

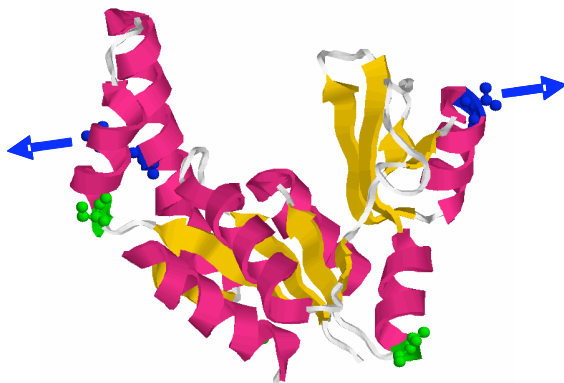
Mechanical Response of Guanylate Kinase.

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The amino acid sequence determines the folded structure of a protein, but this structure is “soft”. Indeed, ligand binding events often elicit large conformational changes of the folded structure – the phenomena of allostery and induced fit. The ability to undergo such mechanical rearrangements of the structure endows proteins with their “molecular device” properties.

Here we ask: can functional conformational changes be elicited by direct application of mechanical stresses? Can we control proteins mechanically?

We have learned how to establish a suitable force field, using “molecular springs”. We are establishing a map of the mechanical response of one model system: the enzyme Guanylate Kinase (GK). The mechanical stress is applied by a molecular spring made of DNA which we covalently couple to the protein using “chemical handles” built in by site-directed mutagenesis; the spring’s stiffness and thus the stress applied to the protein can be controlled externally through hybridization to different DNA sequences. We measure how the stress modulates the enzymatic activity, and more specifically the binding affinities for the two substrates ATP and GMP and the catalytic rate. For example, GK goes paradigmatically from an “open” to a “closed” conformation upon binding the substrates; we have shown that a mechanical force applied at the location of the arrows in the Figure induces the “open” conformation, with corresponding decrease in enzymatic activity. We are proceeding to map out the response of the protein to forces applied at different locations. We believe the insights gained into the dynamic properties of these structures will ultimately translate into a quantitative, predictive understanding of the fundamental property of allostery.



Eliciting functional conformational changes in Guanylate Kinase by mechanical stresses. A force F applied at the locations shown biases the conformations of the molecule towards the “open” form, with corresponding decrease in enzymatic activity.

- B. Choi, G. Zocchi, Y. Wu, S. Chan, L. Jeanne Perry, “Allosteric control through mechanical tension”, *Phys. Rev. Lett.* **95**, 078102 (2005).
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