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A Review of the Miscibility of Binary Monolayers Composed of DPPC and Fluorinated Compounds: Insights from Multivariate and Bayesian Modeling

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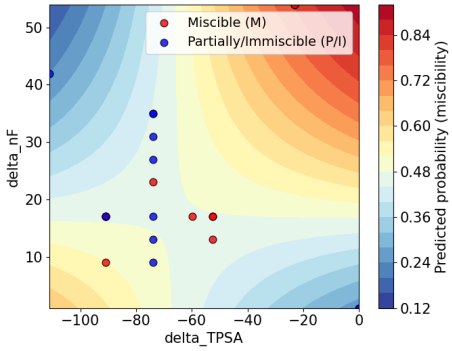
We review the miscibility of binary monolayers composed of dipalmitoylphosphatidylcholine (DPPC) and various fluorinated compounds, summarizing experimental data for both partially and fully fluorinated amphiphiles. Multivariate analysis using molecular descriptors and principal component analysis highlights key factors related to miscibility, including molecular weight and fluorine content. Bayesian logistic regression further suggests that these parameters, along with molecular polarity, contribute positively to miscibility, although no single feature reached statistical significance. Our findings emphasize the multifactorial nature of DPPC/fluorinated compound miscibility and demonstrate the value of integrating systematic data collection with machine learning for guiding the design of functional fluorinated amphiphiles.



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1. Introduction

Recent advances in both synthetic fluorinated amphiphiles and analytical techniques, coupled with growing environmental concerns, have intensified the need for a deeper understanding of their interfacial behavior, especially in model biological systems. Fluorinated amphiphiles had attracted significant interest in the past due to their unique physicochemical properties, including combined hydrophobicity and lipophobicity, high chemical and biological inertness, low surface tension, and remarkable gas-dissolving capacity[1-6]. These characteristics rendered them suitable for a wide array of applications, ranging from materials science (e.g., microelectronics, surface modification) to biomedical engineering, where they served as promising components in drug delivery systems and artificial oxygen carriers[7-10]. However, in recent years, environmental persistence and bioaccumulation of highly fluorinated compounds—classified as PFAS—have led to increasing regulatory restrictions on their use[11-15]. Therefore, current research has shifted toward partially fluorinated or hybrid amphiphiles, which are expected to retain useful interfacial properties while offering improved safety profiles[11,16,17]. Understanding the interactions of these fluorinated amphiphiles with biomembrane constituents is a critical step towards the rational design of functional materials for both industrial and biomedical applications.

A particularly important model system for such investigations is the Langmuir monolayer at the air–water interface, which mimics the two-dimensional organization of biomembrane surfaces[18-20]. In this context, dipalmitoylphosphatidylcholine (DPPC), which is the major component of pulmonary surfactant, serves as a canonical phospholipid[21-23]. The interaction and miscibility of DPPC with various fluorinated compounds in binary monolayers have been studied extensively, providing insight into the molecular determinants of interfacial behavior and phase separation.

This review provides a comprehensive overview of the miscibility of binary monolayers composed of DPPC and various fluorinated compounds, with an emphasis on recent advances in multivariate and machine

learning-based analyses of the molecular features influencing miscibility. In particular, we highlight how a combination of statistical and Bayesian machine learning approaches enables systematic identification and interpretation of key molecular and physicochemical factors that govern miscibility in these complex monolayer systems [24,25].

