Supporting Material for:

Capsaicin Interaction with TRPV1 Channels in a Lipid Bilayer: Molecular Dynamics Simulation

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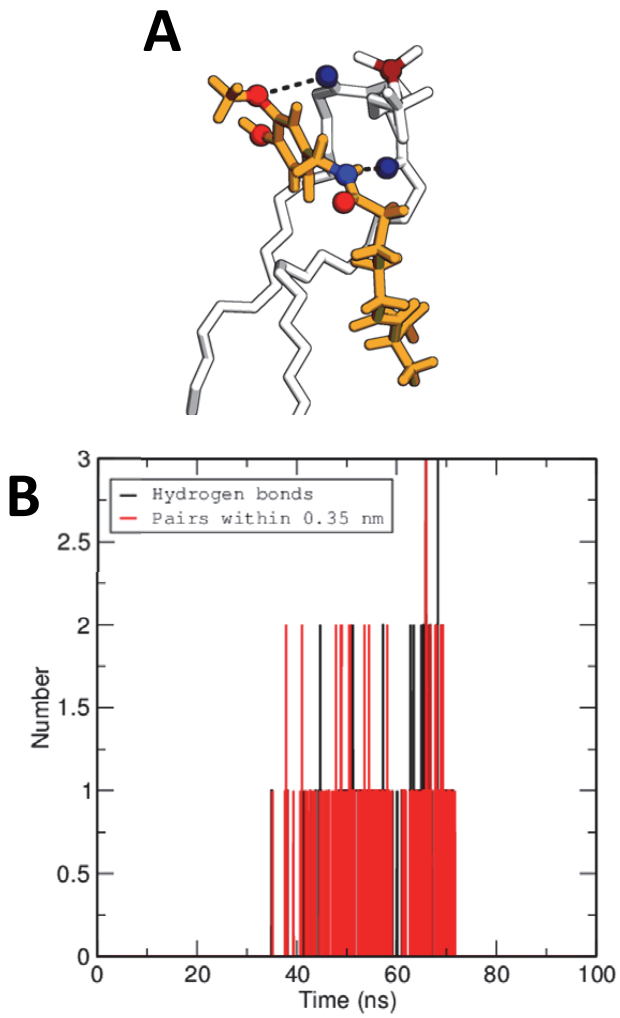

FIGURE S1 **POPC and Capsaicin hydrogen bonding interaction.** *(A)* An example of a long-lived hydrogen bonding interaction between a carbonyl group of a POPC molecule (in white) and the B region of capsaicin (in orange). *(B)* Number of H-bonds vs. time between capsaicin and the selected POPC molecule. This interaction is maintained for more than 30 ns of the simulation.

