

effectively redistributed close to \$1 trillion from older generations, who held most of the stock market, to younger and future generations, who can now purchase the same physical assets at a cheaper price. Because of our failure to assess fiscal policy and economic events in generational terms, we have still to understand that the decline in the stock market was an economic event that was the equivalent of running an extremely fiscally conservative policy. The stock market, in a matter of a few days, effectively did what many had been clamoring after for 8 years. Instead of understanding that more fiscal conservatism is now unwarranted, the general perception is that it is time to really tighten up.

## Conclusion

The development of present value generational budget accounts would greatly improve our description and analysis of fiscal policy. They would be invariant to accounting conventions, capture all fiscal policies, and show at a glance how much each generation is paying to finance the government's consumption. Such accounts would, of course, be sensitive to the choice of interest rates and to projections of future fiscal policy and future economic performance. Whether these accounts will provide more than a very rough road map remains to be seen. But even a rough road map of actual fiscal policy would be preferable to the quite precise road map of accounting whims that constitutes current descriptions of fiscal events.

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3. See *The Economic Report of the President* (Government Printing Office, Washington, DC, 1982), chap. 4.
4. For a discussion of the literature on liquidity constraints and consumption see L. J. Kotlikoff, *What Determines Savings?* (MIT Press, Cambridge, MA, 1988).
5. This statement does not take into account policy-induced changes in the time paths of wages and interest rates that will differently affect the consumption possibilities of successive generations. A full description of the policy requires specifying these general equilibrium changes in factor prices and how they affect successive generations.
6. In the sample presented here, the government's consumption equals zero. Note that the sum of the accounts in the model presented here discounted to time  $t$  is

$$-H + \sum_{j=1}^{\infty} H r_{t+j} \prod_{i=1}^j (1+r_{t+i})^{-1} = -H + \sum_{j=1}^{\infty} H \prod_{i=1}^{j-1} (1+r_{t+i})^{-1} - \sum_{j=1}^{\infty} H \prod_{i=1}^j (1+r_{t+i})^{-1} = 0$$

7. A. J. Auerbach and L. J. Kotlikoff, *Dynamic Fiscal Policy* (Cambridge Univ. Press, Cambridge, MA, 1987), chap. 9.
8. This model is developed and analyzed by Auerbach and Kotlikoff (7).
9. See M. J. Boskin, M. S. Robinson, A. M. Huber, "Government saving, capital formation, and wealth in the United States, 1947-1985" (National Bureau of Economic Research working paper no. 2352, Cambridge, MA, August 1987), table 8, p. 26.

# Forces Between Surfaces in Liquids

JACOB N. ISRAELACHVILI AND PATRICIA M. MCGUIGGAN

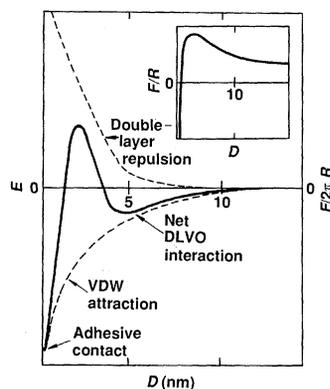
Recent developments in the direct measurements of forces between surfaces in liquids at the ångström resolution level are reviewed. The results reveal a rich variety of interactions and interaction potentials that depend on the nature of the surfaces and intervening liquids. These results also shed new insights into liquid structure adjacent to surfaces and the interactions occurring in complex systems, with implications in many different areas of chemical physics, biology, and technology. The origin of some important fundamental interactions, such as repulsive "hydration" forces and attractive "hydrophobic" forces, are still not understood and offer a challenge for experimental and theoretical work in this area.

**A**LTHOUGH THE NATURE OF INTERMOLECULAR FORCES HAS long interested scientists, rigorous treatments of the subject have tended to concentrate on the "two-body" forces between simple atoms or molecules in vacuum, whereas the vast and important area of the forces between dissolved solute molecules, particles, or surfaces in liquids remained largely unexplored. Howev-

