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1 **The dynamical Matryoshka model: 3. Diffusive nature of the atomic motions contained in a new**
2 **dynamical model for deciphering local lipid dynamics**

3

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25 **Abstract**

26 In accompanying papers [Bicout et al., BioRxiv 10.1101/2021.09.21.461198 (2021); Cissé et al.,
27 BioRxiv 10.1101/2022.03.30.486370 (2022)], a new model called Matryoshka model has been
28 proposed to describe the geometry of atomic motions in phospholipid molecules in bilayers
29 and multilamellar vesicles based on their quasielastic neutron scattering (QENS) spectra. Here,
30 in order to characterize the relaxational aspects of this model, the energy widths of the QENS
31 spectra of the samples were analyzed first in a model-free way. The spectra were decomposed
32 into three Lorentzian functions, which are classified as slow, intermediate, and fast motions
33 depending on their widths. The analysis provides the diffusion coefficients, residence times,
34 and geometrical parameters for the three classes of motions. The results corroborate the
35 parameter values such as the amplitudes and the mobile fractions of atomic motions obtained
36 by the application of the Matryoshka model to the same samples. Since the current analysis
37 was carried out independently of the development of the Matryoshka model, the present
38 results enhance the validity of the model. The model will serve as a powerful tool to decipher
39 the dynamics of lipid molecules not only in model systems, but also in more complex systems
40 such as mixtures of different kinds of lipids or natural cell membranes.

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46 **Keywords (maximum 6)**

47 Matryoshka model, quasielastic neutron scattering, lipids, molecular dynamics, diffusion

48

49 1. Introduction

50 Cell membranes play an essential role in cell function, including the boundary formation of
51 organelles and cells, and the transport of chemical substances exploiting their permeability. It
52 is known that cell membranes consist of various types of lipids and alter their lipid composition
53 to adapt to extracellular environments such as temperature and pH so that they function
54 properly at given environments [1,2]. It is thus important to understand the physical and
55 chemical properties of lipid molecules in detail to reveal the mechanism of their biological
56 functions. Lipid membranes can undergo phase transitions from crystalline, gel, to fluid phases
57 depending on temperature or pressure, which impact their dynamical properties as well as their
58 structures. The motions within membranes span a wide range of time- and space-scales: The
59 intramolecular motions, including the rotation of methylene groups, occur in the picosecond
60 regime, while large-scale motions, such as membrane undulations, take place from the
61 nanosecond to the millisecond regimes [3–7]. In order to understand their dynamical nature in
62 different physicochemical environments, various experimental techniques have been used such
63 as incoherent neutron scattering [8], nuclear magnetic resonance spectroscopy (NMR) [9],
64 fluorescence recovery after photobleaching (FRAP) [10] depending on the time- and space-
65 scale of interest. Together with the advancement in molecular dynamics (MD) simulation
66 techniques and their combination with experiments [11–13], a huge amount of knowledge of
67 individual and collective lipid motions has been accumulated. However, there does not still
68 exist a unified dynamical framework that describes comprehensively the lipid motions
69 occurring at different time domains.

70

71 Among the experimental techniques employed so far, quasielastic neutron scattering (QENS)
72 is a powerful tool to study the dynamics of lipid molecules at the pico-nanosecond timescale

73 and Å–nm length scale, which correspond to the crossover region from localized vibrations to
74 various diffusional processes occurring at a much longer timescale involving bilayer bending
75 and membrane undulation. In particular, QENS provides detailed information on the motions
76 of hydrogen atoms since the incoherent scattering cross-section of the hydrogen atom is much
77 larger than that of any other atom found in biomolecules or its isotope deuterium [14].
78 Moreover, another advantage of this technique is that various motions which occur at different
79 time scales can be focused on by changing the energy resolution of the neutron spectrometers,
80 which is equal to shifting the time window of the observation.

81

82 In order to interpret the QENS spectra, thereby capturing the dynamical properties of lipid
83 molecules in detail, establishment of a theoretical framework that describes relevant atomic
84 motions is indispensable. In 1989, the first theoretical model describing the lipid motions in
85 bilayers was reported [4], where different motional processes were assumed depending on the
86 energy resolutions and the sample conditions. Similar approaches have widely been employed
87 not only for lipid molecules [5,15–17], but also for other molecules such as cholesterol inserted
88 to lipid bilayers [18]. Later, a more sophisticated model has been presented, where QENS
89 spectra were decomposed into three kinds of motions with distinct time scales, i.e. slow,
90 intermediate, and fast motions [19,20]. In this model, each component of these three types of
91 motions was interpreted by various combinations of motions in lipid molecules. Although all
92 of these studies have significantly advanced our understanding of the dynamics of lipid
93 molecules and helped provide a physical picture, a more holistic description of the possible
94 motions contained in the lipid molecules was still missing.

95

96 Based on the dynamical models above, a new theoretical model named Matryoshka model has

97 been presented in the accompanying papers [21,22], where the dynamic structure factor $S(Q,$
98 $\omega)$ is analytically expressed by directly incorporating the scattering functions of various motions
99 that lipid molecules undergo in addition to the decomposition of all the possible motions into
100 three classes, i.e. slow, intermediate, and fast motions. This model successfully accounts for the
101 elastic incoherent structure factor (EISF) and the quasi-elastic incoherent structure factor (QISF)
102 profiles, which are derived from the geometry of atomic motions in the samples, of 1,2-
103 dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) in multi-lamellar bilayers (MLB) and multi-
104 lamellar vesicles (MLV), and 1,2-dimyristoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DMPG) in
105 MLB at various temperatures. This has enabled the detailed investigation of the geometry of
106 motions in lipid molecules placed in various physicochemical environments. On the other hand,
107 although the diffusive nature of the motions classified as the slow, intermediate and fast
108 motions in the Matryoshka model is theoretically characterized through a series of analytical
109 equations of relaxation rates of each of these motions [21], it has not yet been experimentally
110 characterized. In the present paper, this aspect of each of the three types of motions are
111 reported and discussed.

112

113 **2. Materials and methods**

114 *2-1. Sample preparation and neutron scattering experiments*

115 Details of sample preparations, QENS experiments, and the analysis of the QENS spectra are
116 described in the accompanying papers [21,22]. Briefly, the following samples were used for
117 neutron experiments:

- 118 – DMPC in MLB oriented at 135° relative to the incident neutron beam (DMPC MLB135),
119 which mainly focuses on the in-plane motions
- 120 – DMPC in MLB oriented at 45° to focus on the out-of-plane motions (DMPC MLB45)

- 121 – DMPC in MLB oriented at 135° with hydrogen atoms in the tails perdeuterated (d54DMPC)
- 122 – DMPC in MLV (DMPC MLV)
- 123 – DMPG in MLB oriented at 135° relative to the incident neutron beam (DMPG MLB135),
- 124 focusing on the in-plane motions

125 All the samples except for DMPG MLB135 were measured on the IN6 spectrometer
 126 (<https://www.ill.eu/users/instruments/instruments-list/sharp/description/instrument-layout>) at
 127 the Institut Laue-Langevin (ILL; in Grenoble, France) with the energy resolution of ~70 μeV,
 128 which corresponds to a time window of ~20 ps. The spectra of DMPC MLB135 and DMPG
 129 MLB135 were measured on the IN5 spectrometer
 130 (<https://www.ill.eu/users/instruments/instruments-list/in5/description/instrument-layout>) at
 131 the ILL with the energy resolution of ~90 μeV (~15 ps). Each spectrum was fitted by the
 132 following phenomenological equation [14] that contains three types of motions with different
 133 relaxational times:

