Supporting Information

The importance of domain closure for the auto-activation of ERK2

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Table T1. Solvent accessible surface area of Y185.

System	**MD SASA (Å^2)**	**X-Ray SASA (Å^2)**
Inactive[a]	6.0 ± 2.3	4.7
Q103A[a]	10.8 ± 4.3	
I84A[a]	10.0 ± 3.8	
L73P[a]	7.3 ± 3.3	
Mono-phosphorylated[b]	71.1 ± 16.2	67.0
Active[a]	71.4 ± 7.8	71.3

a) ERK2
b) ERK1

Table T2. Mean Correlation Coefficients.

System	Lip-Protein	Whole Protein
Inactive[a]	-0.03070	0.19057
Q103A[a]	-0.01390	0.14649
I84A[a]	-0.01068	0.17141
L73P[a]	-0.03262	0.18115
G83A[a]	-0.01299	0.15649
K162M[a]	0.00970	0.15336
Mono-phosphorylated[b]	0.01246	0.17027
Active[a]	0.00524	0.16801

a) ERK2
b) ERK1

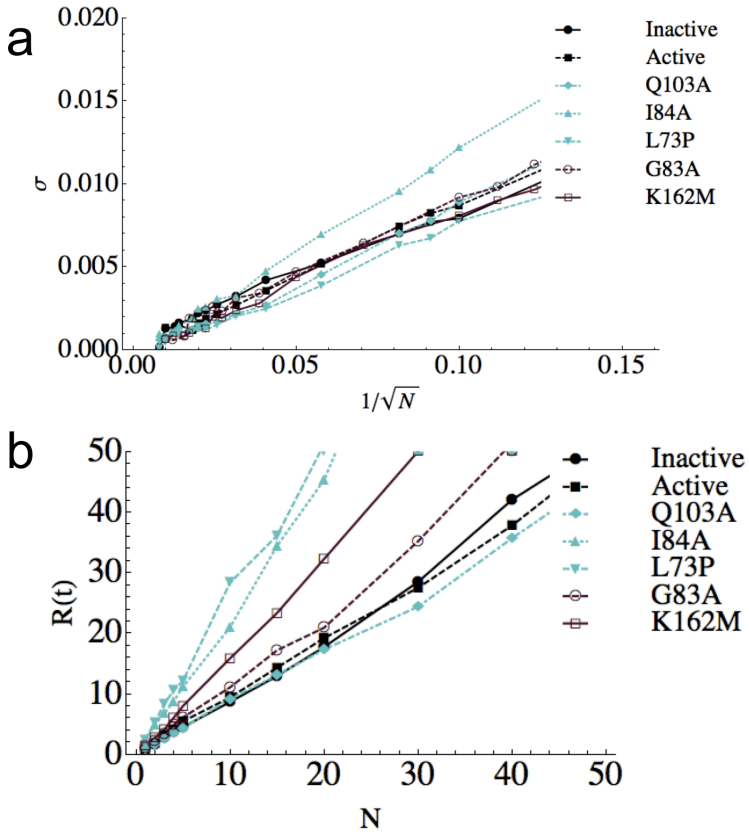

Figure S1. Block based convergence tests of a) the RMSD and b) the variance-covariance matrices (see text).

