On the Analytical Calculation of van der Waals Surfaces and Volumes: Some Numerical Aspects

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ABSTRACT

A fast computer algorithm is presented for complete analytical calculation of van der Waals surfaces and volumes. Connolly's analytical algorithms, computing second- and third-order atomic spheres overlaps, are shown to give insufficient numerical approximations of the exact van der Waals surfaces and volumes. The presented algorithm computes overlaps of any order. Practical situations frequently involve six-order overlaps. Analytical computed surfaces and volumes of 63 chemicals are compared with Monte Carlo measured values. © 1994 by John Wiley & Sons, Inc.

Introduction

The van der Waals spheres model is widely used for interpretation of protein structures[1,2] and for correlation with physicochemical parameters.[3–5] The simplest algorithm is probably the increments method: A volume increment is associated to each of the n atoms, and the total volume is the sum of the n contributions. The value of the increments is optimized with experimental data. Some refinements are possible, adding atom-pairs increments,[6] but the final precision is limited, especially outside the training set. Most methods involve some discretization step, as in Conolly's numerical algorithm,[7] Gavezzotti's algorithm,[4] or Meyer's algorithm.[8] This step requires the generation of a large number of points, either in a grid or at random, such that a good final precision requires a large computing time. The general problem of finding the surface and the volume of n intersecting spheres was not solved analytically until major progress was made when Connolly[7,9] noticed the existence of the Gauss–Bonnet theorem[10,11] and used it to compute surfaces and volumes of third-order spheres intersections. This third-order approximation appears in several other papers.[12–17] It seems that only one paper deals with a complete analytical computation.[18] Various softwares[19] offer surface or volume computation procedures, but they are based on published meth-

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ods, or sometimes the method is not described. The Connolly's analytical algorithms and related methods are often considered to give the best results,[20,21] but they assume that neglecting high-order overlaps constitutes an acceptable approximation. Some numerical information on this approximation is thus needed, leading to the computation of at least fourth-order overlaps. Another interest in computing fourth-order overlaps comes from Helly's theorem.[22] Let us consider n convex sets in the d-dimensional euclidean space. When $n > d$, if every $d + 1$ of the convex sets has a nonempty intersection, the intersection of all n sets is nonempty.

Three-dimensional spheres are convex sets. Thus, when fourth-order overlaps are computed, the number and the list of atomic overlaps of any order can be generated quickly without sophisticated geometric tools. Moreover, the surface and volume of each fifth- and higher-order overlaps are proved to be computable using only first- to fourth-order overlaps.

Methods

The volume (or surface) of the union of n spheres can be expanded following the Poincaré formula (also called the inclusion–exclusion principle[23]) as n summations:

$$V(1 \cup 2 \cup \ldots \cup n) = \sum_{i_1=1}^{i_1=n} V(i_1) - \sum\sum_{i_1>i_2} V(i_1 \cap i_2) + \sum\sum\sum_{i_1>i_2>i_3} V(i_1 \cap i_2 \cap i_3) - \ldots$$

Assume that only the first p summations are kept, and let $V_a - V$ be the difference: approximated volume of the union minus true volume of the union. Using again the Poincaré formula, the sum of the $n - p$ neglected terms is

$$V_a - V = (-1)^{p+1} \cdot \sum_{i_1>\ldots>i_p} \ldots \sum V((1 \cup 2 \cup \ldots \cup i_{p-1}) \cap (i_1 \cap i_2 \cap \ldots \cap i_p))$$

Thus, the approximated volume is a default value when p is even and an excess value when p is odd. The same conclusions also apply to the surfaces.

Assume first that $p = 4$ is set, providing default values for surfaces and volumes. The first term is the sum of the individual atomic contributions. The second term is the sum of the intersections of atomic pairs: The second-order intersection is either a lens or a sphere or is empty. Thus, its contribution to the volume or surface is easy to compute.

Computing Third-Order Intersections

The third-order intersections may be computed with Connolly's algorithm.[7,9] The general three intersecting spheres problem is divided into 14 topological situations (Fig. 1). Among them, six present an empty third-order intersection due to an empty second-order intersection, and one presents an empty third-order intersection without any empty second-order intersection: After projection on the plane containing the three atomic centers, this latter situation is such that the complement of the union (in the plane) is not a connected set (i.e., there is a hole).

This situation, where n spheres have an empty n-order intersection and all the $(n - 1)$-order intersections are nonempty, is called an EST (empty simplicial topology).

The seven remaining situations all present a nonempty third-order intersection. Among them, four are due to an inclusion of a sphere into another sphere, one is due to an inclusion of a sphere in the union of the two others, and one is due to the inclusion of a second-order intersection in the remaining sphere. All the six resulting third-order intersections are computable using only individual and second-order contributions.

The last situation is called the general situation. It means that n spheres have a nonempty n-order intersection and that no partition of the set of indexes $(1, 2, \ldots, n)$ into two nonempty subsets of indexes i and j is such that the common intersection I of all the i spheres is included in the union J of all the j spheres. If such a partition could be exhibited, applying the Poincaré formula to both members of the equality $I \cup J = J$ provides a relation between the n-order intersection and the lower-order intersections.

Thus, for three spheres, the general situation is the only one requiring nontrivial geometric tools. Neither the EST nor the general situation can occur when the centers of the spheres are colinear. The distinction between the 14 topological situations is made by projection on the plane containing the centers: The two contact points (if any) between the two circles are located inside or outside the third circle. When the six contact points exist and are such that any two circles have one contact point

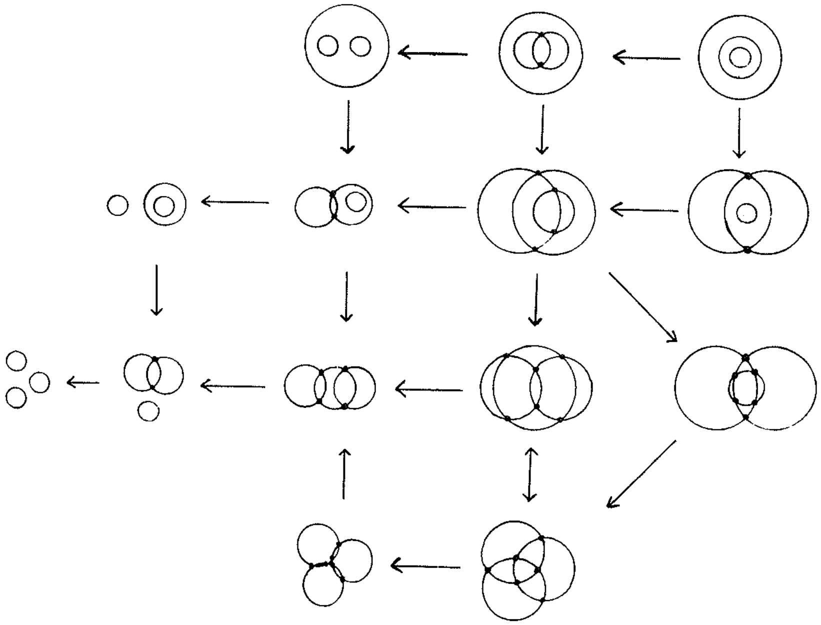


FIGURE 1. The 14 possible topological situations occurring when intersecting three spheres. The arrows show the possible evolutions when a common reduction factor is applied to the three radii: R_1, R_2, R_3 become $a \cdot R_1$, $a \cdot R_2$, $a \cdot R_3$, with $0 < a < 1$.

inside and the other outside the remaining circle, the general situation is detected (see Fig. 1). Then the third-order intersection is symmetrically divided by the plane containing the centers. Let x_i be the contact point inside the i sphere (with center c_i and radius R_i), $i = 1, 2, 3$. Let t_p and t_m be the two triple-intersection points such that $\langle t_p - c_i | t_p - c_i \rangle = R_i \cdot R_i$, $i = 1, 2, 3$, $\langle | \rangle$ denoting the usual scalar product. Thus, the midpoint $t = (t_p + t_m)/2$ lies in the plane containing the centers and is such that the third-order intersection is partitioned into six parts, each of them being the intersection between a trihedron (i.e., the intersection of three halfspaces) and only one sphere (see Appendix 1). The origin of each trihedron is t and is lying inside each sphere. The six trihedrons are $t - x_2$, $t - x_3$, $t - t_p$; $t - x_3$, $t - x_1$, $t - t_p$; $t - x_1$, $t - x_2$, $t - t_p$; $t - x_2$, $t - x_3$, $t - t_m$; $t - x_3$, $t - x_1$, $t - t_m$; $t - x_1$, $t - x_2$, $t - t_m$; and they are intersecting respectively with spheres 1, 2, 3, 1, 2, 3. Some practical information about t, t_p, and t_m is given in Appendix 1.

