

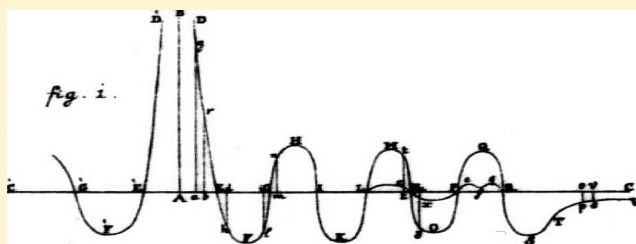
Brief History of Intermolecular and Intersurface Forces in Complex Fluid Systems

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ABSTRACT: We review the developments of ideas, concepts, and theories of intermolecular and intersurface forces and how these were influenced (or ignored) by observations of nature and, later, systematic experimentation. The emphasis of this review is on the way things gradually changed: experimentation replaced rhetoric, measurement and quantification replaced hand waving, energy replaced force in calculations, discrete atoms replaced the (continuum) aether, thermodynamics replaced mechanistic models, randomness and probability replaced certainty, and delicate experiments on the subnanoscale revealed fascinating self-assembling structures and complex behavior of even the simplest systems. We conclude by discussing today's unresolved challenges: how complex "dynamic" multicomponent—especially living biological—systems that receive a continuous supply of energy can be far from equilibrium and not even in any steady state. Such systems, never static but evolving in both space and time, are still far from being understood both experimentally and theoretically.



■ EARLY CONCEPTS OF FORCE

Ancient Egyptians. Ironically, the earliest concepts of forces dealt not with simple liquids or gases but with the most complex of complex fluid systems—with life itself. These essentially abstract concepts of force originated around 1200 B.C. among the ancient Egyptians who considered forces in nature as personal beings emanating from a deity. These "divine forces" included any natural phenomenon (hence the forces of nature) but also what we now consider as chemical or physical interaction forces, producing both violence as well as order,¹ and myths about the deities served to explain both the origin and diverse behavior of natural phenomena.

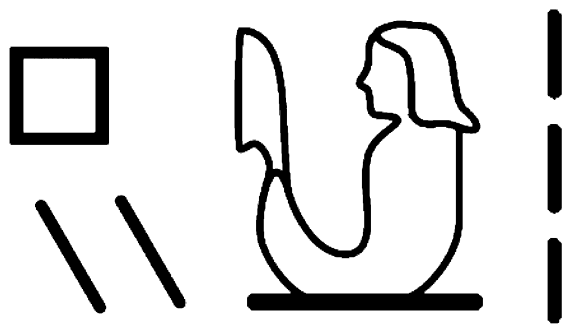


Figure 1. The earliest abstract concept of force can be traced back to ancient Egypt. The hieroglyphic of a figure holding a knife denotes the personification of force, believed to have divine powers.¹

Ancient Greeks. The ancient Greeks were the first to propose explanations of forces that were not based on deities or religion. They observed mysterious forces or influences between certain kinds of matter, which we now recognize as magnetic, electrostatic, and gravitational forces.² At that time, a distinction between the material and immaterial (and living vs nonliving) was only beginning to emerge, and the intriguing action at a distance character of these forces (which was not resolved for many centuries) inspired numerous philosophical thoughts, metaphysical explanations, and, later, scientific theories. The debate initiated in ancient Greece concerned not only the origins of the interactions but also the composition and structure of matter (atomic or particulate or corpuscular vs continuous or aetheral) and the space (fluid or a vacuum) between interacting bodies, both of which were regarded as being connected and crucial to understanding the nature of these interaction forces.

Influenced by the views of earlier philosophers (including Pythagoras) that bodies had qualities independent of their matter, Empedocles (ca. 490–450 B.C.) believed that all matter in the universe was composed of four indestructible and unchangeable roots or elements: earth, air, fire and water. These were in turn combined with two cosmic principles or moving causes: love and strife. Love (harmony) was a uniting force causing *attraction* and creation, which would cause all matter to contract until the increasing power of strife (hate or

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discord) would take over and cause *repulsion* or disorder. The universe would thus contract and expand in an endless cycle. Empedocles also expressed the idea that the sum of all things in the universe was constant. Because the roots or primary elements were unchangeable, Anaxagoras (ca. 500–428 B.C.) believed in a separate moving force external to matter that included mind or reason and possibly viewed it as a type of fluid substance.¹

These thoughts were further elaborated by Plato, who interpreted Empedocles' love and strife as attraction and repulsion, and especially by Aristotle (384–322 B.C.), who proposed two types of forces: those inherent in matter (nature) and others emanating from substances (or other forces) that produce push and pull. The latter would cause motion in a second body in a direction different from that of its inherent or natural motion. Aristotle did not believe in the existence of atoms and voids (vacuum) or that all forms of interaction were mechanical as was then being proposed by the atomists who believed that atoms could collide and attach to one another (with hooks). Because of the influence of his extensive system, Aristotle's views formed the basis of physical and chemical theory for the next two millennia while other lines of thought remained mainly unexplored, although his notion of forces as push and pull did not easily explain, for example, the flight of projectiles.³ The concept of a force linking two bodies simultaneously (sympathy of the like) instead of emanating from one to move the other was developed later by Poseidonius (ca. 135–51 B.C.) and used as an explanation of certain types of forces (including magical and astrological) not explained by Aristotelian physics. Aristotle and Poseidonius' theories were adopted by the Romans and used to explain things well beyond the Middle Ages.

Three Main Forces Known to the Ancients. Several hundred years B.C., it was known that lodestone (naturally magnetized magnetite) attracted iron but also that it could cause repulsion under certain circumstances. Empedocles and others ascribed the attraction to effluxes from pores in the materials that cause air displacement, and there were plenty of other hypotheses.³ The mystery and superstition around these forces led to the use of magnets as love potions and cures for diseases well beyond the 13th century, when the north and south poles of magnets were discovered (not through reasoning or thinking but through experiments, a totally novel procedure at the time). This discovery led to the explanation that magnets received their power from the point of the celestial sphere toward which they pointed,² but the nature of magnetism was to be surrounded by superstition for centuries and not well understood until the 19th century.

Other materials, such as amber, required rubbing in order to (electrostatically) attract small objects. And it was found that certain combinations of different materials acquired attractive or repulsive properties when rubbed together and that in some cases spectacular phenomena such as the generation of crackling sounds and visible sparks could be readily heard or observed.

Yet a third force or phenomenon known to the ancients, that we now recognize as gravitation, was not easily reconciled with the behavior of the other two. In a legendary moment of insight, Archimedes (287–212 B.C.) discovered that the force of gravity on a body can change, even from attractive to repulsive, when placed in a medium that it displaces. Such displacement effects occur also with other forces discovered later (such as van der Waals and electric polarization forces),

with important consequences that have only recently been fully appreciated.

In an era when conclusions were reached mainly by abstract reasoning without any experiments, the acceptance and longevity of explanations of natural phenomena were to a large extent dependent on their self-consistency and the reputation or authority of the person (philosopher) proposing them. Many of the ancient ideas were thus propagated without being confirmed in a manner we naturally expect today. Although the ideas of the ancient philosophers are now considered unscientific or prescientific, many later conceptual breakthroughs originated from the inconsistencies and paradoxes generated by these theories, for example, Galileo's reasoning based on Aristotelian physics regarding the rates at which bodies of different weights fall^{5,7} (see below).

Ancient Experiences with Complex Fluid Systems.

Certain colloidal systems and preparations have been known since prehistoric times.⁴ Stone Age cave paintings (ca. 15 000–20 000 B.C.) were created with ground charcoal and mineral pigments containing wet clay or lime or were mixed with an organic binder such as animal fat, blood, saliva, or honey. Pottery, which was first made in China around 15 000 B.C., has been found from many different eras and was commonly painted with mineral pigments before being fired. Egyptian graves contain paintings on plaster walls using copper compounds (ca. 2700 B.C.), combined with resin or applied as a suspension stabilized by gum arabic.⁴ Glass making is believed to have been discovered in Mesopotamia around 2500 B.C., and copper- and cobalt-containing colored glass was well known to the ancient Egyptians and Greeks. The Romans were familiar with glass blowing, and it is believed that they were the first to develop ruby glass (a solid sol of gold nanoparticles and glass).

Many colloidal systems of ancient origin were (and are) preparations to change the taste or texture of food. Milk and cheese were known in prehistoric times. The brewing of different types of beer was described in Mesopotamia around 3000 B.C.,⁴ and the thickening and gelling properties of hydrocolloids (agar, gum arabic, and gelatin/collagen) were known in several ancient cultures although their first recorded use is as stabilizers or adhesives.

Inks based on soot or vermilion suspensions stabilized by gum arabic, casein (from milk), or albumin (from egg whites) were used in ancient Egypt and China. The preparation of multicomponent oil- or fat-based ointments, emulsions, and suspensions for skin care, medical purposes, and embalming was known both in Mesopotamia and in Egypt,⁴ with the use of similar stabilizers as for the inks. Milk, egg whites, and bone (collagen) also appear as ingredients in ancient Greek recipes for glue, an improvement over the resins that were used as adhesives from before 4000 B.C. (and are still used today, although in a much-improved form).