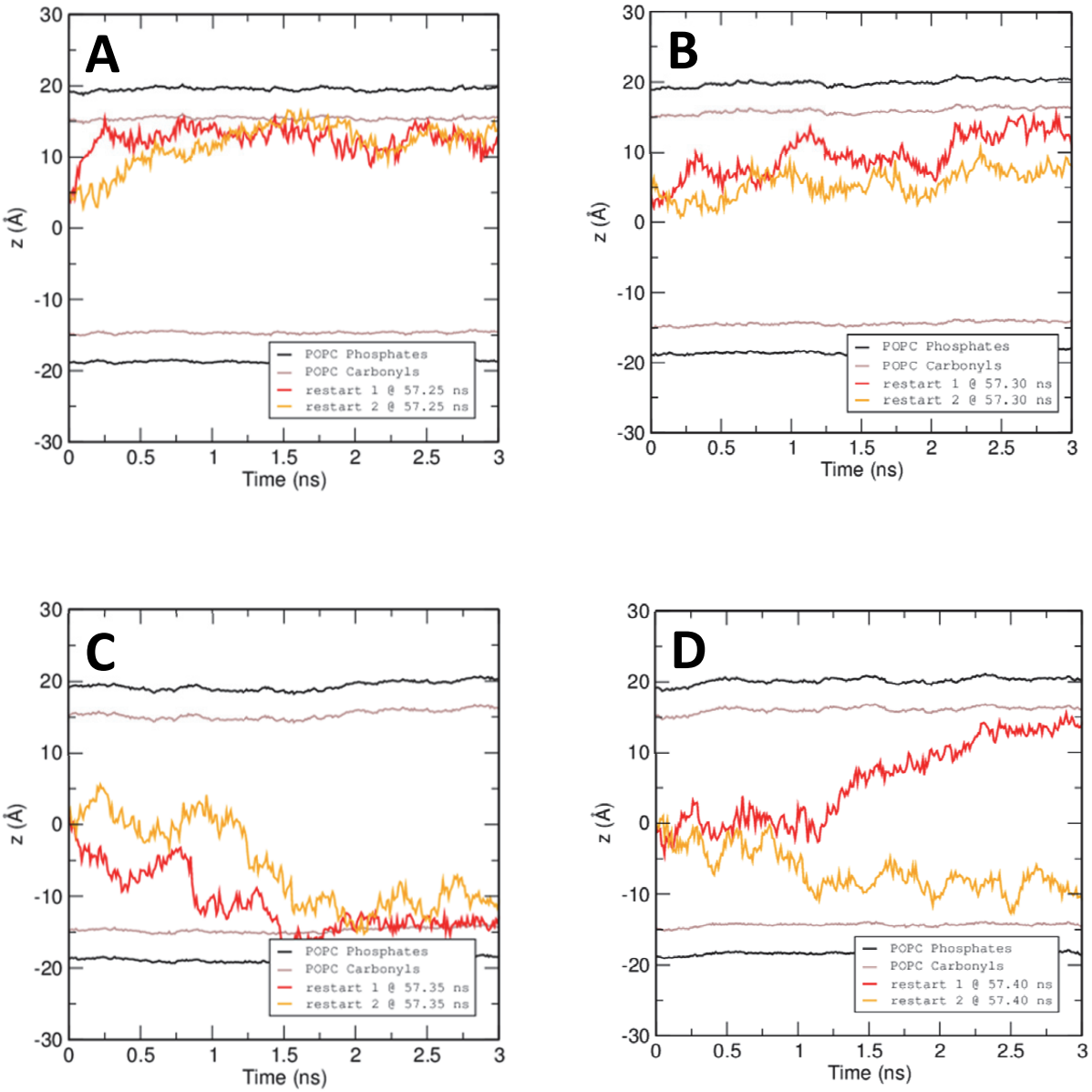

FIGURE S2 **Multiple simulations initiated at selected points along the original capsaicin flip-flop trajectory.** *(A)* Shows two repeats (red and orange lines) with different random velocity seeds using a starting position at 57.25 ns, *(B)* at 57.30 ns, *(C)* at 57.35 ns, and *(D)* at 57.40 ns along the original trajectory which yielded a flip-flop event. Red or orange lines represent the center of mass of capsaicin during different repeats. Black lines represent the phosphate head groups of POPC. Brown lines represent the carbonyls of POPC.