134

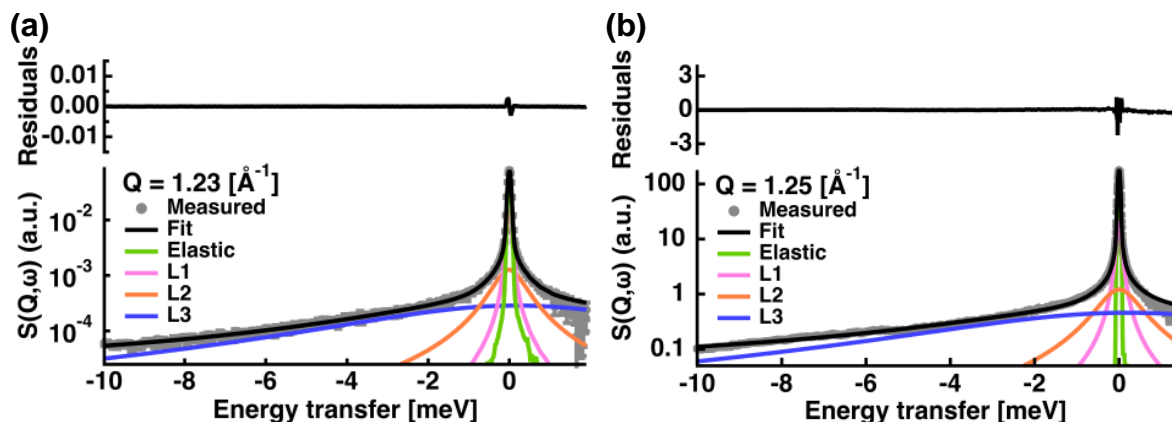
$$135 \quad S_{lipids}(Q, \omega) = C(Q)[A_0(Q)\delta(\omega) + \sum_{i=1}^3 A_i(Q)L_i(Q, \omega)] \otimes R(Q, \omega) + B(Q), \quad (1)$$

136

137 where $C(Q) = C e^{-\langle u^2 \rangle Q^2}$ represents the scaling factor C including the Debye-Waller factor with
 138 $\langle u^2 \rangle$ the mean square amplitude of vibration, $A_0(Q)\delta(\omega)$ is an elastic component with $A_0(Q)$
 139 being the elastic incoherent structure factor (EISF) and $\delta(\omega)$ being the Dirac delta function. $L_i(Q,$
 140 $\omega) = (1/\pi) \times (\Gamma_i(Q) / (\Gamma_i(Q)^2 + \omega^2))$, and $i = 1, 2, 3$ is the i -th Lorentzian function describing the
 141 atomic motion in lipids. $\Gamma_i(Q)$ is the half-width at half-maximum (HWHM) of $L_i(Q, \omega)$. $R(Q, \omega)$
 142 refers to the instrumental resolution function, which is obtained from the Vanadium

143 measurement, $B(Q)$ is a flat background, that includes the instrument contribution, and/or fast
 144 vibrational motions outside the current time window. Finally, \otimes denotes the convolution
 145 operation. In the following, the three Lorentzian functions are classified as the slow motions
 146 (the narrowest Lorentzian), the intermediate motions, and the fast motions (the broadest
 147 Lorentzian). The spectra in the range of $0.37 \text{ \AA}^{-1} \leq Q \leq 2.02 \text{ \AA}^{-1}$ (for the IN6 data) and 0.33 \AA^{-1}
 148 $\leq Q \leq 1.82 \text{ \AA}^{-1}$ (for the IN5 data) were used for the fitting. Note, however, that for the spectra
 149 obtained on IN6, the HWHMs of the Lorentzian functions at the first two lowest Q values were
 150 found to show unrealistically higher values than other data points probably due to multiple
 151 scattering effects. Therefore, the spectra in the range of $0.72 \text{ \AA}^{-1} \leq Q \leq 2.02 \text{ \AA}^{-1}$ were analyzed
 152 for IN6 data and the data points at $Q = 0.37 \text{ \AA}^{-1}$ and 0.55 \AA^{-1} were excluded from the analysis
 153 and not presented in this study. Fits were carried out in the range of $-10 \text{ meV} \leq \Delta E \leq 2 \text{ meV}$
 154 (for the IN6 data) and $-10 \text{ meV} \leq \Delta E \leq 1.3 \text{ meV}$ (for the IN5 data) using IGOR Pro software
 155 (WaveMetrics, Lake Oswego, OR, USA). Some examples of fits are shown in Fig. 1.

156



157

158 **Figure 1.** Examples of fits of the QENS spectra of DMPC MLB135 measured on IN6 (a) and IN5
 159 (b). (a) and (b) are the data at $Q = 1.23 \text{ \AA}^{-1}$ and $T = 283 \text{ K}$, and at $Q = 1.25 \text{ \AA}^{-1}$ and $T = 280 \text{ K}$,

160 respectively. The grey circles are the experimental data points with corresponding statistical
161 errors. The total fit is represented by the black line. The green line corresponds to the elastic
162 peak convoluted by the resolution function, which is directly given by the Vanadium
163 measurements. The magenta, orange and blue curves are the Lorentzian functions convoluted
164 by $R(Q, \omega)$ for slow, intermediate and fast motions, respectively. The upper panels show the
165 residuals of the fits.
166

167 *2-2. Lipid motions contained in the Matryoshka model*

168 In the Matryoshka model [21] as shown schematically in Fig. 2, a lipid molecule is represented
169 by a head group and a tail group (with only one tail instead of two for the sake of simplicity),
170 which contain a fraction z and a fraction $(1-z)$ of the total number of hydrogen atoms,
171 respectively. The values of z are 0.25 and 0.18 for DMPC and DMPG, respectively. The slow,
172 intermediate, and fast motions contain the following internal and/or collective motions of the
173 lipid molecules (Table 1):

174 (i) The slow motions contain the following two movements:

- 175 – A whole lipid molecule undergoes two-dimensional diffusion (2D-diffusion)
176 within the membrane plane. The space where the lipid molecule can move is
177 represented by a cylinder with the radius of $R_{||}$.
- 178 – The whole lipid molecule undergoes one-dimensional diffusion in the direction
179 perpendicular to the membrane plane (in-out of the plane diffusion). This process
180 is characterized by the force constant k , which characterizes the rigidity of the
181 membrane in the normal direction of the membrane plane.

182 (ii) The intermediate motions include the following three motions:

- 183 – The whole lipid molecule undergoes rotational diffusion around its long axis. This
184 process is characterized by the distance between the long axis and the center of
185 inertia of all the hydrogen atoms R_H .

186 – The head group performs a head-flip-flop motion between the angles $\pm\alpha$ with
187 respect to the normal axis. The α values are 32.3° and 30° for DMPC and DMPG,
188 respectively [23,24].

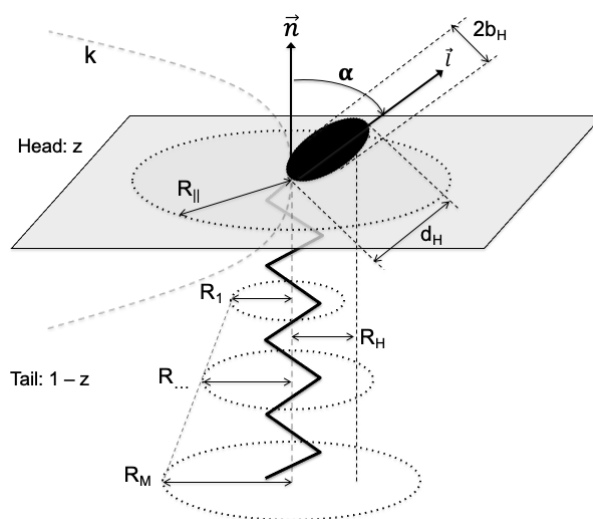
189 – The head group also performs a rotational motion around its own axis with the
190 radius b_H .

