Gradient discontinuities in calculations involving molecular surface area

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The free energy of solvation of a polypeptide or a protein can be expressed in terms of the accessible surface area of the molecule. Algorithms for energy minimization or for molecular dynamics, which involve the first derivatives of the energy, including the free energy of solvation, are commonly used in the conformational analysis of proteins. Discontinuities of the first derivatives, which occur in the accessible surface area and, hence, in the solvation energy, can cause serious numerical problems. In this paper, we describe all the situations in which the gradient of the molecular surface area becomes discontinuous.

0. Introduction

The computation of accessible surface area [1] and its first derivatives is becoming more and more important in the analysis of polypeptide and protein conformations. Partly, this is due to increasing reliance on space-filling graphical representations by molecular models; partly, it is a consequence of the search for reasonably simple approaches to the problem of computing solvation free energies of peptides. One such simple approach associates a free energy density with each atom and calculates the contribution of that atom to the solvation free energy as the product of the free energy density and the accessible surface area; the total solvation free energy is then the sum of the contributions from all atoms exposed to the solvent [2,3].

The most popular, and computationally most efficient methods for computing accessible surface areas analytically are those of Connolly [4] and Richmond [5], which treat the atoms as spheres and use the Gauss–Bonnet theorem from differential geometry to calculate the exposed area of each atom. Both Connolly's and Richmond's methods have been modified by subsequent workers [6–9], and two recent algorithms based on these equations show promise of being fast enough for routine use in computations of the conformational energy of solvated polypeptides and proteins [7,9]. Both of these algorithms also compute the first derivatives of the solvation free energy with respect to the coordinate vectors of the constituent atoms of the peptides. With the availability of these algorithms, the possibility of carrying out energy minimization or molecular dynamics of solvated proteins and other macromolecules, without consuming excessive amounts of CPU time, becomes a reality.

However, there is a difficulty associated with the use of these algorithms. Although the accessible surface area S (i.e. the area of those parts of the surface that are not contained inside any of the spheres of the system) is a continuous function of the spatial positions of the atoms, its gradient is not. When two atoms touch from the outside, there is a discontinuity in the gradient, as follows immediately from the expression for the surface areas of two spheres that intersect [9,10]. The question arises whether this is the only situation that leads to a discontinuity in the gradient. The answer to this question is important practically as well as theoretically, because gradient discontinuities frequently cause problems during searches for local energy minima, and also lead to instability of dynamical trajectories. In this paper, we show that one other spatial arrangement of atoms gives rise to a discontinuity in the gradient, and that these two are the only situations associated with discontinuities.

An additional difficulty arises if a given algorithm computes only that part, S_0, of the total surface area S, which is not buried inside the molecule (a portion of the surface is said to be *buried* inside the molecule, if there is no way to connect points belonging to this portion with points lying outside the molecule by a continuous curve, without entering the interior of at least one atom). An example of this type of algorithm is the MSEED algorithm [7]. Then, the function S_0 itself, as well as its gradient, may be discontinuous. We show, however, that discontinuities of the gradient of S_0 are associated with the same situations as in the case of S, unless the function S_0 is itself discontinuous.

In section 1, we present the main theorem of the paper, and we outline its proof.

In section 2, we define the notion of a circle of intersection of two spheres in space, and we prove that its radius, the position of its center, and the orientation of its plane, are C^∞ [11,12] functions of the centers of the spheres. We also show that, under certain assumptions, the orthogonal projection of the circle on a plane is an ellipse, and its center, the lengths of its axes, and its orientation on the plane, are C^∞ functions of the intersecting spheres.

In section 3, we define C^∞ families of ellipses, and full ellipses (an ellipse plus its interior), so that the projection of a circle of intersection of two spheres, which moves with a change of the positions of their centers, constitutes a C^∞ family of ellipses on the plane of the projection. We prove that the positions of certain points, belonging to ellipses from C^∞ families, are C^∞ functions of all parameters defining these ellipses, i.e. the coordinates of their centers, the lengths of their axes, and their orientations on the plane. We show among other things that the position of the point of intersection of ellipses belonging to two C^∞ families is a C^∞ function of these parameters, unless the ellipses are tangent to each other. We also introduce the definitions of external and internal tangency of ellipses, and show some of their properties.

Section 4 is devoted to C^∞ families of full ellipses. This is the key section of the paper. The two lemmas in this section give estimates of the areas of certain sets in a plane that are bounded by arcs of ellipses belonging to C^∞ families. To prove these lemmas, we apply the results from section 3. The second lemma contains an additional assumption about curvatures of ellipses, which are not satisfied in general by C^∞ families of ellipses; however, in section 5, we show that, for our purposes, this additional assumption is acceptable.

Section 6 presents the main results. Continuity of the gradient of the surface area of the geometrical model of a molecule is shown to be equivalent to a set of simple geometrical relations between the radii and the centers of the spheres constituting the model. The surface area is represented by a linear combination of integrals of functions defining portions of the surface, over sets in a plane that are bounded by arcs of ellipses belonging to C^∞ families; the results of section 4 are applied in section 6.

1. Main theorem and an outline of its proof

As we prove in this paper, the gradient of the accessible surface area S (defined in the introduction), as a function of the Cartesian coordinates of the centers of all spheres modelling the molecule, is discontinuous for those and only for those coordinates for which one of the following situations arises:

(a) two spheres are identical,

(b) two spheres are externally tangent,

(c) there exist three spheres intersecting each other along the same circle of intersection,

and, in addition, both spheres in case (a), or the point of tangency in case (b), or the common circle of intersection in case (c), are not totally contained within the domain bounded by the remaining spheres of the system.

The accessible surface area S can be represented as a sum of surface areas of regions of spheres that are bounded by arcs of circles of intersection. To calculate the surface areas of those regions, we consider their orthogonal projections on suitably oriented planes; the surface areas are computed as integrals of a certain positive, C^∞ function h, over the images of those regions under the projection. The problem of discontinuities of the gradient of S transforms into a problem of discontinuities of the gradients of areas of planar sets bounded by arcs of ellipses.

We investigate all possible kinds of intersections, and all possible types of tangencies of ellipses on a plane, as well as their influence on the continuity of the gradient of the areas bounded by arcs of ellipses. We conclude that a discontinuity of this gradient can arise only if there exists an arc common to two ellipses, or if a new ellipse is created. Since arcs of ellipses on the plane are orthogonal projections of arcs of circles of intersection in space, these situations correspond to the arrangements of spheres listed in the theorem as (a), (b), and (c).

2. Movements of spheres in $\mathbf{R}^3$ space

DEFINITION 2.1

If $u = (x, y, z) \in \mathbf{R}^3$ and $R > 0$ then $O(u, R)$ denotes the sphere O in $\mathbf{R}^3$ with center u and radius R, i.e. the set of all points in $\mathbf{R}^3$ which are at a distance R from the point u.

DEFINITION 2.2

If $O_1(u_1, R_1)$ and $O_2(u_2, R_2)$ are two spheres in $\mathbf{R}^3$ then the set of all points belonging to both O_1 and O_2, is called a circle of intersection of these two spheres.

DEFINITION 2.3

Two spheres $O_1(u_1, R_1)$ and $O_2(u_2, R_2)$ are externally tangent if $|u_1 - u_2| = R_1 + R_2$. Two different spheres $O_1(u_1, R_1)$ and $O_2(u_2, R_2)$ are internally tangent if $|u_1 - u_2| = |R_1 - R_2|$.

REMARK 2.1

If $u_1 = u_2$ and $R_1 = R_2$, then $O_1 = O_2$ and any large circle of the spheres is called a circle of intersection. In the case when O_1 and O_2 are tangent (externally or internally) the circle of intersection is reduced to a single point. If, however, there are no common points of the spheres O_1 and O_2, we do not define the circle of intersection. This means that, whenever we consider a circle of intersection, we always assume that the circle is not empty.

LEMMA 2.1

Let $O_1(u_1, R_1)$ and $O_2(u_2, R_2)$ be two spheres in $\mathbf{R}^3$. The position u_0 of the center of the circle of intersection is a C^∞ function of u_1 and u_2.

Proof

If $R_1 \neq R_2$, then the position u_0 of the center of the circle of intersection is given by the equation:

$$u_0 = \frac{(u_1 + u_2)}{2} + \frac{u_1 - u_2}{|u_1 - u_2|} \cdot \frac{R_1^2 - R_2^2}{2|u_1 - u_2|} . \tag{1}$$

This equation describes a C^∞ function of u_1 and u_2 everywhere with the exception of the situation, in which $u_1 = u_2$, i.e. outside the domain where the circle if intersection is defined.

If $R_1 = R_2$, then the position of u_0 is given by

$$u_0 = \frac{(u_1 + u_2)}{2}, \tag{2}$$

which is a C^∞ function of u_1 and u_2 everywhere. □

LEMMA 2.2

Let $O_1(u_1, R_1)$ and $O_2(u_2, R_2)$ be two spheres in $\mathbf{R}^3$. The radius R_0 of the circle of intersection is a C^∞ function of u_1 and u_2 unless

$$|u_1 - u_2| = |R_1 \pm R_2|, \tag{3}$$

i.e. when the spheres O_1 and O_2 are externally or internally tangent.

Proof

If $R_1 \neq R_2$, then the radius R_0 of the circle of intersection is given by the equation

$$R_0 = \sqrt{R_1^2 - \left[\frac{(R_1 - R_2)(R_1 + R_2)}{2|u_1 - u_2|} + \frac{|u_1 - u_2|}{2}\right]^2}, \tag{4}$$

which describes a C^∞ function of u_1 and u_2 everywhere where the circle of intersection if defined, unless the expression under the square root is zero. This happens, however, if and only if $|u_1 - u_2| = |R_1 \pm R_2|$ and is excluded by the assumption in eq. (3) of the lemma.

If $R_1 = R_2$, then the radius R_0 is given by

$$R_0 = \sqrt{R_1^2 + \frac{|u_1 - u_2|^2}{4}}, \tag{5}$$

which is a C^∞ function of u_1 and u_2 everywhere. □

LEMMA 2.3

Let $O_1(u_1, R_1)$ and $O_2(u_2, R_2)$ be two different, non-tangent (externally or internally) spheres in $\mathbf{R}^3$. The plane O defined by the circle of intersection can be expressed by the equation

$$Ax + By + Cz + D = 0 \tag{6}$$

with the coefficients A, B, C and D given by the following equations:

$$A = x_2 - x_1,$$

$$B = y_2 - y_1,$$

$$C = z_2 - z_1,$$

$$D = -[(x_2 - x_1)x_0 + (y_2 - y_1)y_0 + (z_2 - z_1)z_0]\,, \tag{7}$$

where x_0, y_0, z_0 are the coordinates of the center of the circle of intersection. The coefficients A, B, C, D are C^∞ functions of u_1 and u_2.

