A Central Partition of Molecular Conformational Space.
V. The Hypergraph of \(3D\) Partition Sequences.

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Abstract

In a previous work (Gabarro-Arpa, J. Math. Chem. 42 (2006) 691-706) a procedure was described for dividing the \(3 \times N\)-dimensional conformational space of a molecular system into a number of discrete cells, this partition allowed the building of a combinatorial structure from data sampled in molecular dynamics trajectories: the graph of cells or \(G\), encoding the set of cells in conformational space that are visited by the system in its thermal wandering. In this work we describe the procedures for building from \(G\) an hypergraph allowing to enumerate the basic 3D characteristics of molecular conformations in the cells.

Keywords Molecular Conformational Space, Hyperplane Arrangement, Face Lattice, Molecular Dynamics

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1. Introduction

The aim of this series of papers [1-6] is to build a set of mathematical tools for studying the energy landscape of proteins [7,8,9], and the present paper is a step further towards this goal.

The energy surface of proteins is the essential tool for understanding the physico-chemistry of basic biological processes like catalysis [9]. It is also a complex multidimensional structure that can only be built from the knowledge of the complete dynamical history of the molecule, which is currently out of reach for conventional molecular-dynamics simulations (thereafter referred as MDS) [9]. One reason is that in an MDS trajectory the position of every atom in the molecule is calculated with an accuracy of a hundredth of angström, which quickly overhelms even the most powerful computers. The main tool developed here can be described as a fluctuation amplifier: the small movements of a molecular system, which are easily sampled with the current simulating tools, are encoded by means of a simple combinatorial structure, from which the set of structures corresponding to realizable combinations of these movements can be generated.

Within this approach, the 3D-structures of protein molecules are encoded into binary objects called dominance partition sequences (DPS) [1-6], these are the generalization of a combinatorial structure known as noncrossing partition sequences [10]. They generate a linear partition of molecular conformational space (in what follows abridged to CS) into a set of connected disjoint regions called cells, each harboring the set of 3D-conformations that have the same DPS.

Partitions are a useful tool for studying multi-dimensional spaces, in our case they systematically span a much wider volume range than the set of points along a random trajectory curve generated by a MDS, they have also been used in many other contexts [7,8,11].

The aim of the preceding papers [1-6] was to construct a graph whose nodes are the cells visited by the molecular system in its thermal wandering, two important properties of partition sequences make this construction possible:

1. DPSs are hierarchical structures: partition sequences encoding different sets of cells can be merged into a new partition sequence encoding the union set, and the process can be repeated with the new sets of cells, thus creating a hierarchy. The importance of this property is that climbing the hierarchy ladder the number of cells increases exponentially while the sequence length increases only linearly. This compact coding makes possible the construction of a graph representing huge regions of CS whose size does not exceed the memory of a workstation computer, while keeping at the same time the essential information about the molecular structures.

2. DPSs are modular structures: partition sequences can be decomposed into subsequences that are embedded in different conformational subspaces. This allows to define a composition law: if two partition sequences from two different subspaces share the same sequence for the intersection subspace, then joining both sequences gives a realizable sequence that corresponds to an existing set of cells [4-6].

The first property tells us that the graph can be constructed, the second suggests how to build it: a molecular structure can be decomposed into sets of four atoms, its smallest 3D components,

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1For an N-atom molecule it is a 3 × (N − 1)-dimensional space where each point corresponds to a 3D molecular conformation.

2A structure called partially ordered set (poset). Posets are widely used tools in many theoretical chemistry problems [10,12-20].
by composing the graphs of these one can build the graph of the molecule.

Atoms in MDSs are represented as pointlike structures surrounded by a force field \([22,23]\), the convex envelope of a set of 4 points in 3D-space is an irregular polytope called a **4-simplex** or **simplex**. The conformational space of these sets is relatively small with 13824 cells, of these only a fraction is visited by the system. With a \(CS\) so small it can be plausibly assumed that the accessible cells are all visited during a MDS run.

The method for building the graph that was proposed in [2] consists in

1. Establishing a morphological classification of simplexes, where each class is defined by a set of geometrical constraints.
2. The geometrical constraints that define a class allow to calculate the set of accessible cells in a simplex \(CS\) [4], thus to each class we can associate a graph where the nodes are the cells from this set with edges towards adjacent cells.
3. On the other hand computer simulations of protein dynamics show [2,4] that in a protein structure the majority of simplexes evolve within a reduced number of morphologies. For each 4-atom set in the molecule the graph of its \(CS\) is built by merging the graphs of the visited simplex morphologies.
4. The \(CS\) graph of the molecule, that was called the **graph of cells** or \(G\) in [4], can be built by composing the \(CS\) graphs of the different simplexes.

