Use of random-dot displays in the study of biomolecular conformation

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The perception of random-dot interference patterns is potentially useful in the global characterization of conformational changes occurring in biomolecules. The proposed method can be applied whenever both the structure of the initial and final state of a molecule are known, and an equivalent axis of rotation relating the two forms is desired.

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The 3D structures of many biomolecules have been determined by *X*-ray crystallography. Some of these molecules, such as proteins, undergo conformational changes in response to ligand binding or changes in environmental conditions. Fairly detailed comparisons between conformers, and between structurally similar proteins, are useful and can be achieved by a variety of brute-force computations[1], but sometimes at a cost of the loss of an intuitive feeling for the structures. Differences between structures may obscure the similarities. The approach described here provides a way of summarizing simply global comparisons between structurally related biomolecules.

Random-dot moire patterns[2] are potentially useful in the global characterization of conformational changes occurring in biomolecules. If a pattern of random dots is superimposed on itself and rotated by a small angle, concentric circles are perceived about the point of rotation[2,3]. If the angle of rotation is increased, the perceived circles gradually disappear until a totally unstructured dot display is seen. This effect demonstrates the ability of the human visual system to detect local autocorrelations and may suggest a physiological basis of form perception in higher animals[2,3]. Figure 1 is an example of a dot interference pattern. The pattern is comprised of a set of 10 000 random dots which was superimposed on itself and subsequently rotated and uniformly expanded. Though the pattern was calculated by computer, similar patterns can easily be generated using sprinkled ink and transparencies[4].

In this research, a method is suggested by which random-dot patterns may be used in the study of molecular conformational changes. Many biomolecules undergo changes in their covalent structure in response to ligand binding or changes in their solvent environment. When a substrate molecule is bound to an enzyme, the binding often forces the enzyme into a conformation in which the catalytic groups assume a favourable geometrical position in the transition state; ie, there is an induced fit[5]. A large number of enzymes and other protein molecules consist of two or more distinct domains connected by a few strands of polypeptide chain which may be viewed as hinges. Among the molecules in which a hinged motion of the two domains is suggested by crystallographic studies are hexokinase[6], immunoglobulins[7], and tomato bushy stunt virus[8]. Crystallographic studies on yeast hexokinase[6] show that when glucose binds into the deep cleft, the two lobes move together in a hinged action, closing the cleft and burying the substrate. It has been hypothesized that the substrate may need to be surrounded completely to exclude water or orient catalytic groups.

It is sometimes useful to use simplified models of the relative motion of domains within a protein. In one study of phosphoglycerate kinase, a computer modelling of a proposed cleft-closing conformational change

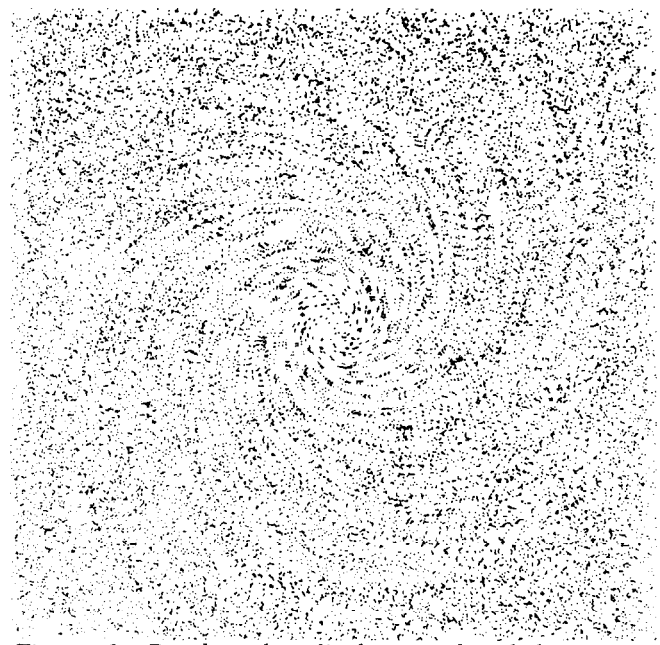

Figure 1. Random-dot display produced by superimposing a figure containing 10 000 random dots upon itself and subsequent rotation by three degrees and uniform expansion by a factor of 1.1