191 (iii) The fast motions include the following two motions:

192 – The tail group undergoes two-dimensional diffusion within the membrane plane
193 with its radius increasing as a function of the distance of the H atoms from the
194 head group along the tail axis. This radius is defined as $\sqrt{m}R_1$, where R_1 is the
195 radius of the 2D-diffusion of H atoms closest to the head group and m denotes
196 the index number of a methylene/methyl group of the tail group. The range of m
197 is $1 \leq m \leq M$, where M is the total number of methylene/methyl groups on the
198 tail ($M = 14$ for both DMPC and DMPG). Such model limits the radius at the
199 bottom of the tail, which is constrained by other lipids in a membrane.

200 – Hydrogen atoms in the methylene and methyl groups in both the head and tail
201 groups undergo rotational jump-diffusion. Two-sites jump diffusion was assumed,
202 where the residence times of the two sites are τ_1 and τ_2 , respectively, with the jump
203 distance corresponding to the H-C-H distance of $d = 2.2$ [Å] [25].

204 The above parameters $R_{||}$, k , R_H , b_H , R_1 , and $\phi (= \tau_1/(\tau_1+\tau_2))$, which characterize the geometry of
205 motions of atoms in the lipids, were determined by the EISF/QISF analysis in the accompanying
206 papers [21,22].



207

208 **Figure 2.** Schematic illustration of the Matryoshka model. A lipid molecule in membranes is
 209 drawn, on which parameters employed in the Matryoshka model are shown (for details of the
 210 parameters, refer to the main text). This figure is taken from Figure 2 of [21].

211

212 **Table 1. Classification of various motions contained in the Matryoshka model.**

	Internal motion	Collective motion
Slow motions		2D-diffusion in-out of the plane diffusion
Intermediate motions	Head-flip-flop Rotation (head)	Rotational diffusion
Fast motions	2D-diffusion (tail) Jump diffusion (tail and head)	

213

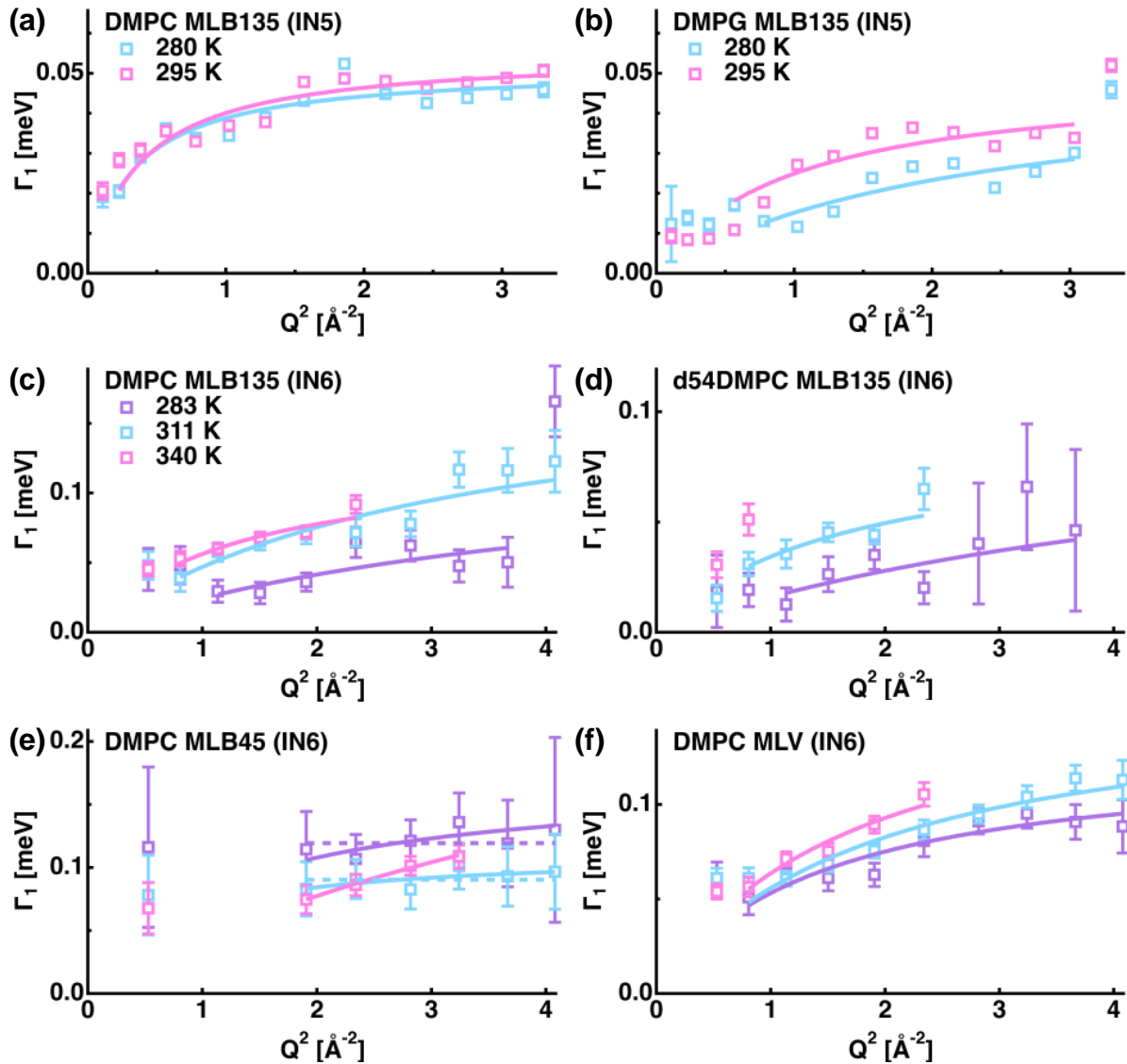
214 3. Results and discussion

215 3.1. Slow motions

216 The Q^2 -dependences of $\Gamma_1(Q)$, which corresponds to the slow motions, of all the samples are
 217 shown in Fig. 3. It is clearly seen that the $\Gamma_1(Q)$ values of all the samples do not reach zero as Q
 218 approaches $0.0 \text{ [\AA}^{-1}]$ while they show asymptotic behavior at higher Q^2 values, suggesting that
 219 the underlying process of this behavior is the jump diffusion within a confined space [14]. Note

220 that in the previous study [19], the narrowest Lorentzian function of the DMPC MLB135 was
221 interpreted as a continuous diffusion within a confined space. This discrepancy is due to the
222 fact that the energy resolutions in the current study are much higher and the accessible Q-
223 ranges are much larger than in the previous study, suggesting that the present data represent
224 faster and smaller-scale motions. Therefore, the jump-diffusional behavior of $\Gamma_1(Q)$ indicates
225 that each step of the global jump diffusion of the entire lipid molecule is resolved here. In the
226 case of DMPC MLB45 at 283 K and 311 K, the $\Gamma_1(Q)$ values might be constant over the Q-range
227 measured, suggesting that these motions are described by a diffusion on a linear segment or
228 by rotational diffusion [26]. Since it is not possible to distinguish the type of motions due to
229 the limited data points and large error bars, analysis was conducted for both types of motions
230 for these two conditions.

231



232

233 **Figure 3.** Q^2 -dependences of $\Gamma_1(Q)$ of DMPC MLB135 (a), DMPG MLB135 (b) measured on IN5,
 234 DMPC MLB135 (c), d54DMPC MLB135 (d), DMPC MLB45 (e), and DMPC MLV (f) measured on
 235 IN6. (a, b): The data points at 280 K and 295 K are shown in cyan and magenta, respectively. (c-
 236 f): The data points at 283 K, 311 K, and 340 K are shown in purple, cyan, and magenta,
 237 respectively. The solid lines show the corresponding fits by the equation describing the jump-
 238 diffusion (Eq. (2)) and the dotted lines (DMPC MLB45 at 283 K and 311 K) are the fits by the
 239 equation describing the diffusion on a linear segment ($\Gamma_1(Q) = 1/\tau_1$, where τ_1 is the correlation
 240 time.). Error bars are within symbols if not shown.

