Four-dimensional Docking: a Fast and Accurate Account of the Receptor Flexibility in Ligand Docking

Giovanni Bottegoni [§], Irina Kufareva [§], Maxim Totrov [‡], and Ruben Abagyan [§‡]*

Dept. of Molecular Biology, The Scripps Research Institute, 10550 N Torrey Pines Rd., La Jolla, CA 92037, USA and Molsoft, LLC, 3366 N Torrey Pines Ct. Suite 300, La Jolla, CA 92037, USA

* To whom correspondence should be addressed: Dept. of Molecular Biology, TPC28, The Scripps Research Institute, 10550 N Torrey Pines Rd., La Jolla, CA 92037, USA. E-mail: abagyan@scripps.edu, Tel: 00 1 (858) 784 8543, Fax: 00 1 (858) 784 8299

§ The Scripps Research Institute; ‡ Molsoft, LLC

Supplementary Information

Materials and Methods

Table 1S. 4D Docking Benchmark: PDB structures

Name	Source	UniProt	PDBid Receptor	PDBid Ligands
CHK1	human	O14757	2BR1, 2HXL, 2HXQ, 2HOG, 2HY0, 2C3K, 2BRG, 2BRH, 2BRB, 2BRM, 2CGU, 1ZLT, 2CGV, 2C3L, 1IA8, 1NVQ, 1NVR, 1NVS, 1ZYS	2BR1, 2C3K, 2BRH, 2BRB, 2BRM, 1NVQ, 1NVR
STK6	human	O14965	2NP8, 2J4Z, 1MQ4, 2DWB	2J4Z
PDPK1	human	O15530	1UU8, 1UU9, 1UU7, 1Z5M, 2PE2, 2PE1, 2PE0, 1H1W, 1OKY, 1OKZ, 1UU3	2PE1, 1OKY, 1OKZ
PTGD2	human	O60760	2CVD, 1IYH, 1IYI	2CVD
PDE5A	human	O76074	1XOZ, 2CHM, 1TBF, 1T9S	1XOZ, 1TBF
DYR	human	P00374	1S3U, 1MVS, 1DHF, 1S3V	1S3U, 1MVS, 1S3V
DYR	human	P00374	1PD8, 1S3W, 1KMS, 1KMV, 1OHJ	1KMS
ABL1	mouse	P00520	1FPU, 1M52, 2HZ0, 2HZI, 2F4J, 2GQG, 2HIW, 1IEP, 2G1T, 2QOH	1M52, 2HZ0, 2HZI, 1IEP, 2QOH
SRC	chick	P00523	2BDF, 2BDJ, 1Y57, 2OIQ, 2H8H, 1FMK, 1YI6, 2SRC	2H8H
THRB	human	P00734	1KTT, 1K22, 1MU6, 2BXT, 2JH0, 1BHX, 1D4P, 1G32, 1MU8, 1MUE, 1O5G, 1QBV, 1T4U, 1TOM, 1ZGI, 2A2X, 2FEQ, 2FES, 2JH5, 2JH6	1KTT, 2JH0, 1G32, 2JH5, 2JH6
