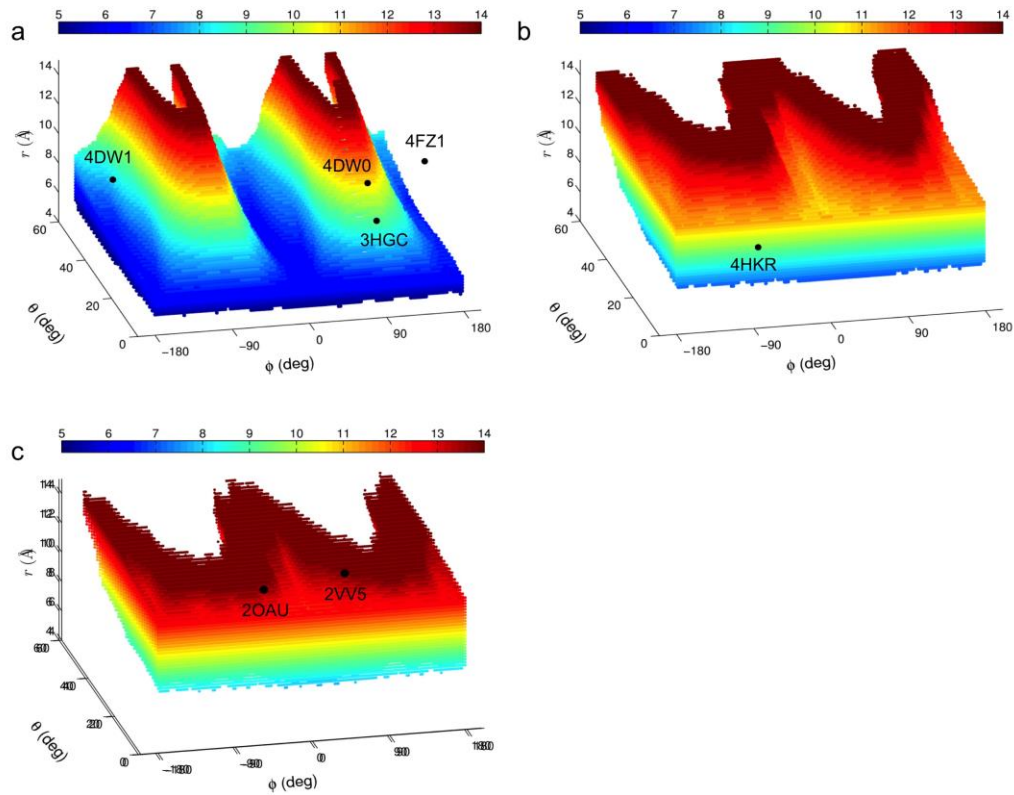
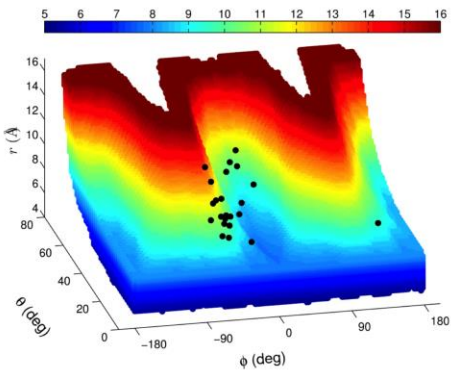


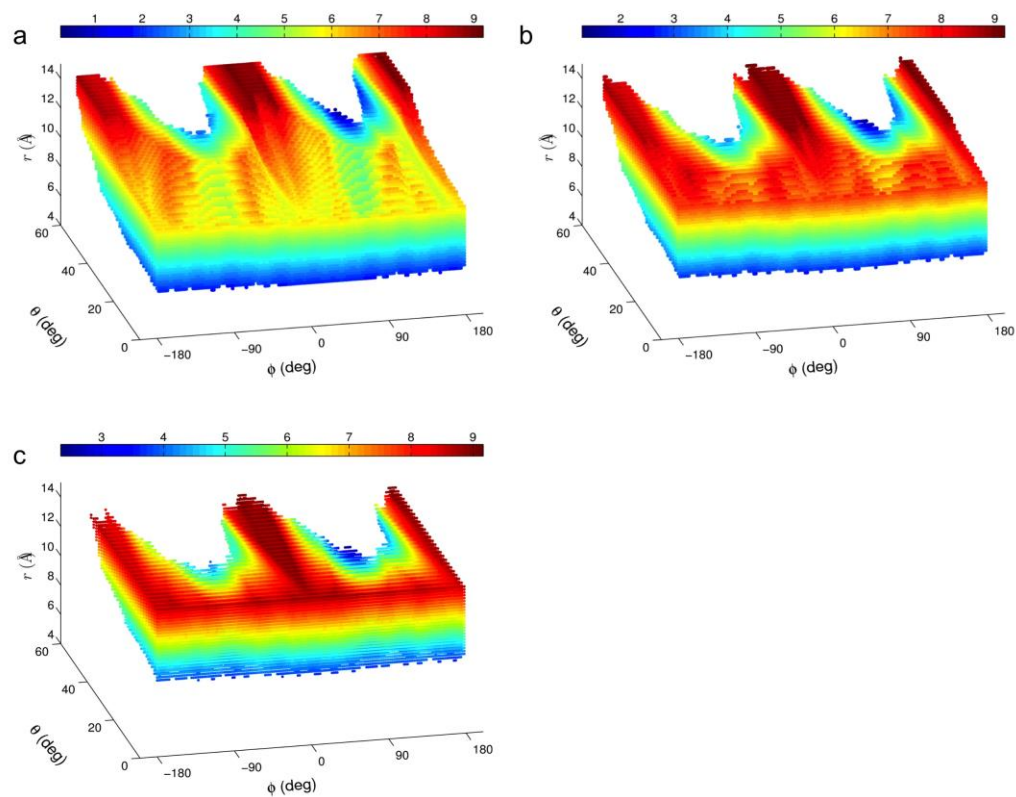
**Supplementary Figure 1 | Distributions of distances and angles for transmembrane helices.** (a) Distribution of the radial distance  $r$  for the pore-lining helix (PLH) bundle in 39 unique ion channel structures. (b) Distribution of the tilt angle  $\theta$  for 171 transmembrane helices in 26 membrane proteins. (c) Distribution of  $\theta$  for the PLH bundles of the 39 channel structures. (d) Distribution of the contact distances of 128 helix pairs in the 26 membrane proteins. (e) Distribution of the contact distances between PLHs and their nearest neighboring helices (not necessarily pore-lining) in the 39 channel structures. (f) Distribution of the contact distances between neighboring PLHs in the 39 channel structures.



