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Is the Focus on "Molecules" Obsolete?

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Abstract

The technologies developed in analytical chemistry have defined in spectacular detail the properties of *molecules*. The field now faces enormously important and interesting problems of which molecules are only a part: for example, understanding the nature of life; helping to manage megacities, oceans, and atmospheres; and making health care (especially diagnostics) affordable and relevant. The emergence of these problems involving molecular *systems* raises the issue of how (and what) analytical chemistry should teach. Historically, it has been essential to chemistry in teaching the science of measurement. As complicated analytical techniques proliferate, it must consider how to balance teaching the *uses* of sophisticated devices and the fundamentals of analysis and measurement. This review (by an admiring but nonanalytical chemist) sketches the essential role of analytical methods—especially *simple* ones made up on the spot—in guiding research in new fields, with examples from self-assembled monolayers, soft lithography, paper diagnostics, and self-assembly; and suggests issues in teaching.

1. INTRODUCTION

Question and answer: "What does analytical chemistry do?" "It determines the composition and structure of matter, and particularly of molecules." Correct answer . . . or so yesterday? Much of science follows the "scientific method." This ponderous but reliable process is a wheel: postulation of theory, formulation of a hypothesis testing the theory, experimental test of the hypothesis, comparison of experimental results with theory, modification of theory, and so on. Measurement (or "analysis," which arguably includes both measurement *and* interpretation) is the axle around which this wheel turns. So, everything in science is—in this sense—"analytical."

Almost everything in science requires some form of "analysis." In chemistry, the specialty that focuses on analysis of matter, and especially of molecules (and the specialty that also develops new *methods* of measurement), is "analytical chemistry." Analytical chemistry sometimes leads chemical science (by enabling new types of experiments); sometimes it follows (by adding useful precision to previously developed capability, or by making methods more user friendly). Regardless, it is essential to the chemical enterprise.

Chemistry defines itself as the science of atoms, molecules, and matter; it tends to focus on molecules. It has become very adept within that definition: Chemists can make, or obtain from nature, an enormous range of molecules and determine their structures, even at extraordinary levels of complexity, with sensitivities now routinely approaching those required to examine single molecules and atoms. This type of work, with its molecular focus, has been the core of the field and will (and must) certainly continue. At the same time, analytical chemistry is blurring around its disciplinary edges. It is increasingly difficult to tell what is "chemistry" and what is "biology" or "materials science" or "cognitive science," or "health care," or "energy." Further, the role that society expects the sciences, and especially chemistry, to play is changing: from developing focused technical methods to solving (or helping to solve) large-scale problems, both in areas of direct, immediate public concern (health care, robots and jobs, environmental monitoring) and in areas of fundamental understanding ("What is life?" "How does climate instability develop?" "How does the human brain think?"). With this broad sweep of *styles* of problems—from sequencing proteins to helping to manage megacities—what will "analytical chemistry" become? Will it be a discipline that focuses on a small part of a bigger problem—one in which molecules may be only a paragraph in a much longer story—or will it lead the integration of measurement, analysis, and interpretation of information across a number of disciplines?

I am not an analytical chemist, and am not competent to answer this broad question; and in any event, I do not know the answer. I am, however, a constant user of analytical methods, someone who often thinks in terms of analysis, a developer of new analytical methods when I need them, and a scientist who is wholly dependent on measurement. And, whether I "know" or not, I have opinions.

Why did I think it might be worth anyone's time to read an essay that I—a nonexpert—might write on analytical chemistry? I have two reasons. First, I have been using analytical methods for 60 years, and the changes in the field in that time have been large, interesting, and instructive for the light they shed on the continuing evolution of chemistry; perhaps the perspective is useful. Second, it seems to me that analytical chemistry is facing some substantial choices, and sometimes "change" is more obvious from outside a field than inside.

In this review, I intend to make five points:

1. Analytical chemistry is extremely important—probably even more important than analytical chemists think. Everything in science requires measurement; analytical chemists are experts in the science of measurement, not just in determining the structures of molecules and the compositions of mixtures of molecules.

2. In new fields—fields in which substantial expertise in analysis does not already exist—*simple* analytical methods often have far greater value than do more precise and sophisticated ones. The rate of progress in a new field often depends as much on the ability to fail rapidly—to understand in the morning why a hypothesis is incorrect, and to try another one in the afternoon—as on precision. Developing simple analytical methods (and teaching students how to develop such methods) is an important and sometimes critical part of exploratory research.
3. "Good enough" is often good enough, even in a developed field. Academic scientists tend to favor complexity and "world-class performance." For users, the balance between convenience, cost, and performance may strongly favor convenience or cost over performance, and it can be as challenging and interesting to develop a truly workable, simple system—one that can be used by others—as it is to develop a highly specialized system that will probably seldom (or never) be replicated.
4. The most important problems for analytical chemistry may be changing from "molecules" to "functions."
5. For all of the value of its technology and methods, and for all the importance of the information that it provides, one of the most important contributions of analytical chemistry may be in teaching new scientists and engineers how to make measurements. As the field has broadened, and as more and more science, instrumental design, and software accumulate in commercial instrumentation, understanding how to balance teaching the fundamentals of measurement with the training needed to operate very sophisticated instrumentation, without letting "analytical chemistry" drift into "the care and feeding of black boxes," is an important challenge, and one that is now without a clear solution.

2. WHAT DOES CHEMICAL ANALYSIS DO? (OR, WHAT DOES "ANALYTICAL CHEMISTRY" SEEM TO BE, TO AN OUTSIDER?)

2.1. Early Impressions Stick

Interestingly (at least to me), my first experiences in laboratory were in analytical chemistry. Even before high school, I worked during the summers as the lowest-level technician in the small company owned by my father. He made a number of products, including (especially at that time) various formulations of coal-tar black and short-fiber chrysotile asbestos designed to fill, for example, the expansion joints between slabs of concrete in roads and runways. My job was to determine pour-point viscosities for coal-tar blacks. These measurements involved taking a sample of hard, black pitch; putting it in a clean copper cup with a small hole in the bottom; heating the cup and its pitch to a temperature specified in an ASTM publication; and then carefully measuring the time required for a specified volume of the melted pitch to drip out of the hole into a volumetric cylinder. Afterward, I cleaned the apparatus again to an immaculate state, using a mixture of benzene and carbon tetrachloride (I quite liked the smell of the mixture). The combination—a mixture of chemicals (polycyclic aromatics, short-fiber chrysotile asbestos, benzene, carbon tetrachloride, and whatever else had been washed into the jug containing it) now known to be splendidly carcinogenic and hepatotoxic—is, if nothing else, a reflection on the carefree state of mind surrounding occupational health and safety at that time. I am, for the moment, still alive.

I carried out this measurement several times a day for three summers. And what did I learn? Cleanliness is good. It's the property—viscosity—that counts, not the molecular composition. Repetition can be soothing. Keep a neat laboratory notebook.

My next experience in chemistry—again in analytical chemistry—was in high school. My only chemistry course was taught by a decent and earnest instructor whose objective in life was to develop experiments for rural schools in Central America. His immediate concern was with the complete absence of equipment in such schools; and he asked, sensibly, "What could be used as a substitute for a beaker or Erlenmeyer flask, when such exotica are not available?" His conclusion—which, in retrospect, I think of as both imaginative and courageous (especially for his students)—was "empty Coca-Cola bottles." So, the job of my class was to carry out, for example, analyses of the product ($SnCl_4$) formed by the reaction of tin granules with concentrated HCl (in a Coca-Cola bottle). The reaction proceeded without difficulty, but it was very exothermic, and required cooling. We soon learned that if one takes a hot Coca-Cola bottle containing a mixture of $SnCl_4$ and HCl and plunges it abruptly into an ice-water bath, the bottom of the bottle immediately cracks off (Coca-Cola bottles are apparently not tempered to withstand large thermal excursions) and dumps its contents into the ice water—at which point there is much sputtering and splattering, and great clouds of HCl vapor, and choking, and surprise. It was great fun, and no one was hurt, although our clothes were in tatters the next day from corrosion by the shower of HCl.

And what did I learn from this second lesson in analytical chemistry? Probably, most importantly, "Good intentions are not enough!" Also, however, the beginning of respect for the invisible infrastructure that makes any field work. After weeks spent trying unsuccessfully to get these experiments in Coca-Cola bottles to work, I always looked at Erlenmeyer flasks (and, later, NMR spectrometers) with affection and respect.

2.2. Historically, Chemistry Has Focused on Atoms and Molecules

Chemistry has developed as a field that manipulates atoms and molecules, and analytical chemistry is the subfield of chemistry that measures compositions, determines structures, and follows rates of reaction. It understands these functions exquisitely. But what happens when the ground begins to shift? When it is routine to determine the structure of a bioactive natural product, but the *important* question is to understand what it does, and how to make a drug of it? When measuring the concentration of CO_2 in air can be done by high school students, but one really wants to know the concentrations of CO_2 in a cubic-meter-scale grid over an entire planetary atmosphere? When—even if one could measure the necessary concentrations of CO_2, and make a whole-atmosphere map of these concentrations—the issue is less the measurements themselves than their validity, their dynamics, and their interpretation? There is no shortage of difficult, important, technically narrowly defined problems with which analytical chemistry can be involved, but the important issues are rapidly becoming the even more difficult, broader, and technically ill-defined ones of systems, costs, policies, and politics.

2.3. New Analytical Methods Have Historically Been "Science Forward"

Analytical chemistry has always been remarkably resourceful in developing new, and relevant, technical methods, when faced with new problems. Its style—as with much of science in the past 60 years—has been "science forward": That is, new science has enabled new types of measurements, and hence new capabilities for analyses. This style of scientific development will, of course, continue to produce interesting and important new analytical procedures. Current examples of active areas include (*a*) methods for examining single molecules; genomics; intracellular analysis; and structures of proteins, nucleic acids, organelles, cells, and organisms; (*b*) methods for measuring processes occurring with rates $>10^{15}$ s^{-1}; and (*c*) methods of writing patterns with dimensions similar to those of molecules. They are extraordinary accomplishments in science.

As, however, the physical and biological sciences turn to problems in which "molecules" are only a part (and sometimes a *small* part), how will analytical chemistry evolve? Will it keep to its knitting in purely atomic and molecular science, or will it become the field that ties other fields together by developing whatever methods of measurement are appropriate for whatever the problem is at hand? Asking the same question in more local terms: As science turns more to materials and biology, to devices, to systems, and to the meaning of the data it produces, how will analytical chemistry choose its problems, and what sorts of new analytical methods will it generate?