241

242 The radius of the confined space (a), which is related to the center-of-mass diffusion, was
 243 estimated from the Q_0 value, at which $\Gamma_1(Q)$ begins to increase, based on the relation $a = \pi/Q_0$
 244 [27]. Since some data points were missing for DMPC MLB45 due to the experimental

245 configuration, the a values were estimated for the other three samples, which were found to
 246 be 2.9–3.5 Å and 3.6–6.6 Å for IN6 and IN5, respectively, as shown in Table 2. The estimated a
 247 values of DMPC MLB135 are largely different between IN6 and IN5. One possibility of this
 248 difference would be the fact that it is not easy to determine the Q_0 value due to the limited
 249 data points and fluctuations of the $\Gamma_1(Q)$ values in the low- Q region. Overall, the estimated a
 250 values here are smaller than the lateral distance between phospholipid molecules. However,
 251 since these values correspond to those resolved by the current time-windows, it is not
 252 surprising to obtain such smaller values.

253

254 **Table 2. Estimated radii of the confined space a [Å] for slow motions**

	280 K	283 K	295 K	311 K	340 K
DMPC MLB135 (IN6)		2.9		2.9	2.9
DMPC MLB135 (IN5)	6.6		6.6		
d45DMPC MLB135 (IN6)		3.5		3.5	n/a
DMPC MLB45 (IN6)		n/a		n/a	n/a
DMPC MLV (IN6)		3.5		3.5	3.5
DMPG MLB135 (IN5)	3.6		4.2		

255

256

257 Next, dynamics' parameters of the slow motions were estimated by the fitting of the $\Gamma_1(Q)$
 258 values using the equation describing the jump diffusion [14];

$$259 \Gamma_1(Q) = D_1 Q^2 / (1 + D_1 Q^2 \tau_1), \quad (2)$$

260 where D_1 is the jump diffusion coefficient and τ_1 is the residence time before the jump.

261 Furthermore, based on these dynamics' parameters, the jump distance l_1 was also estimated

262 by the relation $l_1 = \sqrt{4D_1\tau_1}$ for in-plane motions, $l_1 = \sqrt{2D_1\tau_1}$ for out-of-plane motions, and l_1

263 $= \sqrt{6D_1\tau_1}$ for MLVs. In addition to this analysis, for DMPC MLB45 at 283 K and 311K, the

264 correlation time was also calculated using the relation $\tau_1 = 1/\Gamma_1(Q)$ assuming the diffusion on a

265 linear segment. However, the obtained τ_1 values were the same within the errors as those
266 obtained by the jump-diffusion model (Table S1). Therefore, in the following, discussion is
267 made based on the dynamics' parameters obtained by the jump-diffusion model. The summary
268 of the obtained dynamics' parameters is shown in Fig. 4 (the D_1 and τ_1 values are tabulated in
269 Tables S1 and S2). The obtained parameters of DMPC MLB135 and DMPC MLB45 are found to
270 be similar within the errors except at 340 K. This is in agreement with a MD simulation study
271 showing that the center-of-mass diffusion coefficients of DMPC at 303 K are essentially the
272 same between the in-plane and the out-of-plane directions (the difference is less than 10%)
273 [28].

274

275 When comparing the D_1 values of d54DMPC MLB135 and DMPC MLB135, there is a tendency
276 that D_1 of the former is slightly smaller at both temperatures although these differences are
277 within errors. The former mainly derives from the contribution of the head group and the latter
278 contains contributions of both the head and the tail groups. This result thus implies that the
279 diffusion of the head group might be slower than that of the tail group, which supports an
280 assumption made in the Matryoshka-model, where the tail group motions are faster than the
281 head group motions [21,22]. The tail group would undergo diffusive motions around the hinge
282 between the tail and the head groups while the head group is less mobile, which increases the
283 D_1 value of the whole molecule compared with that of the head group as observed here. In a
284 previous QENS study on the bilayers of dipalmitoyl-phosphatidylcholine (DPPC) with and
285 without deuteration of its tail group, the same tendency has been observed [29]. The EISF/QISF
286 analysis by the Matryoshka model on the same samples has shown that the diffusion radius of
287 the head group (d54DMPC MLB135) on the membrane plane is larger than that of the whole
288 molecule [21,22]. Together with this finding, the present results imply that the head group of

289 DMPC takes more time to explore the available space than the tail group.

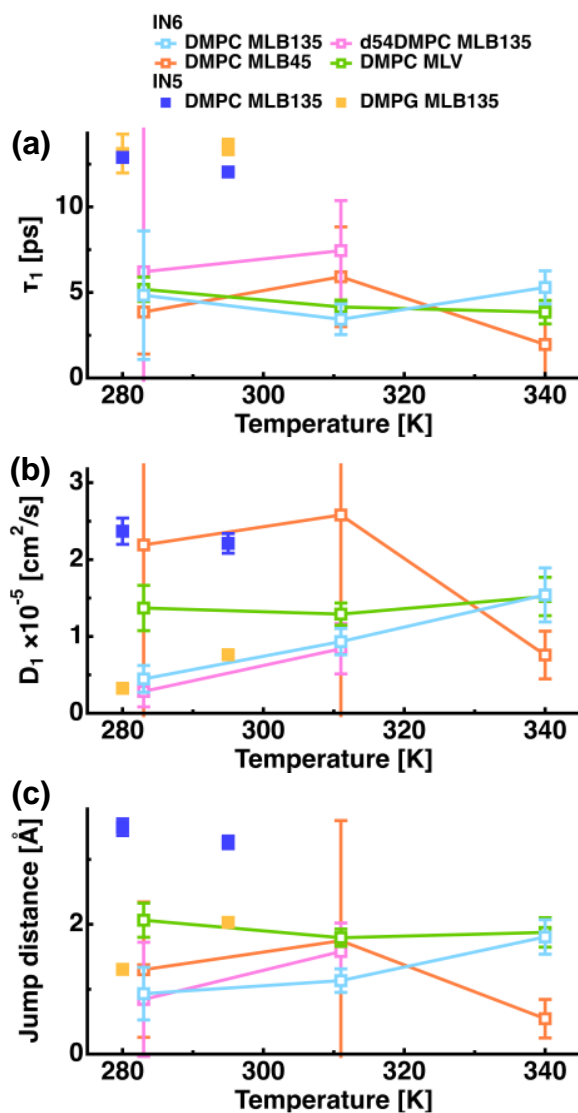
290

291 The dynamics' parameters of the slow motions of DMPC MLB135 were found to be larger for
292 IN5 than for IN6. The geometry of motions for the slow motion of DMPC MLB135 is also slightly
293 different between the measurements on IN6 and those on IN5 [22]. Because MLBs measured
294 on IN6 were more hydrated than those measured on IN5 (27 wt% and 10 wt% hydration for
295 IN6 and IN5 measurements, respectively) and thus enhanced dynamics is expected for IN6, the
296 differences in dynamics' parameters between IN5 and IN6 observed here are not due to the
297 difference in sample environments, but suggest that there is a distribution in the diffusive
298 motions classified as the slow motions. The present results suggest that slight differences in
299 atomic motions are detected by QENS and seen by application of the Matryoshka model, which
300 proves their high sensitivity to decipher the dynamical nature of the samples.