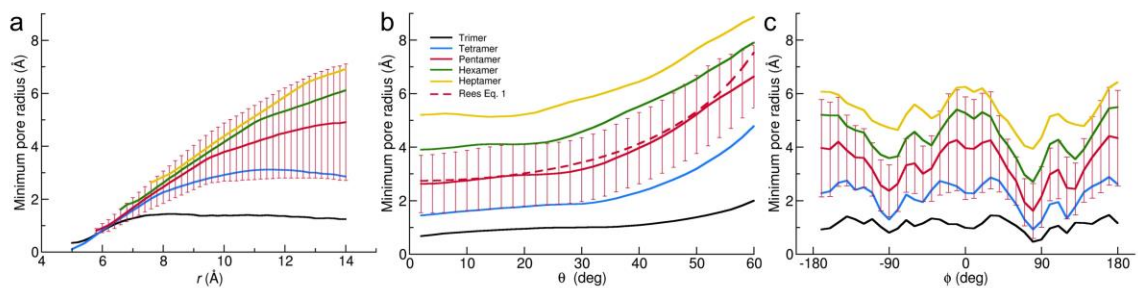
**Supplementary Figure 2 | The W-shaped accessible region in the  $r$ - $\theta$ - $\phi$  space. (a)** The accessible region for trimeric models, along with the conformations of 4 actual pore-lining helix (PLH) bundles. The  $r$  values of the plausible models are displayed according to the color scale at the top. Each black dot represents an actual PLH bundle. The closed-state P2X4 receptor and ASIC1a are within the accessible region, but their open-state counterparts are either near the border of the accessible region (4DW1 for P2X4 receptor) or well outside (4FZ1 for ASIC1a). **(b & c)** Corresponding results for hexamers and heptamers. The hexameric calcium release-activated calcium channel (4HKR) and heptameric MscS (2OAU for closed and 2VV5 for open) are within their respective W-shaped accessible regions.



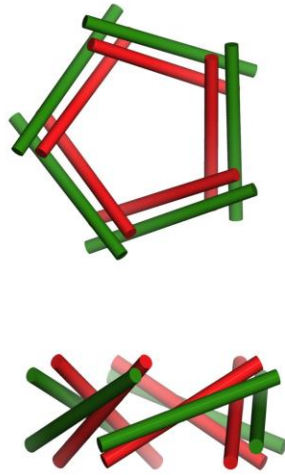
**Supplementary Figure 3 | The W-shaped accessible region in the  $r$ - $\theta$ - $\phi$  space for tetrameric models.** The ranges of parameters are  $5 \text{ \AA} < r < 16 \text{ \AA}$ ,  $0^\circ < \theta < 80^\circ$ , and  $-180^\circ < \phi < 180^\circ$ . Conformations of pore-lining helix bundles in channel structures are displayed as black dots.



**Supplementary Figure 4 | Minimum pore radii of the plausible models. (a)** Hexamers. **(b)** Heptamers. **(c)** Octamers. In each panel, the  $R_0$  values of the plausible models are displayed according to the color scale at the top.



