Characterization of the differences in the cyclopiazonic acid binding mode to mammalian and *P. falciparum* Ca^{2+} pumps: a computational study

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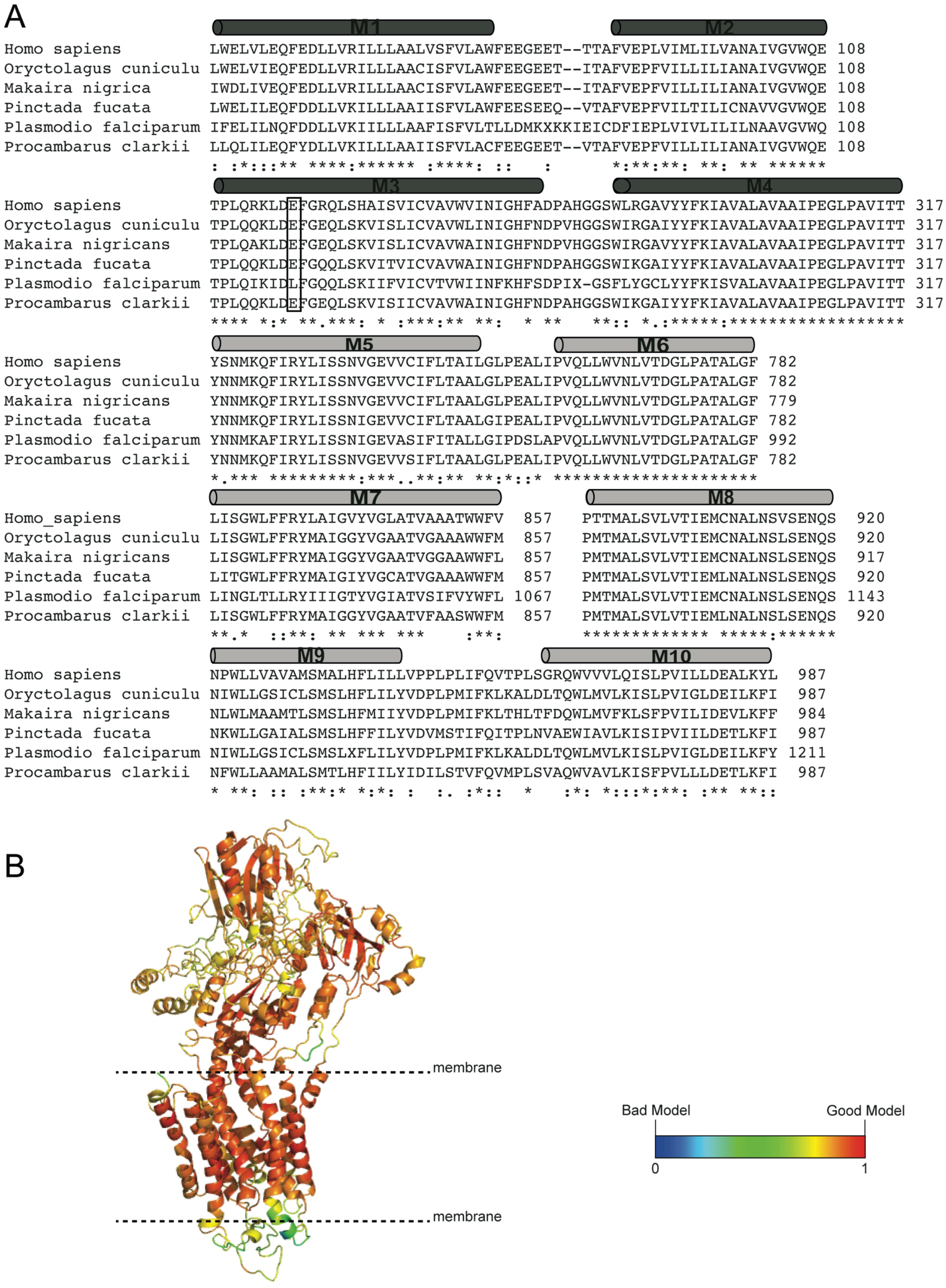
Supporting Information



