New approaches to biomaterials design

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The adoption of combinatorial and computational methods in biomaterials design is a highway towards the discovery and realization of tailored polymeric materials to satisfy the specific requirements of many diverse biomedical or prosthetic applications.

Biomaterials are the backbone of the medical device industry, a critical element of health care. Ever since the development of stainless steel in 1929 opened the path for the implantation of the first artificial hip, advances in materials science have fuelled breakthroughs in the design and use of artificial body parts. With the advent of tissue engineering, biomedical engineers now attempt to restore tissue loss by using temporary implants that support the regeneration of injured tissue, followed by the safe biodegradation of the implant. For this revolutionary concept to become a clinical reality, the medical device industry has to move from permanently implanted prostheses (which are mostly based on metals and commonly used engineering plastics) to the development of a wide range of safe and effective tissue scaffolds. These tissue scaffolds have to be based on biocompatible and biodegradable materials (see Fig. 1). One of the early lessons learned by biomedical engineers was that the mechanical properties of a tissue scaffold should be similar to those of the surrounding tissues. For all body tissues, except bone, this design requirement means that scaffolds have to be relatively soft and pliable, yet relatively tough — properties rarely exhibited by materials based on metals or ceramics. So, future tissue regeneration scaffolds will have to be based predominantly on biodegradable polymers, and these will eventually become the most widely used biomaterials. However, this transition from metals, ceramics and engineering plastics to biodegradable polymers has been surprisingly slow.

The traditional mode of materials design begins with the synthesis of a new material, followed by its characterization, leading to the question: What is that material good for? The ultimate goal of the use of combinatorial and computational approaches in biomaterials design is to turn the traditional mode

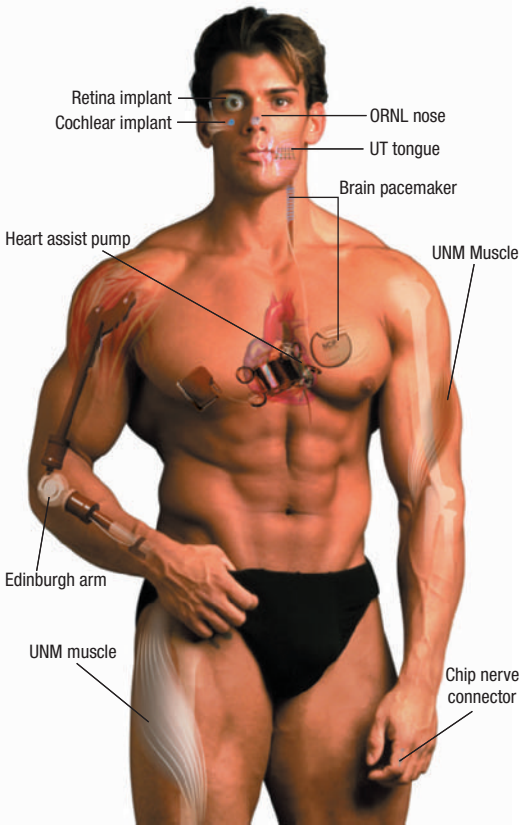

Figure 1 **Implants and prostheses for the bionic man. The goal of tissue engineering is to replace many of the currently used prostheses (shown in this picture) with degradable tissue scaffolds that support the regeneration of lost or damaged tissue. Most of these temporary tissue scaffolds will consist of biodegradable polymers whose physicomechanical, chemical and biological properties need to be tailored to meet application-specific requirements. The emerging discipline of combinatorial and computational materials design should accelerate the discovery of suitable biomaterials.**

Image credit: Danilo Ducak, Popular Mechanics.

Figure 2 **The first degradable, radio-opaque polymer coronary stent[1]. The new polymer used in this stent was developed within a nine-month period through a rational design approach that started from a combinatorially designed polymer library containing approximately 10,000 distinct polymer compositions. Using semi-empirical modelling techniques, only a small number of polymers needed to be synthesized and experimentally explored before a target polymer with optimum properties could be identified. In this process, the materials requirements were defined first, followed by a targeted search for polymers that satisfied the predetermined requirements[1].**

Image credit: REVA Medical, San Diego, California.

of materials discovery around: Virtual biomaterials libraries can be created by computational techniques first. A substantial amount of information about each of the virtual biomaterials can be gathered before a single dollar is spent on synthesis. Rather than relying on the intuition of polymer chemists to select promising candidate materials, the selection of the most promising synthetic targets can, at each step of the discovery process, be based on truly rational design criteria. This approach has recently been used in the design of a new polymer, optimized for use in coronary stents[1] — tubular devices used to prevent arteries from becoming blocked (Fig. 2).

