Supplementary Information (SI) for Soft Matter.

Supplementary Information

Modeling the organizational heterogeneity of cholesterol-enriched microdomains in the neuronal membranes of gray and white matter of Alzheimer's brain: A computational lipidomics study

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Table S1: The representative structures of lipids used in the current study.

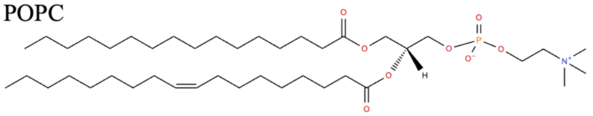
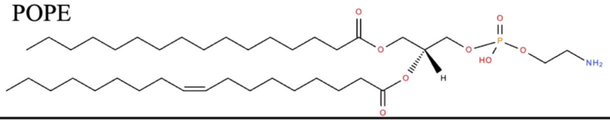
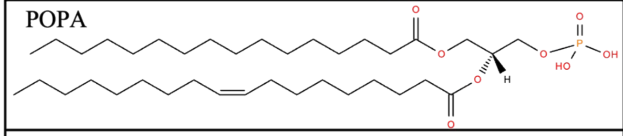
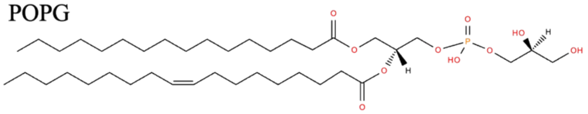
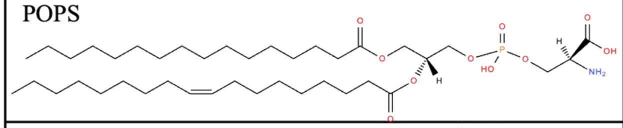
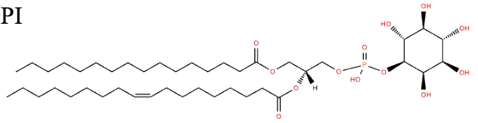
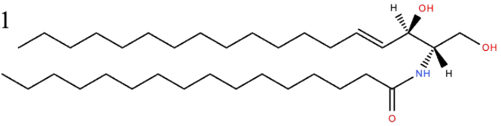
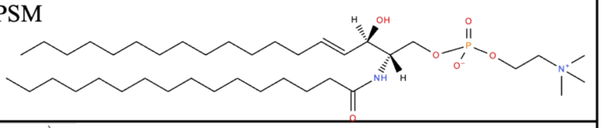
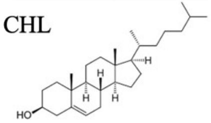
POPC 	POPE 
POPA 	POPG 
POPS 	POPI 
CER1 	PSM 
CHL 	

Table S2: The composition of individual lipid components in outer and inner leaflets for the four systems studied. (OL: outer leaflet, IL: inner leaflet).

Concentration in mol %												
Brain model	Gray matter						White matter					
	Healthy Brain			AD Brain			Healthy Brain			AD Brain		
Lipid	Avg	OL	IL	Avg	OL	IL	Avg	OL	IL	Avg	OL	IL
CHOL	46	46	46	50	50	50	56.5	56.5	56.5	55.5	55.5	55.5
POPA	0.4	0.3	0.5	0.3	0.2	0.4	0.5	0.3	0.7	0.5	0.3	0.7
POPC	17.5	25	10	14.7	21	8.4	11.2	16	6.4	11.4	16	6.8
POPE	14.9	10	19.8	14	9.6	18.4	11.7	7.9	15.5	11.9	8.2	15.6
POPG	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1
POPS	4	2	6	3.8	2	5.6	3	1.2	4.8	3.3	1.6	5
POPI	6	0	12	5	0	10	4	0	8	4	0	8
PSM	8.5	14	3	8	13	3	7	12	2	8	13	3
CER1	2.5	2.5	2.5	4	4	4	6	6	6	5.3	5.3	5.3

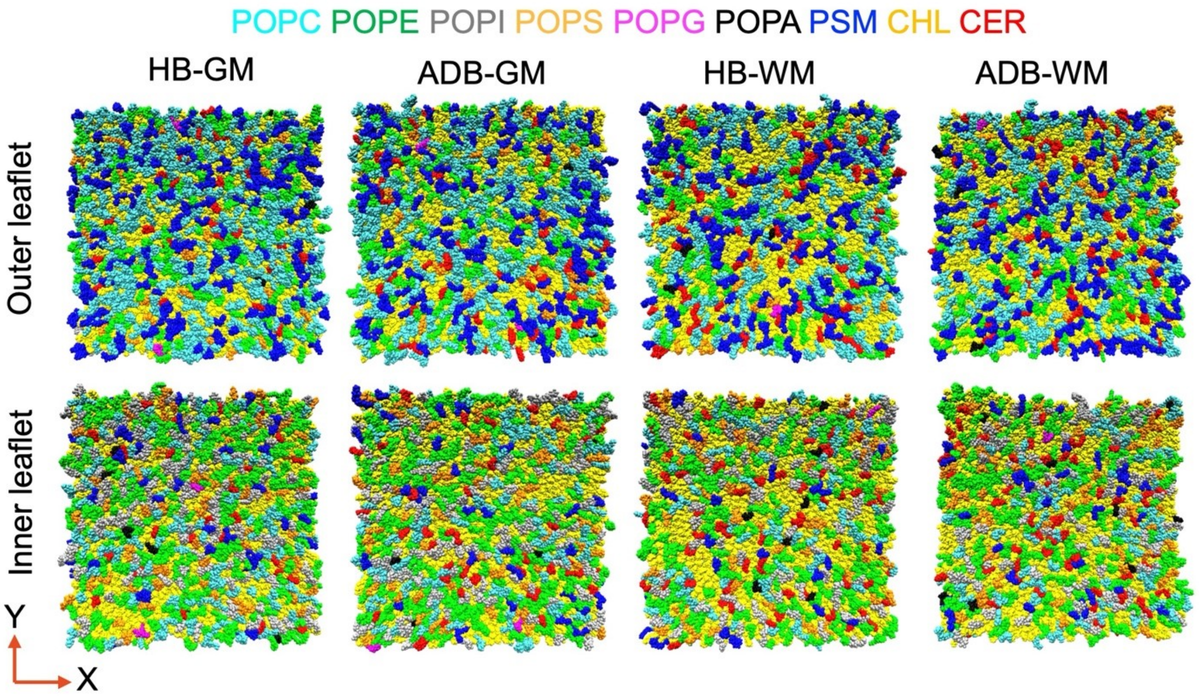


Fig. S1: A representative pre-equilibrated structure showing outer and inner leaflets and the spatial distribution of lipid components in the GM and WM regions modeled from the lipidomics data of postmortem frozen brain tissues of subjects with AD pathology (ADB), and compared to the healthy age-matched controls (HB), with each lipid colored uniquely.