**Supplementary Figure 5 | Average  $R_0$  when only one of the three coordinates is fixed, for oligomeric states. (a) Averaging at fixed  $r$ . (b) Averaging at fixed  $\theta$ . (c) Averaging at fixed  $\phi$ . Error bars representing standard deviations are displayed for pentamers, to indicate the significant variations in  $R_0$  when only one coordinate is fixed. In (b) the dashed curve displays the prediction of Spencer and Rees for a model of infinite cylinders with a diameter of 7.8 Å.**



**Supplementary Figure 6 | Comparison of the open model proposed in this study for MscL (red) with a model proposed by Sukharev et al. (green). Both top and side views are shown.**

**Supplementary Table 1 | Oligomeric arrangements of pore-lining helix bundles in channel structures**

PDB entry	$r$ (Å)	$\theta$ (°)	$\phi$ (°)	Residues of PLHs	Aligned segment	Ideal helix	rmsd (Å)	Description	Ref.
<i>Trimers</i>									
3HGC	4.5	44.7	147.0	A-C: V427-E451	427-450	1-24	1.5	ASIC1 desensitized state	1
4FZ1	12.7	12.5	153.5	A-C: V427-L450	427-450	1-24	2.0	ASIC1-psalmotoxin 1 at high pH	2
4DW0	6.4	49.9	144.5	A-C: I335-I359	335-358	1-24	1.4	P2X4R apo	3
4DW1	8.6	45.3	-159.5	A-C: I335-I359	335-358	1-24	1.1	P2X4R with ATP	3
<i>Tetramers</i>									
1BL8	6.8	32.9	-25.1	A-D: L86-Q119	94-117	1-24	0.7	KcsA	4
1K4C								KcsA + Fab	5
2ITC								KcsA + Fab in NaCl	6
2NLJ								KcsA M96V mutant in KCl	6
3IGA								KcsA in 150 mM Li <sup>+</sup> and 3 mM K <sup>+</sup>	7
3HPL								KcsA closed inactivated. E71H and F103A	8
3OR7								KcsA E71I	9
3OR6								KcsA E71Q	9
3STL								KcsA Y82C with cadmium	10
3FB8								KcsA open conductive. Open 20 Å	11
3EFF								Full length KcsA closed	12
3PJS								Full length KcsA open	13
3F7Y								KcsA partially open. Open 17 Å	11
3FB6	7.8	40.0	-4.0	A-D: L86-F114	94-114	1-21	0.6	KcsA partially open. Open 16 Å	11
3FB5								KcsA partially open. Open 14.5 Å	11
3F5W	9.8	56.1	11.8	A-D: L86-Q117	94-117	1-24	1.7	KcsA open inactivated. Open 32 Å	11
3FB7								KcsA in open state with Rb <sup>+</sup>	8
3F7V								KcsA open inactivated. Open 23 Å	11
2A0L	9.2	57.8	0.4	A-D: P207-K237	214-237	1-24	1.4	KvAP + Fv fragment	14
1ORQ								KvAP + Fab	15
2A79	7.7	48.4	8.6	A-D: I385-T421	394-417	1-24	1.6	Kv1.2	16
3LUT								Full length Kv1.2	17
2R9R								Kv1.2/Kv2.1	18
3LNM								Kv1.2/Kv2.1 F233W	19
4H33	6.2	33.8	4.1	A-D: P68-T102	79-102	1-24	1.1	KvLm closed	20
4H37								KvLm in K <sup>+</sup> condition	20
3LDC	10.2	55.9	2.6	A-D: P70-I99	76-99	1-24	1.7	MthK K <sup>+</sup> channel	21
1LNQ								MthK K <sup>+</sup> channel, Ca <sup>2+</sup> gated	22
4HYO								MthK K <sup>+</sup> channel. S68H & V77C	23
4GX5	12.1	28.0	-53.0	A-D: S78-F108	79-99	1-21	1.4	GsuK wild-type	24
4GX0								GsuK L97D	24
4GX1								GsuK L97D with ADP	24
4GX2								GsuK L97D with NAD <sup>+</sup>	24
3JYC	9.6	35.8	-37.9	A-D:	160-183	1-24	0.6	Kir2.2	25

