https://doi.org/10.1038/s44286-023-00016-y

A bright future in medicine for chemical engineering

Robert Langer & Nicholas A. Peppas

Chemical engineering principles will continue to help scientists design and optimize new medical devices, treatments and modalities. This Comment reflects on historical developments and potential opportunities in medicine for chemical engineering.

In a paper published 20 years ago, we gave a detailed analysis of the early days of biomedical engineering and the influence chemical engineering had in medicine[1]. Indeed, chemical engineers have long used their background in fluid mechanics, materials engineering, mass transfer, reaction systems, control theory and process design to contribute to many areas of medicine. These include the development of artificial organs; blood rheology and thrombosis; tissue engineering; regenerative medicine; advanced biomaterials and medical devices; controlled drug delivery systems; genetic therapies; advanced vaccine development; medical imaging; biosensors; approaches to improved enzyme characteristics by immobilizing them on appropriate supports, placing them in organic solvents or using directed evolution; and contributions to synthetic biology, such as enabling mammalian cells to take on new functions by designing appropriate molecular switching systems[2–6]. Developing linear and nonlinear mathematical models for the analysis of advanced biomedical problems is an area where chemical engineers have been active for many years[7,8]. A recent example where mathematical models are proving useful is in predicting optimal vaccine schedules and developing new vaccines[9]. Biomedical engineering has become an increasingly important part of chemical engineering research and education in the past 60 years. Chemical engineers are well suited to address interdisciplinary problems, in particular, those requiring convergence[10] and the integration of complex molecular systems[8]. This Comment provides our perspectives on several historical developments and future opportunities in medicine for chemical engineering.

Biomaterials, artificial organs and tissue engineering

The development of new biomedical materials, scaffolds for tissue engineering, and synthetic and hybrid materials has enabled the design and optimization of new medical products that exhibit improved selectivity and specificity towards specific analytes or therapeutic agents used for medical applications. For example, artificial organs have been an important and life-saving development. Artificial kidneys are used to provide renal replacement therapy for some 2 million patients yearly. Membrane science and chemical engineering have played an important role in enabling better, safer and more effective systems for kidney dialysis[11]. Artificial hearts and other artificial organs have also provided life-saving technologies.

CREDIT: KELLY REDINGER/ GETTY IMAGES

Tissue engineering, which can manifest itself in creating completely new tissues and organs from first principles, promises to take artificial organs several steps further[12]. For example, by taking specific cells, placing them in a correct configuration often on a specifically designed biomaterial and growing them in an appropriate bioreactor, the cells can reorganize and create a tissue. This type of approach has already led to artificial skin that is now clinically used, and the creation of many other tissues, including blood vessels, tendons, spinal cords, pancreas, vocal cords, cartilage, bone, kidney, corneas and heart muscle, have all been studied in animals or humans[3]. This approach has also led to organs or tissues on a chip that can enable more rapid approaches to drug development, because they can enable high-throughput screening. This may also someday lead to a reduction in the amount of animal and human testing[3].

One of the key areas of research in tissue engineering has been the development of biomaterials. Up until the latter part of the twentieth century, nearly all biomaterials that were used clinically were not initially developed for medical purposes. The individuals responsible for deciding the type of material to be placed in the human body were physicians, not chemical engineers. The strategy they employed was to replace a tissue or organ with an off-the-shelf household object that resembled the organ or tissue they were trying to fix. The material now used in artificial hearts, a polyether urethane, was originally used in ladies' girdles because it had good flex properties. The material used for the artificial kidney was sausage casing, made of cellulose acetate. The material used for a vascular graft (artificial blood vessel) was Dacron (poly(ethylene terephthalate)) because the material was easy to sew with, and the materials used for breast implants were lubricants (such as silicone) or mattress stuffing (such as polyurethane)[6].