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Homo sapiens         LWELVLEQFEDLLVRILLLAALVSFVLAWFEEGEET--TTAFVEPLVIMLILVANAIVGVWQE 108
Oryctolagus cuniculu LWELVIEQFEDLLVRILLLAACISFVLAWFEEGEET--ITAFVEPFVILLILIANAIVGVWQE 108
Makaira nigrica      IWDLIVEQFEDLLVRILLLAACISFVLAWFEEGEET--ITAFVEPFVILLILIANAIVGVWQE 108
Pinctada fucata      LWELILEQFDDLLVKILLLAAIISFVLAWFEESEEQ--VTAFVEPFVILTILICNAVVGVWQE 108
Plasmodio falciparum IFELILNQFDDLLVKIILLLAAFISFVLTLLDMKXKKIEICDFIEPLVIVLILILNAAVGVWQ 108
Procambarus clarkii  LLQLILEQFYDLLVKILLLAAIISFVLACFEEGEET--VTAFVEPFVILLILIANAIVGVWQE 108
                     : :*:::** ****:****** :****: ::   :      *:**:**: **: ** ******

Homo sapiens         TPLQRKLDEFGRQLSHAISVICVAVWVINIGHFADPAHGGSWLRGAVYYFKIAVALAVAAIPEGLPAVITT 317
Oryctolagus cuniculu TPLQQKLDEFGEQLSKVISLICVAVWLINIGHFNDPVHGGSWIRGAIYYFKIAVALAVAAIPEGLPAVITT 317
Makaira nigricans    TPLQAKLDEFGEQLSKVISLICVAVWAINIGHFNDPVHGGSWIRGAVYYFKIAVALAVAAIPEGLPAVITT 317
Pinctada fucata      TPLQQKLDEFGQQLSKVITVICVAVWAINIGHFNDPAHGGSWIKGAIYYFKIAVALAVAAIPEGLPAVITT 317
Plasmodio falciparum TPLQIKIDLFGQQLSKIIFVICVTVWIINFKHFSDPIX-GSFLYGCLYYFKISVALAVAAIPEGLPAVITT 317
Procambarus clarkii  TPLQQKLDEFGEQLSKVISIICVAVWAINIGHFNDPAHGGSWIKGAIYYFKIAVALAVAAIPEGLPAVITT 317
                     **** *:* **.***: * :***:** **:  * **   **:: *.:*****:******************

Homo sapiens         YSNMKQFIRYLISSNVGEVVCIFLTAILGLPEALIPVQLLWVNLVTDGLPATALGF 782
Oryctolagus cuniculu YNNMKQFIRYLISSNVGEVVCIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGF 782
Makaira nigricans    YNNMKQFIRYLISSNVGEVVCIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGF 779
Pinctada fucata      YNNMKQFIRYLISSNIGEVVCIFLTAALGIPEALIPVQLLWVNLVTDGLPATALGF 782
Plasmodio falciparum YNNMKAFIRYLISSNIGEVASIFITALLGIPDSLAPVQLLWVNLVTDGLPATALGF 992
Procambarus clarkii  YNNMKQFIRYLISSNVGEVVSIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGF 782
                     *.*** *********:***..**:** **:*::* *********************

Homo_sapiens         LISGWLFFRYLAIGVYVGLATVAAATWWFV  857   PTTMALSVLVTIEMCNALNSVSENQS  920
Oryctolagus cuniculu LISGWLFFRYMAIGGYVGAATVGAAAWWFM  857   PMTMALSVLVTIEMCNALNSLSENQS  920
Makaira nigricans    LISGWLFFRYMAIGGYVGAATVGGAAWWFL  857   PMTMALSVLVTIEMCNALNSLSENQS  917
Pinctada fucata      LITGWLFFRYMAIGIYVGCATVGAAAWWFM  857   PMTMALSVLVTIEMLNALNSLSENQS  920
Plasmodio falciparum LINGLTLLRYIIIGTYVGIATVSIFVYWFL 1067   PMTMALSVLVTIEMCNALNSLSENQS 1143
Procambarus clarkii  LISGWLFFRYMAIGGYVGAATVFAASWWFM  857   PMTMALSVLVTIEMLNALNSLSENQS  920
                     **.*  ::**: ** *** ***    :**:        ************* *****:******

