J. MAGEE

WHAT CHEMISTS WANT TO KNOW

Chemistry is a key component in all the scientific disciplines. But does that mean it is nothing more than a handy tool — or are there still major chemical questions to crack? **Philip Ball** finds out.

Physicists do not shy away from promoting the big questions that drive their field — how the Universe began, say, or what governs the behaviour of space, time and matter over scales from the atomic to the cosmic. Biologists, too, are happy to point to Erwin Schrödinger's question 'What is life?', which they are attempting to answer by unravelling DNA and mapping out the structures and interactions of proteins.

But what of the third basic science in the curriculum? To judge from the scant attention chemistry gets in the public media, you could be forgiven for thinking that it is a discipline whose time has passed, its grand puzzles all now answered. Does chemistry have any big questions left?

Identifying such frontier questions seems all the more urgent because university chemistry departments are facing an uncertain future. The department at the University of Sussex in Britain, for many years home to Nobel laureate Harry Kroto, co-discoverer of buckminsterfullerene, was the latest in a long line threatened with closure. It has so far resisted an attempt to remodel it as a 'chemical biology' adjunct of the life-sciences division; but several other UK chemistry departments have failed to evade the axe. Following similar moves and concerns in the United States, a 2004 editorial in *Chemical and Engineering News*, published by the American Chemical Society (ACS), proposed changing the organization's name, rebranding it as the Society for Molecular Sciences and Engineering.

With departments closing and student numbers dwindling, can today's chemists be sure that their discipline will continue to be seen as a core science? Some of them complain that many of its most important questions are being framed in terms of the 'chemical' aspect of another discipline, rather than being seen as central to chemistry itself. In an attempt to gauge the prospects for academic chemistry, *Nature* asked many leading chemists what the field's big questions are, and whether in fact chemistry needs big questions to maintain a sense of coherence and identity.

The strongly synthetic character of chemistry sets it apart from the 'discovery' sciences such as physics, biology, astronomy and the Earth sciences. "Chemistry creates its object," as the French chemist Marcelin Berthelot wrote in 1860.

Many chemists still see this creativity as one of the field's strengths. "It makes chemistry able to set goals of a type most other sciences cannot hope to attain," says Ron Breslow, an organic chemist at Columbia University in New York and a past president of the ACS. "Where is synthetic astronomy — changing the gravitational constant to see what effect that has on the properties of the Universe, and thus perhaps improving it?"

And although synthetic biology is now emerging as a genuine discipline, to many chemists this is just another branch of applied chemistry, relying as it does on chemical techniques such as DNA synthesis and protein design. "We are the only science where things can be made that were never made before," says nucleic-acid chemist Jacqueline Barton at the California

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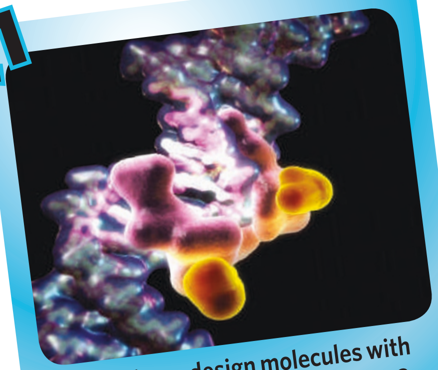

How do we design molecules with specific functions and dynamics?

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Institute of Technology in Pasadena.

The downside of this focus on making stuff is that chemists can be portrayed as inveterate tinkerers — tweaking the molecular world to satisfy their curiosity, sometimes for fun and sometimes for profit. And it makes it especially hard to see where industrial chemistry ends and academic chemistry begins, because important practical challenges provide the motivation for much academic creativity.

"Chemistry is the scientific enterprise that fuels industry," notes Barton. "Not just petrochemicals, but pharmaceuticals, biotechnology and computer chips." Breslow agrees that chemistry faces not so much big questions as big practical challenges, such as "to devise a practical method to derive our needed energy from sunlight; to create a room-temperature superconductor that can carry large currents; to learn now to perform the manufacturing we need without damaging the environment".