Soap was made in Mesopotamia as early as 2800 B.C. by heating fat with ashes, and soaplike substances and plant-based detergents were also prepared by the Egyptians around 1000–1500 B.C. Soap was mainly used for washing textiles or for the treatment of skin diseases. The need to remove contaminants and particulate matter suspended in solution was also recognized, and alum was used in Egypt to purify water.⁴

Processes to make porcelain and paper were invented in China around 100 AD and were not reproduced in the western world until much later. Indeed, the high priests of science in

China at that time were the botanists who also used herbs medicinally, again centuries ahead of Western medicine.

■ FROM THE MYSTICISM OF THE ANCIENTS TO THE EARLY SCIENTIFIC EFFORTS OF THE RENAISSANCE

Prevalence of Ancient Ideas. Only modest progress in the explanation of forces was made during the Middle Ages and the Renaissance. Roger Bacon (ca. 1220–ca. 1292) was a proponent of experiments (as opposed to rhetoric or philosophical speculation),² although it is not clear to what extent he did any, but celestial motion and other force-related problems were still discussed mainly using the same arguments and analogies as among the ancient Greeks. For example, Leonardo da Vinci (1452–1519) believed in the notion of natural versus emanating forces.¹ Although the view that certain qualities of bodies were independent of matter became more common and the first mathematical formulations of a law of motion were put forward around this time, change and movement were still commonly thought to have a divine origin. No action at a distance was thus needed, although William of Occam held the view that it existed. A novel concept at this time was Jean Buridan's (ca. 1300–after 1358) theory of impetus (a step toward our concept of inertia) proposing that a body or object could cause movements of different magnitude in another object. Others suggested that gravity acted between the centers of gravity of bodies rather than between their parts, but they were criticized for assigning occult properties to points in space.¹ All of these natural philosophers struggled with how far their theories were truly objective (scientific) or ultimately relied on some occult properties of matter, atoms, or space.¹

The observations and ideas above were carried well into the 17th century and formed the basis for the first more or less scientific investigations of interaction forces (those acting between two bodies or molecules) at the same time as alchemy, astronomy, and the search for perpetual motion devices shaped the early beginnings of chemistry and physics. For example, the physician and philosopher Antonius Ludovicus (d. 1547) described two types of interaction, sympathy and antipathy, that caused attraction to bind the universe (as well as its parts) together and the concept of like joins like that maintained order.¹ Similar concepts were used around the same time by Nicolaus Copernicus.

Experiments Make Their Debut. With a few exceptions, the concept of experimentation to prove or refute hypotheses was almost unknown in ancient times and became appreciated only toward the end of the Renaissance. In 1600, electric and magnetic phenomena were investigated by William Gilbert (1544–1603).³ Although he still ascribed the origin of the forces (electric, magnetic, and gravitational) to effluvia, he noted that attraction was not induced by heating materials with a flame, although this consumed air. On the basis of his observations, he objected to the then-accepted principle of the attraction of similars outside the areas of magnetism, electricity, and gravitation, for example, to the prescription of medications, and concluded that the opinions of those who ascribed magnetism to “the four elements and the prime qualities, we relinquish to the moths and the worms”.^{2,3}

The first systematic experiments are ascribed to Galileo Galilei (1564–1642) in his classical work on gravity, the motion of bodies, optics, astronomy, and proving the existence of a vacuum.⁵ Galileo avoided speculating on the origin of gravitational force and introduced a new way of thinking that

was not purely metaphysical: for example, his experiment (there is some doubt about whether he actually performed it) of dropping two balls from the Tower of Pisa was done only after he had worked out the answer by applying a new form of reasoning (what we would today call scaling arguments) to Aristotelian physics, arguing that if two balls of different weights were joined together, thereby creating a ball heavier than either, Aristotle's physics leads to the self-contradictory conclusion that the heavier composite mass will fall faster than the heavier single ball while at the same time the different pulls and motions of the two balls would make the composite mass fall more slowly. And testing his hypothesis by direct experiment would also have been novel. In this was, he introduced the modern scientific method.

Galileo's English contemporary, Francis Bacon (1561–1626), may also be credited with the introduction of inductive reasoning and the concept of experimental research. He discarded the ancient notion of matter having a soul and categorized many phenomena showing apparent action at a distance,³ including the forces observed by the ancient Greeks and the mutual attraction of two bubbles. He was more skeptical about some other concepts and phenomena, such as telepathy, the effects of the moon on the tides, and sympathetic medicine.

Another important figure in the scientific revolution occurring during this period was the mathematician and astronomer Johannes Kepler (1571–1630). Kepler's concept of force developed from a soul into a corporeal quantity, an intermediate but quantifiable concept needed to explain the change in distance and speed of a planet along its orbit. Although Kepler believed that gravitational attraction was of magnetic origin, his quantitative mapping of the motions and orbits of planets was of great importance for Newton's development of his laws of motion and the law of gravitation.¹

In many cases, the alleged events related from this time, in particular, some of the alleged experiments, may or may not have taken place, but more importantly, the development of new concepts and ways of thinking can be considered to have formed the basis of our current scientific method.

Quantification of Measurements: Newton and His Contemporaries. There is a famous saying attributed to H. James Harrington: “If you can't measure something, you can't understand it.” The next stage in our historical tour concerns the transition from observation and experimentation to quantification of the results or measured data.

Newton's Gravitational Force Law. A major breakthrough in the understanding of interaction forces came with the discovery by Isaac Newton (1642–1727) of the law of gravitation, which, according to himself, was inspired by contemplating an apple hanging from a branch. Generalizing the concept of gravity acting on an apple to the orbit of the moon around the earth when acted on by the same force is a remarkable thought process, a leap of the imagination by a factor of 10^6 in time, 10^8 in distance, and 10^{24} in mass. And it was not arrived at instantaneously. After proposing this law in 1687, he tried to check it against experimental data, but it was not until 20 years later that new, more accurate astronomical data became available, confirming his predicted inverse-square distance behavior for the gravitational force.⁶ Furthermore, other natural philosophers such as Robert Hooke (1635–1703) were also interested in gravity and were probably aware of the inverse-square law around the time of Newton's discovery but

did not succeed in developing a model describing planetary motion.^{1,3,7}

Newton's contributions to an understanding of matter on the molecular scale consisted of theories on both its structure and interactions. He believed that both matter and light were composed of particles (corpuscles), in contrast to the very influential theory by René Descartes (Cartesius, 1596–1650), who believed that matter was continuous, in eternal motion, and interacted through kinematic vortices. Gravity suggested that particles should attract one another. However, the gas law by Robert Boyle (1627–1691) proposed some 20 years earlier suggested that they *repel*. Newton concluded that at even smaller separations the particles of a gas must *attract* each other because they can condense to form liquids and solids but must ultimately *repel* again because the material does not disappear.

The conclusion that particles attract (the inverse-square law of gravitation) but ultimately repel (as $1/r$), his calculus (developed simultaneously with Gottfried Leibniz (1646–1716) in the 1680s), and many other things were published by Newton in his highly influential book *Principia*.

Confusion, Contradictions, and Controversy. The apparent contradictions between attraction and repulsion were to lead to many conflicting theories about the structure and interactions of matter in the years to come. At this time, matter was believed to consist either of stationary corpuscles (not moving atoms as in the Greek atomists' view) or of vortexes in an aether (an elastic, massless medium). Leibniz was a strong proponent of the latter. The kinetic theory of gases was not to be proposed for another century, there was no thermodynamics, and the concept of potential energy was still unknown. In spite of the tremendous advances made by Newton, the period between his *Principia* and the beginning of the 19th century was marked by confusion, contradictions, and controversy.^{8,9} Most notable of these were the following: (i) An inverse distance law accounting for the behavior of gases was known (even by Newton) to be unphysical (i.e., diverge) when integrated over many molecules and/or large distances. (ii) Newton's law of gravity did not provide an explanation of the cause of forces. Furthermore, it required an instantaneous force to act across a vast vacuum, which by many amounted to invoking some supernatural phenomenon that the new rational thinking was supposed to avoid. Although Newton's work was almost immediately interpreted as a demonstration of the existence of action at a distance, Newton himself was ambivalent about the concept and mentioned it only as a possibility in his later writings, perhaps influenced by his strong interest and beliefs in alchemy.⁶ (iii) When considering the forces between particles over a wide range of distances, a peculiar picture emerged where these forces start off being attractive (the gravitational force) and then become repulsive and then attractive again (to account for solids and liquids) and then finally repulsive (to account for the fact that matter does not disappear into itself). This line of thinking led Roger Boscovich (1711–1787)¹⁰ to propose a generic oscillatory force between all particles (Figure 2). Heat was believed to be a substance ("caloric") that increased the repulsive part of this interaction. Boscovich, who had studied Newton's work, believed that atoms were immaterial centers of force without extension, not Newton's massy corpuscles, and thus impenetrable as a result of force instead of matter. (iv) The phenomenon of capillary rise and capillary forces had puzzled natural philosophers for centuries. The first to describe capillary rise is believed to be Leonardo da Vinci.⁴ Systematic experiments by Francis Hauksbee (1666–

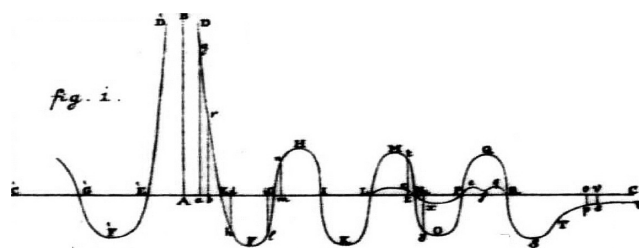


Figure 2. Illustration by Boscovich¹⁰ in 1763 of interparticle force as a function of radial distance, showing (from the right) gravitational attraction followed by an unknown number of arcs representing cohesion (for example, vaporization or sublimation) and a final repulsion at small particle distances attributed to impenetrability enhanced by the presence of caloric. In his own words, "the alternation of the arcs, now repulsive, now attractive, represent[s] fermentations and evaporations of various kinds, as well as sudden conflagrations and explosions".^{8,10}

1713), who was Newton's demonstrator at the Royal Society, showed that the capillary rise of liquids did not depend on the capillary wall thickness, however thin, which implied that interparticle forces must be very *short-ranged*. However, the equally obvious fact that the liquid rises to a substantial height, even in tubes having macroscopic inner radii, suggested that these forces must be *long-ranged* because they are able to reach the liquid molecules in the center of the tube. The investigations by Hauksbee and others^{8,9} would eventually lead to our familiar concepts of surface tension, wetting, and Laplace pressure, which in turn led to the first understanding of the range and strength of intermolecular and surface forces.