2. Miscibility for DPPC/Fluorinated Compound Binary Monolayers

To provide a comprehensive assessment of DPPC miscibility with a diverse range of fluorinated compounds, we systematically compiled and compared published data on binary monolayer systems, as summarized in Table 1. The compounds analyzed include a wide range of partially and fully fluorinated alcohols, acids, phospholipids, and structurally related amphiphiles. The selection criteria for included studies were: availability of miscibility classification based on Langmuir isotherms or microscopy, and consistent reporting of experimental conditions. As summarized in Table 1, the observed miscibility behavior of these binary monolayers ranges from fully miscible to partially or completely immiscible systems. Notably, the partially fluorinated alcohols with chain lengths analogous to DPPC (such as *F*4*H*11OH[26]) tend to form miscible monolayers with DPPC. In contrast, fully fluorinated fatty acids with longer perfluoroalkyl chains (e.g., *F*13COOH, *F*15COOH, and *F*17COOH [32,33]) often exhibit partial miscibility or complete immiscibility, a phenomenon attributed to the limited compatibility of perfluorocarbon chains with the hydrocarbon chains of DPPC. A total of 23 binary monolayer systems were analyzed (n = 23), of which 12 systems were classified as miscible (M), 8 as partially miscible (P), and 3 as immiscible (I). For statistical analysis, the partially miscible and immiscible classes were combined (P/I, n = 11), to focus on the distinction between fully miscible and non-miscible systems.

Table 1. Miscibility of binary monolayers composed of DPPC and various fluorinated compounds.

Compounds	Miscibility	Ref.
*F*4*H*11OH	M	26
*F*6P*H*5PPhNa	M	27
*F*8P*H*5PPhNa	M	27
*F*8*H*5OH	M	28
*F*8*H*5PC	M	28
*F*8*H*7OH	M	29
*F*8*H*9OH	M	30
*F*8*H*11DMP	M	31
*F*11COOH	M	32,33
*H*2BP(*F*13COO)$_2$	M	34
*H*6BP(*F*13COO)$_2$	M	34
*H*10BP(*F*13COO)$_2$	M	34
*F*13COOH	P	32,33
*F*15COOH	P	32,33
*F*4*H*10COOH	P	35
*F*6*H*10COOH	P	35
*F*8*H*10COOH	P	35
*F*8*H*11OH	P	36
F-DPPC	P	37
di(*F*10*H*16)	I	38
*F*17COOH	I	32,33,39

An intriguing trend emerges in the perfluorooctylated long-chain alcohols (*F*8*Hm*OH series), where the miscibility with DPPC is strongly dependent on the length of the methylene spacer (m): shorter analogs such as *F*8*H*5OH are miscible, while longer-chain variants like *F*8*H*11OH tend toward partial miscibility or even immiscibility. This phenomenon reflects a delicate balance among van der Waals interactions, the dipole moment at the hydrocarbon/fluorocarbon interface, and the domain morphologies

observed via Brewster angle and fluorescence microscopy [36].

Furthermore, the introduction of fluorinated phospholipids (e.g., *F*8*H*5PC) also leads to miscible monolayers with DPPC, likely due to structural compatibility and favorable lateral interactions. Conversely, fluorinated DPPC analogues and dimers of partially fluorinated alkanes (e.g., di(*F*10*H*16), which consists of two partially fluorinated alkyl chains connected by a covalent bond, tend to be immiscible, underscoring the importance of both chain structure and headgroup identity in determining monolayer miscibility.

Overall, these findings underscore that the miscibility of binary DPPC/fluorinated compound monolayers is governed by a complex interplay of molecular structure, fluorination degree, and interfacial packing constraints. This rich dataset provides a valuable foundation for subsequent multivariate and machine learning approaches to identify the principal factors driving miscibility in these systems.

3. Bayesian Machine Learning Analysis of Miscibility Determinants

To elucidate the key determinants governing the miscibility of DPPC/fluorinated compound monolayers, we systematically constructed a comprehensive feature set that included both molecular and experimental parameters. For each binary system, molecular descriptors for the fluorinated compound were calculated using RDKit. These descriptors comprised the molecular weight (MolWt), octanol–water partition coefficient (LogP)—a measure of hydrophobicity–hydrophilicity balance—and topological polar surface area (TPSA), which quantifies the contribution of polar atoms to the molecular surface and serves as an indicator of hydrogen bonding potential and overall polarity. In addition, we computed the number of hydrogen bond acceptors (HBA) and donors (HBD), the number of rotatable bonds, the number of fluorine atoms (nF), as well as the number of CF_2 and CF_3 groups. The reason for including both the number of nF and MolWt as parameters is as follows. Although nF is an important factor reflecting the degree of fluorination, the difference in atomic mass between fluorine and hydrogen means that changes in nF can significantly impact the overall molecular weight. Molecular weight itself can also influence packing properties, steric compatibility, and entropy effects within the monolayer, independently of the specific contribution from fluorine atoms. Therefore, both nF and MolWt were included to decouple the effects of fluorine content from those related to the general size and mass of the molecule. The fluorine ratio, defined as the proportion of fluorine atoms relative to the total number of atoms in the molecule, was also included as a descriptor.