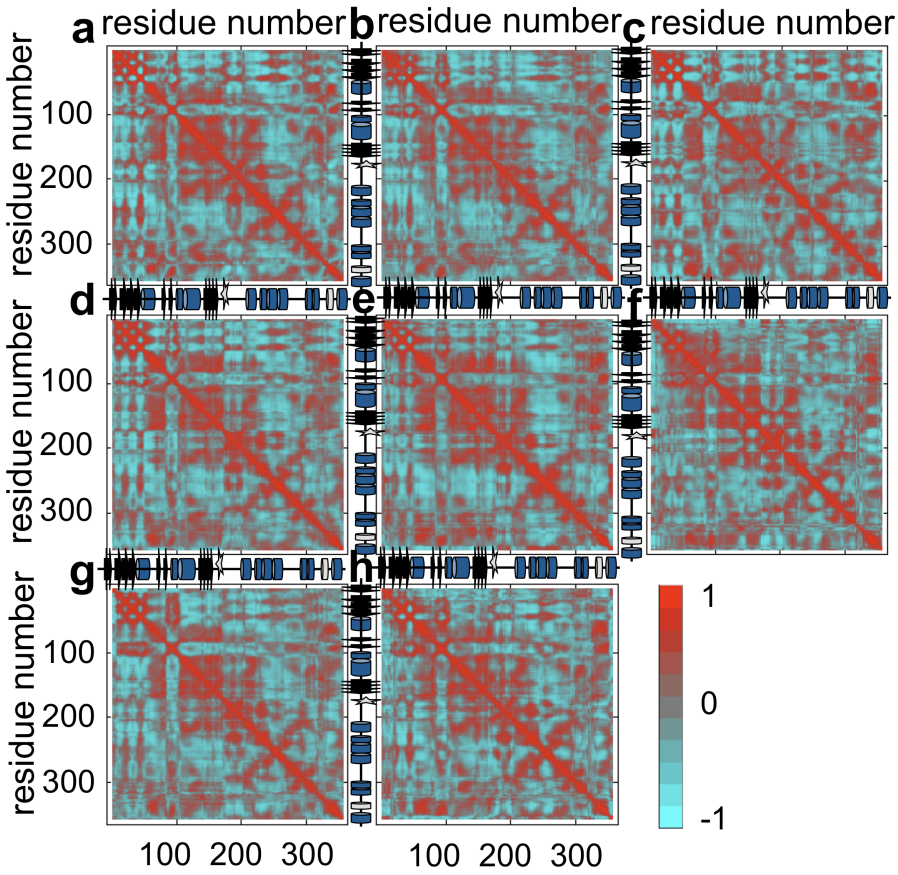

Figure S2. Variance-covariance matrices for: a) inactive ERK2, b) active ERK2, c) monophosphorylated ERK1, d) ERK2 mutant Q103A, e) ERK2 mutant I84A, f) ERK2 mutant L73P g) ERK2 mutant G83A, and h) ERK2 mutant K162M. Secondary structure labels are provided along the axes. The phosphorylation site (TEY motif) is shown by a light grey star, and the 3_{10} helical region of L16 in the active state is shown in light grey.

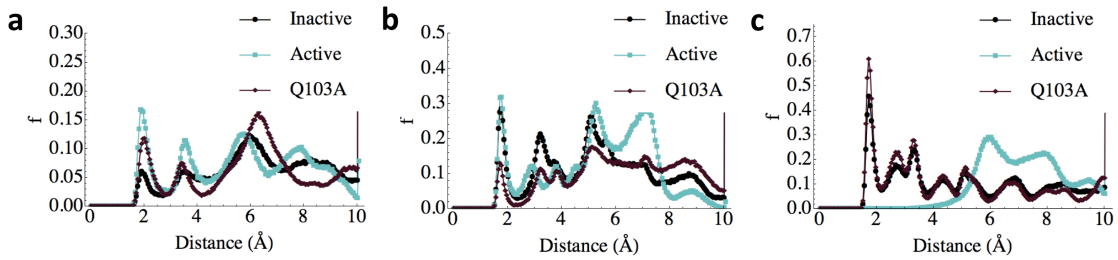

Figure S3. Trajectory-averaged distance histograms for contacts between D334 and a) Q64, b) R68, and c) R170 in the inactive, active and Q103A mutant states.

Figure S4. Sequence alignment of MAKs. The protein name and PDB access code are shown on the left. The sequence for cAPK is included at the bottom for comparison with Ref. (54). The residues mutated in this study are highlighted in yellow.

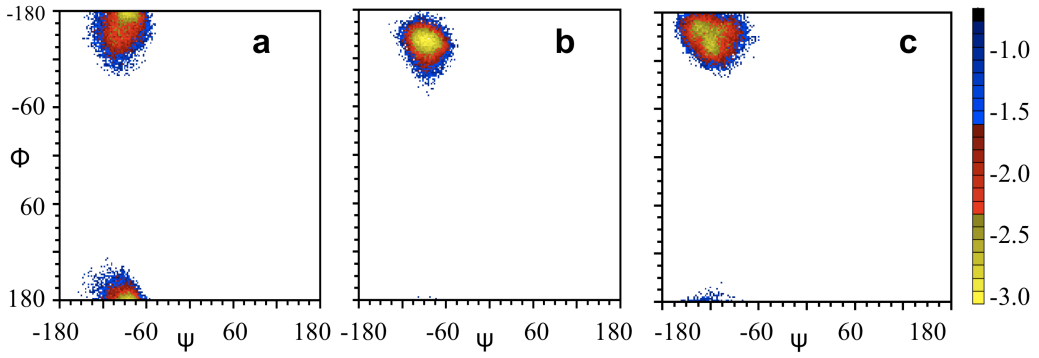

Figure S5. Free energy surfaces (in kcal/mol) for backbone rotation of G83. a) active ERK2, b) inactive ERK2, and c) ERK2 mutant G83A.

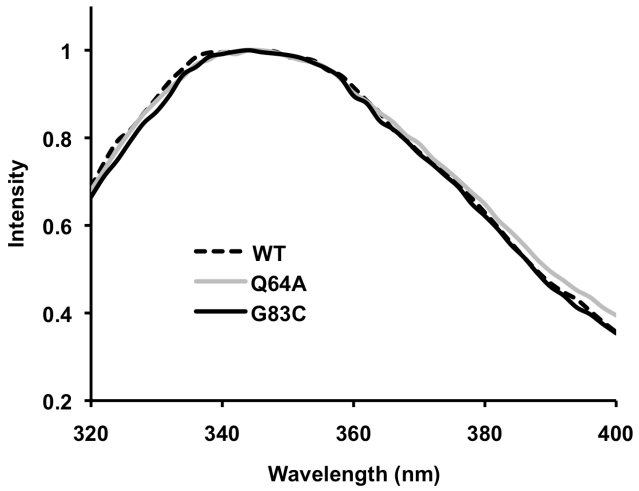

Figure S6. Fluorescence spectra of ERK2 wild type and mutants.

Movie M1. Quasi-harmonic mode 16 of the ERK2 inactive state showing hinge motion.

Movie M2. Quasi-harmonic mode 13 of the ERK2 active state showing hinge motion.

Movie M3. Quasi-harmonic mode 14 of the ERK2 active state showing twisting motion.

Movie M4. TMD transition pathway of ERK2 activation. The movie starts at the inactive and ends at the active state.