An Octanol Hinge Opens the Door to Water Transport

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Despite prevalent use as a surrogate for partitioning of pharmacologically active and natural products across lipid membranes, the mechanism of solute transport across water/octanol phase boundaries remains unexplored. Using classical molecular dynamics with uniquely benchmarked forcefields, graph theoretical and cluster analysis, and Langevin dynamics, we reveal an elegant mechanism for the transport of the simplest solute, water. At equilibrium, small groups of octanol at the instantaneous interface bind water and swing like hinge of a door to bring water into a semi-organized second interfacial layer (octanol `bilayer islands"), where water can then diffuse into bulk octanol or be returned to the aqueous phase. The fundamental forces, collective, and reversible behavior, is well-described by a double well potential energy function, satisfying the basic principles of a simple molecular machine for solute transport. Unlike other transporting machines, this example leverages the interfacial surface fluctuations rather than circumventing them, imparting new design principles for hierarchically organized structures that transport solutes across liquid/liquid phase boundaries.

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Octanol bilayer islands act as a molecular hinge to transport water across the water/octanol phase boundary.
An Octanol Hinge Opens the Door to Water Transport†

Zhu Liu* and Aurora E. Clark*

Despite prevalent use as a surrogate for partitioning of pharmacologically active solutes across lipid membranes, the mechanism of transport across water/octanol phase boundaries remains unexplored. Using molecular dynamics, graph theoretical and cluster analysis, and Langevin dynamics, we reveal an elegant mechanism for the simplest solute, water. Self-assembled octanol at the interface reversibly binds water and swing like the hinge of a door to bring water into a semi-organized second interfacial layer (a "bilayer island"). This mechanism is distinct from well-known lipid flipping and water transport processes in protein-free membranes, highlighting important limitations to the water/octanol proxy. Interestingly, the collective and reversible behavior is well-described by a double well potential energy function, satisfying the basic principles of a molecular machine that is driven by differential free energies of solvation of H₂O across the interface. This example successfully operates within the dynamic motion of instantaneous surface fluctuations, a feature that expands upon the existing transporting machine paradigm that acts to avoid or circumvent the dynamic nature of the interface.

1 Introduction

Liquid/liquid interfaces often act as kinetic gatekeepers for solute transport. This can occur in the context of biological systems, where cell membranes control uptake of pharmacologically active agents, or in separations and purification processes at the industrial scale using methods like solvent extraction. Interestingly, solute transport across a liquid/liquid phase boundary is rarely considered to occur via a mechanism involving a molecular machine - as defined by a driving force that is coupled to work in the form of a "secondary function". Exceptions to this include lipid bilayer macrostructures (e.g. transmembrane proteins) that undergo activation and conformational changes to facilitate solute transport. "Catch and release" strategies for separations of complex mixtures have been developed that utilize photoswitching extractant molecules that are selective for specific solutes under different conformational states interconverted by light. Within these cases, the highly dynamic motion of the instantaneous liquid/liquid interface is controlled or avoided in order for the transporting machine mechanism to operate. The lipid bilayer dampens thermal roughness and imparts mechanical stability that supports the function of the embedded macrostructure. The catch and release extractant utilizes the liquid/liquid interface solely as a depot for the selected solutes.

Apriori, it may not be necessary to moderate or avoid dynamic surface fluctuations to rationally design transporting interfacial machines. Several examples demonstrate collective motion of the instantaneous surface during “non-machine” facilitated solute transport. “Fingers” or “protrusions” are considered amplifications of surface roughness into new structural motifs that facilitate passage of ions across the interface. Modulating protrusion formation has recently begun to be explored; surfactants like tributyl phosphate amplify interfacial heterogeneity and increase the likelihood of water protrusions that are the dominant mechanism for water transport. Anecdotal evidence from molecular dynamics (MD) implicates protrusions as the transporting mechanism of metal-ligand complexes and larger solutes across oil/water phase boundaries. Although protrusion-based mechanisms may exhibit collective motions similar to machine-based transport, reversible and relatively straightforward reaction coordinates have yet to be identified (the closest examples being the recent work of Kikkawa et al.).

Accordingly, what could be potential characteristics of a transporting, reversible, molecular machine that coexists with instantaneous surface fluctuations? One option is a hinge, where one end is embedded within the interfacial region, but where the other end has sufficient steric freedom to dynamically traverse the phase boundary to reversibly transport molecules between the two immiscible solutions. This requires organization of the interface beyond the instantaneous surface, yet at the same time, the interfacial structure should not too organized otherwise the swinging end of the hinge would be sterically hindered.
Metastable configurations are also necessary at both extremes of motion (the organic and aqueous phases) to enable solute binding and release events, where the differential solubility of the solute across the instantaneous surface acts as a driving force. Considering these features a double well potential is a suitable energetic representation, as is employed for molecular shuttles.¹⁹

This work reports the serendipitous observation of a biphasic system that meets the aforementioned requirements, namely, solute transport across the water/octanol interface. This system has significant relevance to the separations and pharmacology communities. Octanol is widely employed as a phase modifier that alters transport kinetics within industrially relevant solvent extraction systems. Additionally, the solute water/octanol partition coefficient is a broadly accepted measure of lipophilicity and octanol is assumed to be a mimetic surrogate for more complicated phospholipids that comprise bilayer membranes.²⁰–²⁸

Over 300 peer-reviewed publications are in print within the last two decades (Google Scholar), with significant recent growth of simulation studies of water/octanol biphasic systems. Although mass transport/kinetic models have been developed for select systems,²⁹,³⁰ and non-equilibrium and potential of mean force simulations have been employed to understand energetic favorability in different bulk phases,³¹ the equilibrium transport mechanism has not (to our knowledge) been examined at a molecular level (the scope of studies from more than 100 simulation-based publications is presented in Table S1). To elucidate the mechanism of H₂O transport across the liquid/liquid phase boundary, classical MD simulations employed a benchmarked set of interaction potentials that reproduced both the experimental mole fraction water solubility in octanol (0.26³²) and the interfacial tension (7.83 ± 0.80³³), as well as key experimental observations regarding interfacial structure associated with octanol orientation and partial bilayer formation.

Thorough statistical analyses of all water transport events verify that nearly all H₂O that migrate from bulk water, through the interface, and into bulk octanol, do so by collectively organized octanol clusters that swing across the interface by reversibly picking up water at the instantaneous surface and depositing them to a semi-bilayer of octanol. From there, water as part of a bilayer island may diffuse into bulk octanol, or be returned to the instantaneous water surface by the reverse transport process. The water transport mechanism identified here sharply contrasts with that identified by MD studies of protein-free lipid membranes (via water defects and the associated formation of water pores³⁴) and as such clearly limits octanol as a mechanistic surrogate for solute transport (although other elements of the proxy may hold). The “hinge” mechanism for water transport across the water/octanol phase boundary is further well-reproduced by Langevin dynamics based upon a double well potential energy function, as in molecular shuttles¹⁹ and other molecular machines. In this case, favorable inter-octanol hydrogen bonding interactions support collective organization of the bilayer islands that have a relatively low barrier toward oscillatory motion, while the high solubility of water in octanol causes stable minima at the instantaneous surface of water with octanol, as well as within the semi-bilayer structure adjacent to, and in dynamic equilibrium with, bulk octanol.