Although the chemical structure of DPPC remains constant across all samples, analogous descriptors for DPPC were calculated to enable the construction of pairwise features. To capture the relative physicochemical contrasts between the two components, we generated pairwise differences and ratios for key descriptors. Specifically, for each parameter, the value for the fluorinated compound was subtracted from or divided by the value for DPPC (for example, delta_MolWt represents the molecular weight of the fluorinated compound

minus that of DPPC; ratio_LogP represents the LogP of the fluorinated compound divided by that of DPPC). Experimental conditions, including ionic strength, pH, and temperature, were also incorporated as features to account for potential environmental effects on miscibility. After data processing, the dataset contained no errors or missing values; all samples were retained, yielding a complete dataset suitable for subsequent statistical and machine learning analyses.

4. Multivariate Feature Analysis and Visualization

To assess the multivariate structure of the constructed feature space and its relationship to miscibility outcomes, we first applied principal component analysis (PCA) to the standardized dataset. The PCA projection enabled visualization of the overall distribution of binary DPPC/fluorinated compound systems according to their computed features. As shown in Figure 1, data points corresponding to miscible (M) and non-miscible (P/I) monolayers exhibit partial clustering; however, substantial overlap remains, indicating that miscibility arises from multifactorial determinants rather than a single descriptor. Figure 1 shows a principal component analysis (PCA) plot, which is a graphical method to summarize high-dimensional data. In this plot, each point represents a binary monolayer system, with the x-axis and y-axis corresponding to the first and second principal components, respectively. The percentage in parentheses indicates the variance explained by each component. Points are colored according to miscibility (red: miscible, blue: partially/immiscible). This allows visual assessment of whether systems with similar properties cluster together or overlap. The plot helps to understand if certain molecular features can separate miscible and non-miscible systems.

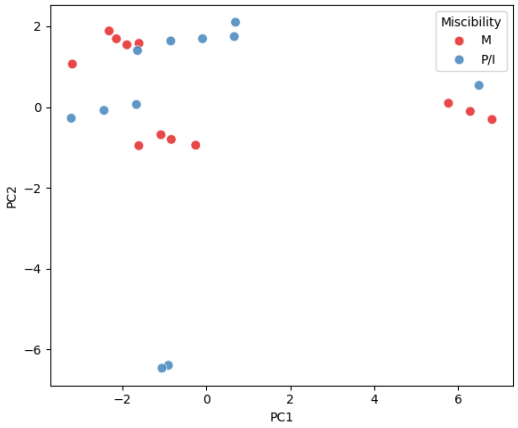

Figure 1. Principal component analysis (PCA) plot of the feature space for binary monolayer systems composed of DPPC and fluorinated compounds. The *x*-axis and *y*-axis represent the first (PC1) and second (PC2) principal components, respectively, with the percentage of variance explained by each component indicated in parentheses. Each point represents a sample, colored by its miscibility class (red: miscible (M); blue: partially or immiscible (P/I)).

Potential redundancy and inter-feature correlations were further explored and inter-feature correlations by generating a Pearson correlation heatmap (Figure 2) of the main molecular descriptors, pairwise differences, and selected interaction terms. Figure 2 presents a Pearson correlation heatmap, where each cell shows the correlation coefficient between two features, ranging from -1 (strong negative correlation, blue) to +1 (strong positive correlation, red). The axes list the various molecular descriptors and their pairwise terms. This visualization helps

identify pairs of features that are highly correlated and may carry redundant information, which is important to avoid overfitting in subsequent regression analyses. This analysis revealed several highly correlated feature pairs, such as molecular weight and its ratio or difference terms, and LogP with its associated pairwise features, highlighting the importance of careful feature selection to avoid multicollinearity in predictive modeling. Based on these insights, representative and non-redundant features were retained for subsequent regression analysis.