The graph of cells allows to enumerate exactly the set of visited cells in conformational space, but since the cells are encoded in a compact form unwrapping them completely is probably algorithmically hopeless. Instead, in [5,6] it was developed a generalization of dominance partition sequences (in what follows abridged to GDPS), that could be geometrically interpreted as a bouquet of cones in \(CS\). Its importance lies in two facts:

1. it encloses the region of \(CS\) that harbours the dynamical states of the molecular system,
2. it can be hierarchically factorised, thus the whole region can be decomposed as a product of smaller partitions of molecular conformational spaces, greatly relieving the computational effort involved in the enumeration of the cells from \(CS\).

This subject is developed in the next five sections:

- Section 2 contains a graphical presentation of dominance partition sequences.
- Section 3 discusses the factorization of the generalized dominance partition sequences.
- Section 4 describes the procedure for merging the graph of cells and the GDPS and introduces the concept of the partition sequences graph.
- Section 5 discusses the construction of the graph, with a detailed description of a set of three algorithmic procedures that make the construction possible.

\[^3\text{In what follows this denomination will be used to designate ordered sets of 4-atoms/points.} \]
2. The Dominance Partition Sequences

Hidden in complex objects like macromolecules there are simple structures that cannot be seen because they are buried under great amounts of information. However, these structures can be made to emerge when information is selectively eliminated from the objects [11].

Here the only information we keep from the 3D-structure of macromolecules are the dominance partition sequences (DPS) [1-4], there are three such sequences: one for each cartesian coordinate $x$, $y$ and $z$. For an $N$-atom molecular system with atoms numbered from 1 to $N$ the DPS of a given coordinate $c$: is the sequence of atom numbers sorted in ascending order of the $c$ coordinate of their respective atoms.

A simple example of DPS can be extracted from Fig. 1, where an $\alpha$-carbon skeleton 3D-conformation from the pancreatic trypsin inhibitor (PTI) [24] is shown

![Figure 1](image)

\textit{α}-carbon skeleton stereoview of the pancreatic trypsin inhibitor [24].

As can be easily seen from Fig. 1 the $(x, y, z)$-dominance partition sequences of the protein conformation are

\[
\{(58)(29)(48)(57)(27)(28)(31)(30)(52), (32)(47)(53)(50)(19)(26)(21)(56)(51)(24)
\]

\[
(33)(20)(23)(55)(46)(25)(22)(34)(54)(18), (1)(45)(17)(5)(6)(35)(44)(2)(8)(43)
\]

\[
(16)(9)(11)(7)(3)(10)(36)(4)(37)(42)(15)(12)(41)(40)(14)(38)(13)(39)\}_{x},
\]

\[
\{(15)(16)(17)(14)(18)(37)(36)(13)(19)(38)(34)(35)(12)(11)(39)(20)(33)(46)(10)(40)
\]

\[
(32)(47)(21)(45)(44)(9)(48)(31)(41)(22)(49)(50)(43)(42)(8)(51)(30)(23)(24)(52)
\]

\[
(7)(29)(54)(53)(5)(27)(55)(26)(25)(4)(6)(28)(57)(56)(58)(3)(2)(1)\}_{y},
\]

\[
\{(26)(27)(10)(8)(25)(7)(24)(11)(6)(9)(12)(28)(13)(33)(34)(15)(31)(32)(29)(17)
\]

\[
(14)(23)(36)(41)(35)(3)(40)(5)(22)(16)(30)(4)(39)(43)(1)(18)(21)(19)(42)(20)
\]

\[
(44)(38)(2)(37)(55)(48)(45)(51)(52)(57)(56)(47)(46)(54)(49)(53)(58)(50)\}_{z}
\]

DPSs like (1) generate an equivalence relation: two 3D-conformations are equivalent if they have the same dominance partition sequence. Further, for a $N$-atom molecular system DPSs generate a partition of the $(3 \times N - 3)$-dimensional molecular conformational space into cells whose points (3D-conformations) all have the same DPS. This partition is known to combinatorialist as a Coxeter reflection hyperplane arrangement and for an $N$-atom molecule is designated as $A^{N-1} \times A^{N-1} \times A^{N-1}$ [25,26].
For clarity purposes we have only taken into consideration the α-carbon atoms from the protein. Notice that this does not matter much, since the procedures used throughout this work are strictly modular and the results obtained for parts or components are also valid for the whole molecule.