er, many important phenomena in condensed matter and liquid state physics, chemistry, biology, materials and surface science, engineering, and many industrial processes, involve such interactions. The reason was that until recently little was actually known or understood about the short-range forces that occur even in simple liquids, let alone more complex multicomponent systems involving dissolved colloidal particles, biological structures, polymers, surfactants, and so forth. Thus, although Langmuir and others published theoretical papers in the 1930s and 1940s on the repulsive screened electrostatic forces operating in aqueous electrolyte (salt) solutions (1), and Lifshitz in the 1950s and 1960s published his general theory of the van der Waals forces between surfaces (and between molecules) in liquids (2), there were no detailed measurements of the magnitude and range of short-range forces, and even their existence remained controversial until the early 1970s. In contrast to this, intermolecular forces across vacuum and air were rigorously studied as early as the 1950s by the Russian School, as well as others in the Netherlands, England, and Germany (3). Only with the development of reliable direct force-measuring techniques in the 1960s and 1970s, and more recent theoretical advances, especially

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**Fig. 1.** Classical DLVO interaction potential energy  $E$  as a function of surface separation  $D$  between two flat surfaces interacting in an aqueous electrolyte (salt) solution through an attractive van der Waals force and a repulsive screened electrostatic “double-layer” force (1, 4). The double-layer potential (or force) is repulsive and roughly exponential in distance dependence; its strength depends on the surface charge density and its range depends on the electrolyte concentration (the higher the concentration, the more effective the screening and the steeper the decay of this force).



The attractive van der Waals potential has an inverse power-law distance dependence (for example,  $E \propto -1/D$  between two spheres, and  $E \propto -1/D^2$  between two flat surfaces) and thus dominates at small separations, which results in strong adhesion at contact. The inset shows a typical interaction potential between surfaces of high charge in dilute electrolyte solution. All curves are schematic. Note that the interaction energy between two flat surfaces is directly proportional to the force  $F$  between two curved surfaces of radius  $R$  through the relation  $F/R = 2\pi E$ , as shown by the right-hand ordinate [this is known as the “Derjaguin approximation” (1)].

Monte Carlo and molecular dynamics computer simulations of “many-body” interactions in liquids, has it been possible to measure and begin to understand the subtle forces that determine the properties of many complex (although familiar) multicomponent systems.

By convention, four types of forces are considered to operate between surfaces or particles in liquids: (i) van der Waals forces, which are normally monotonically attractive and occur between all molecules; (ii) repulsive electrostatic “double-layer” forces, which arise when ionizable surfaces have a net electric charge, as usually occurs in water; (iii) solvation (“structural” or “hydration”) forces, which arise from the structuring or ordering of liquid molecules when confined between two surfaces close together (these can be attractive, repulsive, or oscillatory); and (iv) repulsive entropic (steric or fluctuation) forces, which arise from the thermal motions of protruding surface groups (such as polymers or lipid head groups) or from the thermal fluctuations of flexible fluidlike interfaces (of surfactant or lipid bilayers). For interactions in vacuum, only the van der Waals forces are important, whereas in liquids all four forces may operate simultaneously, although in liquids it is often difficult to separate unambiguously the various contributions into the above categories.

## Van der Waals and Electrostatic Forces: The DLVO Theory

The attractive van der Waals and repulsive electrostatic double-layer forces were the earliest to be considered, both theoretically and experimentally, and until recently only these two forces were believed to be important. Thus, if the former dominated, two particles or surfaces would come together and adhere, whereas if the latter dominated, they would be kept apart. Taken together, the combined but opposing action of these two interactions form the basis of the celebrated “DLVO theory,” after its originators, Derjaguin, Landau, Verwey, and Overbeek (4). The DLVO theory has served since the 1950s as the main theoretical framework for analyzing the properties of colloidal and biocolloidal systems (Fig. 1). Double-layer forces are responsible for stabilizing thick soap films and were indeed first measured from the equilibrium thicknesses of such films (5).

A number of techniques have been developed for measuring the forces between surfaces in liquids. In particular, one may mention osmotic and hydraulic pressure techniques, which allow for the measurements of repulsive forces between colloidal particles and aligned clay sheets (6) or between lipid bilayers (7) in solution. Other techniques have been developed for specific systems, for example, measuring the equilibrium thicknesses of soap films or thick wetting films on surfaces to obtain the forces stabilizing these films (1).