Be specific

No one would deny the importance of applied and industrial chemistry. But if chemistry's questions aren't so much about what we can know but about what we can do, does that make it a form of engineering — a quest for particular solutions to particular problems?

According to inorganic chemist John Meurig Thomas of the Royal Institution in London, it is in the nature of chemistry to be a science of particulars. One can identify general principles of chemical bonding, for example, but what often matters is how these are enacted and modified in specific molecules. Similarly, he says, "it would be ludicrous to look for a general theory of catalysis that applies to all enzymes, materials, surfaces and so on."

With so many chemists happily focused on practical goals, and with other disciplines nibbling away at the edges of chemistry, are there any big questions left at the academic core of the subject? And if there are, do they have the intellectual excitement of those at the frontiers of physics and biology?

Chemists certainly have the tools and concepts to help answer some of the frontier questions arising in these other disciplines. The clearest consensus among the chemists approached by *Nature* was that many of chemistry's most urgent questions are ones that address aspects of biology. "To me, the big unanswered questions concern the chemistry of life processes," says physical chemist Richard Zare of Stanford University. Barton agrees: "A real understanding of biological processes always comes down to understanding the chemistry."

Essence of life

Harvard University chemist George Whitesides goes further. "The nature of the cell is an entirely molecular problem," he says. "It has nothing to do with biology, really." Whitesides suggests that the "really intellectual" parts of biology, such as its more quantitative and molecular aspects, are overlooked whenever biologists study whole organisms. These are strong claims, which biologists might contest. One can claim that the cell has nothing to do with biology, points out molecular biologist and Nobel laureate Sydney Brenner at the Salk Institute for Biological Studies in San Diego, California, but by the same token, one could say that all of chemistry is just quantum mechanics.

"The nature of the cell is an entirely molecular problem. It has nothing to do with biology." — George Whitesides

Still, many of the gaps in scientific understanding of the fundamental processes of molecular biology, such as protein folding, genetic encoding of biomolecular function, and highly selective molecular recognition, are fundamentally chemical problems. And although molecular biologists may assume that these things are broadly understood, from a chemical viewpoint they get more puzzling the closer one looks. Scientific understanding is still not good enough to provide a rational and predictive basis for the kind of molecular-scale interventions needed in biomedicine and drug development.

Meanwhile, the chemical nature of biomolecular processes such as signal transduction, identified as a key question by chemical engineer Matthew Tirrell at the University of California, Santa Barbara, is one of the issues that is positioning chemistry as an information science. The concept of a lock and key to explain biomolecular recognition, proposed by German chemist Emil Fischer in 1894, can now be seen as the start of what supramolecular chemist and Nobel laureate Jean-Marie Lehn of the University Louis Pasteur in Strasbourg, France, has called the science of informed matter.

The concepts behind self-assembly have accustomed chemists to the idea that molecules can be programmed to interact and come together in very specific ways, and artificial replicating molecules have demonstrated the principles by which chemical information can be transmitted and amplified. "For me, chemistry has a most important contribution to make to the biggest question of all: how does self-organization arise and how does it lead the Universe to generate an entity that is able to reflect on its own origin?" Lehn says.

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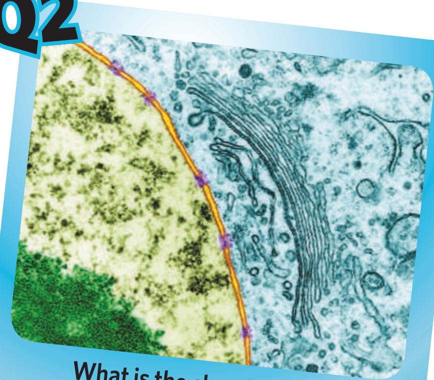

What is the chemical basis of the cell?