Since 1969, when the first degradable sutures based on poly(glycolic acid) became available, only a handful of synthetic, degradable polymers have been used in Food and Drug Administration-approved medical implants. Furthermore, most of these synthetic, degradable polymers are simple polyesters based on glycolic acid, lactic acid and similar α-hydroxy acids. This lack of diversity is a serious problem, because a wide range of degradable materials will be needed so that the implant properties can be appropriately matched to the very specific and unique requirements of each individual medical application. The adoption of combinatorial and computational approaches in biomaterials design can potentially address both of these challenges (i) by accelerating the discovery of new biomaterials and (ii) by increasing the diversity of promising polymer structures.

Combinatorial chemistry has led to dramatic changes in the way lead compounds for the discovery of new drugs are identified[2]. The so-called COMBICHEM approach is based on the simultaneous synthesis of millions (sometimes billions) of random moieties followed by identification of the most active compounds by selective bioassays and advanced analytical techniques. Over the last 20 years, it has led to the development of highly sophisticated methods for the simultaneous synthesis of large numbers of drug candidates, specialized robotic instruments for synthesis and analysis of complex mixtures, and computational approaches of data mining and design optimization[3–5].

Given the impact of combinatorial chemistry on the process of drug discovery, it is not surprising that this approach has also been explored within the framework of materials discovery. The work by Menger *et al.* in 1995[6] is an outstanding example for both the advantages and disadvantages of the use of the COMBICHEM approach in polymer discovery. To discover enzymatically active polymers, Menger used a random reaction scheme to functionalize an inert polymer backbone with mixtures of chemical moieties known to be present in the active sites of various enzymes. This 'brute force' approach resulted indeed in the identification of polymer mixtures that had phosphatase-like catalytic activity (phosphatase enzymes catalyze the formation or hydrolysis of phosphate ester bonds). However, the specific polymer sequences that resulted in the observed enzymatic activity could not be identified, nor could the mixtures of billions of polymer sequences created within each reaction vessel be separated into individual, well-characterized polymer species.

While in the drug-discovery process, it is possible to identify useful lead compounds contained within a complex mixture, in the polymer-discovery process, it is impossible to screen for useful material properties unless the test polymer can be obtained in a state of high purity. This fundamental difference between 'drug discovery' and 'polymer discovery' can be easily explained: the chemical structure of a low-molecular-weight drug candidate is the single most important parameter determining its biological activity and hence its utility. On the other hand, the chemical structure of a polymer is only one of many parameters that affect its ultimate utility. Other, equally important parameters are the molecular weight of the average polymer chain, the molecular weight distribution of polymer chains within the sample, and the presence of trace impurities that can fundamentally change the material properties. Moreover, the way in which a particular test specimen was fabricated can make a big difference. The concept that the properties of a polymer are dramatically affected by the way in which it is shaped into an object is often not appreciated by chemists and biologists who are key participants in the biomaterials design process. Yet, the overriding effect of polymer processing on its properties is easily illustrated by a styrofoam cup, used to dispense hot coffee, and a transparent overhead projection sheet. They are both made of polystyrene, yet the two objects formed are entirely different in their end-use properties.

This leads to two important conclusions: (i) The basic methodology of drug discovery as practised in the pharmaceutical industry is not much use to material scientists, and (ii) the capability of synthesizing large numbers of polymers is of little utility unless it is integrated into an overall experimental work flow that includes effective screening and characterization steps, and advanced methods of computational modelling and data mining.