During the 1970s sophisticated new techniques were introduced for directly measuring the full “force laws” (force versus distance) between a variety of surfaces immersed in vapors and liquids (8, 9). Figure 2 shows one such device, the surface forces apparatus (8, 10), which has become an important tool in many research laboratories. The surfaces are often bare mica, which is molecularly smooth, although these surfaces can have thin films of polymers or metals, or monolayers and bilayers of surfactants or lipids adsorbed (deposited) on them before they are installed in the apparatus. The distance between the two surfaces can be controlled and measured to less than 1 Å, and the force sensitivity is about 10 nN ( $10^{-6}$  g).

By using this apparatus, it became possible for the first time to directly test the DLVO theory by accurately measuring the van der Waals and double-layer forces between surfaces immersed in various aqueous electrolyte solutions (11) and polar liquids (12). The results showed that at separations beyond about ten molecular diameters of the solvent molecules, the net interaction potential is very well described by continuum theories: namely, the so-called “Lifshitz theory” for the van der Waals force (1, 2) and the Poisson-Boltzmann equation for the double-layer force (1). In cases where deviations have been observed, these can usually be attributed to the existence of some additional type of interaction (discussed below), rather than to a breakdown in the validity of the two fundamental forces of the DLVO theory.

There is, however, one important exception that concerns surfaces of high charge interacting in aqueous solutions in the presence of divalent counterions: for example, between negatively charged surfactant and lipid bilayers in  $\text{CaCl}_2$  solutions, where  $\text{Ca}^{2+}$  is the “counterion.” Both theory (13) and experiments (14, 15) have recently shown that for such systems there is a strong additional attraction at small surface separations (less than about 20 to 40 Å). This extra attraction is believed to arise from ion-correlation effects, a sort of additional van der Waals attraction between the divalent ions—an effect that was first predicted theoretically from computer simulations to test the validity of the Poisson-Boltzmann equation (13). The importance of these specific attractive “ion-correlation forces” in different systems has yet to be fully assessed. Such forces can be far stronger than the conventional van der Waals attraction, and thus may be crucial for overcoming the double-layer and other repulsive forces between particles and surfaces, thereby promoting their adhesion (and fusion of micelles, bilayers, and biological membranes, which are known to involve divalent counterions such as  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ ). A quantitative comparison between theory and experiment is still awaited.

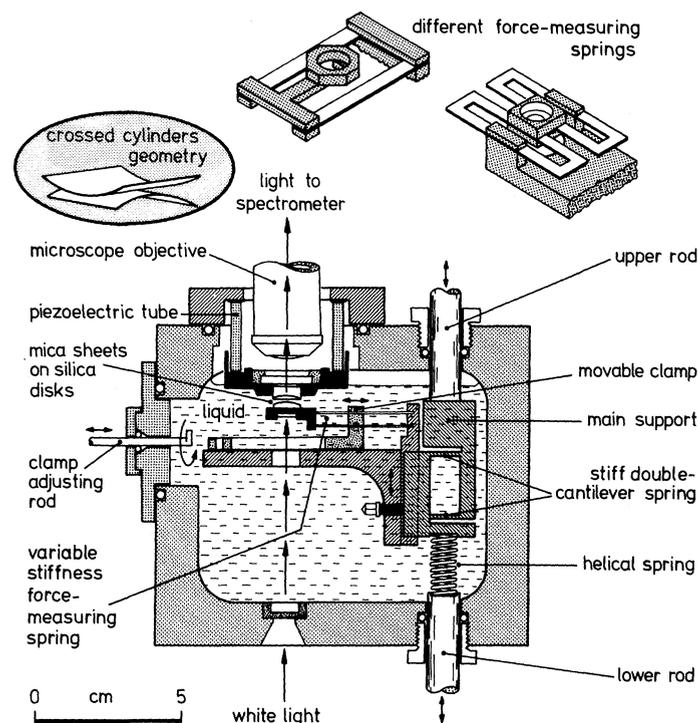
## Solvation Forces: Forces Associated with Solvent (Liquid) Structure

In many cases, however, an additional repulsive rather than attractive force appears to operate. This effect is reflected in the interactions of certain colloidal particles, clay mineral surfaces, and sheetlike structures, such as lipid bilayers and biological membranes in aqueous solutions, which do not always obey the predictions of the DLVO theory. For example, colloidal particles in solution can

remain separated, that is, they do not aggregate, even in the absence of any net surface charge, or two surfaces may separate (swell) spontaneously from contact when immersed in water. Until quite recently, the origin of these discrepancies remained a mystery; was the DLVO theory at fault, or was there some additional repulsive "structural" force of unknown origin, although invariably believed to be related to water structuring effects (16)?

