Controlling Biomedical Processes

Process control engineers can have significant impacts in the area of biomedical control, believe Manfred Morari of ETH Zentrum (Zürich, Switzerland) and Andrea Gentilini (previously at ETH, now with The Boston Consulting Group, Zürich). Biomedical engineering is evolving rapidly through new discoveries in biology that provide new actuators and sensors as well as improved understanding of biological functions, which is a prerequisite for feedback controller design. Moreover, there is very little use of automatic control at present. Thus, thanks to their chemical engineering training, process control engineers are well-positioned to take advantage of the opportunities in this area, they say. Two problems of particular interest to them are blood glucose control via automatic insulin delivery and automation of anesthesia.

Control of insulin delivery. Two pathways for insulin delivery are under consideration for use in a closed-loop system (i.e., an “artificial pancreas”) — the subcutaneous route and the intravenous route. While both methods significantly reduce the injection pain, they exhibit advantages and limitations in terms of long-term reliability and short-term action. The major obstacle to overcome, however, before an artificial pancreas becomes a reality is the development of a reliable glucose sensor.

The technical shortcomings of sensors and actuators located outside the blood pool may be avoided altogether by transforming the glucose/insulin regulation problem into an endogenous feedback system (ENFS), where all the elements of the feedback system lie inside the body. This would be made possible by controlled drug-delivery technology, where the sensor and the actuator are both located inside the blood pool. In this approach, insulin would circulate in the blood stream coated by a synthetic polymer, which swells or degrades in acidic environments.

Control strategies in anesthesia. Clinical anesthesia can be seen as a feedback control system where the anesthesiologist represents the control algorithm. During surgery, the anesthesiologist administers drugs and adjusts various medical devices to control the patient’s muscle relaxation, analgesia and hypnosis, to compensate for the effect of surgical manipulation and blood losses, and to maintain the patient’s vital functions.

Some of the outputs to be regulated are qualitative by nature and thus must be assessed by correlating them with available physiological measures. Although several sensors are available, the correlation remains a subject of vivid debate. Several additional research challenges related to anesthesia control involve modeling and identification, learning systems, signal processing and estimation, multi-objective constrained control, and safety-critical real-time systems.

A more extensive discussion of challenges and opportunities in biomedical process control can be found in the October issue of *AIChE Journal.* Dr. Morari will also discuss the topic at the AIChE Annual Meeting in Reno, NV, Nov. 4–9.

Assessing Uncertainty and Controlling Risk in the R&D Pipeline

Managing an organization’s research-and-development pipeline involves making decisions regarding portfolio selection and project task scheduling in the face of significant uncertainty and an ever-constrained resource pool. In its most general form, the inherent optimization problem is the control of a stochastic discrete-event dynamic system (DEDS) that is performance-oriented and resource-constrained, explains Joseph F. Pekny, professor of chemical engineering at Purdue Univ. (West Lafayette, IN).

Pekny, along with his colleagues PhD candidate Dharmashankar Subramanian and professor Rex Reklaitis, have developed a new computing architecture called simulation-based optimization (Sim-Opt). Sim-Opt merges combinatorial optimization and discrete-event system simulation to assess uncertainty and control the risk present in R&D pipeline management. It incorporates the use of timelines (a timeline is one run through the simulation until either the end of the planning horizon or a predetermined state, such as the completion of all tasks in the pipeline, is reached) to study the evolution of the discrete-event pipeline system. Integration of information across many timelines provides design and operational insights about the system that are difficult to obtain using deterministic methods, says Pekny.

A detailed discussion of Sim-Opt and its implementation can be found in the October issue of *AIChE Journal.*

Dehydration Tailors Molecular Sieve’s Pore Size

A team of engineers and scientists led by Michael Tsapatsis, associate professor of chemical engineering at the Univ. of Massachusetts (Amherst), and Steven M. Kuznicki, senior scientist at Englehard Corp. (Iselin, NJ),
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has demonstrated that the titanium silicate molecular sieve known as ETS-4 (synthesized and patented by Kuznicki) has a flexible framework that can be systematically contracted by dehydration at elevated temperatures (Nature, 412 (6848), pp. 720–724, Aug. 16, 2001). This framework contraction can be manipulated to adjust the effective size of the pores giving access to the interior of the crystal, says Tsapatsis. This “molecular gate” effect can be exploited to tailor the material’s adsorption properties for separating similarly sized molecules in the range of 3–4 Å, such as nitrogen/methane, argon/oxygen, and nitrogen/oxygen, he explains. Although similar framework flexibility has been observed in a few other zeolites, this is the first time it has been reported for mixed octahedral/tetrahedral molecular sieve like ETS-4, he points out.

Tsapatsis explains further that ETS-4 can be considered a thermally unstable molecular sieve. Previous researchers have reported that the pore structure collapses upon dehydration. However, Tsapatis and his colleagues have shown that if the dehydration is performed and monitored carefully, it opens up a new realm of interesting science and applications, and this, he believes, could change the way people look at other “unstable” molecular sieves.