C155-K183									
3SPI								Kir2.2 with PIP <sub>2</sub>	26
3SPC								Kir2.2 with DGPP	26
3SPH								Kir2.2 I223L mutant with PIP <sub>2</sub>	26
3SPJ								Kir2.2 I223L mutant apo	26
3SPG								Kir2.2 R186A mutant with PIP <sub>2</sub>	26
				A-D:					
2QKS	8.2	34.4	-27.9	V103-S132	109-132	1-24	0.6	Kir3.1	27
				A-D:					
4KFM	8.8	43.2	-22.6	P167-S196	173-196	1-24	1.1	GIRK2 (Kir3.2) + PIP <sub>2</sub> + G-protein βγ subunits + Na <sup>+</sup>	28
3SYO								GIRK2 (Kir3.2)	29
3SYA								GIRK2 (Kir3.2) + PIP <sub>2</sub>	29
3SYP								GIRK2 (Kir3.2) R201A mutant	29
								GIRK2 (Kir3.2) R201A mutant + PIP <sub>2</sub>	29
3SYQ								GIRK2 (Kir3.2) D228N mutant	29
3SYC									
				A-D:					
1P7B	8.0	32.7	-31.0	T120-A150	127-150	1-24	0.6	KirBac1.1	30
				A-D:					
2WLJ	7.7	33.7	-23.4	G106-T136	113-136	1-24	0.6	KirBac3.1 semi-latched	31
2WLK								KirBac3.1 latched	31
2WLI								KirBac3.1 semi-latched 3.09 Å	31
2WLO								KirBac3.1 semi-latched 4.20 Å	31
2WLM								KirBac3.1 semi-latched 3.61 Å	31
2WLN								KirBac3.1 unlatched 3.44 Å	31
2WLH								KirBac3.1 unlatched 3.28 Å	31
2X6A								KirBac3.1 Q170A stalled	31
								KirBac3.1 Q170A blocked with Ba <sup>2+</sup>	31
2X6B								KirBac3.1 Q170A conductive	31
2X6C									
				A-D:					
3ZRS	7.6	40.6	-14.3	G106-T136	113-136	1-24	0.9	KirBac3.1 open	32
				A-D:					
3BEH	8.0	35.8	-44.1	S185-G213	190-213	1-24	0.6	MlotiK1	33
				A-D:					
2AHY	9.3	27	-41.7	D74-Q103	80-103	1-24	0.4	NaK closed	34
2Q67								NaK channel with Ca <sup>2+</sup> , D66A	35
								NaK channel chimera with grafted C-terminal of a NaV channel	36
3VOU				A-D:					
3E86	10.7	59.5	13.9	D74-V112	83-103	2-22	1.7	NaK open	37
3K0D								CNG-mimicking NaK channel	38
3OUF								NaK channel K <sup>+</sup> selective mutant	39
3T1C								NaK/NaK2K channel mutant	40
				A-B:Y193-					
3RVY	9.5	34.7	-42.7	M221	198-221	1-24	0.7	NaVAb I217C mutant	41
4DXW								NaVRh	42
3RW0								NaVAb M221C	41
4LTO								NavAe1p	43
4EKW								NaV closed	44
				A-D:					
4F4L	12.0	39.1	-47.7	W71-I93	71-93	2-24	1.0	NaV open	45
				A-D:					
3KG2	7.3	30.2	-36.2	S595-V626	603-626	1-24	0.5	GluA2	46
				A-D:					
2L0J	7.8	26.5	153.1	D24-F47	24-47	1-24	1.2	M2 in hydrated lipid bilayer	47
2RLF								M2 with rimantadine	48
3BKD								M2 crystal structure	49
3C9J								M2 + amantadine crystal structure	49
								M2 transmembrane domain crystal structure	50
3LBW									



2LY0								M2 S31N mutant with M2WJ332	51
2KIX								M2 proton channel influenza B	52
2LJB								M2A-M2B chimera	53
2LJC								M2A-M2B with rimantadine	53
				A-D:					
3HZQ	9.1	48.6	23.7	V14-I46	14-37	1-24	1.0	Tetrameric MscL	54
				A-D:					
3J5P	8.0	38.3	-22.4	F655-I689	666-689	1-24	1.9	TRPV1 closed	55
3J5Q								TRPV1 with RTX	56
3J5R								TRPV1 with capsaicin	56
				<i>Pentamers</i>					
				A-E:					
2OAR	8.4	36.3	28.2	N13-I46	13-36	1-24	0.7	MscL	57
				A-E:					
3RHW	9.4	7.3	68.7	A241-Q266	241-264	1-24	0.8	GluCl receptor with Fab and ivermectin	58
				A-E:					
2M6I	11.8	16.3	79.9	A249-Q266	249-266	1-18	1.0	GlyR receptor transmembrane domain NMR	59
				A-E: K242/248/256/24	242/248/256/242/251-S269				
				/L275/L283	271/279/265/274	1-24	0.8	nAChR closed	60
1OED	9.6	7.4	67.4	/S269/L278				nAChR refined	61
2BG9								nAChR closed class	62
4AQ5								nAChR open class	62
4AQ9									
				A-E:					
2VL0	8.6	9.1	-167.7	S226-L252	229-252	1-24	0.8	ELIC	63
4A97								ELIC with zopiclone	64
								ELIC L240S F247L in 10 mM cysteamine	65
3UQ7								ELIC with acetylcholine	66
3RQW								ELIC apo	66
3RQU								ELIC with bromoform	67
3ZKR									
				A-E:					
3TLS	8.2	10.3	178.8	Y221-P243	221-243	1-23	1.1	GLIC E19'P locally closed LC2	68
								GLIC loop2-22' oxidized locally closed LC3	68
3TLV									
3TLT								GLIC H11'F locally closed LC1	68
								GLIC loop2-20' oxidized locally closed LC1	68
3UU3								GLIC loop2-21' reduced in crystal locally closed LC1	68
3UU4								GLIC loop2-24' oxidized locally closed LC1	68
3TLU								GLIC loop2-21' oxidized locally closed LC2	68
3TLW								GLIC WT resting state	69
4NPQ									
				A-E:					
3EAM	9.4	5.7	92.5	S220-T244	220-243	1-24	0.7	GLIC open	70
3UU5								GLIC loop2-20' reduced open	68
								GLIC loop2-21' reduced in solution open	68
3UUB								GLIC loop2-22' reduced open	68
3UU6								GLIC loop2-24' reduced open	68
3UU8								GLIC open	71
3EHZ								GLIC open	72
4HFI								GLIC wildtype TBSb complex	73
2XQA								GLIC with propofol anesthetic	74
3P50								GLIC with ketamine anesthetic	75
4F8H								GLIC WT open	69
4NPP									
				A-E:					
2KYV	8.0	7.7	179.9	A24-L52	24-47	1-24	0.6	Phospholamban in T-state	76

