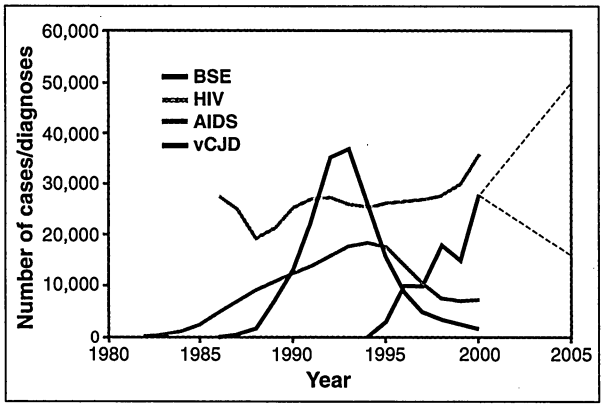
The longer the IPD, the greater the number of people with infections who would have died from other causes before progression to vCJD (*1*). Third, the investigators make use of the only other aspect of the case data: age (the mean age at death is 28 years). The distribution of ages is interesting; it appears constant with time. If the risk of infection and rate of progression were constant with age, then the age distribution should be increasing. However, it is impossible with current data to determine which of these aspects is age-dependent, and, again, inclusion of age effects can only be unsupported speculation. Finally, because all cases so far are of one particular genotype (which represents about 40% of the UK population), any predictions can only pertain to this subpopulation.



Life in a time of epidemics. Diagnoses in the UK (1980 to 2000): BSE (cases by year of confirmation), HIV (diagnoses per year × 10), AIDS (diagnoses per year × 10), and vCJD (diagnoses per year × 1000). The dotted lines show the range of predictions from (*1*) × 1000. Note that the upper 95% confidence limit is essentially exponential.

This situation contrasts with predictions of the recent foot and mouth disease (FMD) epidemic in the UK (*4, 5*), and the BSE epidemic in sheep (*3*). There are more data for these infections (largely derived from experimental infections), and, in the case of FMD, the IPD is well understood. The complications come in defining the infection function. Kao *et al.* (*3*) can predict with some accuracy the time period of the BSE epidemic in sheep (which is IPD dependent), but the predictions of the size (which depend on transmission) are very variable. Again, the lack of data is the source of uncertainty. However, even in the case of FMD, where data are abundant, it is probably wiser to stick with relative rather than absolute predictions of the effects of control measures.

There are several sensible approaches to solving these problems. The first is to ignore the unknown and treat epidemics as statistical processes (*9*). With this strategy only short-term predictions are reliable, and at the beginning of the epidemic the number of infected individuals is usually exponentially increasing. This approach does provide an upper bound to all predictions (see the figure).

The second approach is to extend and complicate the analysis by including additional information that reduces (rather than increases) variability. Present analyses of vCJD assume that the risk of infection is homogeneous, that is, all individuals are at equal risk (apart from the classifications of genetics and age). However, inclusion of risk heterogeneity can potentially reduce uncertainty in absolute predictions, as well as indicate relative incidence between groups. For example, under the (unproven but widely held) assumption that the BSE agent was transmitted by ingestion of infected food, individual variations in diet may be informative (*10, 11*). Similarly, rates of progression are known to increase with dose, so that heterogeneity in degree of exposure could also be informative (*12*). However, until risk factors for infection and progression are identified and the data exist to define their distribution in the general population, inclusion of heterogeneity in risk is unlikely to reduce uncertainty in prediction.

Consequently, predictions of the vCJD epidemic will continue to be plagued by wide confidence intervals. The current epidemic in the UK is a large cohort study: When the vCJD epidemic is over, we will perhaps have a good estimate of the IPD. If there is subsequently an epidemic in another population, we will have the data to enable more accurate predictions to be undertaken.

So are predictions worth the effort? I believe that they are, but not for the numerical values. Their intrinsic importance lies in developing an understanding of the processes underpinning these epidemics, and in providing an external validation of this understanding—if the predictions turn out to be wrong, we have to ask why. Valleron's qualitative prediction (*2*) that the age distribution will become bimodal is intriguing and more valuable than the number of predicted cases that they present. We should also watch how predictions change as case data are accumulated—encouragingly, each new prediction seems to have a lower upper bound.

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PERSPECTIVES: MATERIALS SCIENCE

Putting Metals into Polymers

Ian Manners

The valuable physical and chemical properties of many solids can be attributed to metallic elements. Examples include magnetic materials used in data storage, superconductors, electrochromic materials, and catalysts. It has long been recognized that incorporation of metal atoms into the one-dimensional chains of synthetic polymers may also lead to desirable properties. However, synthetic difficulties with creating macromolecular chains in which metal atoms act as a key structural component have slowed progress in the field (*1*).