2 Methods

2.1 Force fields benchmarking and simulation protocol

Force Field Benchmarking. Extensive benchmarking of the force field implementation has been performed and is based upon the reproduction of two macroscopic equilibrium properties (the interfacial tension and the mole fraction solubility of water in the octanol) as well as experimental resonance enhanced second-harmonic generation studies that has elucidated octanol orientation and organizational features at the interface.³⁷ Finite size effects were also examined by monitoring the convergence of all properties to system box size, where ε = 70 - 170 Å, and x = y = 40 - 98 Å (Table S2).

The four octanol and water force field combinations considered represent the most prevalently employed within the literature for bulk and limited interfacial studies: GROMOS54A7/SPC-E,³⁸ GAFF/TIP4P-EW,³⁹ GAFF/TIP3P,³⁹ and OPLS/TIP3P.⁴⁰ The resulting data compared to two prior studies are presented in the Table 1. Importantly, there is a strong correlation between the calculated interfacial tension and the associated solubility of water in octanol.⁴¹–⁴³ The GROMOS54A7/SPC-E set was observed to reproduce the correct solubility and interfacial tension, with excellent agreement being observed for the interfacial structure, as described in Section 3.1. Using this set of force field parameters, the GROMACS simulation package⁴⁴ was employed to study the equilibrium properties of the water/octanol liquid/liquid interface in a rectangular simulation cell with 3-dimensional periodic boundary conditions (Figure S1). The simulation cell contains 2938 octanol and 12836 water molecules. The nonbonded Lennard-Jones interactions are treated with a spherical cut-off r_c = 15 Å while the long-range Coulomb interaction is evaluated using Ewald summation⁴⁵,⁴⁶ with a relative error of 10⁻⁸. The
Table 1 Summary of intermolecular interactions, mole fraction solubility of water in octanol, and interfacial tension of the liquid/liquid interface predicted with different octanol/water models. CG-MARTINI is the coarse-grained model from Ndao et al. Polarized FF and D-C denote the polarizable octanol force field and polarizable Dang-Chang water model from Wick and Chang. Experimental data are from Šegatin and Klofutar and Demond and Lindner.

| Models          | Intermolecular interactions (kcal/mol) | Mole fraction solubility | Interfacial tension (mN/m) |
|-----------------|---------------------------------------|--------------------------|----------------------------|
| (octanol/water) | octanol-octanol water-water octanol-water |                          |                            |
| GROMOS54A7/SPC-E| -82164.65 -135214.37                  | 0.26                     | 7.83±0.80                  |
| GAFF/TIP4P-Ew   | -74534.51 -138135.00                  | 0.11                     | 16.28±0.33                 |
| GAFF/TIP3P      | -85428.77 -115686.56                  | 0.16                     | 11.57±0.50                 |
| OPLS/TIP3P      | -24240.02 -75472.20                   | 0.14                     | 14.35±1.70                 |
| CG-MARTINI/CG-MARTINI | —        | —                        | —                          |
| Polarized FF/D-C| —                                    | 0.26                     | 3±6                        |
| Expt.           | —                                    | 0.27                     | 8.5                        |

The suggested probe sphere radius 1.5 Å with a grid spacing of 0.2 Å was employed. As illustrated in Figure S1, there exists a non-negligible amount of water molecules within the octanol-rich interfacial region. Thus, H2O that are distributed in the bulk octanol phase will be mistakenly counted as the “true” interfacial H2O in the algorithm. To avoid this issue, a density based cluster approach (Pytim DBSCAN) is adopted to separate these H2O that have penetrated the octanol phase, vs. those truly interfacial H2O that remain connected to the aqueous phase via a hydrogen bond network. Octanol molecules are counted as truly interfacial if their -OH is hydrogen-bonded to at least one truly interfacial H2O.

The Willard-Chandler instantaneous interface. The interfacial surface area of the system is determined using a procedure of continuous representation of a discrete instantaneous configuration of surface water molecules proposed by Willard and Chandler. This procedure provides a reliable definition of the relevant spatial fluctuations in space and time of the interface location, which is otherwise averaged out by using the Gibbs dividing surface. We adopt the suggested coarse-graining length 2.5 Å and 90% water bulk density criterion in obtaining the Willard-Chandler surface of water. Ensemble average values of the interfacial area are obtained by averaging the individual areas of the instantaneous Willard-Chandler interface.

Identification of bilayer islands and organized octanol clusters during water transport. Pytim, a python package that has implemented cutoff-based clustering and DBSCAN density-based cluster algorithm, was employed for the cluster search to identify hydrogen bonded clusters consisting solely of octanol or octanol and water and their position within the interfacial region during water transport. Octanol or water molecules are considered to be in the same cluster if their O-atoms are closer than 3.5 Å, which is the O...O distance criterion for a HB.

2.2 Analyses

The ITIM instantaneous interface. In this work, all hydrogen bond (HB) interactions are analyzed using the ChemNetworks package, in which H2O and octanol molecules are converted to nodes, with any existing hydrogen bond between them as edge connection. Hbs for water-water, water-octanol or octanol-octanol are all defined by an O...O distance with a value less than 3.5 Å and an H-O-O angle 0 - 30°. The strong association of the hydrophilic octanol with water complicates the interpretation of interfacial properties based upon a Gibbs dividing surface (GDS) reference position within the interfacial region. Thus the intrinsic interface (or instantaneous surface) is examined and identified using the Identification of Truly Interfacial (ITIM) algorithm.

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2.3 Langevin dynamics

Many reported molecular machines have simple potential energy landscapes that underpin their fundamental motions. The ability of a simplified potential energy surface to reproduce the observed water transport from molecular dynamics was tested using a Langevin dynamics formalism. Therein, for a system of N particles with masses M, with coordinates X = X(t) that constitute a time-dependent random variable, the equation of motion is MX = −∇U(LD) − γX + √2kBγT R(t), where U(X) is the particle interaction potential; V is the gradient operator such that −∇U(LD)(X) is the force calculated from the particle interaction potentials; the dot is a time derivative such that X is the velocity and X is the acceleration; γ is the friction coefficient; the third term is the noise term with T as the temperature, kB as Boltzmann’s constant; and R(t) as a delta-correlated stationary Gaussian process with zero-mean.
The double well potential energy function is $U = 8.90z^4 - 0.22z^3 - 11.75z^2 + 0.56z + 4.16 + 0.5x^2$. This potential energy landscape is created under the following requirements. First, the activation energy barrier of the potential landscape is located at $x = z = 0$. Second, the left well is located at $z \sim -0.868$ nm ($x = 0$), which value is taken from the average molecular length of octanol in Layer-1 (see Figure 2 in Section 3.1). At the same time, the average Layer-2 octanol molecular length is set to be $z \sim 0.854$ nm ($x = 0$). In this way, the double well structure is representative of the head group clusters of octanol and water being transferred between Layer-1 and Layer-2 (Section 3.2). Last but not the least, the left ramp potential barrier, that is the depth of the left well, is set to $4.16 \pm 0.11$ kcal/mol, which is adopted from the transport activation energy barrier of water from the octanol Layer-1 region to Layer-2 region (Section 3.3). The depth of the right well is $3.51 \pm 0.06$ kcal/mol and also directly obtained from the MD simulation of water transport from Layer-2 to Layer-1. The uncertainties are calculated by splitting the simulations into three blocks and calculating the standard error of the mean.

The particle within the Langevin dynamics will experience the double well potential energy, friction and noise forces and evolve its positions by the Langevin integrator. The temperature (300 K) and sample time (1 ps) of the Langevin dynamics simulation are set to the same as the course the MD simulation. Each Langevin dynamics simulation ran for 100,000 steps to obtain meaningful statistics. The uncertainties are calculated by running the simulation 100 times and calculating the standard error of the mean.