FA10	human	P00742	1NFU, 1NFY, 2J2U, 2J34, 2J38, 1F0R, 1F0S, 1IQM, 1XKA, 2CJI, 2D1J, 2J94, 2J95, 2UWO, 1LPK, 1LPZ, 1NFW, 2BOK, 2UWL, 2UWP	2J2U, 2J34, 2J38, 2CJI, 2J95, 2UWO, 1LPZ, 2UWL
UROK	human	P00749	1SC8, 1SQA, 1GJ9, 1OWD, 1GJ7, 1EJN, 1GJ8, 1GJB, 1O3P, 1OWH, 1SQT, 1GJD, 1OWE, 1U6Q, 1GI9, 1SQO, 1GI7, 1GI8	1GJ7, 1O3P, 1SQT, 1U6Q, 1SQO
TRY1	bovin	P00760	1F0T, 1K1P, 1QB6, 1G36, 1O2R, 1O2U, 1QBN, 1K1L, 1MTW, 1O2T, 1AZ8, 1BJV, 1F0U, 1GJ6	1F0T, 1K1P, 1K1L, 1GJ6
TRY1	bovin	P00760	1Y59, 1Y5A, 1Y5B, 1Y5U	1Y5A, 1Y5U
RENI	human	P00797	2G1R, 2IKU, 2G1Y, 2G22, 2G1S, 2G24, 2G21, 2I4Q, 2IL2, 1BIL, 1HRN, 1RNE, 2BKS, 2BKT, 2FS4, 2G20, 2G26, 2REN, 2V0Z	2G1Y, 2G22, 2G24, 2IL2, 2BKT
AEQ2	aeqvi	P02592	1UHH, 1EJ3, 1UHJ, 1UHK, 1SL8, 1UHI	1UHH, 1UHJ, 1UHK, 1UHI
RETBP	human	P02753	1FEL, 1ERB, 1AQB, 1BRQ, 1FEM, 1FEN, 1HBQ, 1JYD, 1JYJ	1AQB
ALBU	human	P02768	2BXK, 2BXM, 2BXQ, 2BXO, 1H9Z, 1HA2, 2BXA, 2BXH, 1E7A, 2BXL, 1AO6, 1BJ5, 1BM0, 1BM0, 1E78, 1E7B, 1E7C, 1E7E	1HA2
KITH	hhv11	P03176	1KI4, 1E2N, 1E2K, 1OF1, 1E2P, 1E2M, 1E2H, 1KI2, 1KI3, 1KI6, 1KI7, 1KI8, 1QHI, 2KI5	1KI4, 1E2N, 1QHI
ESR1	human	P03372	1ZKY, 2FAI	1ZKY, 2FAI
ESR1	human	P03372	1ERR, 1XQC, 1YIN	1ERR, 1XQC, 1YIN
ESR1	human	P03372	2OUZ, 1XP9, 1XPC, 1YIM, 1XP1, 1XP6, 1L2I	2OUZ, 1XP9, 1XPC, 1YIM, 1L2I
FA11	human	P03951	1ZRK, 1ZSK, 1ZSJ, 1XX9, 1XXF, 1ZHM, 1ZJD	1ZRK, 1ZSK, 1ZSJ
ACES	torca	P04058	1EVE, 1H22, 1UT6, 1E66, 1ODC, 1ZGB, 1ZGC, 1DX6, 1GPN, 1W4L, 1GPK, 1U65, 2ACK, 1VOT, 1EA5, 1H23	1E66, 1W4L
SHBG	human	P04278	1LHN, 1LHO, 1LHU	1LHN, 1LHO, 1LHU
POL	hv1ma	P04588	1EP4, 2BE2, 1S9E, 1C1B, 1C0U, 1VRU, 1C1C, 1RT1, 1TKT, 1FK9, 1REV, 2OPP	1EP4, 2BE2, 1S9E, 1C1B, 1C0U, 1C1C, 1TKT, 1FK9, 2OPP
KAPCA	mouse	P05132	2GU8, 1REJ, 1YDT, 1RE8	2GU8, 1YDT

