chemistry for establishing new benchmarks that test the limits of these bonding theories, by synthesizing molecules that appear to defy generally accepted rules governing bonding. More specifically, these rules describe the extent and nature of overlap of electron density associated with atomic orbitals that contribute to the formation of stable molecular structures (*5*, *6*). For example, the valence s and p orbitals of carbon have similar energies, so they tend to mix according to symmetry requirements to produce a lowest-energy tetrahedral geometry for the four single bonds of carbon atoms. In highly "distressed" (*7*) or "nonclassical" (*8*) organic molecules, such bonding arrangements are severely distorted away from tetrahedral geometries to such an extent that the resulting higher energy of the molecular framework would have been thought impossible to achieve. Successful syntheses of nonclassical molecules can also provide examples of potential new reaction pathways for subsequent synthetic transformations.

A seminal contribution to the advancement of modern theories of structure and bonding was made by Wiberg and co-workers [reviewed in (*9*)]. They predicted the stability of [1.1.1]propellane, a highly strained C_5H_6 hydrocarbon that fuses three rings (see the figure, panel A), and went on to synthesize this molecule under ambient conditions and validate its structure in experimental studies. The formal valence-shell orbitals describe bond paths that require an "inverted umbrella" geometry for the bridgehead carbon atoms that link the rings, which greatly increases the strain energy associated with this molecular framework.

Before attempting the synthesis of such daunting targets, most chemists would want some assurance that the target is actually stable enough to isolate or observe spectroscopically. Predictions of stability (*5–9*) for these nonclassical molecules can now be assessed quantitatively because of advances in computational methods, which include ab initio, semiempirical, and density functional theory. In these methods, the electronic distributions that define atomic positions and bond paths within a molecule are not biased by the artificial construct of isolated molecular orbitals, and the stability of more complex bonding arrangements can be successfully probed and rationalized (*10*).

The work of Peng *et al.* is also related to efforts that refine fundamental concepts of structure and bonding through the computational investigation, synthesis, and characterization of molecules in which the carbon is replaced by the heavier group 14 elements (*11*). The issue is whether these benchmark

molecules can be viewed as "heavy-atom analogs" that follow the same set of bonding and reactivity rules as all-carbon-based organic molecules, or whether their properties require a rethinking of orbital interactions that can better describe differing behavior in structure, bonding, and reactivity. Ironically, a dearth of synthetic methods has led to the discovery of new benchmark molecules and reactions for these heavy-atom analogs, mainly through serendipity. Often, each new discovery has also challenged reconciliations with theory.

By all initial appearances, the forward and reverse chemical processes reported by Peng *et al.* do not conform neatly with what we would expect on the basis of their carbon counterparts. The Woodward-Hoffmann rules predict that cycloaddition of $H_2C{=}CH_2$ to a substituted acetylene ($RC{\equiv}CR$) should be a forbidden process. Similarly, the stability of bicyclo[2.2.0]hexane (BCH), the simplest analog to the product reported by Peng *et al.*, is quite different (see the figure, panel B). Furthermore, the Woodward-Hoffmann rules would predict that the reverse fragmentation of BCH should follow an entirely different ring-opening pathway than that observed for the tin-containing product, 1,4-distannabicyclo[2.2.0]hexane (DSBCH).

One way in which symmetry-based orbital overlap arguments must be refined for carbon's heavier counterparts is that s and p orbitals tend to be further apart in energy and mix more weakly. Valence bonds

are often then made from orbitals with much more p character, and bond angles closer to 90° are more commonly seen. Fortunately, a successful reconciliation of the present observations may not require that any new conceptual models of bonding be invoked for DSBCH.

Further high-level computational investigations of this system will also undoubtedly lead to a better understanding of the changes in free energy for the forward and reverse processes that establish DSBCH as only a "minimally stable" molecule. However, it is the facile nature of the forward and reverse concerted cycloaddition of two $H_2C{=}CH_2$ with one $RSn{\equiv}SnR$ that opens a new, currently blank, chapter describing modern theories that govern structure, bonding, and fundamental chemical processes that we have yet to envision.

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CHEMISTRY

Emergent or Just Complex?