■ FORCE LAWS, INTERACTION POTENTIALS, AND THE STRUCTURE OF MATTER IN THE 19TH CENTURY

Emerging Concept of Energy. Starting with the ancients (e.g., Archimedes) and through to the 17th and 18th centuries, the notion of force was used to describe and analyze very different phenomena, including the ones we now call force, momentum, power, and kinetic energy. This led to controversies over the effects of forces over time and distance. (Why or how did some forces change with time and distance?) A clarification and a new way to analyze interactions and properties, especially of many-body systems, were to come from the new concept of energy that emerged around this time.

Certain manifestations of invariance in nature that we now associate with energy conservation were already known by the ancients through the use of simple machines (levers and pulleys), where it was known empirically that relationships existed between applied force and length or time.¹¹ The (im)possibility of perpetual motion had also been debated through the ages. Galileo noticed that force \times distance was constant for a pulley system and that the velocity of a ball falling from rest depended only on the height fallen. He also discussed momentum, which was a quantitative development of the impetus suggested by Buridan. Leibniz, Newton's contemporary and strong critic, set forth that the living force (vis viva) associated with falling bodies (mv^2) was constant whereas the quantity of motion (mv) proposed by Descartes was not. This controversy was solved by Jean D'Alembert (1717–1783), who showed that momentum is associated with the effect of a force over time and (in modern terms) that the energy is associated with the effect of a force over space.¹¹ A

quantitative and systematic mathematical approach to this problem was introduced by Joseph Lagrange (1736–1813). Other developments in pure and applied mathematics by Euler, Laplace, and others during the 18th century also proved to be crucially important for analyzing and interpreting experimental data.

Search for Unifying Forces. Much of the progress in the understanding of intermolecular forces during the 19th century came from work on liquid surfaces, especially on the long-standing problem of capillarity.^{8,9} Alexis Clairault (1713–1765) was the first to attempt a semiquantitative explanation of intermolecular forces based on Newtonian gravity. He suggested that capillarity could be explained if the attraction between the liquid and glass molecules was different from the attraction of the liquid molecules for themselves. It was confirmed that the height of rise of a liquid column did not depend on the capillary wall thickness, which led to the conclusion that these forces must be very short-ranged or, in the language of the time, extended over insensible distances. Work by John Leslie (1766–1832), Thomas Young (1773–1823), and others in the very early 1800s led to the theory of capillarity based on surface tension, which was expanded on and described in mathematical form by Pierre-Simon Laplace (1749–1827) and Carl Friedrich Gauss (1777–1855).

During the 19th century, it was believed that one simple universal force law, similar to the law of gravitation, would eventually be found to account for all intermolecular attractions. A number of interaction potentials were proposed that contained a $1/r^n$ distance dependence and the masses of the molecules, attesting to the belief at the time that these forces are related to gravitational forces.¹² The power-law index n arose partly from attempts to fit experimental data to equations containing n (>3) as an adjustable parameter and from an appreciation of the fact, first noted by Newton, that if intermolecular forces are not to extend over large distances, the value of n must be greater than 3.⁸

Toward the latter part of the century, it became apparent that no single force law could provide a quantitative explanation of the multitude of phenomena. But the modern concept of surface tension forces (and surface energy, although initially without distinction between free and total energy) was becoming established, as was the recognition that these were the same short-range forces as those that hold molecules together in solids and liquids. A number of long-range (macroscopic) phenomena could be explained on the basis of surface tension, such as capillary rise, the shapes of liquid drops on surfaces, the contact angle between coalescing soap bubbles, and the breakup of a jet of water into spherical droplets. Long-range effects are thus not caused by long-range forces. In fact, the strength of the interaction is more important than the range, and short-range forces tend to be stronger than long-range forces. The next major developments in the understanding of intermolecular interactions were to come from a quite different direction: from work on the properties of gases rather than liquids or surfaces.

First Successful Phenomenological Theories. During the 18th century, little progress was made in establishing the properties of gases beyond the earlier discoveries by Boyle.¹³ The first dynamic or kinetic theory of gases was developed by Daniel Bernoulli (1700–1782) in 1738, who suggested that gases consisted of large numbers of particles in rapid motion (as opposed to the static view by Newton). John Dalton's (1766–1844) law of partial pressures was proposed in 1793,

and the gas laws of Jacques Charles and Joseph Gay-Lussac (1778–1850) were published by the latter in 1802. Although the existence of molecules was still being intensely debated, calculations of the velocities of gas molecules and derivations of the gas laws from a kinetic theory were undertaken in the 1840s and 1850s by James Joule (1818–1889), Rudolf Clausius (1822–1888), and James Clerk Maxwell (1831–1879).

The relationships among temperature, kinetic energy, and internal energy were thus established theoretically, but more accurate experiments revealed that all gases deviate to a larger or smaller degree from the assumed behavior, especially at high pressure.¹³ To explain this deviation, Johannes Diderik van der Waals (1837–1923) considered the effects of attractive forces between molecules. In 1873, he arrived at his famous equation of state for gases and liquids, which quantitatively accounted for both the finite size of molecules and the attractive intermolecular forces between them. These universal forces between all molecules are now known as van der Waals forces.⁸

In 1785, Charles-Augustin de Coulomb (1736–1806) proposed the first force law between electrically charged bodies that is still used today. His equation applies to all charged bodies, including atoms (ions), molecules, and particles: $F(r) = +CQ_1Q_2/\epsilon r^2$, where Q_1 and Q_2 are the charges of the two bodies and ϵ is the dielectric constant of the suspending medium. The Coulomb force, unlike the gravitational and van der Waals forces, is not universal and is repulsive between like bodies.

By the early 20th century, the search for one unifying force law, applicable to all molecules, was largely abandoned because it was realized that intermolecular forces do not have a simple nature, and a number of semiempirical expressions were developed that could account for specific phenomena.¹² In 1903, Gustav Mie (1869–1957) proposed an interaction pair potential (energy–distance function) of the form

$$w(r) = -\frac{A}{r^n} + \frac{B}{r^m} \quad (1)$$

which for the first time included a repulsive (positive energy) term in addition to the attractive van der Waals term. Since then, many similar laws have been proposed that successfully account for a wide range of physical and chemical phenomena. The Mie potential is still used today, as is the van der Waals equation of state. However, it was quickly recognized that many different potentials containing adjustable parameters (A , B , m , and n in the Mie potential) could account for the same experimental data. Thus, whereas such empirical relationships were useful, the origin of van der Waals forces remained a mystery for 57 more years after the van der Waals equation, until the advent of quantum theory when in 1930 Fritz London showed that $n = 6$ and that A is related to the optical polarizability of molecules. Because molecular polarizabilities were (and still are) measured by how gases disperse light, attractive van der Waals forces are now also commonly referred to as dispersion forces. Today, the most commonly used universal interaction potential is the one proposed by John Lennard-Jones (1894–1954) in 1924: $w(r) = -A/r^6 + B/r^{12}$, which is still semiempirical (the second term has no theoretical basis) but is simple and works well in many cases, including computer simulations of many-body interactions (as long as there are no strong electrostatic forces). But we are jumping too far ahead.

Continuum versus Particulate Structure of Light and Matter. The controversy about whether matter was a



Figure 3. View of Clapham pond (a) before and (b) after a teaspoon of olive oil was allowed to spread on its surface in a reconstruction of Franklin's experiment. Photographs by C. H. Giles in ref 17. Reproduced by permission of The Royal Society of Chemistry.

continuum or composed of atoms, molecules (but not yet in the modern sense of molecules), or particles/corpuscles continued well into the 19th century. Interference experiments by Young showed that light behaves as waves, and theoretical progress in explaining phenomena in terms of continuum field theories (electrical or gravitational) also led to a decline in the belief in particles. Maxwell is said to have noted in an introductory lecture on light that the main reason for why, by the mid-19th century, nobody believed in particles (at least of light) any longer was not because anyone had shown that they did not exist but because "all those who believed in the corpuscle theory have died".¹⁴

The first successful attempt to estimate the size of molecules was made in 1815 by Young, who realized that the surface tension γ (in units of J m^{-2} or N m^{-1}) and the cohesive energy or latent heat of a material U (in units of J m^{-3} or N m^{-2}) were related via the range of intermolecular forces and/or the molecular size. The value he obtained for water was 0.09 nm, which is remarkably close to the radius of a water molecule. Unfortunately, Young published his calculation in an encyclopedia article and under a pseudonym, and it was ignored.

