SUPPLEMENTARY INFORMATION

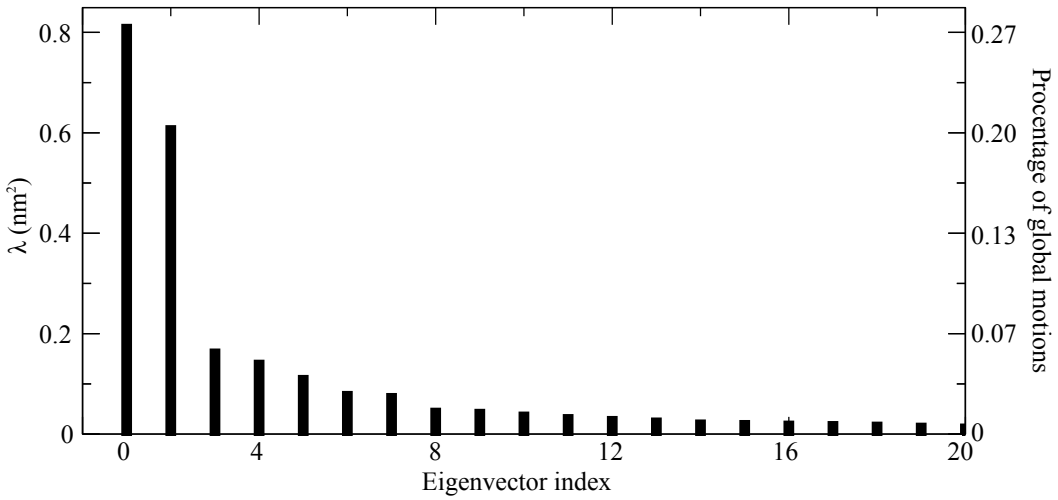

Figure S1: 20 largest eigenvalues from PCA of the kinase domain C_α atoms as observed for the apo-state. The first two eigenvectors account for about 45% of the global protein motion.

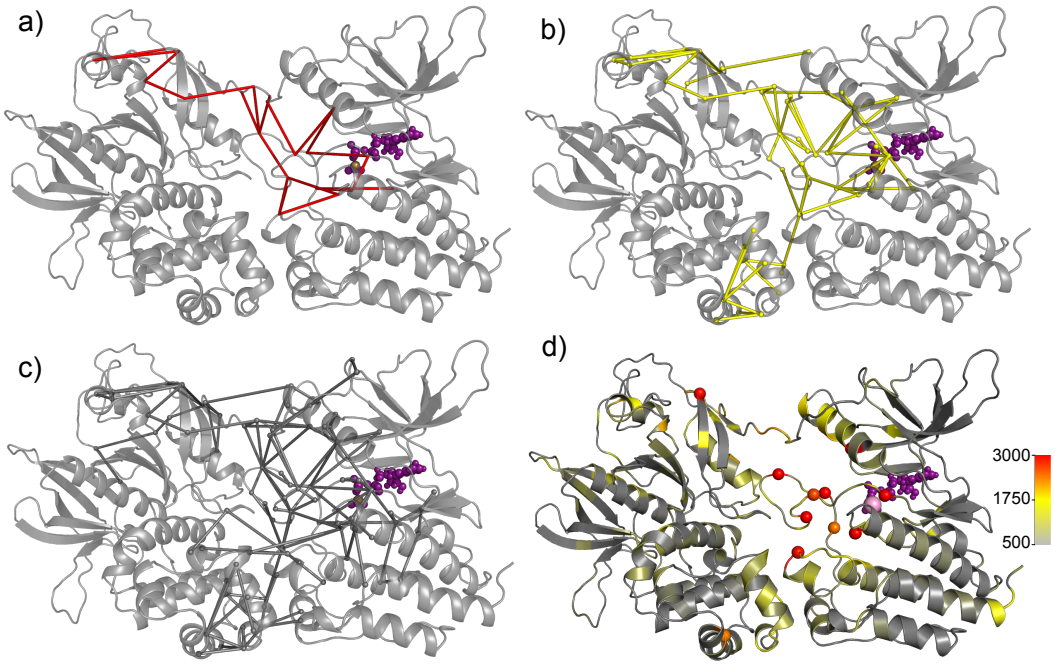

Figure S2: Force distribution upon ATP binding. (a-c) The network of force differences between apo-FK and FK-ATP state simulations is shown as sticks. Only the networks of forces connecting more than 5 residues are shown. ATP (*purple*) is shown at a representative position, as observed during the simulations. The different colors of sticks indicate different force cutoffs, namely at a) 500 pN. b) 300 pN and c) 200 pN. d) Difference of punctual stress, the sum of force differences acting on a given residue. Residues with stresses > 3000 pN are shown as spheres.