Proof

The plane O is obviously perpendicular to the vector $[x_2 - x_1, y_2 - y_1, z_2 - z_1]$ (the assumptions of the lemma imply that it is a non-zero vector), and the center of the circle of intersection lies in this plane. This justifies eqs. (6) and (7). The fact that the coefficients are C^∞ functions of u_1 and u_2 follows from eq. (7) and from lemma 2.1. □

LEMMA 2.4

Let spheres O_1, O_2, and the plane O be defined as in lemma 2.3. In addition, assume that O is not parallel or perpendicular to the plane xy, and that the line of intersection of the planes O and xy is not parallel to either the x or the y axis. The orthogonal projection of the circle of intersection on the xy-plane is an ellipse and

– the coordinates of its center,

– the lengths of its major and minor axes,

– the angles between these axes and the x- and y-axis

are C^∞ functions of u_1 and u_2. This means that this ellipse can be parametrized as follows:

$$x(\omega) = a\cos\alpha\cos\omega - b\sin\alpha\sin\omega + x_0\,,$$

$$y(\omega) = a\sin\alpha\cos\omega + b\cos\alpha\sin\omega + y_0\,, \tag{8}$$

where a, b are the lengths of the major and minor semi-axes, respectively, α is the angle of orientation between the major axis of the ellipse and the x-axis, x_0, y_0 are the coordinates of the center of the ellipse, and ω is a parameter to specify a point on the ellipse; a, b, α, x_0, y_0 are C^∞ functions of u_1 and u_2.

The curvature of the ellipse at the point corresponding to a given value of the parameter ω [according to the parametrization in eqs. (8)] is a C^∞ function of u_1, u_2 and ω.

Proof

Lemma 2.1 implies that the coordinates x_0, y_0, z_0 of the center of the circle of intersection are C^∞ functions of u_1 and u_2. Since the coordinates of the center of the ellipse on the xy-plane are obviously (x_0, y_0), they are C^∞ functions of u_1, u_2 as well.

The length a of the major semi-axis of the ellipse equals the radius R_0 of the circle of intersection, which is a C^∞ function of u_1 and u_2, as follows from Lemma 2.2. The length b of the minor semi-axis is given by the equation

$$b = R_0 \frac{|C|}{\sqrt{A^2 + B^2 + C^2}} \tag{9}$$

with A, B, C being C^∞ functions of u_1, u_2, defined by eqs. (7). Since the plane O is not parallel to the xy-plane, at least one of the coefficients A, B is different from zero; hence, the expression under the square root in eq. (9) is always positive. Since O is not perpendicular to xy, the value of C is either always positive or always negative. Hence, b is a C^∞ function of u_1 and u_2.

The angle between the x-axis and the major axis of the ellipse is equal to the angle between the x-axis and the line of intersection of the planes O and xy, given by the equation $Ax + By + D = 0$. The cosine of this angle equals $|B|/\sqrt{A^2 + B^2}$. Since this line of intersection is not parallel or perpendicular to the x-axis, the expression under the square root is always positive, and the value of B is either always positive or always negative. Hence, the cosine of this angle, and the angle itself, are C^∞ functions of u_1, u_2.

The curvature of the ellipse at a point related to a given value of the parameter ω equals $[\dot{x}(\omega)\ddot{y}(\omega) - \ddot{x}(\omega)\dot{y}(\omega)]/[\ddot{x}(\omega)^2 + \ddot{y}(\omega)^2]^{3/2} = ab/(a^2 \cos^2 \omega + b^2 \sin^2 \omega)^{3/2}$, where x and y are given by eqs. (8), and $\dot{x}, \dot{y}$ and $\ddot{x}, \ddot{y}$ denote the first and second derivatives, respectively, of x and y with respect to the parameter ω. It is a C^∞ function of u_1, u_2 and ω because a and b are such functions, and they are always positive. □

REMARK 2.2

Lemma 2.4 remains true if we replace the plane xy by a plane $\mathcal{P}$, not parallel or perpendicular to O, and supply it with a Cartesian coordinate system $\eta\xi$, such that the line of intersection of the planes $\mathcal{P}$ and O is not parallel or perpendicular to any of the axes η and ξ. The parametrization in eqs. (8) will then take the form

$$\begin{aligned} \eta(\omega) &= a \cos\alpha \cos\omega - b \sin\alpha \sin\omega + \eta_0 , \\ \xi(\omega) &= a \sin\alpha \cos\omega + b \cos\alpha \sin\omega + \xi_0 , \end{aligned} \tag{10}$$

where a, b are the lengths of the major and minor semi-axes of the ellipse, respectively, α is the angle of orientation between the major axis and the η-axis, and η_0, ξ_0 are the coordinates of the center of the ellipse on the plane $\mathcal{P}$ in the $\eta\xi$ coordinate system.

3. Movements of ellipses on a plane

Let us assume that $O_1(u_1, R_1), \ldots, O_n(u_n, R_n)$ is a collection of n spheres in $\mathbf{R}^3$. Furthermore, we assume that the radii $R_1, \ldots, R_n$ are fixed and $u = (u_1, \ldots, u_n) = (x_1, y_1, z_1, \ldots, x_n, y_n, z_n)$ is a collection of independent variables.

With each pair i, j of spheres, and with each plane $\mathcal{P}$ with a Cartesian coordinate system $\eta\xi$, we can associate an ellipse on the plane $\mathcal{P}$ for every value of $(u_1, \ldots, u_i, \ldots, u_j, \ldots, u_n) = u$, provided that, for these values of u_i, u_j, certain conditions are satisfied (see the assumptions in remark 2.2). This ellipse is defined by eqs. (10), and $a, b, \alpha, \eta_0, \xi_0$ are C^∞ functions of u_i and u_j. We can obviously say that a, b, α, η_0 and ξ_0 are also C^∞ functions of all variables $u_k, k = 1, 2, \ldots, n$, since these functions do not depend at all on any quantities other than u_i and u_j. In other words, if the assumptions in remark 2.2 are satisfied for the pair i, j and for a given point $u = (u_1, \ldots, u_n) \in \mathbf{R}^{3n}$, then there exists an open neighborhood [13] $U \subset \mathbf{R}^{3n}$ of this point such that, for every point u belonging to U, the associated ellipse E^u is given by the parametrization of eqs. (10), and $a, b, \alpha, \eta_0, \xi_0$ are C^∞ functions of $u \in U \subset \mathbf{R}^{3n}$.

We introduce the following definition:

DEFINITION 3.1

Let U be an open set [13] in an N-dimensional space $\mathbf{R}^N$ (in our case N will always be equal to $3n$), and for every $u \in U$ let E^u be an ellipse on a plane $\mathcal{P}$ supplied with a Cartesian coordinate system $\eta\xi$. If the family $\{E^u : u \in U\}$ can be parametrized by eqs. (10) with $a, b, \alpha, \eta_0, \xi_0$ being C^∞ functions of $u \in U$, then it is called a C^∞ family of ellipses.

If E is an ellipse on a plane $\mathcal{P}$, $\tilde{E}$ denotes the set of all points on this plane which are inside the ellipse E, including the ellipse itself (i.e. the border of this domain), and is called a *full* ellipse. Consequently, if $\{E^u : u \in U\}$ is a C^∞ family of ellipses, $\{\tilde{E}^u : u \in U\}$ is called a C^∞ family of full ellipses.

LEMMA 3.1

Let $\{E^u : u \in U\}$ be a C^∞ family of ellipses on the $\eta\xi$-plane. Let $\mathbf{v}$ be a unit vector on the plane. There is a unique point on each ellipse E^u, for which the outer normal unit vector equals $\mathbf{v}$. The coordinates (η, ξ) of this point are C^∞ functions of u.

Proof

We will first prove the lemma in the case in which this vector equals [1,0]. Then, our point on the ellipse E^u is the point where the coordinate η takes its maximum value. Hence, its position can be derived from the equation $\dot{\eta}(\omega) = 0$, with $\dot{\xi}(\omega) > 0$:

$$-a \cos\alpha \sin\omega - b \sin\alpha \cos\omega = 0 \tag{11}$$

and

$$-a \sin\alpha \sin\omega + b \cos\alpha \cos\omega > 0\,. \tag{12}$$

For $\alpha \neq \pm 90°$ and lying in the first or fourth quadrant, eqs. (11) and (12) lead to the equation

$$\omega = \arctan[(-b \tan\alpha)/a] \tag{13}$$

and, for $\alpha \neq \pm 90°$ and lying in the second or third quadrant, to the equation

$$\omega = \arctan[(-b \tan\alpha)/a] + 180°\,. \tag{14}$$

The derivatives of both functions (13), (14) with respect to α can be represented as

$$-\frac{ab}{a^2\cos^2\alpha+b^2\sin^2\alpha}\,, \tag{15}$$

which is a C^∞ function for all α, since $a,b>0$. Hence, both functions (13), (14) can be extended [14] uniquely to C^∞ functions on quadrants I and IV, and II and III, respectively, now including $\alpha=\pm 90°$. Moreover, they can be extended to the same common function $\omega(\alpha)$ which is periodic and is a C^∞ function for all real values of α.

Now, the coordinates (η,ξ) can be calculated from the eqs. (10) with ω replaced by $\omega(\alpha)$. Since a,b,α,η_0,ξ_0 are C^∞ functions of u, and ω is a C^∞ function of α, then η and ξ are C^∞ functions of u.

