leq N , j \neq \mu$, and the maximum position is the minimum position plus the number of matrix elements $DR_{\mu j}^c = 0$ , $1 \leq j \leq N , j \neq \mu$.

The index $\mu$ in the dominance sequence must always stay to the right of the elements it dominates if there are $n_+$ of such elements the minimum position of $\mu$ is $n_+ + 1$, on the other hand be $n_0$ the number of indifferent relations, $\mu$ can be either to the right or to the left of any of these then the maximum position of $\mu$ must be $n_+ + n_0 + 1$.

We can also extract from $DR_c$ the set of lower dimensional cells that we can expect to find in $C$. And this is most useful for fragmenting $G$ into a set of subgraphs with more manageable size, to do that we can proceed as follows: we select the indices $c_\mu$ and $c_\nu$ that have the following property

$$DR_{\mu \nu}^c = DR_{\mu \nu}^y = DR_{\mu \nu}^z = 0 \quad (6a)$$

Those are cells of dimension $(N-1) \times (N-1) \times (N-1)$, that occur simultaneously for $x$, $y$ and $z$, this gives a greatly reduced number of possibilities compared with what we would get if we considered only one or two dimensions in (6). In a dominance sequence like (4b) (6a) would form a pattern

$$(\ldots(\mu \nu)\ldots,(\mu \nu)\ldots,\ldots(\mu \nu)\ldots) \quad (7a)$$

Other patterns arise as combinations of equations (6a) with cyclic permutations of indices, for instance

$$DR_{\lambda \mu}^c = DR_{\lambda \mu}^y = DR_{\lambda \mu}^z = 0$$
$$DR_{\lambda \nu}^c = DR_{\lambda \nu}^x = DR_{\lambda \nu}^y = 0 \quad (6b)$$
$$DR_{\lambda \nu}^c = DR_{\lambda \nu}^x = DR_{\lambda \nu}^y = DR_{\lambda \nu}^z = 0$$

would form a pattern

$$(\ldots(\lambda \mu \nu)\ldots,(\lambda \mu \nu)\ldots,\ldots(\lambda \mu \nu)\ldots) \quad (7b)$$

that represents a cell of dimensions $(N-2) \times (N-2) \times (N-2)$.

The set of allowed patterns deduced from the $DR_c$ matrices can be seen in table I. The next step consists in calculating the sequences with maximal combinations of the patterns (7), i.e. that for a given sequence the combination is such that no more patterns like (7) can be squeezed in. We obtained a total of 9955112 possible sequences with an average of 14 patterns (7) per sequence, only a fraction of these sequences is realizable: that correspond to 3D-structures that can be found in $C$.

Each of these sequences can be considered as a mini-cone and from the dominance constraints that (7) generates we can extract subgraphs from $C$ with a manageable size.
IV. Computing discrete 3D-distances between cells.

In ordinary affine spaces the distance between two points is the norm of the vector that results from subtracting the coordinates of the two points. In our discrete space we can also compute the discrete distance between two points by computing first the discrete components of the 3D vector obtained by subtracting the positions of the two points in the dominance sequence. The problem we are going to discuss is how to measure the set of discrete distances between two points \(i\) and \(j\) from the cells in \(G\).

To do this we have to consider the \(\binom{N-1}{2}\) sets of cells from the simplexes that contain \(i\) and \(j\) as vertices and to determine how many conformations there are, and for each conformation how many points there are between the position of \(i\) and \(j\), for each coordinate \(x\), \(y\) and \(z\).

Let us consider as an example the simplex \(S_1 = \{i, j, u, v\}\), there are 8 possible relative positions that \(i\) and \(j\) can take in the dominance sequence of a cell, in this example we consider only those cells that have the interval pattern

\[ (i)(j) \] \[ (i)(j) \] \[ (i)(j) \]

(8)

suppose we have the cell

\[ (i)(u)(v)(j) \] \[ (i)(v)(j) \] \[ (i)(u)(j) \]

(9a)
(for each coordinate we obviously disregard the positions outside the interval \((i, j)\)), if there were only 4 points in our system the distance between \(i\) and \(j\) would be \(d_{ij} = \sqrt{1 + 1 + 1 + 1}\). If we admit the existence of a 5th point \(w\) in our system, and among the cells in \(S_2 = \{i, j, u, w\}\), we find the cell
\[
\text{(i)(u)(w)(j)} \quad \text{(i)(w)(j)} \quad \text{(i)(j)}
\]
(9b)
it is obvious that if we suppress the index \(v\) from (9a) and \(w\) from (9b) we end up with the same pattern and we say that the projections (9a) and (9b) are compatible. On the other hand if (9a) and (9b) correspond to two projections of the same structure then in the simplex \(S_3 = \{i, j, v, w\}\) there must exist a cell with the pattern
\[
\text{(i)(w)(v)(j)} \quad \text{(i)(w)(v)(j)} \quad \text{(i)(j)}
\]
(9c)
which is obviously compatible with (9a) and (9b), again if there were only 5 points in our system we would have \(d_{ij} = \sqrt{1 + 1 + 1 + 1 + 1}\), where each component of the discrete vector \(\vec{ij}\) is the number of different indices that fall in the dominance interval \((i)(j)\) from a set of mutually compatible sequences for every coordinate \(x, y\) and \(z\).

The example above indicates that problem of finding the structures from the projections in the graph \(G\) is equivalent to the problem of finding the clique\(^{[1]}\) of a graph.

**Theorem 6.** For an interval pattern (8) if the projections (9) are the nodes of a graph with edges between compatible projections then the cells that are the projection of a 3D-structure form a clique.

**V. Conclusion**

In [1-4] it was made clear that the graph of cells is the "structure" that contains the dynamical states of a molecular system, thus if a global view of the dynamics of molecular systems is a necessity this is one structure that must be studied.

This paper is a first step in solving the problem of managing this huge graph. Three issues have been addressed:

1. we can give bounds that delimit interesting regions in \(CS\),
2. we can decompose the graph into a hierarchy of smaller components,
3. and the crucial problem of extracting distances that are needed for computing energies has been clearly defined.

These three issues form the basis that is needed for doing phenomenological studies with molecular systems that we expect to be the subject of future works in this series.

**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. J. Gabarro-Arpa, "Combinatorial determination of the volume spanned by a molecular system in conformational space", Lecture Series on Computer and Computational Sciences 4, 1778-1781 (2005).

4. J. Gabarro-Arpa, "A central partition of molecular conformational space. III. Combinatorial determination of the volume spanned by a molecular system in conformational space", Journal of Mathematical Chemistry DOI 10.1007 10910-006-9079-8.url (2006).

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

6. S. Fomin and N. Reading, "Root systems and generalized associahedra", math.CO/0505518 (2005).

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

8. 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).

9. 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).

10. M. Marquart, J. Walter, J. Deisenhofer, W. Bode, R. Huber, "The geometry of the reactive site and of the peptide groups in trypsin, trypsinogen and its complexes with inhibitors", Acta Crystallogr. Sect. B, 39, 480-490 (1983).

11. J. Gabarro-Arpa, R. Revilla, "Clustering of a molecular dynamics trajectory with a Hamming distance", Comp. and Chem., 24, 693698 (2000).

12. W. Kabsch, "A discussion of the solution for the best rotation to relate two sets of vectors", Acta Cryst., A34, 827828 (1978).