And, of course, one can ask: "Why should it even think about changing, or broadening its scope?" After all, molecules will continue to be important, and analytical chemistry is doing very well in dealing with them. The answer, if there is one, is in part a question of purpose and ambition, and returns to the centrality of measurement. Only those who know how to *make* measurements really know what those measurements *mean*. Measurement and analysis are critical contributions of science to society, and analytical chemistry—by the nature of the measurements it makes—is now at the center of some of the questions that are most important to society. Either it can take this position as an opportunity for solving small parts of these big, important problems, making reliable measurements, and then handing the data to others to use (and sometimes misuse) according to their objectives; or it can take a broader view of its opportunities and responsibilities.

2.4. Commercial Development Is Critical to Broad Acceptance of New Analytical Methods

Academic analytical chemistry has another characteristic that makes it unusual among the subfields of chemistry, that is, its very close connection to the companies that commercialize analytical systems. The discovery of magnetic resonance spectroscopy was a great discovery of physics. Defining the value of the information about the structures of molecules that could be obtained from it was a great accomplishment of physical, analytical, and organic chemistry; developing the commercial NMR spectrophotometers that make almost unbelievably sophisticated manipulations of nuclear spins routine even for unsophisticated users was an extraordinary collaborative accomplishment of analytical science and commercial engineering. The same remark holds for spectrophotometry, for HPLC (high-performance liquid chromatography), VPC (vapor phase chromatography), and CE (capillary electrophoresis); for genomic analysis; for mass spectroscopy; and for essentially every area of analysis in widespread (and, thus, high-impact) use. This collaboration between science (making the discoveries and pointing to an initial application) and commercialization (supplying the engineering, building the human interface, and enabling widespread adoption of the technique as a product) has been one of the most productive and useful in American science. Will it work as well in the future for problems that are critically important socially, but perhaps not equally promising as a source of profit (e.g., atmospheric monitoring, low-cost public health)? Time will tell.

2.5. Pasteur's Quadrant

2.5.1. Science as a curiosity-driven art form; science as a solution to practical problems; science as both; science as a starving pigeon. Science is, I believe, in a particularly interesting phase. The United States has arguably been the country in which much of analytical chemistry—particularly the strongly instrumental parts—developed after World War II. Much of the initial scientific development, and proof of concept, on which new analytical methods rest has also taken place in another US invention, that is, the "research university." The idea of governmental support for research carried out in universities (in the United States and elsewhere) has followed, in large part, from Vannevar Bush's enduringly influential report *Science, the Endless Frontier* (1). This

report justified government financial support of research in universities on the grounds that it contributed to three aspects of national well-being: health, jobs, and national security. It was, in that sense, a solidly utilitarian document. It has subsequently been interpreted to favor the idea of "curiosity-driven research." The notion behind this sometimes self-referential interpretation was never that utility was not important, but rather that it was best served by having university researchers unfettered by what were assumed to be the limited goals of solving practical problems, and thus encouraged to pursue ideas that industry might not pursue. In principle, this ambition is an inspiring one: Whether it works in the face of, for example, a reactionary peer review system, in times of limited budgets, is at best uncertain.

For a range of reasons, the assumptions fostering "curiosity-driven" research have become a matter of active debate. Because analytical chemistry has always bridged science and application (that is, understanding and use), this debate is especially relevant to it as a field. The alternative way of thinking about government sponsorship has been—probably most compellingly—argued by Stokes in his book *Pasteur's Quadrant* (2). This argument is that science and engineering—viewed as a whole—proceeds best by realizing that both understanding and application are important but, by themselves, incomplete. The best policy for research (both federally supported and commercial) is thus one that *combines* important but very difficult practical problems with the creation of scientific understanding that can make possible their solution. Currently, the National Science Foundation is responsible for supporting curiosity-driven research (how well it fulfills this responsibility is a separate issue), and the Defense Advanced Research Projects Agency is the exemplar of an agency whose policy is to couple science and technology.

"Science"-derived analytical methods are easy to identify: Examples include single-molecule spectroscopy, mass-spectrometric sequencing of proteins, ultrafast analytic methods, high-throughput biological analyses (of which genomic analyses provide an outstanding example), and electrochemistry with nanoelectrodes. Protein crystallography with synchrotron light sources, scanning probe microscopy, and green fluorescent protein as a marker of protein expression—these also are examples of analytical methods developing from curiosity-based science. What, for the future, are examples of larger-scale problems? I offer four, just to suggest an alternative class of problems for scientists with a strong background in chemistry and an interest in analysis. All these problems would fit within Pasteur's quadrant; that is, they have a very large societal impact, and solutions that will require new kinds of science. In all, analysis/measurement will be a key part of their eventual solution (if, in fact, we can *find* a solution).

2.5.2. Cost of health care: cost-effective public health versus high-technology, end-of-life medicine. Arguably the most important current financial problem facing the United States is the cost of health care. We, in the United States, have a model for health care that involves, inter alia, a focus on expensive, end-of-life treatment of symptomatic disease. In this model, targets are selected in large part (and for compelling financial and regulatory reasons) on the basis of their potential profitability (or return on investment), rather than for their social equity, or even their benefit to the patient. An alternative approach to health care focuses on models that are derived from public health, and thus, in principle, consist of cost-effective methods of health monitoring, epidemiology, prevention of disease, and anticipatory medicine. Although there are strenuous arguments about the costs and benefits of these two approaches, there is little disagreement that the current system, in terms of investment in new technology, strongly favors end-of-life health care: better genomics for cancer, or high-throughput screening for drug development, rather than measurements of immune status among children, or of particulates in urban air. Developing technology for modern epidemiology, point of care, and cost-effective medicine will necessarily focus on new analytical technologies. This problem is an enormous one, and is unfamiliar to many

academic researchers in its focus on "effectiveness" rather than on "academic fashion," but it is particularly rich in opportunities.

2.5.3. Understanding and managing the environment. Monitoring the global environment represents the second problem of enormous social significance, of acknowledged need, of an absolute requirement for new methods of measurement (and on a very large scale), and for new methods for managing data. It is also one in which the usual close collaboration between university-based analytical science and companies specializing in the commercialization of analytical methods may be problematic. This area, again, has the characteristic that successful analytical technologies will probably come from collaborations among the wide variety of disciplines, and to be successful, they must produce relevant information at a very low cost. Collaborative research in new areas is difficult to support in the current, conservative peer review system; and capitalist incentives are weak for inventing low-cost technologies.

2.5.4. National and personal security. The national defense sector has historically been one of the most productive sources of new technology, both in the United States and globally. Much of materials science, the technology for aerospace, the early phases of computation and development of what became the Internet, space technology, and many other areas were derived from the technological requirements of defense systems. Since the end of the Cold War (or perhaps between the end of the last Cold War and the beginning of the next), the needs for "measurement" have not declined, but the incentives have changed. Now, rather than using a very sophisticated satellite to watch the keel of a cruiser being laid down in a shipyard, we want a simple method or device to tell us if the white powder in the elevator is sugar or anthrax, whether a traveler in the airport has been handling ammonium nitrate, what the vaccination status is for the population of a city, who in a crowd has spent time in the Baaka Valley, and whether the nervous passenger on the subway platform has bad intentions. Many of these questions pose sophisticated problems in chemical analysis, and clever solutions (for example, the "artificial nose" and rapid diagnostics) represent initial responses to these problems; but after 25 years of research in microfluidics and portable analytical systems, there are still no satisfactory solutions.

2.5.5. The management of megacities. A "megacity" is a new phenomenon for science and society. Although its definition is still imprecise, one characteristic is a population of more than 50 million people with a very heterogeneous composition, including slums, manufacturing and business areas, and suburbs; systems for transportation, health care, and energy supply; and so on. The "management" of a megacity must ultimately rest on a web of analysis and measurement: quantity and quality of water, food, and power into the city; waste, effluents, and goods out of the city; and detection and management of disease, air quality, education, and endless other parameters. Again, these problems, taken separately, will tend to emphasize low-cost, out-of-laboratory solutions. More importantly, they must be in a form that can be integrated in real time by the city managers who must "drive" the city. If trends in population, and of movement from rural regions to cities, continue, most of us will live in very large cities in the future. The management of these new human constructs, and the analyses on which their management will depend, poses new and pressing problems for analytical chemistry.

These classes of problems—problems in Pasteur's quadrant—are no less interesting intellectually than are the problems of sequencing proteins by mass spectroscopy and of developing biomarkers for asymptomatic cancer. They are, however, very different in the type of technology they involve and in the way that they will attract the scientific and engineering talent, and the funds, they require. And they, as problems, will have an unfamiliar twist: Their solutions will have

the potential to be used on a large scale, and directly, to guide in formulating and implementing policy, and in influencing the quality of life of large numbers of people. Questions of separating meaning from data, and of justifying and supporting the validity of inferences drawn from data, will become much more relevant for these large-scale questions than they were for the much simpler problem of developing NMR spectroscopy for analysis of organic compounds. (The controversies around the data used in claims and counterclaims concerning "global warming" provide both an illustration of future controversies and a warning that analysis relevant to these sorts of problems is really *different*.)

2.6. Theories of Revolutions in Science

If one believes that analytical chemistry and "measurement" (and perhaps interpretation) will become increasingly important in the future as part of a rewriting of the social contract between university science and society, then, in principle, there is the possibility (and perhaps even the requirement) for revolutionary change in the field. Analytical chemistry (and chemistry in general) tends to modesty (in interesting contradistinction to physics and biology). But if analytical chemistry is to be an even more important field than it has been in the past, analytical chemists may have to raise their level of ambition, and consider how to guide the revolution.

There are many theories of revolution in science. The one most familiar to scientists is probably that of Thomas Kuhn, famously expressed in *The Structure of Scientific Revolutions* (3). This theory argues that revolutions occur only when there is no alternative, that is, when experimental measurements are no longer compatible with existing, accepted theory, and the only way to proceed, using the scientific method, is to formulate a new theory. Kuhn's argument is based on physics in the period of the early 1900s, when observations in spectroscopy and thermodynamics forced the development of quantum mechanics. This formulation of revolution in science, thus, applies to one part of the history of physics; how broadly it applies to other fields is up for discussion.

A second theory of revolutions—one that is perhaps more relevant to analytical chemistry than to physics—has no singular parent, but has been advanced by Freeman Dyson, Peter Galison, and others. This theory argues that revolutions in science occur when new analytical tools make possible new types of measurements. I am willing to believe that both descriptions of the origins of revolutions can be correct, but I think that the circumstances that lead to a Kuhnian shift in paradigm are substantially less common than those in which new fields of science come from new tools.