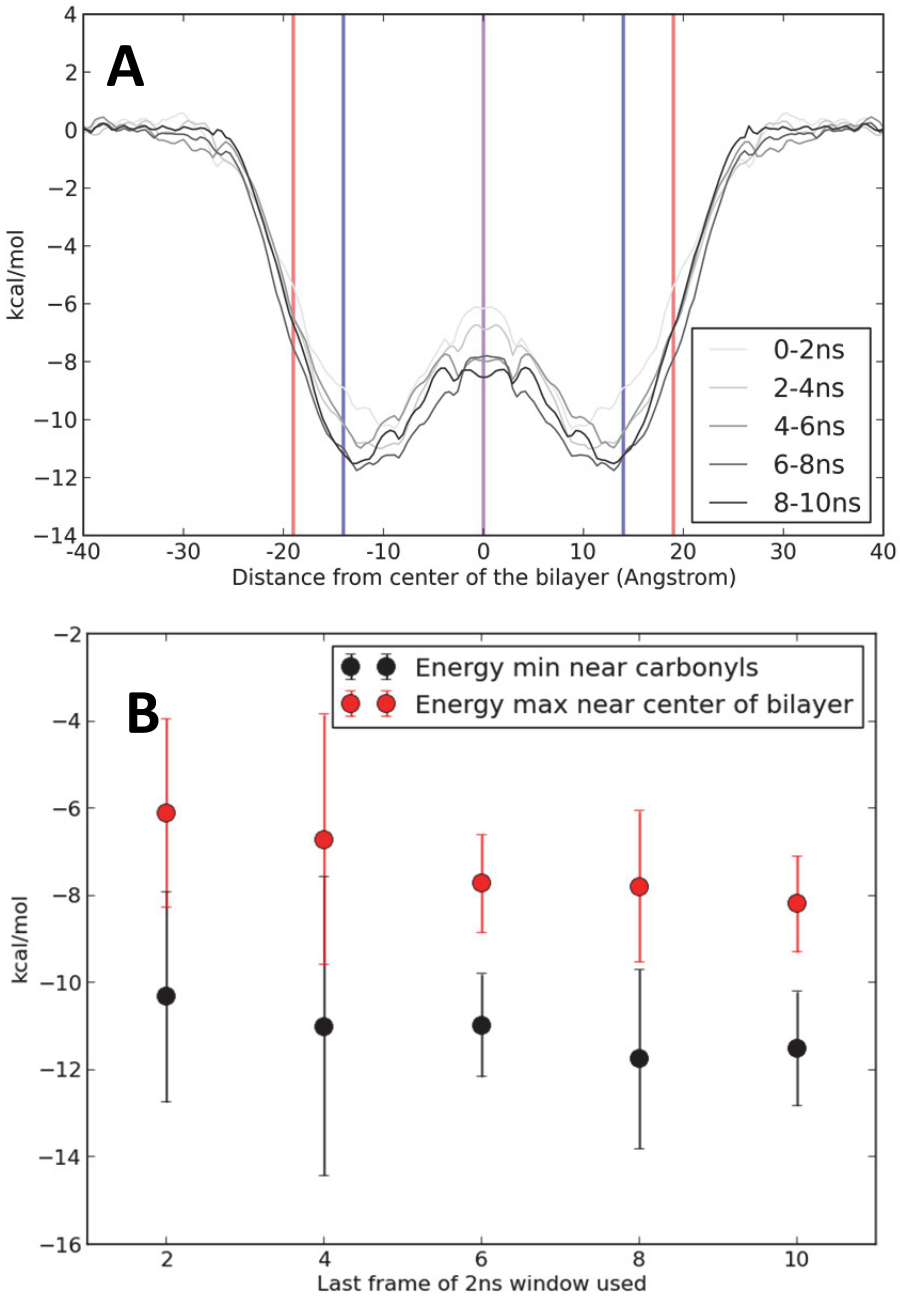

FIGURE S3 **PMF Convergence.** *(A)* PMF profiles as calculated from consecutive 2 ns segments of the full 10 ns simulations of 1 Å windows across the bilayer. *(B)* The values of the energy minima near the carbonyls (z = ±12 Å) and the energy maxima near the center of the bilayer (z = 0 Å) were calculated for the consecutive PMFs in *A* to provide a measure of convergence of the free energy profile.

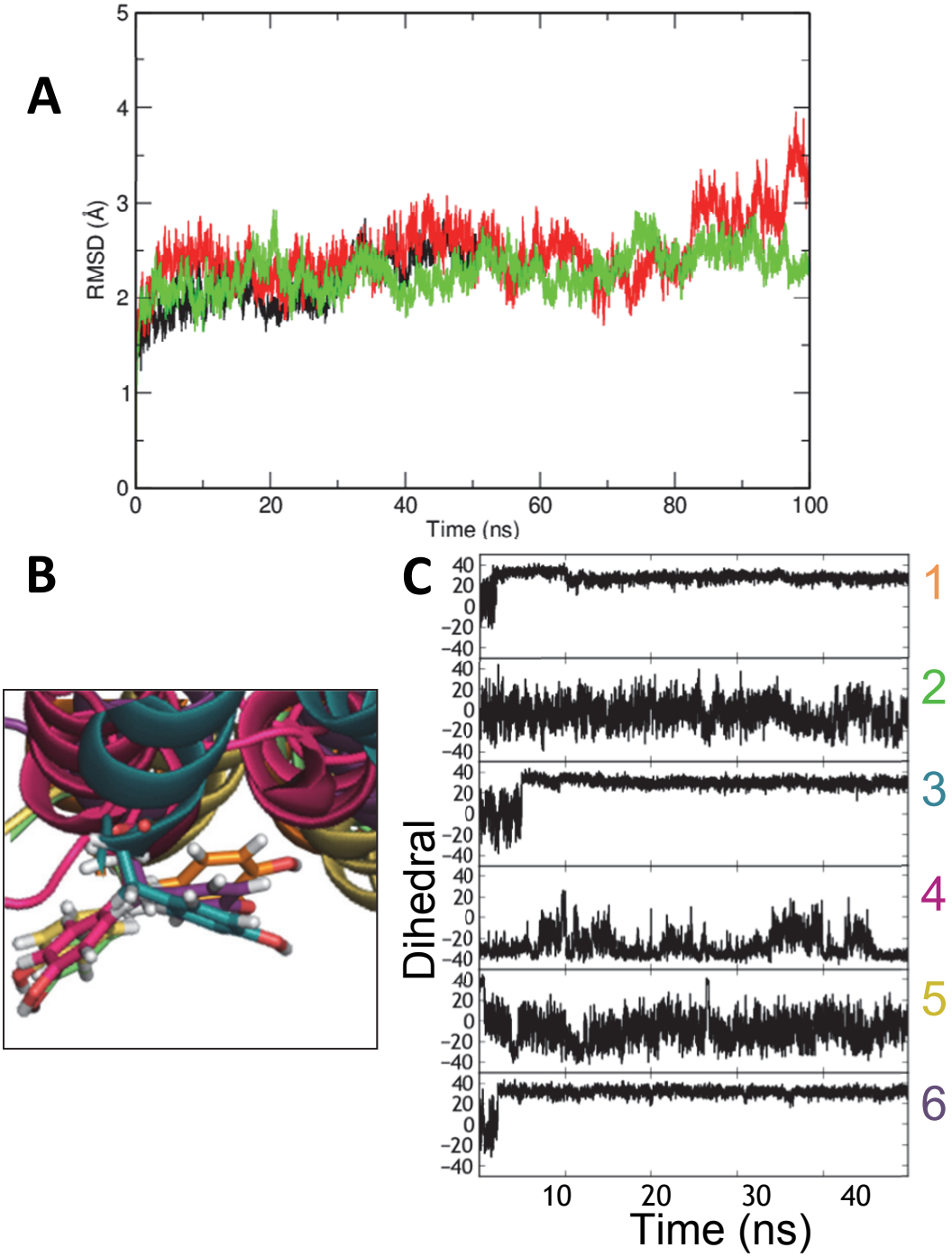

FIGURE S4 **Analysis of stability of the TRPV1 S1-S4 in model membrane.** *(A)* The backbone RMSD from the initial structure of the S1-S4 domain of TRPV1 over the course of three repeat 100 ns simulations. *(B)* The flip from an outward to an inward conformation of the sidechain of tyrosine 511. *(C)* Changes in the X_1 dihedral angle of Tyr511 over time of six separate simulations (colored accordingly) of the S1-S4 of the apo EM structure in a POPC bilayer.