3 Results and discussion

3.1 Octanol interfacial structure in the $z$-direction

A molecular scale understanding of the liquid/liquid interfacial structure is essential toward defining and understanding the water transport mechanism. We focus first upon understanding organization across the interface, along the $z$-direction (Figure 2). The instantaneous interface has significant distribution in $z$ due to local thermal corrugation that exists in combination with longer-range capillary waves. Typical analyses of interfacial organization often begin with density profiles of the respective solvents along $z$, complemented by radial distribution functions of essential functional groups. These data (Figure S2), shown and discussed in detail within the Supplementary Information, are the first intimation of density oscillations in the hydroxyl O-atom and methyl carbons that coincide with a bilayer-like structure where the carbon tails of octanol molecules at the instantaneous surface are organized end-to-end with the alkyl tails of octanol a second layer from the surface. The distance distribution from the hydroxyl O-atom to the terminal C-atom indicates a high probability of the elongated linear configuration (Figure S3), consistent across several force fields and prior work. The octanol bilayer-like structure is depicted in both Figures 2 and S1. The orientation profiles of water and octanol molecules as a function of $z$ is presented in Figure S2, demonstrating that octanol at the interface orient their hydroxyl head groups pointing toward the water phase with a cosine $\theta$ value around 0.7 (45 $^\circ$). Here $\theta$ is the angle between the octanol molecular end-to-end vector passing through the hydroxyl H- and terminal C- atoms and the surface normal along the $z$ axis. The interfacial orientation is in good agreement with the experiment value by Cramb et al.,\textsuperscript{56} obtained from second harmonic generation spectroscopy and measured to be $39 \pm 10^\circ$ to the surface normal. Further into the octanol phase, there is a preference for octanol molecules to point their hydroxyl oxygens in the opposite direction with respect to the interfacial octanol orientation, toward the octanol phase. The orientational data supports the organization of an octanol bilayer-like region in the vicinity of the liquid-liquid interface, as observed in MD simulations using polarizable forcefields.\textsuperscript{36,42} Based upon these data, we then delineate five regions of the chemical system: the bulk aqueous phase, the instantaneous surface of H$_2$O in direct contact with octanol, the octanol molecules at the instantaneous interface with water that have their -OH groups facing the aqueous phase (labelled Layer-1), octanol molecules that form a second semi-organized layer and have their -OH groups facing the organic phase (labelled Layer-2), and the bulk octanol phase. These regions are presented in Figure 2.

![Fig. 2 Schematic representation of the water or octanol molecules in different regions, namely bulk water, Layer-1, Layer-2, bulk octanol phases. Bulk water molecules are depicted with red lines. Water molecules in Layer-1, Layer-2, and the bulk octanol phase are highlighted with red, purple, and orange oxygens, respectively. Octanol molecules in Layer-1 are highlighted with green bonds for alkyl carbon tail and green sphere for oxygens in the hydroxyl head group. The alkyl tails are drawn in blue with the hydroxyl oxygen highlighted in blue sphere for octanol molecules in the Layer-2. Bulk octanol molecules are depicted with gray lines.](image-url)
3.2 Octanol structure parallel to the interface

The bilayer-like structure of the octanol interface can be further quantified by metrics that assess the spatial heterogeneity along (as opposed to across) the surface. Distinct differences are observed between Layer-1 and Layer-2. Within the instantaneous octanol surface (Layer-1), examination of the hydroxyl O-atom density in the \( xy \) plane (Figure 3) reveals a fairly homogeneous distribution of octanol with an average packing density of 2.80 oct/nm\(^2\) (using the Willard Chandler surface), in good agreement with the experimental value (3.56 oct/nm\(^2\)).\(^{57}\) The spatial correlation between octanol molecules in Layer-1 was measured with 2-dimensional radial distribution functions (2D-RDF, Figure S4), which exhibits a correlation peak around 2.4 Å, corresponding to the octanol-octanol dimer (held together by a single hydrogen bond) and a second correlation peak at \( \sim 4.2 \) Å that corresponds to the water-bridged octanol-water-octanol dimer, observed in previous studies.\(^{58,59}\)

In contrast to Layer-1, the \( xy \) plane density heat map of hydroxyl O-atoms in Layer-2 (Figure 3B) exhibits significant heterogeneity, with distinct clustering of octanol surrounded by low-density octanol regions. The Layer-2 RDF presents an outstandingly higher peak at \( \sim 2.4 \) Å as the Layer-1 RDF, and a relative lower height second peak at \( \sim 4.2 \) Å. Interestingly, in the Layer-2 2D-RDF, anti-correlation is observed between 5 to 13 Å, which also indicates octanol deficient regions in the second layer of the octanol bilayer. This feature was further analyzed by calculating the excess coordination number (ECN):

\[
N_{\alpha\beta}^{\text{Excess}}(r) = 4\pi \rho_{\beta} \int_{0}^{r} r^2 \left[ g_{\alpha\beta}(r) - 1 \right] dr,
\]

(2)

where \( g_{\alpha\beta}(r) \) is the Kirkwood-Buff \( g \) factor between species \( \alpha \) and \( \beta \) of interest and \( \rho_{\beta} \) is the number density of \( \beta \) component. From a physical point of view, the ECN \( N_{\alpha\beta}^{\text{Excess}}(r) \) is the difference in the number of \( \beta \) species in the vicinity of a central \( \alpha \) species compared to that found in an equivalent volume of the bulk solution. Therefore, a positive ECN value indicates an excess of \( \beta \) species in the vicinity of species \( \alpha \) over the bulk distribution. While a negative value will corresponds to a depletion of species \( \beta \) surrounding \( \alpha \). In this work, \( g_{\alpha\beta}(r) \) is just the 2D-RDF \( g(r)_{\text{OCTA-OCTA}} \) with \( \alpha, \beta \) referring to octanol only. For the coordination of octanol molecules in Layer-1, beyond 5 Å the ECNs around \( z = 0 \) indicates a uniform octanol distributed at the instantaneous surface. In Layer-2, the relative large ECN value around \( 2.4 \) Å indicates anomalous, higher densities of octanol relative to those in Layer-1. This is consistent with the 2D-RDF, where enhanced peak intensity is consistent with clustering. In the distance range of 5 to 15 Å, negative ECN values correspond to a depletion of the octanol hydroxyl head groups. This indicates significant “gaps” in octanol density between octanol clusters, and thus we adopt the terminology “bilayer islands” for this phenomena (Figure 3 and S4).

Fig. 3 Two-dimensional density distributions of hydroxyl O-atom of octanol molecules in (A) Layer-1 (the instantaneous octanol surface) and (B) Layer-2 (the second layer from the instantaneous surface).