If the unit vector $\mathbf{v}$ is different from [1,0], let $\alpha_{\mathbf{v}}$ denote the angle of orientation between $\mathbf{v}$ and the η-axis. By rotation of every ellipse from the original family $\{E^u : u\in U\}$ by the angle $-\alpha_{\mathbf{v}}$, we obtain a new C^∞ family of ellipses, $\{E'^u : u\in U\}$. This new family of ellipses is parametrized by eqs. (10), with the angle α replaced by $\alpha+\alpha_{\mathbf{v}}$, and the problem of calculating the position of the specified point on the original ellipses for the vector $\mathbf{v}$ is equivalent to the already-solved problem of calculating this point on the rotated ellipses for the vector [1,0]. □

LEMMA 3.2

Let $\{E^u : u\in U\}$ be a C^∞ family of ellipses on the $\eta\xi$-plane. Let $\mathring{u}\in U$ and let $(\mathring{\eta},\mathring{\xi})$ be a point inside $E^{\mathring{u}}$. Denote by l_ϕ the half-line starting at the point $(\mathring{\eta},\mathring{\xi})$, with the angle of orientation ϕ with the η-axis, for all $\phi\in R$. Let $\rho(u,\phi)$ denote the distance between $(\mathring{\eta},\mathring{\xi})$ and the point of intersection of E^u and l_ϕ. Then ρ is a C^∞ function of both variables u and ϕ, for u sufficiently close to $\mathring{u}$.

Proof

We will first prove the lemma with the assumption that $(\mathring{\eta},\mathring{\xi})=(0,0)$. The point of intersection of E^u and l_ϕ satisfies the following equations (for each u which is sufficiently close to $\mathring{u}$):

$$a\cos\alpha\cos\omega-b\sin\alpha\sin\omega+\eta_0=\rho\cos\phi\,,$$

$$a\sin\alpha\cos\omega+b\cos\alpha\sin\omega+\xi_0=\rho\sin\phi\,. \tag{16}$$

If $\phi\neq k\cdot 90°$, for $k=0,1,2,\ldots$, these equations can be transformed into one equation with unknown ω:

$$a\sin(\alpha-\phi)\cos\omega+b\cos(\alpha-\phi)\sin\omega+(\xi_0\cos\phi-\eta_0\sin\phi)=0\,. \tag{17}$$

With $A=a\sin(\alpha-\phi), B=b\cos(\alpha-\phi), C=\xi_0\cos\phi-\eta_0\sin\phi$, we obtain

$$A\cos\omega+B\sin\omega+C=0\,. \tag{18}$$

This equation can be solved to give

$$\sin\,\omega = \frac{-BC \pm A\sqrt{A^2+B^2-C^2}}{A^2+B^2}\,, \tag{19}$$

where the sign is to be chosen to make ρ positive. Since both the denominator and the expression under the square root are positive, eq. (19) describes a C^∞ function with respect to A, B, C. Hence, $\sin\omega$ is a C^∞ function of u and ϕ. Therefore, ω is a C^∞ function of u and ϕ. With the assumption that $\phi \neq k \cdot 90°$, for $k = 0, 1, 2, \ldots,$ eqs. (16) imply the C^∞ dependence of $\rho(u, \phi)$ with respect to both variables.

If $\phi = k \cdot 90°$ for some $k = 0, 1, 2, \ldots,$ then the right-hand side of the first or the second of equations (16) is equal to zero and leads to eqs. (18) and (19). Consequently, ω and ρ are C^∞ functions of the variables u and ϕ.

If the point $(\mathring{\eta}, \mathring{\xi})$ is different from (0,0), we can reduce the problem to the previous case by translating all the ellipses from the family $\{E^u : u \in U\}$ by the vector $[\mathring{\eta}, \mathring{\xi}]$. □

DEFINITION 3.2

Two different ellipses E_1 and E_2 on a plane $\mathcal{P}$ are tangent at a point e if there exists a line l tangent to both E_1 and E_2 at e.

Two ellipses E_1 and E_2 are *externally* tangent at e, if they are tangent at e and, in addition, the common parts of E_1 and $\tilde{E}_2$, as well as E_2 and $\tilde{E}_1$ are both the same single point e, in a neighborhood of this point.

An ellipse E_1 is *internally* tangent to an ellipse E_2 at e, if both ellipses are tangent at e and, in addition, E_1 is contained in $\tilde{E}_2$ in a neighborhood of this point.

REMARK 3.1

Two ellipses E_1, E_2 on a plane can be tangent at a point e and, at the same time, not tangent externally or internally. The ellipses E and E'' in fig. 1 are one example of this situation.

Indeed, let E be an ellipse (but not a circle) and e be a point on E different from

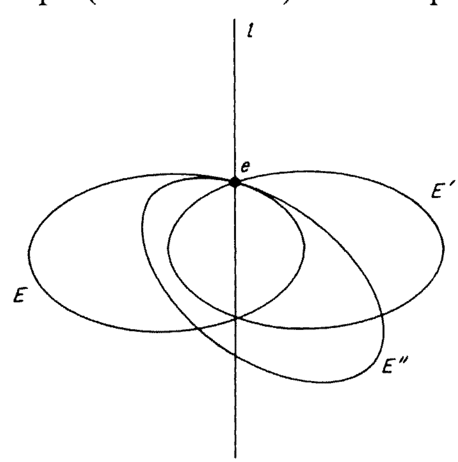

Fig. 1.

those four points where the ellipse is intersected by its major or minor axis (see fig. 1). Denote by l the line parallel to the minor axis, which includes the point e and by E' the symmetric image of E, with l as the symmetry axis. Rotate the ellipse E' around the point e so that the resulting ellipse E'' is tangent (but not externally tangent) to E at the point e. The ellipses $E_1 = E$ and $E_2 = E''$ serve as the example of the situation described in this remark.

LEMMA 3.3

Let ellipses E_1 and E_2 meet the conditions specified in remark 3.1. Then the curvatures of both ellipses at the point e are equal.

Proof

If we supply the plane of both ellipses E_1, E_2 with a Cartesian coordinate system such that the abscissa coincides with the line tangent to both E_1 and E_2 at the point e, and if e is the origin of this coordinate system, then the portions of both curves E_1 and E_2 in a neighborhood of this point can be understood as graphs of two functions f_1 and f_2, respectively. Both functions together with their first derivatives take the value 0, if the abscissa equals 0. As is well known, both are analytical functions (i.e. expandable into a Taylor series) in a neighborhood of zero. Since, in a neighborhood of zero, one of the functions, say f_1, must be greater than f_2 for all negative values of the abscissa and, at the same time, smaller than f_2 for its positive values, then the lowest-order coefficients in both Taylor series, which are different from each other, must be of odd order equal to 3 or more. Hence, the second derivatives of both functions f_1 and f_2 at 0 must be equal. The well-known relation between curvatures and second derivatives completes the proof. □

LEMMA 3.4

Let $\{E_1^u : u \in U\}$ and $\{E_2^u : u \in U\}$ be two C^∞ families of ellipses on the η, ξ-plane. For a given $\mathring{u} \in U$, let $\mathring{p}$ be the point of intersection of $E_1^{\mathring{u}}$ and $E_2^{\mathring{u}}$. Assume that $E_1^{\mathring{u}}$ and $E_2^{\mathring{u}}$ are not tangent at $\mathring{p}$. If p denotes the point of intersection of the ellipses E_1^u and E_2^u, then the coordinates η, ξ of p are C^∞ functions of u, for u sufficiently close to $\mathring{u}$.

Proof

The proof is very similar to that of Lemma 3.2. Parametrizations in eqs. (10) are used for both families of ellipses, and equations in coordinates η, ξ of the point p as unknown are solved. The assumptions of the lemma assure that the resulting η and ξ are C^∞ functions of u. □

4. Movements of full ellipses on a plane

DEFINITION 4.1

If G is a Lebesgue measurable subset [15] of a plane $\mathcal{P}$, $\mu(G)$ denotes the area of G.

DEFINITION 4.2

If $u = (u_1, u_2, \ldots, u_N)$ is a point in the space $\mathbf{R}^N$, the norm $\|u\|$ is defined by the expression $\|u\| = (u_1^2 + u_2^2 + \ldots + u_N^2)^{1/2}$. For two points u' and u'' belonging to $\mathbf{R}^N$, the norm of the difference $u' - u''$ defines the distance between u' and u'' in the space $\mathbf{R}^N$.

DEFINITION 4.3

If A and B are two sets then $A \div B$ denotes the union of the sets $A - B$ and $B - A$, i.e. $A \div B = (A - B) \cup (B - A)$.

REMARK 4.1

Let U be an open set in $\mathbf{R}^N$, and let g be a C^∞ function of the variable $u \in U$. Then, for any point $\mathring{u} \in U$ there exists a constant $c > 0$ such that $|g(u) - g(\mathring{u})| \leqslant c\|u - \mathring{u}\|$ for all u being sufficiently close to $\mathring{u}$.

LEMMA 4.1

Let $\{\tilde{E}_1^u : u \in U\}, \ldots, \{\tilde{E}_m^u : u \in U\}$ be C^∞ families of full ellipses on the η, ξ-plane. Let $\mathcal{E}^u$ denote the intersection (i.e. the common part) of all $\tilde{E}_1^u, \ldots, \tilde{E}_m^u$. Suppose that, for some point $\mathring{u} \in U$, $\mathcal{E}^{\mathring{u}}$ is a single point $\mathring{p}$. Then there exists a constant $c > 0$ such that

(i) $\mu(\mathcal{E}^u) \leqslant c\|u - \mathring{u}\|^{3/2}$ for all u sufficiently close to $\mathring{u}$,

(ii) $\mu(\mathcal{E}^u \div \mathcal{E}^{\mathring{u}'}) \leqslant c\|\mathring{u}' - \mathring{u}\|^{1/2}\|u - \mathring{u}'\|$ for all u and $\mathring{u}'$ sufficiently close to $\mathring{u}$.

Proof

The point $\mathring{p}$ is obviously the intersection of only those full ellipses from $\tilde{E}_1^{\mathring{u}}, \ldots, \tilde{E}_m^{\mathring{u}}$ whose boundaries contain $\mathring{p}$, as well. For simplicity, we may assume in the proof that $\mathring{p}$ belongs to all ellipses $E_1^{\mathring{u}}, \ldots, E_m^{\mathring{u}}$.

The number $\mu(\mathcal{E}^u)$ is smaller than the area of the intersection of any number of full ellipses chosen from $\tilde{E}_1^u, \ldots, \tilde{E}_m^u$. There are only two possible arrangements of these ellipses which satisfy the assumptions of the lemma:

- None of the ellipses $E_1^{\mathring{u}}, \ldots, E_m^{\mathring{u}}$ is externally tangent to any other at $\mathring{p}$. Then there exist three full ellipses, say $\tilde{E}_i^{\mathring{u}}, \tilde{E}_j^{\mathring{u}}, \tilde{E}_k^{\mathring{u}}$, whose intersection is $\mathring{p}$ (see fig. 2(a)); consequently, $\mu(\mathcal{E}^u)$ is smaller than the area of the intersection of the full ellipses $\tilde{E}_i^u, \tilde{E}_j^u$ and $\tilde{E}_k^u$ (see fig. 2(b)).