Another observation that would enable an estimate of molecular size (although not recognized as such at the time) was a report by Benjamin Franklin (1706–1790) to the Royal Society of London in 1774.¹⁵ A few years earlier, inspired by an observation at sea in 1757, he had poured about one teaspoon of oil on Clapham Pond near London and noted that as the oil spread it stilled the waves over "perhaps half an acre" of the pond's surface.¹⁵ This phenomenon was already known to ancient seafarers, divers, and fishermen,^{4,16} and a modern-day illustration of Franklin's experiment is shown in Figure 3.

Remarkably, neither Franklin nor any member of the Royal Society nor any of his contemporaries (for example, Boscovich, who he had met) thought of calculating the film thickness to estimate the size of the molecules from the known area ($\sim 2000 \text{ m}^2$) and volume ($\sim 2 \text{ cm}^3$),¹⁶ which would have given $\sim 1 \text{ nm}$. This connection was not made until more than 100 years later, in 1890, by Lord Rayleigh,¹⁸ who repeated these measurements by accurately measuring the spreading of olive oil on water in a "sponge bath" and obtained a film thickness of 1.6 nm.

In the second half of the 19th century, the growing appreciation of the kinetic theory of gases and the van der Waals equation of state, which both required attracting molecules and corroborated values for the sizes of molecules, led to a return to the belief in molecules. The first calculations of molecular sizes within the framework of the kinetic theory were carried out (much along the lines of Young's work) by van der Waals and others and also by Albert Einstein (1879–1955) in his first paper (on the interaction potential between molecules, submitted in 1900).¹⁹ During the last decades of the 19th century, the new field of statistical mechanics was developed mainly by Clausius, Maxwell, van der Waals, Ludwig Boltzmann (1844–1906), and J. Willard Gibbs (1839–1903) to unify continuum theories such as thermodynamics (discussed below) and mean-field theories with molecular theories. However, the origin of the intermolecular forces themselves remained unresolved until the radically new concepts of quantum theory were put forward the 1920s.

■ THERMODYNAMICS

Nature of Heat. The nature of heat was a mystery well into the 19th century. In the 17th century, it was believed that heat was a substance consisting of particles and that an object that contained such particles became hot through their motion or that it was a volatile substance, phlogiston. In the 1760s, Joseph Black (1728–1799) proposed that phlogiston could be absorbed by bodies and flow from one place to another, a theory that would dominate during the remainder of the 18th century. Black introduced the concepts of latent heat and heat capacity and did early calorimetric experiments, which were further developed by Antoine Lavoisier (1743–1794) and Laplace in the 1780s to measure the heat evolved in chemical reactions. Lavoisier, who had shown that the phlogiston theory was incorrect, strongly supported the notion that heat was a fluid and named it caloric.¹³ Heating a material was believed to add caloric to it, hence the expansion, and frictional heating was due to caloric being squeezed out of the material.

Benjamin Thompson (Count Rumford, 1753–1814) is credited with several inventions related to heat, including improved kitchen and fireplace designs (the Rumford stove) and discussed the propagation of heat in liquids after burning his mouth on a hot apple pie. While overseeing the

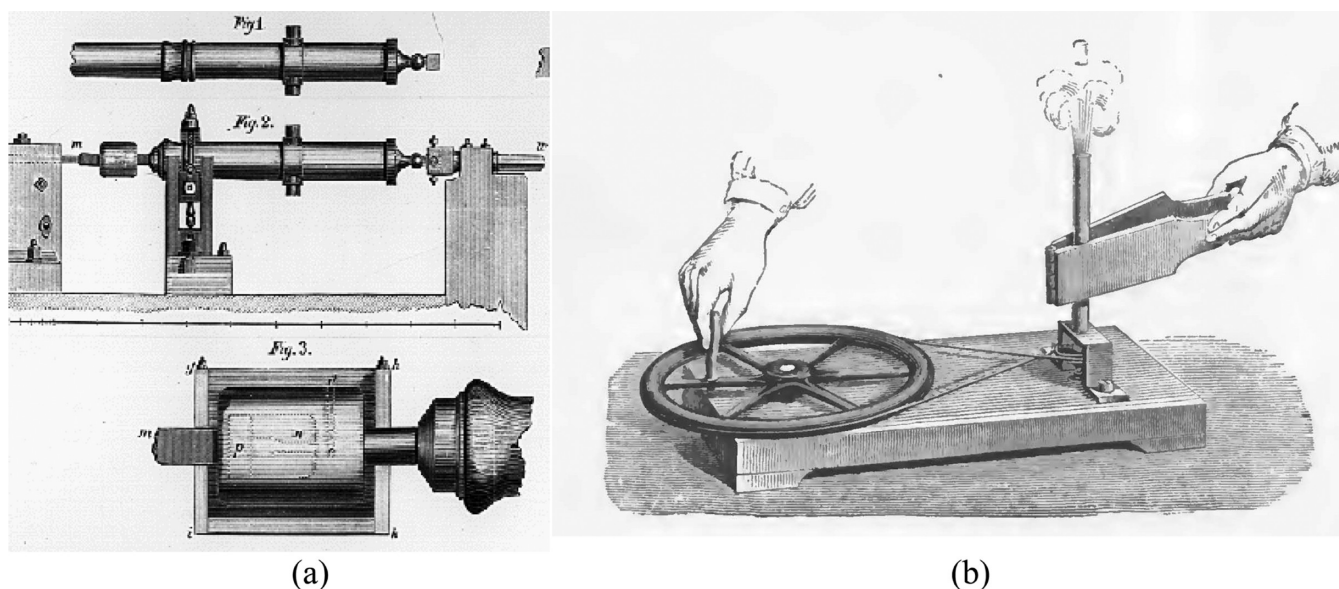


Figure 4. (a) Thompson's cannon-boring experiment. After a few hours of frictional heating of the metal, water in a box surrounding the cylinder and borer (lower figure) started to boil. The heat generated appeared to be "inexhaustible", thereby disproving the caloric theory.²¹ (b) "Tyndall frictional cylinder" for demonstrating the frictional heating of a pipe. When rotated between leather-covered wooded paddles, the water (or alcohol) in the pipe was heated to boiling, at which point the cork popped out.²⁰ Again, the heating continued as long as the wheel was turned.

manufacture of cannon, he made observations on frictional heating that led him to reject the caloric theory in 1798.²¹ Some of Thompson's experiments and a later apparatus for demonstrating the same phenomenon are shown in Figure 4.

In Figure 4a, the metal protruding from the end of an unfinished brass cannon was turned into a solid cylinder (still attached to the cannon by a narrower part), which was either insulated ("wrapped in flannel") or immersed in a box filled with water (bottom part of Figure 4a) and rotated against a stationary, blunt boring tool. The temperature of the cylinder (and the water, when applicable) was monitored. After checking that the heat capacity of the "scaly metallic powder" produced during boring remained the same as for a solid block of brass and that the total amount of brass (the filings and the hollow cylinder) remained the same as that of the original solid cylinder, Thompson stated, "... the heat generated in these experiments, or *excited*, as I would rather choose to express it, was not furnished *at the expense of the latent heat or combined caloric* of the metal ...", and after further elaboration he concluded that "any thing which any *insulated* body, or systems of bodies, can continue to furnish *without limitation*, cannot possibly be a *material substance* ..." He then proposed that some kind of motion was responsible for the observed heating,²¹ which was to become known as the dynamical theory of heat. The nature of the motion remained unknown and was ascribed by others to the movement of atoms, particles, or caloric, a concept that did not die easily.

First Law. The experiments by Thompson, taken together with the observations by Lavoisier and Laplace on the heat evolved in chemical reactions, were the first steps toward a molecular-level understanding of the nature of heat, the formulation of what we now know as the first law of thermodynamics, and the first measurements of the mechanical equivalent of heat.²² Lavoisier and Laplace recognized that the heat evolved in a chemical reaction was equal to that absorbed in the reverse reaction and discovered that the heat released in combustion and respiration were the same. The next

conceptual breakthroughs came almost half a century later. In 1840, Germain Henri Hess (1802–1850) proposed what we now call Hess' law, stating that the heat evolved or taken up in a reaction is the same irrespective of the number of steps needed.