Importantly, the bilayer islands cause an enhanced nonpolar alkane-like region in the vicinity of the interface. As described in Steel and Walker\(^{37}\) solvatochromic surfactants have been used to probe the change in polarity across the water/octanol interface using resonance-enhanced second-harmonic generation. That data provided evidence that the water/octanol interface has a region that is less polar than either of the individual solvents, implying a hydrophobic barrier (exposed alkyl groups) between the two bulk polar phases.\(^{37}\) At the same time, the data also indicated a membrane-like structure. Prior work using polarizable octanol and water has also predicted a semi-organized second layer of octanol relative to the instantaneous surface,\(^{36}\) while most non-polarizable force fields predict a monolayer under equilibrium conditions and mixing/demixing studies sometimes predict a semi-bilayer structure that is dependent upon system configuration.\(^{41,60}\) We compared several classical force field representations (Tables 1 and S3) and analyzed the associated intermolecular pairwise interactions which indicated that strong interactions of the water and octanol hydroxyl group have a dual effect of causing the correct water solubility, and stabilizing water rich octanol islands in the semi-bilayer.
3.3 Water transport mechanism

Initial analysis of the dynamic features of the semi-bilayer structure of the octanol surface reveals characteristics that are reminiscent of analogous protein-free lipid membranes\(^1\) that have more significant organizational structure. For example, individual octanol molecules undergo stochastic flipping events between layers (Layer-1 ⇔ Layer-2) as well as diffusive motion to and from Layer-2 and bulk octanol. Within 30 ns of simulation, 26,650 flipping events were observed, evenly distributed between Layer-1 → Layer-2 and the reverse process (Table S4, Figure 4). With these data, the barrier for flipping on a per octanol basis is estimated using the Arrhenius equation \(\ln k = \ln A - \frac{E_a}{RT}\), where \(k\) is the flipping rate and \(A\) is the pre-exponential factor. The estimated activation energy barrier of these stochastic flipping events is 0.99 ± 0.02 kcal/mol for Layer-1 → Layer-2, and 0.96 ± 0.02 kcal/mol for Layer-1 ← Layer-2 (Tables S5 - S6). The facile nature of octanol stochastic flipping is not entirely surprising, as prior work has shown that the barrier for lipid flipping can be significantly modulated by alkyl chain length, membrane packing, and nature of the hydrophobic head group.\(^2\) Interestingly, prior work has demonstrated that water defects and the associated formation of water pores is essential to lipid flipping in protein-free membranes.\(^3\) However, a distinguishing characteristic in octanol flipping is that the stochastic process consists of single octanol molecules that are not hydrogen bonded to \(\text{H}_2\text{O}\). Out of the 26,650 flipping events, only 350 are observed to involve one octanol hydrogen bonded to one \(\text{H}_2\text{O}\) (Table S4, Figure 4).

Individual water transfer events consist of \(\text{H}_2\text{O}\) adsorbing to instantaneous surface from the bulk (a diffusion limited process), moving from Layer-1 of octanol to Layer-2 of octanol (via a mechanism described below) and then diffusing from Layer-2 to bulk octanol. The analogous transfer from octanol to the aqueous phase also occurs as part of the \(\text{H}_2\text{O}\) partitioning at equilibrium. As observed in Figure S6, nearly 150 ns of equilibration is needed to achieve the dynamic equilibrium of water transfer across the aqueous/octanol interface such that the average water content in octanol is essentially constant. This work focuses upon the rate-limiting process for water transport between the aqueous and octanol phases, namely Layer-1 ⇔ Layer-2.

Using a combination of hydrogen bond and cluster analyses all events where \(\text{H}_2\text{O}\) were transported between Layer-1 ⇔ Layer-2 and between Layer-2 ⇔ bulk octanol were analyzed. The equilibrium transport statistics between Layer-1 ⇔ Layer-2 and between Layer-2 ⇔ bulk octanol are collected in Table S4 and shown graphically in Figure 4. Within the 30 ns of equilibrium MD simulation, 477 instances of water diffusion events are observed, where no \(\text{H}_2\text{O}...\text{oct}\) hydrogen bonding interactions occur during \(\text{H}_2\text{O}\) migration across the interface. This comprises 14% of all instances of \(\text{H}_2\text{O}\) being transferred from the instantaneous surface of water to Layer-2 of octanol. In comparison, 1391 instances of Layer-1 → Layer-2 water transfer events are observed that involve a direct HB between an octanol and \(\text{H}_2\text{O}\) that transport a total of 2931 water molecules to Layer-2. Similarly, there exist 1404 transfer events for Layer-1 ← Layer-2 that transport 2850 water molecules back to Layer-1. Importantly, 87.5% of these instances involve the transport of one or more \(\text{H}_2\text{O}\) to and from a bilayer island by an assembly of octanol molecules, with the remaining 12.5% being the rare instance of one \(\text{H}_2\text{O}\) hydrogen bonded to a stochastically flipping single octanol molecule. Equivalently, the events that employ octanol assemblies transport 94% of all \(\text{H}_2\text{O}\) molecules that migrate between Layer-1 ⇔ Layer-2, while only 6% of waters that are transported involve the stochastically flipping octanol. This important characteristic portends a very different mechanism of water transport, one that relies upon collective motion of octanol and water and small networks of intact HB networks to facilitate \(\text{H}_2\text{O}\) transport across the interface.

To further characterize the distinctive nature of the \(\text{H}_2\text{O}\) transport by octanol assembly, we first analyze the structure and geometric changes during the transport process, which intimately relates to the bilayer island structural features of the interface. Bilayer islands predominantly consist of 4-5 octanol and 1-3 \(\text{H}_2\text{O}\) (Table S7). They are characterized by enhanced water content, as analyzed by their networks of hydrogen bonds between octanol...octanol, water...water and water...octanol (Figures S7 and S8). When a water is transferred between octanol layers by a mechanism that relies upon an octanol...\(\text{H}_2\text{O}\) hydrogen bond network, an entire bilayer island (or a sub-set of bilayer island octanol molecules) is observed to swing from Layer-2 to Layer-1, like the door of a hinge, whereupon one or more \(\text{H}_2\text{O}\) bind to the self-assembled cluster. Then, the cluster swings back from Layer-1 to Layer-2 to deposit the water to this region. The process is graphically represented in Figure 5, where the analogous change to the octanol dipole orientational angle is depicted in Figure S9.
Fig. 5 A Water extraction event, depicted across 1.6 ns. The first frame \( t = 21.510 \text{ ns} \) occurs prior to \( \text{H}_2\text{O} \) binding to two octanol, followed by the binding event and hinge rotation of engaged octanol molecules to Layer-2, then \( \text{H}_2\text{O} \) release and octanol reorientation to Layer-1. Octanol molecules not involved in the event are omitted for clarity. The background blue surface is the instantaneous representation of the water/octanol interface.

This mechanism, hereafter referred to as the “hinge mechanism”, is validated through a number of analyses.

On an average \( 3.71 \pm 0.05 \) octanol molecules are involved in the Layer-1 \( \rightarrow \) Layer-2 transfer of \( 2.28 \pm 0.11 \) \( \text{H}_2\text{O} \) per transfer snapshot, while \( 3.65 \pm 0.05 \) octanol molecules participate in Layer-1 \( \leftrightarrow \) Layer-2 transfer of \( 2.24 \pm 0.07 \) \( \text{H}_2\text{O} \) per transfer snapshot. These are within statistical error and show that the initial and final “states” of the octanol cluster-based hinge are approximately the same (ignoring any affects due to variations in solvation on either side of the phase boundary). The average composition of the non-covalently assembled transporting species is predominantly \( (\text{H}_2\text{O})_{2-5}(\text{oct})_{2-6} \), as can be seen in the ring plot of Figure 4, which labels the three ways in which water can be transported across the water/octanol phase boundary (diffusion 14%, stochastic flipping 5%, and the hinge mechanism 81%, respectively). All percentages are calculated basing on the statistics in Table S4.