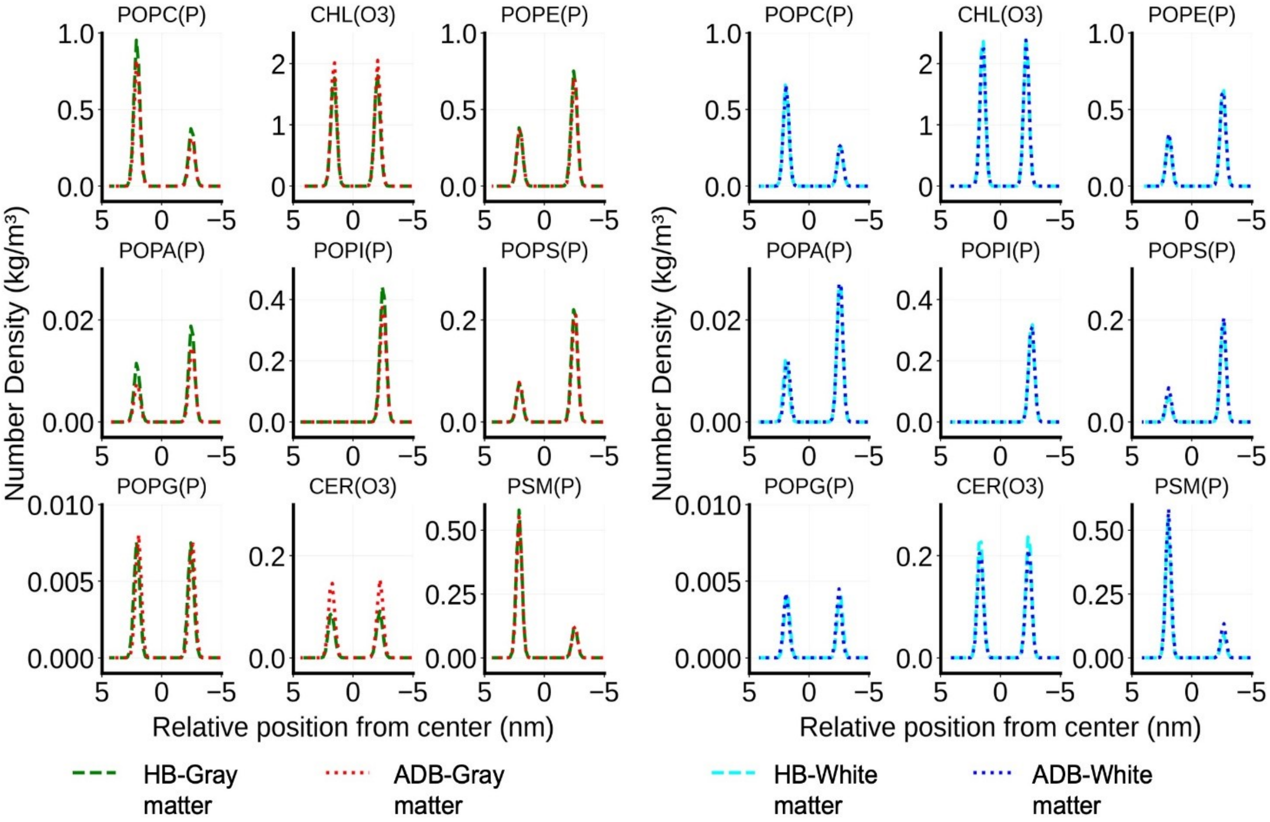


Fig. S2: The number density distribution of all lipids across the four systems. HB: healthy membrane model, ADB: AD-mimicking diseased model membrane.

Table S3: Membrane bilayer structural properties of all the systems. The area per lipid as determined using the "Phosphorous" atom of POPC, POPE, POPS, POPI, POPA, POPG, PSM, and the O3 atom of CER, CHL as reference. The membrane thickness is determined using the "Phosphorous" atom of POPC, POPE, POPS, POPI, POPA, POPG, and PSM as the reference. The data is shown as mean ± standard deviation. Each property is calculated over the concatenated 1.5 μs of the trajectory for each system.

Property	**Gray matter**		**White matter**	
	HB	ADB	HB	ADB
Area per lipid (Phospholipids- 'P', CER- 'O3', CHL- 'O3') (nm^2)	0.42 ± 0.0014	0.42 ± 0.0013	0.41 ± 0.0012	0.41 ± 0.0012
Thickness (Phospholipids- 'P') (nm)	4.59 ± 0.0128	4.57 ± 0.0125	4.53 ± 0.0136	4.54 ± 0.0130
Interdigitation	0.208 ± 0.021	0.205 ± 0.020	0.201 ± 0.187	0.201 ± 0.018
Cholesterol Tilt angle ('C13-C10')	12.05 ± 0.326	11.75 ± 0.314	11.24 ± 0.289	11.27 ±0.285