2M3B									Phosphorylated phospholamban	77
				A-E: N285-						
2BBJ	8.5	20.9	-168.1	M302	285-302	7-24	1.0	CorA		78
2IUB								CorA		79
2HN2								CorA		80
4EEB								CorA in the absence of Mg <sup>2+</sup>		81
4EED								CorA in the presence of Mg <sup>2+</sup>		81
4EV6								CorA		82
								<i>Hexamer</i>		
				A-F:						
4HKR	9.3	1.5	-82.7	T144-Q180	157-180	1-24	1.0	Calcium release-activated calcium channel (CRAC)		83
								<i>Heptamers</i>		
				A-G:						
2OAU	10.9	26.9	-12.3	T93-L111	93-111	6-24	0.9	<i>E. Coli</i> MscS		84
								<i>Thermoanaerobacter</i>		
3T9N								<i>Tengcongensis</i> MscS		85
4HW9								<i>helicobacter pylori</i> MscS		86
				A-G:						
2VV5	14.0	9.3	55.0	T93-L111	93-111	1-19	0.6	<i>E. Coli</i> MscS A106V mutant		87
2HWA								<i>E. Coli</i> open wild type MscS		86
4AGE								<i>E. Coli</i> open D67C MscS		88
4AGF								<i>E. Coli</i> open L124C MscS		88

Only entries shown in black were deemed “unique”; entries in gray were deemed similar to the preceding entries in black. There are a total of 138 entries, of which 39 are unique.

## Supplementary References

1. Gonzales, E.B., Kawate, T. & Gouaux, E. Pore architecture and ion sites in acid-sensing ion channels and P2X receptors. *Nature* **460**, 599-604 (2009).
2. Bacongus, I. & Gouaux, E. Structural plasticity and dynamic selectivity of acid-sensing ion channel-spider toxin complexes. *Nature* **489**, 400-5 (2012).
3. Hattori, M. & Gouaux, E. Molecular mechanism of ATP binding and ion channel activation in P2X receptors. *Nature* **485**, 207-12 (2012).
4. Doyle, D.A. et al. The structure of the potassium channel: molecular basis of K<sup>+</sup> conduction and selectivity. *Science* **280**, 69-77 (1998).
5. Zhou, Y., Morais-Cabral, J.H., Kaufman, A. & MacKinnon, R. Chemistry of ion coordination and hydration revealed by a K<sup>+</sup> channel-Fab complex at 2.0 Å resolution. *Nature* **414**, 43-8 (2001).
6. Lockless, S.W., Zhou, M. & MacKinnon, R. Structural and thermodynamic properties of selective ion binding in a K<sup>+</sup> channel. *PLoS Biol* **5**, e121 (2007).
7. Thompson, A.N. et al. Mechanism of potassium-channel selectivity revealed by Na<sup>(+)</sup> and Li<sup>(+)</sup> binding sites within the KcsA pore. *Nat Struct Mol Biol* **16**, 1317-24 (2009).
8. Cuello, L.G. et al. Structural basis for the coupling between activation and inactivation gates in K<sup>(+)</sup> channels. *Nature* **466**, 272-5 (2010).
9. Chakrapani, S. et al. On the structural basis of modal gating behavior in K<sup>(+)</sup> channels. *Nat Struct Mol Biol* **18**, 67-74 (2011).
10. Raghuraman, H. et al. Mechanism of Cd<sup>2+</sup> coordination during slow inactivation in potassium channels. *Structure* **20**, 1332-42 (2012).
11. Cuello, L.G., Jogini, V., Cortes, D.M. & Perozo, E. Structural mechanism of C-type inactivation in K<sup>(+)</sup> channels. *Nature* **466**, 203-8 (2010).
12. Uysal, S. et al. Crystal structure of full-length KcsA in its closed conformation. *Proc Natl Acad Sci U S A* **106**, 6644-9 (2009).
13. Uysal, S. et al. Mechanism of activation gating in the full-length KcsA K<sup>+</sup> channel. *Proc Natl Acad Sci U S A* **108**, 11896-9 (2011).
14. Lee, S.Y., Lee, A., Chen, J. & MacKinnon, R. Structure of the KvAP voltage-