In addition to the fundamental variance in the composition of the transporting species, and the fact that water transport via the hinge mechanism is correlated to the presence of bilayer islands, the energetics of water transport via the hinge mechanism is decidedly different from stochastic octanol flipping processes. In this case, although each bilayer island is a relatively stable \( (\text{oct})_{2-n} \) species, it is useful to consider the simplified stoichiometry of the transporting reaction on a per \( \text{H}_2\text{O} \) basis. Dividing the average composition of the transferring octanol island by the average number of \( \text{H}_2\text{O} \) transferred yields \( 1.62 \pm 0.06 \) octanol + \( \text{H}_2\text{O} \) for Layer-1 \( \rightarrow \) Layer-2 transport, and \( 1.63 \pm 0.03 \) octanol + \( \text{H}_2\text{O} \) for the Layer-1 \( \leftrightarrow \) Layer-2 transport. With these data, the Arrhenius estimated \( E_a \) for Layer-1 \( \rightarrow \) Layer-2 water transport is \( 4.16 \pm 0.11 \) kcal/mol and \( 3.51 \pm 0.06 \) kcal/mol for Layer-1 \( \leftrightarrow \) Layer-2. A simplified model of water transport was then tested using single particle Langevin dynamics (LD) simulation in a double-well potential in the \( z \)-dimension with a parabolic shape in the \( x \)-dimension (centered at \( x = z = 0 \)), ensuring that the particle is confined in one of two minima located at \( z \sim -0.868 \text{ nm} \) and \( z \sim 0.854 \text{ nm} (x = 0) \), as depicted in the panel A of Figure 6. The minima are representative of the head group clusters of octanol and water being transferred between Layer-1 and Layer-2, whose locations are based on the average octanol molecular lengths in Layer-1 and Layer-2, respectively. The energy barrier utilizes the estimated Arrhenius \( E_a \). The dynamics trajectory of the particle from the LD simulation are pictorially represented in Figure 6B. Importantly, after 100,000 LD steps, the ratio of the transferred concentration of the particle confined to the Layer-1 and Layer-2 minima is \( 1.22 \pm 0.11 \), which is in excellent agreement with the average water transfer concentrations from Layer-1 and Layer-2 (2931/2850 within the trajectory analyzed).
4 Conclusions

The water/octanol interface is of fundamental importance to separations science, both in the context of biological partitioning of solutes across cell membranes as well as industrial purification. To date the mechanism for solute transport has not been elucidated. The current MD study reveals collectively organized transporting units of octanol at the interface and a well-defined and reversible mechanism that is reproduced using Langevin dynamics employing a double-well potential. The ability of the transporting octanol “hinge” motif to successfully operate within the surface fluctuations of the interface is a testament to the balance of hierarchical organization and energetic driving forces associated with the mutual solubility of water in the biphasic system. Although the instantaneous surface of octanol in direct contact with water is highly organized, a second bilayer-like organization exists a layer away from the interface that consists of hydrogen bonded octanol islands. The dynamic fluctuations within the interfacial region provide sufficient steric flexibility for bilayer islands (or sub-components) to swing to and from the instantaneous surface to the second layer of octanol in equilibrium with the bulk octanol phase. The reported transport mechanism is further distinct from recent reports regarding water transport through protein-free lipid membranes. The current work thus provides additional context to the generally accepted paradigm that water/octanol phase. The reported transport mechanism is further distinct to the second layer of octanol in equilibrium with the bulk octanol “hinge” motif to successfully operate within the surface fluctuations of the interface is a testament to the balance of hierarchical organization and energetic driving forces associated with the mutual solubility of water in the biphasic system. Although the instantaneous surface of octanol in direct contact with water is highly organized, a second bilayer-like organization exists a layer away from the interface that consists of hydrogen bonded octanol islands. The dynamic fluctuations within the interfacial region provide sufficient steric flexibility for bilayer islands (or sub-components) to swing to and from the instantaneous surface to the second layer of octanol in equilibrium with the bulk octanol phase. The reported transport mechanism is further distinct from recent reports regarding water transport through protein-free lipid membranes. The current work thus provides additional context to the generally accepted paradigm that water/octanol system is a surrogate of biological membranes as it pertains to lipophilicity, solute partitioning, and kinetics of partitioning. On-going work is investigating how the well depths, widths, and concurrent barrier height in the double well model of the hinge mechanism can be modulated by parameters of the interfacial structure and intermolecular forces. These include surfactant packing within the instantaneous surface, the second layer of the surface, the strength of surfactant...surfactant and surfactant...solute interactions.

Conflicts of interest

There are no conflicts to declare.

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Supporting Information for
An Octanol Hinge Opens the Door to Water Transport
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S1 Literature Analysis

Table S1: Previous theoretical and computational publications that have focused upon the water/octanol biphasic systems. Note that the works of Wipff and coworkers[1, 2, 3, 4] have examined metal-ligand complex distributions across water/octanol interfaces as it pertains to liquid-liquid extraction. Computational protocols involved mixing/demixing (non-equilibrium) and potential of mean force were employed to understand the energetic favorability in the two bulk phases (where the distance coordinate is not the transport reaction coordinate).[5, 6] adopt mass-transfer models to understand the extraction equilibria and kinetics solute complexes between the aqueous and octanol phases.

