Supporting Information

Predicting and interpreting EPR spectra of POPC lipid bilayers with transmembrane α-helical peptides from all-atom Molecular Dynamics simulations

Andrea Catte and Vasily S. Oganesyan

School of Chemistry, Pharmacy and Pharmacology, University of East Anglia, Norwich, NR4 7TJ, UK

Corresponding author: v.oganesyan@uea.ac.uk

1. Parametrisation of 5-PC nitroxide spin probe

Quantum chemical calculations of 5PC spin probe were performed with the Gaussian16[1] software package, to obtain partial charges using the restricted electrostatic potential approach (RESP) carried out with the RED software[2]. Force-field parameters for the new atom types of the nitroxide moiety in 5-PC (the unsaturated carbon atoms of the nitroxide ring, the saturated carbon atoms of the nitroxide ring, the nitrogen and the oxygen) were taken from a combination of geometry optimisation calculations in the gas phase and previous calculations. Equilibrium bond lengths and angles were taken directly from the minimised energy structures. Force constants were interpolated using the reference values in the AMBER99 force field[3] and the quantum mechanical calculations of Barone and co-workers[4]. Torsional parameters were calculated as described previously[5].

2. Prediction of EPR spectra from MD simulations

A trajectory-based approach for prediction of the spectral line shapes employs the Liouville von Neumann equation in the semi-classical approximation, often called the Langevin form of the Stochastic Liouville Equation:[6–8]

$$\frac{d\rho(t)}{dt} = -i\hat{\hat{L}}(t)\rho(t) \qquad \text{(S1)}$$

where $\rho(t)$ is a density matrix of the system and the Liouvillian $\hat{\hat{L}}$ is a superoperator anticommutator of the spin-Hamiltonian (expressed in the units of $\hbar$), $\hat{\hat{L}}(t) = [\hat{H}(t),\ \cdot]$. The spin-Hamiltonian of the nitroxide probe is given by[7,9]:

$$\hat{H}(t) = \beta \hat{S}_z g_{zz}(t) B + \hat{S}_z A_{zz}(t) \hat{I}_z + \hat{S}_z A_{zx}(t) \hat{I}_x + \hat{S}_z A_{zy}(t) \hat{I}_y \tag{S2}$$

For each orientation of the spin probe in the laboratory frame $\Omega(\mathrm{t})$ the appropriate elements of the **g**- and **A**-tensors are determined from:

$$\mathbf{g}(t) = R\big(\Omega(\mathrm{t})\big)\mathbf{g}_{\boldsymbol{d}} R^T\big(\Omega(\mathrm{t})\big) \tag{S3}$$

$$\mathbf{A}(t) = R\big(\Omega(\mathrm{t})\big)\mathbf{A}_{\boldsymbol{d}} R^T\big(\Omega(\mathrm{t})\big) \tag{S4}$$

where $\mathbf{g}_\mathrm{d}$ and $\mathbf{A}_\mathrm{d}$ are the tensors diagonalised in the frame of the nitroxide and $R\big(\Omega(\mathrm{t})\big)$ is the Euler matrix for the rotation from the nitroxide to the laboratory frame[6,7,10] .

The form of spin-Hamiltonian (S2) allows explicit analytical solutions for both the eigenvalues and eigenvectors[7]. At each time increment Δt the initial propagation of the spin density matrix is achieved analytically in Hilbert space using the expressions for both eigenvalues and eigenvectors of the Spin-Hamiltonian as reported previously[7,11]. For sufficiently small Δt propagation is carried out using the following approximation:

$$\rho(t + \Delta t) \approx \exp\left(-i\hat{\hat{L}}(t)\Delta t\right)\rho(t) \tag{S5}$$

In the Hilbert space Eq (S5) is equivalent to the following unitary transformation of the density matrix occurring during Δt time interval:

$$\rho(t + \Delta t) \approx \exp\left(-i\hat{H}(t)\Delta t\right)\rho(t)\exp\left(i\hat{H}(t)\Delta t\right) \tag{S6}$$

where the unitary transformation:

$$\exp\big(-i\hat{H}(t)\Delta t\big) = \hat{V}(t)\exp\left(i\hat{D}(t)\Delta t\right)\hat{V}^{+}(t) \tag{S7}$$

is expressed in terms of $\hat{V}$ and $\hat{D}$ which are the matrix of the eigenvector columns and diagonal matrix of the eigenvalues, respectively, of the SH (S2) for each orientation $\Omega(t)$. A sufficient

number of propagations from randomly selected initial points in the MD trajectory are generated and used for statistical averaging. Statistical averaging was achieved by the "sliding time window technique" allowing the use of single MD trajectories for predicting EPR line shapes[6,11]. Additional angular averaging is carried out in order to account for even distribution of lipid bilayers in the sample.

In most cases the rotational dynamics associated with the nitroxide spin labels and probes falls within the 0.1 ns - 100 ns timescale. In the current work relatively long total MD trajectories allowed the simulation of EPR spectra directly by propagation of the spin density matrix along the required sampling time using Equations (S5) - (S7) without further approximations.