An argument for revolution in science based on the development of revolutionary tools for measurement and analysis (inter alia) is (to use a sporting analogy) a very soft pitch served up to analytical chemistry, and it should be one that deserves a fearless swing. But, of course, one must be thinking of a distant fence, and a home run, rather than a single that just drags out the inning. New science requires new types of analyses; new analyses also make it possible to raise new questions in science.

2.7. "Style" in Measurement and Analysis: From Rococo to Minimalist

Analytical chemistry—like every other field in science—has fashions, and fashions involve as much matters of taste and style as they do matters of substance. Dresses on a runway in Paris or London are generally not intended to be useful in working on the farm.

The question of style and fashion is, nonetheless, very important for the field: It strongly biases the choices of the peer review system, and thus enables (or disables) new fields; it influences the choices of research made by graduate students; and it ultimately strongly influences the "curiosity-based" research that will be available for the solution of applied problems. Consider four examples:

1. Detailed molecular analysis by NMR, MS (mass spectrometry), and X-ray crystallography. These techniques have made extraordinary progress in the past few decades; it is now routine to analyze molecules in detail that was fundamentally unknowable only a few years ago. The instruments required for these analyses are also very sophisticated, expensive, and specialized.
2. Biomedical imaging methods: imaging NMR, computer axial tomography (CAT), and positron emission tomography (PET). This set of techniques is interesting for its history. Although, of course, analytical chemistry played a critical role in the development of NMR spectroscopy, imaging NMR, like CAT and PET, developed largely outside of traditional analytical chemistry. Why? I do not know the answer, but speculate that the users who guided the development of these techniques were not chemists but doctors, and even though the resulting methods have fundamentally changed the way medicine is practiced, they have never been embraced by analytical chemistry. If the reason is that "imaging is not molecules," then the field may have difficulty in making the step to "imaging Mumbai" as a part of the management of megacities.
3. Scanning probe microscopy (SPM). SPM offers another interesting case study. It provides a perfect example of the Dyson–Galison doctrine that new tools provide the basis for revolutions in science. Scanning tunneling microscopy (STM) and atomic force microscopy (AFM) catalyzed the formation of the new field of nanoscience. Although the examination of small things was well established before the work of Gerd Binnig and Heinrich Rohrer, and although the electron microscopic methods used in these prior examinations were highly developed, the ability to "see" (or to have the computer generate images that appeared to make it possible to "see") individual atoms captured the attention of scientists across essentially all disciplines. Why was SPM developed in physics, rather than in analytical chemistry?
4. "Breath figures." My fourth example of style is almost embarrassingly simple by comparison with the three foregoing, and very sophisticated, examples. I wear glasses. When I want to clean them, I hold them near my mouth and exhale gently. The water vapor in my breath condenses on the cooler glass, and generates a field of small droplets of water that scatters light; smudges and fingerprints on the surface of the unwiped glasses appear as patterns in these droplets. And why does this primitive example deserve a place among the much more sophisticated examples that have preceded it? The answer is that sophistication and expense can be impediments in analytical chemistry, and a method that is very convenient and inexpensive will often do more to guide a field—especially a new field—than much more elaborate methods that are also far less accessible. Breath figures (also known as condensation figures) were an analytical technique that made patterns in monolayer-thick organic films [self-assembled monolayers (SAMs)] readily visible to the unaided eye, and were enormously useful in developing organic surface chemistry and especially contact printing of SAMs (where the printed pattern was recognizable in the patterns of breath figures, with no instrumentation at all!) (**Figure 1**).

2.8. Molecular Composition to Systems

So, if science is perhaps rewriting its social contract with society, analysis and measurement will be a crucial part of what society needs in the future. Analytical chemistry is in the business of analysis and measurement. What kinds of questions will it answer? "What is the pour viscosity of this lump of coal-tar pitch?" "What is the concentration of chromium in this sample of steel?" "How many compounds in a random collection of low-molecular-weight molecules bind to the insulin receptor?" "Is the wastewater from Mumbai clean enough?" "What fraction of the population of Haiti is immune to dengue?" "What is the composition of the atmosphere?" The possible questions

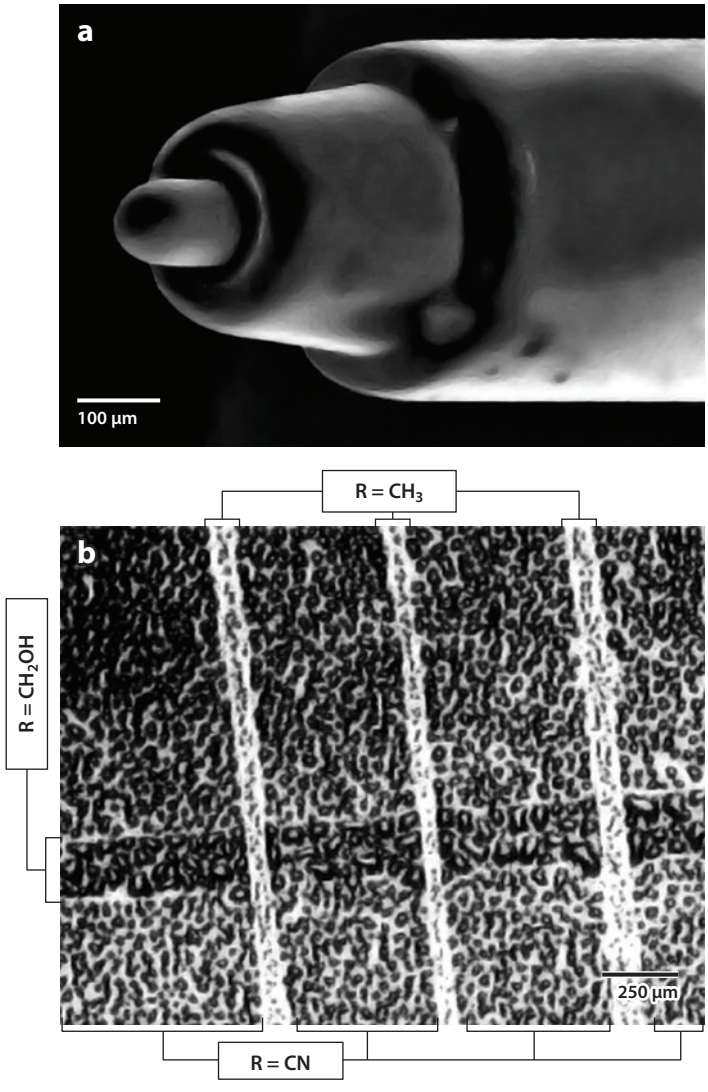


Figure 1

Imaging of features on surfaces by condensation figures. (*a*) Scanning electron image of a micropen used to write lines of self-assembled monolayers (SAMs) derived from $HS(CH_2)_{15}CH_3$ on a gold film. A micropipette was used to write a SAM derived from $HS(CH_2)_{15}CH_2OH$. The background, derived from $[S(CH_2)_{16}CN]_2$, was formed in the last step. (*b*) Optical micrograph of condensation figures of the patterns of SAMs formed from $R(CH_2)_{15}S$-($R = CH_3$, CO_2H, CN). Modified from Reference 4.

range from purely supportive and technical to broadly important questions that strongly influence human behavior and large-scale public expenditure and behavior.

The issue is whether analytical chemistry will focus on the important and technically challenging problems at which it has been historically so successful—that is, measuring compositions and structures of molecules—or whether it should aim to develop methods to measure, analyze, and interpret that are applicable to the broader problems of systems analysis and policy. The two classes of problems are different; both are interesting.

The old saw from business school is, "You can't manage it if you can't measure it." Analytical chemistry is in a position to make measurements that directly influence the management of large-scale societal concerns. To the question "Why bother? Molecular analysis is more than challenging enough, and we already do it well," four answers might be: "Other problems are more important," "With important problems come the resources to solve them," "Important problems can sometimes stimulate creative ideas in a way that familiar problems cannot," and "Taxpayers pay for your research, and you have an ethical obligation to give them back something for their money."

2.9. Data and the Meaning of Meaning: What Else Does Analysis Teach?

There is one other, very important, role that analytical chemistry has historically served in chemistry, that is, teaching students what a "measurement" is, and how to make one. At one time, physical chemistry and analytical chemistry shared this responsibility. As physical chemistry has concerned itself more with quantum mechanics than with more macroscopic subjects, its concern with teaching students how to think about data, statistics, and measurement has declined. E.B. Wilson's *An Introduction to Scientific Research* is now ancient history, although the lessons it taught certainly should not be.

One last story about my childhood: My first course in college was a course in analytical chemistry. The core subject matter was squarely along the lines of: "How much chromium is present in this sample of steel?" I remember nothing about most of it. The very first laboratory exercise, however, did forever change my view of science.

All weighing for the laboratory part of the course was done using a beautiful double-pan balance, together with tweezers, and a set of brass weights that snuggled in a wooden case with a blue velvet lining: very decorative! One was never allowed to touch the weights with fingers because fingerprints themselves had a weight, and because they also caused corrosion of the brass. The weights had nominal values, but their accuracy was insufficient for precision weighing: a 5-g weight plus two 2-g weights plus one 1-g weight did not exactly equal the weight of the 10-g weight. The task of the student was to develop a set of calibration factors for each weight that would give the "true" value of that weight. There was a fairly straightforward procedure for determining these corrections. Most of the students in the course claimed to have solved this problem in the first afternoon. I personally worked on it for the entire semester, and never got it right. To this day, I don't know why.

Why is this small failure in pedagogy important? The answer is that I have never, since, trusted data. The problem presented in calibration of weights was the simplest possible. Without question, there was an answer. The answer should not even have been all that difficult to get. And I couldn't get it. My response to this failure has been—I think, reasonably—to assume that if I could not solve even this simplest problem, then I certainly could not trust my solutions to more complicated ones. Even with this burden, I have carried on bravely with my career, and it has worked out reasonably well; but when a student comes to me with numbers, my first instinct is: "They're probably wrong."

Instilling a deep distrust of the accuracy of data has, for generations of students, been one of the great services of analytical chemistry. Unlike studies of metabolism, or of the fracture toughness of elastomers, in elementary analytical chemistry there *are* answers, and the answers are well defined. Instruction in analysis taught the manipulation and organization of data, and the standard methods of statistics (for example, calculating a mean value correctly, and understanding what a normal distribution and the central limit theorem might be; interpreting standard deviations and confidence limits)—all crucial parts of the foundation of being a scientist.

These issues—especially issues concerning the kinds of conclusions that one can draw from a given set of data—are unquestionably important in determining the composition of steel, but are

much, much more important in asking questions about the composition of the atmosphere, and the relationship, if any, between that composition and (to pick a small topic) climate instability. Part of the job of science is to help people who are not professional scientists—but who have the responsibility for using the information produced by science—to understand the difference between data, information, and meaning and uncertainty. Most students leaving undergraduate school (and many leaving graduate school) now have very little notion of these issues. And if their analytical courses do not teach them, then what will?