In 1842, the physician J. Robert von Mayer (1814–1878) published an article on the numerical equivalence between mechanical work and heat,^{23,24} which was inspired by his recognition that the different color of venous blood of people in tropical climates meant that less food is needed to be "burned" to heat their bodies. He was the first to suggest that the body obtains its energy from oxidation processes and, perhaps unwittingly, was the first to write down what amounts to the first law of thermodynamics. At first, his work did not attract any attention, and later it was misunderstood (partly because of his ambiguous use of the word *force* instead of what we now call *energy*). James Joule published his work on the equivalence between mechanical and electrical energy and heat in 1843. The importance of this observation (which also made caloric unnecessary) became recognized as Hermann von Helmholtz (1821–1894) formulated the first law of thermodynamics (on the conservation of energy, which also he called *force*) in 1847, which was more explicitly stated by Clausius in 1850. After learning about Joule's work a few years after its publication, Mayer tried to claim priority, which was eventually recognized by John Tyndall (1820–1893) in a lecture at the Royal Institution in 1862.²⁴

Second Law. In the early 19th century, substantial effort was put into obtaining a better understanding of the efficiency of steam engines. In 1824, Sadi Carnot (1796–1832) proposed an idealized heat engine and showed that the two temperatures of the reservoirs between which it operates limit its efficiency. However, he noted that in reality some heat (caloric) would be irreversibly lost and thus not converted into work. These ideas were further refined by Clapeyron, Clausius, and William Thomson (Lord Kelvin, 1824–1907) and provided the basis for the formulation of the second law of thermodynamics in 1850 on the basis of the concepts that heat cannot flow from a

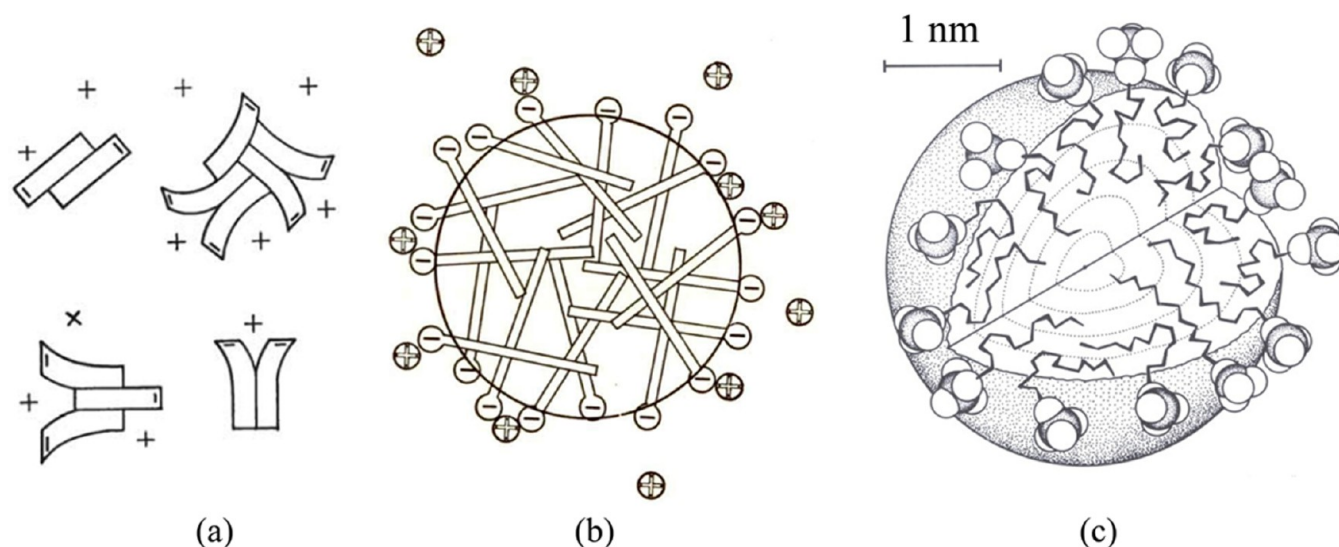


Figure 5. Early models of how amphiphilic molecules, or amphiphiles, containing a nonpolar region (usually one to four hydrocarbon chains) and a hydrophilic (water-loving) region or headgroup that is either charged or can hydrogen bond with water associate to form micelles. (a) McBain's micelle model and (b) Hartley's spherical ionic micelle, from ref 29. (c) Modern model based on molecular dynamics simulations, showing a micelle containing 60 sodium dodecylsulfate molecules with fluid hydrocarbon chains, drawn to scale. In the core, the hydrocarbon chains pack at liquid hydrocarbon density and are almost as disordered as in the bulk liquid state. Reprinted from ref 8, copyright 2011, with permission from Elsevier.

colder object to a warmer one and that heat cannot be converted into work without some "loss" of energy (or energy that is not work). Taken together, these two concepts form the notion of entropy. Thermodynamics (a term coined by Kelvin in 1854) was (and is) a highly successful description of natural and engineering processes that did not require knowledge of the structure of matter, which was important at a time when this was being hotly debated and even led Kelvin to abandon his belief in the existence of atoms and molecules temporarily.

Once the relationship between heat and work had become clarified, Hess' law was seen as an example of the first law. However, with increasing understanding of information arising from experiments, it became clear that the work that could be done by chemical forces was not the heat but the largest amount of work available when the reaction was carried out reversibly. These concepts were further refined in the 1870s, when Gibbs (1839–1903) introduced the concept of the chemical potential. He also proposed a geometric representation of thermodynamic quantities (thermodynamic surfaces), extended this analysis to multiphase systems,²⁵ and formulated what is now known as the phase rule. Gibbs was instrumental in developing the applications of thermodynamics and, later, statistical mechanics to all branches of chemistry and physics, including the understanding it provides of surfaces, interfacial tension, adsorption, self-assembling structures (discussed below), and physical phenomena such as radiation.

Gibbs' thermodynamic equations are probably the most used equations in science today, addressing phenomena that were totally unknown in Gibbs' days. It is ironic that toward the end of his life, with new elementary particles and rays being discovered every year, he felt his ideas were already passé.

■ INTERMOLECULAR AND INTERPARTICLE (COLLOIDAL AND BIOCOLLOIDAL) FORCES IN COMPLEX LIQUID, SELF-ASSEMBLING, AND NONEQUILIBRIUM SYSTEMS

Micelles: First Scientific Concept of Self-Assembling Systems. Soap has been used since antiquity. However, the

behavior of aqueous solutions of soaps (fatty acid salts) was first investigated systematically by James W. McBain (1882–1953) and co-workers in the early 1900s. At low concentrations, these salts behaved as ordinary electrolytes, whereas above some particular concentration, properties such as the conductivity and osmotic pressure changed, eventually leading to the conclusion that small colloidal particles (the term colloid was first used by Thomas Graham in 1861²⁶ for organic colloids) or micelles²⁷ formed in the solution and that these colloidal electrolytes were thermodynamically stable. This concept contrasted with the prevalent view at the time, where colloids were believed not to have easily reproducible properties or to conduct electricity. And thermodynamically, micelles at equilibrium appeared to contradict the Gibbs phase rule. According to McBain, "So novel was this finding that when in 1925 some of the evidence for it was presented to the Colloid Committee for the [British Association for the] Advancement of Science in London, it was dismissed by the Chairman, a leading international authority, with the words, 'Nonsense, McBain'."²⁸

Both the proposed structure of these micelles and their possible existence as a separate phase were controversial. Several different models were proposed for these self-assembled structures (although this term was not to be used until the 1950s by virologists to describe the self-assembly of the molecules that spontaneously combine to form a virus particle). Figure 5a,b shows some of the structures originally proposed for micelles, which also included lamellae,²⁹ and many others. It is now recognized that the commonly assumed spherical shape (Figure 5c) is dynamic and easily distorted because of the sensitive balance of the intermolecular forces that include van der Waals, electrostatic, hydrophobic, and steric hydration forces.⁸ Beginning in the 1980s, NMR studies and computer simulations showed that all segments of the chains spend an appreciable proportion of time near the micelle surface. Thus, even though the core is almost completely devoid of water each segment samples the hydrophilic (aqueous) environment.

Quantum Theory and Interaction Potentials. By the beginning of the 20th century, inquiry into the nature of intermolecular, interparticle, and intersurface forces had reached the end of its first scientific phase, coinciding (not unexpectedly) with the end of the classical era of physics and chemistry. A number of significant conceptual changes had occurred during the preceding centuries, where a purely mechanistic view of intermolecular forces had been replaced with thermodynamics and the probabilistic concepts of free energy and entropy. It had become appreciated that heat is a form of energy that does not arise from some substance or intermolecular potential and that gravitation is too weak to cause significant intermolecular forces. Furthermore, it became apparent that a knowledge of the force law between two molecules does not provide an understanding of how an ensemble of such molecules will behave. For example, the fact that certain molecules attract each other does not mean that they will condense into a liquid or a solid at any given temperature or pressure, and there is no easy process available for deriving the properties of the resulting condensed phases from their intermolecular pair potentials and vice versa.

The description of the electronic structure of atoms and molecules in the first decade of the 20th century and the development of quantum mechanics in the 1920s finally provided a rigorous and quantitative understanding of the origin of intermolecular forces and enabled derivations of their interaction potentials.¹² The emerging concept of electric dipoles interacting through Coulomb forces appeared to be a plausible explanation for the intermolecular forces postulated by van der Waals. It was initially thought that all molecules were permanent dipoles, but the indisputable attraction between the atoms of the noble gases (e.g., argon) that obviously had no permanent dipole led to a dead end for this approach. An understanding of the physical (and chemical) forces between nonpolar molecules required a quantum mechanical approach, which developed during the late 1920s into the description of dispersion forces by Fritz London (1900–1954) in 1930, as already mentioned above.

Even with the advent of quantum theory, it became clear that all intermolecular forces are essentially electrostatic in origin. This follows from what is now called the Hellman–Feynman theorem, according to which the spatial distribution of the electron clouds (determined by solving the Schrödinger equation) can be treated as a classical charge distribution from which the intermolecular forces may be calculated. This theorem greatly simplified the concepts involved for understanding the nature of intermolecular forces: two charges interact through the inverse-square Coulomb force; for moving charges, one has electromagnetic forces, and for the complex fluctuating charge distributions occurring in and around atoms, one obtains the various interatomic and intermolecular bonding forces familiar to physics, chemistry, and biology. Argon does have a dipole moment, albeit a fluctuating one about zero.

