In retrospect

Sixty years of living polymers

In the 1950s, the discovery of a class of 'living' polymerization reaction revolutionized the field of polymer science by providing a way of controlling the molecular-weight distribution of polymers. The effects reverberate to this day.

GARY PATTERSON

One of the triumphs of modern polymer science is the exquisite control that synthetic chemists have achieved in the design and execution of polymerization reactions[1]. A key concept on which this control is based was discussed 60 years ago by Michael Szwarc[2] in a classic paper in *Nature*. He reported 'living' polymerization reactions, in which each addition of a monomer to a growing chain is irreversible and, when the pool of monomers is exhausted, the ends of the polymer chain remain active so that further chemistry can take place. Szwarc's findings have been applied to a wide range of polymerizations, and are responsible not only for major industrial applications, but also for advancing the theory of polymer science[3].

In the early 1950s, typical laboratory polymerizations produced a mixture of molecules of different chain lengths because the reactions were reversible — monomers could detach from polymer chains, rather than irreversibly adding to them, and random termination reactions could occur, preventing further chain growth and causing even broader chain-length distributions. Theoretical considerations suggested that many of the properties of polymers depend on both the average molecular chain length and the chain-length distribution. Polymer scientists therefore required samples that were both well characterized and of controlled length to test fundamental theories. Early efforts to carry out such evaluations required extremely tedious fractionations of polymer samples to obtain appropriate test materials. The idea that irreversible polymerizations would produce polymers that have narrow molecular-weight distributions had been proposed by the chemist Paul Flory[4] in 1940, but little progress towards such reactions was made until Szwarc's paper appeared.

Szwarc received his degree in chemical engineering from the Warsaw University of Technology in 1932, but wisely chose to emigrate to Israel in 1935, before the start of the Second World War. He received his PhD in organic chemistry in 1942 from the Hebrew University of Jerusalem. In 1945, he joined the research group of Michael Polanyi — a polymath who made great contributions to physical chemistry — at the University of Manchester, UK, earning another PhD in physical chemistry in 1947, and a DSc in 1949. He joined the faculty as a senior lecturer, but then moved to the United States in 1952 to become professor of physical chemistry and polymers at the New York State College of Forestry in Syracuse. The University of Manchester was the pre-eminent place for research in polymers in Britain during the period Szwarc was there, and he was determined to continue this research at Syracuse.

Good things happen when a truly prepared mind is exposed to an otherwise disappointing result, and so it was for Szwarc. He heard reports of an 'unwanted' polymerization reaction that occurs between the radical anion of naphthalene and the monomer styrene (a radical anion is a compound that bears both a negative charge and an unpaired electron; in this case, the electron serves as an initiator for the polymerization reaction). Further studies by Szwarc found that the initial product of this reaction is another chemically active radical anion that reacts irreversibly with more styrene to produce an intriguing polymer. This reactive polymer was indefinitely stable when stored in a dry, oxygen-free solvent, but the active chain ends could be terminated — chemically inactivated — at will by adding a little moisture. This is the kind of polymer envisaged by Flory in 1940.

The realization of a chemical route to a living polymer produced a flurry of research[5], and many different polymers with narrow molecular-weight distributions were produced. Polymer physicists (such as myself) were thrilled, because it allowed materials to be prepared that could test our theories. But Szwarc realized that synthetic organic chemists would be even more pleased, because a different monomer could be added to the

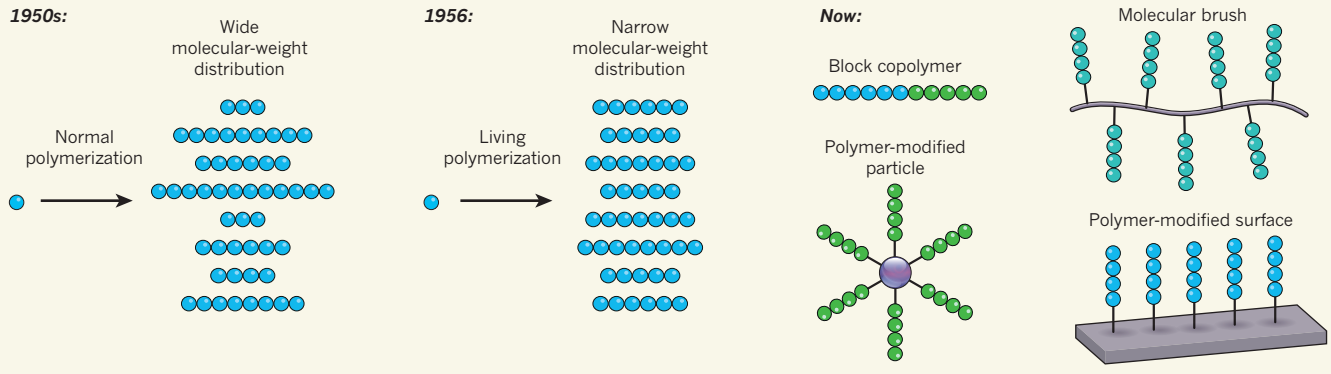

Figure 1 | Living polymerization reactions allow control of polymeric structures. In the early 1950s, most polymerization reactions produced a mixture of molecules of different chain lengths — a wide molecular-weight distribution. In 1956, Szwarc[2] reported a 'living' polymerization reaction that allowed much greater control of the products, and which therefore yielded a much narrower molecular-weight distribution. Living polymerizations have since been used to make a wide array of polymer structures, including block copolymers (which contain more than one type of monomer), molecular brushes and polymer-modified particles and surfaces.