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Lehn believes the next step is the design of chemical 'learning systems' that are not just programmed for assembly but can be trained. Indeed, another of the key questions in chemical biology raised by several chemists was the chemical basis of memory.

"Once we know the answer, maybe we can design new thoughts and memories, or even just learn how to retain old ones," Barton suggests. Whitesides wants to know how to use chemistry to merge silicon electronics with grey matter. "How do I plug my computer into my brain?" he asks. That might sound like a matter for neuroscientists and electrical engineers — but as the signals between neurons are chemically mediated, this kind of interfacing demands command of a chemical language.

These are appealing directions for chemists to study, but do they qualify as truly chemical questions? To Whitesides, that couldn't be more the case. "I take the view that most of what is interesting in science is now chemistry," he says. He argues that even some of the key questions in a field as apparently remote from chemistry as astronomy, such as 'How many Earth-like

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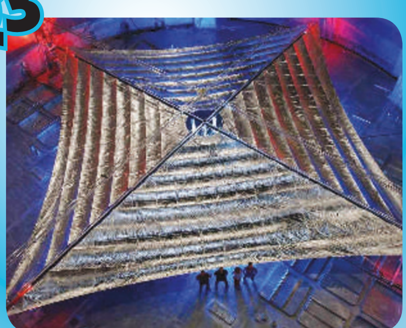


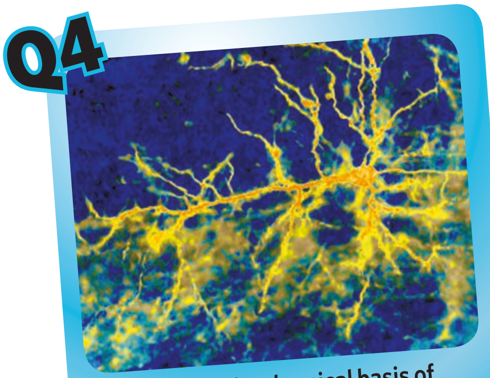
How do we make the materials needed for the future, in energy, aerospace or medicine?

T. VAN SANT/NASA

planets are there?' or 'What is on Saturn's moon Titan?' are fundamentally molecular ones.

When addressing interdisciplinary questions, what truly distinguishes chemists from physicists and biologists is that they are not content to ignore molecular-scale mechanisms. Tackling these issues confronts chemists with what is perhaps the core challenge of their discipline: to understand and predict the relationship between molecular structure and function.

Structure–property relationships are crucial to drug design, for example — one of chemistry's major concerns. "How do



What is the chemical basis of thought and memory?

PHOTOTAKE/ALAMY

we encode specificity for particular cells, organelles or tissues into molecules?" asks Barton. "How do we make molecules go where we want them to go?" It is also essential for designing catalysts for use in industrial synthesis. But at present, a full understanding of the link between structure and function is often possible only for relatively simple, small molecules — and even then there are many details of the problem that have yet to be clarified.

Action heroes

For example, Nobel laureate Ahmed Zewail, a physical chemist at the California Institute of Technology, points out that the dynamic behaviour of molecules can play as big a role in their reactivity as their molecular structure. It is now clear that the interactions between biomolecules aren't simply a matter of fitting a key into a lock — getting a good geometric match between the binding site and its target — but may depend on the dynamics of the interacting molecules and the solvent.

Chemists now think of reactions as happening on a complex, multidimensional energy surface, or landscape, which can be as rugged as a mountain range. So understanding protein folding is a question of how the molecule's peptide chain negotiates a trajectory across this energy landscape so that it ends up in the 'valley' corresponding to the correctly folded conformation. "In biology, thinking about the relationship between structure and function is not enough," says Thomas. "You've got to think about movement around the energy landscape." In other words the dynamics are key.