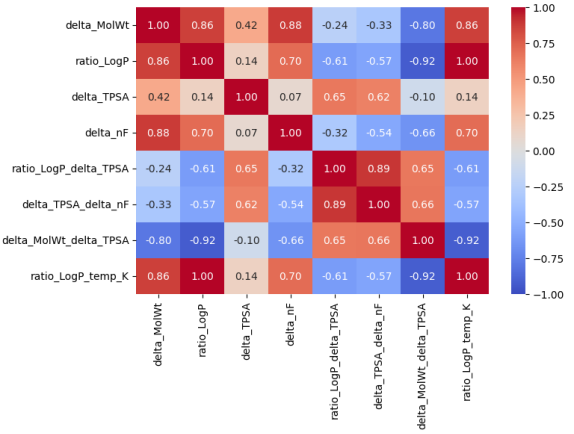

Figure 2. Correlation heatmap of selected features used for the miscibility analysis. The heatmap visualizes Pearson correlation coefficients between the main molecular descriptors, pairwise differences, and selected interaction terms.

5. Bayesian Logistic Regression Modeling

To quantitatively assess the contribution of individual features and their interactions to miscibility, we implemented a Bayesian logistic regression model. The binary miscibility label (M as 1, P/I as 0) was used as the dependent variable, while selected molecular descriptors, pairwise features, and interaction terms served as predictors. Model fitting was performed using PyMC, and model diagnostics, including posterior predictive checks and information criteria (LOO and WAIC), confirmed the adequacy and robustness of the model.

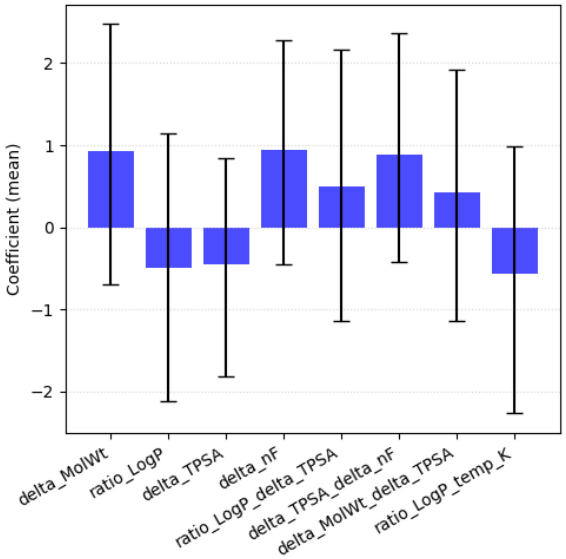

Figure 3. Estimated coefficients (posterior means and 95% credible intervals) for main effects and selected interaction terms in the Bayesian logistic regression model predicting miscibility.

The results are summarized in Figure 3, which present the estimated posterior means and 95% credible intervals for the main effects and selected interaction terms. Figure 3 provides a visual summary of the estimated regression coefficients for each feature included in the Bayesian logistic regression model. In the figure, each feature (molecular descriptor or interaction term) is listed on the vertical axis, and the corresponding coefficient value is plotted on the horizontal axis. The dot represents the posterior mean estimate, while the horizontal bar indicates the 95% credible interval for that coefficient. If the credible interval crosses zero, it means

that the effect of the feature is not statistically significant given the current data. This graphical representation allows readers to compare both the relative importance and the uncertainty of each variable in predicting miscibility. For example, the coefficient for delta_MolWt had a posterior mean of 0.93 with a 95% credible interval (CI) of (−0.69, 2.47), and delta_nF also showed a positive mean of 0.95 (−0.45, 2.27). In contrast, other features such as ratio_LogP (mean: −0.49, 95% CI: −2.12, 1.14) and delta_TPSA (mean: −0.46, 95% CI: −1.81, 0.84) displayed mean effects near zero or with wide intervals. Among interaction terms, both ratio_LogP × delta_TPSA (mean: 0.49, 95% CI: −1.14, 2.16) and delta_TPSA × delta_nF (mean: 0.89, 95% CI: −0.41, 2.36) exhibited positive mean effects, but their intervals also crossed zero. Overall, all credible intervals included zero, indicating no statistically robust effect could be established with the current sample size. Nonetheless, the positive trends observed for features such as delta_MolWt, delta_nF, and the interaction term delta_TPSA × delta_nF suggest that these parameters may emerge as statistically significant predictors as more data become available.