  Indeed, let $l_1, \ldots, l_m$ be lines tangent to the ellipses $E_1^{\mathring{u}}, \ldots, E_m^{\mathring{u}}$, respectively, at the point $\mathring{p}$. It may happen that, for some indices i, j, $1 \leqslant i, j \leqslant m$, $i \neq j$, the lines l_i and l_j coincide, i.e. the ellipses $E_i^{\mathring{u}}$ and $E_j^{\mathring{u}}$ are tangent (although not externally tangent) to each other at $\mathring{p}$. Denote by $\mathcal{L}_1, \ldots, \mathcal{L}_M$, for a suitable M, $M \leqslant m$, the largest collection of these lines from $l_1, \ldots, l_m$ all of which differ from each other. If, for any I, $1 \leqslant I \leqslant M$, there is more than one line from $l_1, \ldots, l_m$, which coincides with $\mathcal{L}_I$, then the respective ellipses must be tangent to each other at $\mathring{p}$. Since they cannot be externally tangent, all of them must lie in the same closed

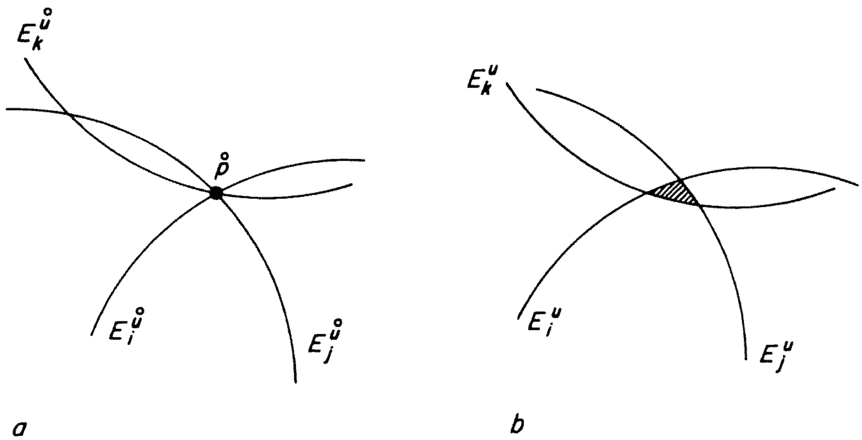

Fig. 2.

half-plane $\mathcal{P}_I$ defined by the line $\mathcal{L}_I$. Hence, if $\Gamma_I^\epsilon, 0<\epsilon<1°$, denotes the set of all points p from $\mathcal{P}_I$ such that the angle between the line $\mathcal{L}_I$, and the line connecting $\mathring{p}$ and p is smaller than ϵ, then the set $\overline{\Gamma_I^\epsilon}$ [13] is contained in each of the full ellipses tangent to $\mathcal{L}_I$ at $\mathring{p}$, in a sufficiently small neighborhood of $\mathring{p}$. Therefore, for any $\epsilon, 0<\epsilon<1°$, the intersection of all full ellipses $\tilde{E}_1^{\mathring{u}} \ldots, \tilde{E}_m^{\mathring{u}}$ contains the intersection of all sets $\overline{\Gamma_I^\epsilon}, \ldots, \overline{\Gamma_M^\epsilon}$, in a sufficiently small neighborhood of $\mathring{p}$. Moreover, the point $\mathring{p}$ belongs to the latter intersection because it belongs to each of the sets $\overline{\Gamma_I^\epsilon}, \ldots, \overline{\Gamma_M^\epsilon}$ and, at the same time, $\mathring{p}$ is the single common point of all full ellipses $\tilde{E}_1^{\mathring{u}}, \ldots, \tilde{E}_m^{\mathring{u}}$; hence, $\mathring{p}$ must be the intersection of $\overline{\Gamma_I^\epsilon}, \ldots, \overline{\Gamma_M^\epsilon}$, for every $\epsilon, 0<\epsilon<1°$. Denote by $\mathcal{P}^I$ the intersection of the half-planes $\mathcal{P}_1, \mathcal{P}_2, \ldots, \mathcal{P}_I$, for $3 \leqslant I \leqslant M$. For any such I, since all the lines $\mathcal{L}_1, \ldots, \mathcal{L}_M$ are different from each other, the set $\mathcal{P}^I$ is either the single point $\mathring{p}$, or a closed set bounded by two of the lines $\mathcal{L}_1, \mathcal{L}_2, \ldots, \mathcal{L}_I$, i.e. $\mathcal{P}^I$ is the intersection of only two of the half-planes $\mathcal{P}_1, \mathcal{P}_2, \ldots, \mathcal{P}_I$. Assume that $\mathcal{P}^M$ is not a single point, i.e. it is of the second type. Then, for a sufficiently small $\epsilon > 0$, the intersection of the sets $\overline{\Gamma_1^\epsilon}, \ldots, \overline{\Gamma_M^\epsilon}$ would be larger than the single point $\mathring{p}$ in any neighborhood of this point. This contradiction shows that $\mathcal{P}^M$ must consist of the single point $\mathring{p}$ only. We can define the smallest integer $K, 3 \leqslant K \leqslant M$, such that $\mathcal{P}^K$ is a single point, and $\mathcal{P}^{K-1}$ is the intersection of two half-planes, say, $\mathcal{P}_I$ and $\mathcal{P}_J$. In other words, the intersection of $\mathcal{P}_I, \mathcal{P}_J$, and $\mathcal{P}_K$ is the single point $\mathring{p}$. Let $E_i^{\mathring{u}}, E_j^{\mathring{u}}$ and $E_k^{\mathring{u}}$ be the ellipses tangent to the lines $\mathcal{L}_I, \mathcal{L}_J$, and $\mathcal{L}_K$, respectively. All of the full ellipses $\tilde{E}_i^{\mathring{u}}, \tilde{E}_j^{\mathring{u}}, \tilde{E}_k^{\mathring{u}}$ contain the point $\mathring{p}$, and are obviously contained in the respective half-planes $\mathcal{P}_I, \mathcal{P}_J$, and $\mathcal{P}_K$, whose intersection is the single point $\mathring{p}$; therefore, the intersection of the full ellipses $\tilde{E}_i^{\mathring{u}}, \tilde{E}_j^{\mathring{u}}, \tilde{E}_k^{\mathring{u}}$ is this single point.

There exist two ellipses, say $E_i^{\mathring{u}}, E_j^{\mathring{u}}$ among $E_1^{\mathring{u}}, \ldots, E_m^{\mathring{u}}$, which are externally tangent to each other at $\mathring{p}$ (see fig. 3(a)). Then $\mu(\mathcal{E}^u)$ is smaller than the area of the intersection of the full ellipses $\tilde{E}_i^u$ and $\tilde{E}_j^u$ (see fig. 3(b)).

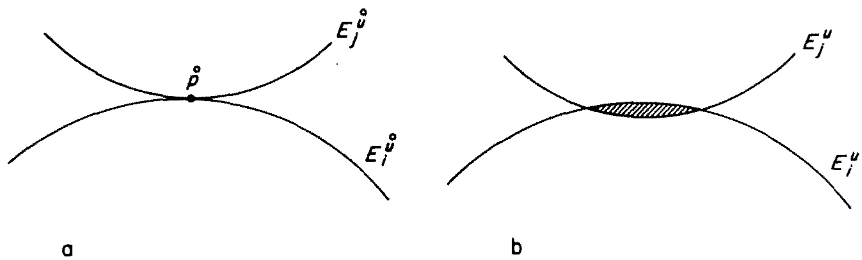

Fig. 3.

In the first arrangement, for every u which is sufficiently close to $\mathring{u}$, the intersection of $\tilde{E}_i^u, \tilde{E}_j^u, \tilde{E}_k^u$ is either an empty set, or a single point, or an "ellipsoidal convex triangle" as shown in fig. 2(b). Lemma 3.4 and remark 4.1 imply that the distances between any two vertices of this "triangle" are smaller than $c\|u - \mathring{u}\|$ for a suitable constant c, and for any u sufficiently close to $\mathring{u}$. Simple geometrical considerations, utilizing the facts that the curvature and the lengths of the large and small axes of the ellipses belonging to a C^∞ family are C^∞ functions of u (see lemma 2.4 and remark 2.2), lead to the conclusion that the area of the "triangle", i.e. $\mu(\mathcal{E}^u)$, can be estimated by $c\|u - \mathring{u}\|^2$, for another suitable constant c, and for any u which is sufficiently close to $\mathring{u}$.

In the second arrangement, for every u which is sufficiently close to $\mathring{u}$, the intersection of $\tilde{E}_i^u$ and $\tilde{E}_j^u$ is either an empty set, or a single point, or an "ellipsoidal convex lens" as shown in fig. 3(b). To estimate the area of this "lens", we consider two oppositely directed unit vectors $\mathring{\mathbf{v}}_i$ and $\mathring{\mathbf{v}}_j$, externally normal to the ellipses $E_i^{\mathring{u}}$ and $E_j^{\mathring{u}}$ at the point $\mathring{p}$, respectively (see fig. 4). For every u, sufficiently close to $\mathring{u}$, the

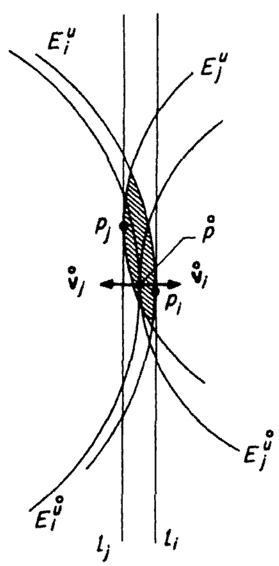

Fig. 4.

"lens" will be totally contained in the strip restricted by two lines l_i and l_j, parallel to each other, perpendicular to both vectors $\mathring{\mathbf{v}}_i$ and $\mathring{\mathbf{v}}_j$, and tangent to the ellipses E_i^u and E_j^u at the points in which $\mathring{\mathbf{v}}_i$ and $\mathring{\mathbf{v}}_j$ are externally normal to them, respectively. The coordinates of the respective tangency points p_i and p_j are C^∞ functions of u, as follows from lemma 3.1; hence, the distance between the lines l_i and l_j can be estimated by $c\|u - \mathring{u}\|$ for a suitable constant c, and for any u which is close enough to $\mathring{u}$. Again, using lemma 2.4 and remark 2.2, simple geometrical calculations show that the area of the "lens", i.e. $\mu(\mathcal{E}^u)$, is smaller than $c\|u - \mathring{u}\|^{3/2}$ for another suitable constant c, and any u which is close enough to $\mathring{u}$.

