Conformational Flexibility of Human Casein Kinase Catalytic Subunit Explored by Metadynamics

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SUPPORTING MATERIAL

Details of free energy surface reconstruction. After metadynamics simulations, the free energy surfaces are reconstructed with the sum of the Gaussians added during the simulation as a function of CVs:

$$V_G(S(x),t) = w \sum_{\substack{t'=\tau_G,2\tau_G,\ldots \\ t'<t}} \exp\left(-\frac{(S(x)-S(x(t')))^2}{2\delta s^2}\right) \quad (1)$$

where V_G corresponds to the sum of the Gaussians centred along the trajectory (x) in the space of the CVs, S(x(t')) is the value taken by the CV at time t', w is the Gaussian height, δs is the Gaussian width which is deposited every τ_G .

The opposite of the sum of the Gaussians added during the simulation converges to the free energy surface $\lim_{t\to\infty} -V_G(S(x),t) \approx F(S(x))$.

In the well-tempered variant of metadynamics (2), the height of the Gaussian terms is $w = w_0 e^{-\frac{V_G(S,t)}{k_B \Delta T}}$ with w_0 the initial Gaussian height and ΔT is the difference between the fictitious temperature of the CV and the temperature of the simulation. The ratio $(T+\Delta T)/T$ is referred as bias factor. $\Delta T \rightarrow 0$ corresponds to a ordinary MD and $\Delta T \rightarrow \infty$ to a standard metadynamics. The bias potential does not oscillate around the FES value but slowly converges.

$$\lim_{t\to\infty} -V_G(S(x),t) \approx \frac{\Delta T}{T+\Delta T} F(S(x))$$

Parameters of metadynamics and CVs chosen to generate the first guess path. 6 metadynamics were performed for the p-loop equilibrium and 3 for the hinge region equilibrium. For the p-loop equilibrium, metadynamics were performed with the collapsed or the stretched p-loop conformations as starting point and with the Gaussian deposition rate of 1ps. The CVs chosen were the distance between the atoms:
d1 : Arg47 : HE– His160 : O (along the H-bond)
d2: Lys49 : NZ – Asp156:CG
d3: Tyr50:HO– Asp156:OD2 (along the H-bond)
d4 : Arg47:CZ – Asp120:CG
and the dihedral angle : an1: Arg47(Cβ, Cα,C),Gly48(N)

CV1	CV2	H (kcal/mol)	∂CV1	∂CV2	Simulation time	Starting point
d1	d2	0.3	0.4 A	1 A	0.9 ns	collapsed
d1	d3	0.3	0.8 A	0.5 A	0.35 ns	collapsed
d2	d4	0.3	1 A	2 A	0.75 ns	collapsed
d1	an1	0.3	1 A	0.35 rad	0.6 ns	collapsed
d1	d2	0.3	1.5 A	2 A	0.45 ns	stretched
d1	an1	0.3	1.5 A	0.35 rad	1.0 ns	stretched

For the hinge region equilibrium, the open and closed hinge region were used as starting point and the deposition rate was 1 ps or 0.25 ps for the metadynamics with 2 or 3 CVs respectively. The CVs chosen were the distance between the atoms:
d5: Thr119:O - Ile164:H (along the H-bond)
d6: Phe121:H - Val162:O (along the H-bond)
and the dihedral angle an2 : Phe121(Cγ, Cβ, Cα, C)

CV1	CV2	CV3	H (kcal/mol)	∂CV1	∂CV2	∂CV3	Simulation time	Starting point
d5	an2		0.3	0.3	0.25		0.5 ns	open
d5	an2	d6	0.3	0.3	0.25	0.3	0.5 ns	open
d5	an2		0.3	0.3	0.25		0.4 ns	closed

The parameters of the Gaussians for these metadynamics were rude because the aim is to provide intermediate frames to define the path collective variables.

Table S1. Atoms included in the PCV calculation.

Figure S1. For the p-loop equilibrium, the variable s(R), the progression along the guess path, is plotted as a function of simulation time.

Figure S2. Convergence rate of free energy for the p-loop equilibrium. The difference of free energy between the two minima, the collapsed and the stretched p-loop conformations, is plotted as a function of simulation time.