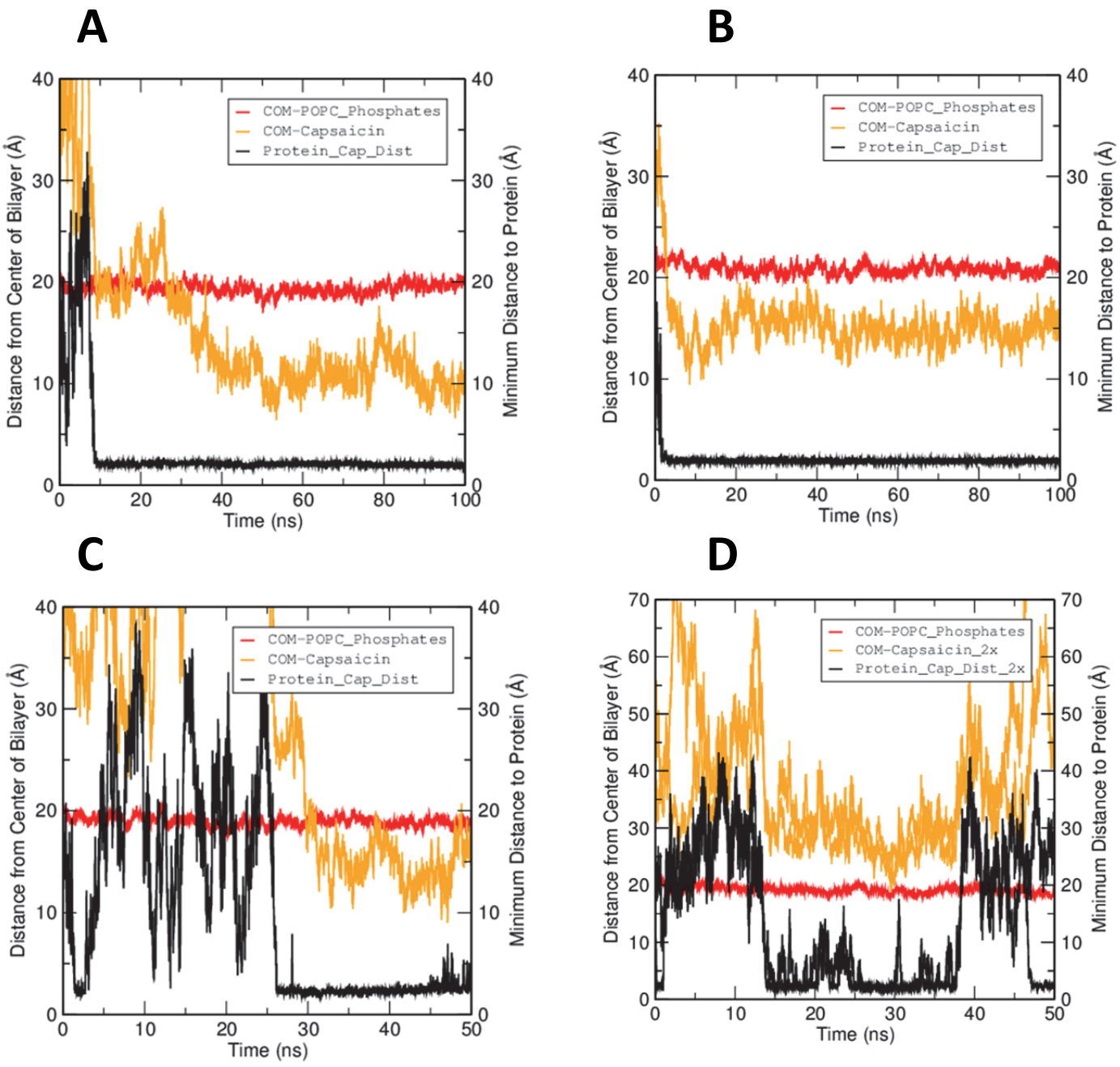

FIGURE S5 **Capsaicin interaction with TRPV1 S1-S4 compared to its membrane penetration.** Plots of the minimum distance of interacting capsaicin molecules to the TRPV1 S1-S4 domain over the course of four simulations (black), overlayed with the bilayer penetration as shown by the center of mass of capsaicin (orange) relative to that of the phosphates of the intracellular leaflet (red). This is shown for two capsaicin molecules that interact with the S1 helix *(A)* and *(B)*, and for three capsaicin molecules that interact with the S2-S3 loop *(C)* and *(D)*. *(D)* is an interaction between a two-capsaicin aggregate and the TRPV1 S1-S4. Notice how in A-C the capsaicin interacts with the protein before and during bilayer penetration.