Combining the two cases, we have the estimate $c\|u - \mathring{u}\|^{3/2}$ for $\mu(\mathcal{E}^u)$.

In both the first and the second arrangements, the length of the boundary of $\mathcal{E}^{\mathring{u}'}$ is of order $\|\mathring{u} - \mathring{u}'\|^{1/2}$, and the boundary of $\mathcal{E}^u$ is contained in the set of all points on the plane distant from $\mathcal{E}^{\mathring{u}'}$ by less than $c\|u - \mathring{u}'\|$, for a suitable constant c and all u, $\mathring{u}'$ sufficiently close to $\mathring{u}$. Hence, $\mu(\mathcal{E}^u \div \mathcal{E}^{\mathring{u}'})$ must be of order $\|\mathring{u} - \mathring{u}'\|^{1/2}\|u - \mathring{u}'\|$. □

LEMMA 4.2

Let $\{\tilde{E}_1^u : u \in U\}, \ldots, \{\tilde{E}_m^u : u \in U\}$ be C^∞ families of full ellipses on the $\eta\xi$-plane. Let $\mathcal{E}^u$ denote the intersection of all $\tilde{E}_1^u, \ldots, \tilde{E}_m^u$ and assume that, for a given point $\mathring{u} \in U$, $\mathcal{E}^{\mathring{u}}$ has a non-empty interior. Assume that there exist an index $k, 1 \leqslant k \leqslant m, \mathring{p} \in \mathcal{P}$, and an open neighborhood $\mathcal{O}(\mathring{p})$ of the point $\mathring{p}$ on the plane $\mathcal{P}$, such that $\mathring{p}$ is the only common point of the sets $\mathcal{E}^{\mathring{u}}$ and $E_k^{\mathring{u}}$ in this neighborhood; i.e. the intersection of the sets $\mathcal{E}^{\mathring{u}}$, $E_k^{\mathring{u}}$ and $\mathcal{O}(\mathring{p})$ is the single point $\mathring{p}$.

In addition, if for some $i, 1 \leqslant i \leqslant m, i \neq k$, the ellipse $E_i^{\mathring{u}}$ is tangent to $E_k^{\mathring{u}}$ at $\mathring{p}$, then we assume that the curvature of $E_i^{\mathring{u}}$ is larger than the curvature of $E_k^{\mathring{u}}$ at this point (this assumption, together with lemma 3.3, excludes tangencies other than those of the internal or external type; the latter, however, is automatically excluded by the above assumption that the set $\mathcal{E}^{\mathring{u}}$ has a non-empty interior, so the only acceptable type of tangency under these conditions is the internal one).

Let $\mathcal{R}^u$ denote the intersection of the sets $\mathcal{E}^u, \mathcal{P} - \tilde{E}_k^u$, and $\mathcal{O}(\mathring{p})$, i.e. the common part of the sets $\mathcal{E}^u$ and $\mathcal{P} - \tilde{E}_k^u$, included in the neighborhood $\mathcal{O}(\mathring{p})$ of the point $\mathring{p}$.

The above assumptions imply that there exists a constant $c > 0$ such that

(i) $\mu(\mathcal{R}^u) \leqslant c\|u - \mathring{u}\|^{3/2}$ for all u sufficiently close to $\mathring{u}$

(ii) $\mu(\mathcal{R}^u \div \mathcal{R}^{\mathring{u}'}) \leqslant c\|\mathring{u}' - \mathring{u}\|^{1/2}\|u - \mathring{u}'\|$ for all $u, \mathring{u}'$ sufficiently close to $\mathring{u}$.

Proof

Obviously, the number $\mu(\mathcal{R}^u)$ is smaller than the area bounded by any number of ellipses chosen from $E_1^u, \ldots, E_{k-1}^u, E_{k+1}^u, \ldots, E_m^u$, and contained inside both $\mathcal{P} - \tilde{E}_k^u$ and $\mathcal{O}(\mathring{p})$. As in the case of lemma 4.1, there are only two possible arrangements of these ellipses which satisfy the assumptions of this lemma:

- None of the ellipses $E_1^{\mathring{u}}, \ldots, E_{k-1}^{\mathring{u}}, E_{k+1}^{\mathring{u}}, \ldots, E_m^{\mathring{u}}$ is tangent to $E_k^{\mathring{u}}$ at $\mathring{p}$. Then there exist two ellipses among them, say E_i^u and E_j^u, not tangent to each other at $\mathring{p}$,

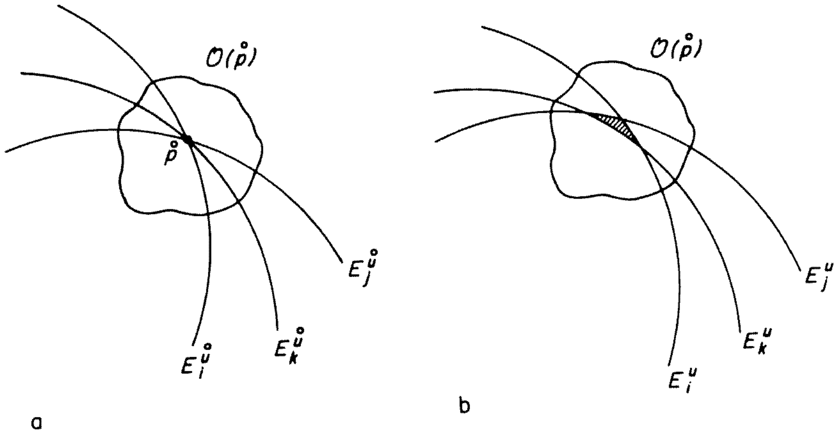

Fig. 5.

and such that $\mathring{p}$ is the only common point of $\tilde{E}_i^{\mathring{u}}, \tilde{E}_j^{\mathring{u}}$ and $E_k^{\mathring{u}}$ in the neighborhood $\mathcal{O}(\mathring{p})$ (see fig. 5(a)). Consequently, $\mu(\mathcal{R}^u)$ is smaller than the area bounded by E_i^u, E_j^u and contained in both $\mathcal{P} - \tilde{E}_k^u$ and $\mathcal{O}(\mathring{p})$ (see fig. 5(b)).

- There exists an ellipse, $E_i^{\mathring{u}}$, among $E_1^{\mathring{u}}, \ldots, E_{k-1}^{\mathring{u}}, E_{k+1}^{\mathring{u}}, \ldots, E_m^{\mathring{u}}$, internally tangent to $E_k^{\mathring{u}}$ (see fig. 6(a)). Then $\mu(\mathcal{R}^u)$ is smaller than the area bounded by E_i^u and contained in both $\mathcal{P} - \tilde{E}_k^u$ and $\mathcal{O}(\mathring{p})$ (see fig. 6(b)).

In the first case, the proof is practically the same as the analogous part of the proof of lemma 4.1.

In the second case, we use the additional assumption about the curvatures of internally tangent ellipses. This additional assumption assures that the area restricted by the ellipse E_i^u and contained in both $\mathcal{P} - \tilde{E}_k^u$ and $\mathcal{O}(\mathring{p})$, has the shape of

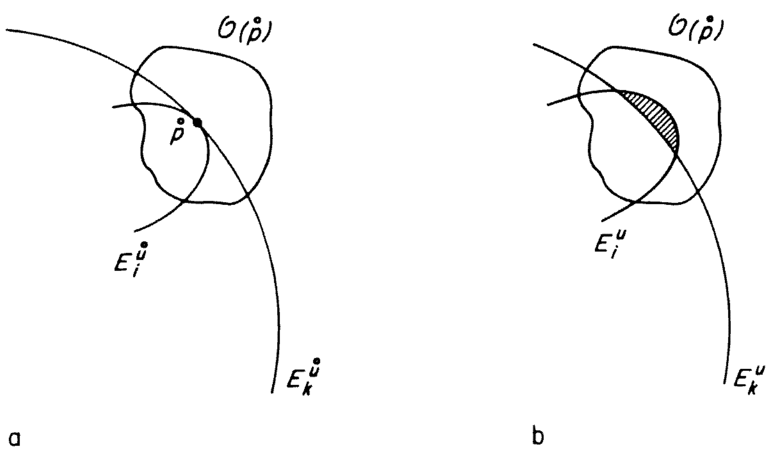

Fig. 6.

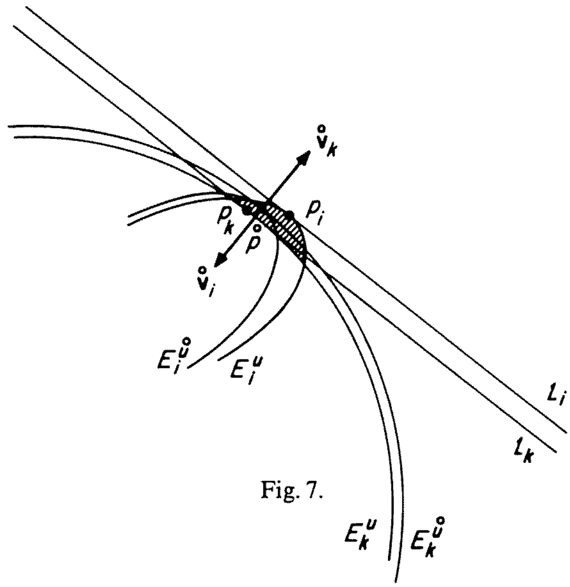

Fig. 7.

a "lens", convex on one side, and concave on the other one, with the larger curvature of the ellipse on the convex side (E_i^u), as shown in fig. 7. The rest of the proof follows the corresponding part of the proof of lemma 4.1. □

5. Projections of circles of intersection

DEFINITION 5.1

Let O_1, O_2 and O be three different spheres in $\mathbf{R}^3$, O_1 and O_2 not tangent (externally or internally) to O, and $\mathcal{C}_1$, $\mathcal{C}_2$ be the circles of intersection of the spheres O with O_1 and O_2, respectively. The circles $\mathcal{C}_1$ and $\mathcal{C}_2$ are said to be spherically tangent on the sphere O, if there exists only one common point of the circles $\mathcal{C}_1$ and $\mathcal{C}_2$. In this case there exists a common line l, tangent to both circles at this point. This line is called the common line of tangency of the circles $\mathcal{C}_1$ and $\mathcal{C}_2$.