Thus, the volume (and surface) of the third-order intersection can be computed analytically because it is possible to compute analytically the volume (and surface) of the intersection between a sphere and any trihedron using the Gauss–Bonnet theorem (see Appendix 2).

Computing Fourth-Order Intersections

The general four intersecting spheres problem presents many particular situations that are easy to handle: If some three-order intersection is empty, the fourth-order intersection is empty. When the set of indexes (1, 2, 3, 4) is partitioned into two nonempty subsets of indexes i and j, such that the common intersection I of all the i spheres is included in the union J of all the j spheres, there is a relation between the fourth-order intersection and the lower-order intersections. When such an inclusion ($I \subset J$) is encountered for three spheres, it is also encountered for four spheres: The fourth index is added to the j indexes. This means that the existence of the general situation for four spheres needs the existence of the general situations for all three-tuples of spheres. When all three-tuples of spheres are in the general situation, the four spheres are either in the general situation or constitute an EST (i.e., the complement of the union is not a connected set; there is a hole). The distinction between these several situations is made with the location of the contact points between three spheres: These contact points (named previously t_p and t_m) may be inside or outside the remaining sphere.

Thus, as in the three spheres problem, only the general situation requires some nontrivial geometric tool. This situation corresponds to the general intersection of two lenses (without one of the inclusions mentioned previously) and cannot occur when the centers are coplanar. Each of the six lenses associated with a second-order intersection has two spherical caps separated by a plane. It may be shown (see Appendix 1) that these six planes intersects in an unique point q lying inside the fourth-order intersection. Let t_1, t_2, t_3, t_4 be the three spheres contact points lying respectively inside the remaining sphere 1, 2, 3, 4. Thus, the fourth-order intersection is partitioned into four parts, each of them being the intersection between a trihedron and only one sphere (see Appendix 1). The origin of each trihedron is q, and the four trihedrons are $q - t_2, q - t_3, q - t_4; q - t_3, q - t_4, q - t_1; q - t_4, q - t_1, q - t_2; q - t_1, q - t_2, q - t_3$; and they are respectively intersecting with spheres 1, 2, 3, 4.

Thus, as third-order intersections, the volume and the surface of the fourth-order intersection can be computed analytically using the Gauss–Bonnet theorem: It needs only to compute analytically the volume (and surface) of the intersection between a sphere and any trihedron (see Appendix 2).

Computing Fifth- and Higher-Order Intersections

Although the atomic overlap list of fifth- and higher-order intersections is known using Helly's theorem, the surface and the volume of any of these intersections are computable using the three spheres theorem (see Appendix 4): Let n spheres have a common nonempty intersection. When $n > 4$, there is at most $m = 3$ spheres such that the intersection I of the $n - m$ remaining spheres is included in the union J of the m spheres.

Thus, applying the Poincaré formula to both members of the equality $I \cup J = J$ provides a relation between the n-order intersection and the $(n - 1)$-order intersections. Starting from fourth-order intersections, fifth-order intersection thus computed, then sixth-order intersections so on. Thus, the analytical calculation of va Waals surfaces and volumes is completed wi approximation, using all the expansion of the caré formula.

A similar simplified computation of high- overlaps was outlined previously by Gibson Scheraga.[18]

Results and Discussion

A FORTRAN program analytically compu both the surface and the volume of the union spheres in any position was developed on a V VAX Station 3100, storing real values in do precision real words (2 · 32 bits; 56 bits are m ingful). Except for some OPEN and FORMAT s ments in the main, the program and al subroutines have been compiled without mo cation on AIX-IBM RISC 6000 and UNICOS C Y-MP and ran successfully on these computers following numerical informations apply to the version of the program.

Sixty-three compounds and their hydro suppressed connection tables have been sele from a large CAS file.[24] The three-dimensi atomic coordinates have been generated using CONCORD software.[25] These compounds are li in Table I and displayed in Figure 2. The atomic were taken from Gavezzotti's paper.[4] All values u in this article are assumed given in angstroms. G ezzotti's atomic radii are $r(H) = 1.17$, $r(C) = 1$ $r(N) = 1.55$, $r(O) = 1.40$, $r(F) = 1.30$, $r(Cl) = 1$ $r(Br) = 1.95$, $r(I) = 2.10$.

For each compound, the volumes and surface all atomic overlaps were computed, but only number of these overlaps (Table II) and the sum their contributions to each order (Tables III and are reported here, thus avoiding outputs that are large.

The average computation time was less than per compound, including reading input file and c puting results. The relative precision varies ab from 10^{-7} to 10^{-9}, both for surfaces and volum depending on the compounds. This precision v evaluated by comparing results when random ro tions and random atomic renumbering are appl to input coordinates. Most of the central processi unit (CPU) cost and precision lost both come fr fourth-order overlaps. For example, aromatic co pounds frequently need the resolution of quasi-singular linear systems. Thus, a random perturbation of each atomic position was sometimes applied: Perturbations are distributed uniformly and isotropically around the atomic position. The radius of the largest perturbation was 10^{-6} angstroms, but most of the 63 compounds did not require this perturbation. When no perturbation was applied, the precision was about 10^{-9}.

The total volumes and surfaces were also measured accurately with the Monte Carlo method, using 10,000,000 observations for each measure (see Appendix 3). The comparison between computed and measured values is performed in Table V. The measured values needed about 70 min average computation time to get a relative precision of about 10^{-3}.

The absolute and relative differences between approximated and exact values have been computed over the 63-compounds population. The average values and their associated standard deviations are as follows:

Third-order approximation:

	$V_a - V$	$S_a - S$	$100 \cdot (V_a - V)/V$	$100 \cdot (S_a - S)/S$
Average	10.423	87.124	5.280	36.286
Standard deviation	7.279	51.058	3.401	20.126

Fourth-order approximation:

	$V_a - V$	$S_a - S$	$100 \cdot (V_a - V)/V$	$100 \cdot (S_a - S)/S$
Average	−1.988	−17.258	−1.043	−7.543
Standard deviation	1.821	14.550	0.950	6.591

Thus, the third-order approximation is insufficient for surfaces: The average relative error is about 36%. The fourth-order approximation reduced this error to −7%. For volumes, the third-order approximation presents an average relative error about 5%. The fourth-order approximation reduced this error to about −1%. The computation times are not reduced significantly when the algorithm is stopped after the fourth-order overlaps.

The last example is provided as a common test set for comparison with various other methods. The atomic coordinates of saxitoxin and tetrodotoxin published in ref. 27 are merged to get a single unthinkable compound containing 43 atoms. Analytically computed surface and volume are, respectively, $S = 273.073465$ and $V = 277.763739$ (all digits are meaningful; no random perturbation was needed). The highest overlap order is 13. The number of overlaps are (from 1- to 13-order overlaps) 43, 373, 1463, 3385, 5242, 5843, 4910, 3192, 1605, 604, 159, 26, 2.

A listing of the volume and surface of any overlap of this test compound can be obtained from the author of this article. The Monte Carlo FORTRAN subroutines are also available free of charge.