Such forces are now commonly referred to as "solvation" or "structural" forces, or, if the solvent medium is water, "hydration" forces, and during the past few years many measurements have been made of the solvation forces in a variety of different liquids (10). In most cases the results show that when two molecularly smooth surfaces are separated by more than five to ten molecular diameters, the force laws are as expected from continuum theories (1), that is, an attractive van der Waals force and—if the surfaces are charged—a repulsive double-layer force (the two DLVO forces). At smaller separations, however, a liquid can no longer be treated as a structureless continuum and an additional solvation force is present that generally oscillates with distance (Fig. 3) (17, 18), varying between attraction and repulsion, with a periodicity equal to the mean diameter of the liquid molecules.

The origin of oscillatory forces between surfaces is now well understood theoretically (18, 19), at least for pure simple liquids, and it is recognized that the exponentially decaying peak-to-peak profiles characteristic of these solvation forces are related to, and



**Fig. 2.** A version of the surface forces apparatus (SFA) for measuring the forces between two curved molecularly smooth surfaces in liquids at the angstrom resolution level. Forces are measured from the deflection of the "variable-stiffness force-measuring spring," whose stiffness can be varied by shifting the position of the "movable clamp" by using the "clamp adjusting rod." A variety of interchangeable force-measuring springs (two shown on top) can also be used to allow greater versatility in measuring both repulsive or attractive forces over a range of greater than six orders of magnitude (8). During the past few years this apparatus has been used to identify and quantify most of the fundamental interactions occurring between surfaces in various liquids and vapors (1, 10), such as van der Waals and double-layer forces, solvation (hydration and hydrophobic) forces, adhesion and capillary forces, and the interactions between polymer-covered and surfactant-coated surfaces.

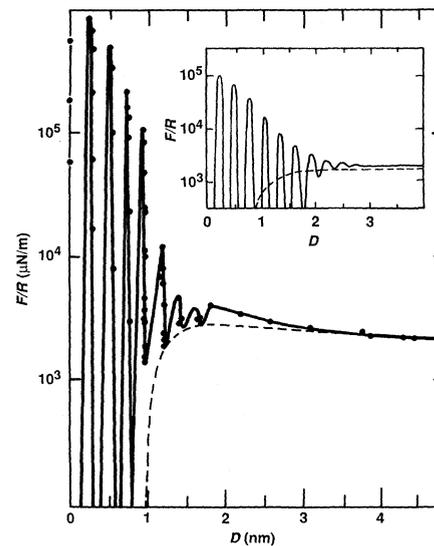
have the same origin as, the "radial distribution functions" and oscillatory "potentials of mean force" that are the basis for theoretical descriptions of intermolecular interactions in liquids. Oscillatory solvation forces cannot be described by continuum or "mean-field" theories, since such forces arise from the finite size of molecules, and they therefore depend critically on the molecular size and shape as well as on the local bonding or "structure" of the liquid medium. Thus oscillatory forces occur even between two totally inert surfaces because the liquid molecules prefer to order, or pack, into discrete but diffuse layers as the two surfaces approach each other. However, the effect is more general and occurs for molecules confined between any two boundaries, including two curved surfaces or even between two solute molecules in solution.

By studying the oscillatory forces between different surfaces across both aqueous and nonaqueous liquids, a host of interesting data has steadily accumulated and has revealed their subtle nature (10), such as their great sensitivity to the shape and rigidity of the liquid molecules (20), to the presence of other components (21), and to surface roughness. In particular, the oscillations can be smeared out if the liquid molecules are irregularly shaped (such as branched linear-chain molecules) and therefore unable to pack into ordered layers, or when surfaces are rough even at the angstrom level (22).