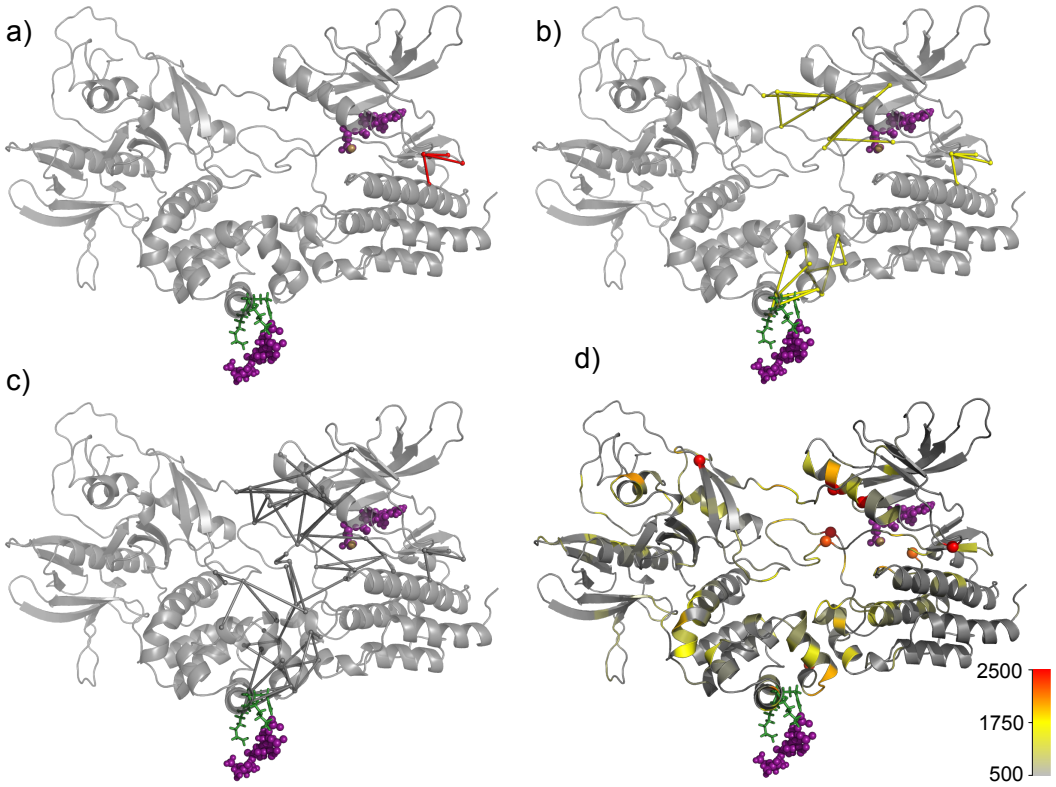

Figure S3: Force distribution upon PIP_2 binding. (a-c) The network of force differences between FK-ATP and FK-ATP-PIP_2 state simulations is shown as sticks. Only the networks of forces connecting more than 5 residues are shown. ATP and PIP_2 (*purple*) are shown at representative position, as observed during the simulations. The different colors of sticks indicate different force cutoffs, namely at a) 350 pN, b) 300 pN and c) 200 pN. d) Difference of punctual stress, the sum of force differences acting on a given residue. Residues with stresses > 3000 pN are shown as spheres.