301

302 The D_1 values and the jump distance of DMPC MLB135 obtained on IN5 were found to be
303 larger than those of DMPG MLB135, indicating that the diffusive motions are restrained in
304 DMPG. Since the head group of DMPC has a larger mass than that of DMPG (the molecular
305 weights are 104 and 92 Da for the head groups of DMPC and DMPG, respectively), it is expected
306 that DMPC undergoes slower diffusive motions. However, the head group of DMPC possesses
307 a positive charge, but is more hydrophobic than that of DMPG, which has two hydroxyl groups
308 and thus polarity. It is likely that the hydration water molecules form less H-bonding with the
309 head groups of DMPC than those of DMPG, indicating that the atoms in the head group of
310 DMPC can move more freely. Because of these differences, the motions of the whole lipid
311 molecule would also be enhanced for DMPC compared with DMPG.

312



313

314 **Figure 4.** Temperature dependence of the residence time (τ_1), the diffusion coefficient (D_1), and
 315 the jump distance (l_1) of the slow motions. The parameter values of DMPC MLB135, d54DMPC
 316 MLB135, DMPC MLB45, and DMPC MLV measured on IN6 are shown in cyan, magenta, orange,
 317 and green, respectively. Those of DMPC MLB135 and DMPG MLB135 measured on IN5 are
 318 shown in blue and pale orange, respectively.
 319

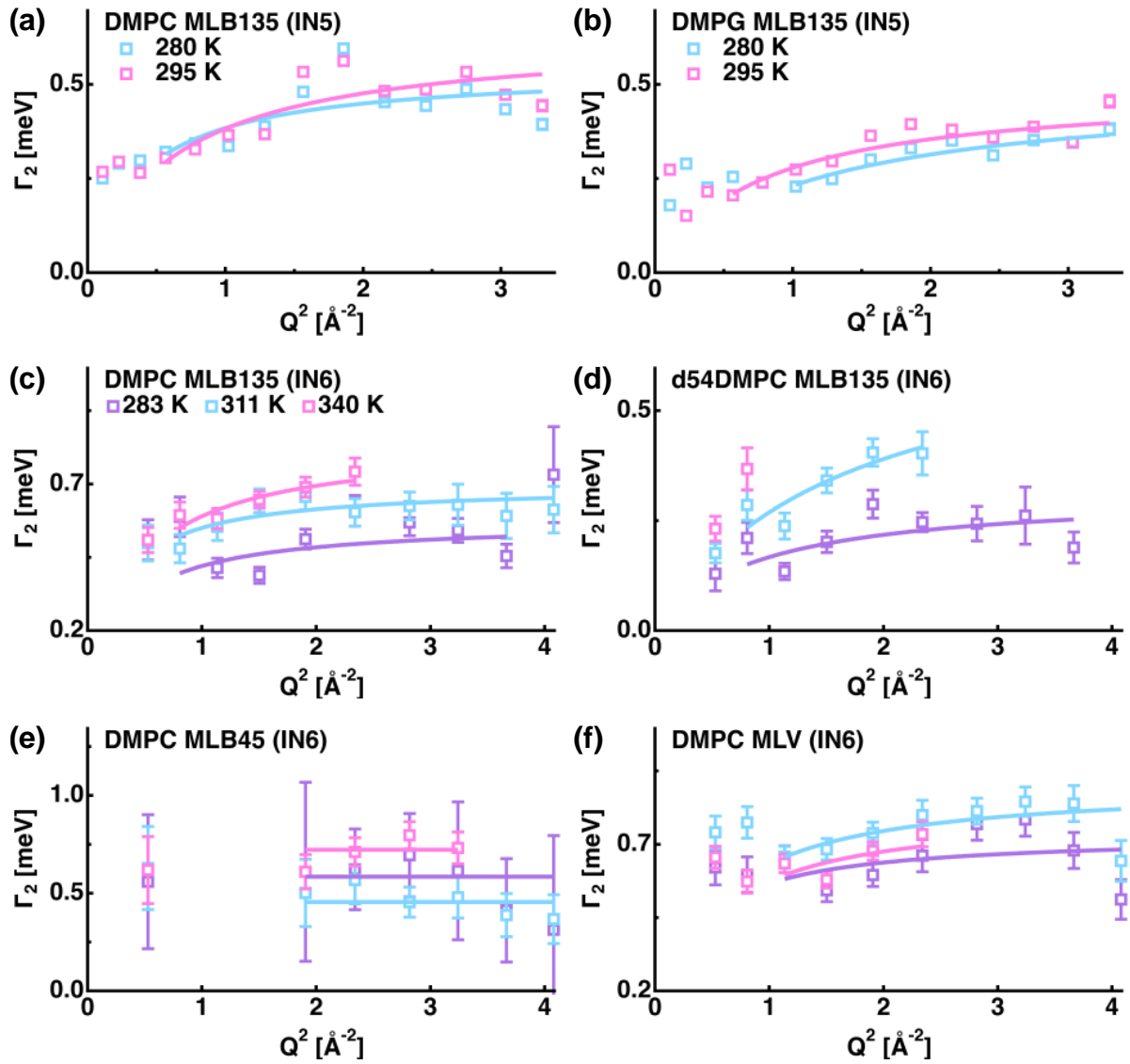
320 Regarding the comparison between DMPC MLB135 and DMPC MLV on IN6, it is found that
 321 while the τ_1 values are similar within the errors, the D_1 value and the jump distance are larger
 322 for MLVs at 283 K and 311 K. This could be due to the fact that the MLVs are generally more
 323 hydrated than MLBs [13]. The present results are also consistent with the results of the
 324 EISF/QISF analysis using the Matryoshka model, where the radius of a circle within which the
 325 whole lipid molecule can diffuse is larger for MLVs than MLBs [22].

326

327 *3.2. Intermediate motions*

328 The Q^2 -dependences of $\Gamma_2(Q)$ of all the samples are shown in Fig. 5. The profiles of all the
329 samples, except for DMPC MLB45, show non-zero values at low- Q regions, followed by an
330 asymptotic behavior, suggesting that these motions are described by jump diffusion within a
331 confined space [14]. On the other hand, the profiles for DMPC MLB45 do not show a Q^2 -
332 dependent behavior, indicating that this motion is described by a diffusion on a linear segment
333 or rotational diffusion [26]. Since the measurement of DMPC MLB45 mainly observes the
334 motion perpendicular to the membrane plane, it is reasonable that only a one-dimensional
335 motion is observed.

336

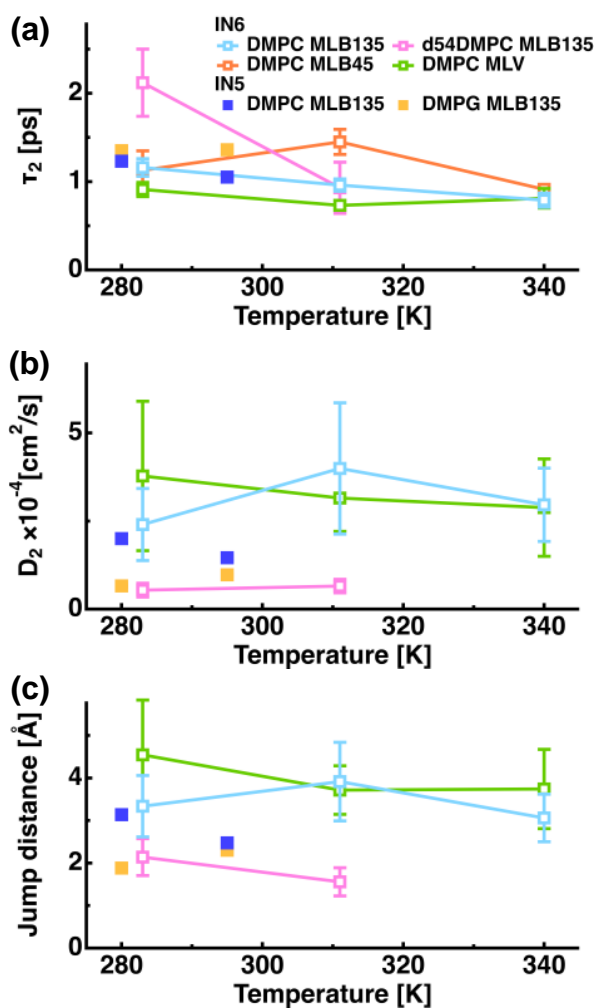


337

338 **Figure 5.** Q^2 -dependences of $\Gamma_2(Q)$ of the intermediate motions. The color scheme is the same
 339 as in Fig. 3. The solid lines show the fits by the equation describing the jump diffusion ($\Gamma_2(Q) =$
 340 $D_2 Q^2 / (1 + D_2 Q^2 \tau_2)$) or by the equation describing the diffusion on a linear segment ($\Gamma_2(Q) = 1/\tau_2$)
 341 for DMPC MLB45 (for the definition of the parameters, see the main text). Note that the scales
 342 on the ordinates are not the same in all the panels such that the fitting curves are better seen.
 343