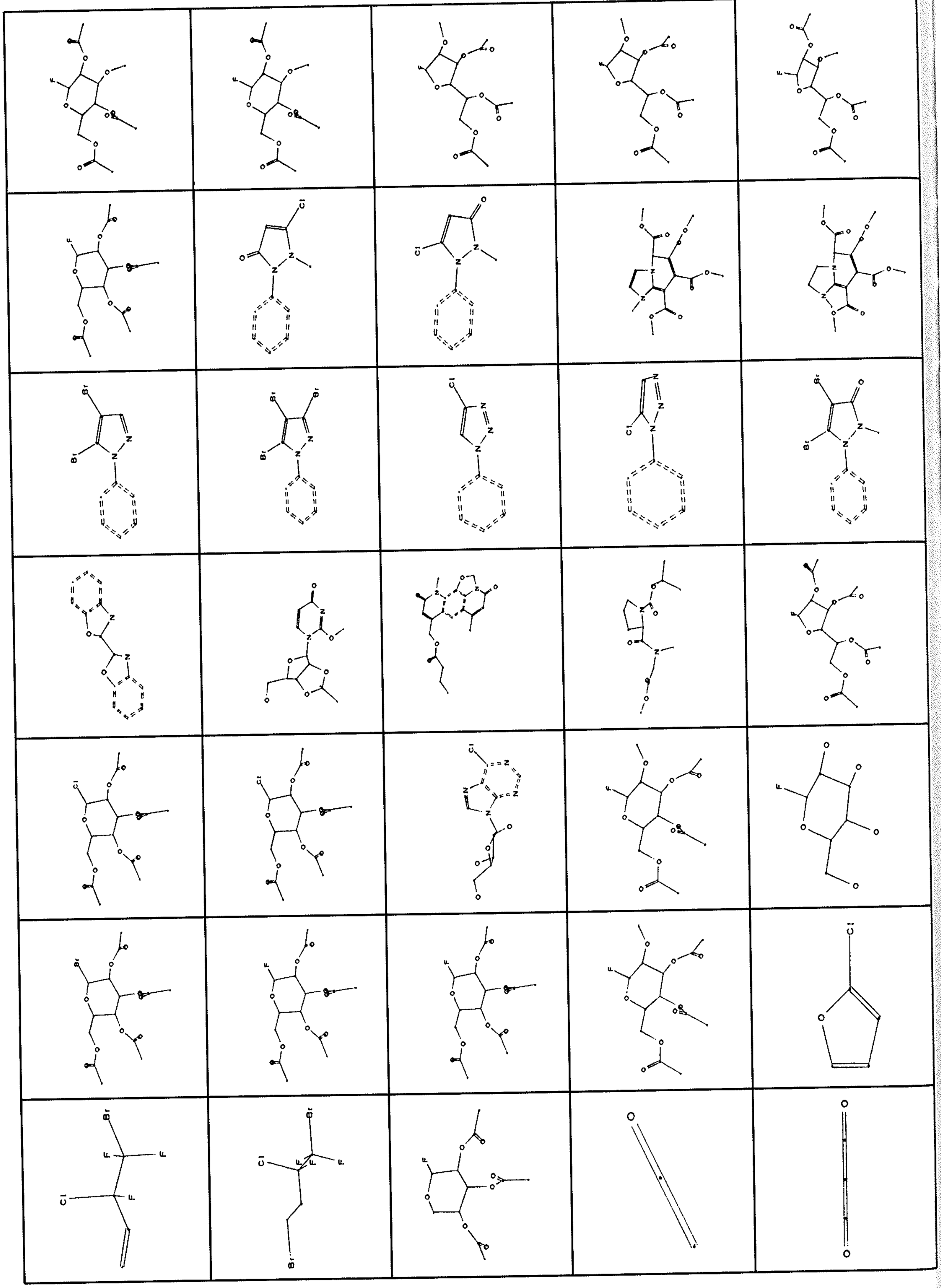
Conclusion

The analytical calculation of van der Waals surfaces and volumes is fast and accurate. The third-order approximation is not acceptable, especially for surface computation: This relative error is often greater than 30%. For volume computation, this relative error is often greater than 5%. Practical situations frequently involve sixth-order overlaps (e.g., aromatic compounds) and sometimes seventh-order overlaps. Many applications using van der Waals surfaces or volumes should benefit from this suppression of undesirable error source, particularly those requiring accurate, discrete approximations of derivatives.

Appendix 1: Existence and Location of Some Remarkable Points in Spheres Intersections

In this appendix, n spheres in the d-dimensional Euclidean space are considered. Unless otherwise stated, $n < d + 2$ is assumed.

Let R_i be the radius of the d-sphere centered on c_i, and $RR_i = R_i \cdot R_i$. DD_{ij} is the square of the distance $c_i - c_j$: $DD_{ij} = \langle c_i - c_j | c_i - c_j \rangle = D_{ij} \cdot D_{ij}$. SS_{ijk} is the square of the area of the triangle $c_i - c_j - c_k$. Let $g_{ij} = (c_i + c_j)/2$, and $m_{ij} = g_{ij} + (c_j - c_i)$