Recently, materials scientists have started to develop new approaches, unique to the process of materials discovery. One creative solution to the inability of resolving complex mixtures of materials was the use of spatially resolved libraries: When a test library is spread within a grid of x,y coordinates such that the material composition changes along x and y, a wide range of material properties can be explored by simply scanning over the film surface with an appropriate analytical technique. This approach has been used with

great success by Amis and his co-workers at the National Institute for Standards and Technology to investigate the properties of polymer blends whereby all possible blend compositions were represented by a pair of *x,y* coordinates[7,8].

An alternative to simultaneous synthesis of many species within the same reaction vessel is to implement a combinatorial search for optimized polymer structures through parallel synthesis, that is, the synthesis of a large number of individual polymers at the same time, but each one within its own reaction vessel. In this way each individual material of the library is obtained in pure form[9,10].

Irrespective of the way in which the test polymers are obtained, the unavoidable next step in the materials discovery paradigm is a thorough characterization of most (perhaps even all) of the individual polymers contained within a library. This requirement poses the most significant hurdle for materials scientists, as there are very few good equivalents to high-throughput assays when it comes to polymer characterization. Although some commercial solutions are available (see for example: Symyx, Inc. at http://www.symyx.com), smaller companies and academic laboratories cannot easily afford expensive commercial tools, and building the necessary high-throughput experimental infrastructure 'in-house' is a time and labour-intensive effort. Any progress that makes high-throughput screening and characterization of polymers more widely available can have substantial impact in accelerating the overall pace at which new materials are discovered.

The lack of suitable high-throughput assays is particularly problematic in the field of biomaterials research where, to evaluate a polymer for medical applications, a wide range of specialized tests are required. Examples of key biomaterial properties include surface protein adsorption, rate and mechanism of degradation, specific biological responses of cells contacting the material surface, cytotoxicity, and degree of biocompatibility in vivo. For such biologically relevant properties, no generally accepted and widely applicable high-throughput assays exist. Instead, each of the above-mentioned properties has to be explored through rather laborious experiments. This is a critical bottleneck in the implementation of a combinatorial biomaterials discovery process.

Fortunately, there are at least two valid approaches to address this problem: The first is to develop the missing assays, validate them, and make them available to the scientific community, as three research groups have started doing[11–13]. The second approach is to use computational modelling to eliminate, as much as possible, the need for detailed characterization of large numbers of polymers by high-throughput screening. For example, the prediction of the glass-transition temperature of individual polymers contained within a library of polyarylates was based on the 'total flexibility index', an empirically derived parameter that can be calculated from the chemical structure of the polymers[10]. The use of computational methodologies has been sparse in the field of biomaterials — mostly because it has been difficult to establish appropriate computational models that can describe the complicated interactions between biomaterials and living cells (or tissues). However, computational modelling techniques have progressed to the point where one can envision the discovery process to start with the creation of large virtual polymer libraries.

Virtual polymer libraries are an extraordinary means to explore a wide range of new polymer compositions in a time- and cost-effective fashion. Briefly, virtual polymer libraries are large collections of polymer structures created using various molecular-modelling tools. The model structures are then used to derive predictions on polymer properties, thereby creating a rational way to select a smaller subset of these virtual polymers for actual synthesis and exploration. This approach, commonly used in drug discovery, is only now being explored as a tool in biomaterials design. In this context, biomaterials scientists can learn a lot from the field of drug discovery where two powerful techniques, molecular similarity–diversity analysis and quantitative structure–property relationship models enable prediction of target properties for a library of compounds, thereby accelerating and optimizing the discovery process.

In a recent Commentary[14], Eberhart and Clougherty write that "materials design is still science fiction". Referring to the '*ab initio*' modelling of structure–property relationships across all length scales, this comment is certainly correct. However, the initial wave of publications exploring combinatorial and computational approaches in biomaterials research indicates that one does not have to wait for the rigorous solution of equations of quantum mechanics to derive substantial benefits from computational modelling approaches in materials design. The real challenges in the adaptation of these techniques in a wide range of material-design programs are the lack of knowledge of many materials scientists of the powerful high-throughput and modelling techniques already available for drug discovery, and the high cost of acquiring the necessary high-throughput instrumentation and computational resources in the laboratory. However, these learning and financial hurdles will eventually need to be overcome because, as Eberhart and Clougherty also note[14], both scientists and society-at-large have a stake in seeing the emerging discipline of combinatorial and computational materials design reach its full potential.

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