Over the past decade or so, these synthetic difficulties have been overcome through the discovery of ring-opening polymerization and metal-catalyzed polycondensation methods. Substantial progress has been made toward the generation of hybrid metal/polymer materials with novel and useful properties (*1, 2*). Self-assembly is emerging as a powerful tool to create supramolecular metal-containing polymeric structures. This approach helps to create self-organized, functional materials whose properties complement those of purely organic systems.

The first metal-containing polymers were materials with metallic substituents in polymer side chains (**1**) (see the first figure) (*3*). Related polymers with Os complexes attached to the polymer side chains (**2**) have recently attracted attention. Electron transfer between electrodes and the relatively inaccessible redox centers of enzymes can be slow, hindering electrochemical detection processes. Thin films of Os polymers can be used to mediate electron transfer or "wire" enzymes

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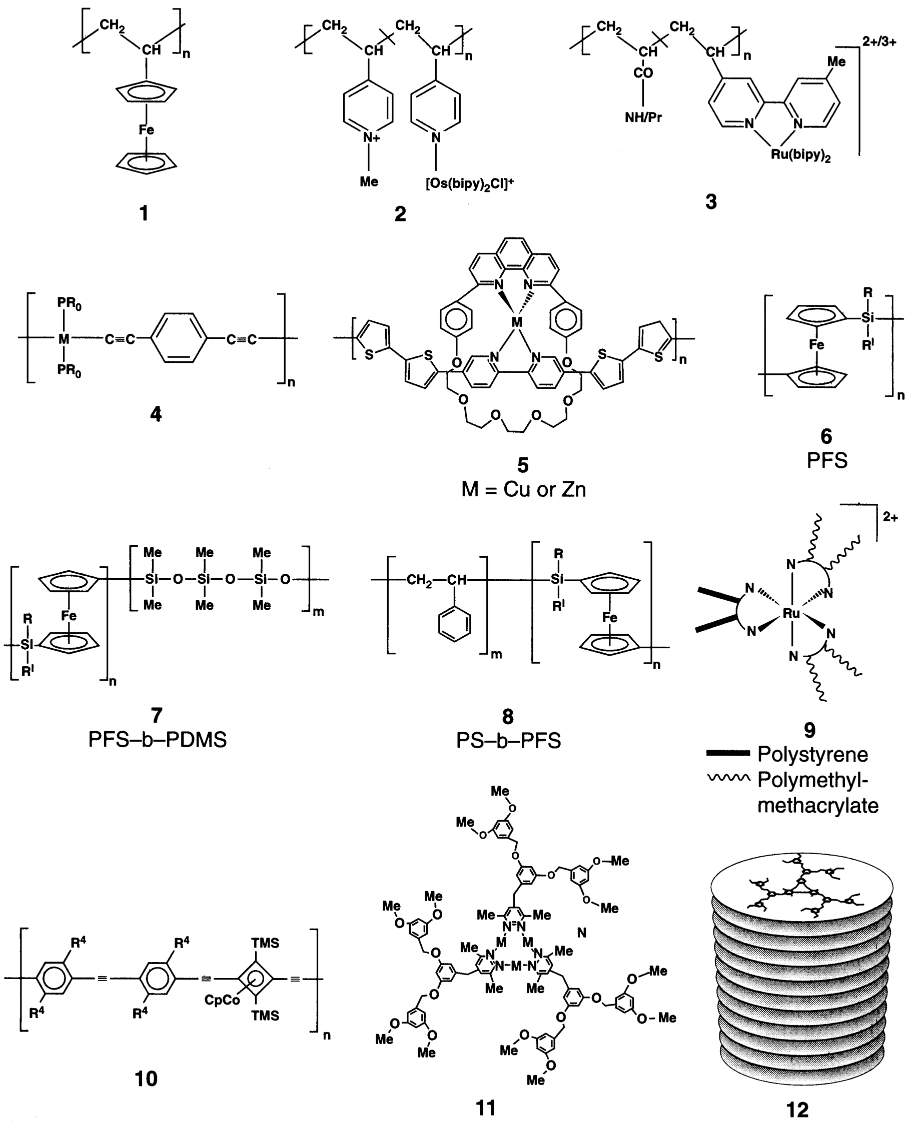
The author is in the Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, M5S 3H6, Canada. E-mail: imanners@chem.utoronto.ca



Structures of polymers, molecules, and self-assembled materials.

such as glucose oxidase to electrodes. Such systems have allowed the creation of glucose sensors. Enzyme-based devices containing related Os polymers are able to detect a single base pair mismatch in an 18-base oligonucleotide (*4*).