344 In order to obtain the dynamical parameters related to intermediate motions, the profiles in
 345 Fig. 5 were fitted by the equation describing the jump diffusion model, $\Gamma_2(Q) = D_2 Q^2 / (1 + D_2 Q^2 \tau_2)$,
 346 where D_2 is the jump diffusion coefficient and τ_2 is the residence time before the jump [14] in
 347 the Q^2 -range between 0.81 \AA^{-2} and 4.08 \AA^{-2} for the IN6 data and the Q^2 -range between 0.58 \AA^{-2}
 348 2 and 3.30 \AA^{-2} for the IN5 data. Furthermore, based on these dynamics' parameters, the jump

349 distance l_2 was also estimated by the relation $l_2 = \sqrt{(4D_2\tau_2)}$ for in-plane motions and $l_2 = \sqrt{(6D_2\tau_2)}$
 350 for MLVs. The correlation time of DMPC MLB45 was calculated using the relation $\tau_2 = 1/\Gamma_2(Q)$.
 351
 352 The residence time (correlation time), jump diffusion coefficient, and the jump distance
 353 parameters obtained by the above fits are shown in Fig. 6 (a), (b), and (c), respectively (the
 354 parameter values are tabulated in Tables S1 and S2). It is found that as the temperature
 355 increases, the τ_2 values slightly decrease. There are no significant differences in the τ_2 values
 356 between DMPC MLB135 and DMPC MLB45, suggesting that the degree of interaction between
 357 atoms is similar in directions both parallel and perpendicular to the membrane plane.



358
 359 **Figure 6.** Temperature dependence of the residence time (τ_2), the diffusion coefficient (D_2), and
 360 the jump distance (l_2) of the intermediate motions. The color scheme is the same as in Fig. 4.

361

362 The τ_2 values of DMPC MLV were found to be smaller than those of DMPC MLB135, especially
363 at 283 K and 311 K, while the D_2 values and the l_2 values were similar between them. This
364 suggests that the atoms in MLVs move more rapidly than those in MLBs. Since lipid molecules
365 are generally more hydrated in MLVs than in MLBs [13], it is likely that more hydration water
366 enhances the frequency of the local motions in MLVs. Moreover, the mobile fraction of atoms,
367 which is estimated by the Matryoshka model [22], is smaller for DMPC MLB135 than for DMPC
368 MLV, suggesting that there exist more hydrogen atoms in MLBs that undergo slower motions
369 than those in MLVs.

370

371 The D_2 values shown in Fig. 6 (b) were larger than the translational diffusion coefficients of bulk
372 water, which are $2.0\text{--}2.3 \times 10^{-5} \text{ cm}^2/\text{s}$ at 293–300 K [30–32] although the residence times were
373 larger than that of bulk water. The same phenomenon was previously reported for protein
374 dynamics: A QENS study on human acetylcholinesterase (hAChE) has shown that the jump-
375 diffusion coefficients of atoms in hAChE were lower or even higher than those of bulk water at
376 90 μeV and 50 μeV energy resolutions, respectively [33]. Since the time-scale and the length-
377 scale of the observable motions depend on the energy resolution employed, the D_2 values
378 obtained in this study for atomic motions in lipids should be regarded as “effective” jump-
379 diffusion coefficients, which depend on the instrumental energy resolution. It would thus be
380 crucial to study the diffusive nature of local atomic motions in a wide range of time- and length-
381 scale to obtain the holistic physical picture of the dynamical behavior of lipid molecules.

382

383 The D_2 values of d54DMPC MLB135 were found to be much smaller than those of DMPC
384 MLB135 while the τ_2 values tend to be larger for the former, resulting in smaller l_2 values for

385 d54DMPC MLB135 than for DMPC MLB135. This suggests that the local atomic motions of the
386 tails are faster than those of the head groups. This is in good agreement with the Matryoshka
387 model [21], where it was necessary to ascribe the contribution of the tail groups to the fast
388 motions in order to fully account for the EISFs and QISFs of the current samples. Since the
389 Matryoshka model was established independently of the width analysis of Lorentzian functions
390 described in this paper, this agreement further enhances the validity of the Matryoshka model.
391 Moreover, it has been shown that the energetic barrier between conformational substates is
392 higher for the head groups than for the tail groups [34], which is consistent with the present
393 results.

394

395 The jump distances of the in-plane motions of the head group and whole molecule of DMPC
396 were found to be ~ 2 Å and 3–4 Å, respectively. The latter value corresponds to the distance
397 between the neighboring alkyl chains in the lipid molecules. On the other hand, according to
398 the analysis based on the Matryoshka model, the radii within which the whole molecules can
399 diffuse around are 1.8–2.4 Å (i.e. 3.6–4.8 Å in diameter) and 1.1–2.1 Å (2.2–4.2 Å in diameter)
400 for the corresponding samples, respectively [22]. The comparison of these values suggests that
401 while the whole DMPC molecule undergoes a jump motion over a distance corresponding to
402 the neighboring alkyl chains, its head group moves by about half of the maximum distance
403 available for it. This behavior of the head group could be due to the head-flip-flop motion as
404 introduced in the intermediate motion of the Matryoshka model, which changes the distance
405 between the centers of mass of the head group and the tail groups projected onto the
406 membrane plane. Furthermore, the current study suggests that all of the above motions take
407 place during the timescale of 1–2 ps on average.

408

409 As for DMPC MLB135, all of the three parameter values obtained from the IN5 data were similar
410 to those obtained from the IN6 data, showing that the identical motions are resolved at both
411 energy resolutions unlike the slow motions described above. When comparing the parameters
412 between DMPC MLB135 and DMPG MLB135 on IN5, the residence time of DMPC was smaller
413 than that of DMPG while the jump diffusion coefficient of DMPC is larger, resulting in a slightly
414 larger jump distance for DMPC. This indicates that the local motions are enhanced for DMPC
415 compared to DMPG, which is in agreement with the findings for the slow motions. The
416 reduction in local dynamics of DMPG MLB135 compared with DMPC MLB135 is consistent with
417 the results obtained from the EISF/QISF analysis by the Matryoshka model where the radius of
418 the two-dimensional diffusion of the tail group on the membrane plane is smaller for DMPG
419 [22].