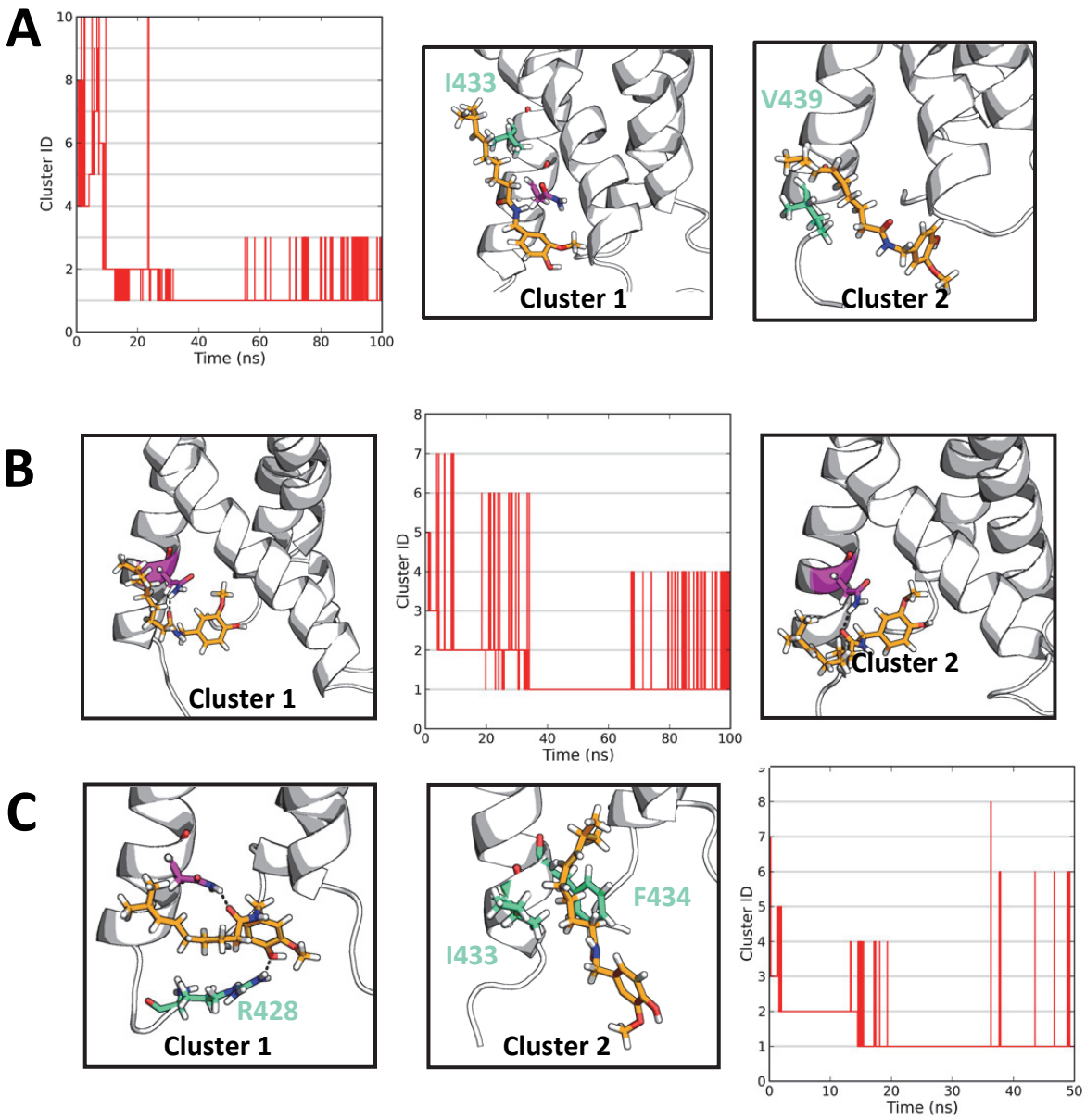

FIGURE S6 **Results of cluster analysis for 'encounter complex' simulations in which interactions are seen between capsaicin and the S1 helix.** *(A)* Cluster analysis of one 100 ns simulation results in a final cluster that involves N437 (magenta), but also I433 (teal). In the second-most dominant cluster the interaction with N437 is not seen, and V439 (teal) instead is seen to interact with capsaicin, perhaps on it's way to a more stable pose. *(B)* This 100 ns simulation is also the one shown in Fig. *7*. Cluster analysis shows a dominant cluster in which capsaicin interacts with N437 (magenta). The second-most dominant cluster also shares this interaction, but the C group acyl chain tail is in a different orientation. *(C)* In this 50 ns simulation, an interaction between capsaicin and the S1 helix is also seen, and the N437 (magenta) interaction is once again observed in the most dominant cluster. However, the R428 (teal) interaction is also seen. This interaction may be an artifact of the S1-S4 helices being truncated from the rest of the full length protein, although it is not seen in the other two simulations.