This approach of taking off-the-shelf materials enabled medical problems to be solved to an extent. However, the solutions had limitations. For example, large-diameter vascular grafts can be made with

Dacron; however, vascular grafts with a diameter of less than 6 mm may cause clots and be non-functional. The artificial heart can function and has saved lives. However, when blood contacts the surface of the artificial heart, it can form a clot that can go to the patient's brain and cause a stroke. One area where chemical engineers have made major contributions, and we expect will continue to do so, is to develop synthetic strategies for creating improved biomaterials. An approach the Langer laboratory and several other research groups have used is rather than to take off-the-shelf materials, is to ask the question what one wants in a biomaterial from an engineering, chemistry and biological standpoint, and then design and synthesize the biomaterial from first principles. One example of this was the development of polymers that have specific amino acids to enable cell attachment. Another example is the development of surface-eroding polymers such as certain polyanhydrides that can prevent dose dumping (and hence prevent toxicity) for more complex drug delivery systems[6].

Drug delivery systems

Controlled-release systems deliver a drug at a pre-determined rate for a finite time and/or can target drugs to specific organs or tissues. They can also protect sensitive drugs (such as peptides and nucleic acids) from being destroyed before they can perform their function. Among the earliest forms of controlled-release systems designed were transdermal systems that, upon placement on the skin, could deliver drugs to the systemic circulation. Chemical engineers and other scientists in the 1960s examined how membranes could control the flux of different molecules through the skin. They also developed mathematical models to predict quantitively to what extent different drugs could pass through the skin. Companies such as ALZA Corporation developed numerous transdermal drug delivery systems for drugs such as nitroglycerin, estradiol and nicotine.

In the early 1970s, the Langer laboratory began to address the possibility of delivering large molecules such as proteins and nucleic acids to the body. Up until that time, controlled-release delivery systems were limited in that they could only slowly release very low molecular weight ($M_w < 300$) lipophilic molecules. In fact, it was a fairly common conception that large molecules could not be delivered from biocompatible biomaterials. However, it was discovered that, by adding certain powders of large-molecular-weight molecules to organic solvents containing hydrophobic or lipophilic materials, microparticles or nanoparticles could be formed[4]. Peppas[7,8] and other chemical engineers studied methods to release small and large therapeutic agents from hydrogels and other hydrophilic and lipophilic carriers. All these studies led to the development of new products for the treatment of numerous cardiovascular, autoimmune and other diseases.

There now exist a variety of delivery systems for macromolecules such as luteinizing-hormone-releasing hormone (LHRH) analogues and other biomolecules. For example, controlled-release systems such as Lupron Depot, Zoladex and Decapeptyl are available in microcapsules or rods that can be injected or implanted. These systems slowly release LHRH analogues (M_w of 1,200) for up to 6 months and have been used by millions of patients to treat advanced prostate cancer or endometriosis. Similar systems are being used to treat other forms of cancer, heart disease, opioid addiction, arthritis, schizophrenia and many other diseases. Most recently, drug delivery systems in the form of lipid nanoparticles have been used to deliver siRNA (OnPattro) to knock down genes that cause ATTR amyloidosis, a nerve disease. Lipid nanoparticles have also enabled messenger RNA to be protected and delivered to billions of people worldwide to provide vaccinations and boosters for COVID-19, saving millions of lives[5]. Chemical engineers have played a key role not only in designing numerous systems to enable drug delivery, but in creating new materials for delivery systems, mathematical models to guide drug delivery system development and new approaches for manufacturing such as 3D printing.

Future directions

There have been other recent advances in this field, including the design of 'intelligent carriers' that act on thermodynamic changes in the surrounding biological or physiological fluids to deliver therapeutic agents at will. This is indeed important as patient treatment has turned towards systems responding to external forces[13], much as chemical systems would do the same in non-biological applications.

Advances in computation, molecular design, and advanced thermodynamic models and theories that were developed in classical chemical engineering are now being applied directly to the solution of medical problems. For example, the advent of powerful computational methods allows calculations of thermodynamic properties in multifunctional systems, leading to predictions of novel medical devices in 'real' biological systems that include protein, antibody, lipid and cell interactions[13].