F
Cl
Br
N
O

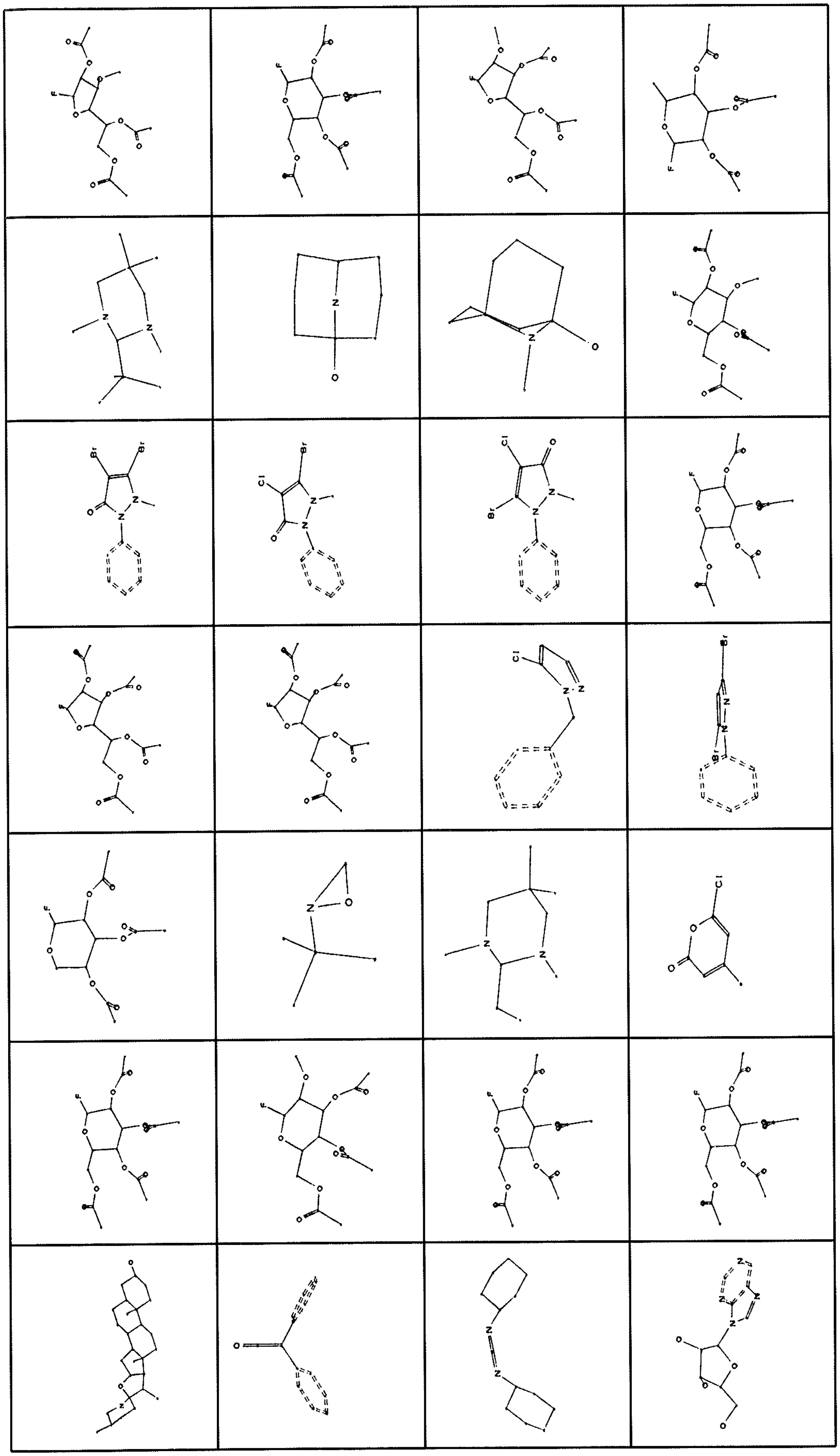


FIGURE 2. The 63 compounds extracted from the CAS file. CAS Registry Numbers are increasing column by column. Molecular formulas are also listed in Table I.

TABLE I.
CAS Registry Numbers and Molecular Formulas of the 63 Compounds Displayed in Figure 1.

	RN	Mol. formula		RN	Mol. formula
1	374-25-4	$C_4H_3BrClF_3$	33	40031-25-2	$C_{14}H_{19}FO_9$
2	378-13-2	$C_4H_4Br_2ClF_3$	34	40031-26-3	$C_{14}H_{19}FO_9$
3	440-05-1	$C_{11}H_{15}FO_7$	35	50877-39-9	$C_{10}H_9ClN_2$
4	463-51-4	C_2H_2O	36	51039-44-2	$C_9H_6Br_2N_2$
5	504-64-3	C_3O_2	37	51039-45-3	$C_9H_6Br_2N_2$
6	511-98-8	$C_{27}H_{45}NO_2$	38	51039-46-4	$C_9H_5Br_3N_2$
7	525-06-4	$C_{14}H_{10}O$	39	51039-47-5	$C_8H_6ClN_3$
8	538-75-0	$C_{13}H_{22}N_2$	40	50139-48-6	$C_8H_6ClN_3$
9	550-33-4	$C_{10}H_{12}N_4O_4$	41	51620-38-3	$C_{10}H_8Br_2N_2O$
10	572-09-8	$C_{14}H_{19}BrO_9$	42	51620-41-8	$C_{10}H_8Br_2N_2O$
11	2823-44-1	$C_{14}H_{19}FO_9$	43	51620-42-9	$C_{10}H_8BrClN_2O$
12	2823-46-3	$C_{14}H_{19}FO_9$	44	51620-43-0	$C_{10}H_8BrClN_2O$
13	2994-38-9	$C_{13}H_{19}FO_8$	45	51897-75-7	$C_{14}H_{19}FO_9$
14	3187-94-8	C_4H_3ClO	46	51897-76-8	$C_{14}H_{19}FO_9$
15	3934-29-0	$C_{14}H_{19}FO_9$	47	52128-79-7	$C_{10}H_9ClN_2O$
16	3935-67-9	$C_{13}H_{19}FO_8$	48	52128-81-1	$C_{10}H_9ClN_2O$
17	4163-44-4	$C_{14}H_{19}FO_9$	49	52839-10-8	$C_{16}H_{18}N_2O_8$
18	4163-45-5	$C_{14}H_{19}FO_9$	50	52839-12-0	$C_{16}H_{20}N_2O_8$
19	4451-35-8	$C_{14}H_{19}ClO_9$	51	54572-01-9	$C_{12}H_{26}N_2$
20	4451-36-9	$C_{14}H_{19}ClO_9$	52	56258-83-4	$C_8H_{15}NO$
21	5399-87-1	$C_{10}H_{11}ClN_4O_4$	53	56258-84-5	$C_9H_{17}NO$
22	7130-50-9	$C_{13}H_{19}FO_8$	54	57558-23-3	$C_{13}H_{19}FO_8$
23	7617-95-0	$C_6H_{11}FO_5$	55	57558-24-4	$C_{13}H_{19}FO_8$
24	10369-23-0	$C_{11}H_{15}FO_7$	56	57558-25-5	$C_{13}H_{19}FO_8$
25	16479-80-4	$C_5H_{11}NO$	57	57558-28-8	$C_{13}H_{19}FO_8$
26	22385-52-0	$C_{10}H_{22}N_2$	58	57558-29-9	$C_{13}H_{19}FO_8$
27	22682-15-1	$C_6H_5ClO_2$	59	57558-30-2	$C_{13}H_{19}FO_8$
28	26903-08-2	$C_{14}H_{12}N_2O_2$	60	57558-31-3	$C_{13}H_{19}FO_8$
29	29507-92-4	$C_{13}H_{18}N_2O_6$	61	57573-38-3	$C_{14}H_{19}FO_9$
30	30408-36-7	$C_{20}H_{20}N_2O_5$	62	57578-79-7	$C_{13}H_{19}FO_8$
31	38074-74-7	$C_{14}H_{24}N_2O_5$	63	62509-89-1	$C_{12}H_{17}FO_7$
32	40031-22-9	$C_{14}H_{19}FO_9$			

TABLE II.
Number of Computed *k*-Order Intersections for Each of the 63 Compounds.

Compound	$k = 1$	$k = 2$	$k = 3$	$k = 4$	$k = 5$	$k = 6$	$k = 7$
1	9	28	35	17	2	0	0
2	10	30	36	17	2	0	0
3	19	57	65	31	6	1	0
4	3	3	1	0	0	0	0
5	5	7	3	0	0	0	0
6	30	124	209	173	72	14	1
7	15	50	67	41	12	2	0
8	15	45	57	36	12	2	0
9	18	58	73	40	9	1	0
10	24	77	92	45	8	1	0
11	24	75	88	43	8	1	0
12	24	75	88	43	8	1	0
13	22	69	82	41	8	1	0
14	6	13	13	6	1	0	0
15	24	75	88	43	8	1	0

TABLE II.
(Continued)

Compound	*k* = 1	*k* = 2	*k* = 3	*k* = 4	*k* = 5	*k* = 6	*k* = 7
16	22	69	82	41	8	1	0
17	24	75	88	43	8	1	0
18	24	75	88	43	8	1	0
19	24	76	90	44	8	1	0
20	24	76	90	44	8	1	0
21	19	62	78	42	9	1	0
22	22	69	82	41	8	1	0
23	12	35	43	25	7	1	0
24	19	57	65	31	6	1	0
25	7	19	24	14	3	0	0
26	12	41	60	41	12	1	0
27	9	24	29	18	6	1	0
28	18	58	76	47	14	2	0
29	21	68	88	53	15	2	0
30	27	92	120	70	19	3	0
31	21	68	84	44	9	1	0
32	24	73	81	34	3	0	0
33	24	73	81	34	3	0	0
34	24	73	81	34	3	0	0
35	13	39	48	27	7	1	0
36	13	41	52	29	7	1	0
37	13	42	54	30	7	1	0
38	14	46	59	32	7	1	0
39	12	35	43	25	7	1	0
40	12	38	49	28	7	1	0
41	15	49	62	33	7	1	0
42	15	49	62	33	7	1	0
43	15	49	62	33	7	1	0
44	15	49	62	33	7	1	0
45	24	75	88	43	8	1	0
46	24	75	88	43	8	1	0
47	14	44	55	30	7	1	0
48	14	44	55	30	7	1	0
49	26	101	143	85	19	1	0
50	26	99	138	82	20	2	0
51	14	50	74	50	14	1	0
52	10	38	76	88	59	21	3
53	11	44	89	101	65	22	3
54	22	69	82	41	8	1	0
55	22	69	82	41	8	1	0
56	22	69	82	41	8	1	0
57	22	67	75	32	3	0	0
58	22	67	75	32	3	0	0
59	22	65	72	32	4	0	0
60	22	65	72	32	4	0	0
61	24	75	88	43	8	1	0
62	22	67	75	32	3	0	0
63	20	62	72	34	6	1	0

TABLE III.
Summations of the Volumes of the *k*-Order Intersections for Each of the 63 Compounds.