However, exact solutions of the Schrödinger equation are not easily obtained, even for two interacting hydrogen molecules. It has therefore been found useful to classify intermolecular forces into different categories, and the separation of interactions into ionic bonds, metallic bonds, van der Waals forces, hydrophobic interactions, hydrogen bonds, and solvation forces is a result of this classification, although they have the same fundamental origin. This grouping is often divided further into strong and weak interactions and short-range and long-range forces. These distinctions are common and can be very useful, but they can

also be misleading, for example, causing the same interaction to be counted twice, or in cases where two normally distinct interactions are strongly coupled.

Colloidal and Biocolloidal Structures and Interactions in Aqueous Solutions. As a result of work initiated by Galileo and others in the 17th century, optical microscopy developed to a point where it would eventually enable direct observation of the structure of certain self-assembling systems. Robert Hooke was the first to publish detailed drawings of his observations of insects, plant material, and many other things in his book *Micrographia* in 1665 and coined the term “cell” to describe the features of sections of cork.⁷ The period just before, during, and after World War II saw much progress in both imaging small (microscopic) colloidal particles or self-assembling “coacervate” particles and measuring and calculating many of their properties, including the forces between them. Coacervates are what we would now call small unilamellar surfactant or lipid bilayer vesicles (SUVs), multilamellar vesicles (MLVs or liposomes), microemulsion droplets (oil droplets in water, O/W, or water-in-oil droplets, W/O), protein aggregates (e.g., virus particles), or a multicomponent assembly of hydrophobic (oil), hydrophilic (water), and amphiphilic molecules (Figure 6). Coacervates were first investigated by the chemist Hendrik Gerard Bungenberg de Jong (1893–1977) in 1932.³⁰

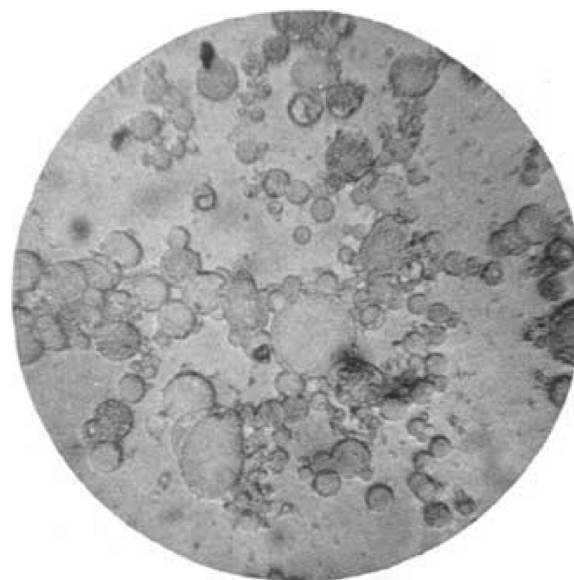


Figure 6. One of the first microscope images of a coacervate, here a mixture of gelatin and soy bean lecithin in water, as reported by Bungenberg de Jong in 1932.³⁰

Coacervates could be thermodynamically stable or long-lived metastable structures if the forces between them were repulsive, thus preventing them from aggregating or coalescing. Thus, an understanding of these long-range colloidal forces was required to understand the stability of colloidal systems. The two major forces are the attractive van der Waals forces and repulsive electrostatic double-layer forces, which form the basis of the so-called Derjaguin–Landau–Verwey–Overbeek (DLVO) theory^{31,32} that was developed independently by Russian and Dutch scientists during World War II, although these two forces were already fairly well understood before the war by Hamaker, Langmuir, and others.

Although understanding the interactions of microscopic particles (nanoscopic particles such as micelles, vesicles, and submicroscopic coacervates had to await the development of high-resolution electron microscopes in the early 1940s) in terms of the interplay of the long-range attractive van der Waals and the repulsive electric double-layer force was beginning to explain many colloidal properties, the short-range forces holding the molecules together to form these structures remained a mystery: calculations showed that the van der Waals forces were simply too weak to bring together the nonpolar regions of amphiphilic molecules or proteins whereas their hydrophilic headgroups or regions repelled in water. Some strong additional attraction was needed at short range, which in the 1950s, based on research on protein folding and virus self-assembly, was postulated by Kauzmann and others to be due to the existence of hydrophobic bonds between all nonpolar groups and surfaces in water. The precise nature (magnitude and range or force law) of hydrophobic (from the Greek, water-fearing) interactions is still not fully understood, and these forces are discussed further in the section on Structural Forces.

Interactions in water turned out to be even more subtle: in certain cases, there appeared to be an extra short-range repulsion, even between uncharged groups or surfaces. Such hydrophilic (from the Greek water-loving) groups and surfaces invariably contain hydrogen bonding groups, but as in the case of hydrophobic forces, these repulsive hydration forces, as they have come to be known, have still not been fully characterized or understood and are also discussed further in the section on Structural Forces.

Water has turned out to be an extremely complex molecule, exhibiting many peculiar physical properties such as high surface tension, the ability to dissolve many substances, expansion on freezing, and a high dielectric constant (that increases when water freezes into ice, which is totally unexpected because the free rotation of molecular dipoles is supposed to cease when a liquid solidifies). Unlike most other liquids, water, the most important liquid on earth, has been found to be very difficult to model, even with the most modern and sophisticated computers. And its history is full of interesting episodes, which space does not allow us to go into but which involve anomalous or polywater, memory water, and cold fusion. We briefly discuss one of these episodes.

Polywater Episode. Experiments by Russian scientists (notably Nikolai Fedyakin and Boris Derjaguin) on water sealed in glass or quartz capillaries, first reported in 1962, appeared to show the condensation of a different form of water with a much higher density and viscosity at the top of the capillary, first near the surfaces (later termed viscinal water) and then growing into the bulk phase.³³ This suggested a different water structure with a lower vapor pressure than ordinary water as well as a memory effect within the liquid. By the end of the 1960s, this substance had gained attention worldwide and was being investigated both spectroscopically and through computer modeling with the beneficial side effect of stimulating technique developments in both research fields. Various linked ring- or polymer chainlike water structures were proposed. Concerns were raised that because this “polywater” was alleged to be more stable than ordinary water and possibly gel-like, all water on earth would eventually turn into it, resulting, for example, in the freezing of all of the oceans (very much as described in Kurt Vonnegut’s science fiction novel *Cat’s Cradle* (1963) that actually preceded or maybe exactly coincided with the polywater discovery). Eventually, in the early 1970s, it was

shown that the physical properties of this anomalous water arose from various types of contamination such as silicic acid hairs slowly growing out of silica surfaces forming a silica gel layer.³³

Structural Forces. In 1936, the famous colloid scientist G. S. Hartley commented prophetically, “There is a widespread tendency to use ‘hydration’ in colloid chemistry as a sort of universal explanation of puzzling phenomena. Its inaccessibility to direct experimental determination fortifies this tendency.” The notion that there must be a new, as-yet undiscovered, repulsive force between some macromolecules, particles, and surfaces, especially in aqueous solutions, arose from the observations that some uncharged particles did not aggregate in water, which, in the absence of any repulsive electrostatic force, was expected because of the dominating effect of the attractive van der Waals force. It is curious that no analogous conclusions were made until much later that there must be some unknown attractive force between particles or molecules that had a negligible van der Waals attraction yet aggregated or phase separated. This new attractive force was (much later, in 1959) termed the “hydrophobic interaction” by Walter Kauzmann (1916–2009).³⁴

The new repulsive force was termed the hydration force, and work on various hydrophilic surfaces, including inorganic surfaces such as silica and swelling clays by Boris Derjaguin (1902–1994) and co-workers in the USSR and on surfactant and lipid bilayers (lyotropic liquid crystals) and biological membranes by many groups worldwide, appeared to show exponentially repulsive hydration forces with decay lengths ranging from ~ 1 nm (for highly hydrophilic inorganic surfaces) to ~ 0.25 nm (for bilayers), where the latter value suggested a correlation with the size of the water molecule. This correlation further suggested a connection with water structure, and these forces were therefore also referred to as structural forces to indicate their possible generality to other, nonaqueous, liquids. They are also referred to as solvation forces to indicate their existence in (liquid) solvents in general.

By the late 1970s, computer simulations of liquid structure—both in the bulk, at a single surface, and between two surfaces—had recovered from the polywater fiasco (which, in the early heady days of computer simulations confirmed the existence of polywater³³), and attention was turned to the theoretical investigation of hydration forces and, more generally, structural forces.^{35–37} To almost everyone’s surprise, these simulations suggested that when liquids are forced to adopt a different structure at or between surfaces the resulting force profile is oscillatory³⁷ (Figure 7a), and not the expected monotonic repulsion. These predictions were soon confirmed by another Australian group,³⁸ who used a surface forces apparatus (SFA) to measure the first oscillatory force profiles directly between two molecularly smooth surfaces across a nonpolar silicone liquid (OMCTS) whose large, ~ 1 nm, quasi-spherical molecules allowed for accurate measurement of the force profiles with submolecular resolution (Figure 7b). These experimental results were followed by similar findings for other simple molecules, including linear alkanes and eventually water as well as simulations that agreed quite well with measured force–distance profiles (ref 7, chapter 15).