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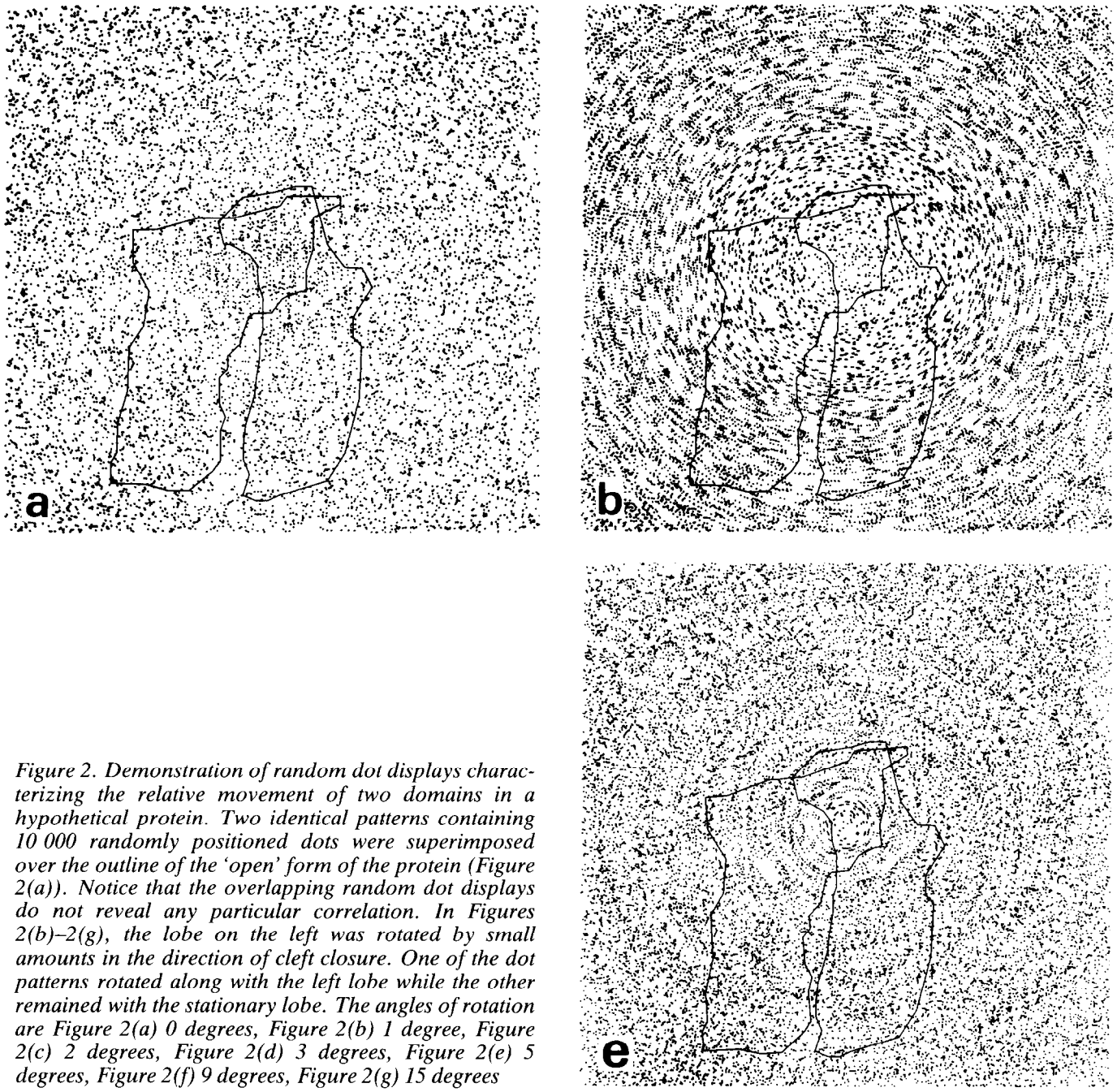
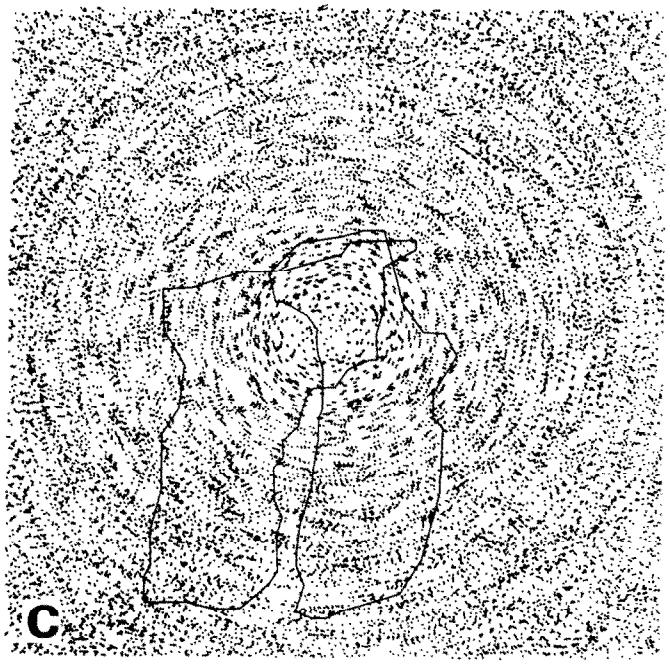