Along these lines, one potential future direction involves modeling the roles of cell condensates. For example, modeling of nucleic acids in transcriptional control suggests a non-equilibrium feedback control mechanism, where low levels of RNA promote condensates formed by electrostatic interactions and high levels promote dissolution of these condensates[9]. Understanding such phenomena could lead to a better understanding of disease development as well as the design of new therapeutics. Advances in understanding thermodynamic behavior of multicomponent systems are expected to predict characteristics of mimetic systems with the associated ability to design surfaces that include tethers, antibodies and cells, and that can act as attractants or repellents of beneficial or non-beneficial compounds, respectively.

Artificial intelligence is another area that will help chemical engineers develop new diagnostics and therapeutics. There will also be important research in better understanding vascular biology[14] and predicting brain function, and in particular, the mechanisms that enable molecules to cross the blood–brain barrier. Transport through other biological barriers, including the intestine, eye and ear, also represent fundamental areas of study.

The principles of convergence[10] and the development of interdisciplinary institutes within universities are expected to enable medical advances to occur that might not have otherwise been possible. The ongoing 'revolution' in biology, coupled with a deep understanding of chemical engineering science, will lead to educational and research opportunities for chemical engineers in the biomedical field.

Robert Langer [1,2] ✉ **& Nicholas A. Peppas** [3,4,5,6,7,8] ✉

[1]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA. [2]Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA. [3]McKetta Department of Chemical Engineering, The University of Texas at Austin, Austin, TX, USA. [4]Department of Biomedical Engineering, The University of Texas at Austin, Austin, TX, USA. [5]Institute of Biomaterials, Drug Delivery and Regenerative Medicine, The University of Texas at Austin, Austin, TX, USA. [6]Department of Surgery and Perioperative Care, Dell Medical School, The University of Texas at Austin, Austin, TX, USA. [7]Department of Pediatrics, Dell Medical School, The University of Texas at Austin,

Austin, TX, USA. [8]Division of Molecular Pharmaceutics and Drug Delivery, The University of Texas at Austin, Austin, TX, USA.
✉e-mail: rlanger@mit.edu; peppas@che.utexas.edu

Published online: 11 January 2024

References

1. Peppas, N. A. & Langer, R. *AIChE J.* **50**, 536–546 (2004).
2. Nair, L. S. & Laurencin, C. T. *Prog. Polymer Sci.* **32**, 762–798 (2007).
3. Langer, R. *Molecul. Front. J.* **3**, 122–128 (2019).
4. Langer, R. & Folkman, J. *Nature* **263**, 797–800 (1976).
5. Conde, J., Langer, R. & Rueff, J. *Nat. Nanotechnol.* **18**, 537–540 (2023).
6. Peppas, N. A. & Langer, R. *Science* **263**, 1715–1720 (1994).
7. Peppas, N. A. & Narasimhan, B. *J. Control. Rel.* **190**, 75–81 (2014).
8. Parker, R. S., Doyle, F. J. III & Peppas, N. A. *IEEE Trans. Biomed. Eng.* **46**, 148–157 (1999).
9. Scott, J. S., Moore, P. L., Kardar, M. & Chakraborty, A. K. *Proc. Natl Acad. Sci. USA* **113**, E7039–E7048 (2016).
10. Sharp, P. & Langer, R. *Science* **333**, 527 (2011).
11. Di Paola, L. in *Current Trends and Future Developments on (Bio-) Membranes* (eds Basile, A. et al.) Ch. 1, 1–20 (Elsevier, 2020).
12. Griffith, L. G. & Naughton, G. *Science* **295**, 1009–1014 (2022).
13. Clegg, J. R., Wechsler, M. E. & Peppas, N. A. *Regen. Eng. Transl. Med.* **3**, 166–175 (2017).
14. Carmeliet, P. & Jain, R. K. *Nature* **407**, 249–257 (2000).

Competing interests

N.A.P. declares no competing interests. For a list of entities with which R.L. is, or has been recently involved, compensated or uncompensated, see https://www.dropbox.com/s/yc3xqb5s8s94v7x/Rev%20Langer%20COI.pdf?dl=0.