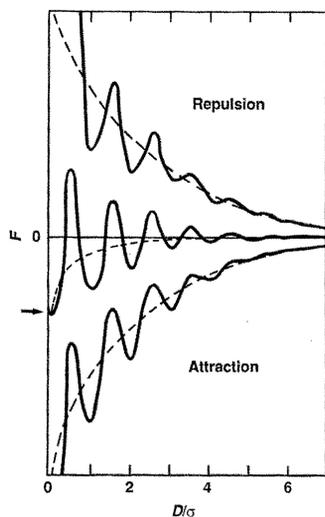
### Solvation in Water: Repulsive "Hydration" Forces and Attractive "Hydrophobic" Forces

More intriguing, however, has been the finding that in aqueous solutions the hydration force can also have a smoothly varying (monotonic) component that can be repulsive or attractive (Fig. 4). Between "hydrophilic" ("water-loving") surfaces, this monotonic force is repulsive, its strength depending on the hydration of the surfaces or surface groups (1, 11). Between "hydrophobic" ("water-fearing") surfaces, the force is attractive, its strength in this case depending on the hydrophobicity of the surfaces or surface groups (23). Hydrophobic surfaces, such as hydrocarbon and fluorocarbon surfaces, are those that are "inert" to water in the sense that they are unable to bind with water either electrostatically or through hydro-

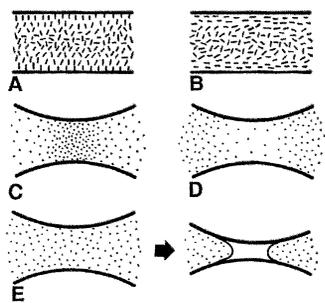
**Fig. 3.** Experimental and theoretical interaction potentials between two mica surfaces in  $10^{-3}M$  KCl solution, in which the concentration of  $K^+$  ions bound to the surfaces is about  $1/nm^2$ . In more dilute electrolyte solutions, the interaction is purely DLVO (compare with the dashed line and Fig. 1 inset). At higher electrolyte concentrations (solid line), more cations adsorb (bind) onto the surfaces along with their water of hydration, which causes an additional hydration force characterized by short-range oscillations (of periodicity 2.2 to 2.6 Å, about the diameter of the water molecule) superimposed on a longer ranged monotonically repulsive tail. Similar results have been obtained with other electrolytes. The main figure shows the measured force law (17); the inset (same units) is a recent theoretical computation for the same system (18). Because of elastic flattening of the supporting glue at distances less than 1 nm, the experimental values of  $F/R$  are overestimated (17).



**Fig. 4.** Typical surface forces in liquids as a function of distance  $D$  normalized by the molecular diameter of the liquid  $\sigma$ . The solvation (hydration) forces in water differ from those in other liquids in that there is a monotonic component in addition to the normal purely oscillatory component. Depending on the local density and orientation of the water molecules at the surfaces (see Fig. 5), the monotonic component can be attractive or repulsive, and thus dominate the oscillatory component. For hydrophilic surfaces the monotonic component is repulsive (upper curve), whereas for hydrophobic surfaces it is attractive (lower curve). For simpler liquids there are no such monotonic components, and both theory and experiments show that the oscillations simply decay with distance with the maxima and minima, respectively, above and below the base line of the van der Waals force (middle curve) or are superimposed on the net DLVO interaction. Note that for such liquids the strength of the final adhesion energy (or force) at molecular contact (the point indicated by the arrow, at  $D = 0$ ) is often accurately given by the continuum Lifshitz theory of van der Waals forces, although this theory fails to describe the force law at finite distances.



**Fig. 5.** Schematic illustration of how solvation forces arise depending on the altered orientation or density, or both, of the intervening liquid (solvent) molecules in the gap between two surfaces as they approach each other. (A) Antiparallel orientation (alignment) of water molecules at hydrophilic surfaces leading to (i) a diffuse layering near each surface (oscillatory hydration force regime) and (ii) a monotonic hydration force regime at larger separations that is repulsive because the molecules are antiparallel to each other as they abut at the midplane. (B) Parallel cooperative alignment of water molecules between two inert hydrophobic surfaces, leading to an attractive hydration (hydrophobic) force. (C) Increased liquid density in the gap leading to repulsion. (D) Decreased density leading to attraction. (E) Surface-induced phase-separation transition of a cavity (such as water vapor between two very hydrophobic surfaces) or of a bulk liquid phase (for example, capillary condensation of water from an organic solvent) as two surfaces approach each other. Such phase separations (or nucleation) can occur spontaneously between two surfaces while they are still well separated (26).



gen bonds. The hydrophobic interaction is a long-range force (23) and operates at even greater distances than the van der Waals force does. As in the case of the specific attractive ion-correlation forces mentioned above, the importance of the hydrophobic interaction has probably not been fully realized. Both of these monotonic hydration forces appear to decay exponentially with distance, with a characteristic decay length of 6 to 15 Å, which makes them rather long ranged, and they can dominate over the DLVO forces even at relatively large distances.