Parenthetically, a small but important sidelight on this issue comes from a discussion of the correctness of *most* of the results reported in science. The argument runs something like this: In the beginning of a new field, results are scattered, with possible results lying far from a true value. Outliers seem, of course, very interesting, and thus are selected by the peer review system and editors of fashionable journals for publication. As more observations in the field accumulate, the shape of the distribution becomes clearer, and results tend closer to the (uninteresting) null hypothesis—that is, reversion to the mean. The result is the slow evaporation of initially exciting results. All of that would be fine, except that the peer review system and editors (for different reasons) are not particularly interested in publishing smaller, more accurate results that might correct the larger, more newsworthy ones. The result is that a combination of ignorance of statistics, the competitive desire to be first, and a dislike for being proved wrong provides a kind of instability in published science. In purely technical matters, these instabilities are, in fact, corrected over time. The closer one gets to policy, however, the more abruptly (and sometimes difficultly reversibly) unreliable data can be converted into doubtful policy.

3. IDIOSYNCRATIC OBSERVATIONS: EXPLORING A LANDSCAPE IN SCIENCE THAT IS CHANGING RAPIDLY, SIMPLICITY AS A STRATEGY IN ANALYTICAL SCIENCE

Before writing this perspective, I read those from two previous volumes, both by good friends and wise scientists. Fred McLafferty (5) described—amazingly—the entire history of development of MS; Royce Murray (6) covered more than any individual could possibly know about the breadth of analytical chemistry, from the perspective of the editor of *Analytical Chemistry*. I make no pretense of understanding either the field or even a small subfield with a fraction of the sophistication of these scientists. In fact, I cannot claim to be an analytical chemist, only a constant user of the techniques created by analytical chemistry. I have also worked at the border between chemistry and other fields, from which comes my interest in broadening the scope of analysis and measurement. This type of research has, however, also made me an admirer of another theme in analysis, that is, *simplicity*. The most sophisticated analytical techniques tend to require specialization for their most effective use. As a nonspecialist, I need analytical techniques that let me get on with whatever I'm doing. Quickly! Failing rapidly is one hallmark of good science.

Let me describe a little of the history of my own research, and the importance of analytical chemistry in it, with an emphasis on two precepts: The first is that, particularly in exploring something relatively new—where you really don't have much of an idea of what you're doing—the analytical methods that guide the way most effectively are often those that are simplest, fastest, and least expensive. The second is that it helps to understand the fundamental, freshman-level science really, really well if you want to develop simple, intuitive, analytical methods. Each of the vignettes that follow has a point, and not all the points are the same, but these are the common themes.

3.1. Graduate School, and Retraining

I went to graduate school at Caltech. By happy—and complete—accident, I worked with Professor J.D. (Jack) Roberts. Jack Roberts was a physical-organic chemist, and one of the pioneers who first applied the techniques of physical chemistry to the messy problems of mechanism and structure in organic chemistry. He was there at the beginning of the use of isotopes in tracing mechanisms; he discovered benzyne; he helped to demystify nonclassical carbonium ions; he brought molecular orbital theory into organic chemistry; and he was one of the first to use NMR spectroscopy to solve real problems in organic chemistry.

After a certain amount of thrashing around as a new graduate student, I picked a problem in research that used proton NMR spectroscopy to study simple dynamical processes (initially processes involving Grignard reagents). NMR spectroscopy has always been a wonderful place to learn quantum mechanics, which I largely refused to do: The seductive characteristic of NMR at that time was that the correspondence between intellectually easy classical treatments (the Bloch equations) and the more difficult quantum mechanical treatments was sufficiently close that if you were lazy, you really didn't have to struggle with quantum mechanics.

But finally, I had to. After a few years, I finished my research, and had my first job lined up (in organic chemistry, at MIT), and wrote my thesis. All was well, until two months before I was supposed to teach my first course, when I realized that the thesis was completely wrong (because, of course, I had not learned quantum mechanics). In the end, it all worked out: I compromised by learning how to use density matrices; I threw myself on the mercies of Harden Connell's postdoctoral fellows (particularly Al Quiram); I finally got the analysis right. I particularly benefited from Harden's approach to chemical physics in general, and magnetic resonance in particular, which I remember as, "If you know what you're doing, you should be able to get it 80% right on the back of an envelope. Someone else can clean up the rest." A compelling argument for simplicity.

An important part of this period came from the spectrometers themselves: The first, commercial NMR spectrometers really did not work very well (in fact, they barely worked at all). Roberts had a very close collaboration with Varian (at the beginning) and Bruker (later). My earliest experiences were with spectrometers whose magnetic fields were largely unstabilized: One had only to put a tube of ethanol in the spectrometer, turn on the machine, and watch field drift scan the spectrum first from low to high field, and then from high to low, and then back again; it was most entertaining. The instrument broke easily, but was usually easily fixed with unsophisticated tools. Later spectrometers became more and more stable, and complicated, and the computers that manipulated the magnetic fields more and more magical.

Why is any of this relevant to the issue of the present and future of analytical chemistry? The answer is that these first, primitive, commercial instruments—instruments in which I could understand the details of how the machine worked, and learn what Fourier transform actually did—were enormously instructive. Very sophisticated instrumentation, controlled by very complex software, enables incredible feats of analysis, but may not be so good in teaching how analysis is developed, and what it actually means. This observation is not an argument for using other than the best instrumentation available. It is an argument for spending some time as one is learning how to do science in developing "first-of-its-kind" analytical methods in new fields, and also for remembering that teaching fundamentals—applied mathematics, statistics, control theory, spectrophotometry, equilibria, and rates—may ultimately be much more useful to students than training on the latest and most sophisticated widget. (I am endlessly bemused to talk to students and colleagues who use NMR, MS, and X-ray crystallography daily, and have literally *no* idea what a Fourier transform is! The Lamarckian propagation of intellectual blind spots cannot bode well for the future invention of new analytical methods.)

3.2. Surfaces: Heterogeneous Catalysis to Polymers to Self-Assembled Monolayers

After graduate school, I worked first in organometallic chemistry (where everything depended on VPC and NMR for analysis), and then in applied enzymology (where everything depended on liquid-phase chromatography and spectrophotometry), and finally heterogeneous organometallic reactivity (VPC and MS). We used what was available. But the progression was from solution (where many analytical techniques were available) to solid state and surfaces (where the techniques that were available were designed for other purposes). In this period, physical chemists interested in surface science (and, ostensibly and occasionally, in heterogeneous catalysis), developed a wonderfully sophisticated set of tools [Auger and X-ray photoelectron spectroscopy (XPS), various reflection-based optical methods, low-angle X-ray scattering] for surface analysis. The difficulty with these tools was that they were very expensive, and operated best in ultrahigh-vacuum (UHV) conditions; as a result, only a few laboratories could afford to use them. Also, they required that the students working with them attend almost full time to their multiple idiosyncrasies. Although we were interested in surfaces, our interest was focused on organic materials: polymers, organic liquids, adsorbed proteins, and ultimately, we hoped, living cells, rather than on nickel single crystals. For organic surface science, there were few really useful analytical techniques.

Lacking a better-formed idea, we took the physical-organic approach, and started with the simplest organic material that we knew, which was polyethylene (PE) film. To study the surface chemistry of this material, we needed to functionalize it. To know if we had functionalized it, we needed an analytical method. Our fundamental reaction consisted of treating PE film with a strong oxidant (chromic acid in sulfuric acid), which—the literature claimed—introduced carboxylic acid groups onto the surface, and generated a material we named polyethylene carboxylic acid (PE-CO_2H). Every physical-organic chemist knew that by starting with carboxylic acid groups, you could do anything. Although we ultimately put IR spectroscopy to some use, by far the most valuable guide to reactivity in this early work on organic surfaces was estimation (I hesitate to call it measurement) of contact angles. The surface of unfunctionalized PE film is very hydrophobic; the surface of PE-CO_2H film is hydrophilic. A drop of water—applied to a surface using a fingertip—either beaded or spread. (One could get more precise information by using a contact angle goniometer, but the increased precision did not increase understanding.) Treating PE-CO_2H with diazomethane generated a more hydrophobic surface, which we assumed (and later demonstrated) to be PE-CO_2CH_3. We developed an entire synthetic chemistry for PE-CO_2H based on bouncing between hydrophobic and hydrophilic surfaces, using contact angle as our guide!

The characteristic of these and similar experiments was not that they were very detailed, but that they were very cheap and very fast. Using them, we could do many experiments a day, whereas high-vacuum spectroscopy might take months or years to generate useful data. Everyone in the group had a fingertip, could apply a drop of water, and get a reasonable idea of the success or failure of an appropriately designed experiment in a minute or two.

Studies of PE-CO_2H and its derivatives demonstrated the power of the application of very ordinary ideas from physical-organic chemistry to organic surface science, and generated (quickly and easily) interesting ideas about reactivity; the surface of PE-CO_2H was, however, very heterogeneous, and this heterogeneity made any hypothesis difficult to test. We began to work on alternatives (for example, Langmuir–Blodgett films). These systems were also fragile, only partially ordered, and difficult to make. Everything changed in the early 1980s when Ralph Nuzzo—an ex-student, then at Bell Labs—visited one afternoon, and mentioned (with his usual scientific generosity and openness) a system that he and his colleague Dave Allara had characterized. This system was generated by exposing an evaporated gold film to a solution of an alkanethiol in ethanol

for a few minutes. Ralph and Dave had characterized the alkyl groups in the resulting system as being "highly ordered." And that work was, of course, the real beginning of the field of SAMs of alkanethiolates on gold.

3.2.1. Self-assembled monolayers of alkanethiolates on gold and silver. Ralph described the techniques he used to make SAMs, and we concluded quickly that the ease with which they could be prepared, the flexibility with which organic groups could be introduced into them, and the range of analytical techniques that could be used with them made them superior to other systems as substrates with which to study organic surface science. We quickly built a program based on studying their physical-organic chemistry (roughly, here, the relation between the structures of the molecules making up the SAMs and the chemical and materials properties of the SAMs). Ralph, Dave, and I (and exceptional students, especially Colin Bain and Paul Laibinis) collaborated productively in exploring these surfaces. Ralph and Dave did careful spectroscopy; we did organic chemistry and bioorganic chemistry. Because SAMs were so easy to make, and because the analytical methods that emerged were so straightforward, we could make rapid progress. This system—SAMs on evaporated gold, and sometimes silver, films—rapidly became, and remains, the standard for organic surface chemistry.