LEMMA 5.1

Let $\mathcal{C}_1$, $\mathcal{C}_2$ be the circles of intersection of a sphere O with spheres O_1 and O_2, respectively (O_1, O_2 not being tangent to O), and let $\mathcal{C}_1 \neq \mathcal{C}_2$. Assume that c is a common point of $\mathcal{C}_1$ and $\mathcal{C}_2$, and l_1, l_2 are lines tangent to $\mathcal{C}_1$, $\mathcal{C}_2$ at the point c, respectively. Denote by $\mathcal{P}$ a plane not perpendicular to any of the planes defined by the circles $\mathcal{C}_1$ and $\mathcal{C}_2$, not parallel to any of the lines l_1 and l_2, not intersecting the sphere O, and such that the point c lies between $\mathcal{P}$ and the plane parallel to $\mathcal{P}$ through the center of the sphere. Let π be the orthogonal projection of $\mathbf{R}^3$ onto $\mathcal{P}$.

If ellipses E_1, E_2, being images of the circles $\mathcal{C}_1, \mathcal{C}_2$, respectively, on the plane $\mathcal{P}$, under the projection π, are tangent to each other at the point $e = \pi(c)$, then:

- E_1 and E_2 are either externally tangent at e,

or

- E_1 is internally tangent to E_2 at e, and the curvature of E_1 is larger than the curvature of E_2 at e,

or

- E_2 is internally tangent to E_1 at e, and the curvature of E_2 is larger than the curvature of E_1 at e.

Proof

Indeed, if E_1 and E_2 are tangent at the point e, then the line tangent to both E_1 and E_2 at e is an image under π of both lines l_1, l_2, tangent to $\mathcal{C}_1$ and $\mathcal{C}_2$, respectively, at the point c. Since the point c does not lie on the large circle of the sphere O parallel to $\mathcal{P}$, the lines l_1 and l_2 coincide, and hence the circles $\mathcal{C}_1$ and $\mathcal{C}_2$ are spherically tangent on the sphere O at the point c. Consequently, the ellipses E_1 and E_2 are externally tangent, or one of them is internally tangent to the other one at the point e, say, E_1 is internally tangent to E_2.

Define the plane $\mathcal{P}'$ containing the circle $\mathcal{C}_2$, and denote by π' the projection of the space $\mathbf{R}^3$ onto $\mathcal{P}'$ along the same lines as the projection π, i.e. along a line perpendicular to $\mathcal{P}$. The image of the circle $\mathcal{C}_2$ under π' is obviously the same circle, and the image of $\mathcal{C}_1$ under π' is an ellipse E_1' on the plane $\mathcal{P}'$, internally tangent to $\mathcal{C}_2$ at the point $e' = \pi'(c) = c$. Hence, the curvature of E_1' at e' cannot be smaller than the curvature of the circle $\mathcal{C}_2$ which is of course the same at all points belonging to $\mathcal{C}_2$. If these two curvatures were equal, the point e' would be the point of intersection of the ellipse E_1' and its minor axis, because the curvature of E_1' at points neighbouring e' cannot be smaller than the constant curvature of the circle $\mathcal{C}_2$; consequently, this minor axis would be an axis of symmetry of both the circle $\mathcal{C}_2$ and the ellipse E_1', and the direction of the projection π' (which is the same as the direction of the projection π) would be perpendicular to the line l_2, and hence l_2 would be parallel to $\mathcal{P}$. This is excluded by one of the assumptions of the lemma. Hence, the curvature of the ellipse E_1' must be larger than the curvature of the circle $\mathcal{C}_2$ at the point e'. Since E_1' and $\mathcal{C}_2$ lie in the same plane, and $\pi(E_1') = E_1, \pi(\mathcal{C}_2) = E_2, \pi(e') = e$, the same property must hold for the curvatures of E_1 and E_2 at the point e. □

6. Main results

The total surface area, i.e. the sum of those parts of the surface areas of all the spheres $O_1(u_1, R_1), \ldots, O_n(u_n, R_n)$ which are not contained in any of the domains bounded by other spheres of the system, is a function $S(u)$ of the $3n$-dimensional variable u. Here, the function $S(u)$ relates to the entire geometrical boundary of the molecule including those parts of the surface which are buried inside the molecule. By $S_0(u)$, we will denote the area of that fraction of the surface which is not buried inside the molecule [16]. It is obvious that S is a continuous function, and that S_0 is not. The following theorems, together with concluding remarks in this section, describe all the situations in which the gradients of S and S_0 are discontinuous.

THEOREM 6.1

Let $O_1(u_1, R_1), \ldots, O_n(u_n, R_n)$ be a collection of n spheres in $\mathbf{R}^3$, with variable coordinates of the centers $u_1, \ldots, u_n$, and fixed radii $R_1, \ldots, R_n$. If, for some $\mathring{u} \in \mathbf{R}^{3n}$, the spheres $O_1(\mathring{u}_1, R_1), \ldots, O_n(\mathring{u}_n, R_n)$ satisfy the following conditions:
(a) no two spheres are identical,

(b) $\mathrm{dist}(\mathring{u}_i, \mathring{u}_j) \neq R_i + R_j$ for all $i, j = 1, 2, \ldots, n, i \neq j$,

(c) $O_i(\mathring{u}_i, R_i) \cap O_j(\mathring{u}_j, R_j) \neq O_i(\mathring{u}_i, R_i) \cap O_k(\mathring{u}_k, R_k)$ for all $i, j, k = 1, 2, \ldots, n, i \neq j$, $i \neq k, j \neq k$, such that $O_i(\mathring{u}_i, R_i) \cap O_j(\mathring{u}_j, R_j)$ and $O_i(\mathring{u}_i, R_i) \cap O_k(\mathring{u}_k, R_k)$ are not empty, then the gradient of the function S is continuous at $\mathring{u}$.

Proof

We will first prove this theorem when assumption (b) is replaced by a stronger condition:

(b′) $\mathrm{dist}(\mathring{u}_i, \mathring{u}_j) \neq |R_i \pm R_j|$ for all $i, j = 1, 2, \ldots, n, i \neq j$.

For simplicity, denote by O_i and $\mathring{O}_i$ the spheres $O_i(u_i, R_i)$ and $O_i(\mathring{u}_i, R_i)$, for $i = 1, 2, \ldots, n$, respectively.

For all $i = 1, 2, \ldots, n$, and for any $u \in \mathbf{R}^{3n}$, denote by D_i that part of the surface of the sphere O_i, which is not contained in the open balls bounded by the other spheres of the system. Obviously, the set D_i may be empty for some indices i, and it is closed for $i = 1, 2, \ldots, n$, i.e. $D_i = \bar{D}_i$ [13]. Divide each of the spheres O_i into 8 pieces $O_i^1, \ldots, O_i^8$ by splitting it along three large circles parallel to the planes xy, xz, yz. We may assume here that none of these three circles coincides with any of the circles of intersection of the system; otherwise, we would properly rotate the coordinate system xyz. Denote by $\mathcal{D}_i^1, \ldots, \mathcal{D}_i^8$ the intersections of the set D_i and the sets $\overline{O_i^1}, \ldots, \overline{O_i^8}$, respectively. We can represent the function S by the sum $\sum_{i=1}^{n} \sum_{m=1}^{8} S_i^m$, where S_i^m is the area of the surface $\mathcal{D}_i^m$. The gradient of S can be represented as an analogous sum and, consequently, to prove the continuity of grad S, it is sufficient to prove this property for the functions S_i^m, for each choice of the indices i and m. Let i and m be any fixed indices such that $1 \leqslant i \leqslant n$ and $1 \leqslant m \leqslant 8$ and, for simplicity, let $O = O_i$, $\Delta = \overline{O_i^m}$, and $\mathcal{D} = \mathcal{D}_i^m = \overline{\mathcal{D}_i^m}$. We may also assume without loss of generality that $i = 1$.

For the specific case $u = \mathring{u}$, denote by $\mathring{\Delta}, \mathring{\mathcal{D}}$, and $\mathring{O}$ the respective sets $\Delta, \mathcal{D}$, and O. Let o denote either the center of the surface $\mathring{\Delta}$, or a point on $\mathring{\Delta}$, very close to the center, such that the plane $\mathcal{P}$ tangent to $\mathring{\Delta}$ at o is not parallel or perpendicular to any of the planes defined by the circles of intersection which appear in the system, when $u = \mathring{u}$, i.e. the circles related to the spheres $\mathring{O}_1, \ldots, \mathring{O}_n$; furthermore, if there exist two circles of intersection related to these spheres, spherically tangent to each other on the sphere $\mathring{O}$, and the point of tangency lies on the surface $\mathring{\Delta}$, then the plane $\mathcal{P}$ is not parallel to the common line of tangency of these two circles. Obviously, such a point o exists because there is only a finite number of circles of intersection for $u = \mathring{u}$; moreover, if the center of the surface $\mathring{\Delta}$ can not be accepted as o because of the above conditions, the point o can be chosen as close to this center as we wish.

There exists a number $\epsilon > 0$ such that the open neighborhood [13] $\mathring{\Delta}_\epsilon$ of the set $\mathring{\Delta}$ on the sphere $\mathring{O}$, consisting of all points belonging to $\mathring{O}$ whose distance from $\mathring{\Delta}$ is less than ϵ, satisfies the following condition: the plane $\mathcal{P}$ is not orthogonal to any plane tangent to $\mathring{O}$ at any point belonging to $\mathring{\Delta}_\epsilon$. If π is the orthogonal projection of $\mathring{\Delta}_\epsilon$ on the plane $\mathcal{P}$ then, obviously, the images under π of any two different points from $\mathring{\Delta}_\epsilon$ are different points on the plane $\mathcal{P}$. The image $\pi(\mathring{\Delta})$ of $\mathring{\Delta}$ has the shape of a convex, slightly distorted (if o is not the center of $\mathring{\Delta}$) "regular elliptic triangle". The image $\pi(\mathcal{D})$ of $\mathcal{D}$ is a subset of $\pi(\mathring{\Delta})$, for any $u \in \mathbf{R}^{3n}$. For u sufficiently close to $\mathring{u}$, the set $\pi(\mathcal{D})$ is an area with a boundary consisting of arcs of several non-degenerate ellipses, different from each other, i.e.