KAPCA	mouse	P05132	2F7E, 2JDS, 2OH0, 2C1B, 2OJF, 2C1A, 2F7X, 2UZW, 2UZT, 2UZV, 1SVH	2JDS
IPNS	emeni	P05326	1QJF, 1BK0, 1HB1, 1HB2, 1IPS, 1OBN, 1QIQ, 1QJE, 1UZW, 1W03, 1W05, 1W3V	1W3V
HEPS	human	P05981	1O5F, 1P57	1O5E
PRGR	human	P06401	1A28, 1SR7, 1SQN, 1ZUC	1A28, 1SR7, 1SQN
NRAM	iatok	P06820	1ING, 1INH, 1IVD, 1IVC, 1IVE, 1INW, 1INX, 1IVF, 1IVG, 1IVG, 1NN2, 2BAT	1IVF
HS90A	human	P07900	1UYF, 1UYE, 2H55, 1UYD, 2BYI, 2FWY, 2FWZ, 1UY6, 1UYI, 1YC1, 2BSM, 2UWD, 1UYH, 2BT0, 2BYH, 1UYC, 1UYK, 1UY9	1UYF, 1UYE, 1UYD, 2FWZ, 1UY6, 1UYI, 1YC1, 2BSM, 2UWD, 2BYH, 1UYC, 1UYK, 1UY9
MCR	human	P08235	2AAX, 2AB2, 1YA3, 1Y9R	2AAX, 2AB2, 1YA3, 1Y9R
FA7	human	P08709	2BZ6, 2F9B, 1O5D, 2FLR, 2FLB, 2AEI, 2C4F, 1CVW, 1DAN, 1KLI, 1WQV, 1WSS, 1WTG, 1WUN, 1YGC	2BZ6, 2FLB
MYS2	dicdi	P08799	1YV3, 1FMV, 1JWY, 1JX2, 1LVK, 1MMA, 1MMD, 1MND, 1VOM	1YV3
CP51	myctu	P0A512	1EA1, 1E9X, 1U13, 1X8V, 2BZ9	1X8V
INHA	myctu	P0A5Y6	2H7M, 2H7N, 2H7P, 2H7L, 2H7I, 1ENY, 1P45, 2AQ8, 2AQH, 2AQI, 2AQK, 2H9I, 2IDZ, 2IE0, 2IEB, 2NSD, 2NTJ	2H7M, 2H7P, 2H7L, 2H7I
TETR4	ecolx	P0ACT4	2O7O, 2TRT, 1ORK	2O7O
AMPM	ecoli	P0AE18	2GG0, 2GG2, 2GG5, 2EVC, 2GG7, 2EVM, 2EVO, 2GG3, 1XNZ, 2BB7, 1YVM, 1C21, 1C22, 1C23, 1C24, 1C27, 1MAT, 2GG8, 2GG9, 2GGB	2GG0
THB1	human	P10828	1N46, 1NQ0, 1XZX	1N46, 1XZX
PNMT	human	P11086	2G8N, 2G72, 2G70, 1HNN, 1YZ3, 2AN3, 2AN5, 2AN4, 2ONY	2G8N, 2G72
PIM1	human	P11309	1XWS, 1YI3, 2C3I, 2O63, 2O64, 2OBJ, 2O3P, 1YXX, 1YXV, 1XQZ, 1XR1, 1YHS, 1YI4, 1YWV, 1YXU, 2BZH	1XWS, 1YI3, 2C3I, 1YHS
VDR	human	P11473	1DB1, 1S19, 1TXI, 2HB8, 1IE8, 1S0Z, 2HAM, 2HAR, 1IE9, 2HAS, 2HB7	1DB1, 1S19, 1TXI, 2HB8, 1IE8, 1S0Z, 2HAM, 2HAR, 1IE9, 2HAS, 2HB7
UNG	human	P13051	2HXM, 1AKZ, 1EMH, 1EMJ, 1Q3F, 1UGH, 1YUO	2HXM
VDR	rat	P13053	1DB1, 1RJK, 1RKH, 2O4J, 1IE8, 1RKG, 1IE9	1DB1, 1RJK, 2O4J, 1IE8, 1RKG, 1IE9
FABPA	human	P15090	2NNQ, 1TOU, 1TOW	2NNQ
ALDR	human	P15121	1PWL, 1T40, 1EL3, 2NVC, 1IEI, 1Z3N, 2IKJ, 1US0, 2FZB, 2IKI, 2PEV, 2NVD, 1Z89, 1X97, 1X98, 2IKG	1PWL, 1T40, 1IEI, 1Z3N, 2IKJ, 1US0, 2IKI, 1Z89, 2IKG
ANDR	rat	P15207	2AMB, 2IHQ, 2AX9, 1E3G, 1I37, 1T5Z	2AMB, 1E3G, 1T5Z
ANDR	rat	P15207	1XNN, 2AX7, 2OZ7, 2AX6	1XNN, 2AX7, 2OZ7
DYR	pneca	P16184	1KLK, 1VJ3, 2FZI, 1S3Y, 1LY3, 1LY4, 2FZH, 1DYR, 1CD2, 1DAJ, 1E26, 3CD2	2FZI, 1S3Y, 1LY3, 1LY4, 2FZH
PTN1	human	P18031	1KAV, 1Q1M, 1BZC, 1L8G, 1XBO, 2F6V, 1T48, 2F70, 2F71, 2CMC, 1ONZ, 2CM7, 2F6T, 2F6Y, 2F6Z, 1NO6, 2CNF, 1KAK, 2CNG	2F6T, 2F6Y
RXRA	human	P19793	1RDT, 1MVC, 1XVP, 1FM6, 1G1U, 1G5Y, 1MV9, 2P1T, 2P1U, 2P1V	1FM6, 2P1T, 2P1U, 2P1V
ITAL	human	P20701	1CQP, 1RD4, 1LFA, 1XDD, 1XDG, 1XUO, 1ZON, 1ZOP	1CQP
ACES	mouse	P21836	1N5R, 2GYV, 1J07, 2GYU, 2GYW, 1J06, 1KU6, 1N5M, 1Q84, 2HA3	2GYW
COMT	rat	P22734	1H1D, 1JR4, 2CL5, 1VID	1JR4
GRIK1	rat	P22756	2F34, 2F35, 2PBW, 1VSO, 1TXF, 1YCJ, 1YCJ, 2F36	2F34, 2PBW