420

421 *3.3. Fast motions*

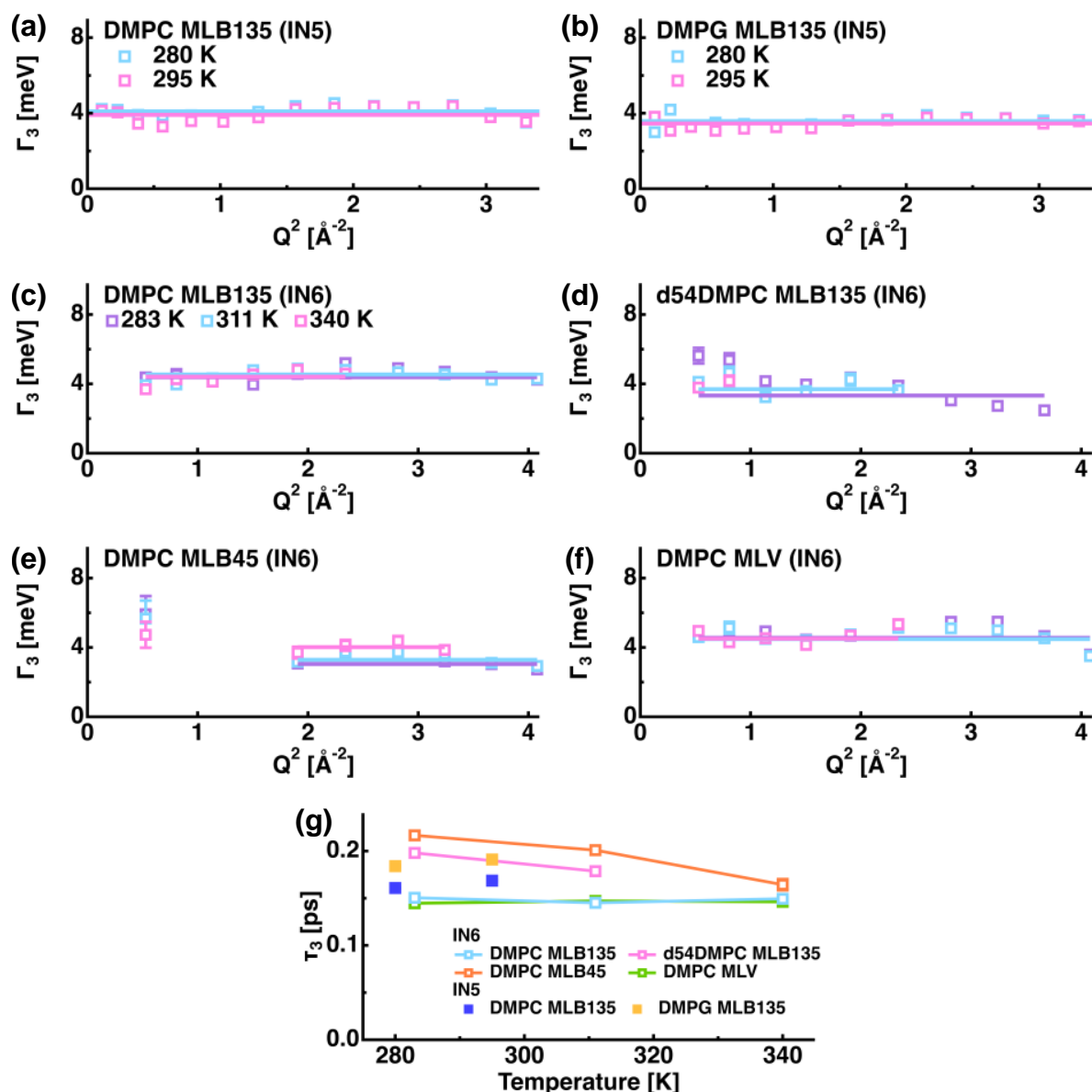
422 As shown in Fig. 7 (a-f), the widths of the broadest Lorentzian functions corresponding to the
423 fast motions were found to be independent of Q for all the samples, suggesting that these
424 motions are mainly described by rotational jump diffusion [14] as seen in hydrogen atoms in
425 the methylene and methyl groups. On the other hand, the Matryoshka model assumes another
426 kind of motions in addition to the rotational jump diffusion for the fast motions, which is the
427 two-dimensional diffusion of the hydrogen atoms in the tail groups within the membrane plane.
428 The width of the Lorentzian function describing this motion would increase as the Q^2 values
429 rise, which is not observed for $\Gamma_3(Q)$ here, suggesting that the contribution of the rotational
430 jump diffusion to $\Gamma_3(Q)$ is dominant. This is in line with the result of the analysis based on the
431 Matryoshka model in that the integrated value of the $A_{\text{jump}}(Q)$ over the Q -range employed is
432 much larger than that of $A_{\text{tail}}(Q)$ [21].

433

434 The correlation time of these motions was calculated from the relation $\tau_3 = 1/\Gamma_3(Q)$, and its
435 dependence on the temperature is shown in Fig. 7 (g) (the τ_3 values are tabulated in Tables S1
436 and S2). The τ_3 values of DMPC MLB135 on IN6 and DMPC MLV are found to be independent
437 of the temperature and to be the same within the errors, suggesting that the frequency of the
438 methyl and methylene rotations is independent of the local environments in which they reside
439 (i.e. in the MLB or in the MLV). The τ_3 values of d54DMPC MLB135 are larger than those of
440 DMPC MLB135, indicating that the rotational jump diffusion is enhanced for the tail group
441 compared with for the head group, which is consistent with the basic assumption of the
442 Matryoshka model that the tail motions are faster than the head group motions [21,22]. The τ_3
443 values of DMPC MLB45 are found to be larger than those of DMPC MLB135, implying that the
444 fast motions show anisotropy (i.e. parallel or perpendicular to the membrane plane).

445

446 The τ_3 values of DMPC MLB135 measured on IN5 were found to be slightly smaller than those
447 of DMPG MLB135, suggesting that the frequency of the rotational jump diffusion of the methyl
448 and methylene groups is higher for DMPC MLB135, which is consistent with the enhanced
449 dynamics of DMPC MLB135 for the slow and the intermediate motions. Furthermore, the τ_3
450 values of DMPC MLB135 were similar between IN5 and IN6, suggesting that the same type of
451 motions is observed on both spectrometers as the intermediate motions. It thus appears that
452 the different hydration state of the DMPC MLB135 between IN5 and IN6 as described above
453 does not significantly affect the intermediate and fast motions. In the Matryoshka model, it
454 was necessary to include the contribution of the rotational jump diffusion in the methyl and
455 methylene groups in order to describe the QISF of the fast motion [21,22]. The present results
456 indicate that the rotational jump in these chemical groups occurs every 0.2 ps.



458

459 **Figure 7.** Summary of the parameters obtained for the fast motions. (a-f): Q^2 -dependences of
 460 $\Gamma_3(Q)$. The color scheme is the same as in Figs. 3 and 5. The solid lines show the corresponding
 461 fits by the equation describing the rotational jump diffusion ($\Gamma_3(Q) = 1/\tau_3$) (see also the text).
 462 (g): Temperature dependence of the correlation time (τ_3) of the fast motions. The color scheme
 463 is the same as in Figs. 4 and 6.