Interestingly, SAMs were so much more convenient, and so much less expensive to work with, than were clean metal surfaces in UHV, and so much more relevant to emerging questions in biological chemistry, that the attention of the community of surface scientists largely shifted to them. Again, however, the analytical techniques that worked particularly well in guiding the first, baby steps in this field were the simplest: Studies of wetting, as a function of pH, and as a function of the contacting liquid, were particularly informative. More elaborate and sophisticated techniques—surface plasmon resonance (SPR) spectroscopy, XPS, reflection absorption IR spectroscopy, electrochemistry—were invaluable in confirming results, but it is astonishing how much information was available in a contact angle, especially when it was combined with an understanding of the properties and reactivities of organic functional groups.

These early studies of SAMs provided an example of another kind of experiment that has subsequently become important, that is, "materials by molecular design." By changing the nature of the organic group at the position farthest removed from the surface of the gold (that is, at the position exposed at the surface), one could change not just wetting, but a range of related properties (adhesion, adsorption, biocompatibility, and others) that depended on the molecular-level structure of that interface. It was, thus, possible to go from *design* (at the level of molecules) to *properties* (at the level of macroscopic materials) in the time required to synthesize the required thiol. This ability, in many different forms, has proven remarkably useful in a wide range of applications in materials science.

3.2.2. Biochemistry: absorption of proteins on self-assembled monolayers, and "inert surfaces." One of the motivations for working with SAMs was that they provided an entry into organic surface chemistry that was potentially relevant to biochemistry and biology. Developing that opportunity required three new capabilities: (*a*) the ability to absorb proteins on SAMs noncovalently; (*b*) the ability to attach biomolecules (proteins, nucleic acids, and carbohydrates) to SAMs covalently; and (*c*) the ability to design and generate SAMs that were "inert" (that is, to which biologically relevant macromolecules would *not* adsorb). The first problem was easy. Most proteins adsorbed to hydrophobic surfaces (often by unfolding to expose their hydrophobic interiors), and methyl-terminated SAMs quickly formed a monolayer of adsorbed protein. The solution to the second problem was also easy, if messy. The carboxylic acid groups of carboxyl-terminated

SAMs could be activated using many of the standard procedures employed in synthetic organic chemistry, and the resulting active esters would react with the amino groups of lysine residues on the surfaces of proteins. The problem with this reaction is one common to much of protein biochemistry; that is, it is difficult to select *which* amino group reacts, and the resulting covalently attached monolayer of protein was thus a mixture. (Achieving position-specific linkage between the surface and a protein, without the labor of site-specific genetic engineering, is a problem for which there is still no general solution.) The third problem—that of generating an inert surface—was solved, in essence, by screening. The most successful solution involved the attachment of oligo(ethylene glycol) (EG_n) moieties to the surface, although a number of other, more complicated, groups also work, some possibly better than EG_n. The mechanism by which these surfaces resist the adsorption of proteins has been explored extensively by Michael Grunze and others using a range of techniques, and remains the subject of discussion.

The interesting characteristic of these studies is that the analytical methods used—at least those used to guide the synthetic procedures—were (as with many of the early developments in SAMs) relatively straightforward. The most useful technique in this area was SPR—another easy-to-use technique. The characteristics of the problem limited analytical techniques to those that could be used in situ. After an experiment (particularly one focused on either noncovalent adsorption, or on forming inert surfaces), it was not possible to remove the surface from solution and wash and dry it, given that these procedures could plausibly remove weakly adsorbed proteins; it was also not practical to remove them and *not* wash them, because deposition of protein and buffer salts on the surface on drying would be a complication. It was thus not possible to use many of the techniques so important with dry surfaces (contact angle, reflectance IR, XPS) with samples still immersed in a solution containing protein. SPR provided an ideal match of an analytical technique to a problem, however, because the adsorption of a monolayer of protein to the surface of a SAM produced a substantial change in the index of refraction of the medium immediately adjacent to that surface. Further, SPR simultaneously provided information about the kinetics of adsorption and desorption and about the equilibrium constant for adsorption. It was both operationally very simple and applicable to SAMs of any structure, and it required an acceptably small amount of protein. (It did not, unfortunately, provide any useful information about the structure of the adsorbed protein—another still-unsolved problem.)

These studies using SPR to characterize the adsorption of proteins on SAMs have evolved into equally useful procedures operating in reverse: For many applications in biochemistry, the best substrate to use in SPR is in fact one based on a SAM on gold. Similarly, by attaching functional ligands to the SAM composed mostly of a nonabsorbing group, using straightforward organic chemistry, it is possible to study the adsorption of proteins to ligands at interfaces, and thus to screen for protein–ligand interactions.

3.2.3. Pinholes in self-assembled monolayers: etching. A final example of the use of a "simple" method for characterization of SAMs concerns pinholes. Formation of a SAM is operationally straightforward: A glass or silicon wafer—supporting a thin film of evaporated gold or silver—is simply immersed in a solution (typically ethanolic) of the organic thiol to be absorbed. The early, schematic pictures of SAMs were highly idealized: The substrate was considered atomically flat, and the organic monolayer—typically an *n*-alkanethiolate—was an extended, two-dimensional crystal. In fact, the structures of these surfaces are much more complicated: The metal film is rough and irregular on the atomic scale; there may be impurities absorbed on the surface; and there are almost always particles of dust that deposit on the surface. The result is that the SAM has disordered regions and pinholes. How does one detect these defects?

Electrochemistry provided one approach, and was thoroughly explored by Crooks, Chidsey, and others. The *n*-alkanethiolates are insulating; defects in them allow access of electroactive species in a solution to the metal surface, and thus can be inferred through measurement of currents in redox reactions. Studies of electrochemistry make it possible to infer many characteristics of SAMs, and have been extensively and productively used for that purpose. One of the simpler methods of detecting defects, however, is, again, operational: One reason we wished to have low defect densities was to improve the utility of SAMs as resists in microcontact printing. In that application, their function is to protect the metal from an etching agent. The failure of the SAM to protect against etching is then the basis for a defect, but also the basis for an analytical method. The most sensitive method for detecting pinholes (or at least, pinholes relevant to microcontact printing) was to use a two-step process: In the first step, exposure of a SAM on gold, and supported on a silicon wafer, to an etchant generated a small hole in the metal film where there was a pinhole in the SAM; in the second step, subsequent exposure of that system to a solution that etched silicon produced a large pit, easily detected by electron microscopy.

3.2.4. Serious instrumental methods applied to self-assembled monolayers. I emphasize the value of simple analytical methods, especially when combined with an understanding of chemical reactivity and the properties of materials, as a guide to research in a new area. This emphasis downplays the enormously important role that more sophisticated types of surface analysis have played in organic surface science. Reflectance IR methods, especially reflectance adsorption IR spectroscopy using polarized light, were absolutely indispensable in improving the order (or, perhaps, the existence) of highly ordered regions in SAMs. SPR has been especially important in biological studies, in which the SAM must remain in contact with aqueous solution. Ellipsometry, XPS, second-harmonic generation, HREELS (high-resolution electron energy loss spectroscopy), and SFG (sum-frequency generation) have all provided invaluable information. XPS and electron microscopy have also been useful, and TEM (transmission electron microscopy) has provided one of the first demonstrations of multiple types of ordered phases in the SAM; both suffer, however, from the fact that thin organic films rapidly become damaged on exposure to high-energy radiation or particles. Electrochemistry has both contributed to the characterization of SAMs (and especially, heterogeneity in them) and provided the basis for analytical methods that use electroactive SAMs. SPM has, perhaps surprisingly, not been as useful as one might have expected: SAMs are not conductive, and thus are not good substrates for STM; AFM has been extremely useful in characterizing the overall roughness of surfaces supporting SAMs, but much of that roughness comes from the metal film rather than the SAM, and the information is thus only indirectly useful. In the hands of artists—for example, Paul Weiss—scanning probe methods have generated important information, especially about ordered regions of SAMs.

3.3. Microcontact Printing and Micro- and Nanomolding

In principle, SAMs—as flat, relatively homogeneous, films—were excellent substrates for studies of a variety of physical-organic studies of organic surface chemistry. In practice, they were used primarily in detailed studies of wetting and related subjects. Partly to examine the influence of heterogeneity on wetting, and partly as a step into lithography (**Figure 2**), we developed methods to pattern SAMs on surfaces.

3.3.1. Microcontact printing. The earliest of these methods—initially explored by Nick Abbott—involved forming patterns by physically scratching a SAM, and then forming a second

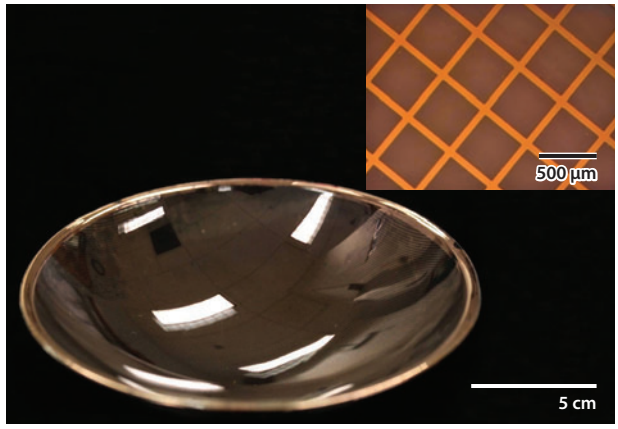


Figure 2

Grid of 100-µm gold wires printed on a curved surface. Microcontact printing was used to form a layer of a protective self-assembled monolayer; then, the unprotected gold was removed by etching. Photograph by NanoTerra. Modified from Reference 7.

SAM, with very different wettability, in the scratches. A more successful, and more flexible, technique originated as an accidental result of a sabbatical spent by Manoj Chaudhury in our laboratory. At that time, Manoj worked with Dow Corning, and had extensive experience with silicone elastomers; his visit introduced these exceptionally useful materials into the laboratory. A series of experiments carried out by Amit Kumar, Hans Biebuyck, Younan Xia, Dong Qin, and others developed a remarkably simple technique that introduced micrometer- (and ultimately submicrometer-) scale bas-relief patterns into the surface of a slab of poly(dimethylsiloxane) (PDMS). (These experiments were really the beginning of what is now known as "soft lithography.") "Inking" this topographically patterned slab with an organic thiol, and using it to print that thiol onto the surface of a gold film, formed patterns of SAMs. Immersing a patterned surface into a solution of a second alkanethiol filled in the spaces not covered by the first SAM. The analytical question in these experiments was: "How do you know what has happened?" Using imaging spectroscopic methods to answer this question would have been possible (and these methods ultimately *were* useful); for exploratory work, however, they were too slow, complicated, and expensive to guide research.