Homo sapiens         NPWLLVAVAMSMALHFLILLVPPLPLIFQVTPLSGRQWVVVLQISLPVILLDEALKYL  987
Oryctolagus cuniculu NIWLLGSICLSMSLHFLILYVDPLPMIFKLKALDLTQWLMVLKISLPVIGLDEILKFI  987
Makaira nigricans    NLWLMAAMTLSMSLHFMIIYVDPLPMIFKLTHLTFDQWLMVFKLSFPVILIDEVLKFF  984
Pinctada fucata      NKWLLGAIALSMSLHFFILYVDVMSTIFQITPLNVAEWIAVLKISIPVIILDETLKFI  987
Plasmodio falciparum NIWLLGSICLSMSLXFLILYVDPLPMIFKLKALDLTQWLMVLKISLPVIGLDEILKFY 1211
Procambarus clarkii  NFWLLAAMALSMTLHFIILYIDILSTVFQVMPLSVAQWVAVLKISFPVLLLDETLKFI  987
                     * **: :: :**:* *:*: :  :. :*::  *   :*: *:::*:**: :** **::
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Figure S1. (**A**) Multi-sequence alignment of the transmembrane (TM) region comprising sequences coming from different species. The boxes at the top of the alignment indicate the TM helices. The rectangular box highlights the glutamic acid conserved in the sequences from all species but *P. falciparum* and indirectly involved in the binding of CPA. (**B**) Three-dimensional arrangement of the TM bundle of helices in the X-ray structure of rabbit SERCA (PDB: 3FGO). Ribbon representation of the PfATP6 model built using the X-ray structure of rabbit SERCA1a (PDB: 3FGO) as template. The structure is colored according to the color scale of QMEANBrane, the quality estimation method for membrane proteins used to evaluate the quality of the PfATP6 model.

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P. falciparum     1 MEEVIKNAHTYDVEDVLKFLDVNKDNGLKNEELDDRRLKYGLNELEVEKK   50
                    ||.    ||:...|:.|.:..|::..||..:::.....|||.|||..|:.
Rabbit            1 MEA----AHSKSTEECLAYFGVSETTGLTPDQVKRHLEKYGHNELPAEEG   46

P. falciparum    51 KSIFELILNQFDDLLVKILLLAAFISFVLTLLDMKHKKIEICDFIEPLVI  100
                    ||::||::.||:||||:||||||.|||||...:...:.|..  |:||.||
Rabbit           47 KSLWELVIEQFEDLLVRILLLAACISFVLAWFEEGEETITA--FVEPFVI   94

P. falciparum   101 VLILILNAAVGVWQECNAEKSLEALKELQPTKAKVLRDGKWEI--IDSKY  148
                    :||||.||.||||||.|||.::|||||.:|...||.|..:..:  |.::.
Rabbit           95 LLILIANAIVGVWQERNAENAIEALKEYEPEMGKVYRADRKSVQRIKARD  144

P. falciparum   149 LYVGDIIELSVGNKTPADARIIKIYSTSLKVEQSMLTGESCSVDKYAEKM  198
                    :..|||:|::||:|.|||.||:.|.||:|:|:||:|||||.||.|:.|.:
Rabbit          145 IVPGDIVEVAVGDKVPADIRILSIKSTTLRVDQSILTGESVSVIKHTEPV  194

P. falciparum   199 EDSYKNCEIQLKKNILFSSTAIVCGRCIAVVINIGMKTEIGHIQHAVIES  248
                    .|  .....|.|||:|||.|.|..|:.:.:|...|:.||||.|:..:  :
Rabbit          195 PD--PRAVNQDKKNMLFSGTNIAAGKALGIVATTGVSTEIGKIRDQM--A  240

P. falciparum   249 NSEDTQTPLQIKIDLFGQQLSKIIFVICVTVWIINFKHFSDPIHG-SFLY  297
                    .:|..:||||.|:|.||:||||:|.:|||.||:||..||:||:|| |::.
Rabbit          241 ATEQDKTPLQQKLDEFGEQLSKVISLICVAVWLINIGHFNDPVHGGSWIR  290

P. falciparum   298 GCLYYFKISVALAVAAIPEGLPAVITTCLALGTRRMVKKNAIVRKLQSVE  347
                    |.:|||||:|||||||||||||||||||||||||||.|||||||.|.|||
Rabbit          291 GAIYYFKIAVALAVAAIPEGLPAVITTCLALGTRRMAKKNAIVRSLPSVE  340

P. falciparum   348 TLGCTTVICSDKTGTLTTNQMTTTVFHLFRESD----SLTEYQLCQKGDT  397
                    |||||:|||||||||||||||:.....:..:.|    ||.|:.:  .|.|
Rabbit          341 TLGCTSVICSDKTGTLTTNQMSVCKMFIIDKVDGDFCSLNEFSI--TGST  380