- dependent K<sup>+</sup> channel and its dependence on the lipid membrane. *Proc Natl Acad Sci U S A* **102**, 15441-6 (2005).
15. Jiang, Y. et al. X-ray structure of a voltage-dependent K<sup>+</sup> channel. *Nature* **423**, 33-41 (2003).
  16. Long, S.B., Campbell, E.B. & MacKinnon, R. Crystal structure of a mammalian voltage-dependent Shaker family K<sup>+</sup> channel. *Science* **309**, 897-903 (2005).
  17. Chen, X., Wang, Q., Ni, F. & Ma, J. Structure of the full-length Shaker potassium channel Kv1.2 by normal-mode-based X-ray crystallographic refinement. *Proc Natl Acad Sci U S A* **107**, 11352-7 (2010).
  18. Long, S.B., Tao, X., Campbell, E.B. & MacKinnon, R. Atomic structure of a voltage-dependent K<sup>+</sup> channel in a lipid membrane-like environment. *Nature* **450**, 376-82 (2007).
  19. Tao, X., Lee, A., Limapichat, W., Dougherty, D.A. & MacKinnon, R. A gating charge transfer center in voltage sensors. *Science* **328**, 67-73 (2010).
  20. Santos, J.S. et al. Crystal structure of a voltage-gated K<sup>+</sup> channel pore module in a closed state in lipid membranes. *J Biol Chem* **287**, 43063-70 (2012).
  21. Ye, S., Li, Y. & Jiang, Y. Novel insights into K<sup>+</sup> selectivity from high-resolution structures of an open K<sup>+</sup> channel pore. *Nat Struct Mol Biol* **17**, 1019-23 (2010).
  22. Jiang, Y. et al. Crystal structure and mechanism of a calcium-gated potassium channel. *Nature* **417**, 515-22 (2002).
  23. Posson, D.J., McCoy, J.G. & Nimigean, C.M. The voltage-dependent gate in MthK potassium channels is located at the selectivity filter. *Nat Struct Mol Biol* **20**, 159-66 (2013).
  24. Kong, C. et al. Distinct gating mechanisms revealed by the structures of a multi-ligand gated K(+) channel. *Elife* **1**, e00184 (2012).
  25. Tao, X., Avalos, J.L., Chen, J. & MacKinnon, R. Crystal structure of the eukaryotic strong inward-rectifier K<sup>+</sup> channel Kir2.2 at 3.1 Å resolution. *Science* **326**, 1668-74 (2009).
  26. Hansen, S.B., Tao, X. & MacKinnon, R. Structural basis of PIP<sub>2</sub> activation of the classical inward rectifier K<sup>+</sup> channel Kir2.2. *Nature* **477**, 495-8 (2011).
  27. Nishida, M., Cadene, M., Chait, B.T. & MacKinnon, R. Crystal structure of a

- Kir3.1-prokaryotic Kir channel chimera. *EMBO J* **26**, 4005-15 (2007).
28. Whorton, M.R. & MacKinnon, R. X-ray structure of the mammalian GIRK2-beta gamma G-protein complex. *Nature* **498**, 190-7 (2013).
  29. Whorton, M.R. & MacKinnon, R. Crystal structure of the mammalian GIRK2 K<sup>+</sup> channel and gating regulation by G proteins, PIP<sub>2</sub>, and sodium. *Cell* **147**, 199-208 (2011).
  30. Kuo, A. et al. Crystal structure of the potassium channel KirBac1.1 in the closed state. *Science* **300**, 1922-6 (2003).
  31. Clarke, O.B. et al. Domain reorientation and rotation of an intracellular assembly regulate conduction in Kir potassium channels. *Cell* **141**, 1018-29 (2010).
  32. Bavro, V.N. et al. Structure of a KirBac potassium channel with an open bundle crossing indicates a mechanism of channel gating. *Nat Struct Mol Biol* **19**, 158-63 (2012).
  33. Clayton, G.M., Altieri, S., Heginbotham, L., Unger, V.M. & Morais-Cabral, J.H. Structure of the transmembrane regions of a bacterial cyclic nucleotide-regulated channel. *Proc Natl Acad Sci U S A* **105**, 1511-5 (2008).
  34. Shi, N., Ye, S., Alam, A., Chen, L. & Jiang, Y. Atomic structure of a Na<sup>+</sup>- and K<sup>+</sup>-conducting channel. *Nature* **440**, 570-4 (2006).
  35. Alam, A., Shi, N. & Jiang, Y. Structural insight into Ca<sup>2+</sup> specificity in tetrameric cation channels. *Proc Natl Acad Sci U S A* **104**, 15334-9 (2007).
  36. Irie, K., Shimomura, T. & Fujiyoshi, Y. The C-terminal helical bundle of the tetrameric prokaryotic sodium channel accelerates the inactivation rate. *Nat Commun* **3**, 793 (2012).
  37. Alam, A. & Jiang, Y. High-resolution structure of the open NaK channel. *Nat Struct Mol Biol* **16**, 30-4 (2009).
  38. Derebe, M.G., Zeng, W., Li, Y., Alam, A. & Jiang, Y. Structural studies of ion permeation and Ca<sup>2+</sup> blockage of a bacterial channel mimicking the cyclic nucleotide-gated channel pore. *Proc Natl Acad Sci U S A* **108**, 592-7 (2011).
  39. Derebe, M.G. et al. Tuning the ion selectivity of tetrameric cation channels by changing the number of ion binding sites. *Proc Natl Acad Sci U S A* **108**, 598-602 (2011).