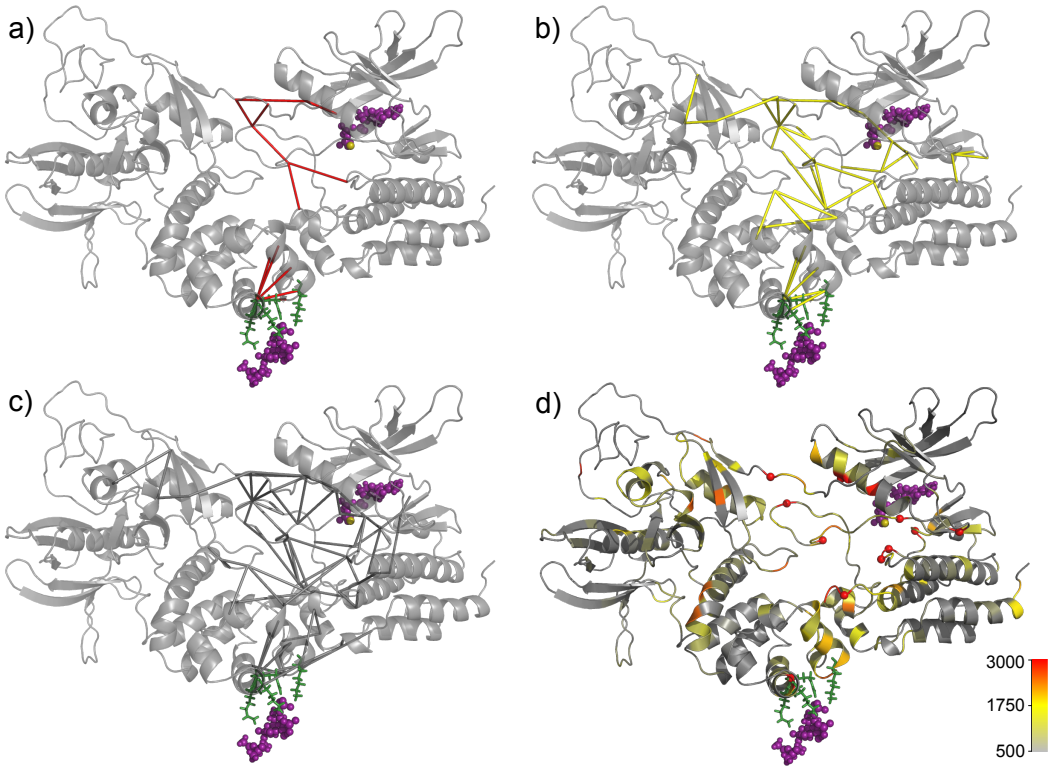

Figure S4: Force distribution upon ATP and PIP_2 binding. (a-c) The network of force differences between apo-FK and FK-ATP-PIP_2 state simulations is shown as sticks. Only the networks of forces connecting more than 5 residues are shown. ATP and PIP_2 (*purple*) are shown at representative positions, as observed during the simulations. The different colors of sticks indicate different force cutoffs, namely at a) 500 pN. b) 300 pN. c) 200 pN. d) Difference of punctual stress, the sum of force differences acting on a given residue. Residues with stresses > 3000 pN are shown as spheres.

Table S1: Average residue pairwise forces within connected networks upon ATP and PIP_2 binding as pointed out by FDA and as shown in Fig. 4, S2 and S3. Residue pairs with a change > 250 pN upon ATP binding and a reverse change of > 250 pN upon PIP_2 binding are marked in red and highlighted in Fig. 4 *c*. All of them except one are saltbridges.

Residue pair		APO (pN)	ATP (pN)	ATP-PIP_2 (pN)	Residue pair		APO (pN)	ATP (pN)	ATP-PIP_2 (pN)
R35	D60	-559	-937	-403	E404	R569	-104	-447	-195
R35	R108	637	1014	796	K454	E471	-538	-941	-630
R35	E109	-7	-988	-114	K454	K581	1.473	322	3
R35	E112	-829	-1179	-1082	K467	E403	-258	-489	-14
R35	E118	-885	-8	-330	K467	E471	-108	-418	-757
R35	D395	0	-351	-105	K467	K578	266	554	125
K38	E403	-785	-26	-9	E471	Q470	270	582	378
R57	D462	-635	-50	0	E471	D564	16	413	378
D60	R108	-552	-234	-668	E471	R569	-952	-74	-682
D60	E109	15	521	232	E471	K581	0	-845	2
D60	D395	1	400	245	H482	Q529	91	49	773
E109	E112	130	458	168	H482	D558	32	-62	481
E118	K38	-185	-1272	-1144	H482	C559	64	6	1084
R177	E182	-174	-620	-410	H482	V560	-124	-67	1352
R177	R184	120	466	173	R545	E572	-126	-1038	-1094
E182	M183	636	309	300	D546	K583	-779	-1675	-1158
E182	R184	-649	-943	-546	D564	H544	-80	256	194
E182	R597	-502	-176	-397	D564	D546	677	2231	2381
R184	K190	164	10	319	D564	R550	-986	-528	-324
R184	E636	-367	-76	-693	D564	F565	391	-37	111
E189	R221	-6	-546	-650	D564	K583	-222	-557	-412
E189	K222	-109	-419	-294	R569	D405	-202	-725	-765
E189	R229	-915	-477	-675	E572	Y570	-289	135	105
K190	E592	-799	-563	-37	E572	D573	400	725	681
K191	K218	155	143	475	K578	E404	-4	-669	-905
K191	R221	339	455	858	K578	E572	-1215	6	1
R221	E195	-1109	-505	-151	K578	Y576	120	583	604
R221	E198	-1178	-479	-168	K578	S580	361	-32	-1
R221	K199	608	174	73	L580	A579	-190	178	112
R221	K222	488	671	1277	K581	D564	-8	-542	-2
D395	R57	0	-405	-393	K583	R550	492	1166	475
D395	D63	532	119	22	R597	R545	-9	540	316
D402	K467	-1068	-620	-44	R597	E572	-32	-874	-568
D402	K578	-136	-1193	-1248	R597	D573	-1025	-439	-663
E403	D402	609	916	664	R597	T575	309	-3	-3
E403	K578	-3	-723	-358	E636	E592	458	365	61

Table S2: Data collection and refinement statistics for K-FAK structures.