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living polymer to produce a block copolymer: molecules that contain long, uniform runs of different monomers.

Block copolymers have become major commercial successes — for example, the whole field of thermoplastic elastomers is based on this technology. Thermoplastic elastomers are rubbery solids that, unlike conventional rubbers, can be reused by heating them to temperatures above their glass transition temperature, remoulding them and then rapidly cooling them (the glass transition temperature is the range of temperatures in which amorphous materials pass from a liquid state to a hard, glassy substance). Apart from block copolymers, a dizzying number of other polymeric molecular structures engineered by living polymerization are also now available (Fig. 1). Szwarc received international recognition for the synthetic aspect of his work when he was awarded the Kyoto Prize for advanced technology in 1991.

A development that was greatly aided by the routine availability of polymers with a narrow molecular-weight distribution was the scaling theory that allows many polymer properties to be expressed in terms of molecular weight. For example, in 1950, Flory and Thomas Fox determined an equation[6] that accurately expressed the glass transition temperature as a function of molecular weight. The improved polystyrene samples available after 1956 confirmed this prediction[7].

A crucial property of pure liquid polymers is their viscosity. Flory and Fox discovered[8] that, for high-molecular-weight polymers, the viscosity increases in proportion to the molecular weight raised to the power of 3.4, and they proposed a theory to explain this finding. This means that, even well above the glass transition temperature, such polymers can have a high viscosity and behave like a soft solid. That may seem an obscure finding, but it has practical applications — such as the polymeric 'solvent' used in advanced batteries that do not leak. Again, Szwarc's discovery allowed Flory and Fox's theory to be validated.

One of the theoretically most challenging issues in scaling theory was the molecular-weight dependence of the osmotic pressure of polymer solutions. This is of interest because many industrial polymers are used in solution, and because biologists require an understanding of naturally occurring polymer solutions. The physicist Pierre-Gilles de Gennes correctly intuited[9] that, because linear polymer chains in solution are 'swollen' by the solvent, the osmotic pressure will have a different molecular-weight dependence from that predicted by classical theory. Measurements[10] of osmotic pressure for solutions encompassing wide ranges of concentration and molecular weight confirmed de Gennes' predictions. Both Flory and de Gennes received a Nobel prize for their work in polymer science and condensed-matter science, respectively.

Many theoretically challenging issues remain to be solved in polymer science, and the synergistic relationship between theory and the availability of well-defined polymer samples will greatly aid this effort. For instance, rubbery materials are widespread in industry and in biology, yet the theory of rubber elasticity is yet to be fully validated. The chemistry of living polymers also remains a highly active area[11], with hundreds of investigators worldwide. Many synthetic routes to living polymers have been developed, and a wide range of monomers can now be used in this approach. The concept of living polymers has truly revolutionized the practice of polymer science. ■

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HUMAN GENOMICS

A deep dive into genetic variation

The exome is the portion of the genome that encodes proteins. Aggregation of 60,706 human exome sequences from 14 studies provides in-depth insight into genetic variation in humans. SEE ARTICLE P.285

JAY SHENDURE

Just seven years ago, my colleagues and I reported the protein-coding DNA sequences, called exomes, of 12 individuals[1] — among the first to be produced with a new generation of sequencing technologies[2]. Exome sequencing is much less expensive than whole-genome sequencing and, for cancers and Mendelian disorders (the latter caused by mutations in single genes), there is much more disease-associated genetic variation in the exome than in the rest of the genome. On page 285, the Exome Aggregation Consortium (ExAC) and collaborators[3] report the exome sequences of 60,706 individuals, collected from diverse studies: a venture 5,000 times larger than our initial study.

The current work highlights the pace at which human genetics is being scaled up. The project is almost ten times bigger than the Exome Sequencing Project (ESP) reported in 2013 (ref. 4), which was an important forerunner of ExAC. Indeed, this may be the deepest dive into the well of human genetic variation so far.

The study and accompanying database are noteworthy on several counts. First, for the sheer number of individuals sequenced and the depth of coverage — that is, the number of times each nucleotide in each individual's exome was sequenced. In the recently completed 1000 Genomes Project, 2,504 genomes were shallowly sequenced[5], a cost-saving strategy that favours the discovery of common over rare genetic variation. By contrast, each exome in ExAC has been sequenced deeply. Consequently, even genetic variants observed in just one individual can be confidently considered to be real (Fig. 1).

More than half of the approximately 7.5 million variants found by ExAC are seen only once. But collectively, they occur at a remarkably high density — at one out of every eight sites in the exome. For each gene, the authors contrasted the expected and observed numbers of variants that cause the production of truncated proteins, to search for regions containing lower-than-predicted levels of protein-truncating variants. This allowed them to identify several thousand genes that are highly sensitive to such variants — that is, unable to function normally after loss of one copy of the gene, even if the other copy is intact. Most of these genes have not yet been associated with disease, but mutation probably leads to embryonic death or strongly affects fitness in some other way. These genes are also intolerant of variants in regulatory DNA sequences that markedly alter levels of RNA synthesis from the gene[6], and are more likely than other genes to be implicated in genome-wide association studies of common disease.

The second noteworthy achievement of the research is that it provides a glimpse

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