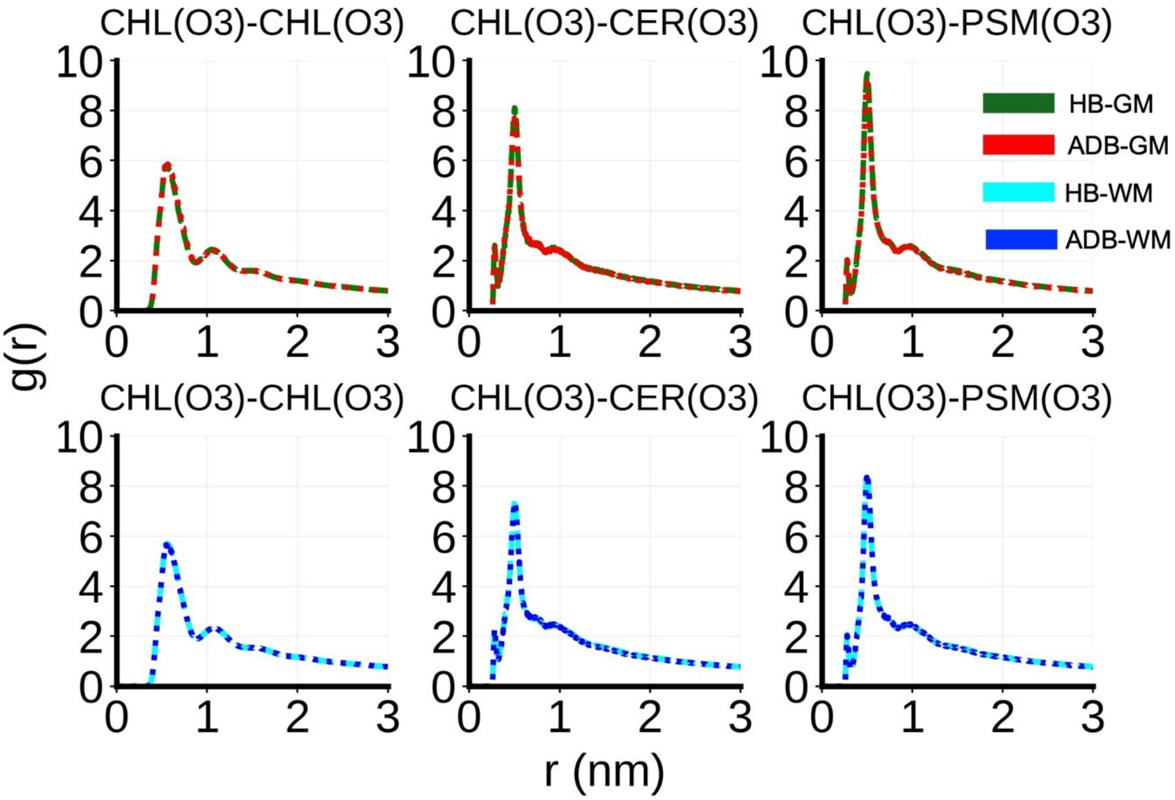


Fig. S3: The radial density function (RDF) profile of cholesterol, ceramide, and sphingomyelin around cholesterol. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, GM: gray matter, WM: white matter).

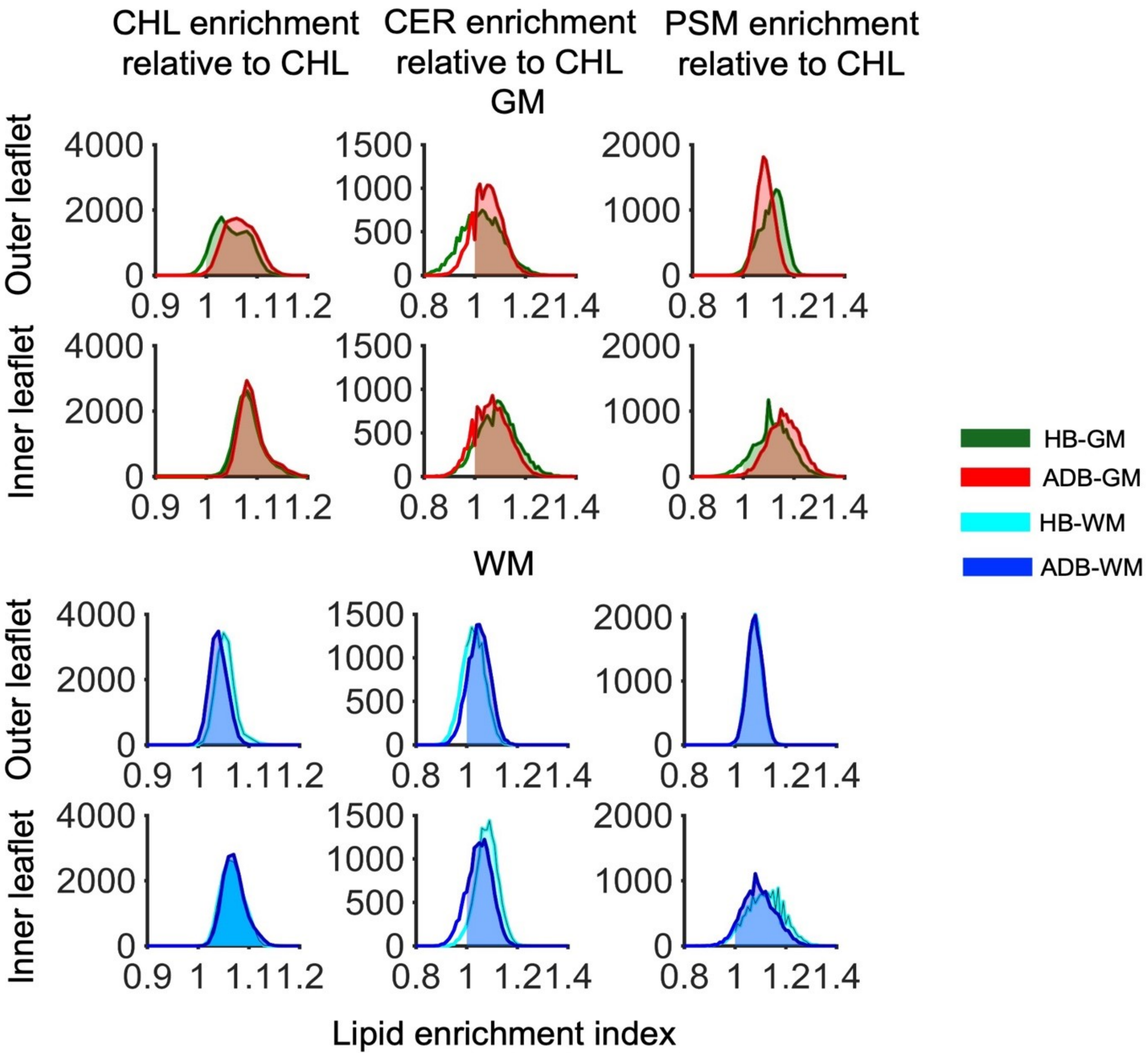


Fig. S4: The distribution of enrichment index of cholesterol, ceramide, and sphingomyelin relative to cholesterol across the leaflets of healthy (HB) and diseased membranes (ADB) in the GM (gray matter) and WM (white matter) region. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, GM: gray matter, WM: white matter).