MMP8	human	P22894	1BZS, 1ZS0, 1ZVX, 1MNC, 1JJ9, 1ZP5, 1A85, 1A86, 1I73, 1JAN, 1JAO, 1JAP, 1JAQ, 1KBC, 1MMB, 2OY2, 2OY2, 2OY4, 2OY4	1BZS, 1JJ9, 1ZP5
RARG2	human	P22932	1EXA, 1EXX, 1FCX, 1FCZ, 1FCY, 1FD0, 2LBD	1EXA, 1FCX, 1FCZ, 1FCY, 2LBD
PTPRB	human	P23467	2H02, 2H04, 2I5X, 2AHS, 2H03, 2HC1, 2HC2, 2I3R, 2I4E, 2I4G	2H04
CDK2	human	P24941	1YKR, 2B54, 2FVD, 1H08, 2B52, 1H1S, 1OIU, 2C5Y	2B54, 2FVD, 1H1S, 1OIU
CDK2	human	P24941	1CKP, 1G5S, 2B55, 2BHH, 1KE7, 1R78	2B55, 2BHH, 1KE7
POLG	hcvj6	P26660	1YVZ, 1YVX, 1YUY, 1YV2	1YVX
POLG	hcvja	P26662	2GIQ, 2FVC, 1YVF, 2D41, 2I1R, 2JC0, 2JC1, 1NHU, 2D3U, 2GIR, 2D3Z, 2HWI, 1OS5, 2HWH, 2O5D, 2GC8, 1C2P	2JC1
DPP4	human	P27487	2FJP, 2P8S, 1X70, 2IIT, 1RWQ, 2HHA, 2IIV, 2OGZ, 2OPH, 1N1M, 1J2E, 1NU6, 1NU8, 1PFQ, 1R9M, 1R9N, 1TK3, 1WCY, 2AJL	1X70
DCK	human	P27707	1P62, 2NO6, 2NO9, 2NOA, 1P5Z, 1P60, 2A7Q, 2NO7	2A7Q
NRAM	inbbe	P27907	1B9V, 1B9T, 1B9S, 1INF, 1IVB, 1A4G, 1A4Q, 1INV, 1NSB, 1NSC, 1NSD	1B9V, 1B9T, 1B9S
CFI1	medsa	P28012	1EYQ, 1FM7, 1FM8, 1JEP, 1EYP	1EYQ
MK01	human	P28482	2OJJ, 1WZY, 2OJI, 1TVO, 3ERK, 4ERK, 2OJG, 1ERK, 2ERK, 2FYS, 2GPH	2OJJ, 1WZY, 1TVO
TGT	zymmo	P28720	1Y5X, 1Y5W, 1Y5V, 1Q66, 1N2V, 1F3E, 1ENU, 1P0B, 1Q4W, 1S38, 1K4G, 1K4H, 1P0D, 1PUD	1Y5W
DHI1	human	P28845	2ILT, 2BEL, 1XU7	2ILT, 2BEL
RABP2	human	P29373	2CBS, 1CBQ, 1CBS, 2FS6, 2FS7, 3CBS	2CBS, 1CBQ, 1CBS, 3CBS