As it has extensively discussed in [10,26] these sequences have interesting combinatorial properties. Suppose we have two molecular conformations that for some coordinate axis the atoms, say 3 and 10, get past each other, obviously these two conformations will have DPSs (encoding \((N-1)\)-dimensional cells in CS [4]) that differ in only two positions: \(\{3\} \{10\}\) and \(\{3\} \{10\}\) respectively.

These can be aggregated in a new sequence \(\{3\} \{10\}\) representing the permutations of 3 and 10 and encoding an \((N-2)\)-dimensional cell in CS [4,6]. More generally a DPS with a sequence of \(n\) atom numbers enclosed in parenthesis \(\{i_1, i_2, ... i_{n-1}, i_n\}\) represents the set of \(n!\) DPSs corresponding to the permutations of the indices \(i_1, i_2, ... i_{n-1}, i_n\) and encodes an \((N-n)\)-dimensional cell.

3. Generalized Dominance Partition Sequences

To analyse molecular simulations with this procedure DPSs codes need to be further generalized in order to handle more complex situations. The sequence below is a valid example of the generalization we try to achieve

\[
\{(49 48 29 27 28) 30 31 52\}_c
\]

where (2) encloses \{(49 48 29 27 28)(30 31 52)\}_c and \{(49 48)(27 28 30 31 52)\}_c as subsequences.

This means, for instance, that (2) encodes a set of cells from CS where the \(c\)-coordinates of atom pairs 27 and 48, 27 and 31 can be permuted, but not those of the pair 48 and 31.

It was shown in [6] that the DPSs from the conformations generated in a molecular dynamics trajectory of the PTI protein [27] like (1), are all subsequences of the generalized DPS

\[
\{(49 48 29 27 28 30 31 52) 47 32 50 (26) 51 21 23 24 (19) (20) (25 33) 46 55 (54) 22 18 34 45 (17) (5 44) 35 43 (9) (16) (11) (7) 36 (3 4) (10) (42) (37) (15) (12) (41) (40) (38) (14) (13) (39)\}_x,
\]

\[
\{(15 16 (17) (14) (18) (36 (13) 37) (19) (34) 12 35 38) (11) 20 33 (39) (46 (10) 32) 40 47) (21) (45) 44 (31) (9 48) (41) (22) (42 49 50) 8 30 43 51) (23) (24) (7 52 (29 (4 53 54) 24 (26 27) 5) 6 25 28 55) 3) 24\}_y,
\]

\[
\{(26 (27 (8 10 (7 25 (11 (13) 9) 6 24 (12 (28 33) 31) (34) (15) 32 (29 (17) (14) 5 23 (4 22 35 36 40 41 (3) 30) 39) 16 21 43) (38) (18 19) 20) 37 42 44) (55) (45 48 (52) 51) (46 47) 54 (49 53) 22\}_z
\]

a graphical, more intuitive form of (13) can be seen in Fig. 2. Also (13) can be thought as a pattern: all the DPSs from the protein dynamical conformations match (13). Also, a great number of DPSs matching (13) do not correspond to any dynamical conformation.

Thus, the problem addressed in this paper is: what subset of DPSs matching (13) correspond to the molecule’s dynamical states?
Figure 2

The generalized partition function (13) in graphical form. With the permutation sequences enclosed in squares.
4. Merging the Graph of Cells with the GDPS

While (13) contains approximate information about the whole system, the graph of cells \( G \) contains exact information on the system fragments. Thus, the problem above could be solved by merging both.

To do this we must proceed to decompose (13) into its component DPSs, first by enumerating the complete set of non-intersecting sequences of permutations. These can be extracted with a three-step recursive procedure from the graph in Fig. 3, whose nodes are the sets of permutations with forward edges towards the adjacent non-intersecting permutation sets:

1st by taking the paths that go through non-decreasing node numbers, starting at a node with no backward links and ending at one with no forward links,
2nd the DPSs are formed by discarding in (13) the permutations that are not in the path,
3rd the intervening sequences inherit the structure from (13) restricted to them, this again generates GDPSs and the procedure has to be applied recursively to each of them.