Compound	$k = 1$	$k = 2$	$k = 3$	$k = 4$	$k = 5$	$k = 6$	$k = 7$
1	171.6927	77.2995	19.6656	1.7224	0.0123		
2	202.7520	85.0630	21.2158	1.7522	0.0110		
3	336.6033	179.8464	46.9773	5.9325	0.8430	0.0817	
4	56.3926	18.8839	1.0438				
5	90.3360	40.6560	4.4783				
6	644.7176	438.2758	184.2904	47.3853	8.4162	0.8267	0.00005
7	325.7842	214.8926	80.8624	23.4291	6.4059	0.9618	
8	323.0379	177.6673	52.4188	11.2348	2.8928	0.3842	
9	332.8633	217.2411	83.9707	21.7321	3.7993	0.2734	
10	448.7959	233.3313	60.8193	6.9027	0.8566	0.0816	
11	426.9393	229.4432	59.4137	6.8016	0.8562	0.0815	
12	426.9393	229.4433	59.4137	6.8016	0.8562	0.0815	
13	392.9960	208.7991	54.8455	6.3720	0.8564	0.0816	
14	124.5190	64.6947	22.1055	5.9431	0.8837		
15	426.9393	229.4433	59.4137	6.8016	0.8561	0.0815	
16	392.9960	208.7991	54.8455	6.3720	0.8564	0.0816	
17	426.9393	229.4433	59.4137	6.8016	0.8561	0.0815	
18	426.9393	229.4433	59.4137	6.8016	0.8561	0.0815	
19	440.9643	232.4340	60.4494	6.8584	0.8562	0.0815	
20	440.9643	232.4341	60.4494	6.8584	0.8562	0.0815	
21	356.0911	227.7054	87.0361	21.9306	3.7992	0.2735	
22	392.9960	208.7992	54.8456	6.3720	0.8564	0.0816	
23	201.3688	110.8885	31.4067	5.0521	0.8562	0.0816	
24	336.6033	179.8464	46.9773	5.9324	0.8430	0.0817	
25	139.3391	70.2304	24.5142	3.9368	0.2877		
26	255.6900	141.6297	52.1443	9.5292	1.1005	0.1145	
27	180.9117	99.6238	31.0443	6.7197	1.4394	0.1584	
28	368.4753	256.0732	104.4419	31.8205	7.6532	0.9618	
29	392.0022	240.9694	86.9094	18.9498	3.0407	0.2569	
30	537.6532	368.4026	149.3370	39.3321	8.4179	1.1349	
31	402.9574	226.2982	74.8334	12.2737	0.9504	0.0008	
32	426.9393	232.7630	63.7768	8.3832	0.7431		
33	426.9393	232.7630	63.7769	8.3832	0.7431		
34	426.9393	232.7630	63.7769	8.3832	0.7431		
35	278.9179	170.6608	64.0080	18.3559	4.3158	0.4809	
36	295.3595	173.1398	66.1537	18.8541	4.3138	0.4810	
37	295.3595	173.9491	67.1274	19.1198	4.3137	0.4809	
38	326.4188	185.2601	70.4393	19.4757	4.3138	0.4809	
39	249.6178	156.2630	60.9232	18.0642	4.1313	0.4809	
40	249.6178	155.3008	59.5735	17.4852	4.1310	0.4808	
41	329.3028	193.2504	73.1435	19.5731	4.2324	0.4809	
42	329.3028	193.2041	73.1004	19.5595	4.2328	0.4809	
43	321.4713	191.8825	72.3951	19.4267	4.2325	0.4808	
44	321.4713	191.9299	72.4406	19.4418	4.2327	0.4809	
45	426.9393	229.4432	59.4136	6.8016	0.8561	0.0815	
46	426.9393	229.4433	59.4137	6.8016	0.8562	0.0815	
47	290.4119	180.0368	68.4261	18.9572	4.2320	0.4809	
48	290.4119	180.0610	68.4438	18.9603	4.2320	0.4809	
49	482.3381	311.6599	121.3671	26.4606	3.7710	0.3284	
50	482.3381	301.9426	113.4570	23.5735	3.4669	0.3563	
51	300.5886	179.4424	72.4359	15.0102	1.8929	0.1144	
52	206.6870	128.2747	49.9183	14.5669	3.2873	0.3638	0.00031
53	229.1362	143.2623	58.5614	16.7535	3.5205	0.3861	0.00031

TABLE III.
(Continued)

Compound	*k* = 1	*k* = 2	*k* = 3	*k* = 4	*k* = 5	*k* = 6	*k* = 7
54	392.9960	208.7940	54.8402	6.3699	0.8564	0.0816	
55	392.9960	208.7940	54.8402	6.3699	0.8564	0.0816	
56	392.9960	208.7940	54.8402	6.3699	0.8564	0.0816	
57	392.9960	212.1189	59.2158	7.9576	0.7430		
58	392.9960	212.1188	59.2158	7.9576	0.7430		
59	392.9960	212.2835	58.9656	7.5684	0.6197		
60	392.9960	212.2835	58.9656	7.5684	0.6197		
61	426.9393	229.4433	59.4137	6.8016	0.8562	0.0815	
62	392.9960	212.1189	59.2158	7.9576	0.7430		
63	359.0526	192.3262	50.8596	6.2049	0.8424	0.0815	

TABLE IV.
Summations of the Surfaces of the *k*-Order Intersections for Each of the 63 Compounds.

Compound	*k* = 1	*k* = 2	*k* = 3	*k* = 4	*k* = 5	*k* = 6	*k* = 7
1	304.8023	268.6542	133.3509	24.9791	0.3897		
2	352.5860	297.2250	141.8719	24.9344	0.3653		
3	616.9774	603.6537	293.8223	66.3172	10.6905	1.3497	
4	101.5991	49.7374	6.6238				
5	164.7137	111.0490	24.1634				
6	1118.5326	1485.0774	1074.5278	421.0002	93.0571	10.4528	0.01985
7	563.4132	655.0858	426.7951	171.2965	46.4034	7.0536	
8	560.6800	561.6835	301.9722	103.0339	28.4458	3.9519	
9	604.1283	707.0074	444.3865	150.4446	28.6393	2.6212	
10	808.2375	788.1841	381.5245	80.7746	11.1461	1.3372	
11	781.6911	774.0025	372.4854	78.7594	11.1435	1.3367	
12	781.6911	774.0027	372.4855	78.7594	11.1435	1.3367	
13	718.5765	706.2461	341.0860	73.4849	11.1449	1.3371	
14	217.9373	192.7077	102.4358	32.6720	5.2714		
15	781.6911	774.0026	372.4853	78.7593	11.1435	1.3367	
16	718.5765	706.2460	341.0860	73.4849	11.1449	1.3371	
17	781.6911	774.0026	372.4853	78.7593	11.1435	1.3367	
18	781.6911	774.0026	372.4853	78.7593	11.1435	1.3367	
19	799.8231	783.7035	378.7405	80.0603	11.1440	1.3368	
20	799.8231	783.7036	378.7405	80.0603	11.1439	1.3368	
21	643.4975	744.3077	464.4133	153.4981	28.6397	2.6214	
22	718.5765	706.2462	341.0862	73.4850	11.1450	1.3371	
23	375.2947	380.3780	199.2000	54.3044	11.0974	1.3372	
24	616.9774	603.6536	293.8222	66.3171	10.6905	1.3497	
25	247.2433	229.4571	130.4843	35.4674	3.8778		
26	445.2265	476.5236	294.9267	89.7084	13.6838	1.4984	
27	319.5364	314.2228	173.8339	57.3954	14.7437	1.9740	
28	648.4247	798.2415	535.4346	214.2260	55.1247	7.0536	
29	708.4606	806.5333	491.8073	154.7777	28.5411	2.8837	
30	953.2220	1189.1552	792.8792	287.7229	66.3872	9.3244	
31	722.3150	762.9099	430.5137	108.5271	9.4295	0.0617	
32	781.6911	780.8146	380.2802	76.3920	6.2705		
33	781.6911	780.8147	380.2804	76.3921	6.2705		
34	781.6911	780.8148	380.2804	76.3921	6.2705		
35	484.5957	523.4045	321.5165	118.8445	29.0927	3.5269	
36	502.3092	536.8784	338.3363	124.2734	29.0870	3.5271	