The origin of these monotonic hydration forces is as yet unclear. Their long range makes it difficult to carry out Monte Carlo or molecular dynamics simulations because—unlike the relatively short-range oscillatory solvation forces—these much longer ranged forces would require many hundreds of water molecules for a successful simulation. The repulsive force may simply be a negative form of the attractive force, depending on whether water molecules are aligned parallel or antiparallel to each other (Fig. 5, A and B).

Simple theoretical considerations (24) also suggest that a repulsive force would arise if the density of water between the two surfaces increased as the surfaces approached each other, whereas an attractive interaction would arise if the density decreased, that is, if the region between the two surfaces became depleted of water (Fig. 5, C and D). For sufficiently hydrophobic surfaces, this decrease in density could result in the spontaneous nucleation of a vapor phase, or cavity, between the two surfaces (Fig. 5E), an effect that has been observed recently (25). However, unlike the oscillatory forces, the molecular origin of the monotonic solvation forces is not yet understood, but they may both have the same origin, since both are exponential and have similar decay lengths.

These effects are closely related to the phenomenon of the spontaneous condensation of a liquid phase (of solute) from solvent, such as the spontaneous capillary condensation of a bulk water phase from oil between two hydrophilic surfaces (26). Once such condensation occurs, capillary forces act strongly to pull the two surfaces together. Such surface-induced nucleation can occur even when two surfaces are very far apart, as much as 100 Å. Both of these phenomena can have a dramatic effect on the interactions of surfaces and particles in solvents containing small, or even trace, amounts of a second, sparingly soluble (immiscible) component (27). As in the case of the monotonic solvation forces, the origin of surface-induced phase transitions is not well understood, but Evans and Marconi (28) have recently proposed a unified thermodynamic treatment of these phenomena that likens them to the gas-liquid transition of a van der Waals gas.

## Entropic and Fluctuation Forces Between Fluidlike Surfaces

The three interactions described so far may be considered to be the three fundamental interactions occurring in liquids; the first two (the van der Waals and electrostatic forces) being described by idealizing the liquid medium as a continuum, whereas the real interaction also includes the solvation forces. Other types of interactions are basically variations or perturbations of these under special situations. A particularly important case arises when the surfaces of the interacting structures are composed of amphiphilic molecules (such as surfactants or lipids), which are usually in the fluid state at ambient temperatures, so that the interacting surfaces are not smooth and rigid, but effectively rough and mobile. In particular, this occurs for structures such as micelles, vesicles, lipid bilayers, microemulsion droplets, surfactant-coated colloidal particles, and biological membranes in aqueous solutions (1). Any oscillatory component that may be intrinsic to the solvation (or hydration) force is now smeared out, partly because of the intrinsic “roughness” of these macromolecular interfaces, but mainly because of the thermal fluctuations of the hydrophilic surface groups (the “head-groups”), leaving only an effectively monotonic repulsive “hydration-fluctuation” force between the surfaces. These repulsive forces were first studied with soap films (29) and later measured in detail by Rand, Parsegian, and co-workers (7) using the osmotic pressure technique on lipid multibilayers composed of a variety of lecithin lipids (an important class of uncharged biological lipids). The hydration repulsion between the lecithin bilayers decayed exponentially with distance with decay lengths varying between 1.5 and 3.5 Å (notably shorter than observed between rigid surfaces of mica and silica). The more fluid or flexible the bilayers were, the greater the range of the repulsive forces, which extended from below 20 Å for frozen bilayers to above 30 Å for fluidlike bilayers, an effect that arises from the additional fluctuation repulsion of more fluid bilayers.

Subsequent measurements between lecithin and other lipid bilayers deposited on mica surfaces made with the surface forces apparatus basically confirmed these findings (30, 31) and, as might be expected, it was further established that the shorter the range of the repulsive forces, the stronger the van der Waals adhesion between bilayers at their equilibrium "contact" separation (Fig. 6). These short-range interactions are difficult to separate into their pure solvation (hydration) and thermal (entropic-fluctuation) components, which act together to give the total interaction potential. Indeed, the repulsive forces between lecithin bilayers in ethylene glycol, a polar but nonaqueous liquid, are very similar to those measured in water (32), highlighting the difficulty of trying to separate these forces into their two components.