- there are no straight lines bounding $\pi(\mathcal{D})$; this follows from the above conditions for the choice of the point o,
- none of the ellipses is reduced to a single point; such an ellipse would have to be the image under π of a circle of intersection which is a single point, and this situation is excluded by assumption (b′),
- the ellipses are distinct from each other; this follows from assumptions (a) and (c).

If the plane $\mathcal{P}$ is supplied with a Cartesian coordinate system $\eta\xi$ (chosen so that the axis η is not parallel or perpendicular to any of the lines of intersection of the plane $\mathcal{P}$ with the planes defined by the circles of intersection which appear in the system for $u = \mathring{u}$), then the surface area of $\mathcal{D}$ equals $\int_{\pi(\mathcal{D})} h(\eta,\xi)\, d\eta\, d\xi$, where $h(\eta,\xi) = [1 + g_\eta^2(\eta,\xi) + g_\xi^2(\eta,\xi)]^{1/2}$. Here $g(\eta,\xi) = (R^2 - \eta^2 - \xi^2)^{1/2}$, R being the radius of the sphere $\mathring{O}$, and g_η, g_ξ denote the respective partial derivatives of g. The function h is a positive, C^∞ function of η, ξ in the subset $\pi(\mathring{\Delta}_\epsilon)$ of the plane $\mathcal{P}$.

If, for any index j, $2 \leqslant j \leqslant n$, a part of the set $\mathring{\Delta}$ is contained inside the sphere O_j, or lies on the surface of O_j, denote this part by C_j. C_j is a closed set, and so is the set $\Delta C_j = \mathring{\Delta} - C_j$. The image of one of the sets C_j or ΔC_j on the plane $\mathcal{P}$ is convex. For all other indices j, $2 \leqslant j \leqslant n$, $C_j = \emptyset$ and $\Delta C_j = \mathring{\Delta}$.

If μ denotes the measure [15] of surface area on the sphere $\mathring{O}$ then, for $u = \mathring{u}$, the surface area of $\mathring{\mathcal{D}}$ equals

$$\mu(\mathring{\mathcal{D}}) = \mu(\mathring{\Delta}) - \sum_{i=2}^{n} \mu(\mathring{C}_i) + \sum_{i,j=2}^{n} \mu(\mathring{C}_i \cap \mathring{C}_j) - \sum_{i,j,k=2}^{n} \mu(\mathring{C}_i \cap \mathring{C}_j \cap \mathring{C}_k) + \dots$$
$$- (-1)^n \mu(\mathring{C}_2 \cap \mathring{C}_3 \cap \dots \cap \mathring{C}_n)\,, \tag{20}$$

where the indices $i, j, k, \dots$ in the multiple sums are all distinct from each other, and the sets $\mathring{C}_2, \mathring{C}_3, \dots, \mathring{C}_n$ are the respective sets $C_2, C_3, \dots, C_n$, for $u = \mathring{u}$. By replacing $\mathring{C}_i$ by $\mathring{\Delta} - \Delta\mathring{C}_i$ wherever the image under π of $\mathring{C}_i$ is not convex, this equation is transformed into a linear combination of areas of sets which are closed sets with convex images. Each of these convex images is obviously a convex set bounded by arcs of several non-degenerate ellipses, distinct from each other. It may happen, however, that such a set takes the form of a single point (e.g. when two of the circles of intersection, whose images under π are the respective ellipses, are spherically tangent on $\mathring{O}$). The final equation for the surface area of $\mathring{\mathcal{D}}$ must contain also those terms which represent the surface areas of all non-empty sets (including single points), even if the surface areas equal zero.

Thus, the area of $\mathring{\mathcal{D}}$ is a linear combination of integrals of the function h over convex sets bounded by arcs of distinct, non-degenerate ellipses on the plane $\mathcal{P}$.

To prove the continuity of the gradient of the function S at the point $\mathring{u}$, we must examine the values of the function S (i.e. the related surface areas) for points u which are close but distinct from $\mathring{u}$. Since $u_1, u_2, \dots, u_n$ denote the coordinates of the centers of spheres, it is sufficient to change only the variables $u_2, u_3, \dots, u_n$ because the change of u_1 can be compensated by a translation of the whole system. Any sufficiently small change of the variables $u_2, u_3, \dots, u_n$ maintains the conditions imposed on the choice of the coordinate system xyz, and the plane $\mathcal{P}$ with the coordinate system $\eta\xi$, as well as the assumptions (a), (b′), and (c) of the theorem. Hence, for u sufficiently close to $\mathring{u}$, the final form of the equation for the area of $\mathcal{D}$ remains valid, and is the same linear combination of integrals of the function h over convex sets bounded by arcs of ellipses on the plane. Each of these ellipses corresponds to an ellipse that appears in the equation for the surface area of $\mathring{\mathcal{D}}$ calculated for the coordinates $\mathring{u}$. Both are simply projections under π of the same circle of intersection of the sphere $\mathring{O}$ with one of the spheres $O_2, O_3, \dots, O_n$, which moves slightly in $\mathbf{R}^3$ with a small change of $u_2, u_3, \dots, u_n$. Direct application of lemma 2.4 and remark 2.2 shows that both ellipses are members of the same C^∞ family of ellipses on the plane $\mathcal{P}$.

Consider only one term of the final linear combination of integrals of the function h. For any u close enough to $\mathring{u}$, the set $\mathcal{E}^u$ over which we integrate is a convex set bounded by arcs of several ellipses, say $E_1^u, E_2^u, \dots, E_m^u$, which belong to respective C^∞ families of ellipses, such that

- none of the ellipses $E_1^{\mathring{u}}, \dots, E_m^{\mathring{u}}$ is degenerate, i.e, both axes of each of these ellipses have lengths greater than zero,
- $E_i^{\mathring{u}} \neq E_j^{\mathring{u}}$ for any $i, j = 1, 2, \dots, m, i \neq j$.

The set $\mathcal{E}^{\mathring{u}}$ may take the form of a convex set with a non-empty interior, or the form of a single point; $\mathcal{E}^{\mathring{u}}$ cannot be an empty set because integrals over empty sets are not included in the final linear combination of integrals. We emphasize here that all the integrals of h over sets consisting of single points must be considered, although their contributions to the area of $\mathring{\mathcal{D}}$ are zero. Such integrals can take positive values, when $\mathring{u}$ is replaced by u; a change of u causes "movements" of ellipses belonging to C^∞ families and a single-point set $\mathcal{E}^{\mathring{u}}$ can expand to a set with a non-empty interior, resulting in a positive value of the respective integral.

To prove the continuity of the gradient of S, we must consider the limits of $[S(u) - S(\mathring{u}')]/\|u - \mathring{u}'\|$, where $\|u - \mathring{u}'\|$ converges to zero and $\mathring{u}'$ is close or equal to $\mathring{u}$; however, because of the method of linear decomposition of S, shown above, it is only necessary to examine the limit

$$\lim_{u \to \mathring{u}'} [S_{\mathcal{E}}(u) - S_{\mathcal{E}}(\mathring{u}')]/\|u - \mathring{u}'\|, \tag{21}$$

where $S_{\mathcal{E}}(u) = \int\int_{\mathcal{E}^u} h(\eta, \xi)\, \mathrm{d}\eta\, \mathrm{d}\xi$.

If $\mathcal{E}^{\mathring{u}}$ is a single point, $\mathcal{E}^{\mathring{u}}$ must be an intersection of full ellipses $\tilde{E}_1^{\mathring{u}}, \dots, \tilde{E}_m^{\mathring{u}}$; moreover, the absolute value of the limit in expression (21) is smaller than

$$\lim_{u \to \mathring{u}'} \frac{1}{\|u - \mathring{u}'\|} \int\int_{\mathcal{E}^u \div \mathcal{E}^{\mathring{u}'}} h(\eta, \xi)\, \mathrm{d}\eta\, \mathrm{d}\xi\,. \tag{22}$$

Since the families $\{\tilde{E}_1^u : u \in U\}, \dots, \{\tilde{E}_m^u : u \in U\}$, and the intersection $\mathcal{E}^u$ satisfy the assumptions of lemma 4.1, for a sufficiently small neighborhood U of $\mathring{u}$, then $\mu(\mathcal{E}^u \div \mathcal{E}^{\mathring{u}'}) \leqslant c\|\mathring{u}' - \mathring{u}\|^{1/2}\|u - \mathring{u}'\|$, and the limit in expression (22) is of order $\|\mathring{u}' - \mathring{u}\|^{1/2}$. Hence, the limit in expression (21) equals zero for $\mathring{u}' = \mathring{u}$, and is a continuous function of $\mathring{u}'$ at $\mathring{u}$.

If $\mathcal{E}^{\mathring{u}}$ is a convex set with a non-empty interior, the function $S_{\mathcal{E}}(u)$ can be represented, for every u which is close enough to $\mathring{u}$, by

$$\begin{aligned} S_{\mathcal{E}}(u) &= \int_0^{2\pi} \int_0^{\rho(u,\phi)} h(r\cos\phi, r\sin\phi) r\, \mathrm{d}r\, \mathrm{d}\phi \\ &= \int_0^{2\pi} H(\rho(u,\phi), \phi)\, \mathrm{d}\phi\,, \end{aligned} \tag{23}$$

where the function $\rho(u, \phi)$ is the distance from a pre-fixed point in the interior of $\mathcal{E}^{\mathring{u}}$, to the border of $\mathcal{E}^u$, and in the direction indicated by the angle ϕ relative to the η-axis of the coordinate system on the plane $\mathcal{P}$. $H(r, \phi)$ is the primitive [17] of the function under the double integral sign over the variable r; it is a C^∞ function of both variables r and ϕ, with $H(0, \phi)$ equal to zero for all ϕ.

Let us first assume that each of the vertices $\mathring{q}_1, \dots, \mathring{q}_l$ on the boundary of the set $\mathcal{E}^{\mathring{u}}$ belongs to only two of the ellipses $E_1^{\mathring{u}}, \dots, E_m^{\mathring{u}}$. Moreover, assume that none of the arcs comprising the boundary of $\mathcal{E}^{\mathring{u}}$ is tangent to any of the ellipses $E_1^{\mathring{u}}, \dots, E_m^{\mathring{u}}$. In this case the number of vertices remains the same for all u sufficiently close to $\mathring{u}$, and lemma 3.4 implies that their positions are C^∞ functions of u. This fact, together with lemma 3.2, implies that the function $S_{\mathcal{E}}$ is a C^{∞} function at $\mathring{u}$. In this case, we do not even need to consider the difference quotient in expression (21).