Once propagation of the spin density matrix is completed EPR line shapes are obtained by applying a Fourier transform to the time dependent averaged transverse magnetisation $\langle M_+(t)\rangle$ into the frequency of field domain. $\langle M_+(t)\rangle$ is calculated according to:

$$\langle M_+(t)\rangle \propto Tr\left(\hat{S}_+\rho(t)\right) \tag{S8}$$

All spectra have been simulated using the MD-EPR simulation suite SpinMolDyn (formerly EPRSSP_DYN)[6,10–13]

3. Fitting of the correlation functions of the z-axis of POPC lipid at C position 5 in the sn-1 chain

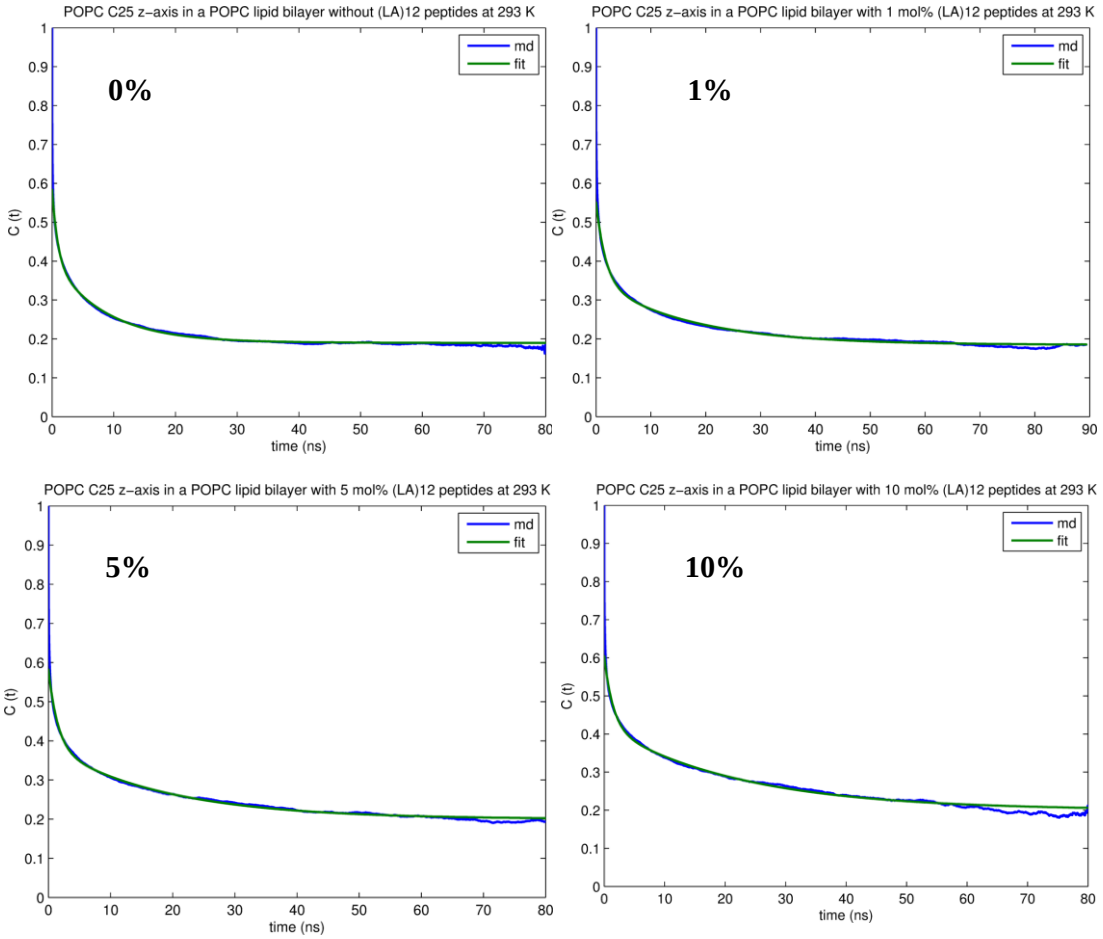

Figure S1. Autocorrelation functions of the molecular z-axis of POPC lipid at carbon position 5 in the sn-1 chain, defined as the cross product between two C-H adjoin bond, for different % mol concentrations of $(LA)_{12}$ peptides at 293 K. Autocorrelation functions calculated from MD trajectories using Eq (1) and their bi-exponential fittings using Eq (3) from the main text are shown by blue and green lines, respectively.

References:

1 M. J. Frisch et al., *Gaussian16, Revision C0.1*, Gaussian, Inc., Wallingford CT, 2016.

2 F.-Y. Dupradeau, A. Pigache, T. Zaffran, C. Savineau, R. Lelong, N. Grivel, D. Lelong, W. Rosanski and P. Cieplak, *Physical Chemistry Chemical Physics*, 2010, **12**, 7821.

3 W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell and P. A. Kollman, *J Am Chem Soc*, 1995, **117**, 5179–5197.

4 V. Barone, A. Bencini, M. Cossi, A. Di Matteo, M. Mattesini and F. Totti, *J Am Chem Soc*, 1998, **120**, 7069–7078.

5 F. Chami, M. R. Wilson and V. S. Oganesyan, *Soft Matter*, 2012, **8**, 6823.

6 V. S. Oganesyan, *Phys. Chem. Chem. Phys.*, 2011, **13**, 4724–4737.

7 S. DeSensi, D. P. Rangel, A. H. Beth, T. P. Lybrand and E. J. Hustedt, *Biophys J*, 2008, **94**, 3798–3809.

8 D. Sezer, J. H. Freed and B. Roux, *J Phys Chem B*, 2008, **112**, 5755–5767.

9 H. Steinhoff and W. L. Hubbell, *Biophys J*, 1996, **71**, 2201–2212.

10 V. Oganesyan, *SPR: Electron Paramagnetic Resonance, ed Gilbert B, Chechik V, Murphy DM (Royal Society of Chemistry, London)*, 2015, **24**, 32–61.

11 V. S. Oganesyan, *Liq Cryst*, 2018, **45**, 2139–2157.

12 V. S. Oganesyan, *Journal of Magnetic Resonance*, 2007, **188**, 196–205.

13 SpinMolDyn, https://www.uea.ac.uk/groups-and-centres/projects/spinmoldyn.