464

465 3.4 Comparison of $\Gamma_1(Q)$, $\Gamma_2(Q)$, and $\Gamma_3(Q)$ between experiments and Matryoshka model

466 All of the above analyses were carried out independently of the application of the Matryoshka

467 model and despite this fact, the present findings support the results obtained by the EISF/QISF

468 analysis using this model [21,22]. In order to see further whether the Matryoshka model can
469 reproduce the energy widths of the QENS spectra, the experimental $\Gamma_1(Q)$, $\Gamma_2(Q)$, and $\Gamma_3(Q)$
470 values were compared with those based on the Matryoshka model. Analytical equations of
471 $\Gamma_1(Q)$, $\Gamma_2(Q)$, and $\Gamma_3(Q)$ based on this model, which are given in the Supplementary material, were
472 fitted to the measured corresponding profiles. Note that only the samples other than MLVs were
473 used for the fitting, because the derivation of the analytical expressions of $\Gamma_1(Q)$, $\Gamma_2(Q)$, and $\Gamma_3(Q)$
474 for MLVs is not straightforward. In the fitting, the values of the parameters ($R_{||}$, k , R_H , b_H , R_1 , and
475 ϕ), which were determined by the EISF/QISF analysis [22], were fixed except for the fitting of
476 $\Gamma_2(Q)$ with the following cases:

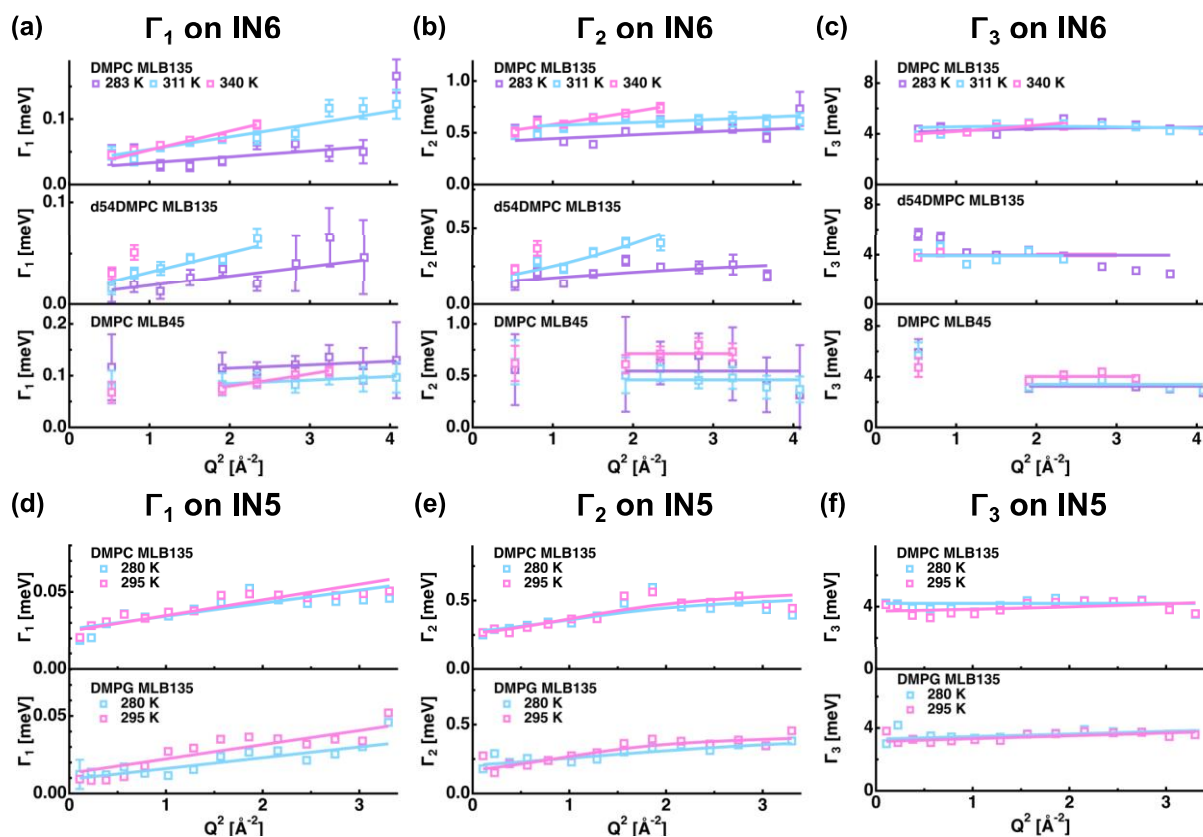
- 477 – R_H of DMPC MLB135 at 283 K on IN6
- 478 – R_1 of DMPC MLB135 at 340 K on IN6
- 479 – b_H of d54DMPC MLB135 at 283 K and 311 K on IN6
- 480 – b_H of DMPC MLB135 and DMPG MLB135 at 280 K and 295 K on IN5

481 The above parameters were allowed to change during the fitting because of their large errors
482 estimated by the EISF/QISF analysis [22]. The fitting results are shown in Fig. 8 (the values of
483 each parameter are tabulated in Tables S3 and S4). Although in some cases, the above
484 parameter values were outside the range determined at the corresponding temperature by the
485 EISF/QISF analysis [22] (these values are shown with asterisk in Tables S3 and S4), all of these
486 parameter values were still within the range determined at other temperatures, suggesting that
487 these values are not physically unrealistic ones. From Fig. 8, it is seen that the resultant fitting
488 curves are able to reproduce the experimental $\Gamma_1(Q)$, $\Gamma_2(Q)$, and $\Gamma_3(Q)$ values quite well regardless
489 of the instruments. Regarding the $\Gamma_1(Q)$ of in-plane motions, i.e. DMPC MLB135, DMPG MLB135,
490 and d54DMPC MLB135, as already discussed in the section 3.1 (see also Fig. 3), because of the
491 wide Q-range and the low energy resolutions, our experimental data appear to permit to see

492 the discrete steps of the global diffusion of the whole lipid molecules. Thus, description of such
 493 detailed motions, which are independent of EISF/QISFs, would improve further the quality of
 494 the fitting. All in all, the Matryoshka model can reproduce not only the EISF/QISF profiles, but
 495 also the energy widths of the QENS spectra, enhancing the reliability of this model to describe
 496 the lipid dynamics.

497

498



499

500 **Figure 8.** Comparison of the experimental $\Gamma_1(Q)$, $\Gamma_2(Q)$, and $\Gamma_3(Q)$ profiles with those predicted
 501 by the Matryoshka model. Q^2 -dependences of $\Gamma_1(Q)$, $\Gamma_2(Q)$, and $\Gamma_3(Q)$ on IN6 are shown in (a),
 502 (b), and (c), respectively. The data points at 283 K, 311 K, and 340 K are shown in purple, cyan,
 503 and magenta, respectively. (d), (e), and (f) show the Q^2 -dependences of $\Gamma_1(Q)$, $\Gamma_2(Q)$, and $\Gamma_3(Q)$
 504 on IN5, respectively. The data points at 280 K and 295 K are shown in cyan and magenta,
 505 respectively. The solid lines show the corresponding fits based on the Matryoshka model (Eq.
 506 (1-12) in the Supplementary material).

507

508

509 *4. Concluding remarks*

510 In this study, the diffusive nature of the motions contained in the QENS spectra of DMPC and
511 DMPG in various forms was analyzed and thus relaxational aspects of the Matryoshka model
512 were characterized. The three Lorentzian functions, which were obtained by decomposing the
513 QENS spectra, showed significantly distinctive relaxational features with their widths spanning
514 about two orders of magnitude. Regardless of this variety, the Matryoshka model can
515 satisfactorily describe the various motions contained in each of these components. The current
516 results of the analysis of the widths of these Lorentzian functions, which was carried out
517 independently of the development of the Matryoshka model, not only provides information
518 on the relaxational aspects of the motions contained in this model, but also corroborates the
519 parameter values such as the amplitudes and the mobile fractions of atomic motions obtained
520 by the EISF/QISF analysis using the Matryoshka model, which enhances the validity of the
521 model. The Matryoshka model can thus serve as a powerful tool to decipher the intramolecular
522 motions of lipid molecules and demonstrate its power in characterizations of more complex
523 systems such as the mixtures of different kinds of lipids, protein-lipid complexes, and eventually
524 natural cell membranes in the near future.

525

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530

531 **Supplementary material**

532 Parameter values obtained from the QENS spectra, analytical expressions of $\Gamma_1(Q)$, $\Gamma_2(Q)$, and

533 $\Gamma_3(Q)$ based on the Matryoshka model are found in the Supplementary material.

534

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