| References                          | partitioning coefficient (solute solubility, distribution coefficient) | interfacial structure | water solubility in octanol | water/solute transport mechanism |
|-------------------------------------|------------------------------------------------------------------------|-----------------------|-----------------------------|---------------------------------|
| Campos-Villalobos2019[7]            | ✓                                                                      | ✓                     | ✓                           | ✓                              |
| Qiao2018[8]                         |                                                                         |                       |                             |                                 |
| Cevc2018[9]                         |                                                                         |                       |                             |                                 |
| Biswas2018Partitioning[10]          | ✓                                                                      | ✓                     | ✓                           | ✓                              |
| Schottl2018[11]                     |                                                                         |                       |                             |                                 |
| Zhang2018[12]                       |                                                                         |                       |                             |                                 |
| Biswas2018Alkalai[13]               | ✓                                                                      | ✓                     | ✓                           | ✓                              |
| Lopez2018[14]                       |                                                                         |                       |                             |                                 |
| Zolgahd2017[15]                     | ✓                                                                      | ✓                     |                             |                                 |
| Taddese2017[16]                     |                                                                         |                       |                             |                                 |
| Mondal2017[17]                      |                                                                         |                       | ✓                           |                                 |
| Tang2017[18]                        | ✓                                                                      | ✓                     |                             |                                 |
| Atsmon-Raz2017[19]                  |                                                                         |                       |                             |                                 |
| Tabrizi2017[20]                     |                                                                         |                       |                             |                                 |
| Saeedi2017[21]                      |                                                                         |                       |                             |                                 |
| Singh2016[22]                       |                                                                         |                       |                             |                                 |
| Bannan2016[23]                      |                                                                         |                       |                             |                                 |
| Abramko-Rideg[24]                   |                                                                         |                       |                             |                                 |
| Ndao[25]                            |                                                                         | ✓                     |                             |                                 |
| Schottl[26]                         |                                                                         | ✓                     |                             |                                 |
| Sun2015[27]                         |                                                                         | ✓                     |                             |                                 |
| Garrido2015[28]                     |                                                                         | ✓                     |                             |                                 |
| Wagner2015[29]                      |                                                                         | ✓                     |                             |                                 |
| Huang2015[30]                       |                                                                         | ✓                     |                             |                                 |
| Liyana-Arachchi2014[31]             |                                                                         | ✓                     |                             |                                 |
| Wick2014[32]                        |                                                                         | ✓                     |                             |                                 |
| Martin2014[33]                      |                                                                         | ✓                     |                             |                                 |
| Schottl2014[34]                     |                                                                         | ✓                     |                             |                                 |
| Liyana-Arachchi2013[35]             |                                                                         | ✓                     |                             |                                 |
| Abramko-Rideg2013[36]               |                                                                         | ✓                     |                             |                                 |
| Bhatnagar2013[37]                   |                                                                         | ✓                     |                             |                                 |
| Samanta2013[38]                     |                                                                         | ✓                     |                             |                                 |
| Reference               | Valid? | Valid? | Valid? | Valid? | Valid? |
|-------------------------|--------|--------|--------|--------|--------|
| Kozbial2013[39]         | ✓      |        |        |        |        |
| Benay2013[4]            | ✓      |        |        |        | ✓      |
| Liyana-Arachchi2012[40] | ✓      |        |        |        |        |
| Samanta2012[41]         | ✓      |        |        |        |        |
| Mohsen-Nia2012[42]      | ✓      |        |        |        |        |
| Kamath2012[43]          | ✓      |        |        |        |        |
| Bhatnagar2012[44]       | ✓      |        |        |        |        |
| Park2011[45]            | ✓      |        |        |        |        |
| Stein2011[46]           | ✓      |        |        |        |        |
| Petersen2010[6]         | ✓      |        |        |        |        |
| Palombo2010[47]         |        | ✓      |        |        |        |
| Wick2010[48]            |        |        | ✓      |        |        |
| Prasanna Rani2010[5]    | ✓      |        |        |        |        |
| Economou2010[49]        | ✓      |        |        |        |        |
| Goudarzi2010[50]        | ✓      |        |        |        |        |
| Benay2010[1]            |        | ✓      |        |        |        |
| Noubigh2010[51]         | ✓      |        |        |        |        |
| Garrido2009[52]         | ✓      |        |        |        |        |
| Giri2009[53]            | ✓      |        |        |        |        |
| Redmill2009[54]         | ✓      |        |        |        |        |
| Carmosini2008[55]       | ✓      |        |        |        |        |
| Nanzai2008[56]          | ✓      |        |        |        |        |
| MacCallum2007[57]       | ✓      |        |        |        |        |
| White2007[58]           | ✓      |        |        |        |        |
| Chevrot2007[2]          | ✓      |        |        |        |        |
| Cheng2007[59]           | ✓      |        |        |        |        |
| Mintz2007[60]           | ✓      |        |        |        |        |
| Held2007[61]            | ✓      |        |        |        |        |
| Kazuya2007[62]          | ✓      |        |        |        |        |
| Marrink2007[63]         | ✓      |        |        |        |        |
| Ghasemi2007[64]         | ✓      |        |        |        |        |
| Engelmann2007[65]       | ✓      |        |        |        |        |
| Chevrot2007[3]          | ✓      |        |        |        |        |
| Jedlovszky2007[66]      | ✓      |        |        |        |        |
| Chapeaux2007[67]        | ✓      |        |        |        |        |
| Napoleon2006[68]        | ✓      |        |        |        |        |
| Chen2006[69]            | ✓      |        |        |        |        |
| Lamber2006[70]          | ✓      |        |        |        |        |
| Zhao2005[71]            | ✓      |        |        |        |        |
| DeOliveira2005[72]      | ✓      |        |        |        |        |
| Paolantoni2005[73]      | ✓      |        |        |        |        |
| Jabusch2005[74]         | ✓      |        |        |        |        |
| Meylan2005[75]          | ✓      |        |        |        |        |
| Sassi2004[76]           | ✓      |        |        |        |        |
| Steel2004[77]           | ✓      |        |        |        |        |
| Rahb2004[78]            | ✓      |        |        |        |        |
| Benjamin2004[79]        | ✓      |        |        |        |        |
| Jedlovsky2004[80]       | ✓      |        |        |        |        |
| Zhang2003[81]           | ✓      |        |        |        |        |
| Abraham2003[82]         | ✓      |        |        |        |        |
| Steel2003[83]           | ✓      |        |        |        |        |
| Aliste2003[84]          | ✓      |        |        |        |        |
| Bas2002[85]             | ✓      |        |        |        |        |
| DeOliveira2002[86]      | ✓      |        |        |        |        |
| Roberts2002[87]         | ✓      |        |        |        |        |
| Kovalchuk2000[88]       | ✓      |        |        |        |        |
| Grassi2002[89]          | ✓      |        |        |        |        |
| Peretti2002[90]         | ✓      |        |        |        |        |
| MacCallum2002[91]       | ✓      |        |        |        |        |
| Tetko2001[92]           | ✓      |        |        |        |        |
| Michael2001[93]         | ✓      |        |        |        |        |
Figure S1: Schematic representation of the octanol/water liquid-liquid interface simulation box. Bulk water and octanol molecules are depicted in gray and cyan lines respectively. Extracted water molecules into the octanol phase and the interfacial water layer are described with red oxygens, while two adjacent water layers that directly beneath the interfacial water layer with green and blue oxygens, respectively (only shown in the right half cell). The bilayer structure of octanol molecules in the vicinity of the interface (left half box) is highlighted with cyan bonds for alkyl carbon tail and orange sphere for oxygens in the hydroxyl head group.
Table S2: The compositions and simulation periodic unit cell box sizes, interfacial tensions, water solubilities after equilibration using the GROMOS54A7/SPC-E force field. Note that after 30 ns equilibration, a system with 60 Å z-length (40 Å of octanol phase along the z axis) is not sufficient enough to adequately describe the octanol long-range structure, as a consequence, no liquid-liquid interface is generated.

| Water | Octanol | X   | Y   | Z   | Interfacial Tension (mN/m) | Water fraction solubility |
|-------|---------|-----|-----|-----|-----------------------------|--------------------------|
| 4279  | 979     | 77.96 | 77.96 | 60.42 | —                           | —                        |
| 8557  | 1959    | 78.24 | 78.24 | 119.32 | 7.89 ± 1.30                | 0.31                     |
| 12836 | 2845    | 79.77 | 79.77 | 173.61 | 7.83 ± 0.80                | 0.26                     |
| 17115 | 3917    | 78.54 | 78.54 | 237.59 | 7.43 ± 0.80                | 0.20                     |
| 3209  | 734     | 40.60 | 40.60 | 166.92 | 7.44 ± 1.95                | 0.24                     |
| 7220  | 1653    | 60.16 | 60.16 | 171.22 | 6.75 ± 0.65                | 0.25                     |
| 20056 | 4591    | 98.16 | 98.16 | 178.64 | 7.76 ± 0.85                | 0.22                     |

S3 Results and Discussion

The black curve in the left panel of Figure S2 shows the scaled water density profile along the z axis by its bulk density in the octanol-rich phase. It can be observed that there presents a significant region of enhanced water concentration around 17 Å from the GDS toward the octanol phase, which is in good agreement with the previous simulation. The average densities of water and octanol more than 1 nm from the GDS in the octanol-rich phase yields an average mole fraction of water of 0.26, in good agreement with the experimental water solubility in octanol[103] (see Table 1).