NOS1	rat	P29476	1VAG, 1K2U, 1K2R, 1K2S, 1LZX, 1OM5, 1QWC, 1K2T, 1LZZ, 1M00, 1MMV, 1MMW, 1OM4, 1P6H, 1P6I, 1P6J, 1QW6, 1RS6, 1RS7	1VAG
WEE1	human	P30291	1X8B, 2IN6, 2IO6	1X8B, 2IN6, 2IO6
AKT2	human	P31751	2JDR, 2JDO, 2UW9, 1GZK, 1GZN, 1O6K	2JDR, 2UW9
MMP13	mouse	P33435	1XUD, 1YOU, 1XUC, 2OW9, 456C, 1XUR, 1ZTQ, 2D1N, 2E2D, 2OZR	2OW9
KES1	yeast	P35844	1ZHZ, 1ZHW, 1ZHX, 1ZHY, 1ZI7	1ZHZ, 1ZHT, 1ZHX, 1ZHY
POL	hv1y2	P35963	1EP4, 2BE2, 1S9E, 1C1B, 1C0U, 1VRU, 1C1C, 1RT1, 1TKT, 1FK9, 1REV, 2OPP	1EP4, 2BE2, 1S9E, 1C1B, 1C0U, 1C1C, 1TKT, 1FK9, 2OPP
POL	hv1y2	P35963	1EP4, 2BE2, 1S9E, 1C1B, 1C0U, 1VRU, 1C1C, 1RT1, 1TKT, 1FK9, 1REV, 2OPP	1EP4, 2BE2, 1S9E, 1C1B, 1C0U, 1C1C, 1TKT, 1FK9, 2OPP
PPARG	human	P37231	2G0G, 2I4J, 2I4P, 2ATH, 1FM6, 2G0H, 1K74, 2F4B, 2HFP, 1PRG, 2I4Z	1FM6, 2F4B
MMP12	human	P39900	2HU6, 1UTZ, 1JIZ, 1UTT, 1ROS, 1RMZ, 1OS2, 1OS9, 1Y93, 2OXU, 2OXW, 2OXZ	1UTT, 1ROS, 1RMZ
ENPL	canfa	P41148	2FYP, 1QY5, 1QY8, 1QYE, 1TBW, 1TC0, 1U0Y, 1U0Z, 1YT1	1QY5, 1U0Y
ENPL	canfa	P41148	1U0Z, 2H8M, 2HCH, 2HG1	2HCH
AK1C3	human	P42330	1ZQ5, 1S2A, 1S2C, 1RY0, 1RY8, 1S1P, 1S1R, 1XF0, 2F38	1ZQ5
KSYK	human	P43405	1XBB, 1XBA, 1XBC	1XBC
MK14	mouse	P47811	1W83, 1WBN, 2GTM, 1A9U, 1M7Q, 1WBS, 1WBT, 1W82, 1BL7, 1WBV	2GTM, 1M7Q
MK14	mouse	P47811	2GTN, 2BAL, 1ZZ2	2GTN, 2BAL
PK3CG	human	P48736	1E7V, 1E8W, 1E8X, 1E8Y, 1E8Z, 2CHW, 2CHX, 2CHZ	1E7V, 1E8W
AMPM2	human	P50579	1YW9, 1QZY, 1R58, 1R5H, 2OAZ, 1YW7, 2ADU, 1BN5, 1KQ0, 1KQ9, 1R5G, 2GA2	1QZY, 1R58, 1R5G