TABLE IV.
(Continued)

Compound	$k = 1$	$k = 2$	$k = 3$	$k = 4$	$k = 5$	$k = 6$	$k = 7$
37	502.3092	542.4433	345.5635	127.2185	29.0859	3.5268	
38	550.0929	583.9524	368.8156	131.7860	29.0860	3.5268	
39	437.8174	487.4745	312.1379	119.1457	28.4650	3.5266	
40	437.8174	484.0316	308.2714	117.5098	28.4639	3.5265	
41	565.4238	616.8662	390.6563	136.4814	28.8217	3.5266	
42	565.4238	616.9047	390.7693	136.5164	28.8232	3.5268	
43	557.0094	611.8160	386.2331	134.9633	28.8220	3.5266	
44	557.0094	611.7805	386.1277	134.9342	28.8227	3.5267	
45	781.6911	774.0024	372.4851	78.7592	11.1434	1.3367	
46	781.6911	774.0026	372.4853	78.7593	11.1435	1.3367	
47	509.2258	568.2231	359.8726	129.3934	28.8211	3.5267	
48	509.2258	568.1923	359.7435	129.3495	28.8212	3.5267	
49	873.1743	1045.2335	664.7437	205.9902	31.9582	2.8213	
50	873.1743	1017.6557	635.9102	193.7434	31.5372	3.5765	
51	522.1955	607.0191	401.0128	130.5291	20.6229	1.4978	
52	362.6969	441.2558	325.7932	150.7954	43.1147	5.8729	0.04861
53	401.1814	500.6414	379.0558	173.5652	47.7251	6.4039	0.04848
54	718.5765	706.2515	341.1059	73.4964	11.1447	1.3371	
55	718.5765	706.2514	341.1057	73.4963	11.1447	1.3371	
56	718.5765	706.2516	341.1060	73.4964	11.1447	1.3371	
57	718.5765	712.9942	348.7638	71.0587	6.2699		
58	718.5765	712.9942	348.7638	71.0587	6.2699		
59	718.5765	712.0317	346.3571	69.9186	6.4227		
60	718.5765	712.0317	346.3570	69.9186	6.4227		
61	781.6911	774.0025	372.4853	78.7593	11.1435	1.3367	
62	718.5765	712.9943	348.7639	71.0587	6.2699		
63	655.4619	646.0092	317.3405	70.3045	10.6576	1.3368	

TABLE V.
For Each of the 63 Compounds: Computed Volume (V), Monte Carlo Measured Volume (V_m) and Its Standard Deviation, Computed Surface (S), Measured Surface (S_m) and its Standard Deviation.

Compound	V	V_m	Standard deviation	S	S_m	Standard deviation
1	112.349	112.244	0.049	144.910	144.946	0.048
2	137.164	137.257	0.066	172.664	172.622	0.056
3	198.563	198.382	0.111	250.170	250.183	0.096
4	38.552	38.547	0.014	58.486	58.514	0.016
5	54.158	54.164	0.017	77.828	77.794	0.026
6	350.936	351.127	0.176	369.607	369.574	0.166
7	173.769	173.765	0.087	203.176	203.129	0.086
8	189.063	188.938	0.097	222.429	222.181	0.087
9	181.387	181.422	0.099	217.081	217.323	0.092
10	270.156	270.262	0.156	330.612	330.749	0.126
11	250.883	250.885	0.143	311.221	311.246	0.121
12	250.883	250.922	0.143	311.221	311.142	0.121
13	233.445	233.448	0.120	289.739	289.520	0.111
14	76.870	76.832	0.027	100.265	100.273	0.034
15	250.883	250.814	0.143	311.221	311.220	0.121
16	233.445	233.478	0.120	289.739	289.786	0.111
17	250.883	250.708	0.143	311.221	311.238	0.121
18	250.883	250.954	0.143	311.221	311.199	0.121
19	262.896	262.871	0.152	324.607	324.371	0.124

TABLE V.
(Continued)

Compound	V	V_m	Standard deviation	S	S_m	Standard deviation
20	262.896	262.756	0.152	324.607	324.524	0.124
21	197.017	197.150	0.102	236.123	236.177	0.098
22	233.445	233.404	0.120	289.739	289.880	0.111
23	117.610	117.660	0.054	149.572	149.623	0.058
24	198.563	198.382	0.111	250.170	250.241	0.096
25	89.974	89.921	0.038	116.681	116.773	0.039
26	157.661	157.809	0.071	186.107	186.200	0.069
27	106.894	106.891	0.051	134.522	134.530	0.050
28	191.715	191.765	0.110	219.463	219.601	0.097
29	221.776	221.678	0.138	264.614	264.811	0.108
30	286.538	286.468	0.173	326.286	326.336	0.143
31	240.169	240.176	0.142	290.760	290.803	0.112
32	250.313	250.408	0.155	311.035	311.085	0.121
33	250.313	250.480	0.155	311.035	310.957	0.121
34	250.313	250.532	0.155	311.035	311.096	0.121
35	157.744	157.810	0.066	189.429	189.366	0.075
36	173.352	173.466	0.082	205.054	205.012	0.078
37	173.251	173.300	0.078	203.770	203.662	0.078
38	195.955	195.978	0.086	228.729	228.668	0.086
39	139.864	139.902	0.059	168.274	168.191	0.067
40	140.056	139.947	0.059	169.485	169.379	0.067
41	193.374	193.355	0.093	228.028	228.056	0.088
42	193.391	193.356	0.084	228.068	228.017	0.088
43	186.309	186.388	0.096	221.759	221.743	0.086
44	186.292	186.358	0.090	221.718	221.907	0.086
45	250.883	250.630	0.143	311.221	311.154	0.121
46	250.883	250.727	0.143	311.221	311.109	0.121
47	163.595	163.603	0.071	196.776	196.762	0.078
48	163.586	163.441	0.078	196.722	196.718	0.078
49	269.027	268.955	0.143	315.831	315.716	0.133
50	273.390	273.348	0.150	325.646	325.899	0.134
51	180.350	180.526	0.076	204.785	204.791	0.081
52	116.687	116.637	0.040	133.729	133.749	0.055
53	130.817	130.865	0.055	147.400	147.438	0.061
54	233.447	233.252	0.130	289.742	289.807	0.111
55	233.447	233.563	0.130	289.742	289.442	0.111
56	233.447	233.500	0.130	289.742	289.854	0.111
57	232.878	232.577	0.136	289.557	289.685	0.111
58	232.878	232.781	0.136	289.557	289.635	0.111
59	232.729	232.726	0.147	289.406	289.508	0.111
60	232.729	232.620	0.147	289.406	289.596	0.111
61	250.883	250.841	0.143	311.221	311.174	0.121
62	232.878	232.747	0.136	289.557	289.326	0.111
63	212.142	212.040	0.119	265.809	266.050	0.102

$\cdot\ (RR_i - RR_j)/(2 \cdot DD_{ij})$. To avoid some trivial situations, all centers are assumed to be distinct. Let H_{ij} be the $(d - 1)$-hyperplane containing m_{ij} and orthogonal to $c_i - c_j$.