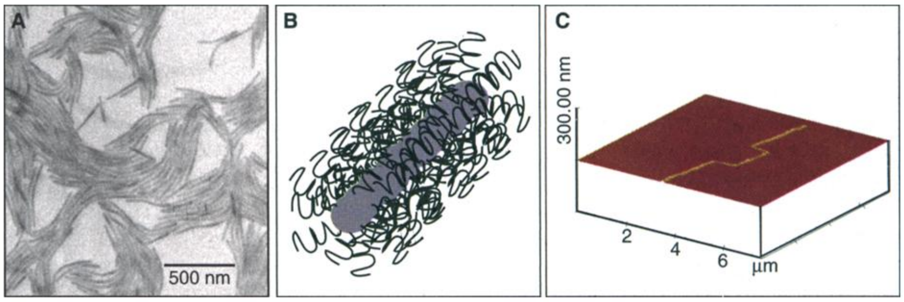
Similar polymers with Ru complexes (**3**) have been used to create self-oscillating gels, which may be used for example in pulsatile drug delivery devices. In contrast to conventional gels, the Ru polymers swell and contract periodically at constant temperature without need for external stimuli. The oscillatory Belousov-Zhabotinsky reaction is used to drive the swelling and deswelling, which occurs as the Ru center fluctuates in oxidation state and hydrophilicity between Ru^{3+} (green) and Ru^{2+} (orange) (*5*).

The discovery of electrically conducting organic polymers has led to increased interest in macromolecules in which metal atoms are inserted into a conjugated carbon framework. Rigid-rod polymers (**4**) with metals such as Pd and Pt in the backbone were first developed in the late 1970s. The structural diversity has now been expanded to include elements such as Fe and Rh (*3*). These systems exhibit liquid crystalline ordering in solution and have interesting nonlinear optical properties. In addition, materials such as **5** offer potential for metal-ion sensing based on enhanced conductivity (*6*).

Ring-opening polymerization methods have enabled the synthesis of metallocene-based polymer systems such as polyferrocenylsilanes (PFSs) (**6**) (*7*). These organometallic materials are easily processed. Pyrolysis yields nanocomposites containing magnetic Fe clusters; the magnetic ceramic retains the shape of the PFS precursor. The size of the Fe nanoparticles can be controlled through the pyrolysis temperature, allowing the magnetic properties to be tuned from superparamagnetic to ferromagnetic (*8*). Such materials may be useful for data storage or electromagnetic shielding applications. PFS materials also show promise as precursors to electrostatically charged microspheres, as protective charge dissipation coatings, and as sensors that detect changes in refractive index in the presence of an analyte (*9*, *10*).

Anionic ring-opening polymerization methods permit PFS block copolymers to be formed. For example, the diblock copolymer material **7** contains a polydimethylsiloxane (PDMS) coblock (*11*). The material dissolves in hexane, a selective solvent for the PDMS block, to yield cylindrical micelles (see panel A, second figure) with a PFS core surrounded by a PDMS corona (panel B). The structures are sufficiently stable to permit deposition onto substrates. Deposition in grooves fashioned by electron beam lithography followed by plasma etching results in oriented, 10- to 20-nm-wide ceramic lines (panel C) with potentially interesting conductive or magnetic properties (*12*). Ceramic structures with such small dimensions are very difficult to fabricate with other currently available lithographic techniques.

Other block copolymers have also been prepared. For example, **8** contains an organic polystyrene (PS) coblock. Thin films of these materials phase separate, leading to periodic nanoscale domains of PFS and PS (*11*). Because PFS is more etch resistant than PS, such films can be used for patterning substrates



Toward nanometer-scale ceramic structures. (**A**) Transmission electron microscope image and (**B**) the structure of cylindrical PFS-b-PDMS micelles. (**C**) An oriented ceramic line on a silicon wafer derived from oriented cylindrical PFS-b-PDMS micelles via hydrogen plasma etching.

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such as cobalt. With this approach, arrays of magnetic nanodots with potential applications in data storage can be obtained (*13*).

Several other materials containing metallic units within potentially self-assembling polymer architectures are also being pursued. Star-shaped block copolymers with metal cores (**9**) have been prepared by controlled polymerization methods. These materials should exhibit rich and interesting supramolecular behavior (*14*). Block copolymers containing main chain and side chain nonmetallocene coordination complexes have been developed and are of similar interest (*15–17*).