BLAB	serma	P52699	1DD6, 1JJT, 2DOO, 1JJE	1JJT
BLA1	xanma	P52700	2AIO, 2GFJ, 2GFK, 2FU9, 2HB9, 1SML, 2FM6, 2FU8, 2QDT	2AIO, 2GFJ
KIF11	human	P52732	2FKY, 2G1Q, 2FL2, 2UYM, 2UYI, 2FL6, 2FME, 2GM1, 2PG2, 1YRS, 1Q0B, 1II6, 2Q2Y	2UYM, 2UYI, 2FME, 2GM1, 2PG2
MK10	human	P53779	2P33, 1PMN, 2O0U, 1PMQ, 1PMV	1PMN
ADA	bovin	P56658	1WXY, 1NDV, 1V7A, 1NDZ, 1V79, 1NDW, 1KRM, 1NDY, 1O5R, 1QXL, 1UML, 1VFL, 2E1W	1WXY, 1V79, 2E1W
ERR3	human	P62508	1S9Q, 2EWP, 2GPP, 1TFC, 2E2R, 2GP7, 2GPO	1S9Q, 2GPP
ADA17	human	P78536	2FV5, 2A8H, 1ZXC, 2I47, 2FV9	2A8H, 1ZXC
PDXK	sheep	P82197	1YGK, 1LHP, 1LHP, 1LHR	1YGK
CPXJ	sacen	Q00441	1JIN, 1EGY, 1EUP, 1JIO	1JIN
MDM2	human	Q00987	1T4E, 1RV1, 1T4F, 1YCR, 2AXI, 2GV2	1T4E
PYRD	human	Q02127	2FPT, 2FPY, 2BXV, 2FQI, 1D3G, 2FPV, 2B0M, 1D3H	1D3G, 2B0M
PDE4B	human	Q07343	1XOT, 1XLX, 1XLZ, 1Y2J, 1RO6, 1Y2H, 1F0J, 1XMY, 1RO9, 1ROR	1XLX, 1XMY
CDC2H	plafk	Q07785	1V0P, 1V0O, 1OB3, 1V0B	1V0P, 1V0O
PDE4D	human	Q08499	1XOQ, 1XOM, 1XON, 2FM0, 2FM5, 1Y2K, 1OYN, 1Y2D, 1XOR, 1XOR, 1Y2E, 1Y2C, 1Y2B, 1PTW, 1Q9M, 1ZKN	2FM0
BGLA	thema	Q08638	2CET, 2J7C, 2J7D, 2J7F, 2CBV, 2J78, 2J79, 1OD0, 1OIF, 1OIM, 1UZ1, 1W3J, 2CBU, 2CES, 2J75, 2J7B, 2J7E, 2J7G	2CET
MTAP	human	Q13126	1K27, 1CB0, 1CG6, 1SD1, 1SD2	1SD2
QDOI	aspja	Q7SIC2	1H1I, 1H1M, 1GQH	1H1I
ESR2	human	Q92731	2FSZ, 1U3R, 1U3S, 1YYE, 1QKM, 1X78, 2GIU, 1X76, 1ZAF, 1U3Q, 1U9E, 1X7B, 2J7X, 2J7Y, 2JJ3, 2NV7	1QKM, 2GIU, 2JJ3