Obviously, when the d-spheres i and j are not one included in the other and have a nonempty intersection, this latter is a d-dimensional lens bounded by a $(d - 1)$-sphere centered on m_{ij} and lying in H_{ij}.

Consider the intersection of H_{ij} and H_{jk}, i, j, k being distinct. This intersection is a $(d - 2)$-hyperplane. Any point z pertaining both to H_{ij} and H_{jk} satisfies

$$\langle z - m_{ij} | c_i - c_j \rangle = \langle z - g_{ij} | c_i - c_j \rangle + (RR_i - RR_j)/2 = 0$$

and

$$\langle z - m_{jk} | c_j - c_k \rangle = \langle z - g_{jk} | c_j - c_k \rangle + (RR_j - RR_k)/2 = 0$$

Adding these equalities gives $\langle z - g_{ik} | c_i - c_k \rangle + (RR_i - RR_k)/2 = 0$. Thus $\langle z - m_{ik} | c_i - c_k \rangle = 0$. It means that the $(d - 1)$-hyperplanes H_{ij}, H_{jk}, and H_{ik} have a unique and common intersection, which is a $(d - 2)$-hyperplane. Using the same technique, it is easy to show that all the $n \cdot (n - 1)/2$ $(d - 1)$-hyperplanes H_{12}, H_{13}, . . . , associated with each couple of centers, intersects all on a unique and common $(d - n + 1)$-hyperplane.

Let us compare R_i with the distance between z and c_i:

$$RR_i - \langle z - c_i | z - c_i \rangle = RR_i - \langle z - m_{ij} | z - m_{ij} \rangle - \langle m_{ij} - c_i | m_{ij} - c_i \rangle$$

Using the m_{ij} expression, we get

$$RR_i - \langle z - c_i | z - c_i \rangle = LL_{ij} - \langle z - m_{ij} | z - m_{ij} \rangle$$

with

$$LL_{ij} = (R_i + R_j + D_{ij}) \cdot (-R_i + R_j + D_{ij}) \cdot (R_i - R_j + D_{ij}) \cdot (R_i + R_j - D_{ij})$$

The expression of $RR_i - \langle z - c_i | z - c_i \rangle$ is symmetric for i and j. Thus,

$$RR_i - \langle z - c_i | z - c_i \rangle = RR_j - \langle z - c_j | z - c_j \rangle$$

When the d-spheres i and j have a nonempty intersection and are not one included in the other, LL_{ij} is the square of the radius of the $(d - 1)$-sphere bounding this intersection (obviously, this d-lens exists if and only if LL_{ij} is not negative). Thus, z is always either inside or outside both d-spheres. When z is on the boundary of one of the d-spheres, z is on the boundary of both d-spheres.

This result is extended easily to all the n d-spheres: The z-points pertaining to the common $(d - n + 1)$-hyperplane defined previously [i.e., the intersection of all the $(d - 1)$-hyperplanes containing the boundary of the d-lens] are either inside all the n d-spheres or outside all the n d-spheres. If z is on the boundary of one of the n d-spheres, it is on the boundary of all the n d-spheres.

EXISTENCE OF THIS COMMON $(d - n + 1)$-HYPERPLANE

This hyperplane is orthogonal to all the directions $c_i - c_j$. Thus, the common $(d - n + 1)$-hyperplane exists if and only if its intersection z_0 with the $(n - 1)$-hyperplane containing the n centers exists.

Let a_i $(i = 1, 2, \ldots, n)$ be the z_0 barycentric coordinates:

$$z_0 = a_1 \cdot c_1 + a_2 \cdot c_2 + \ldots + a_n \cdot c_n, \quad \text{with} \quad a_1 + a_2 + \ldots + a_n = 1$$

The orthogonality relations are

$$\langle z_0 - m_{ij} | c_i - c_j \rangle = \langle z_0 - g_{ij} | c_i - c_j \rangle + (RR_i - RR_j)/2 = 0$$

and n equations are needed to compute the a_i coefficients. Thus, let us select $i = 1$, and $j = 2, 3, \ldots, n$. The a_i are solutions of a linear n-order system. The coefficients matrix of this system is

$$\begin{array}{ccc} 1 & \cdots & 1 \\ \langle c_1 | c_1 - c_2 \rangle & \cdots & \langle c_n | c_1 - c_2 \rangle \\ \langle c_1 | c_1 - c_3 \rangle & \cdots & \langle c_n | c_1 - c_3 \rangle \\ \cdots & \cdots & \cdots \\ \langle c_1 | c_1 - c_n \rangle & \cdots & \langle c_n | c_1 - c_n \rangle \end{array}$$

The determinant is computed by subtracting columns 2, 3, . . . , n from column 1 and developing from this first column. The determinant is then equal to $(-1)^n$ multiplied by the $(n - 1)$-order determinant:

$$\begin{array}{ccc} \langle c_2 - c_1 | c_2 - c_1 \rangle & \cdots & \langle c_n - c_1 | c_2 - c_1 \rangle \\ \langle c_2 - c_1 | c_3 - c_1 \rangle & \cdots & \langle c_n - c_1 | c_3 - c_1 \rangle \\ \cdots & \cdots & \cdots \\ \langle c_2 - c_1 | c_n - c_1 \rangle & \cdots & \langle c_n - c_1 | c_n - c_1 \rangle \end{array}$$

which is the square of the determinant of the oriented $(n - 1)$-simplex: $c_2 - c_1, c_3 - c_1, \ldots, c_n -$

c_1. Thus, z_0 exists if and only if the $(n-1)$-simplex $c_1, c_2, \ldots, c_n$ is nondegenerate, and the same conclusion is reached if another set of n equations (i.e., $i > 1$) had been selected among the $n \cdot (n-1)/2$ orthogonality relations.

APPLICATION WHEN $d = 3$ AND $n = 2$

We have simply $z_0 = m_{12}$. The radius L_{12} of the lens (if any) is the square root of LL_{12}. So m_{12} exists if and only if the segment $c_1 - c_2$ is not degenerate i.e., when D_{12} is not null (the spheres are not concentric). The second-order intersection is a lens partitioned by H_{12} into two parts, each of them being the intersection between a halfspace and only one sphere.

APPLICATION WHEN $d = 3$ AND $n = 3$

The common $(d + n - 1)$-hyperplane is a line orthogonal to the plane containing the three centers. The intersection z_0 of this line with the plane is named t in the Methods section. The third-order intersection is divided symmetrically by the plane containing c_1, c_2, c_3. Thus, there is zero or two z-points lying on the boundaries of the three spheres. They are named t_m and t_p in the Methods section. When t_m and t_p exist, t is the midpoint of the $t_p - t_m$ segment. This segment is on the common line where H_{12}, H_{23}, and H_{31} are intersecting. Thus, in the general situation, the third-order intersection is partitioned into three parts by the halfplanes included in H_{12}, H_{13}, and H_{23} and bounded by the common line containing t_p and t_m. Each part is the intersection between a dihedron and only one sphere. Each of these three parts is divided by the plane containing c_1, c_2, c_3 into two symmetric parts.

The barycentric t coordinates, relative to c_1, c_2, c_3, are

$$t = (a_1 \cdot c_1 + a_2 \cdot c_2 + a_3 \cdot c_3)/(16 \cdot SS_{123})$$

$$\begin{aligned} a_i = {} & RR_i \cdot (-2DD_{jk}) \\ & + RR_j \cdot (DD_{jk} + DD_{ki} - DD_{ij}) \\ & + RR_k \cdot (DD_{jk} - DD_{ki} + DD_{ij}) \\ & + DD_{jk} \cdot (-DD_{jk} + DD_{ki} + DD_{ij}) \end{aligned}$$

where i, j, k are circular permutations of 1, 2, 3.