Figure S3. For the hinge region equilibrium, the variable s(R), the progression along the guess path, is plotted as a function of simulation time.

Figure S4. Convergence rate of free energy for the hinge region equilibrium. The difference of free energy between the two minima, the closed and the open hinge region conformations, is plotted as a function of simulation time.

Table S1:

For the collapsed p-loop equilibrium, the RMSD calculated for the path collective variable is between 54 atoms from the p-loop region:
Arg42 N, Ca,C ; Lys43 N, Ca, C ; Leu44, N, Ca, C ; Gly45 N, Ca, C ; Arg46 N, Ca, Cb, Cg, C ; Gly47 N, Ca, C ; Lys48 N, Ca, Cb, Cg, C ; Tyr49 N, Ca, Cb, Cg, C ; Ser50 N, Ca, C ; Glu51 N, Ca, C ; Val52 N, Ca, C ; Phe53 N, Ca, C
For the closure of the hinge region equilibrium, the RMSD calculated for the path collective variable is between 63 atoms:
Val111 N, Ca ; Phe112 N, Ca ; Glu113 N, Ca ; Hie114 N, Ca ; Val115 N, Ca, C ; Asn116 N, Ca, Cb, C ; Asn117 N, Ca, Cb, C ; Thr118 N, Ca, Cb, C ; Asp119 N, Ca, Cb, C ; Phe120 N, Ca, Cb, Cg, Cd1, Cd2, Ce1, Ce2, C ; Lys 121 N, Ca, C ; Gln122 N, Ca, C ; Leu123 N, Ca ; Tyr124 N, Ca ; Gln125 N, Ca ; Thr126 N, Ca ; Leu127 N, Ca

Figure S1:

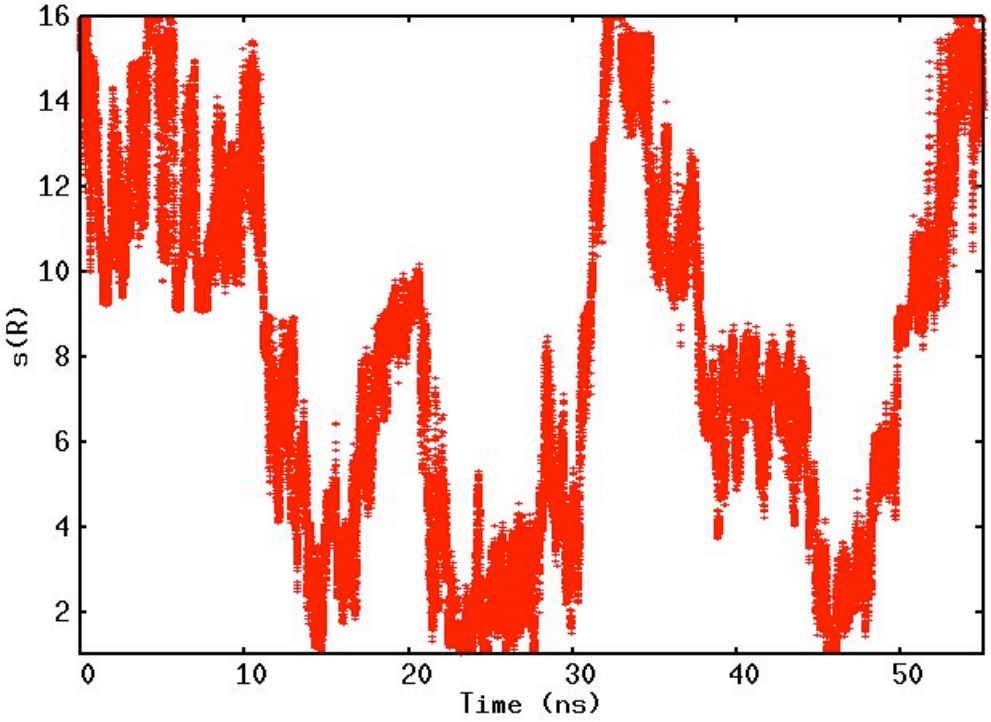


Figure S2:

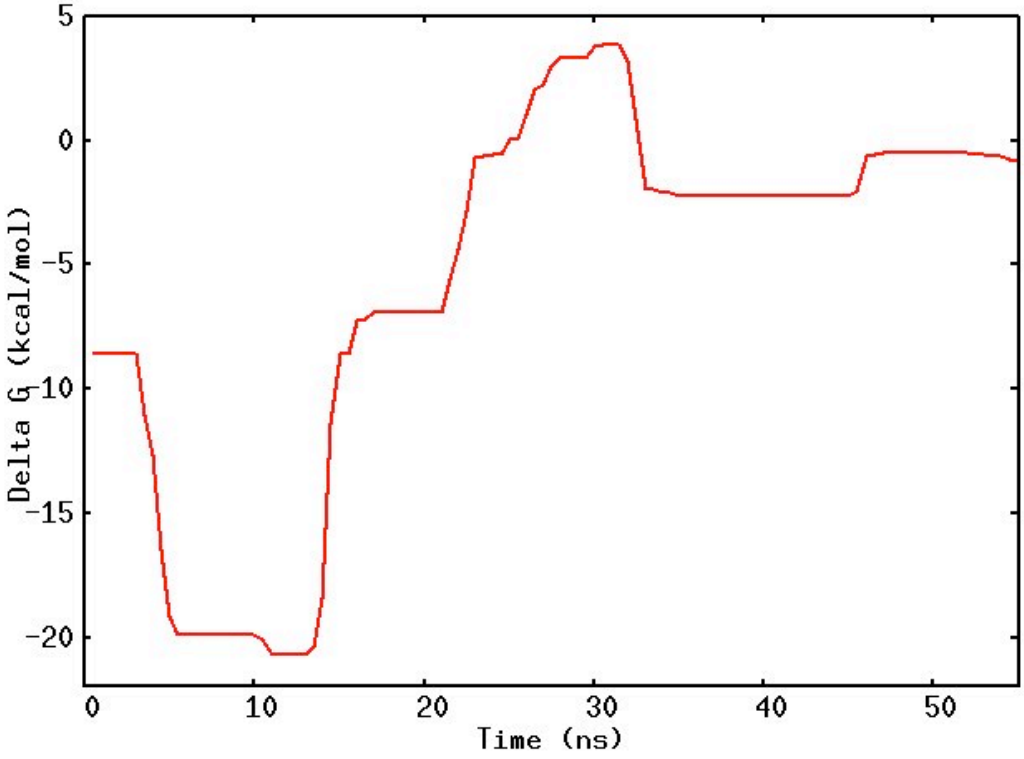


Figure S3:

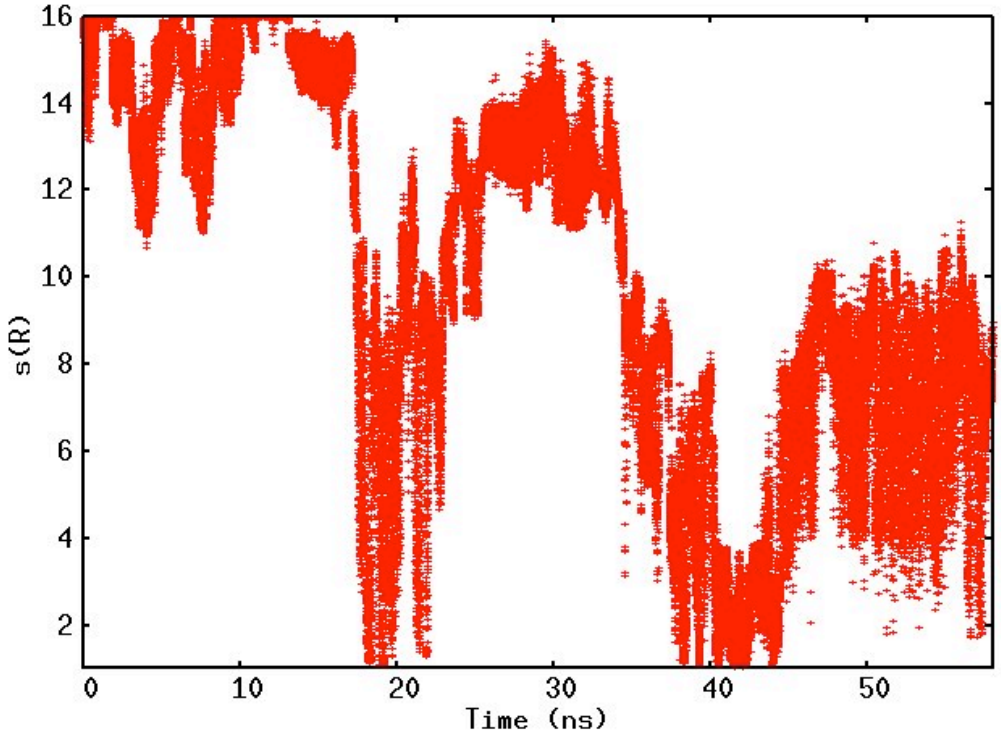
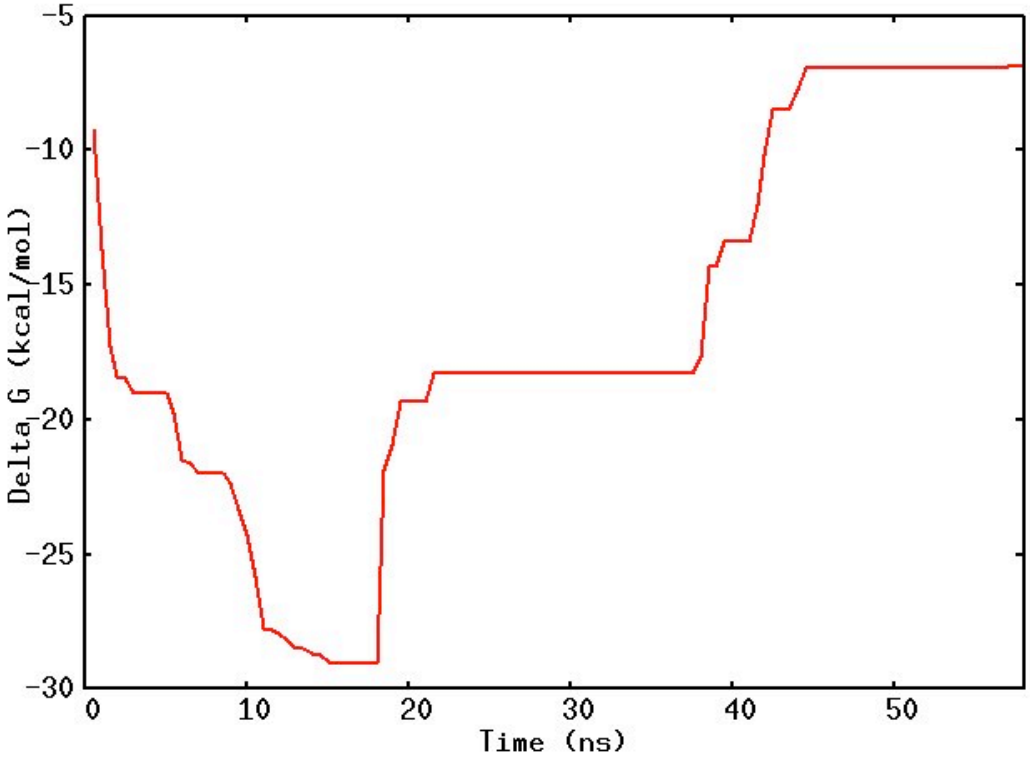


Figure S4:



SUPPORTING REFERENCES

(1) Laio, A., and F.L. Gervasio. 2008. Metadynamics: a method to simulate rare events and reconstruct the free energy in biophysics, chemistry and material science. Rep. Prog. Phys. 71: 126601.
(2) Barducci, A., G. Bussi, and M. Parrinello. 2008. Well-Tempered Metadynamics: A Smoothly Converging and Tunable Free-Energy Method. *Phys. Rev. Lett.* 100:020603.