Results and Discussion

Table 2S. Docking Results – Structures correctly reproduced in the top ranking solution (Detailed)

Name	UniProt	RC[a]	L[b]	MRC[c]	4D[d]	XRC[e]	X4D[f]	Name	UniProt	RC[a]	L[b]	MRC[c]	4D[d]	XRC[e]	X4D[f]
ESR1	P03372	3	3	3	3	3	3	GRIK1	P22756	9	2	2	2	0	0
SHBG	P04278	3	3	3	3	2	2	AK1C3	P42330	9	1	1	1	0	0
HEPS	P05981	3	1	0	1	1	1	ABL1	P00520	10	5	5	5	4	3
THB1	P10828	3	2	2	2	2	2	ITAL	P20701	10	1	1	0	0	0
FABPA	P15090	3	1	1	0	0	0	MMP13	P33435	10	1	1	1	1	0
WEE1	P30291	3	3	3	3	3	3	ENPL	P41148	10	2	2	2	2	2
KSYK	P43405	3	1	1	1	1	1	MK14	P47811	10	2	0	1	0	0
MK14	P47811	3	2	1	1	1	1	ERR3	P62508	10	2	2	2	1	2
QDOI	Q7SIC2	3	1	1	1	1	1	PDPK1	O15530	11	3	2	2	2	2
STK6	O14965	4	1	1	1	1	1	KAPCA	P05132	11	1	1	1	1	0
PDE5A	O76074	4	2	1	1	1	1	PNMT	P11086	11	2	1	1	1	1
TRY1	P00760	4	2	1	1	0	2	VDR	P11473	11	11	11	11	11	11
ESR1	P03372	4	4	4	4	4	4	RXRA	P19793	11	4	4	4	4	4
KAPCA	P05132	4	2	2	2	1	2	PDE4B	Q07343	11	2	1	1	1	1
PRGR	P06401	4	3	3	3	2	2	NRAM	P06820	12	1	1	1	1	1
MCR	P08235	4	4	4	4	4	4	DYR	P16184	12	5	4	5	3	4
ANDR	P15207	4	3	3	2	1	1	ACES	P21836	12	1	0	0	0	0
COMT	P22734	4	1	1	0	0	0	MK01	P28482	12	3	3	3	1	2
POLG	P26660	4	1	0	0	0	1	POL	P35963	12	9	9	8	8	8
DHI1	P28845	4	3	3	3	2	2	AMPM2	P50579	12	3	1	1	1	1
ENPL	P41148	4	1	0	0	0	0	IPNS	P05326	13	1	0	0	0	0
BLAB	P52699	4	1	1	1	1	0	PTPRB	P23467	13	1	1	1	1	1
CPXJ	Q00441	4	1	1	1	0	0	NRAM	P27907	13	3	3	3	3	3
PTGD2	O60760	5	1	0	0	0	0	ADA	P56658	13	3	0	1	0	1
CP51	P0A512	5	1	1	1	0	0	TRY1	P00760	14	4	1	2	2	2
MK10	P53779	5	1	1	1	1	1	KITH	P03176	14	3	3	3	2	2
ADA17	P78536	5	2	2	1	2	1	POL	P04588	14	9	8	8	8	8
PDXK	P82197	5	1	1	0	0	0	TGT	P28720	14	1	1	1	1	1
MTAP	Q13126	5	1	1	1	1	1	POL	P35963	14	9	9	9	8	9
ANDR	P15207	6	3	3	3	3	3	MMP12	P39900	14	3	1	0	2	1
CDK2	P24941	6	3	2	2	0	1	KIF11	P52732	14	5	5	4	4	2
AKT2	P31751	6	2	2	2	1	1	FA7	P08709	15	2	2	1	2	1
KES1	P35844	6	4	4	4	4	4	ACES	P04058	16	2	1	1	1	1
MDM2	Q00987	6	1	0	1	0	0	PIM1	P11309	16	4	1	3	0	1
CDC2H	Q07785	6	2	2	2	0	1	ALDR	P15121	16	9	9	9	9	9
ESR1	P03372	7	5	5	5	4	4	PPARG	P37231	16	2	2	2	1	1
UNG	P13051	7	1	1	1	1	1	BLA1	P52700	16	2	1	0	0	0
VDR	P13053	7	6	6	6	6	6	PDE4D	Q08499	16	1	0	0	0	0
RARG2	P22932	7	5	5	5	5	5	ESR2	Q92731	16	3	3	3	1	1
CFI1	P28012	7	1	1	1	1	1	UROK	P00749	18	5	3	4	2	3
AEQ2	P02592	8	4	4	4	4	4	HS90A	P07900	18	13	3	3	3	3
TETR4	P0ACT4	8	1	1	1	1	1	MYS2	P08799	18	1	1	1	0	0
CDK2	P24941	8	4	3	3	3	2	CHK1	O14757	19	7	5	5	5	5
DCK	P27707	8	1	1	1	0	0	PTN1	P18031	19	2	2	2	2	2
RABP2	P29373	8	4	3	2	2	1	MMP8	P22894	19	3	1	0	0	0
PK3CG	P48736	8	2	2	2	2	2	BGLA	Q08638	19	1	0	0	0	0
PYRD	Q02127	8	2	2	2	2	2	THRB	P00734	20	5	3	2	3	4

		a	b	c	d	e	f			a	b	c	d	e	f
DYR	P00374	9	3	2	2	1	2	FA10	P00742	20	8	8	7	7	6
DYR	P00374	9	1	1	1	1	1	INHA	P0A5Y6	20	4	4	4	4	4
SRC	P00523	9	1	0	0	1	0	AMPM	P0AE18	20	1	0	0	0	1
RETBP	P02753	9	1	1	1	1	1	RENI	P00797	22	5	4	3	4	5
FA11	P03951	9	3	3	3	3	3	ALBU	P02768	23	1	0	0	0	0
GRIK1	P22756	9	2	2	2	0	0	NOS1	P29476	23	1	1	0	1	0
AK1C3	P42330	9	1	1	1	0	0	POLG	P26662	28	1	1	1	0	1
								DPP4	P27487	29	1	0	1	1	0

[a] Receptor Structures/Conformations; [b] Ligands; [c] Multiple Receptor Conformations Docking Results – Cognate Receptor Included; [d] 4D Docking Results – Cognate Receptor Included; [e] Multiple Receptor Conformations Docking Results – Cognate Receptor Excluded; [f] 4D Docking Results – Cognate Receptor Excluded.