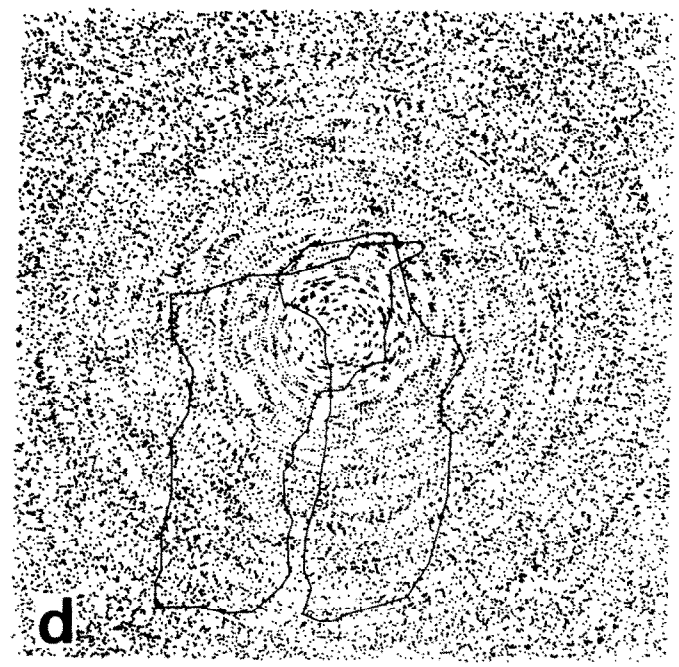
Figure 2. Demonstration of random dot displays characterizing the relative movement of two domains in a hypothetical protein. Two identical patterns containing 10 000 randomly positioned dots were superimposed over the outline of the 'open' form of the protein (Figure 2(a)). Notice that the overlapping random dot displays do not reveal any particular correlation. In Figures 2(b)–2(g), the lobe on the left was rotated by small amounts in the direction of cleft closure. One of the dot patterns rotated along with the left lobe while the other remained with the stationary lobe. The angles of rotation are Figure 2(a) 0 degrees, Figure 2(b) 1 degree, Figure 2(c) 2 degrees, Figure 2(d) 3 degrees, Figure 2(e) 5 degrees, Figure 2(f) 9 degrees, Figure 2(g) 15 degrees

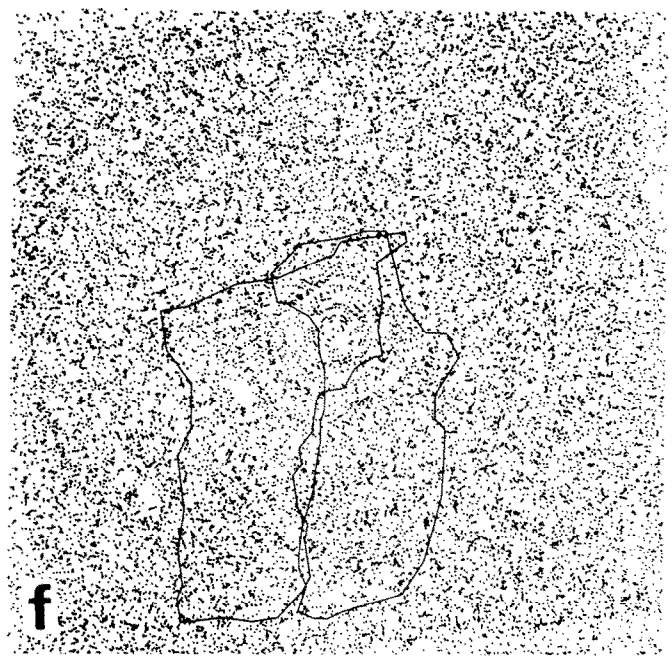
was used in order to produce observed solution-scattering measurements; however, the hypothetical axis of rotation in which one lobe of the molecule rotates relative to the other was chosen somewhat arbitrarily[9]. A similar simulated cleft closure was performed in a study of the arabinose-binding protein (see Discussion in [9]). In addition, simplified dynamic molecular models (eg the oscillation of the hinged lobes in lysozyme[10]) sometimes represent domain motion with simplified hinged motions.