40. Sauer, D.B., Zeng, W., Raghunathan, S. & Jiang, Y. Protein interactions central to stabilizing the K<sup>+</sup> channel selectivity filter in a four-sited configuration for selective K<sup>+</sup> permeation. *Proc Natl Acad Sci U S A* **108**, 16634-9 (2011).
41. Payandeh, J., Scheuer, T., Zheng, N. & Catterall, W.A. The crystal structure of a voltage-gated sodium channel. *Nature* **475**, 353-8 (2011).
42. Zhang, X. et al. Crystal structure of an orthologue of the NaChBac voltage-gated sodium channel. *Nature* **486**, 130-4 (2012).
43. Shaya, D. et al. Structure of a prokaryotic sodium channel pore reveals essential gating elements and an outer ion binding site common to eukaryotic channels. *J Mol Biol* **426**, 467-83 (2014).
44. Payandeh, J., Gamal El-Din, T.M., Scheuer, T., Zheng, N. & Catterall, W.A. Crystal structure of a voltage-gated sodium channel in two potentially inactivated states. *Nature* **486**, 135-9 (2012).
45. McCusker, E.C. et al. Structure of a bacterial voltage-gated sodium channel pore reveals mechanisms of opening and closing. *Nat Commun* **3**, 1102 (2012).
46. Sobolevsky, A.I., Rosconi, M.P. & Gouaux, E. X-ray structure, symmetry and mechanism of an AMPA-subtype glutamate receptor. *Nature* **462**, 745-56 (2009).
47. Sharma, M. et al. Insight into the mechanism of the influenza A proton channel from a structure in a lipid bilayer. *Science* **330**, 509-12 (2010).
48. Schnell, J.R. & Chou, J.J. Structure and mechanism of the M2 proton channel of influenza A virus. *Nature* **451**, 591-5 (2008).
49. Stouffer, A.L. et al. Structural basis for the function and inhibition of an influenza virus proton channel. *Nature* **451**, 596-9 (2008).
50. Acharya, R. et al. Structure and mechanism of proton transport through the transmembrane tetrameric M2 protein bundle of the influenza A virus. *Proc Natl Acad Sci U S A* **107**, 15075-80 (2010).
51. Wang, J. et al. Structure and inhibition of the drug-resistant S31N mutant of the M2 ion channel of influenza A virus. *Proc Natl Acad Sci U S A* **110**, 1315-20 (2013).
52. Wang, J., Pielak, R.M., McClintock, M.A. & Chou, J.J. Solution structure and functional analysis of the influenza B proton channel. *Nat Struct Mol Biol* **16**,

- 1267-71 (2009).
53. Pielak, R.M., Oxenoid, K. & Chou, J.J. Structural investigation of rimantadine inhibition of the AM2-BM2 chimera channel of influenza viruses. *Structure* **19**, 1655-63 (2011).
  54. Liu, Z., Gandhi, C.S. & Rees, D.C. Structure of a tetrameric MscL in an expanded intermediate state. *Nature* **461**, 120-4 (2009).
  55. Liao, M., Cao, E., Julius, D. & Cheng, Y. Structure of the TRPV1 ion channel determined by electron cryo-microscopy. *Nature* **504**, 107-12 (2013).
  56. Cao, E., Liao, M., Cheng, Y. & Julius, D. TRPV1 structures in distinct conformations reveal activation mechanisms. *Nature* **504**, 113-8 (2013).
  57. Chang, G., Spencer, R.H., Lee, A.T., Barclay, M.T. & Rees, D.C. Structure of the MscL homolog from Mycobacterium tuberculosis: a gated mechanosensitive ion channel. *Science* **282**, 2220-6 (1998).
  58. Hibbs, R.E. & Gouaux, E. Principles of activation and permeation in an anion-selective Cys-loop receptor. *Nature* **474**, 54-60 (2011).
  59. Mowrey, D.D. et al. Open-channel structures of the human glycine receptor alpha1 full-length transmembrane domain. *Structure* **21**, 1897-904 (2013).
  60. Miyazawa, A., Fujiyoshi, Y. & Unwin, N. Structure and gating mechanism of the acetylcholine receptor pore. *Nature* **423**, 949-55 (2003).
  61. Unwin, N. Refined structure of the nicotinic acetylcholine receptor at 4A resolution. *J Mol Biol* **346**, 967-89 (2005).
  62. Unwin, N. & Fujiyoshi, Y. Gating movement of acetylcholine receptor caught by plunge-freezing. *J Mol Biol* **422**, 617-34 (2012).
  63. Hilf, R.J. & Dutzler, R. X-ray structure of a prokaryotic pentameric ligand-gated ion channel. *Nature* **452**, 375-9 (2008).
  64. Spurny, R. et al. Pentameric ligand-gated ion channel ELIC is activated by GABA and modulated by benzodiazepines. *Proc Natl Acad Sci U S A* **109**, E3028-34 (2012).
  65. Gonzalez-Gutierrez, G. et al. Mutations that stabilize the open state of the Erwinia chrisanthemi ligand-gated ion channel fail to change the conformation of the pore domain in crystals. *Proc Natl Acad Sci U S A* **109**, 6331-6 (2012).

