Functioning-dependent structures

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Abstract

Numerous studies have shown that proteins involved in metabolic or signalling pathways are often distributed non-randomly as multimolecular assemblies. Such assemblies range from quasi-static, multi-enzyme complexes (such as the fatty acid synthase or the (-oxo acid dehydrogenase systems) to transient, dynamic protein associations. Multi-molecular assemblies may comprise proteins but also nucleic acids, lipids, small molecules and inorganic ions. Such assemblies may interact with membranes, skeletal elements and/or cell organelles. They have been termed *metabolons*, *transducons* and *repairosomes* in the case of metabolic pathways, signal transduction and DNA repair, respectively, or, more generally, *hyperstructures*.

Although channelling is sometimes challenged, most authors have assumed that, in many molecular assemblies, intermediates are channelled from each enzyme to the next without diffusion of the intermediates into the surrounding cytoplasm. Potential advantages of channelling are:

1. reduction in the size of the pools of intermediates (a point however contested by some authors),
2. protection of unstable or scarce intermediates by maintaining them in a protein-bound state,
3. avoidance of an "underground" metabolism in which intermediates become the substrates of other enzymes and
4. protection of the cytoplasm from toxic or very reactive intermediates.

In the case of transient, dynamic multi-molecular assemblies, certain only form in an activity-dependent manner due, for example, to an association between enzymes that only occurs when they are engaged in transporting or transforming substrates or transducing a signal. We have proposed to term *functioning-dependent structure* (FDS) any such type of dynamic, multi-molecular structure; in other words, an FDS assembles when functioning and disassembles when no longer functioning and thus is created and maintained by the very fact that it is in the process of accomplishing a task.

The formation of an FDS adds protein-protein interactions to the classical protein-substrate (or protein-signal) interactions and is therefore likely to generate novel kinetic behaviours. Given the extremely diverse mechanisms at work in the variety of biological systems quoted above, it is difficult to devise a single approach that would be appropriate to model them all. Therefore, in the following, we begin by determining whether the metabolite-induced association of two enzymes into an FDS (a so-called metabolite-induced metabolon) may, under steady-state conditions, confer to the overall FDS kinetic features that the individual enzymes do not have; this particular two-enzyme FDS is fairly straightforward to model, which is why we have chosen it. We then discuss how the type of approach used here to analyse the metabolite-induced metabolon may be used to analyse other varied assemblies. Finally, we speculate on the relevance of such concepts to the debate on the nature of life.