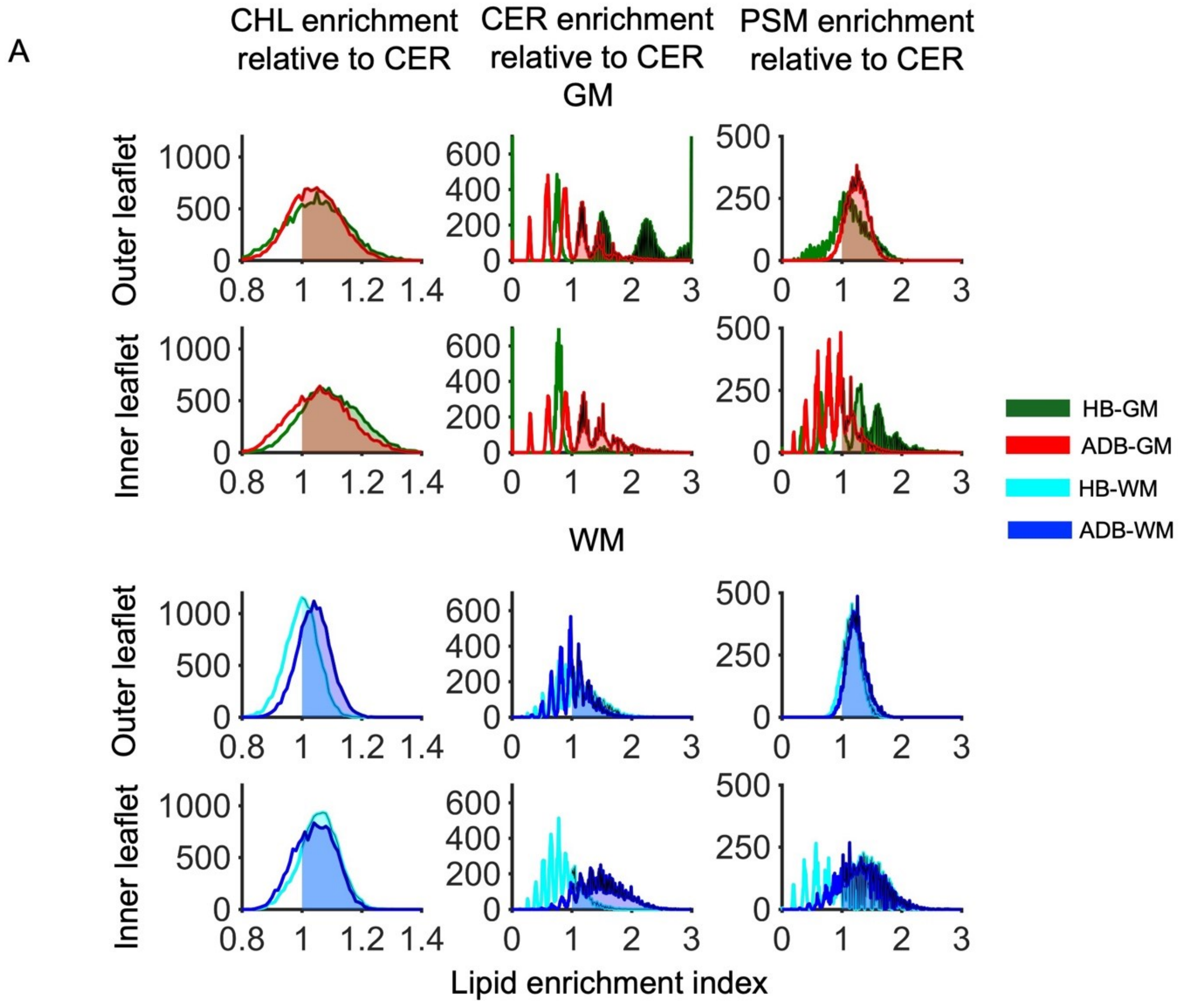


Fig. S5: The enrichment index distribution of cholesterol, ceramide, and sphingomyelin relative to ceramide across the leaflets of healthy (HB) and diseased membranes (ADB) in the GM (gray matter) and WM (white matter) region. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, GM: gray matter, WM: white matter).

Table S4: Area under the curve values, obtained from the enrichment index value distribution curve (Fig. S4), for regions with enrichment values greater than or equal to 1. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, OL: outer leaflet, IL: inner leaflet, GM: gray matter, WM: white matter, CHL-Cholesterol, CER- *N*-palmitoyl-d-erythro-sphingosine, PSM- *N*-palmitoyl-d-erythro-sphingosine phosphorylcholine).

Membrane type	**CHL-CHL**		**CER-CHL**		**PSM-CHL**	
	OL	IL	OL	IL	OL	IL
HB-GM	141.85	150.03	94.29	132.43	148.27	141.21
ADB-GM	149.25	150.03	120.71	123.96	149.48	149.18
HB-WM	149.98	150.02	109.19	143.88	149.5	142.4
ADB-WM	149.07	150.02	129.07	125.61	149.5	139.7

Table S5: Area under the curve values, obtained from the enrichment index value distribution curve (Fig. S5), for regions with enrichment values greater than or equal to 1. (HB: healthy membrane model, ADB: AD-mimicking diseased neuronal model membrane, OL: outer leaflet, IL: inner leaflet, GM: gray matter, WM: white matter, CHL-Cholesterol, CER- *N*-palmitoyl-d-erythro-sphingosine, PSM- *N*-palmitoyl-d-erythro-sphingosine phosphorylcholine).