Pairs of adjacent permutations, however, are far less complex GDPSs than (13) and decomposing them into simple sequences is much less computationally demanding.

The graph from Fig. 3 suggest how to obtain the DPSs representing dynamical conformations from (13) and the graph of cells \( G \)

1. We arbitrarily consider only one the axis from Fig. 3, \( x \) for instance. The result would be the same with any other axis, this because (13) is used only as a guideline for aggregating DPSs from the simplexes in \( G \)
2. In the graph of Fig. 3 we take in succession the linked pairs of permutations sets, say \( \mathcal{P}_i \) and \( \mathcal{P}_j \), together with the intervening sequence \( \mathcal{I}_{ij} \) in between, and form the \( x \)-dominance partition sequence
   \[
   \{(\mathcal{P}_i)(\mathcal{I}_{ij})(\mathcal{P}_j)\}_x
   \] (14)
   Let \( \mathcal{N}_{i,j} = \{n_1, n_2, n_3, ...\} \) be the set of atom numbers in (14), for \( y \) and \( z \) we simply reduce (13)\( y \) and (13)\( z \) by eliminating the indices that are not in the set \( \mathcal{N}_{i,j} \), this gives a GDPS \( \mathcal{D}_{\mathcal{N}_{i,j}} \).
3. Similarly we eliminate from \( G \) the simplexes with vertices numbers that are not in \( \mathcal{N}_{i,j} \), and from the CS of each remaining simplex we eliminate the cells whose DPS does not match \( \mathcal{D}_{\mathcal{N}_{i,j}} \). We call the resulting graph \( G_{\mathcal{N}_{i,j}} \).
4. As described in [5] the \( (N-1) \)-dimensional cells from \( G_{\mathcal{N}_{i,j}} \) are aggregated into a smaller number of lower dimensional cells, giving the final compact form \( C_{\mathcal{N}_{i,j}} \) of the reduced graph of cells.

5. Building the Dominance Partition Sequences Graph

Constructing every DPS from \( G \) is algorithmically hopeless, instead the approach developed here is built upon the fact that DP sequences can be factorized on two levels:

\[ \text{So that no permutation set can be added to the sequence without intersecting one of the sets in it.} \]
Figure 3

GDPS skeleton graph: the nodes are the permutation sequences from (13) with links towards adjacent non-intersecting sequences.
first as shown in the previous section GDPS can be factorized into pairs of connected adjacent permutation sequences,

second DPSs can be aggregated so that specific segments inside the sequence form permutation sequences (thereafter abridged to PS) encoding great amounts of information [1-4]. Moreover, a given PS frequently appears in many other aggregated DPSs. Thus we can think of PSs as the nodes of a directed graph with incoming arcs from the left-DPSs and outgoing arcs towards the right-DPSs. For sake of simplicity we call this graph \( D \).

In what follows we proceed with the second factorization level. That is, a procedure is described for factoring linked adjacent pairs of PSs from the GDPS (13) into a directed graph of PS patterns. Later these graphs can be easily joined together. All the information needed to build \( D \) can be found in \( C \) and it can be done in 4 steps.

The first step consists in finding the nodes of \( D \), these can be found in the DPS set associated with each simplex in \( C \). As discussed in [5], the DPSs for each simplex in \( C \) are projections of DPSs from the molecule. For instance we have the DPS for the simplex with vertex numbers \( \{12, 14, 40, 41\} \):

\[
\{[(12 41)(40)]_x, [(14)(12)(40)(41)]_x, [(12)(14 40 41)]_z, \}
\]

a glance gives the potential permutation sequence nodes \((12, 41)_x\), \((14, 40, 41)_z\) as well as \((14)_x, (41)_z, (14)_y, ... \)

In the second step we need to determine for each PS vertex the positions it can have inside a DPS. Again this information can be obtained from \( C \), if for coordinate \( c \) we have a PS \( P \) this number is determined with the procedure below.

Assume that for the coordinate \( c \) we have the PS \((P_\chi)_c\) with set of indices \( \chi \), let \( S_\chi \) be a simplex with vertices set \( V = \{v_1, v_2, v_3, v_4\} \) such that \( \chi \subset V \), and let \( \mathcal{S}_\chi \) be the adjacent set of simplexes such that the union of their vertices sets is \( \mathcal{N} \) and \( \mathcal{S}_\chi \) is minimal. Also, let \( DPS_{P_\chi} \) be the set of DPSs from \( S_\chi \) that have \((P_\chi)_c\) as a subsequence.