Figure S2: Scaled density profiles from the octanol-water liquid-liquid interface system for water (black line), octanol hydroxy oxygens (red line), octanol methylene carbons (green line), and octanol methyl carbons (blue line) (left panel). Average orientation of water dipoles (black lines) and end-to-end atoms (hydrogen from OH groups and methyl carbon) for octanol (blue lines). The angle is with respect to the z axis, with zero representing no orientational preference for both profiles (right panel).

The left panel of Figure S2 presents the density profiles of octanol atom types in the right half the simulation box along the z axis (scaled by their bulk densities in the octanol phase). The oscillation in the hydroxyl O-atom density profile draws the further interest, with its first peak sitting exactly at the position of the Gibbs Dividing surface (GDS) (z = 0). The density has a minimum near 9 Å from the GDS, which is in good agreement with previous simulations having a similar distances of 8[79] or 9 Å[32]. We further calculate the average octanol molecular end-to-end distance (hydroxyl oxygen to methyl carbon) to be 8.68 Å, coinciding with the difference between the first maximum and minimum of the hydroxyl oxygen density profile. The density oscillation propagates further along the z dimension of the simulation box, with the second peak sitting ∼17 Å from the GDS, a value comparable to twice the octanol molecular end-to-end length. The
average end-to-end distance of octanol molecules in the second layer of the bilayer structure has a value is 8.54 Å. It is worth to note that the sum of this obtained value and the average interfacial octanol molecular end-to-end distance is confirmed to be equal to the difference between the aboved-mentioned maxima of the hydroxyl oxygen density profile. The distribution of the molecular end-to-end distance of the octanol backbone (hydroxyl oxygen to methyl carbon) in Layer-1 and Layer-2 are shown in Figure S3.

Figure S3: The distribution of the molecular end-to-end distance for octanol in Layer-1 and Layer-2.

Figure S4: Left panel: two dimensional RDF of bilayer octanol molecules in the water-octanol interface system. Right panel: Excess coordination numbers between octanol molecules in Layer-1 and Layer-2.
Table S3: Summary of calculated intermolecular interactions for water and octanol molecules with different octanol/water models. Here SR, Disper.-corr., and Coul.-recip. denote short-range, dispersion correction and coulombic interactions in reciprocal space.

| Model               | Intermolecular Energy Term | E (Octanol+Water)      | E (Octanol)  | E (Water)   | Δ E (Octanol-Water) |
|---------------------|----------------------------|------------------------|--------------|-------------|---------------------|
| GROMOS47A7/SPCE     | VDW                        | Lj (SR)                | -3681.57±6.69| -3077.81±13.15| 26710.08±10.04     | 354.16 |
|                     |                            | Coulomb (SR)           | -1743.01±1   | -761.86     | 1168.13±0.10       | 14.52 |
|                     |                            | Coulomb (Coulomb)      | -2304±2.6    | -5156±2.8   | 1622±2.10          | -1664.68 |
|                     |                            | Coulomb (Coulomb)      | 1697.73±1.34 | 968±2.8    | 422.4±2.10         | -323.56 |
|                     |                            | Coulomb (Coulomb)      | -2377.32±12.9| -41068.83±14.34 | 16475.66±5.26     | -7968.93 |
|                     |                            | Coulomb (Coulomb)      | 672.33±0.19  | 492.34±0.57 | 329.73±0.38        | -149.83 |
|                     |                            | Coulomb (Coulomb)      | -2149.67±13.44 | -39972.04±18.64 | 18552.15±3.82     | -79.18 |
|                     |                            | Coulomb (Coulomb)      | -1610.52    | 920.39      | 320.14             | -623.55 |
|                     |                            | Coulomb (Coulomb)      | -1891.07±3.25 | -44996.18±19.32 | 134518.16±14.82   | -965.83 |
|                     |                            | Coulomb (Coulomb)      | 683.38±0.88  | 499.75±1.36 | 384.92±0.74        | -161.29 |
|                     |                            | Coulomb (Coulomb)      | -9892.33±4.54 | -21459.39±13.82 | 11743.38±3.11     | -176.32 |
|                     |                            | Coulomb (Coulomb)      | -937.52     | 504.49      | -66.48             | -966.55 |
|                     |                            | Coulomb (Coulomb)      | -9374.33±9.80 | -2559.99±11.23 | 8761.38±1.41      | -3829.96 |
|                     |                            | Coulomb (Coulomb)      | -966.17±0.45 | 283.85±0.10 | 21228±0.10         | -1239.96 |

S3.1 Water and octanol transport dynamics.

In order to analyze the dynamics and mechanism of water extraction into octanol organic phase, we perform MD simulations by starting with an initial configuration consisting of a pure water phase sandwiched by two octanol layers, as shown in Figure S1, in NPT ensemble to equilibrate for 250 ns. During equilibration, water molecules are observed to rapidly diffuse into the octanol phase. Figure S6 presents the time evolution of the octanol layers, as shown in Figure S1, in NPT ensemble to equilibrate for 250 ns. During equilibration, water molecules are observed to rapidly diffuse into the octanol phase. Figure S6 presents the time evolution of the number of water molecules transferring into the octanol phase as a function of simulation time. It indicates that over 200 ns of equilibration time, the equilibrium of the water extraction can be reached.

Table S4: The dataset of transferred water and octanol clusters among the transport between Layer-1 and Layer-2 and between Layer-2 and octanol organic phase for all examined 3000 frames of simulation data.

| Cluster composition | Layer-1 → Layer-2 | Layer-2 → Layer-1 | Layer-2 → Organic | Organic → Layer-2 |
|---------------------|-------------------|-------------------|--------------------|-------------------|
| 1Octanol            | 153269            | 13024             | 79248              | 79465             |
| 2Octanol            | 128               | 135               | 1399               | 1529              |
| 3Octanol            | 21                | 26                | 406                | 448               |
| 4Octanol            | 1                 | 2                 | 68                 | 57                |
| 5Octanol            | 1                 | –                 | 12                 | 16                |
| 6Octanol            | –                 | –                 | 2                  | 4                 |
| 7Octanol            | –                 | –                 | –                  | 2                 |
| 1Water              | 477               | 413               | 18554              | 18573             |
| 2Water              | –                 | 1                 | 201                | 202               |
| 3Water              | –                 | –                 | 46                 | 50                |
| 4Water              | –                 | –                 | 9                  | 11                |
| 1Water-1Octanol     | 168               | 182               | 2540               | 2716              |
| 1Water-2Octanol     | 293               | 310               | 1332               | 1191              |
| 1Water-3Octanol     | 243               | 231               | 233                | 226               |
| 1Water-4Octanol     | 67                | 81                | 44                 | 35                |
| 1Water-5Octanol     | 14                | 11                | 13                 | 10                |
| 1Water-6Octanol     | –                 | –                 | 2                  | 4                 |
| 1Water-7Octanol     | –                 | –                 | 1                  | 1                 |
| 1Water-8Octanol     | –                 | –                 | –                  | –                 |
| 2Water-1Octanol     | 3                 | 3                 | 1009               | 975               |
| 2Water-2Octanol     | 39                | 35                | 386                | 385               |
| 2Water-3Octanol     | 84                | 101               | 69                 | 94                |
| 2Water-4Octanol     | 88                | 79                | 31                 | 22                |
| 2Water-5Octanol     | 44                | 38                | 10                 | 7                 |
| 2Water-6Octanol     | 12                | 12                | 3                  | 1                 |
| 2Water-7Octanol     | –                 | 1                 | 1                  | 1                 |
| 2Water-8Octanol     | –                 | –                 | –                  | –                 |
| 3Water-1Octanol     | –                 | 1                 | 149                | 149               |
| 3Water-2Octanol     | 2                 | 4                 | 72                 | 93                |
| 3Water-3Octanol     | 23                | 19                | 34                 | 30                |
| 3Water-4Octanol     | 42                | 37                | 12                 | 4                 |
| 3Water-5Octanol     | 31                | 40                | 4                  | 2                 |