If, on the contrary, there exists a vertex on the boundary of $\mathcal{E}^{\mathring{u}}$ belonging to more than two ellipses, or if there is an arc of boundary of $\mathcal{E}^{\mathring{u}}$ that is tangent to one of the ellipses, then more vertices can appear on the boundary of $\mathcal{E}^{u}$ even for very small changes of u. In the first case, there exist two ellipses, say, $E_i^{\mathring{u}}, E_j^{\mathring{u}}$, having this vertex as a common point, but not tangent there to each other, and there exists a neighborhood of the vertex such that there are no common points of $\tilde{E}_i^{\mathring{u}}, \tilde{E}_j^{\mathring{u}}$, and $E_k^{\mathring{u}}$ in this neighborhood, with the exception of this vertex, for all $k = 1, 2, \ldots, m$, $k \neq i, j$. Then there exists a k, $1 \leqslant k \leqslant m, k \neq i, j$ such that $E_k^{\mathring{u}}$ contains the vertex. If, in addition, $E_k^{\mathring{u}}$ is tangent to one of the ellipses $E_i^{\mathring{u}}$ or $E_j^{\mathring{u}}$, say, $E_i^{\mathring{u}}$, then lemma 5.1 and the assumptions made about the choice of the point o and the plane $\mathcal{P}$ imply that $E_i^{\mathring{u}}$ is internally tangent to $E_k^{\mathring{u}}$ at the vertex, and the curvature of $E_i^{\mathring{u}}$ is larger than the curvature of $E_k^{\mathring{u}}$ there.

In the second case, there exists an ellipse $E_i^{\mathring{u}}$ bordering $\mathcal{E}^{\mathring{u}}$, and an ellipse $E_k^{\mathring{u}}$, such that $E_i^{\mathring{u}}$ is internally tangent to $E_k^{\mathring{u}}$ at a point on the boundary of $\mathcal{E}^{\mathring{u}}$, which is not a vertex of $\mathcal{E}^{\mathring{u}}$; the curvature of $E_i^{\mathring{u}}$ is larger than the curvature of $E_k^{\mathring{u}}$ at this point.

All these situations are shown in fig. 8, and are covered by lemma 4.2.

The value of $S_{\mathcal{E}}(u)$ can be now computed exactly as in the previous case (i.e. we would ignore the appearance of extra vertices), if we add (or subtract) some compensating terms being integrals of the function h, over sets which have shapes fully described in lemma 4.2, and denoted there by $\mathcal{R}^u$. The areas of these sets are of order $\|u - \mathring{u}\|^{3/2}$, and the area of the sets $\mathcal{R}^u \div \mathcal{R}^{\mathring{u}'}$ are of order $\|\mathring{u}' - \mathring{u}\|^{1/2}\|u - \mathring{u}'\|$; hence, the respective integrals give zero contributions in the limit in expression (21), and this limit represents a continuous function of $\mathring{u}'$ at $\mathring{u}$.

This completes the proof of the theorem, with the stronger assumption (b′) replacing the original assumption (b). However, if two spheres are internally tangent, simple geometrical calculations show that the gradient of the accessible surface area is continuous. □

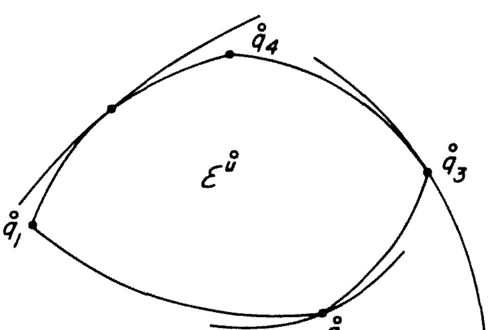

Fig. 8.

REMARK 6.1

The gradient of S is discontinuous if assumptions (a), (b), or (c) of theorem 6.1 are not satisfied, unless

– in the case (a), both spheres,

– in the case (b), the point of tangency,

– in the case (c), the common circle of intersection

are contained in the open balls defined by all the spheres of the system.

Proof

It is well-known that the gradient is discontinuous in cases (a) and (b), and then the proof of this fact is trivial.

In case (c), if spheres O_1, O_2, and O_3 have a circle of intersection which is common for all the pairs O_1O_2, O_2O_3, and O_1O_3 (see fig. 9), then one of the spheres, say, O_3, must be contained in the union of the remaining two, say $O_1 \cup O_2$. Let O be the plane of the circle of intersection. The radius of the sphere O_3 is larger than or equal to the radius of the circle of intersection. In the first case, the center u_3 of O_3 does not lie in the plane O, and in the second case, it does. In the first case, if the center of O_3 is moved orthogonally towards O while the centers of O_1 and O_2 are preserved, the combined surface area of O_1, O_2, and O_3 decreases, and the first derivative in the component of the coordinates u_3 orthogonal to O would be more negative than a negative constant; the value of this constant follows from the geometrical relations between the radii and the centers of the three spheres in their original positions, and is related to the ratio between the "gained" area of the sphere O_3, and the "lost" area of the combined spheres O_1 and O_2, and to the length of the accessible portion of the common circle of intersection. If the center of O_3 is moved in the opposite direction, there is no change in the combined surface areas

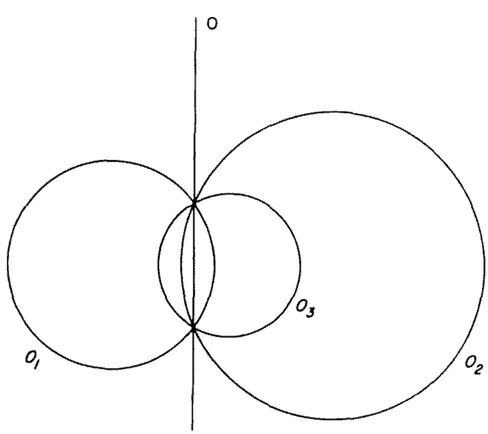

Fig. 9.

of the three spheres, and the first derivative would be zero; thus, the gradient is discontinuous.

In the second case, opposite movements of the center u_3 parallel to O, may be considered to show the discontinuity of the gradient.

THEOREM 6.2

Theorem 6.1 remains valid for the function S_0, unless the point $\mathring{u}$ is a point of discontinuity of S_0.

Proof

Let $\mathring{u}$ satisfy the assumptions of this theorem. The area $S_0(\mathring{u})$ is a linear combination of integrals of the function h over convex sets bounded by arcs of distinct, non-degenerate ellipses on a plane, as in theorem 6.1. The only difference is that, for the point $\mathring{u}$, all the integrals which appear in the linear combination for the function S, and account for those parts of the surface, that are buried inside the molecule, are removed for the calculation of S_0. Each of these integrals represents a continuous function of u, with continuous first derivatives at the point $\mathring{u}$. Thus, the function S_0 is discontinuous at $\mathring{u}$, if and only if an infinitesimally small change of the variable u from its original position at $\mathring{u}$, will change the number of integrals with positive values, in the linear combination of integrals for S_0; this is associated with the situation in which a surface, buried inside the molecule for $u = \mathring{u}$, becomes accessible from the outside of the molecule, for u infinitesimally close to $\mathring{u}$. □

REMARK 6.2

Remark 6.1 remains valid for the function S_0, unless the point $\mathring{u}$ is a point of discontinuity of S_0, and then the gradient cannot be defined at this point.

7. Conclusion

The situations described in theorems 6.1 and 6.2, in which the gradient of the accessible surface area is discontinuous, can occur during any local energy minimization or molecular dynamics simulation of a macromolecule. External contact of two atomic spheres occurs quite frequently during simulations in which a macromolecule is allowed to fold or unfold ([9], and our unpublished observations). The second type of discontinuity, in which two circles of intersection overlap, has been observed in simulations in which linear hydrogen bonds were forming (our unpublished observations). Techniques for avoiding the effects of such discontinuities will be discussed elsewhere.

Acknowledgements

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[11] R. Sikorski, *Advanced Calculus, Functions of Several Variables* (Polish Scientific Publ., Warsaw, 1969).
[12] A function f of a variable $\zeta \in \mathbf{R}^\nu$ is a C^∞ function in a neighborhood [13] of $\mathring{\zeta}$, if all derivatives of f of any order exist, and are continuous in this neighborhood; see also ref. [11], chap. IV, sect. 3, p. 140, and sect. 5, p. 150.
[13] (i) A set Ω in $\mathbf{R}^\nu$ is open, if for any $\mathring{\zeta} \in \Omega$, there exists $\epsilon > 0$, such that any point $\zeta \in \mathbf{R}^\nu$ distant from $\mathring{\zeta}$ by less than ϵ, belongs to Ω;
(ii) a set Γ in $\mathbf{R}^\nu$ is closed, if $\mathbf{R}^\nu - \Gamma$ is open;
(iii) if Λ is any set in $\mathbf{R}^\nu$, then $\bar{\Lambda}$ denotes the smallest closed set in $\mathbf{R}^\nu$ containing Λ, and is called a closure of Λ.
(iv) if $\mathring{\zeta} \in \mathbf{R}^\nu$, then any open set in $\mathbf{R}^\nu$ containing this point is called a neighborhood (or an open neighborhood) of $\mathring{\zeta}$.
The above definitions can be extended to any space $\mathbf{X}$ (playing the role of $\mathbf{R}^\nu$), for which the distance between any two points in $\mathbf{X}$ is defined; precise definitions can also be found in ref. [11], chap. III, sect. 3.
[14] If f and F are functions defined on sets $\mathbf{X}$ and $\mathbf{Y}$, respectively, and $\mathbf{X} \subset \mathbf{Y}$ then F is called an extension of f, if $F(x) = f(x)$ for all $x \in \mathbf{X}$.
[15] The ν-dimensional Lebesgue measure μ is defined for a class of the so-called measurable subsets of $\mathbf{R}^\nu$ large enough to contain all the sets which may appear in practical problems; it is an extension of the intuitive notion of length, area, or volume, depending on ν, for virtually any sets which may be of practical use. For a precise definition see ref. [11], chap. VI.
[16] The MSEED algorithm computes the quantity $S_0(u)$.
[17] If f is a C^∞ function of a variable $\zeta \in \mathbf{R}^\nu$, the function $F(\zeta) = F(\zeta_1, \ldots, \zeta_\nu) = \int_0^{\zeta_1} \ldots \int_0^{\zeta_\nu} f(\xi_1, \ldots, \xi_\nu) d\xi_1 \ldots d\xi_\nu$ is called a primitive of f.