P. falciparum   398 YYFYESSNLTNDIYAGESSFFNKLKDEGNVEALTDDGEEGSIDEADPYSD  447
                    |.  |....||     .|. |: | : ..
Rabbit          381 Y-APEGEVLKNDKPI-RSGQFDGLVELAT---------------------  395

P. falciparum   448 YFSSDSKKMKNDLNNNNNNNNNSSRSGAKRNIPLKEMKSNENTIISRGSK  497

Rabbit          396 --------------------------------------------------  415

P. falciparum   498 ILEDKINKYCYSEYDYNFYMCLVNCNEANIFCNDNSQIVKKFGDSTELAL  547
                                       :|.: ||::::..|:...:.:|.|::||.||
Rabbit          416 -------------------ICAL-CNDSSLDFNETKGVYEKVGEATETAL  445

P. falciparum   548 LHFVHNFDILPTFSKNNKMPAEYEKNTTPVQSSNKKDKSPRGINKFFSSK  597
                    ||.|.::::: |  :|
Rabbit          446 TTLVEKMNVFNTEVRNLSKV------------------------------  453

P. falciparum   598 NDNSHITSTLNENDKNLKNANHSNYTTAQATTNGYEAIGENTFEHGTSFE  647

Rabbit          454 --------------------------------------------------  469

P. falciparum   648 NCFHSKLGNKINTTSTHNNNNNNNNNSNSVPSECISSWRNECKQIKIIEF  697
                                                    .|.|..|...|:...:||
Rabbit          470 ----------------------------ERANACNSVIRQLMKKEFTLEF  491

P. falciparum   698 TRERKLMSVIVENKKKEII-----LYCKGAPENIIKNCKYYLTKNDIRPL  742
                    :|:||.|||.....|....     ::.|||||.:|..|.|........|:
Rabbit          492 SRDRKSMSVYCSPAKSSRAAVGNKMFVKGAPEGVIDRCNYVRVGTTRVPM  541

P. falciparum   743 NETLKNEIHNKIQNMG--KRALRTLSFAYKKLSSK--DLNIKNTDDYYKL  788
                    ...:|.:|.:.|:..|  :..||.|:.|.:....|  ::.:.::..:.:.
Rabbit          542 TGPVKEKILSVIKEWGTGRDTLRCLALATRDTPPKREEMVLDDSSRFMEY  591

P. falciparum   789 EQDLIYLGGLGIIDPPRKYVGRAIRLCHMAGIRVFMITGDNINTARAIAK  838
                    |.||.::|.:|::|||||.|..:|:||..|||||.||||||..||.||.:
Rabbit          592 ETDLTFVGVVGMLDPPRKEVMGSIQLCRDAGIRVIMITGDNKGTAIAICR  641

P. falciparum   839 EINILNKNEGDDEKDNYTNNKNTQICCYNGREFEDFSLEKQKHILKNTPR  888
                    .|.|..:||...::            .|.||||:|..|.:|:...:..
Rabbit          642 RIGIFGENEEVADR------------AYTGREFDDLPLAEQREACRRA--  677

P. falciparum   889 IVFCRTEPKHKKQIVKVLKDLGETVAMTGDGVNDAPALKSADIGIAMGIN  938
                    ..|.|.||.||.:||:.|:...|..||||||||||||||.|:|||||| :
Rabbit          678 CCFARVEPSHKSKIVEYLQSYDEITAMTGDGVNDAPALKKAEIGIAMG-S  726

P. falciparum   939 GTEVAKEASDIVLADDNFNTIVEAIKEGRCIYNNMKAFIRYLISSNIGEV  988
                    ||.|||.||::|||||||:|||.|::|||.||||||.|||||||||:|||
Rabbit          727 GTAVAKTASEMVLADDNFSTIVAAVEEGRAIYNNMKQFIRYLISSNVGEV  776

P. falciparum   989 ASIFITALLGIPDSLAPVQLLWVNLVTDGLPATALGFNPPEHDVMKCKPR 1038
                    ..||:||.||:|::|.||||||||||||||||||||||||:.|:|...||
Rabbit          777 VCIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMDRPPR  826

P. falciparum  1039 HKNDNLINGLTLLRYIIIGTYVGIATVSIFVYWFLFYPDSDMHTLINFYQ 1088
                    ...:.||:|....||:.||.|||.|||....:||::..|...   :.::|
Rabbit          827 SPKEPLISGWLFFRYMAIGGYVGAATVGAAAWWFMYAEDGPG---VTYHQ  873