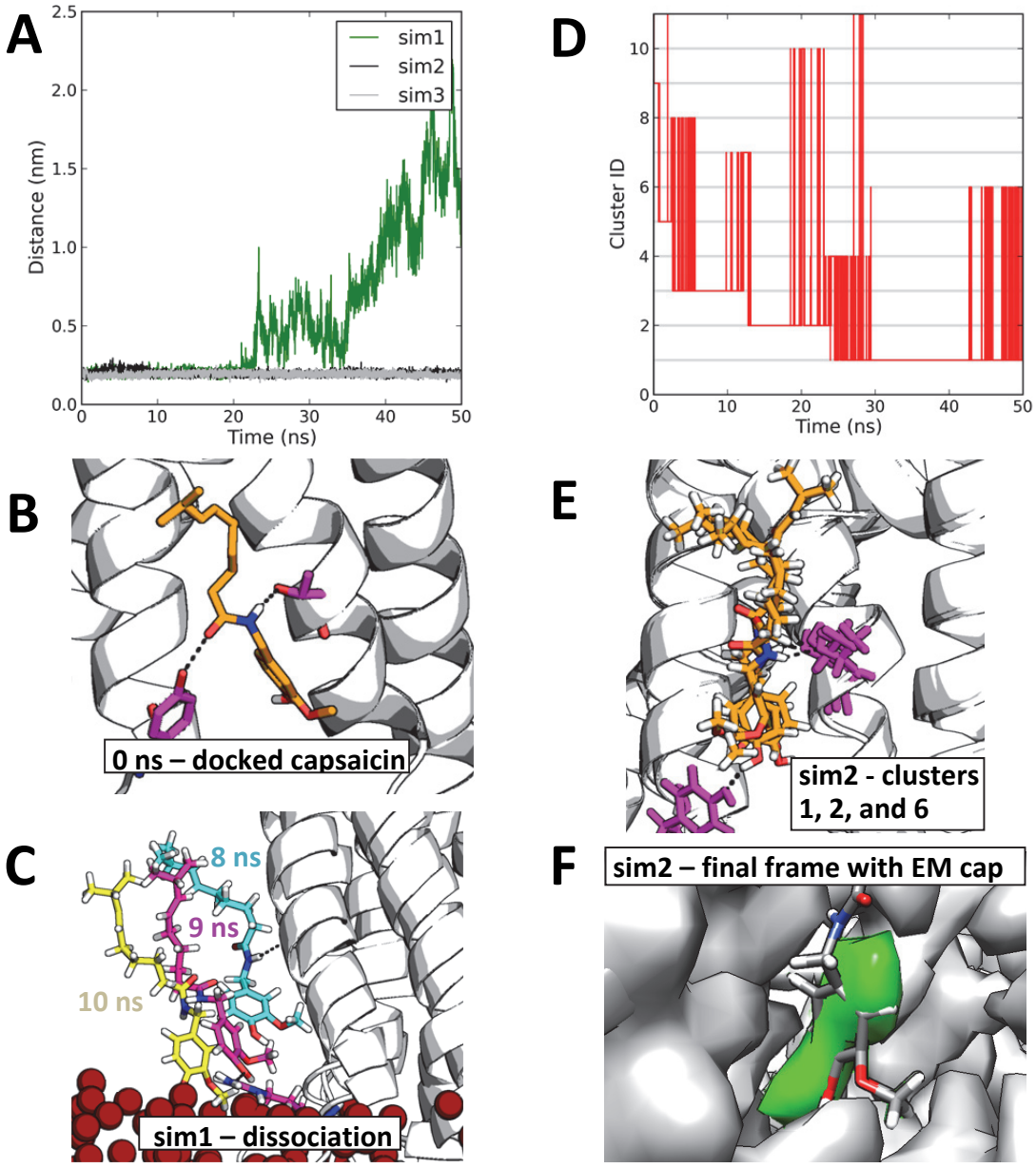

FIGURE S7 **Results of 50ns simulation of capsaicin docked to TRPV1.** *(A)* In two out of three simulations capsaicin continued to equilibrate within the docked position between the S3 and S4. *(B)* The docked pose of capsaicin was the top-ranked pose found using the Autodock Vina program and the full-length TRPV1 (PDB ID: 3J5R). T550 and Y511 are shown in magenta. *(C)* In the simulation in which capsaicin dissociated from the S1-S4 helices it initially had formed a hydrogen bond with T550 (cyan) and then began to dissociate, interacting with an arginine at the intracellular side of the S4 (magenta) and then finally with only the POPC molecules (yellow) in a position seen in the capsaicin-bilayer only simulations. *(D)* Cluster analysis of one of the simulations in which capsaicin remained in the docked pose shows small shifts toward a final cluster. *(E)* Three of the dominant clusters from D (1, 2, and 6) are shown. A change from the initial docked pose is that now Y511 forms a hydrogen bonding interaction with the A group aromatic region instead of the B group. *(F)* An overlay of the final frame of this simulation shows that the A group of capsaicin overlaps with density suspected to correspond to capsaicin in the sharpened EM density (deep green) of the capsaicin bound structure (temperature factor -200 Å, filtered to 4.2 Å, shown at sigma level 8).