66. Pan, J. et al. Structure of the pentameric ligand-gated ion channel ELIC cocrystallized with its competitive antagonist acetylcholine. *Nat Commun* **3**, 714 (2012).
67. Spurny, R. et al. Multisite binding of a general anesthetic to the prokaryotic pentameric *Erwinia chrysanthemi* ligand-gated ion channel (ELIC). *J Biol Chem* **288**, 8355-64 (2013).
68. Prevost, M.S. et al. A locally closed conformation of a bacterial pentameric proton-gated ion channel. *Nat Struct Mol Biol* **19**, 642-9 (2012).
69. Sauguet, L. et al. Crystal structures of a pentameric ligand-gated ion channel provide a mechanism for activation. *Proc Natl Acad Sci U S A* **111**, 966-71 (2014).
70. Bocquet, N. et al. X-ray structure of a pentameric ligand-gated ion channel in an apparently open conformation. *Nature* **457**, 111-4 (2009).
71. Hilf, R.J. & Dutzler, R. Structure of a potentially open state of a proton-activated pentameric ligand-gated ion channel. *Nature* **457**, 115-8 (2009).
72. Sauguet, L. et al. Structural basis for ion permeation mechanism in pentameric ligand-gated ion channels. *EMBO J* **32**, 728-41 (2013).
73. Hilf, R.J. et al. Structural basis of open channel block in a prokaryotic pentameric ligand-gated ion channel. *Nat Struct Mol Biol* **17**, 1330-6 (2010).
74. Nury, H. et al. X-ray structures of general anaesthetics bound to a pentameric ligand-gated ion channel. *Nature* **469**, 428-31 (2011).
75. Pan, J. et al. Structure of the pentameric ligand-gated ion channel GLIC bound with anesthetic ketamine. *Structure* **20**, 1463-9 (2012).
76. Verardi, R., Shi, L., Traaseth, N.J., Walsh, N. & Veglia, G. Structural topology of phospholamban pentamer in lipid bilayers by a hybrid solution and solid-state NMR method. *Proc Natl Acad Sci U S A* **108**, 9101-6 (2011).
77. Vostrikov, V.V., Mote, K.R., Verardi, R. & Veglia, G. Structural dynamics and topology of phosphorylated phospholamban homopentamer reveal its role in the regulation of calcium transport. *Structure* **21**, 2119-30 (2013).
78. Lunin, V.V. et al. Crystal structure of the CorA Mg<sup>2+</sup> transporter. *Nature* **440**, 833-7 (2006).



79. Eshaghi, S. et al. Crystal structure of a divalent metal ion transporter CorA at 2.9 angstrom resolution. *Science* **313**, 354-7 (2006).
80. Payandeh, J. & Pai, E.F. A structural basis for Mg<sup>2+</sup> homeostasis and the CorA translocation cycle. *EMBO J* **25**, 3762-73 (2006).
81. Pfoh, R. et al. Structural asymmetry in the magnesium channel CorA points to sequential allosteric regulation. *Proc Natl Acad Sci U S A* **109**, 18809-14 (2012).
82. Guskov, A. et al. Structural insights into the mechanisms of Mg<sup>2+</sup> uptake, transport, and gating by CorA. *Proc Natl Acad Sci U S A* **109**, 18459-64 (2012).
83. Hou, X., Pedi, L., Diver, M.M. & Long, S.B. Crystal structure of the calcium release-activated calcium channel Orai. *Science* **338**, 1308-13 (2012).
84. Bass, R.B., Strop, P., Barclay, M. & Rees, D.C. Crystal structure of Escherichia coli MscS, a voltage-modulated and mechanosensitive channel. *Science* **298**, 1582-7 (2002).
85. Zhang, X. et al. Structure and molecular mechanism of an anion-selective mechanosensitive channel of small conductance. *Proc Natl Acad Sci U S A* **109**, 18180-5 (2012).
86. Lai, J.Y., Poon, Y.S., Kaiser, J.T. & Rees, D.C. Open and shut: crystal structures of the dodecylmaltoside solubilized mechanosensitive channel of small conductance from Escherichia coli and Helicobacter pylori at 4.4 Å and 4.1 Å resolutions. *Protein Sci* **22**, 502-9 (2013).
87. Wang, W. et al. The structure of an open form of an E. coli mechanosensitive channel at 3.45 Å resolution. *Science* **321**, 1179-83 (2008).
88. Pliotas, C. et al. Conformational state of the MscS mechanosensitive channel in solution revealed by pulsed electron-electron double resonance (PELDOR) spectroscopy. *Proc Natl Acad Sci U S A* **109**, E2675-82 (2012).