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Efforts toward creating artificial cells are shedding light on how life may have emerged.

The concept of emergence in the physical and biological sciences is an elusive one. The term refers to phenomena in which the complexity of structures or behaviors in systems with many interacting components exceeds that predicted from knowledge of the individual components and the forces between them. A recent conference (*1*) provided an opportunity to probe the notion of emergence from a wide range of viewpoints, loosely linked by the themes of

increasing complexity and molecular organization. The scope of the conference is exemplified by S. Rasmussen's characterization of hydrogen as "a colorless, odorless gas, which, given enough time, turns into people." Perhaps the prototypical emergent phenomenon is the origin of entities that can plausibly be called alive (*2*). How does one get from atoms to simple molecules to systems that can grow, reproduce, metabolize, move, and adapt?

Carbonaceous meteorites (*3*) may offer a glimpse into the organic chemistry of presolar environments that resulted in the production of the first chiral amino acids, which may have served as early building blocks and/or as asymmetric catalysts. However, many steps

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from these amino acids to living cells remain to be elucidated. For example, how did small monomers polymerize into longer chain species, such as nucleic acids (4), and how were the developing reaction networks compartmentalized into protocells (5)? None of these processes contradicts or is inherently incomprehensible in terms of our current understanding of thermodynamics, chemical kinetics, and catalysis. Yet, a coherent, explanatory, conceptual synthesis is far enough away that it still seems reasonable to characterize early life as emergent.
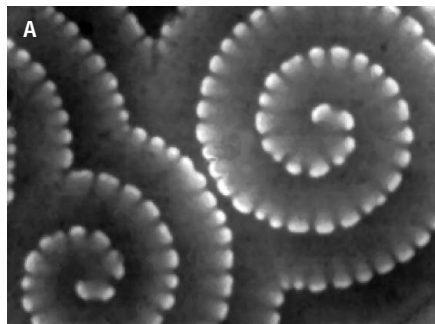
Spirals and worms. (**A**) Segmented spirals emerge from about one million interacting nanodrops of aqueous BZ solution in an oil-water microemulsion (15). Frame size, 3.72 × 4.82 mm². (**B**) In a simulation (16), a BZ gel "worm" autonomously reorients itself to localize in the dark region.
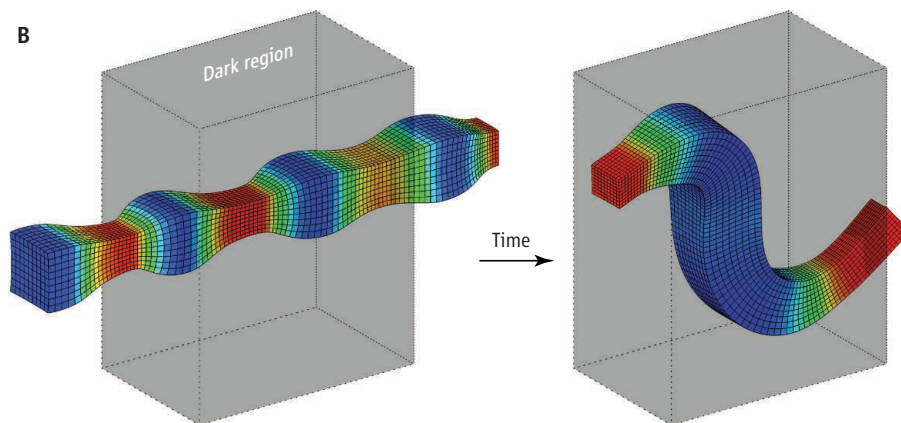
One popular example of emergence is Conway's "Game of Life" (6). In this game, a rectangular grid of sites is populated by "cells." A simple set of rules determines whether those cells live, die, or multiply, based on the number of neighboring sites that are populated. Depending on the rules chosen and the initial conditions specified, repeated iteration yields a remarkable variety of moving and stationary patterns that seem far more intricate than the simple elements and rules of the game should allow. This game is a simple example of cellular automata (7), whose richness continues to surprise.