Supporting Material - Parameter (*.itp) file for capsaicin

```
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; name  nrexcl
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[ constraints ]
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[ pairs ]
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    17      5  1       ;    C8-   H13
     3      7  1       ;    C2-   H14
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      41      49  1       ;    H2-   H24

[ angles ]
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     4     6     8   1     120.000    527.1840     ;    C3-    C4-    C5
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     7     6     8   1     120.000    292.8800     ;   H14-    C4-    C5
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    18    17    20   1     109.500    292.8800     ;   H10-    C8-    N1
    19    17    20   1     109.500    292.8800     ;   H11-    C8-    N1
    17    20    22   1     121.900    418.4000     ;    C8-    N1-    C9
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17    20    21    1     118.400    317.9840    ;    C8-    N1-   H21
21    20    22    1     119.800    292.8800    ;   H21-    N1-    C9
20    22    23    1     116.600    585.7600    ;    N1-    C9-   C10
20    22    26    1     122.900    669.4400    ;    N1-    C9-    O3
26    22    23    1     120.400    669.4400    ;    O3-    C9-   C10
22    23    27    1     111.100    527.1840    ;    C9-   C10-   C11
22    23    24    1     109.500    292.8800    ;    C9-   C10-    H8
22    23    25    1     109.500    292.8800    ;    C9-   C10-    H9
24    23    27    1     110.700    313.8000    ;    H8-   C10-   C11
25    23    27    1     110.700    313.8000    ;    H9-   C10-   C11
23    27    30    1     112.700    488.2730    ;   C10-   C11-   C12
23    27    28    1     110.700    313.8000    ;   C10-   C11-    H7
23    27    29    1     110.700    313.8000    ;   C10-   C11-   H16
28    27    30    1     110.700    313.8000    ;    H7-   C11-   C12
29    27    30    1     110.700    313.8000    ;   H16-   C11-   C12
27    30    33    1     112.700    488.2730    ;   C11-   C12-   C13
27    30    31    1     110.700    313.8000    ;   C11-   C12-    H5
27    30    32    1     110.700    313.8000    ;   C11-   C12-    H6
31    30    33    1     110.700    313.8000    ;    H5-   C12-   C13
32    30    33    1     110.700    313.8000    ;    H6-   C12-   C13
30    33    36    1     111.100    527.1840    ;   C12-   C13-   C14
30    33    34    1     110.700    313.8000    ;   C12-   C13-    H4
30    33    35    1     110.700    313.8000    ;   C12-   C13-   H15
34    33    36    1     109.500    292.8800    ;    H4-   C13-   C14
35    33    36    1     109.500    292.8800    ;   H15-   C13-   C14
33    36    38    1     124.000    585.7600    ;   C13-   C14-   C15
33    36    37    1     117.000    292.8800    ;   filled
37    36    38    1     120.000    292.8800    ;    H3-   C14-   C15
36    38    40    1     124.000    585.7600    ;   C14-   C15-   C16
36    38    39    1     120.000    292.8800    ;   C14-   C15-    H1
39    38    40    1     117.000    292.8800    ;   filled
38    40    42    1     111.100    527.1840    ;   C15-   C16-   C17
38    40    46    1     111.100    527.1840    ;   C15-   C16-   C18
38    40    41    1     109.500    292.8800    ;   C15-   C16-    H2
46    40    42    1     112.700    488.2730    ;   C18-   C16-   C17
41    40    42    1     110.700    313.8000    ;    H2-   C16-   C17
40    42    43    1     110.700    313.8000    ;   C16-   C17-   H25
40    42    44    1     110.700    313.8000    ;   C16-   C17-   H26
40    42    45    1     110.700    313.8000    ;   C16-   C17-   H27
41    40    46    1     110.700    313.8000    ;    H2-   C16-   C18
40    46    47    1     110.700    313.8000    ;   C16-   C18-   H22
40    46    48    1     110.700    313.8000    ;   C16-   C18-   H23
40    46    49    1     110.700    313.8000    ;   C16-   C18-   H24
35    33    34    1     107.800    276.1440    ;   H15-   C13-    H4
32    30    31    1     107.800    276.1440    ;    H6-   C12-    H5
29    27    28    1     107.800    276.1440    ;   H16-   C11-    H7
25    23    24    1     107.800    276.1440    ;    H9-   C10-    H8
19    17    18    1     107.800    276.1440    ;   H11-    C8-   H10
13    11    12    1     107.800    276.1440    ;   H18-    C7-   H17