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| 3Water-6Octanol | 16 | 22 | 1 | 2 |
| 3Water-7Octanol | 8 | 3 | – | – |
| 3Water-8Octanol | 1 | – | – | – |
| 3Water-9Octanol | 1 | – | – | – |
| 4Water-1Octanol | – | 1 | 18 | 16 |
| 4Water-2Octanol | 1 | 1 | 24 | 21 |
| 4Water-3Octanol | 4 | 4 | 10 | 4 |
| 4Water-4Octanol | 10 | 14 | 3 | 2 |
| 4Water-5Octanol | 18 | 25 | – | 1 |
| 4Water-6Octanol | 28 | 13 | – | 1 |
| 4Water-7Octanol | 5 | 5 | 1 | – |
| 4Water-8Octanol | 7 | 2 | – | – |
| 4Water-9Octanol | – | – | – | 1 |
| 5Water-1Octanol | – | – | 2 | 3 |
| 5Water-2Octanol | – | 1 | 3 | 7 |
| 5Water-3Octanol | – | 2 | 4 | 1 |
| 5Water-4Octanol | 9 | 5 | 2 | – |
| 5Water-5Octanol | 7 | 5 | – | 1 |
| 5Water-6Octanol | 15 | 13 | – | – |
| 5Water-7Octanol | 12 | 8 | – | – |
| 5Water-8Octanol | 5 | 7 | – | – |
| 5Water-9Octanol | 4 | 3 | – | – |
| 6Water-1Octanol | – | – | 1 | – |
| 6Water-2Octanol | – | 1 | – | – |
| 6Water-3Octanol | 2 | 1 | – | – |
| 6Water-4Octanol | 5 | 4 | – | – |
| 6Water-5Octanol | 5 | 5 | – | – |
| 6Water-6Octanol | 5 | 13 | – | – |
| 6Water-7Octanol | 8 | 5 | – | – |
| 6Water-8Octanol | 1 | 6 | – | – |
| 7Water-1Octanol | 1 | 2 | 1 | – |
| 7Water-2Octanol | 3 | 1 | – | – |
| 7Water-3Octanol | 2 | – | – | – |
| 7Water-4Octanol | 4 | 2 | – | – |
| 7Water-5Octanol | 4 | 4 | – | – |
| 7Water-6Octanol | 3 | 4 | – | – |
| 7Water-7Octanol | 2 | 1 | – | – |
| 7Water-10Octanol | – | 1 | – | – |
| 7Water-11Octanol | – | 2 | – | – |
| 8Water-1Octanol | 3 | – | – | – |
| 8Water-2Octanol | 1 | 1 | – | – |
| 8Water-3Octanol | 1 | 2 | – | – |
| 8Water-4Octanol | 3 | 7 | – | – |
| 8Water-5Octanol | 3 | 4 | – | – |
| 8Water-6Octanol | 3 | 2 | – | – |
| 8Water-10Octanol | 2 | – | – | – |
| 8Water-12Octanol | 1 | – | – | – |
| 9Water-1Octanol | 1 | – | – | – |
| 9Water-2Octanol | 2 | 1 | – | – |
| 9Water-3Octanol | – | 2 | – | – |
| 9Water-4Octanol | 3 | – | – | – |
| 9Water-5Octanol | 1 | – | – | – |
| 9Water-10Octanol | – | – | – | – |
| 10Water-1Octanol | 1 | – | – | – |
| 10Water-2Octanol | 3 | 2 | – | – |
| 10Water-3Octanol | 1 | – | – | – |
| 10Water-11Octanol | 1 | – | – | – |
| 10Water-12Octanol | – | 1 | – | – |
| 11Water-1Octanol | 1 | – | – | – |
| 11Water-2Octanol | 3 | 1 | – | – |
| 11Water-3Octanol | 2 | 1 | – | – |
| 11Water-4Octanol | 1 | – | – | – |
| 11Water-5Octanol | – | – | – | – |
| 11Water-10Octanol | 2 | 1 | – | – |
| 11Water-12Octanol | – | – | – | – |
| 12Water-1Octanol | 2 | – | – | – |
| 12Water-2Octanol | – | 1 | – | – |
| 12Water-3Octanol | 1 | 2 | – | – |
| 13Water-1Octanol | – | 1 | – | – |
| 14Water-1Octanol | – | 1 | – | – |
Table S5: Arrhenius equation fitting data for the molecular transport in the process of Layer-1 → Layer-2.

| Transfer “reaction” | A |  \( E_a \) (kcal/mol) |
|---------------------|---|----------------------|
| octanol stochastic flipping | 1 | 0.99±0.02 |
| water molecular machine transfer | 1 | 4.16±0.11 |

Table S6: Arrhenius equation fitting data for the molecular transport in the process of Layer-2 → Layer-1.

| Transfer “reaction” | A |  \( E_a \) (kcal/mol) |
|---------------------|---|----------------------|
| octanol stochastic flipping | 1 | 0.99±0.02 |
| water molecular machine transfer | 1 | 3.51±0.06 |

Figure S5: The average compositions of transporting species in the Layer-2 → Layer-1 transport. Only transport species with a percentage above 5% are listed.
Figure S6: Simulated number of water molecules in octanol phase as a function of simulation time.

Figure S7: Left panel: The average distribution of the composition of clusters formed by water and octanol hydroxyl atoms in the Layer-2. Right panel: Correlation of water and octanol molecules in the composition of clusters. (The used data are listed in the Table S7)
Figure S8: Two-dimensional normed density distributions of water molecules that are hydrogen bonded to octanol molecules in Layer-1 and Layer-2 with 1.0 representing the bulk uniform distribution.

Table S7: The dataset of compositions of islands formed by water and octanol hydroxyl atoms in the Layer-2 for all examined 3000 frames of simulation data.

| Composition | 0water | 1water | 2water | 3water | 4water | 5water | 6water | 7water | 8water | 9water | 10water | 11water | 12water | 13water | 14water | 15water |
|-------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|----------|----------|----------|----------|----------|----------|
| octanol     |        |        |        |        |        |        |        |        |        |        |          |          |          |          |          |          |
| 0octanol    | 15     | 18     | 17     | 22     | 19     | 22     | 18     | 17     | 22     | 19     | 18       | 17       | 17       | 17       | 17       | 17       |
| 1octanol    | 0      | 2      | 3      | 4      | 5      | 6      | 7      | 8      | 9      | 10     | 11       | 12       | 13       | 14       | 15       | 16       |
| 2octanol    | 0      | 1      | 1      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 3octanol    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 4octanol    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 5octanol    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 6octanol    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 7octanol    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 8octanol    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 9octanol    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 10octanol   | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 11octanol   | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 12octanol   | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 13octanol   | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 14octanol   | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
| 15octanol   | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0         | 0         | 0         | 0         | 0         | 0         |
Figure S9: Orientation profiles of the octanol molecular machine in the process of transporting water molecules between Layer-1 and Layer-2. The angle is between the octanol molecular end-to-end atoms (hydroxyl hydrogen and methyl carbon) and the $z$ axis (see Figure S1). The color code is described in Figure 3.
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