Membrane type	**CHL-CER**		**CER-CER**		**PSM-CER**	
	OL	IL	OL	IL	OL	IL
HB-GM	101.37	125.61	86.5	2.9	107.91	100.8
ADB-GM	103.36	107.54	64.7	85.5	138.12	50.8
HB-WM	76.51	122.76	87.1	45.2	130.98	92.53
ADB-WM	114.53	108.13	77.2	136.3	142.34	121.62

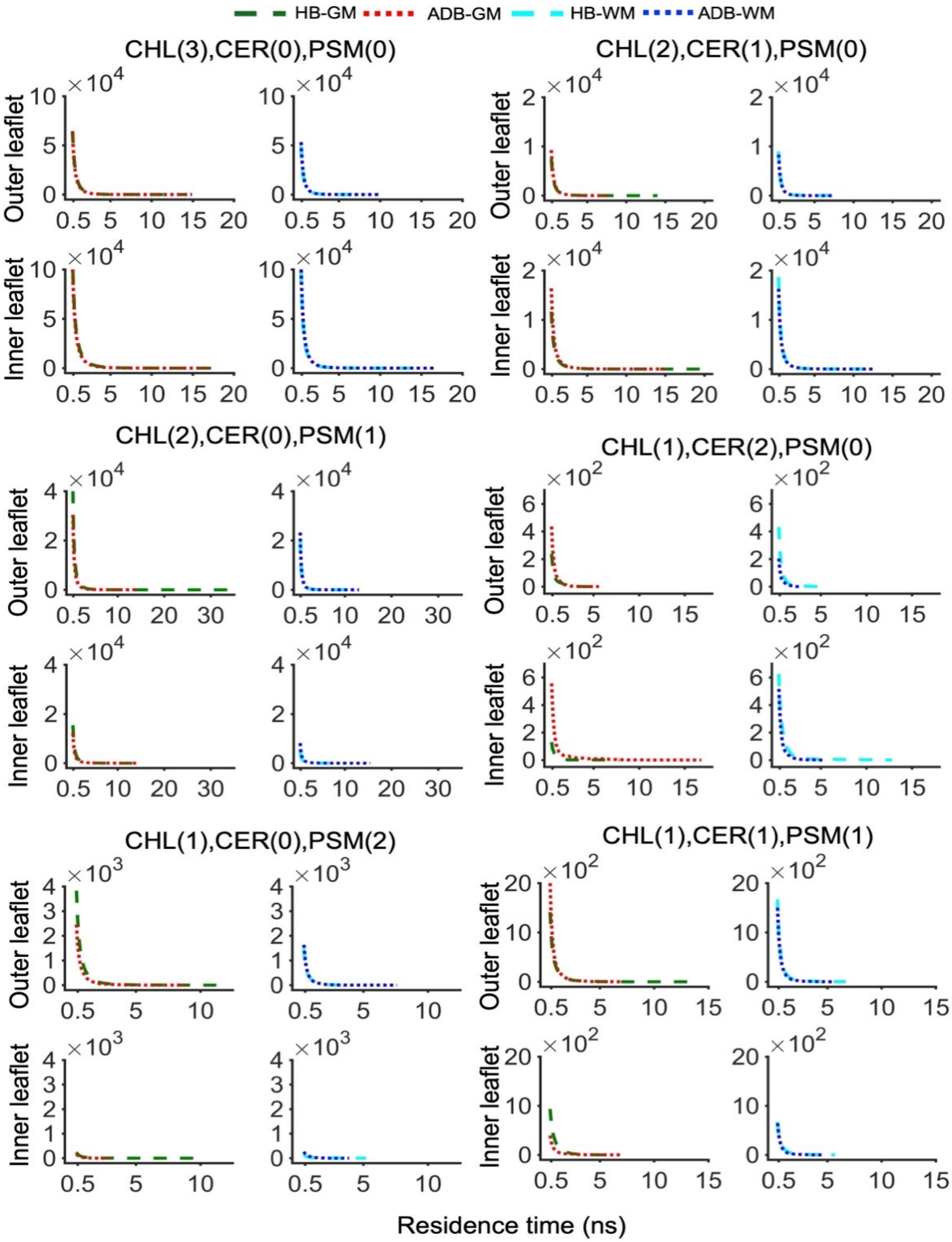


Fig. S6: Residence time distributions of different compositions of microdomains of size 3 calculated from the 1.5 µs concatenated trajectory. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, GM: gray matter, WM: white matter).