PDB code	**4D4Y**	**4D55**	**4D4S**	**4D58**
Data collection				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell dimensions				
a, *b*, *c* (Å)	44.90, 122.99, 50.83	45.01, 44.49, 66.99	45.27, 124.88, 50.81	44.98, 123.37, 50.84
α, β, γ(°)	90.00, 94.94, 90.00	90.0, 95.0, 90.0	90.00, 93.33, 90.00	90.00, 94.65, 90.00
Resolution (Å)*	61.49–1.8 (1.9–1.8)	66.73–2.3 (2.42–2.3)	62.44–2.0 (2.11– 2.0)	61.68 –1.95 (2.06 – 1.95)
R_{sym}*	4.1 (36.3)	4.6 (26.1)	4.4 (35.5)	4.1 (31.5)
I/σ(I)*	11.8 (2.0)	11.2 (2.9)	12.7 (2.1)	11.2 (2.2)
Completeness (%)*	97.3 (96.0)	99.9 (99.8)	99.9 (99.9)	99.9 (100.0)
Redundancy *	4.3 (4.4)	3.8 (3.8)	4.8 (4.7)	3.8 (3.7)
Refinement				
Resolution (Å)	61.49 –1.8	44.88 – 2.3	62.44 – 2.0	61.68 –1.95
No. reflections	46837	11320	36003	38091
R_{work}/R_{free}	18.68/22.67	19.83/25.71	20.6/22.5	19.56/22.85
No. atoms				
Protein	4176	2105	4146	4167
Ligand	24	5	61	48
Water	230	58	148	185
Average B-factor	32.0	47.0	41.4	34.9
Name of ligands	DMSO and $(SO_4)^{2-}$	$(SO_4)^{2-}$	$(SO_4)^{2-}$ and TAE226†	$(SO_4)^{2-}$ and TAE226†
R.m.s deviation				
Bond lengths (Å)	0.0102	0.0095	0.005	0.0086
Bond angles (°)	1.386	1.334	1.049	1.267
PDB code	**4D4V**	**4D4R**	**4D5H**	**4D5K**
Data collection				
Space group	$P2_1$	I_2	$P2_1$	$P2_1$
Cell dimensions				
a, *b*, *c* (Å)	45.00, 123.60, 51.01	115.76, 44.81, 118.08	44.89, 123.59, 50.80	44.93, 122.85, 50.88
α, β, γ (°)	90.00, 94.49, 90.00	90.00, 106.54, 90.00	90.00, 95.00, 90.00	90.00, 94.75, 90.00
Resolution (Å)*	50.85 – 2.1 (2.21–2.10)	56.60 – 1.55 (1.63 – 1.55)	61.79 – 1.75 (1.84 – 1.75)	61.43 – 1.75 (1.84 – 1.75)
R_{sym}*	3.2 (17.6)	3.6 (34.5)	3.4 (37.2)	3.4 (33.6)
I/σ(I)*	15.6 (4.3)	7.9 (2.2)	11.8 (2.1)	9.1 (2.3)
Completeness (%)*	100.0 (100.0)	99.9 (100.0)	99.9 (99.9)	97.7 (91.4)
Redundancy*	4.3 (4.3)	4.1 (4.1)	3.8 (3.9)	3.8 (3.5)
Refinement				
Resolution (Å)	50.85 – 2.1	56.49 – 1.55	50.66 – 1.75	61.43 – 1.75
No. reflections	30740	80385	52597	51212
R_{work}/R_{free}	19.2/22.7	20.1/22.1	18.14/20.50	18.91/21.44
No. atoms				
Protein	4105	4200	4207	4162
Ligand	53	12	39	24
Water	134	330	215	218
Name of ligand	DMSO, $(SO_4)^{2-}$ and compound A‡	$(SO_4)^{2-}$	DMSO, $(SO_4)^{2-}$ and compound B§	DMSO and $(SO_4)^{2-}$
Average B-factor	46.7	26.0	33.7	33.7
R.m.s deviation				
Bond lengths (Å)	0.008	0.0058	0.0094	0.0096
Bond angles (°)	1.231	1.148	1.312	1.330

*Highest resolution range shown in parentheses

†a.k.a 2-[[5-chloro-2-(2-methoxy-4-morpholin-4-ylanilino)pyrim-idin-4-yl]amino]-N-methylbenzamide

‡6-methyl-4-(piperazin-1-yl)-2-(trifluoromethyl)quinoline

§6-methyl-5-[3-(trifluoromethyl)phenyl]amino-2,3-dihydro-1,2,4-triazin-3-one