P. falciparum  1089 LSHYNQCKAWNNFRVNKVYDMSEDHCSYFSAGKIKASTLSLSVLVLIEMF 1138
                    |:|:.||..      :..:....| |..|.|.  :..|::|||||.|||.
Rabbit          874 LTHFMQCTE------DHPHFEGLD-CEIFEAP--EPMTMALSVLVTIEMC  914

P. falciparum  1139 NALNALSEYNSLFEIPPWRNMYLVLATIGSLLLHVLILYIPPLARIFGVV 1188
                    ||||:|||..||..:|||.|::|:.:...|:.||.||||:.||..||.:.
Rabbit          915 NALNSLSENQSLMRMPPWVNIWLLGSICLSMSLHFLILYVDPLPMIFKLK  964

P. falciparum  1189 PLSAYDWFLVFLWSFPVIILDEIIKFYAKRKLKEEQRTKKIKID 1228
                    .|....|.:|...|.|||.||||:||.|:..|::.:..::
Rabbit          965 ALDLTQWLMVLKISLPVIGLDEILKFIARNYLEDPEDERR---K 1001
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Figure S2. Pairwise sequence alignment of the target (PfATP6) and template (rabbit SERCA1a) proteins.

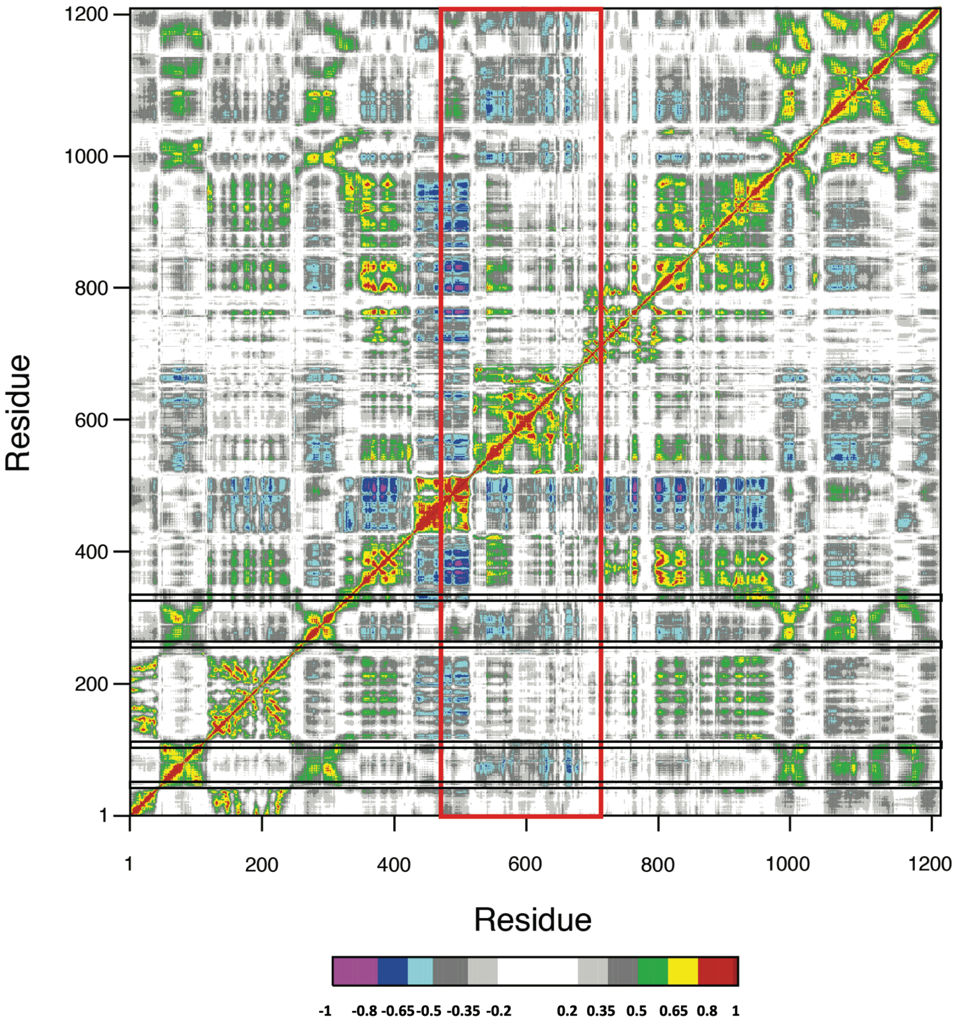

Figure S3. Cross correlation matrix calculated for the Cα atoms of PfATP6. The residues of the CPA binding site are highlighted by black rectangles and the residues belonging to the LCR regions by a red rectangle. White-colored matrix cells indicate uncorrelated residues.