A big question for Zewail is how to control chemical function through dynamics. Compared with their ability to determine molecular structure, chemists have only just begun to understand what can be done to control reaction pathways in this energy landscape. In principle, this can be done by guiding molecules, perhaps using laser beams, into particular quantum states. So far this has been achieved for simple molecules, but looks extremely daunting for larger, 'floppier' ones.

And even if they crack the principles of molecular design, how do chemists apply them? "Until we reach the stage when someone can go in the lab and synthesize an arbitrary molecule in 100% yield in pure form without having a graduate student spend a year working it out, we have not really mastered synthesis," says Barton. "So the big question concerns the nature and rules governing how to assemble atoms into new molecules in a predictable and effective way. Then we could make whatever substances we want."

Creative force

Only chemists know how truly difficult it is to engineer atoms and molecules — something that many other scientific disciplines rely on. If room-temperature superconductors or synthetic bacteria are ever created, it will not be physicists and biologists who make them. And if chemistry is chopped up and parcelled off to other disciplines, there will be no training ground for those who achieve such mastery over matter.

It would be wrong, moreover, to suggest that the heart of chemistry — rational synthesis — lacks intellectual appeal. Some argue that, rather than trying to understand the world, chemists are attempting to understand all possible worlds. "Chemistry has a useful aspect, but that is not the basic science," says Breslow. "The basic science is clear once we realize that the limited examples of molecules and reactions that nature has supplied are a microdrop in an enormous bucket compared with the wonderful chemical world still to be created and examined."

It has been estimated that there are

How did life on Earth begin, and how and where might it begin on other worlds?

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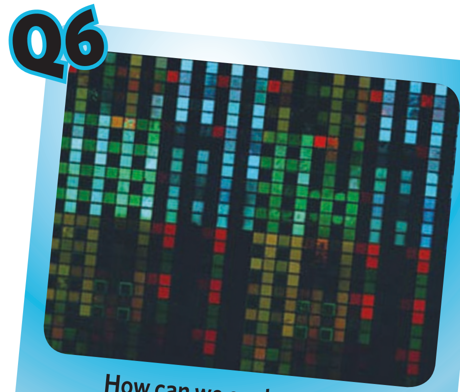

How can we explore all the possible permutations of all the elements?

H. KOINUMA & I. TEKEUCHI *NATURE MATER.* **2**, 429–438 (2004)

about 10^{40} possible molecules that could be made from common elements with a molecular size comparable to that of a typical drug. "The known chemical world, including the expansion of the natural world that chemists have achieved, is nowhere near 1% of that," says Breslow.

It is this profusion that defies attempts to reduce chemistry to a handful of objectives. "Its universe is defined not by reduction to a few elementary particles, or even the hundred or so elements," says theoretical chemist and Nobel laureate Roald Hoffmann of Cornell University in Ithaca, New York, "but by reaching out to the infinities of molecules that can be synthesized. There is no end to the range of structure and function that molecules exhibit."

Most chemists seem content to work without big frontier questions to guide them. Such questions can be helpful to a discipline's sense of identity and direction, but they risk narrowing the possibilities of an inherently creative discipline. Some might argue that an excessive focus (at least in the public eye) on 'theories of everything' or decoding the human genome has not been terribly productive for physics or biology.

Besides, in chemistry, as in any science, the biggest breakthroughs often come from unexpected directions. "I do not think that I have ever identified in advance any of the major directions or key questions of chemical research that I witnessed in the past half century," confesses inorganic chemist Hubert Schmidbaur at the Technical University of Munich in Germany. "And it seems to me that the situation will be not very different in the next five decades."

"There is no Holy Grail in chemistry," Hoffmann admits happily. "Occasionally some are held up for public view," he says, but they are just "gimmicky candidates for the chalice". He adds that in a fundamentally creative field, the satisfaction comes from the chase, not the catch. "My natural philosophical disposition is not to work on big questions," says Hoffmann. "I like working on many detailed small problems in this wonderful chemical garden, while keeping my eyes open for the connections." ■

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For more on this topic, see Editorial, page 486.