Oscillatory structural forces are now recognized as being quite general and have been measured in polymer melts and micellar solutions, where the final drop in the interaction potential into the adhesive well is now recognized as being the same as the attractive depletion force originally investigated by

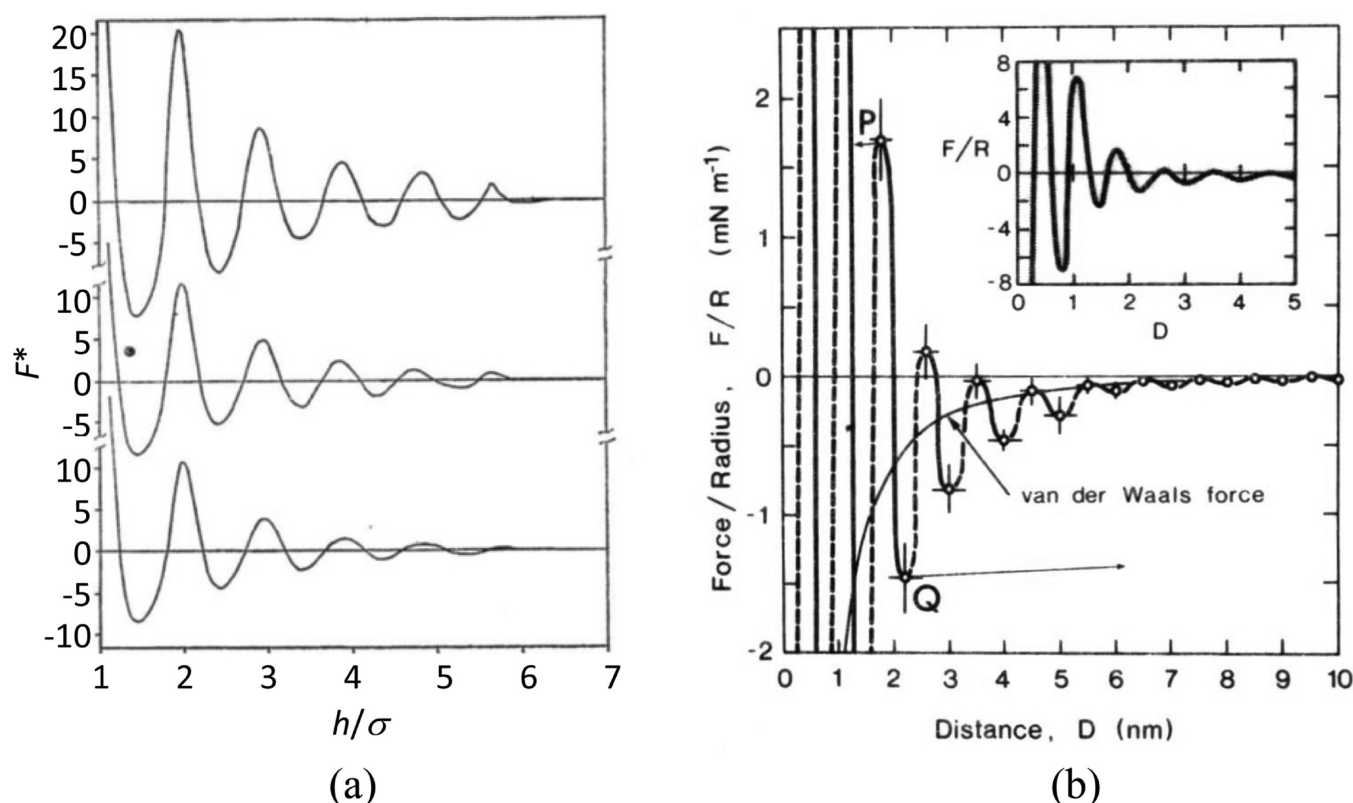


Figure 7. (a) Results from an early Monte Carlo simulation of Lennard-Jones fluids showing normalized solvation forces $F^* = \sigma^3 F/kT$ at three different fluid densities as a function of the normalized distance between two solid plates, h/σ , where σ is the diameter of the atoms. From ref 37. Reproduced by permission of The Royal Society of Chemistry. (b) First experimentally measured oscillatory (solvation) forces in octamethylcyclotetrasiloxane between mica surfaces. From ref 38, copyright 1980, with permission from Elsevier.

Asakura and Oosawa³⁹ in 1954 for colloidal interactions in concentrated polymer solutions.

Branched or highly asymmetric molecules and nanorough surfaces do not always exhibit oscillatory forces, either because the liquid molecules cannot order into discrete layers or because the oscillations become smeared out. Surfaces with highly mobile groups, such as the headgroups of surfactants and lipids in micelles and bilayers, also behave as dynamically rough surfaces where again any intrinsic oscillatory force is smeared out (thermally or osmotically) into a monotonic repulsion that is roughly exponential with decay lengths that, as previously mentioned, are often fortuitously close to the size of a water molecule.

Today, the question of the existence or otherwise of intrinsically monotonic hydration forces, both repulsive and attractive, remains open: there is evidence that even molecularly smooth hydrophilic surfaces can give rise to a monotonic repulsion that is not (quantitatively) accounted for by any current theories. The same is true for the apparently monotonically attractive hydrophobic forces measured between smooth hydrophobic surfaces and molecules in water. There are currently no analytic equations or theories, computer simulations, or definitive experiments that can be said to describe the hydrophobic interaction potential quantitatively (if one exists) and many other aspects of hydrophobic (and hydrophilic) interactions. These two interactions (or maybe the positive and negative manifestations of the same basic interaction) are probably the two most important interactions that have yet to be fully characterized experimentally and explained theoretically.

The interactions of particles with surface-bound polymers or polyelectrolytes that extend into the solution like seaweed can be attractive or repulsive, and the force can change sign, for example, from attraction to repulsion at some separation as the particles approach each other. The same is true for particles immersed in nonadsorbing polymer solutions, where the forces can also be oscillatory, as already mentioned above. Pierre-Gilles de Gennes (1932–2007) did much of the complex theoretical work associated with the highly complex interactions between particles and surfaces mediated by polymers.

Time Effects in Complex Systems. Many complex fluid systems, including some known since ancient times, have very long equilibrium times that may render them stable for practical purposes also when they are not at thermodynamic equilibrium. Some involve slow molecular relaxations in the bulk, and others involve the thin films or gaps between two interacting particles or macromolecules that affect their interaction, including slow adsorption/exchange rates.

During investigations of the optical properties of gold films in 1856, Michael Faraday (1791–1867) noticed that the rinse water from the film preparation had a red tint. Subsequent investigations of these “ruby fluids” and the discovery that they scattered light (the Faraday–Tyndall effect) led him to the conclusion that they contained very small particles of gold.⁴⁰ Such fluids, now recognized as metallic colloids, were known since antiquity and “colloidal gold was prepared even in the days of the alchemists by the reduction of gold salts by all kinds of organic substances, including urine.”⁴¹ However, they are not thermodynamically stable but are kept apart by the electric double-layer force; their lowest free-energy state is the

aggregated or, more correctly, the two-phase water–gold state. Some of Faraday's samples (Figure 8) still survive at the Royal Institution of Great Britain, demonstrating the long-term stability possible in certain systems resulting from the high energy barriers to precipitation.

Another example of a system with a long equilibrium time is the pitch drop experiment (Figure 9), an ongoing experiment that shows pitch to be a normal liquid albeit with a high viscosity. A total of eight drops have fallen since the stem of the funnel was cut in 1930, and the room-temperature viscosity of the pitch (which on shorter time scales behaves as a brittle solid) has been estimated to be about 11 orders of magnitude higher than that of water.⁴³

The so-called von Schroeder paradox is another type of equilibration issue: in experiments on the swelling of gelatin in contact with saturated water vapor, von Schroeder discovered that less solvent was taken up than for gelatin in contact with liquid water, although the chemical potential of water was the same in both cases.⁴⁴ This paradox has since been observed for several different swelling clays, gels, and membranes and ascribed to various experimental artifacts or to the existence of micropores in the polymer network. Recent work suggests that under certain sets of conditions for a nonporous network two thermodynamic equilibrium situations can be found, corresponding to different volume fractions of solvent, with a formation of clusters of solvent molecules within the network.⁴⁵ von Schroeder's paradox remains an important but unresolved issue in understanding interparticle interactions.

Polymer-mediated interactions can also take very long times to equilibrate, mainly because of the high molecular weight, and therefore large number of segments, of many polymers, especially biopolymers and proteins, which can exceed many million Daltons. A still unresolved question in protein folding is whether proteins naturally fold into their lowest free energy state or just some kinetically trapped metastable state.

Self-Assembly versus Directed Assembly. Closely related to the issue of how long it takes a system involving interacting molecules or particles to reach its equilibrium state is whether a self-assembling system is assembling into its true thermodynamic equilibrium state (as would appear on the phase diagram of the system) or into some state that depends on the way the sample has been treated or prepared. One may distinguish between two basic kinds of molecular assembly processes: the spontaneous assembly of molecules into clusters, nanoparticles, or colloidal aggregates that truly self-assemble into their equilibrium configurations and directed assembly, where the end result is not the ultimate equilibrium state. (The term coassembly is also commonly used to describe the self-assembly of two different molecular species; for example, RNA and protein capsomers that only when mixed together will assemble into a virus.)

Directed-assembly processes often require external energy (mechanical work, heat, or electromagnetic or chemical energy) that leads to long-lived metastable or steady-state structures that do not necessarily represent the lowest-energy, true equilibrium state. Or the system may simply appear to assemble spontaneously, as in the case of a folding protein, but not into its lowest-energy state. The products of a directed assembly process may be long-lived, and in a biological (living) system, their finite lifetime may be just what is required for the molecule to perform its function. But the distinction between these two very different processes is always important to bear in mind, especially as new materials are being constantly

produced, many of which slowly change (age) with time, often in unwanted ways.