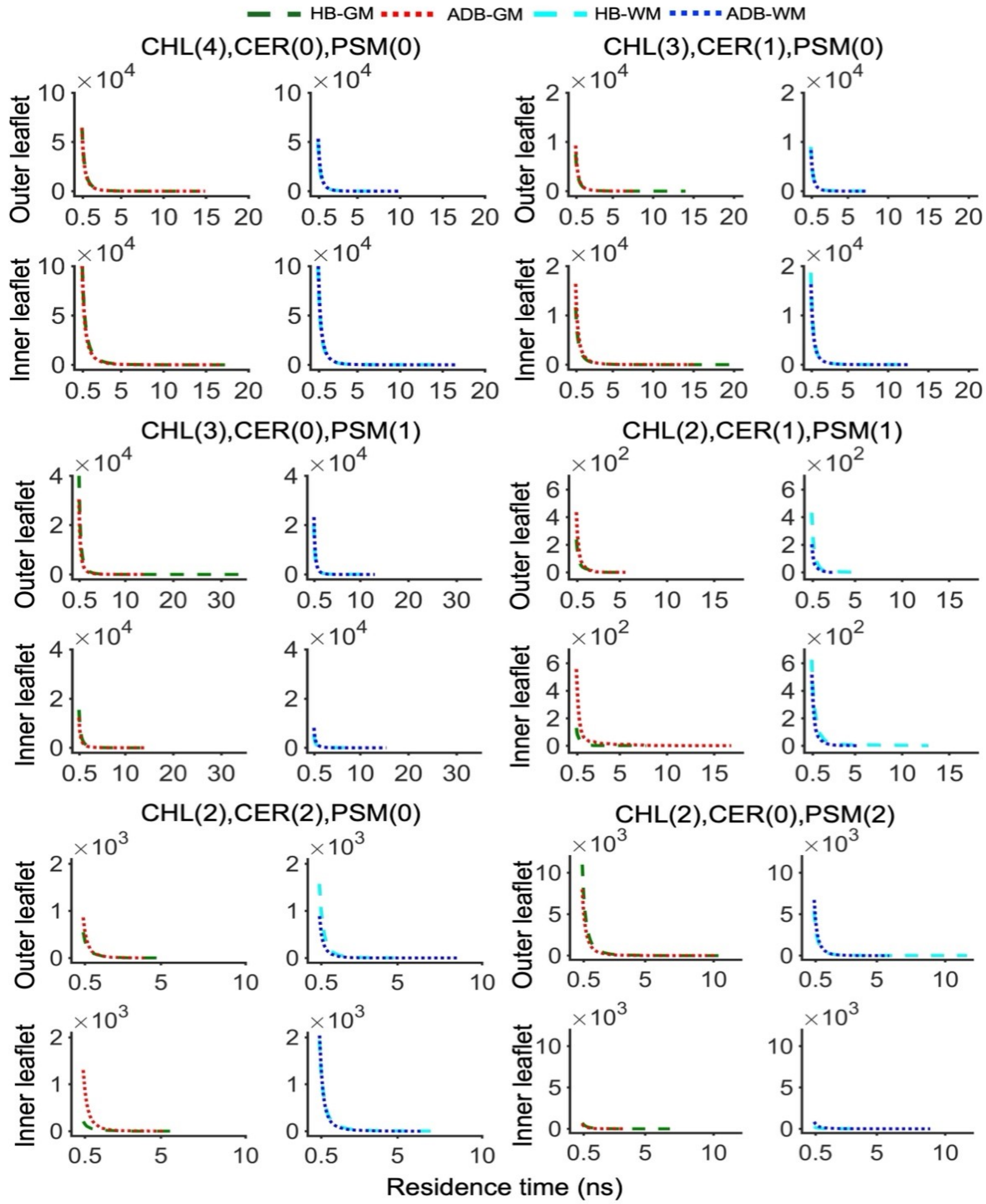


Fig. S7: Residence time distributions of different compositions of microdomains of size 4 calculated from the 1.5 μs concatenated trajectory. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, GM: gray matter, WM: white matter).

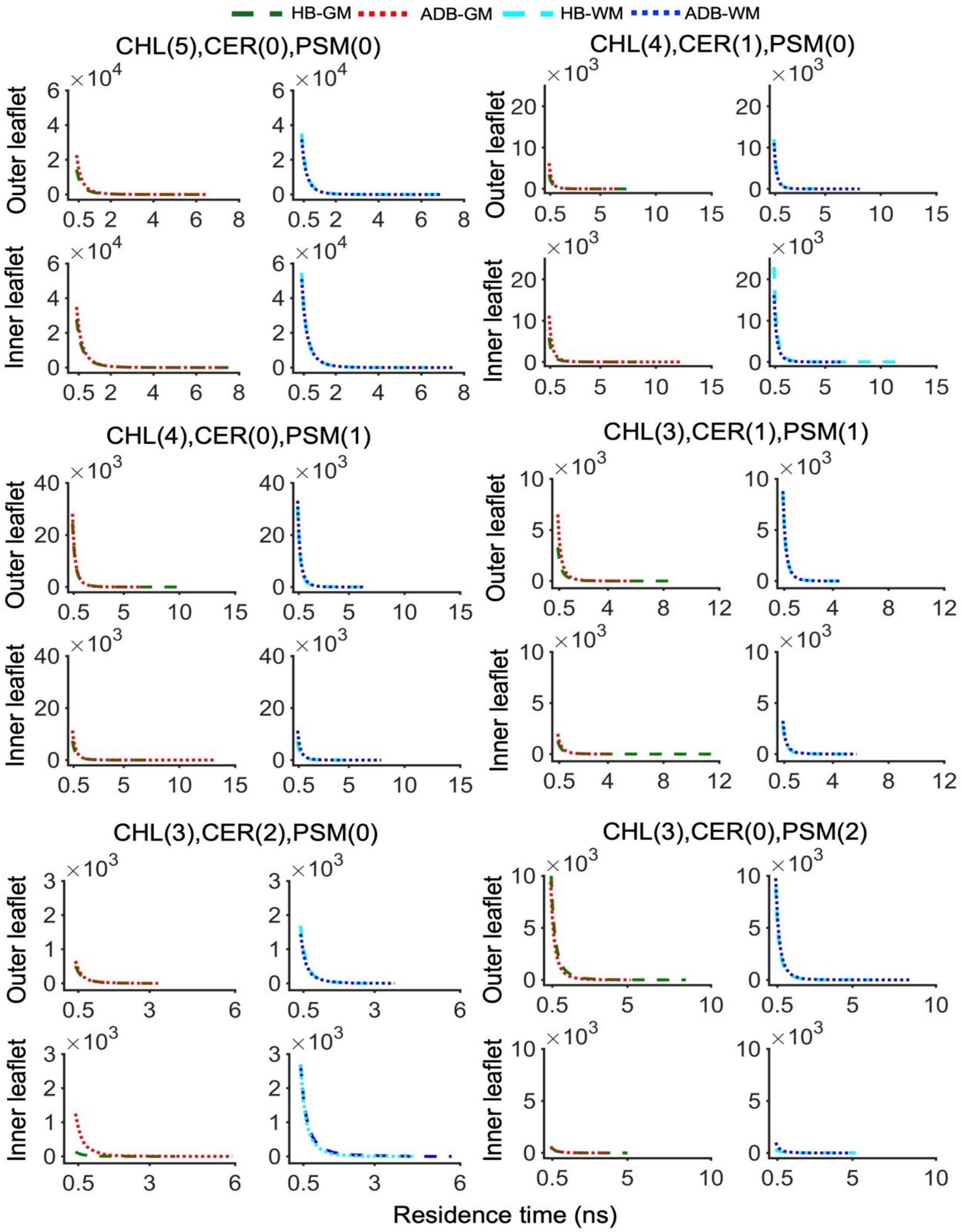


Fig. S8: Residence time distributions of different compositions of microdomains of size 5 calculated from the 1.5 µs concatenated trajectory. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, GM: gray matter, WM: white matter).