For very flexible bilayers, the interaction between them should be dominated by the repulsive entropic-fluctuation forces [referred to as "undulation forces" by Helfrich (33), who first investigated their theoretical origin and suggested their importance]. Helfrich predicted that the repulsive undulation force between two planar fluid surfaces, such as two bilayers, varies as the inverse cube of their separation (the same distance dependence but the opposite sign to the attractive van der Waals force), and that the strength of the interaction should increase in proportion to the increasing flexibility (decreasing bending modulus) of the membranes (33). For bilayers of moderate flexibility, such as lecithin, the fluctuation forces simply enhance the range of the hydration forces by a few angstroms (34), whereas for highly fluid bilayers, the long-range repulsion can be totally dominated by the undulation forces, as has recently been confirmed experimentally (35). Servuss and Helfrich (36) have also recently shown that for bilayers that are somehow restricted from

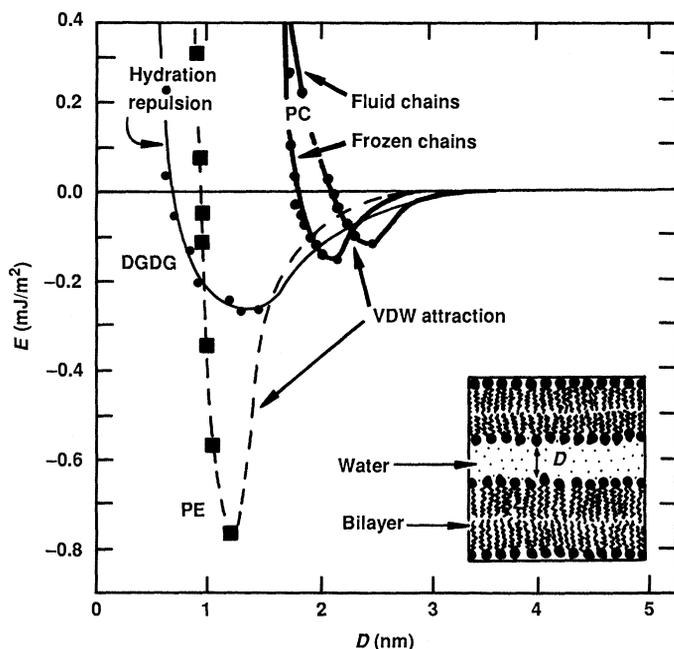
undergoing free thermal motions, for example, when they are under tension or when they are immobilized by being adsorbed onto a solid surface (as in Fig. 6), then the range of their fluctuation repulsion must decrease and their adhesion correspondingly increase.

Thus for amphiphilic surfaces one might expect that, in addition to the usual DLVO interaction, the short-range force should be dominated by a strongly repulsive hydration-fluctuation force that keeps these surfaces from coming close together. However, some bilayers appear to have no short-range hydration repulsion at all, or else a repulsion that extends only a few angstroms (14, 37). In other cases there appears to be an additional attraction either due to a hydrophobic interaction (30, 38) or, for charged bilayers in the presence of divalent counterions, due to "ion-correlation" forces (14, 37). For these surfaces the attractive forces dominate at small distances, which leads to very strong adhesion or fusion.

Although we are still some way from a full understanding of all these forces, we know that the interactions of fluidlike structures and especially of surfactant and lipid surfaces can be extremely varied and specific. Given that the lipid bilayer is the basic structural framework of biological membranes, it is more than likely that biological cells make full use of this diversity and specificity in regulating the interactions of their membranes and membrane-bound components.

## Future Directions

The subtleties that can occur in the last few nanometers as two surfaces, particles, or solute molecules approach each other in a medium can be quite remarkable. Sometimes the forces are well described by "continuum" or "mean-field" theories, such as the DLVO theory, but more often they are not. Important fundamental questions remain concerning the origin of long-range attractive and repulsive hydration forces in water, the spontaneous nucleation of a bulk liquid or vapor phase between two surfaces close together, and the nature of entropic-fluctuation forces between two fluidlike interfaces. The elucidation of these interactions both at the fundamental level and when applied to specific systems (where a number of different interactions may be occurring simultaneously) present a challenge to experimentalists and theoreticians. On the purely experimental side, new techniques are constantly being introduced for extending the range and scope of surface force measurements. For example, one may anticipate that the atomic force microscope (39) will soon provide the first direct measurements of the forces between molecules, as opposed to between surfaces.



