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Enable Catalytic Activity in Phosphoglycerate Kinase, Biophysical Journal

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Kinase?

fundamental questions regarding the mechanism by which allosteric effects can

antar conformational fluctuations of RdRp by observing the structural coupling

nature of allosteric inhibition by using molecular simulations to study the

dynamics of the enzyme, both in a free state and bound to different inhibitors.

We seek to delineate the link between ligand binding and functionally impor-

tant conformational fluctuations of RdRp by observing the structural coupling

which results from the internal motions of the enzyme. In addition to answering

fundamental questions regarding the mechanism by which allosteric effects can

occur, these studies may provide information which can aid in the development of

novel and more effective RdRp inhibitors.

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Domain Fluctuations Enable Catalytic Activity in Phosphoglycerate Kinase?

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The biological function of enzymes is often related to large-scale domain

movements. The configuration changes are observed by methods like x-ray

crystallography, which give a static image of the protein structure in the crystal

confinement. The question is, if these configuration changes are due to the sub-

strate binding or if they are also related to the crystal packing which favors spe-

ific configurations. The structure of a protein in solution can deviate from the

crystal structure but the protein has also the ability to fluctuate between differ-

cent configurations. Are these fluctuations important for protein function?

Phosphoglycerate kinase (PGK) has a widely open domain structure with a

hinge near to the active center between the two domains. The hypothesis of a

substrate-induced configuration change, was first proposed by Banks et al.
based on the comparison of crystal structures.

We have recently investigated the domain dynamics of PGK (1). Structural

analysis by small angle neutron scattering revealed that the structure of the hol-

oprotein in solution is more compact as compared to the crystal structure, but

would not allow the functionally important phosphoryl transfer between the

substrates, if the protein would be static. Brownian large scale domain fluctua-

tions on a timescale of 50 ns was revealed by neutron spin echo spectroscopy.

In particular, the domain movements facilitate a close encounter of the key

residues in the active center to build the active configuration. The observed dy-

namics shows that the protein has the flexibility to allow fluctuations and dis-

placements that seem to enable function. The presence of the substrates

increases the rigidity, which is deduced from a faster dynamics with smaller

amplitude.

(1) in press: Inoue et al., Large Domain Fluctuations on 50-ns Timescale

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Coarse-Grained and Atomistic Modeling of Anisotropic Atomic Fluctua-

tions in Protein Crystal Structures

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Protein atomic fluctuations can be probed by x-ray crystallography in the form

of Anisotropic Displacement Parameters (ADP). In this study, we assess the

accuracy of different coarse-grained and atomistic models that include pro-

tein-environment interactions in a protein crystal in comparison with experi-

mental ADPs. We use a coarse-grained Elastic Network Model (ENM) with

different boundary conditions (see figure) to model protein-environment

interactions, and an atomistic model using a CHARMM force-field. For a large

list of high-resolution protein crystal structures, we find that optimal ADP model-

ing is achieved by weak protein-environment interactions as compared to internal

interactions within a protein structure. There-

fore, the internal dynamics of a protein is only weakly perturbed by crystal pack-

ing. We also find no improvement in the accuracy of ADP modeling by using the

atomistic model over the coarse-grained ENM.

Figure. A protein-environment system constructed from a protein crystal of

oxy-myoglobin (PDB code: 1a6m) with the main protein in red, the nearest

neighbors in green, and the next nearest neighbors in blue. The main protein

and the nearest neighbors are unconstrained while the next nearest neighbors

are fixed.

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Intersubatomic Dynamics: How Does Protein Structure and Function Relate to

Allostery?

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Dynamic properties are functionally important in many proteins, including the

ezyme adenylyl kinase (AK), for which two small domains (LID and NMP) close

over the larger CORE domain; the reverse (opening) motion limits the rate of
catalytic turnover. Here, we compare our previously published coarse-grained
double-well G[Unable to Display Character: Ï]) simulation of mesophilic AK from

E. coli (AKmeso) to simulations of thermophilic AK from

Aquifex aeolicus (AKthermo) in terms of the critical rigid-body, backbone
dihedral, and contact motions in open, closed, and transition state (TS) ensem-

bles. Like AKmeso, AKthermo follows a LID-first closure pathway in the presence

of ligand, but the amplitude of LID rigid-body motions in the O ensemble

decreases significantly. Backbone unfolding in O and/or TS ensembles
decreases significantly relative to AKmeso in most of the interdomain hinges

and within LID. In contact space, the TS of AKthermo has a weaker CORE-

LID interface but a stronger contact network surrounding the CORE-NMP in-

terface than the TS of AKmeso. A “heated” simulation of AKthermo at 375K

and the simulation of AKmeso at 300K show similar conformational ensem-

bles, both in the amplitude of CORE-LID motions in O ensemble and in the

flexibility of some hinge regions, which supports the corresponding states hy-

pothesis. Furthermore, mutation of 7 prolines unique to AKthermo to the cor-

responding residues from AKmeso more fully shifts the dynamics toward the

more flexible behavior of AKmeso in most of the key hinges and even in

some regions distant from any mutation. However, some prolines in AKthermo

appear to strengthen or even substitute for nearby contacts from AKmeso so

that local flexibility increases excessively upon mutating the proline. Finally,

this mutagenic framework can inform the rational design of functionally impor-

tant dynamics and allostery in other proteins toward engineering novel biolog-

cal control systems.

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Dynamosome: How Does Protein Structure and Function Relate to

Dynamics?

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Background. Proteins have been very successfully classified according to

amino acid sequence or structure, which enabled improved prediction of func-

tion. In this study, we carried this idea one step further and developed a mini-

mally biased scheme to compare and classify proteins purely according to their

motion patterns. This approach is based on the notion that proteins, which

fold into often recurring structural motives might also be exhibiting a distinct