Can cluster analysis improve the 4D Docking performance? In order to improve the 4D docking accuracy when a large number of conformers were included in the calculation, a hierarchical cluster analysis was carried out on each ensemble before building the 4D grids. The distance between two conformers was measured as the RMSD among the positions of the non-hydrogen atoms in the binding site side chains. According to the average linkage partition function, two structures were considered part of the same cluster when the distance between them was lower than a given threshold. Two thresholds, 0.5 Å and 1.0 Å, were used to provide a functional partition. When a 0.5 Å threshold was considered, the average number of conformations in each ensemble decreased by 30%. The overall success rate decreased from 77.3 % to 74 %. When a 1.0 Å threshold was considered, the average number of conformations in each ensemble decreased by 62 %. The success rate decreased from 77.3 % to 68.6 %. Neither of the two partitions was able to improve the 4D docking performance (see also Figure 1S).
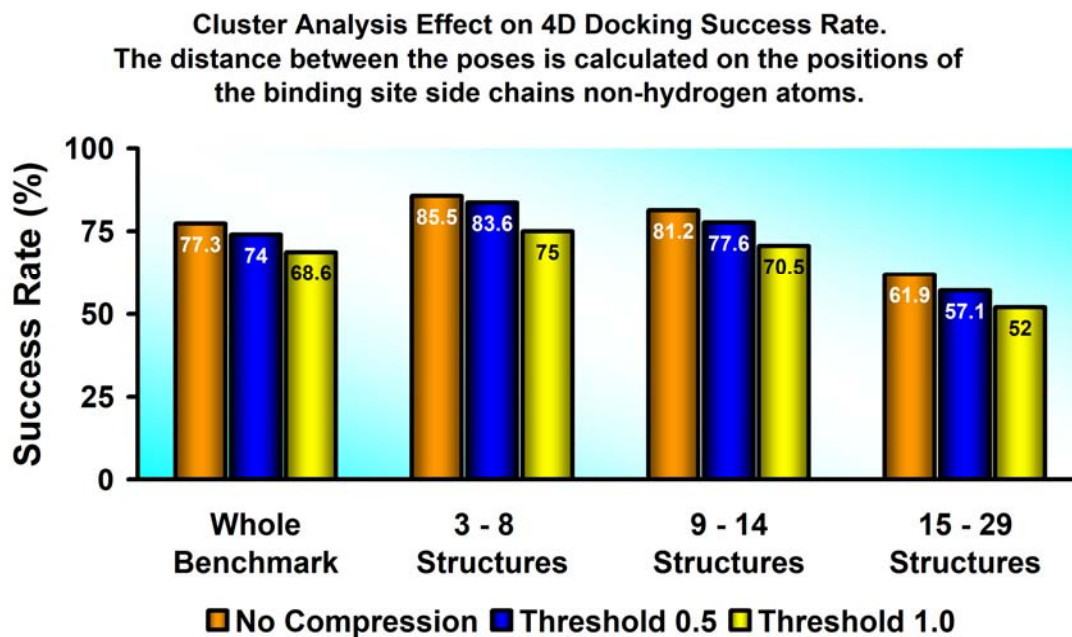
Cluster Analysis Effect on 4D Docking Success Rate.
The distance between the poses is calculated on the positions of the binding site side chains non-hydrogen atoms.

Figure 1S. Effects of geometrical hierarchical cluster analysis performed on the receptor conformers on the 4D docking accuracy. General results for the whole benchmark as well as detailed results according to the initial ensemble size are reported. The 4D docking accuracy rate when no cluster analysis, when a cluster analysis with a grouping distance of 0.5 Å, and a cluster analysis with a grouping distance of 1.0 Å are performed, are reported in orange, blue, and yellow histograms, respectively. Cognate receptors are included in the calculations.