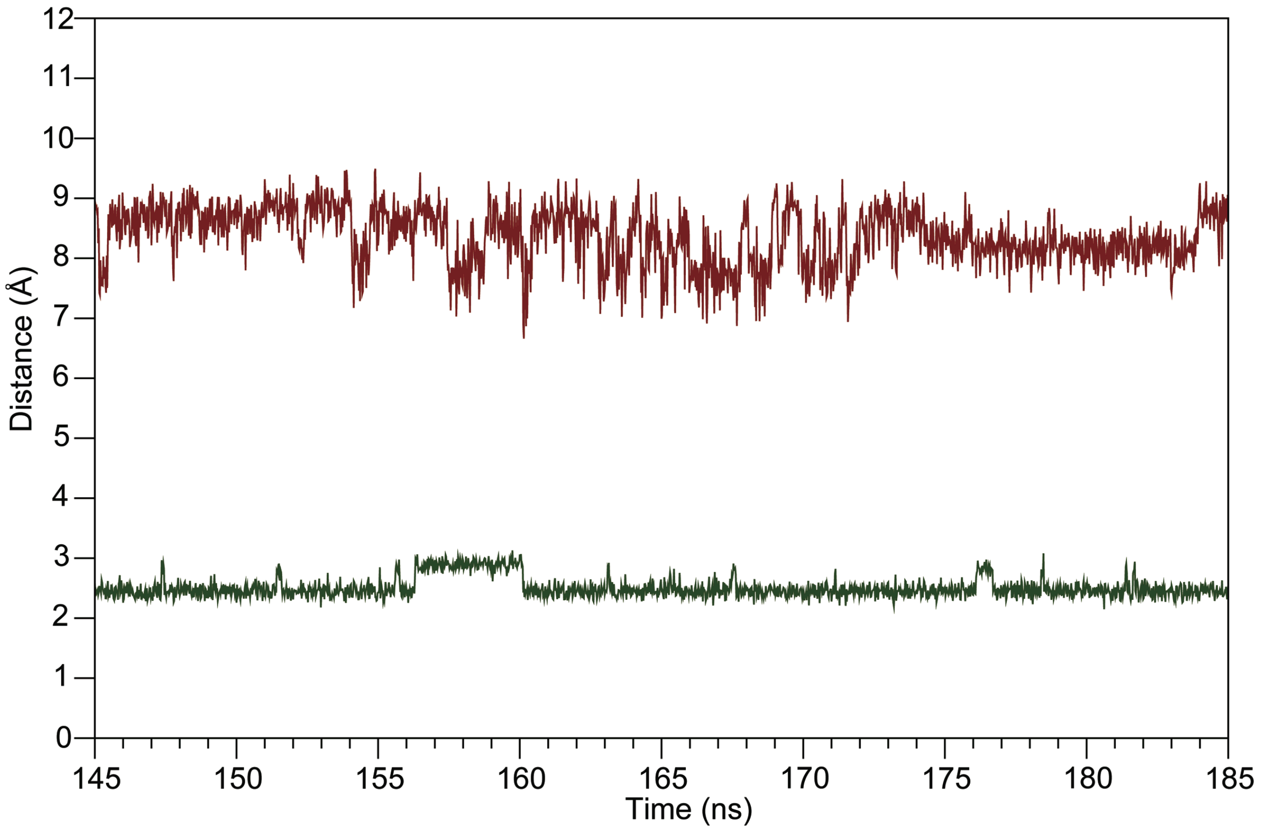

Figure S4. Evolution during the simulation time of the distance between the centers of masses of the carboxylic groups of $_{\mathrm{m}}$Glu255 and $_{\mathrm{m}}$Asp254 in SERCA1a (red line) and between the centers of masses of the carboxylic group of $_{\mathrm{p}}$Asp262 and the δ1 and δ2 carbons of $_{\mathrm{p}}$Leu263 of PfATP6 (green line).