**Fig. 6.** Measured attractive van der Waals and repulsive hydration-fluctuation forces in water between adsorbed bilayers of the most common uncharged lipids of biological membranes (30, 31): (i) phosphatidylcholine or "lecithin" (PC) lipids, showing the effect of increased thermal mobility (fluidity) in enhancing the monotonically repulsive hydration-fluctuation force above the bilayer melting temperature; (ii) phosphatidylethanolamine (PE) bilayers, whose head groups are smaller, less hydrated, and less mobile than those of PC, resulting in a much reduced hydration repulsion and increased adhesion; (iii) DGDG, one of the most common lipids of plant membranes [for the molecular structure of these lipids, see (1)]. The attractive forces beyond the minima were obtained from jump distances, which give the slopes of the forces from which the force curves were constructed (30, 31).

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# From Epinephrine to Cyclic AMP

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**Binding of catecholamines to the  $\beta$ -adrenergic receptor results in the activation of adenylate cyclase and the intracellular formation of adenosine 3',5'-monophosphate (cAMP). In the past 20 years the events that lead from hormone binding at the cell surface receptor site to the synthesis of cAMP at the inner layer of the membrane have been intensively studied. Signal transduction in this system involves the sequential interaction of the  $\beta$ -adrenergic receptor with the guanine nucleotide-binding protein ( $G_s$ ) and the adenylate cyclase catalyst (C). The mechanism of signal transduction from the receptor through  $G_s$  to C, as well as the role of the adenylate cyclase inhibitory G protein  $G_i$ , is discussed.**

**A**DENOSINE 3',5'-MONOPHOSPHATE (cAMP) AND THE ENZYME that synthesizes the molecule, adenylate cyclase, exist in almost every form of life and in every tissue of higher organisms. The ubiquitous role of cAMP and its involvement in the regulation of a multitude of biochemical pathways is now well established. Adenylate cyclase is usually activated as a response to external stimuli—hormones and neurotransmitters in mammalian tissues and glucose in yeast. An experimental system that has become

a focus in the study of transmembrane signaling is the  $\beta$ -adrenergic receptor-dependent adenylate cyclase. This system was originally studied in avian erythrocytes by the discoverers of cAMP, who were also the first to show that epinephrine (adrenaline) activates adenylate cyclase and that all the activity resides in the cell membrane (1). Pharmacological and physiological experiments (2) substantiated by biochemical data (3) have defined three types of adrenergic receptors: the  $\beta_1$ - and  $\beta_2$ -adrenergic receptors, which activate adenylate cyclase; the  $\alpha_2$ -adrenergic receptor, which inhibits adenylate cyclase; and the  $\alpha_1$ -adrenergic receptor, which activates phospholipase C.

The clinical importance of all the receptor subtypes has induced pharmaceutical chemists to develop a wide spectrum of selective drugs that show high affinity for these receptors. These drugs became the basis for the biochemical identification and characterization of these receptors. In 1974 the biochemical criteria for the identification of  $\beta$ -adrenergic receptors were established and, by the use of [ $^3$ H]propranolol (4), [ $^3$ H]dihydroalprenolol (5), and [ $^{125}$ I]-labeled hydroxybenzylpindolol (6), it was possible to identify and quantitate  $\beta$ -adrenergic receptors in a radioreceptor assay. Since 1981 the ligand of choice has been [ $^{125}$ I]-labeled (–)-cyanopindolol (7) because it exhibits 40 times as high affinity and 45 times as high specific radioactivity as either (–)-propranolol or (–)-dihydroalprenolol and is more selective than (–)-hydroxybenzylpindolol. When accurate binding experiments were possible, then substantiation of the pharmacological evidence (8) for the existence of two closely related classes of  $\beta$ -adrenergic receptors,  $\beta_1$  and  $\beta_2$  (9), could be achieved.

(–)-Propranolol was the basis for the design of the first radioactively labeled  $\beta$ -adrenergic affinity label. A bromoacetyl analog of

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