EFFECT OF FRACTAL NATURE ON ENZYMATIC REACTIONS

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SUMMARY

Modeling immobilized enzymes as a fractal object in the form of a DLA and each enzyme molecule as another fractal object in the form of a percolation cluster, the present work simulates the performance for a sequence of elementary reactions and transport on the surface. The results show that non-idealities in the performance, such as multi-stationarity and substrate inhibition, can also arise in this simple description.

INTRODUCTION

Surface representations of proteins have provided a powerful approach for characterization of the structure, folding, interactions and properties of proteins. A fundamental feature of proteins that has not been characterized by these representations, however, is the texture (roughness) of protein surfaces and its role in molecular interactions. The degree of irregularity of a surface may be described by the fractal dimension D (Lewis and Rees, 1985). The ensuing fractal surface dimension controls biologically relevant processes.

Mandelbrot's fractal geometry provides a descriptive and a mathematical way to model many of the seemingly complex forms found in nature (Mandelbrot, 1983). Statistical self-similarity is the essential quality of fractals in nature. Although the fractal dimensionality is but a single parameter, it is nevertheless a useful indicator of protein conformation because it provides a quantitative measure of the degree to which a structure fills the space in which it resides (Wako, 1989).

The rate of substrate arrival (by diffusion) at a biological receptor depends very much on whether the diffusion space is 3-, 2- or 1-dimensional. The maximum rate of a reaction will depend on the encounter probability of the components. The diffusion process can be treated in terms of Brownian motion, or the random walk process. It has been shown in the case of lysozyme that substrate molecules close to the surface are trapped and then migrate along the surface to the active site (Pfeifer et al, 1985). Such diffusion on complex proteins with fractal structures may have important biological implications (Voss, 1988).
In the present work, we have considered an enzymatic reaction in which the substrate molecules can attach to certain points on the enzyme surface, other than the active site, and then diffuse towards the active site. The amount of substrate that can attach to the surface will greatly depend on the fractal dimension of the surface, surface area of enzyme exposed to the medium and the size and bulkiness of the substrate. On reaching the active site, the reaction occurs and the substrate is converted to product. Either the intrinsic rate of conversion of the substrate or the availability of it due to surface diffusion would then determine the rate of the reaction. Diffusion on fractal structures is known to be anomalous (Argyrakis and Kopelman, 1990) and a particularly simple illustration of a random fractal is a percolation lattice (Stauffer, 1985). If movement is allowed from one site of the percolation cluster occupied by the substrate only to a nearest neighbour site of the cluster, the motion is restricted. The aim of this work is to elucidate the effect of the fractal nature of enzymes, and surface diffusion on them, on rates of enzymatic reactions.

**SIMULATION DETAILS**

Considering attachment of a substrate molecule to the enzyme surface, the reaction mechanism is depicted in figure 1. The following assumptions were made to simplify the simulation.

1) A simple method frequently used for enzyme immobilization is chemical aggregation using glutaraldehyde as a bifunctional reagent (Khare and Gupta, 1990). We have modelled such an aggregate as a DLA cluster which is a random fractal (Witten and Sander, 1981).

2) A number of protein molecules are known to possess a fractal dimension and a number of investigators have reported such a dimension for different proteins (Lewis and Rees, 1985; Wako, 1989). In the present work we consider such a protein with a fractal dimension of ~1.89. It is known that the different conformations of proteins may give rise to the same value of fractal dimension. Therefore we can generally represent such a protein as a percolation cluster with the same fractal dimension.

3) There is no interaction between individual substrate molecules.

4) The substrates can attach only to the edges of the percolation cluster to account for the fact that only certain patches on the enzyme surface are capable of interacting with the substrate.

5) Once the substrate is bound to the surface, it moves towards the active site through the shortest available distance.

**FIGURE 1**: Schematic representation of the reaction mechanism: $E_a$ -- enzyme active site; $E_o$ -- enzyme surface other than the active site; $E_oS$ -- complex of substrate at enzyme active site; $E_o$ -- substrate molecule attached to enzyme surface; $P$ -- product; $k_1$ and $k_2$ are proportional to the surface area of the enzyme other than the active site and the enzyme active site, respectively; $k_3$ is proportional to the probability of colliding at the active site and attaching there $k_5$ in proportional to the probability of attachment to the enzyme surface on colliding there; $k_6$ and $k_8$ are proportional to the dissociation constants of $E_o$ and $E_oS$, respectively; $k_7$ is proportional to the reaction probability on complex formation; $k_8$ is proportional to the surface diffusion coefficient and the number of surface bound substrate molecules.