The most valuable early methods for imaging patterns in SAMs relied on condensation figures, and on studies of wetting. Both revealed, rapidly and inexpensively, patterns in the hydrophobicity of a surface, and could be used—often in conjunction with simple microscopy—to judge the fidelity of pattern transfer. The results of these studies could be confirmed spectroscopically through function (for example, by observing patterns of adhering cells), or by destructive methods such as etching. Condensation figures were, however, remarkably accurate for survey experiments.

3.3.2. Micro- and nanomolding. The PDMS stamps used for contact printing also served another type of function: as molds. Rather than printing with their exposed surfaces, their declivities provided the basis for molds that could be used in forming topographically structured polymers. Both optical microscopy and electron microscopy were useful in characterizing these structures, but an interesting problem—also requiring a new analytical method—emerged, for example, determining the ultimate limit to the size of the structure that could be replicated using this type of technique.

One motivation in trying to address this question came from another technology, that is, photolithography. Photolithography makes possible the fabrication of microelectronic devices. It

is an immensely important technology, and one that was (incorrectly) thought to be nearing its limits of resolution in the 1990s. The much-heralded "end of Moore's law" prompted development of alternative methods of making small patterned features. The limits of the sizes of features that can be generated using photolithography is determined, ultimately, by diffraction; molding is limited (perhaps) to smaller features by van der Waals interactions, and has the potential to provide very small features. It thus seemed to be relevant to the future of photonics, and perhaps microelectronics. (In practice, the engineers responsible for the development of photolithography have carried this technique to feature sizes far, far smaller than I, or most other people, would ever have thought possible. The technology required to do so is, however, extraordinarily expensive, and although the end of Moore's law may be at features with dimensions less than 10 nm, soft-lithographic molding has proven important in fields other than fabrication of CMOS devices.) The initial technical issue in exploring the ultimate limits to resolution in molding was analytical: What test does one use to measure replication of three-dimensional structures with feature sizes less than 20 nm, especially if one does not wish to move to electron- or particle-beam writing, and a high-quality clean room?

A simple solution made rapid progress possible: taking a silicon wafer, and introducing a crack into it that progressed only partway through the wafer, generated a test structure—a step in the surface of the wafer—that decreased from an easily detectable 100 μm at the edge to 0 μm when it melted into the uncracked surface of the wafer. Replication of this step into PDMS, followed by the replication into polyurethane and comparing the images of all three features by AFM, demonstrated the ability of nanomolding to replicate the step height at a value of less than 0.5 nm; this demonstration was subsequently confirmed by replicating single steps on the face of an inorganic crystal (**Figure 3**). (The exact meaning of this demonstration remains, however, obscure, because the measurement confounds the shape of the step with the shape of the tip of the AFM, and exceeds the resolution capability of this—or probably any other currently available—analytical technique.) This test does, however, provide another example of the usefulness of simplicity.

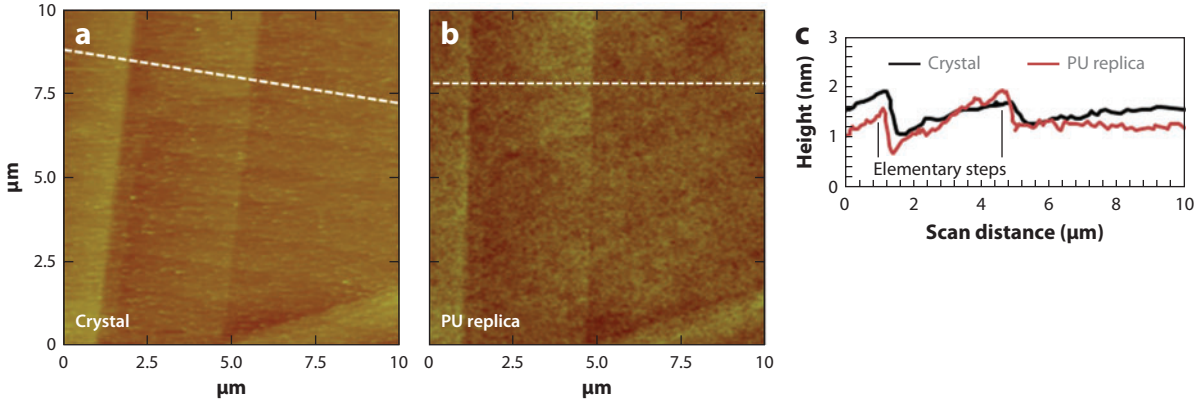


Figure 3

Replication of elementary steps (3–5 Å in height) that define the minimum separation between crystalline layers in the lattices of calcite. (*a*) Atomic force microscopy (AFM) image of a calcite crystal. (*b*) Polyurethane (PU) replica of the region shown in panel *a*. (*c*) Height profiles and root-mean-square surface roughness measured by AFM for calcite crystal and PU replica surfaces. In the AFM images, the white dashed lines indicate the location of the line scans reported in the corresponding height-profile plots, where the elementary steps are indicated. Modified from Reference 8.

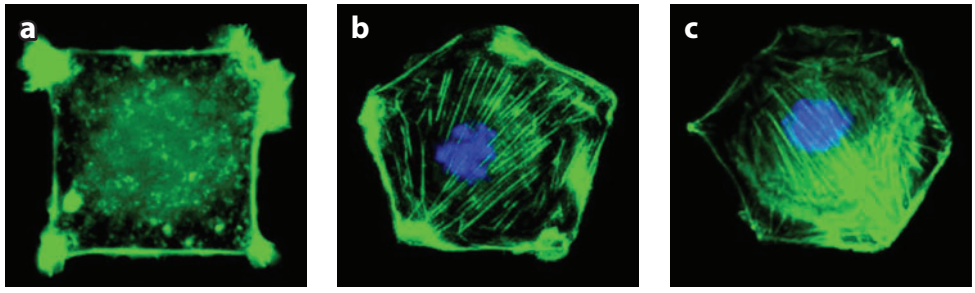


Figure 4

(*a*) Images obtained by fluorescence microscopy of a cell spread on a square 30 × 30 μm island; the cell was stained for F-actin with fluorophore-labeled phalloidin. (*b*,*c*) Cells confined to a pentagon and hexagon (with areas of 900 μm^2) were stimulated with PDGF and stained with phalloidin and 4′-6-diamidino-2-phenylindole to visualize F-actin (*green*) and nuclei (*blue*).

3.4. Cell Biology and Self-Assembled Monolayers

An early application of patterned SAMs—in combination with inert surfaces that resisted the adsorption of proteins involved in the patterning of attachment of cells—was to force mammalian cells attached to a surface to adopt unnatural shapes. The ability of a mammalian cell to attach and spread on a surface depends upon the attachment of peptides, or adsorption of proteins, presenting specific amino acid sequences (most commonly, GRGD) on that surface; inert surfaces—surfaces terminated in EG_n moieties—would resist the attachment of these peptides or proteins, and thus prevent cellular attachment. Initial exploratory experiments carried out with Don Ingber demonstrated that combining microcontact printing, SAMs, inert surfaces, and simple techniques in cell biology could produce patterns that caused mammalian cells to adopt shapes (e.g., squares and triangles) that allowed tests of the relationship between the shape of cells and their phenotypic behavior (**Figure 4**). For example, the ability to use soft lithography to restrict mammalian cells on a surface to the shape of a square of predetermined size made it possible to examine the influence of the area of attachment on the propensity of the cell to undergo apoptosis (programmed cell death). On large squares, cells would divide; on small ones, they would die.

This technique provides a unique capability to cell biology. It has, however, resulted in only modest further development, for a reason intimately related to analysis: Using patterns formed by microcontact printing, it is possible to influence the shape of the cell and the area of its contact with the surface. A cell is, however, an enormously complicated entity, and the amount of information about it, and control over it, that can be obtained just by changing its contact area or shape is limited. Thus, although cell biology seems an enormously promising area for application of patterned, molecularly controlled organic surfaces, it has proven difficult to ask usefully focused questions using such surfaces. The capability provided by SAMs has not, so far, been that required by cell biologists.

3.5. Electrical Properties of Self-Assembled Monolayers: Charge Transport by Tunneling

A second area of research involving SAMs that illustrates the limitations imposed when good assays are not available has to do with studying charge transport across them. This subject is a part of a broader interest in the subject of so-called molecular or organic electronics. The underlying motivation for this field was that silicon-based electronics was considered to be approaching

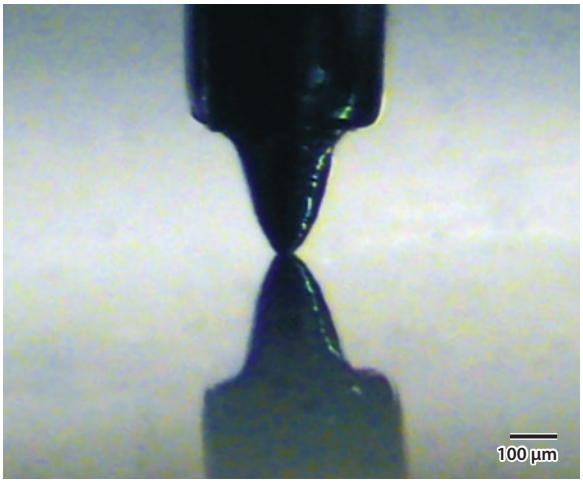


Figure 5

Microscopic image of a conical tip of eutectic gallium-indium alloy (EGaIn) contacting a self-assembled monolayer supported on a silver film. The tip (*top*) is imaged by reflection in the silver (*bottom*). A thin film of Ga_2O_3 maintains the shape of the tip. Photograph by Hyo Jae Yoon. Modified from Reference 9.

physical limits imposed by (inter alia) heterogeneities in the electrical properties of the structures in the semiconductors—particularly the channels—making up transistors. The possibility that single organic molecules might serve as channels through which to transport charge was exciting, and SAMs seemed to offer test systems with which to examine this possibility. Following initial reports of remarkable phenomena ostensibly involving charge transport by tunneling across SAMs, a very substantial amount of research was devoted to developing these organic structures as test beds. SAMs are, however, physically delicate, and the techniques used to fabricate the top electrodes that form a junction from a SAM supported on gold or silver often used procedures such as evaporation of metals onto them; this procedure, not surprisingly, damaged the SAMs. These measurements also generated an entire zoo of artifacts (due to, for example, thin metallic filaments formed by electromigration in the very high electrical field gradients used for measurements, disordered organic structures presumed to be ordered, displacement of the SAM from the surface by solvent or other molecules used in the fabrication, and others). Most of the initial, exciting measurements have never been reproduced.