More generally, computer programming provides an attractive metaphor for emergent behavior in chemical and biological systems. If one imagines molecules and reactions as analogous to the primitive operations and instructions in a programming language, one can build complex chemical "programs" to accomplish specified tasks. Because molecules, such as the complementary base pairs in DNA, can have natural affinities for one another without forming covalent bonds (8), much of the "work" of this sort of programming occurs very efficiently via self-assembly. Complex supramolecular structures can be designed from DNA "origami" seeds and

tiles (9). Deoxyribozyme-based molecular automata can play tic-tac-toe (10).

Even relatively simple chemistry can yield a remarkable array of dynamic behavior resembling that displayed by multicellular organisms. For example, when a few dozen nickel electrodes undergoing electrodissolution are coupled to each other, they form a small set of clusters that oscillate in phase with one another, resembling behavior seen in brain slices (11). Another system, catalyst-impregnated beads in a solution containing the reactants of the Belousov-Zhabotinsky

(BZ) reaction, displays the phenomenon of "quorum sensing:" when the bead density reaches a critical value, the population of independent, quiescent beads undergoes a sharp transition to coherent oscillation (12). Biomolecules—notably proteins and nucleic acids—provide particularly impressive examples of emergent phenomena. Networks of such molecules can perform functions analogous to associative learning (13).

The various threads of the above research could provide useful guidelines for creating artificial cells that can simultaneously perform multiple functions, such as self-propulsion, self-sensing, and a form of communication that leads to cooperative activity. Researchers have designed self-propelled microscopic "swimmers" and colloids and identified conditions where hydrodynamic interactions between these objects drive them to swim together in a concerted manner (14). Such self-propelled entities could exhibit greater "intelligence" if they incorporated some internal chemical dynamics, such as provided by the BZ reaction. In the case of the oscillating beads (12) and that of microemulsions consisting of nanodrops of aqueous BZ solution suspended in an oil phase (15), the state of one entity affects the behavior of the rest, and, in this respect, different units communicate with each other (see the figure, panel A). Further-

more, simulations have shown that light can be used to direct the movement of a small BZ gel "worm" (see the figure, panel B) (16).

It may also be possible to exploit recent synthetic advances to direct the conglomerates to fight or flee—two other hallmarks of biological entities. For example, magnetically driven microspheres at liquid-liquid interfaces can be manipulated such that some microspheres raid and attack others, resulting in the formation of larger snakelike figures (17). Under certain conditions, these snakes divide into smaller entities, thereby

undergoing a simple form of reproduction.

Finally, advances in manipulating DNA (9) may be harnessed to further direct such "intelligent" microscopic objects. For example, functionalization of colloid particles with complementary strands of DNA (18) leads to a new class of synthetic materials designed to self-replicate and, as a result, grow exponentially. Coupling this technology to beads that communicate, fight, flee, and consume energy would open the door to objects displaying essential hallmarks of living systems.

The notion of emergence as an area of scientific inquiry is inherently paradoxical, in that emergent phenomena are defined as those whose origins we do not completely understand. As we probe more deeply, what is perceived to be emergent necessarily recedes into the distance as we begin to see more clearly how interactions between components give rise to more complex structures and behaviors. Nonetheless, how life emerged from atoms and molecules is a question that, whatever we choose to call it, will challenge scientists for many years, if not centuries, to come.

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MATERIALS SCIENCE

Simulating Multifunctional Structures

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More powerful computers and better algorithms are making it possible to probe and engineer the atomic-level properties of nanostructures.

Electronic devices, sensors, and electromechanical systems are now reaching nanoscale dimensions at which they contain only hundreds of millions to billions of atoms. Developments in materials simulation, driven by algorithmic advances and rapid increases in computer power, now allow systems of tens of millions of atoms to be routinely simulated, while systems of billions of atoms can be simulated on the largest supercomputers (*1*). This is leading to new capabilities in interfacial engineering design, development of nanostructures with prescribed properties, tuning of functionality under typical or extreme conditions, and prototyping of nanostructures in silico.