Then the positions of \((P_\chi)_c\) in the DPSs can be determined with the following recursive procedure

**Procedure 1.**

1. Let \( LEFT = \{\} \) and \( POS = \{\} \)
2. for each \( Q \in DPS_{P_\chi} \) let \( n = 0 \)
3. for each \( S \in \mathcal{S}_\chi \) we select from its \( DPS \) set the subset \( DPS_Q \) of sequences compatible with \( Q \),
4. for each \( X_C \in DPS_Q \) let \( \Lambda \) be the set of indices to the left of \((P_\chi)_c\) then \( n = n + |\Lambda \setminus LEFT| \) and \( LEFT = LEFT \cup \Lambda \)
5. \( POS = POS \cup \{n\} \) go to step 4

the algorithm above has been purposely restricted to \( |\chi| \leq 4 \) only for sake of clarity, it can be straightforwardly extended beyond.

In the third step we seek to determine the connexions between the permutation sequences: two

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5 That share three vertices.

6 Two DPSs from two adjacent simplexes when reduced to their common indices give the same sequence are said to be compatible [6].
PSs \((P_1)_c\) and \((P_2)_c\) with positions \(p1\) and \(p2\) such that \(p2 = p1 + |(P_1)_c|\) can be adjacent subsequences in some DPS. This can be checked with the following procedure:

**Procedure 2.**

1. Let \(\chi_1 = \{i_1, i_2, ..., i_n\}\) and \(\chi_2 = \{j_1, j_2, ..., j_m\}\) be the set of indices for \((P_1)_c\) and \((P_2)_c\) respectively,
2. let us define the sets of PSs \(X_1\) and \(X_2\):
   \[
   \{(i_\alpha, i_\beta)_c \in X_1 : 1 \leq \alpha < n , \alpha < \beta \leq n\} \quad \text{and} \quad \{(j_\alpha, j_\beta)_c \in X_2 : 1 \leq \alpha < m , \alpha < \beta \leq m\},
   \]
3. let us define the set of \(\binom{n}{2} \times \binom{m}{2}\) simplexes \(S_{1,2}\) such that \(S \in S_{1,2}\) has the set of vertices \(\{v_1, v_2, v_3, v_4\}\) with two indices from \(\chi_1\) and the other two from \(\chi_2\),
4. for each \(X_{1,\alpha,\beta} \in X_1\),
   for each \(X_{2,\alpha,\beta} \in X_2\)
   let us select the simplex \(S \in S_{1,2}\) such that its set of vertices is \(X_{1,\alpha,\beta} \cup X_{2,\alpha,\beta}\),
5. let \(Q\) be a sequence from the DPS set of \(S\) such that \(\{(X_{1,\alpha,\beta})(X_{2,\alpha,\beta})\}_c \subset Q\), if \(Q\) does not exist, the check is negative and we exit the procedure,
6. the check is positive and the procedure is terminated.

The fourth step consists in transforming \(D\) into an hypergraph. The reason for this is that DPSs in \(x, y\) and \(z\) are not independent, in fact there are constraints arising from the 3D structure of objects that result in connexions between PSs in one coordinate being associated with specific connexions in another coordinate.

The procedure for determining if two connexions, say \(((P_1)(P_2))_{c_1}\) and \(((Q_1)(Q_2))_{c_2}\) are simultaneously present in any one 3D-DPS can be described as follows:

**Procedure 3.**

1. Let \(\chi_{P_1}\) and \(\chi_{P_2}\) be the set of indices of \((P_1)_{c_1}\) and \((P_2)_{c_1}\) respectively, and let \(\chi_{Q_1}\) and \(\chi_{Q_2}\) be the set of indices of \((Q_1)_{c_2}\) and \((Q_2)_{c_2}\) respectively,
2. let \(S_{P_{1,2}}\) and \(S_{Q_{1,2}}\) be a set of simplex defined exactly as in step 3 of procedure 3,
3. for each \(S_P \in S_{P_{1,2}}\) let \(Q_P\) a DPS defined exactly as in step 5 from procedure 3 for \(S_P\) respectively.
4. for each \(S_P\) we progressively substitute one by one the indices from the vertices \(\chi_{P_{1,2}}\) by the indices \(\chi_{Q_{1,2}}\) until \(S_P\) becomes some \(S_Q\), this generates 4 simplexes: \(S^s(1 < s \leq 4)\),
5. for each intermediate stage we build the set \(DPS^s\) \((1 < s \leq 4)\), starting with \(DPS^1 = \{Q_P\}\), each \(DPS^s\) is the subset of DPSs from \(S^s\) that are compatible with those from \(DPS^{s-1}\).
6. let \(DPS_{Q_{1,2}} \in DPS_Q\) the subset of sequences from \(S^4\) each being defined as in step 5 of procedure 3. If \(DPS_{Q_{1,2}} \cap DPS^4 = \emptyset\) the check is negative and we exit the procedure
7. steps 3 to 6 are repeated for each \(S_Q \in S_{Q_{1,2}}\).

\(^7\)In ordinary graphs, an edge in a simple graph is a pair of vertices. In hypergraphs an edge can be an arbitrary subset of vertices [28].
8. the check is positive and the procedure is terminated.

6. Conclusion

This paper addresses the algorithmic issues that arise in enumerating the sets of cells in CS corresponding to the dynamical states of a molecule. More precisely it introduces an important structure: the graph of partition sequences, allowing to enumerate the realizable partition sequences and hence the accessible cells in CS.

This is shown to be possible because the generalized partition sequences make possible a second factorization of DPSs, thus generating a reduction in algorithmic complexity making possible the construction of $D$, as shown by the 3 procedures described in this work.

This is most important, since DPSs are some sort of skeleton of the 3$D$ molecular structure and methods for reconstructing molecular structures from this skeleton are to be developed in forthcoming works of this series.
References

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

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

[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 (2005) 1778-1781.

[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 42 (2006) 691-706.

[5] J. Gabarro-Arpa, Heuristic decomposition of cones in molecular conformational space. physics.comp-ph:0710.2529v1 (2007)

[6] J. Gabarro-Arpa, A central partition of molecular conformational space. IV. Extracting information from the graph of cells, J. Math. Chem. 44 (2008) 872883.

[7] P.G. Mezey Potential Energy Hypersurfaces, (Elsevier, Amsterdam, 1987).

[8] D.J. Wales, Energy Landscapes, (Cambridge University Press, Cambridge, 2003).

[9] K. Henzler-Wildman, D. Kern, Dynamic personalities of proteins, Nature 450 (2007) 964-972.

[10] S. Fomin and N. Reading, Root systems and generalized associahedra, math.CO/0505518 (2005).

[11] C.R. Shalizi and C. Moore, What is a macrostate? Subjective observations and objective dynamics, cond-mat/0303625 (2003).

[12] R. Brügemann, L. Carlsen, Partial Order in Environmental Sciences and Chemistry, (Springer, Berlin, 2006).

[13] G. Restrepo, R. Brügemann, K. Voigt, Croat. Chem. Acta. 80 (2007) 261.

[14] G. Restrepo, R. Brügemann, J. Math. Chem. 44 (2008) 577602.

[15] J.R. Dias, J. Math. Chem. 4 (1990) 17.

[16] E.E. Daza, A. Bernal, J. Math. Chem. 38 (2005) 247.

[17] A. Bernal, Ordenamientos moleculares basados en la energia (BSc Thesis, Universidad Nacional de Colombia, Bogot, 2004).

[18] Papers in MATCH Commun. Math. Comput. Chem. 42,7 (2000); 54, 489 (2005).

[19] D.J. Klein, J. Math. Chem. 18, 321 (1995).

[20] D.J. Klein, D. Babi J. Chem. Inf. Comput. Sci. 37, 656 (1997).

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

[22] 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 (2001) 211-243.
[24] 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 (1983) 480-490.

[25] H.S.M. Coxeter, Regular polytopes, (Dover Publications Inc., New York, 1973).

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

[27] J. Gabarro-Arpa, R. Revilla, Clustering of a molecular dynamics trajectory with a Hamming distance, Comp. and Chem. 24 (2000) 693-698.

[28] K.H. Rosen Ed. in Chief Handbook of Discrete and Combinatorial Mathematics (CRC Press, Boca Raton, USA, chap. 8 sect 12, 2000).