Supramolecular self-assembly is not limited to metal-containing block copolymers. For example, Co polymers **10** form liquid crystalline phases in solution, whereas lamellar and irregular honeycomb-shaped morphologies have been identified in the solid state (*18*). Weak metal-metal interactions involving the heavy transition elements Cu, Ag, and Au have been used to guide the self-assembly of cyclic building blocks (**11**) into luminescent, superhelical fibers based on stacked structures (**12**) (*19*).

Metal-based polymers are emerging as interesting and useful materials. Further synthetic breakthroughs are still needed, but with the immense structural diversity and range of properties and intermolecular interactions made possible by the presence of metallic elements, supramolecular metallopolymers will be a particularly fruitful area of future research.

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PERSPECTIVES: ATOMIC CLOCKS

Raising the Standards

Patrick Gill

From the Global Positioning System to international timekeeping standards, accurate clocks play a fundamental role in science and technology. The higher the frequency of the oscillator used in the clock, the higher is the clock's accuracy. Quartz clocks operate at frequencies in the megahertz range, whereas atomic clocks are based on microwave absorptions in the gigahertz range. At the Sixth Symposium on Frequency Standards and Metrology, held from 9 to 14 September 2001 at the University of St. Andrews, Scotland, researchers presented tantalizing evidence for atomic clocks based on optical absorptions. These "optical clocks" offer even higher accuracies, providing a tool for better timekeeping and improved tests of the fundamental laws of physics.

The symposium opened with a review by N. Ramsey, regarded by many as father of modern frequency standards. In 1949, he developed the separated oscillatory field technique, in which an atomic absorption is probed by two pulses of radiation separated in time or space to give improved spectral resolution. This approach is still applied to both microwave and optical atomic frequency standards and underlies the atomic fountain (*1*).

In an atomic fountain, laser-cooled atoms are launched up a meter or so and fall back under gravity. In the process, they pass twice through a microwave probe region. Interference between the two time-separated probe fields allows the microwave absorption signal to be subdivided to provide higher resolution, achieving typical absorption features of ~1 Hz width. Cesium fountains of this kind are currently the most accurate clocks in the world. Some of these, together with slightly less accurate nonfountain clocks, comprise the international group of clocks that define Coordinated Universal Time (UTC), the official world time.

State-of-the-art fountains (A. Clairon, Laboratoire Primaire du Temps et des Fréquences, Paris) achieve clock frequency uncertainties of about 1 part in 10^{15} after averaging for a day or so but are eventually limited by small shifts in the center frequency of the absorption due to collisional perturbations between the cold atoms in the fountain. It should be possible to reduce this uncertainty to a few parts in 10^{16} for cesium and to 1 part in 10^{16} for cold rubidium fountains, which are affected much less by collisions.

For even faster clocks, we must go beyond microwave atomic clocks to optical clocks. A standard based on an absorption of much higher frequency (~10^{15} Hz in the optical, compared with ~10^{10} Hz in the microwave) but a similarly narrow experimental spectral width of ~1 Hz is much more monochromatic. The achievable frequency stability is proportional to the monochromaticity (or Q) of the absorption, so optical clocks promise better standards.

Direct optical analogs of the atomic fountain have not yet been demonstrated. Two groups have reported good progress (*2*, *3*) toward a neutral atom optical clock based on the weak Ca absorption at 657 nm, despite the relatively large natural linewidth of this absorption. Katori (University of Tokyo) (*4*) described the cooling of neutral Sr, which has a highly "forbidden" and hence very weak absorption at 671 nm with megahertz natural linewidth. Several groups plan to observe this high-Q transition in an optical fountain.

A high-Q optical frequency standard may also be achieved by probing a weak "forbidden" absorption in a single laser-cooled ion held in an electromagnetic trap. Experimental absorption linewidths for different trapped ion candidates discussed at the symposium include mercury (*5*), strontium (*6*, *7*), indium (*8*), and ytterbium (*9*, *10*). Most of these ions have "forbidden" absorptions with limiting natural linewidths between 0.1 and 3 Hz, offering Q values of ~10^{15}. Bergquist and co-workers (*5*) have achieved a linewidth of 6.7 Hz in Hg^+, not much above its natural width. Tamm *et al.* (*9*) have demonstrated a linewidth of 30 Hz for the 435-nm Yb^+ absorption. Other species have smaller natural linewidths but experiments have not yet reached these levels. In particular, the natural linewidth of the extremely weak Yb^+ 467-nm absorption is orders of magnitude below 1 Hz (*10*). In this case, the experimentally achievable linewidth will be limited not by the natural linewidth but by the probe laser linewidth.

The potential use of these high-stability optical absorptions as frequency standards

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The author is at the National Physical Laboratory, Teddington TW11 0LW, UK. E-mail: patrick.gill@npl.co.uk