After a decade of research, several groups are now generating reproducible measurements by using top electrodes formed by very careful metal evaporation, and by using nondamaging contacts based on graphene, mercury, and (perhaps) electrically conducting polymers. Ryan Chiechi and Chris Nijhuis developed a system whose top electrode is the eutectic alloy of gallium and indium (EGaIn), which now seems to us to be the most convenient for physical-organic studies (**Figure 5**). The results from these different types of measurements are still not easily comparable, and the field has not yet coalesced into one in which there is a general agreement concerning the best type of analytical measurement (or even what "best" might mean; that is, that would provide the best balance between convenience, cost, ease of making statistically significant numbers of measurements, contact area, and interfacial chemistry and properties).

Whether SAMs or other organic films ever become an important part of electronics is presently an open question: They have the advantages of being easily designed and engineered at the molecular level, but have substantial disadvantages in terms of stability and ease of patterning into scales

required for current electronic systems. The issue of practicality aside, however, charge transport by tunneling in organic matter is an important subject for a number of other areas (especially for electron-transport pathways in biology), and the availability of good test systems to understand the fundamental physical and biophysical chemistry of these systems could make a substantial contribution to understanding the flow of energy, and certain types of chemical reactivity, in cells. The major impediment in the development of this field—and one that has held it up for almost a decade—has been the absence of assay systems sufficiently simple and reproducible to allow different laboratories to produce data that can be compared directly, and used to build a common understanding of the processes involved.

3.6. Biophysics: From Elementary Interactions to Development of Drugs

I have chosen to focus most of this discussion on analytical systems that are important for organic surface science, and particularly for SAMs. More briefly, however, I would like to touch on two other subjects that raise questions about analysis and measurement: The first concerns an important, but particularly puzzling, topic in biophysics—the hydrophobic effect—and the second is a project whose objective is to develop low-cost diagnostic systems for use in the developing world, and in applications related to point of care.

The hydrophobic effect is the name given to the exclusion of hydrophobic substances from water: It (whatever it is) is the reason that olive oil and gasoline do not dissolve in water. The hydrophobic effect is centrally important in biochemistry: The folding of proteins, the formation of lipid bilayers, the formation of structured nucleic acids, and many other molecular processes in biochemistry depend upon hydrophobic interactions for significant (and often dominant) contributions to their free energy. The question is: "What is the hydrophobic effect, and what is its mechanism?"

The mechanism of the hydrophobic effect has been a confused and controversial subject for more than 50 years. It is unusual—and perhaps unique—in that it intimately involves water, and water is a liquid like no other. The association of hydrophobic surfaces involves a balance between enthalpic and entropic terms, and can only be interpreted in terms of detailed information about the interface between them. The thermodynamic terms are estimated, experimentally, from isothermal calorimetry (ITC); the biostructural information comes from X-ray crystallography, NMR spectroscopy, and ideally the combination of the two. Why, given the power and the availability of the techniques that are now available, has determining the mechanism of the hydrophobic effect remained so difficult?

The answer is, in large part, that the analytical techniques are still not good enough, and that they do not answer the most important question. ITC has eliminated many of the artifacts associated with van 't Hoff analysis (the class of calorimetric methods previously used to obtain most thermodynamic descriptions of association constants). Unfortunately, the sensitivity of ITC is still too low to provide the information needed when substances have low solubilities, and when only small quantities (as with proteins) are available. X-ray crystallography has become enormously more accessible—almost, in fact, routine in some applications—as a result of high-intensity beam lines located at synchrotrons. X-ray crystallography of proteins has the weakness, however, that it provides only marginal information about the locations of water molecules, and the hydrophobic effect is centrally concerned with the structure of water in the active site and around the ligand. NMR spectroscopy, although enormously useful in helping to define the conformational mobility of the proteins and ligand, also provides little information about water.

There are two separate and quite distinct lessons to draw from the problem of understanding the hydrophobic effect.

1. The first lesson concerns analytical technology. Water is the most important liquid that we know; all of life occurs in water; the hydrophobic effect—an interaction central to the molecular events in life—does not occur in the absence of water; and molecular recognition in biology may depend more on the properties of the water than on the properties of the proteins and ligands. Given all of these arguments for understanding water, we still do not have the analytical tools to answer the most basic questions about the physical chemistry, structure, and interaction of water with dissolved biomolecules. The techniques that are most useful are complex and expensive; new, simple techniques to analyze the characteristics of water in new ways could make an enormous difference in our fundamental understanding of this remarkable liquid.
2. The second lesson has less to do with analyses of the hydrophobic effect per se, and more to do with the value that analytical chemistry provides (when it is properly taught and used) in understanding how to think about measurement and analysis. Thermochemistry is intrinsically difficult. No amount of instrumentation or robotic handling will reduce calorimetry in biochemical systems to a black box (although commercial calorimeters are designed to simulate just that effect!). Analytical and physical chemistry are the only subjects that can teach the management and interpretation of data at the level required to produce meaningful results in a subject of this experimental difficulty. X-ray crystallography and complex techniques in NMR spectroscopy can also be used in a mode in which the investigator can generate data without fully understanding either the principles of the techniques or the uncertainties in the results they produce. Understanding whether an apparent "blob" of electron density in a crystallographic map corresponds to a molecule of water, or an artifact of the Fourier transform, requires a sophisticated understanding of the basis of the techniques.

3.7. Low-Cost Diagnostics: Analytical Chemistry in Its Most Stripped-Down Form

My last example from our own research concerns a problem that is—for the first time in this review—explicitly "analytical chemistry." The United States has a highly evolved medical system, in which diagnosis plays a critical part. Diagnosis, of course, involves consideration of many factors, but one is the set of results obtained from diagnostic tests. These tests can range from simple examinations of blood chemistry, through expensive and sophisticated analyses of genome sequences and protein biomarkers, to imaging. Diagnostics contribute, directly, to less than 20% of the cost of health care, but their results influence a larger fraction of expenditures, since diagnosis determines treatment.

Health care in the developing world presents a different set of problems than in the economically developed countries. In the former, everything is in short supply: money, doctors, refrigeration, clean water, medical supplies, and so on. Diagnostics must be very inexpensive; very easy to use; and appropriate to the needs, characteristics, and oddities of the medical and public health systems of those countries. Interestingly, however, medical systems in the developed and developing worlds share one common characteristic. Both need low-cost, simple systems: in the United States, to reduce the costs of health care and to enable point of care testing; in the developing world, to provide minimal but necessary information to health-care workers.

In 2007, we started a program whose objective is to produce diagnostic systems that minimize cost. The strategy that we follow is to start with an intrinsically low-cost material and low-cost methods of manufacturing (paper, and ultimately, reel-to-reel printing). We generate a series of channels in hydrophilic paper using hydrophobic, printed boundaries, and then use these channels to distribute biological samples from the point of collection (for example, a port onto which is

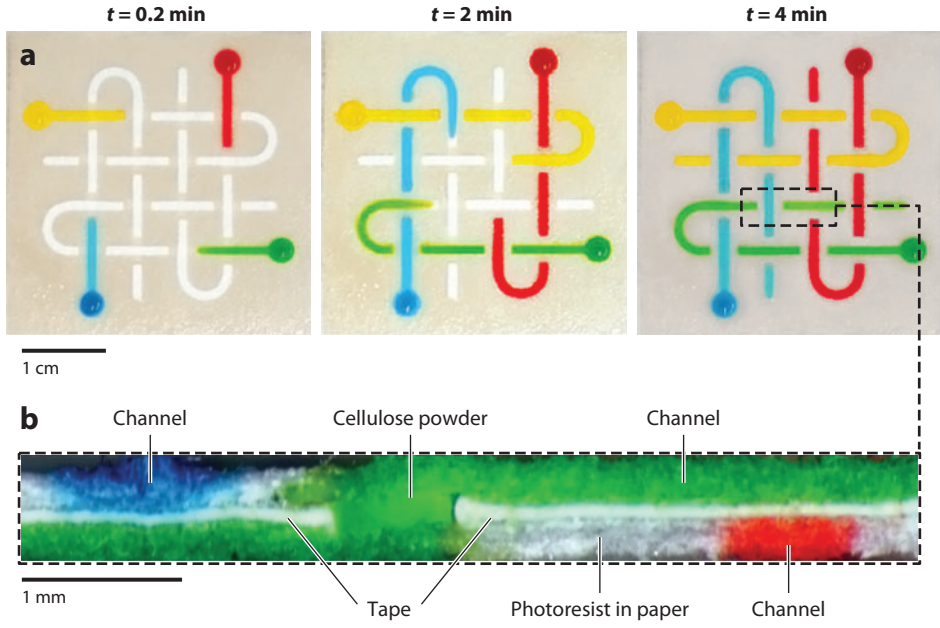


Figure 6

Three-dimensional microfluidic paper-based device demonstrating the principles used in constructing paper-based analytical devices (μPADs). (*a*) A three-dimensional paper chip with four channels that cross, each in a different plane, without mixing fluids. (*b*) Cross section of the device shown in panel *a*. The device is made from two layers of paper patterned with hydrophobic lines and one layer of double-sided adhesive tape. Channels patterned in the paper wick aqueous solutions of dyes in the plane of the paper, and holes cut through the tape provide contact points between adjacent layers of paper. Modified from Reference 10.

applied a drop of blood) to test zones where colorimetric or electrochemical assays can be carried out (**Figure 6**). The requirements for a very low-cost technology have been very stimulating both technologically, in forcing us to think about paper and printing as plausible systems for bioanalytical devices, and scientifically, in requiring information about wicking, fluid flows, and chemical properties (stabilities of proteins and reagents, rates of reaction) in porous, hydrophilic media. These problems are all interesting, but I bring up this program to illustrate two different points concerning the value of thinking about simple, low-cost systems (as opposed to analytical systems relying on synchrotrons or incredible feats of electrical engineering and optics) as still a part of analytical chemistry.

3.7.1. Objective. We do not think of our project in paper diagnostics as primarily a project in academic bioanalysis, with the main objective being to publish papers. Instead, our intention is to try to develop techniques that will actually appear in the hands of patients and physicians in a short period of time. Trying to provide health-care services in the developing world, and being forced—by the characteristics of that problem—to consider science and technology that we would almost certainly not otherwise consider, is a Pasteur's quadrant problem. Without thinking about cost, simplicity, feasibility of transmitting information through cell phones, stability, manufacturing, clinical testing, and other factors in designing the program, there would be little chance that it would succeed in reaching users in any plausible time. By thinking "simple," it was possible for our collaborators in Diagnostics for All (a not-for-profit company founded to carry out the

development of working technology from our simple prototypes) to introduce paper chips into field trials in 2012 (a short time by the standards of bioanalytical chemistry). The rapid progress of this program is a small example of a different way of thinking about research in analytical chemistry, in which the objective is to contribute to the solution of a problem that is much more complicated than a problem in chemical analysis, rather than to generate a "publishable result."