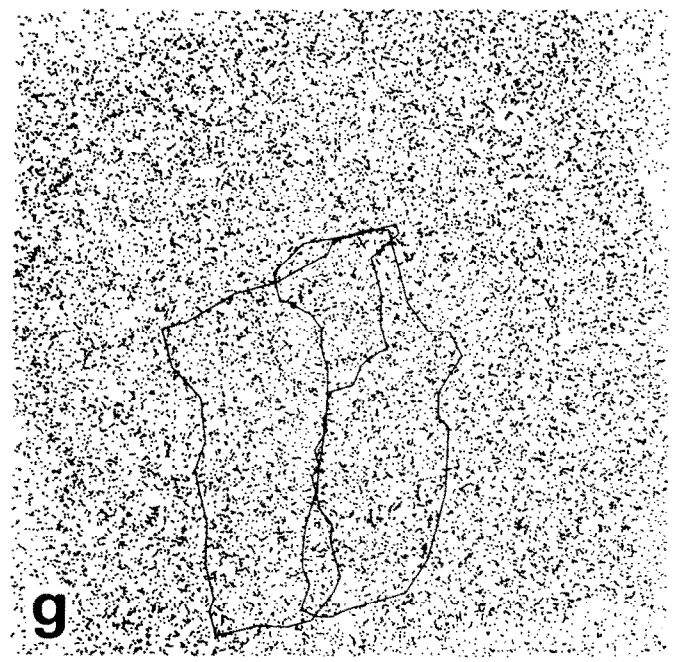
Figure 2 is a demonstration of the suggested use of random dot displays in the characterization of domain relationships for a hypothetical two-lobed protein undergoing a conformational change. First, two identical random-dot patterns were superimposed over the outline of the 'open' form of the protein (Figure 2(a)). Note that the overlapping random dot displays do not reveal any particular correlations. In Figures 2(b)–(g), the lobe on the left was rotated by small amounts in the direction of cleft closure. One of the dot patterns rotated along with the left lobe while the other remained with the stationary lobe. Even a small change, represented by a one degree rotation of one lobe relative to the other, creates a picture where the axis of rotation can begin to be perceived at the centre of the concentric circles (Figure 2(b)). It becomes difficult to perceive the axis of rotation after about 15 degrees (Figure 2(g)). If the rotation involved is more than roughly 15 degrees, the human visual system can no longer perform the dot correlations. Thus, the method described here would be useful in studies where the conformational change is not large.

This graphical technique may be used in situations where two conformers of a molecule are known and an equivalent axis of rotation relating the two is desired. As an example, let us assume that we have a structural









description of a protein with two lobes, lobe *a* and lobe *b*, in 'open' and 'closed' conformations. First, two identical random dot patterns are arbitrarily superimposed over the entire 'open' conformer. Next, lobe *b* is repositioned along with one of the random dot sets such that its relation to lobe *a* matches the 'closed' conformer. The equivalent axis of rotation will lie in the centre of the resultant circles of dots. Often it is desirable to ascertain an equivalent axis of rotation relating two structures in conformational space regardless of the fact that the actual transformation between the starting and ending form of the molecule may have involved many small intermediate rotational and translational components. Such knowledge would be useful in correlating the position of specific secondary structural elements with the tertiary change. As discussed above, this method would also be useful in simulated cleft closures and simplified dynamic models.

In summary, the random dot displays are potentially useful in the global characterization of conformational changes occurring in biomolecules. They would be used in situations where both the structure of the initial and final state of the molecule are known, and an equivalent axis of rotation relating the two forms is desired. The random dot method is not restricted to characterization of domain motion, but may be applied to protein subunit relationships as well. Since the method can characterize broad relationships, it may also have value in the comparison of structurally related proteins with little primary structure homology. In general, useful patterns will result if there is both a rotation and translation, provided that the changes are not too large. Since the initial and final states are merely placed upon one another, no assumption about the specifics of the transformation process are required. A computer is not required to implement this method, although the use of

a vector graphics display is ideal for performing the superpositions. Future work could be directed to researching the usefulness of the process described here in three dimensions. A 3D random dot pattern would be superimposed over the biomolecule's structure, and transformations would be applied in a manner identical to the method described here and viewed binocularly. It is hoped that the random dot method presented here will provide a useful tool for the characterization of small structural changes occurring in biomolecules.

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