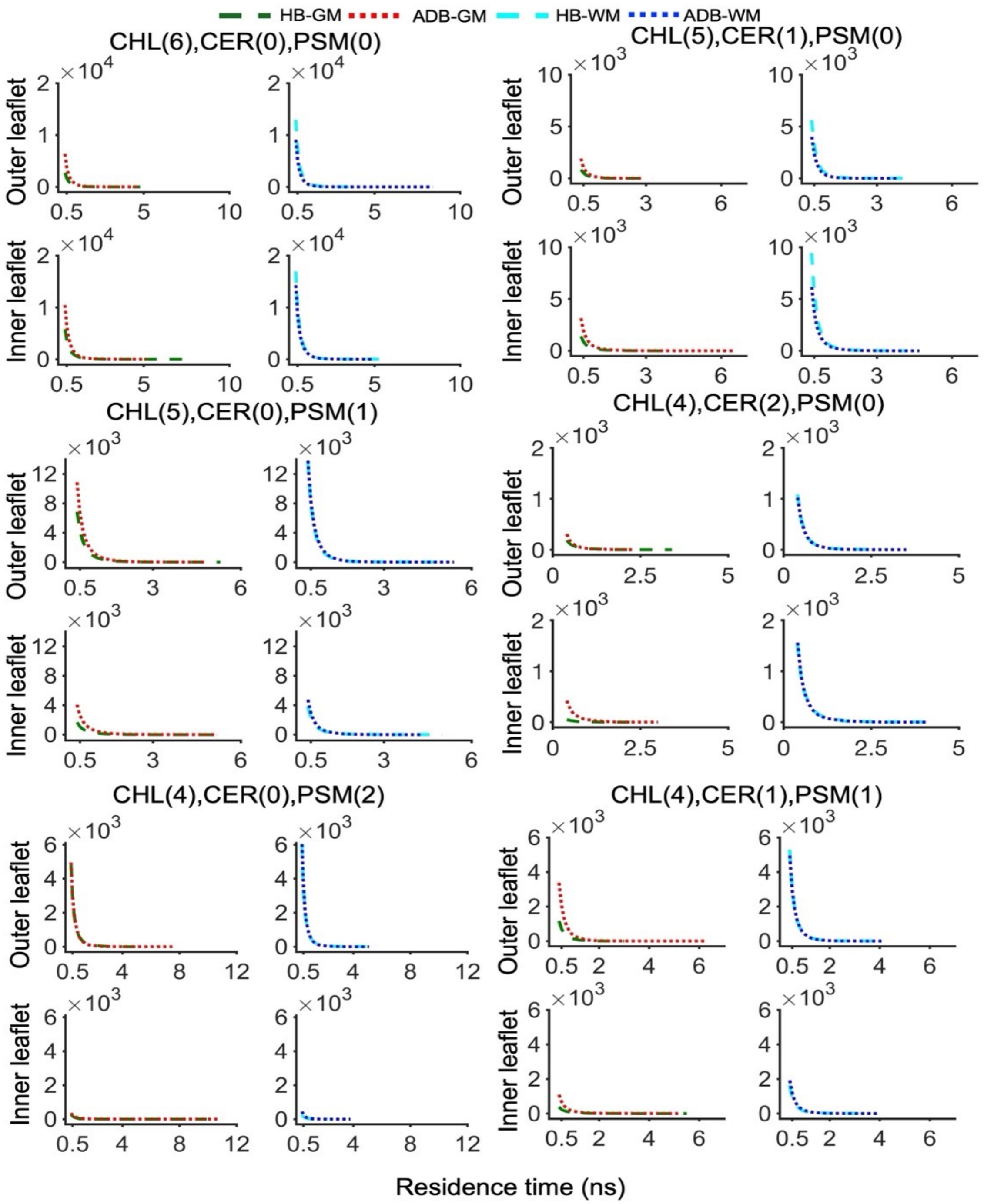


Fig. S9: Residence time distributions of different compositions of microdomains of size 6 calculated from the 1.5 μs concatenated trajectory. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, GM: gray matter, WM: white matter).