3.7.2. Community building. A second aspect of this project that rests on its strategy of simplicity is its ability to attract other researchers. "Paper diagnostics" (as the field has come to be known) is—as far as making the paper-based microfluidic systems is concerned—easy to learn and easy to do (developing the biological tests that provide function in diagnostic devices is substantially more demanding and complicated, but also, at least, clearly defined in terms of their technical requirements). It is, thus, straightforward for other research groups to define for themselves parts of this problem that are interesting, and to which they can contribute. We have no illusion that, as a single research group, we can make a significant contribution to solving a problem of the degree of difficulty provided by health-care diagnostics for the developing world. If we can develop a system whose simplicity and flexibility attract others, and that system nucleates and helps to create a substantial community of researchers—from analytical chemistry, from public health, from diagnostics, from paper technology, and so on—who are interested in this common problem, it is possible that we will make progress; without a community, we will not. "Simplicity" is not just a technical issue; it is also a strategic idea that contributes to the formation of groups of scientists, technologists, and users, and provides a common focus.

4. LOOKING FORWARD

4.1. The Good News: There Is No Shortage of Problems That Require Analysis

The Complication: Many of Them Are Not What We Have Called "Analytical Chemistry." In a sense, and as with so many things, it all comes down to ambition, ability, fashion, incentives, and style. "Measurement" and "analysis" are very broadly important; analytical chemistry is also important, but more focused and specialized. The tools developed by analytical chemistry can be generalized to a broad range of problems; substantial contributions to those problems, however, may require thinking about the strategies for research, and the design of experiments, in different ways. I offer examples from three areas.

4.1.1. Problems where "function" is important, not "molecular structure." One important set of opportunities for analytical chemistry lies in areas where chemical analysis is only a small part of a bigger problem. *Biomedicine*, for example, is a problem of enormous breadth and importance, and one with many important problems in analysis, of which most have never been fashionable in analytical chemistry. The first, and most familiar, involves the sorts of analyses—of molecules or binding constants, of rates of reaction—routinely carried out in bioanalytical laboratories. The second includes the types of analysis and measurement required in more difficult activities such as those involved in the development of new drugs. Here, the broad problem is to produce a compound that safely and effectively treats a disease. Analytical chemistry is, of course, already a part of this process. The pharmaceutical industry, however, does not really understand the complex interactions between a drug and a patient, or more broadly, how to develop a drug that is safe and effective in patients, cleared by the FDA, reimbursable, and accepted by physicians and patients. The chemical view of drug development has tended to be biased by the perspective of synthetic chemists, that is, that synthesizing and testing of drug leads are the key parts of the problem, and the

activities that occur after that are important, but "not chemistry." Perhaps, but these downstream activities are more difficult than the simple identification of leads: Binding assays, high-throughput screening, and combinatorial methods are a small part of developing a drug. Problems centered around so-called ADME/PK/PD (adsorption, distribution, metabolism, excretion, pharmacokinetics, pharmacodynamics), and the very difficult issues associated with translation of results from animal models to heterogeneous populations of humans, are much more important. What, exactly, are the *analyses* that are needed to measure these biological functions, and who should/will develop them? These problems will obviously require chemical analyses for their solutions, given that most matters in biology involve molecules interacting with one another. Understanding the entire complicated process in drug development, in enough detail to contribute new and more useful measurements using existing types of assays, is, however, the real challenge. Meeting this challenge will require analytical chemists to know much more than analytical chemistry, and developing "human-on-a-chip" technology, or predicting the response of individual patients to treatment, will require cell biology, genomics, biomaterials science, bioengineering, physiology, and analytical chemistry, and it may or may not be led by analytical chemists.

The second problem characteristic of biomedicine is that the development of analyses will probably, in the future, increasingly invert the usual process used in chemistry. Analytical methods have tended to be "science forward." That is, new analytical methods have evolved from new discoveries in science. In biomedicine, however, and particularly in clinical medicine, doctors lead. Understanding what information doctors would find useful, and translating that understanding into new analytical methods, requires an understanding of medicine *as it is practiced* that leads to types of research that are quite different from those most commonly used in chemistry.

A third problem, particularly relevant now in medicine, is cost containment; this problem will provide many opportunities for new types of analysis. It is, I believe, entirely possible that many bioassays that are now in widespread use will be discarded as cost-ineffective (and even potentially harmful to patients: Immunoassay for prostate-specific antigen to screen for asymptomatic prostate cancer provides an example). There will be many older assays that must be reworked into less expensive formats, and new assays will have completely different cost constraints if they are to be adopted. All assays will have to be designed to transfer information efficiently into systems for storage and use in public health. Thinking about research projects in bioanalysis in terms of cost and information will require a new type of planning for research projects.

4.1.2. Materials and materials science and engineering. A second area of opportunity for chemical analysis—and one that will also require new approaches—is materials science. Again, a characteristic of this area is that its principal concern is with function, and molecules and chemistry are important only to the extent that they influence function. Structural materials provide an example. The delamination and failure of epoxy composites are a matter of great interest to (for example) the airframe and automotive industries. The toughness of a composite structure under load, or on impact, is the result of a set of chemical events, beginning with the syntheses of monomers used to synthesize polymers, and ending with the rupture of bonds. What types of analyses can we contribute to understanding this chain of events in a way that would allow composite parts to be produced more economically, and to function more reliably? This question has been clearly defined for 40 years, but progress in answering it has been slow and largely empirical. To make progress requires an interest in the entire problem, and a focus on function rather than chemistry.

The example of composites illustrates—in a well-defined case—a problem that chemical analysis faces. Relevant analyses will certainly have a molecular component (for composites, mass

spectroscopy of the fragments evolved on laser-stimulated desorption from a fracture interface may be helpful in defining why failure occurred, for example), but the molecular component is relevant only to the extent that it helps us to understand "function." It is still analytical chemistry, but in the context of a larger and much more complicated problem.

It is straightforward to list many other areas in which relevant questions will involve the same focus on function. Lifetimes-to-failure in organic electronic components; biocompatibility, and mechanisms of biodegradation of implanted synthetic materials and structures; failures in large-scale manufacturing; performance of organic elastomers in soft robots; fouling of membranes in desalination equipment; the fate of CO_2 dissolved in seawater; corrosion of catalyst supports and separators in fuel cells—the list is almost endless! The focus of these problems is, however, almost always functional rather than molecular. Learning to "think functionally," and both to integrate chemical analyses with (for example) structural analyses to solve functional problems, and—more importantly—to design entirely new types of analyses that combine the chemical, structural, and functional into practical methods to solve difficult problems in complex systems, will require new ways of thinking about "analysis."

4.2. Systems

A second, major, new class of opportunities for chemical analysis lies in its potential to help manage large systems. Again, the list of opportunities is long, and includes managing energy systems, understanding biomedical outcomes, managing megacities, and monitoring climate. These are enormous problems, to which any specific technical discipline can contribute only a small amount. Analytical chemistry has something to contribute to all of them. The analyses that are most relevant to these problems, however, are not necessarily going to be the types that make the best and most highly cited papers in scientific journals. How, for example, does one measure—ideally at zero cost—the spectrum of pollutants carried by a river flowing through a megacity? How does one measure changes in pH of an ocean on a fairly fine-grained grid, ideally at zero cost? How does one tell if taking baby aspirin starting in adolescence decreases the incidence of Alzheimer's disease in old age, ideally at zero cost? What is the rate of errors in the analytical methods used in forensics and criminal justice? What are the changes that occur in the human brain during depression? The thinking that goes into this kind of analysis is quite different from that to which we are accustomed as academic chemists.

4.3. Big Data

A third set of problems emerging for analytical chemistry includes those that will be posed by "big data"—the enormous sets of data, with variable and often uncertain provenance, and with difficult-to-determine accuracies and biases, that will emerge from areas such as environmental monitoring, management of energy, and discovering correlations in public health by aggregating information in heterogeneous databases in genomics, individual personal medical histories, and large-scale studies in epidemiology. A few fields—astronomy, genomics, economics, high-energy physics, for example—have begun to wrestle with the multitude of problems that these tsunamis of data will pose. Particularly if analytical chemistry extends its scope to reach into areas such as systems analysis or biomedical outcomes, understanding how to work with them will become both an opportunity and a difficult and important problem. Understanding how to prepare students to work in them will also require rethinking what, and how, we teach.

4.4. Teaching and Learning: Which Babies Must Be Thrown Overboard?

As society generates more and more information—some of it derived from chemical analysis, and thus, at least in part, from analytical chemistry—the question of what one *teaches* to enable students to deal competently with this mass of information becomes more and more complicated. Simply dealing with the myriad of sophisticated tools now used for chemical analysis already requires more time than students have, or the curricula allow; what happens when one adds, for example, the additional information required to think about biomedical outcomes, big data, the systems analysis of flows of pollutants, or the analytical aspects of city management? It seems impossible: "It can't be done! There isn't enough time!" And yet, we do have to decide what to include in the course time we do have, and in the time spent in postgraduate education. The choice will probably depend on matters of opinion: Does one teach a narrow and deep course in a specialized subject to instill technical rigor? Does one teach with much greater breadth to give perspective and to enable the student to learn more effectively on his/her own as the career develops? Regardless of the answer, every teacher will probably have to abandon favorite subjects.

What would my choices be? I think I would favor breadth, but breadth in hard subjects. My experience is that the student who understands the design of experiments; statistics, applied mathematics, physics, and chemistry that support major methods of analyses; electricity and magnetism; and biochemistry can learn the details of a specific instrumental technique. A student who knows the instrumental technique in great depth, but little else, is more limited. (It is also easier to learn difficult, mathematical subjects when you are younger than when you are older!)

5. CODA: ANALYSIS OF THE CHEMISTRY THAT DETERMINES "FUNCTION" MAY BE TOO IMPORTANT TO BE CALLED "ANALYTICAL CHEMISTRY"

Perhaps we need a new name? Perhaps the issue of a name is not important, because analytical chemistry has already migrated into many fields: biophysics, applied physical chemistry, condensed matter physics, chemical engineering, clinical analysis, biochemistry, and any number of others. Still, having a sense of whether the *subject* of the field is really "the basics of measurement of physical phenomena, the management of data, and the extraction of information and meaning appropriate for specific uses," or "how to do high-quality analysis of protein sequence and structure" is important. Both are essential, but they are different.

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