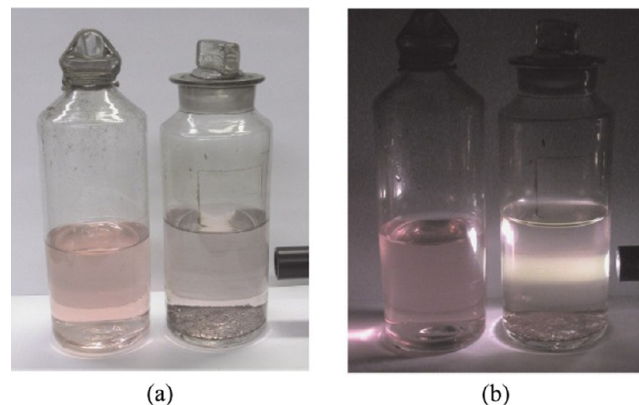


Figure 8. Samples prepared by Faraday in 1856. In both photographs, the flask on the right contains a gold colloid and the flask on the left contains a pink solution. The flasks are shown (a) in ambient light and (b) with light transmitted through the flasks, showing the scattering by the colloid.^{40,41} Photographs by R. Tweney in ref 42 reproduced with permission.



Figure 9. Pitch drop experiment. Photograph courtesy of Prof. J. S. Mainstone, University of Queensland, reproduced with permission.

Lock-and-Key Mechanisms: Interactions That Cannot Be Described by Interaction Potentials. Certain so-called “specific interactions” are molecule-specific and cannot be described in simple terms of pair potentials or as resulting from the surface energies of materials. Such interactions are common among biomolecules and commonly depend on the complementary geometry of molecules (induced-fit interactions) coupled with ionic or noncovalent bonding (often hydrogen bonds), which can lead to the association of molecules in specific configurations.⁸ An early example of such an interaction

scheme is the lock-and-key paradigm^{46,47} (Figure 10) proposed by Emil Fisher (1852–1919) in 1894 to explain the specificity of enzyme action in yeast fermentation of sugars.

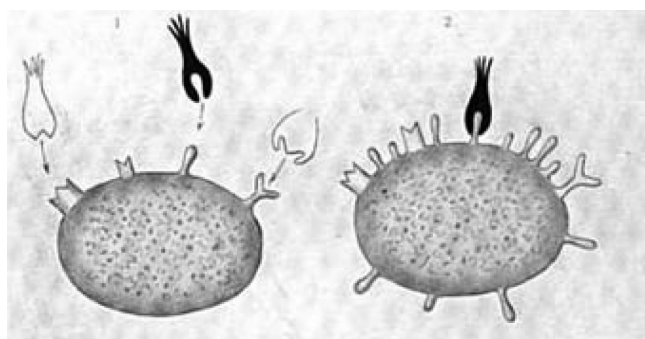


Figure 10. Lock-and-key concept first introduced into immunology by Paul Ehrlich (1854–1915) who suggested that cell surfaces are equipped with specific side chains to which stereocomplementary toxins can bind.⁴⁸ Neither the lock-and-key representation nor the side-chain model is an exact description of molecular events, but they were helpful in describing the level of complexity involved in specific interactions, and cartoons such as the one shown here are still used today to illustrate biospecific, ligand–receptor, antibody–antigen, and other types of complementary noncovalent interactions.

Fisher also noted that enzymes, which were yet to be characterized, were likely to be asymmetric molecules. Unlike traditional interactions, such as van der Waals or electrostatic (Coulomb), that can be written in terms of some force law or interaction potential, such complementary interactions are specific to each ligand–receptor pair and (at least so far) have not been successfully described in terms of an analytical equation or even a series of equations that can be easily solved, offering a daunting challenge to those attempting to model such systems or interactions quantitatively.

Importance of Rare Events. There has been a recent appreciation of the importance of rare events, especially in immunological recognition interactions in biology, but also more generally. This phenomenon is illustrated in Figure 11 for a binding and unbinding process, showing how two cell surfaces may be made to bind by the initial linking of a single molecule (ligand) to a receptor molecule on the opposite surface, which then brings the rest of the two surfaces together. This is an example of a rare event, where the probability of the ligand extending out as far as it did is, according to mean-field theories, very low but that when it does occur the resulting ligand–receptor bond triggers a process that brings the two cells together. One hears of single molecules pollinating a flower, which is another example of a major event occurring that is not determined by mean-field theories or averaged quantities.

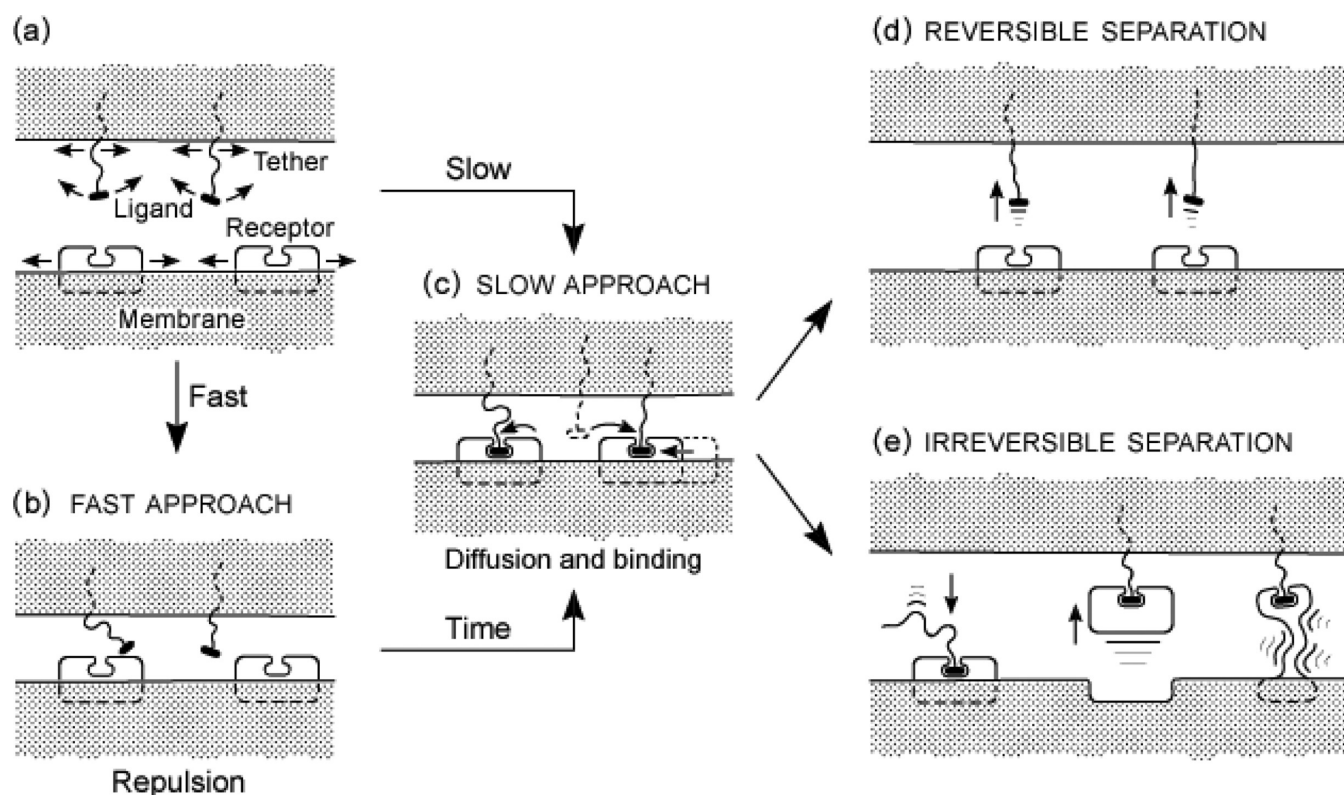


Figure 11. Examples of the complexity of biological interactions involving the molecular binding and unbinding of a ligand and receptor on a biological cell surface (such as the cell membrane). On fast approach (a → b), there is an additional kinetic force barrier because the ligand does not have time to find the binding site until some finite time after the surfaces have been close together (b → c). On separation (c → d, e), depending on the relative bond energies, bond lengths, and the rate of separation, the original ligand–receptor bonds may break (d), lipid molecules may be pulled out of the membrane, the receptor molecules may be pulled out, or the protein may unfold (e). Other scenarios are also possible, including statistical combinations of the above. Note how such systems involve many different bonds acting (binding and unbinding) in parallel and/or in series, both of which are very difficult to model. Reprinted from ref 8, copyright 2011, with permission from Elsevier.

Modern Issues and Challenges. Some of the examples discussed above—nonequilibrium systems, self-assembly versus directed-assembly processes, specific interactions, rare events, and processes that evolve in both space and time—all involve a very complex interplay of different interactions occurring sequentially in both space and time. Understanding the way complex fluid systems behave requires first an appreciation of these subtle processes and interactions and then a means to analyze and model them. Unfortunately, no longer can a simple equation (force law or interaction potential) adequately describe some interaction or process. Instead, complex algorithms appear to be needed to model many complex fluids and especially biological systems, which can apparently be done only with the fastest computers. We hope that some future theories may turn out to enable us to understand at least some of these systems and processes with the same simplicity and beauty as their earlier ones.

AUTHOR INFORMATION

Notes

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