The key missing piece to such device-size simulations has been flexible and powerful descriptions of interatomic interactions that allow materials of different bonding types (metallic, covalent, and ionic) to be treated in an integrated manner. On the one hand, mesoscopic and continuum-level modeling methods are not designed to reach down to the atomic dimensions at which discrete physical and chemical processes take place. On the other hand, electronic structure methods have long been able to simulate heterogeneous systems; indeed, they provide the highest materials fidelity of currently available simulation methods (*2*). However, because they treat the electronic deg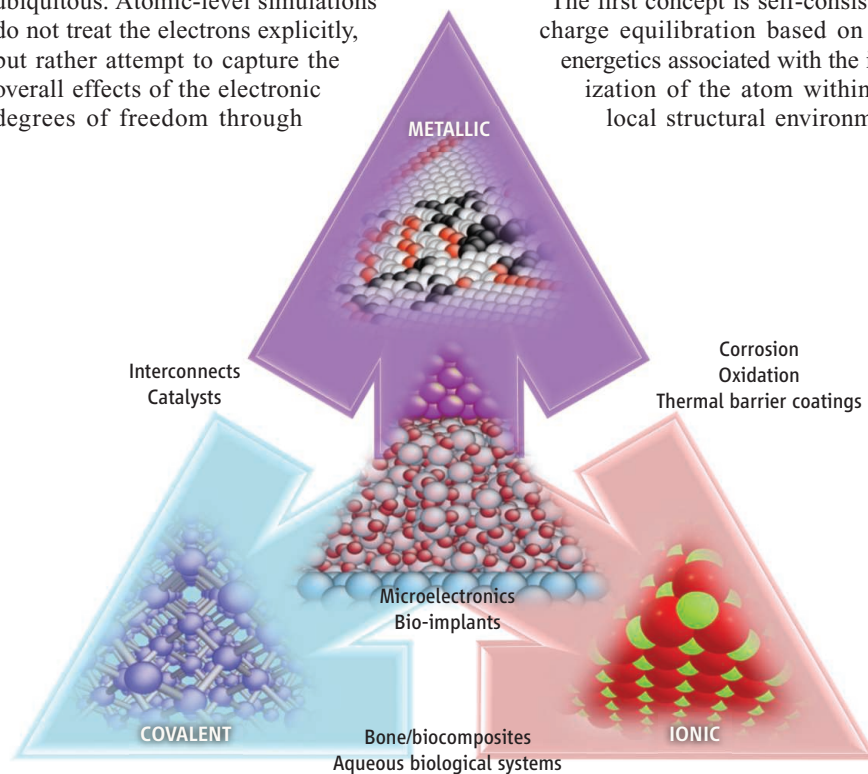rees of freedom of the system explicitly, they are computationally expensive and cannot reach up to the scale of many experimental nanostructures. The gap between these two approaches is filled by atomic-level simulation methods, of which classical molecular dynamics simulation is the most ubiquitous. Atomic-level simulations do not treat the electrons explicitly, but rather attempt to capture the overall effects of the electronic degrees of freedom through effective interatomic interactions among the atoms and ions in the system.

The very different physics and chemistry associated with metallic, covalent, ionic, and van der Waals bonding have led to the development of very different paradigms for the encapsulation of these electronic effects in atomic-level simulations (see the figure). Within its own domain of materials, each has proved very successful: for example, the embedded atom method (EAM) describes a broad range of structural phenomena in metals (*3*). Similarly, fixed-charge approaches have been used successfully to model ionic solids (*1*) and biomaterials in aqueous environments (*4*). However, the approaches for different bonding types are so different that it has not been easy to establish whether, or how, a single framework could capture them all in the absence of a self-consistent electronic structure treatment.

Nevertheless, such a framework has now emerged and is opening up the possibility of simulating structurally and chemically complex nanostructures and nanoscale processes. This framework is built on two key concepts, which in combination appear to provide the power and flexibility to describe the effects of complex electronic-level behavior without simulating the electrons themselves.

The first concept is self-consistent charge equilibration based on the energetics associated with the ionization of the atom within its local structural environment

The modelers' playground. Many of the most challenging and important applications of materials involve interfaces between disparate bonding environments. The ability to simulate such interfaces promises new capabilities in computationally prototyping nanostructures or devices at experimental length scales.

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