The square of the distance $t - t_p$ (or $t - t_m$) is

$$\begin{aligned} \langle t_p - t | t_p - t \rangle = {} & -\langle t - g_{123} | t - g_{123} \rangle \\ & + (R_1 \cdot R_1 + R_2 \cdot R_2 + R_3 \cdot R_3)/3 \\ & + (\langle c_2 - c_3 | c_2 - c_3 \rangle + \langle c_3 - c_1 | c_3 - c_1 \rangle \\ & + \langle c_1 - c_2 | c_1 - c_2 \rangle)/9 \end{aligned}$$

where $g_{123} = (c_1 + c_2 + c_3)/3$.

APPLICATION WHEN $d = 3$ AND $n = 4$

The common $(d - n + 1)$-hyperplane is reduced to a unique point, named q in the Methods section. When the four spheres present a fourth-order intersection in the general situation, q is inside all spheres and inside all contact circles bounding the lenses (i.e., the second-order intersections). It is also at the intersection of the four $t_p - t_m$ segments bounding the third-order intersections. The fourth-order intersection is partitioned into four parts, each of them being the intersection between a trihedron originated in q and only one sphere.

Appendix 2: Intersecting a Sphere with a Trihedron

Let z be the origin of the trihedron; z is assumed to lie inside the sphere. Let x_1, x_2, x_3 be the intersections of the sphere with the halflines bounding the trihedron. The trihedron $z - x_1$, $z - x_2$, $z - x_3$ is assumed to be salient (i.e., the three associated dihedrons are smaller than the halfspace; if not, the volume and surface are deduced by complementation) and ordered in the direct sense. The surface of the intersection S is the surface of the spherical triangle $x_1 - x_2 - x_3$. Let P_1, P_2, P_3 be the planes respectively tangent to the sphere at x_1, x_2, x_3. Each dihedron associated with x_i ($i = 1, 2, 3$) has an intersection with the P_i plane, and a_i is the angle of this intersection ($a_i \in [0; \Pi]$). The spherical triangle is bounded by three arcs of circle: $x_1 - x_2$, $x_2 - x_3$, $x_3 - x_1$, corresponding respectively to angles b_{12}, b_{23}, b_{31} (these angles pertain to $[0; 2 \cdot \Pi]$). Each of these circles has a center (respectively, c_{12}, c_{23}, and c_{31}) and a radius (respectively, R_{12}, R_{23}, and R_{31}). Let K_{ij} ($ij = 12, 23, 31$) be the cosine of the angle $x_i - c - c_{ij}$ (or $x_j - c - c_{ij}$), such that K_{ij} is positive when the $c_{ij} - c$ vector has the same sense as the positive normal to the circle (i.e., oriented by the $x_i - x_j$ arc), and negative if not.

Thus, R being the radius of the sphere, the following analytical S expression is deduced from the

Gauss–Bonnet theorem[10,11]:

$$S/R^2 = (a_1 + a_2 + a_3 - \Pi) - (b_{12} \cdot K_{12} + b_{23} \cdot K_{23} + b_{31} \cdot K_{31})$$

After integration, the following analytical expression of the volume is deduced:

$$\begin{aligned} V = {} & K_{12} \cdot R_{12} \cdot R_{12} \cdot R \cdot (\sin(b_{12}) - b_{12}) \\ & + K_{23} \cdot R_{23} \cdot R_{23} \cdot R \cdot (\sin(b_{23}) - b_{23}) \\ & + K_{31} \cdot R_{31} \cdot R_{31} \cdot R \cdot (\sin(b_{31}) - b_{31}) \\ & + V_x - V_c + A \cdot R/3 \end{aligned}$$

V_x is the signed volume of the oriented tetrahedron $x_1 - z_0$, $x_2 - z_0$, $x_3 - z_0$, and V_c is the signed volume of the oriented tetrahedron $x_1 - c$, $x_2 - c$, $x_3 - c$.

APPENDIX 3: The Monte Carlo Measure of Volumes and Surfaces

The Monte Carlo measure of the volume of some region in a d-dimensional space (i.e., some spheres union or intersection) may be performed as follows (see ref. 26 for theoretical aspects):

1. Build a routine able to detect if a point is inside the region or not.
2. Find a d-parallelepipedic window (the smallest possible) including the region.
3. Generate N d-dimensional points uniformly distributed in the window, and count the number N_i of points falling inside the region.

Let $p = N_i/N$, and $q = 1 - p$. Thus, the Monte Carlo estimate of the volume is $V = W \cdot p$, W being the volume of the window. The expectation of V is the true volume of the region. The standard deviation is $s = W \cdot (p \cdot q/N)^{1/2}$, and V is asymptotically normally distributed.

The Monte Carlo measure of the surface of the union of n d-dimensional spheres may be performed as follows (the surface of their intersection is deduced with the Poincaré formula):

1. Let S_i be the surface of the i sphere and T the sum of all these surfaces: $T = S_1 + S_2 + \ldots + S_n$.
2. Generate N d-dimensional points distributed uniformly on the total surface of all the spheres. This is performed with the following substeps:
   a. Select one of the n spheres, such that each i sphere has a probability equal to S_i/T to be selected (i.e., get a random number y uniformly distributed over $[0; T]$; the selected sphere index i is the smallest one such that $y \langle S_1 + S_2 + \ldots + S_i)$.
   b. Generate a d-dimensional point x distributed uniformly in the i sphere, and norm it to get $\langle x - c_i | x - c_i \rangle = R_i \cdot R_i$.
   c. If x falls inside one of the $n - 1$ other spheres, x is not pertaining to the surface of the union. If x falls outside, x pertains to the surface of this union.
3. Count the number N_u of points lying on the surface of the union.

Let $p = N_u/N$ and $q = 1 - p$. Thus, the Monte Carlo estimate of the surface is $S = T \cdot p$. The expectation of S is the true surface of the union. The standard deviation is $s = T \cdot (p \cdot q/N)^{1/2}$, and S is asymptotically normally distributed.

Thus, the Monte Carlo measure of volumes and surfaces has a precision such that the standard deviation is divided by 10 each time the number of points (and then the CPU time) is multiplied by 100. This is to compare to some methods using a tridimensional grid, for which a multiplication of the CPU time by about 1000 is required to divide the error by 10.

Appendix 4: The Three-Spheres Theorem

Let n spheres have a common nonempty intersection. When $n > 4$, there is at most $m = 3$ spheres such that the intersection I of the $n - m$ remaining spheres is included in the union J of the m spheres.

PROOF

Assume first that $n = 5$. The five spheres have a common nonempty intersection, and thus any four-tuple of these spheres has a common nonempty intersection. If one of these four-tuples is such that the union of $m = 1, 2$, or 3 spheres contains the intersection of the $4 - m$ remaining spheres, the union of these m spheres also contains the intersection of the $5 - m$ remaining spheres, and the theorem stands. As stated in the Methods section, a four-tuple with nonempty common intersection which is not in this particular situation is in the general situation. Then the theorem has to be proved when the five four-tuples are in the general situation. This means that, for each four-tuple, the four contact points pairs between three spheres are such that one of these contact points lies inside the fourth sphere and the other contact point lies outside this fourth sphere (see the computing fourth-order intersections subsection in the Methods section). Thus, denumbering the spatial arrangements of the five spheres leads to only two situations:

1. One sphere contains the intersection of the four others, and, simultaneously, the union of these four spheres contains the first one. The associated common fifth-order intersection is reduced to a fourth-order intersection of the four spheres in the general situation, which is topologically related to a tetrahedron.
2. Two spheres contains the intersection of the three others, and, simultaneously, the union of these three spheres contains the intersection of the two first ones. The associated common fifth-order intersection is a spherical polyhedron related topologically to a triangular prism (i.e., bounded by two triangles and three tetragons, nine arcs and six vertexes).

Obviously, the theorem stands for both situations and thus stands always for $n = 5$. It stands then for any $n > 5$, because the intersection of the $5 - m$ spheres is itself included in the intersection of the $n - m$ spheres.

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