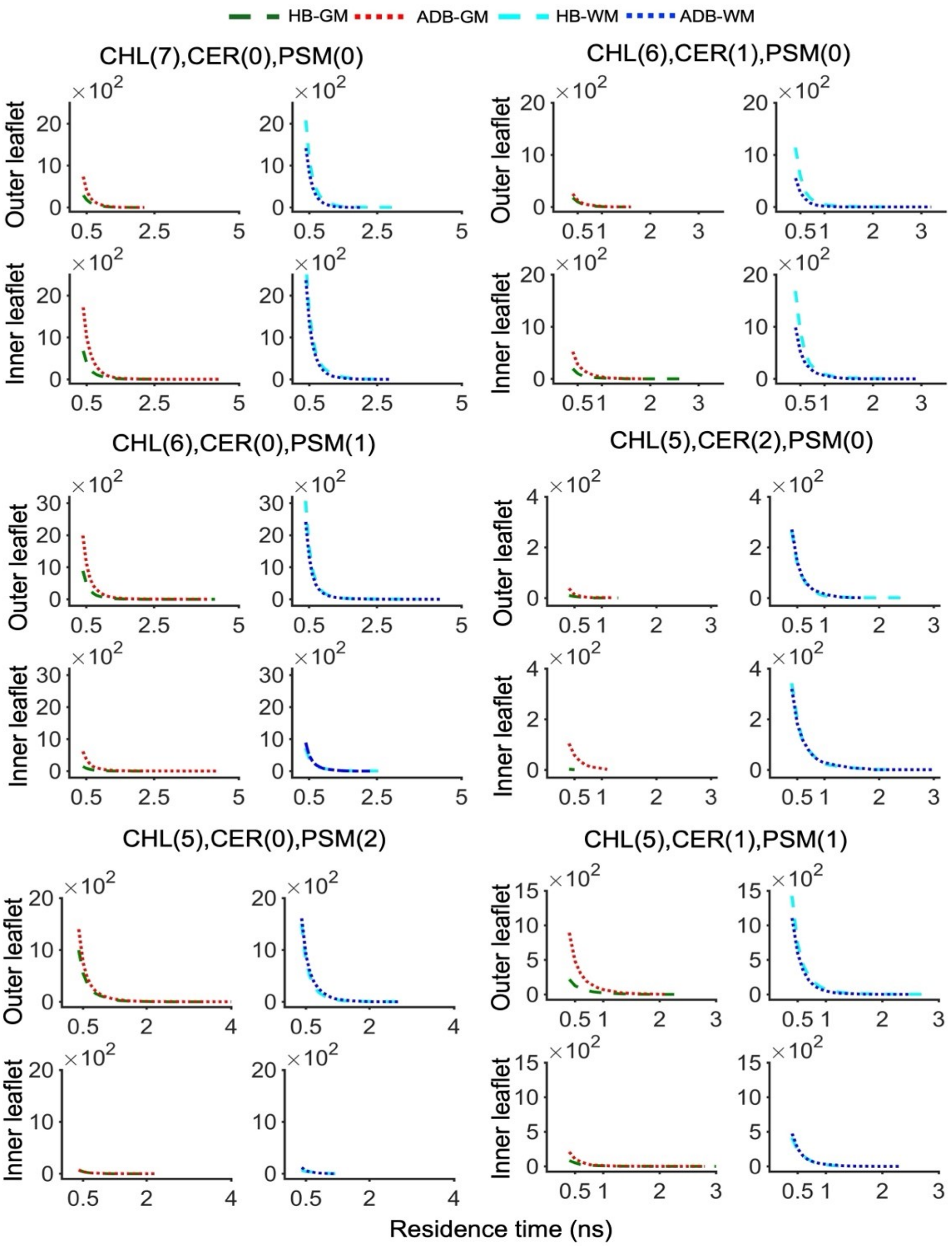


Fig. S10: Residence time distributions of different compositions of microdomains of size 7 calculated from the 1.5 μs concatenated trajectory. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, GM: gray matter, WM: white matter).

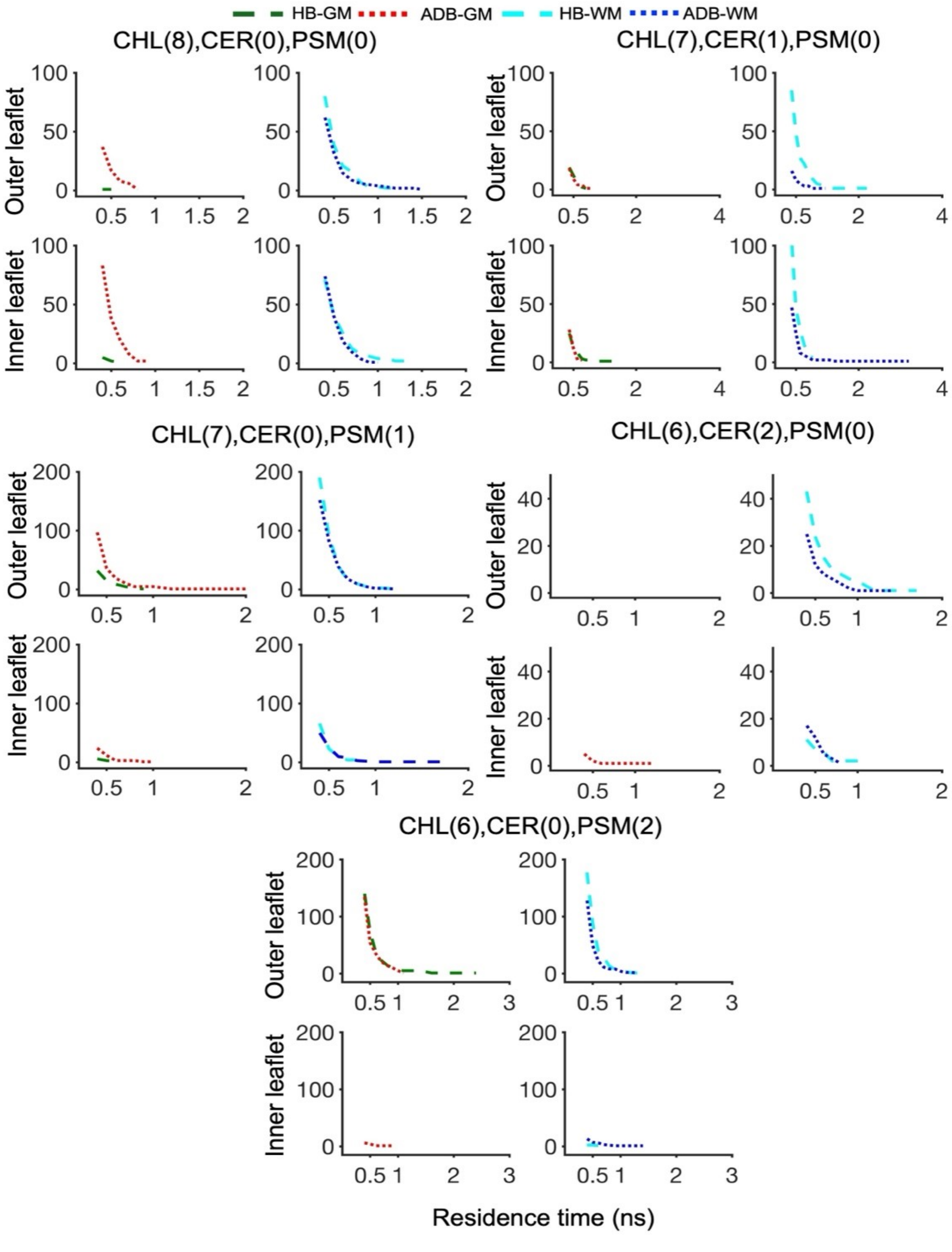


Fig. S11: Residence time distributions of different compositions of microdomains of size 8 calculated from the 1.5 μs concatenated trajectory. (HB: healthy membrane model, ADB: AD-mimicking diseased model membrane, GM: gray matter, WM: white matter).