14    11    12    1     107.800    276.1440    ;   H19-    C7-   H17
14    11    13    1     107.800    276.1440    ;   H19-    C7-   H18
48    46    47    1     107.800    276.1440    ;   H23-   C18-   H22
49    46    47    1     107.800    276.1440    ;   H24-   C18-   H22
49    46    48    1     107.800    276.1440    ;   H24-   C18-   H23
44    42    43    1     107.800    276.1440    ;   H26-   C17-   H25
45    42    43    1     107.800    276.1440    ;   H27-   C17-   H25
45    42    44    1     107.800    276.1440    ;   H27-   C17-   H26
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[ dihedrals ]
;  ai    aj    ak    al funct            c0            c1            c2            c3            c4            c5
     9     1     3     4   3  30.33400   0.00000 -30.33400   0.00000   0.00000   0.00000 ; dih      C6-    C1-    C2-     C3
     3     1     9     8   3  30.33400   0.00000 -30.33400   0.00000   0.00000   0.00000 ; dih      C2-    C1-    C6-     C5
     1     3     4     6   3  30.33400   0.00000 -30.33400   0.00000   0.00000   0.00000 ; dih      C1-    C2-    C3-     C4
     3     4     6     8   3  30.33400   0.00000 -30.33400   0.00000   0.00000   0.00000 ; dih      C2-    C3-    C4-     C5
     4     6     8     9   3  30.33400   0.00000 -30.33400   0.00000   0.00000   0.00000 ; dih      C3-    C4-    C5-     C6
     6     8     9     1   3  30.33400   0.00000 -30.33400   0.00000   0.00000   0.00000 ; dih      C4-    C5-    C6-     C1
     1     9    10    11   3  12.55200   0.00000 -12.55200   0.00000   0.00000   0.00000 ; dih      C1-    C6-    O1-     C7
     9    10    11    12   3   1.58992   4.76976   0.00000  -6.35968   0.00000   0.00000 ; dih      C6-    O1-    C7-    H17
     6     8    15    16   3   7.03749   0.00000  -7.03749   0.00000   0.00000   0.00000 ; dih      C4-    C5-    O2-    H20
     1     3    17    20   3   0.00000   0.00000   0.00000   0.00000   0.00000   0.00000 ; dih      C1-    C2-    C8-     N1
     3    17    20    22   3  -4.70700   2.92044   1.78656   0.00000   0.00000   0.00000 ; dih      C2-    C8-    N1-     C9
    17    20    22    23   3  30.28798  -4.81160 -25.47638   0.00000   0.00000   0.00000 ; dih      C8-    N1-    C9-    C10
    20    22    23    27   3   4.83252  -7.65254   1.68196   1.13805   0.00000   0.00000 ; dih      N1-    C9-   C10-    C11
    22    23    27    30   3  -4.96013   6.28646   1.30959  -2.63592   0.00000   0.00000 ; dih      C9-   C10-   C11-    C12
    23    27    30    33   3   2.92880  -1.46440   0.20920  -1.67360   0.00000   0.00000 ; dih     C10-   C11-   C12-    C13
    27    30    33    36   3   2.92880  -1.46440   0.20920  -1.67360   0.00000   0.00000 ; dih     C11-   C12-   C13-    C14
    30    33    36    38   3   0.52719  -6.39734  -1.69452   7.56467   0.00000   0.00000 ; dih     C12-   C13-   C14-    C15
    33    36    38    40   3  58.57600   0.00000 -58.57600   0.00000   0.00000   0.00000 ; dih     C13-   C14-   C15-    C16
    36    38    40    42   3   0.52719  -6.39734  -1.69452   7.56467   0.00000   0.00000 ; dih     C14-   C15-   C16-    C17
    38    40    42    43   3   0.76567   2.29701   0.00000  -3.06269   0.00000   0.00000 ; dih     C15-   C16-   C17-    H25
    38    40    46    47   3   0.76567   2.29701   0.00000  -3.06269   0.00000   0.00000 ; dih     C15-   C16-   C18-    H22

[ dihedrals ]
; ai  aj   ak  al  funct    phi0          cp      mult
     1     3     9     2   1     180.000       4.602   2        ; imp      C1-    C2-    C6-   H12
     3     1     4    17   1     180.000       4.602   2        ; imp      C2-    C1-    C3-    C8
     4     3     6     5   1     180.000       4.602   2        ; imp      C3-    C2-    C4-   H13
     6     4     8     7   1     180.000       4.602   2        ; imp      C4-    C3-    C5-   H14
     8     6     9    15   1     180.000       4.602   2        ; imp      C5-    C4-    C6-    O2
     9     1     8    10   1     180.000       4.602   2        ; imp      C6-    C1-    C5-    O1
    22    20    23    26   1     180.000      43.932   2        ; imp      C9-    N1-   C10-    O3
    36    33    38    37   1     180.000      62.760   2        ; imp     C14-   C13-   C15-    H3
    38    36    40    39   1     180.000      62.760   2        ; imp     C15-   C14-   C16-    H1
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