6. Interpretation and Mechanistic Implications

The results of the Bayesian logistic regression analysis reveal that, while no single molecular descriptor or interaction term reached strict statistical significance in predicting miscibility—since all 95% credible intervals included zero—many key features, such as delta_MolWt (mean: 0.93, 95% CI: −0.69, 2.47), delta_nF (mean: 0.95, 95% CI: −0.45, 2.27), and the interaction term delta_TPSA × delta_nF (mean: 0.89, 95% CI: −0.41, 2.36), exhibited consistently positive effects. The posterior means for these parameters were close to or above 0.9, and the majority of the credible intervals lay on the positive side, suggesting that these features are likely to be important determinants of miscibility, particularly as the dataset expands or modeling approaches are further refined. In contrast, parameters such as ratio_LogP (mean: −0.49, 95% CI: −2.12, 1.14) and delta_TPSA (mean: −0.46, 95% CI: −1.81, 0.84) had mean estimates near zero or with broad intervals, indicating weaker or more uncertain relationships.

Assuming these observed positive trends are confirmed in larger or more diverse datasets, several mechanistic implications emerge for the miscibility of fluorinated compounds with DPPC. A positive effect for delta_MolWt would suggest that fluorinated compounds with greater molecular weight relative to DPPC may have improved packing compatibility or provide enhanced entropic stabilization within the monolayer, thereby favoring miscibility. Similarly, a positive coefficient for delta_nF would highlight the role of increased fluorine content in promoting miscibility, likely due to strengthened van der Waals or dipole interactions at the hydrocarbon–fluorocarbon interface. The significance of the interaction between would further imply that a combination of high fluorine content and increased molecular polarity acts synergistically to enhance miscibility. Such a synergy could arise from an optimal balance between hydrophobic (fluorinated) and polar regions, allowing the fluorinated compound to integrate more

effectively within the DPPC matrix.

While our analysis primarily highlights the roles of molecular weight and fluorine content in determining miscibility, the influence of the hydrophilic headgroup should also be acknowledged. In this study, most of the investigated fluorinated compounds share similar headgroup types, such as phosphocholine, carboxyl, or hydroxyl groups. This relative uniformity means that, within our dataset, the headgroup effect on miscibility is less discernible in statistical terms compared to the broader variability seen in hydrophobic moieties. However, it is well established in the literature that substantial modifications to the headgroup—such as introducing larger, more polar, or charged functionalities—can substantially impact monolayer behavior and miscibility with DPPC. Therefore, while our findings suggest that molecular weight and fluorine content are primary determinants within the studied compound set, a systematic exploration of diverse headgroup chemistries may reveal additional contributions to miscibility, warranting further investigation.

Overall, these findings support a model in which miscibility with DPPC is dictated not by a single molecular property, but rather by the interplay between molecular size, fluorine content, and polarity, and their combined effects. This perspective provides a rational framework for designing novel fluorinated amphiphiles with tailored miscibility profiles and highlights the value of systematic feature engineering together with flexible, probabilistic modeling. Further expansion of the dataset and refinement of molecular descriptors will likely enable identification of truly predictive features and promote the rational development of functional fluorinated materials. These findings should be considered provisional and hypothesis-generating; further studies involving larger and more diverse datasets will be essential to validate and refine the identified molecular determinants of miscibility in DPPC/fluorinated compound systems.

7. Acknowledgement

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Code Availability

All scripts for molecular descriptor calculation, feature engineering, multivariate analysis, and Bayesian logistic regression are available at https://github.com/Hiromichinakahara123/DPPC-fluoro-miscibility-ML. Please note that input data are not included in the repository due to data sharing policy.

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