Engelhard has been operating a field demonstration unit employing the molecular gate phenomenon to remove nitrogen from natural gas at well-head pressure. It upgrades 210,000 scfh natural gas containing 80–150 ppm water from a nitrogen content of 18% to less than 5%, with methane recovery of at least 90%. The researchers are now attempting to expand the range of commercial separations using these materials and to fabricate membranes of ETS-4.

Another Step Closer to an Insulin Pill …

Chemical engineers at Purdue Univ. (West Lafayette, IN) are developing a method for taking insulin and other medications orally instead of by injection. Currently, such medicines cannot be administered orally because they are broken down in the acidic environment of the stomach.

To avoid this problem, Nicholas A. Peppas, professor of chemical and biomedical engineering, and graduate student Aaron Foss have made microscopic (approximately 1 micron in diameter) particles for drug delivery that protect the medicines from the harsh environment of the stomach. When the particles enter the less-acidic environment of the upper small intestine, they expand and use chemical tethers to latch onto the mucosal areas and cells that line the intestine. The tethers help prevent the stomach acids from breaking down the particles, and keep the particles anchored long enough for the medication to be released into the small intestine, where it is absorbed by capillaries into the blood. The particles are then flushed out naturally by the body’s digestive system after releasing their medication. Furthermore, the particles are not toxic to the cells in the intestine, Peppas adds.

Peppas and Foss tested the particles in a “physiological medium” that mimics the acidity found in the stomach and intestines. The particles remained constricted, protecting the insulin inside, for at least two hours in a highly acidic stomach-like environment, which would be enough time for them to pass from the stomach into the intestines, Foss explains. Then, when the acidity was decreased to a level comparable to the upper small intestine’s, the particles expanded, enabling the insulin to escape, he notes.

The researchers are now studying particles made of different materials to learn how to optimize the technique.

... And a Glucose Sensor and Insulin Dispenser

In another project, Peppas is working with graduate student Mark Byrne to create a biological glucose sensor that may prove useful in “intelligent drug delivery” devices. They formed a mesh-like “biomimetic” gel containing glucose molecules and then used a slightly acidic chemical to remove the glucose, leaving behind spaces where the glucose used to be. If placed in a liquid such
as blood, glucose in the liquid diffuses into the gel and binds to the empty spaces.

Artificial sensing mechanisms might one day be incorporated into medical devices implanted inside the body of a diabetic patient, Byrne predicts. The sensing mechanism would be part of a meshwork containing medications inside numerous microscopic cavities. Sensing glucose in the blood would automatically trigger the meshwork to expand, opening pores and releasing insulin or a medication that would enable the body to more efficiently absorb insulin. Then when the glucose level drops, the polymer gel would stop the release of insulin, he explains.

Such applications would probably be at least five years in the future, he notes. He and Peppas are also working on systems that bind other molecules that are important for the treatment of other conditions.

**Glow-in-the-Dark Pollution Detection**

A team of scientists at Brigham Young Univ. (BYU; Provo, UT) has created molecules that glow in the presence of certain metal pollutants. This could lead to an early warning system that detects contamination of drinking water and waste streams, predicts Paul B. Savage, associate professor of chemistry. Current methods of tracking metals in water are labor intensive and can be very slow, he says. “Our work will let us create a sensor that continually measures metal in a sample of water as it flows by, making it easier to respond to any problems quickly.”

To detect metals such as zinc in water, the BYU researchers first created compounds that seek out and bind to metal ions. Then they created small molecules that attach to the metal-binding compounds. These molecules reveal the presence of bound metal ions by glowing brightly when ultraviolet light is shined on them. If no metal ion is bound, the compounds remain dark. The color of the glow depends on the type and concentration of the metal ions present.

Plans are underway to develop a device that will allow industrial plants and water treatment facilities to track the concentration of metal ions in water and waste streams over time, Savage says.

**Designing Colloids with Desired Properties**

Findings from a NASA-funded study in materials science at the Univ. of Illinois at Urbana-Champaign may change the way the electronics, paint, cosmetics and pharmaceutical industries develop products, predicts Jennifer Lewis, professor of materials science and engineering. She and her colleagues have devised a process that stabilizes colloidal suspensions to prevent the particles from otherwise organizing themselves or coagulating into a disordered gel-like structure. They call this approach “nanoparticle haloing.”

Lewis’s team studied the effects of highly charged nanoparticles on the behavior of negligibly charged colloidal microsphere mixtures, which undergo a transition from a colloidal gel to a stable fluid and back to a colloidal gel with increasing nanoparticle additions. “We attribute the stabilizing transition to nanoparticle haloing around the microspheres, which serves to mitigate their long-range van der Waals attraction,” she explains. The system stability ultimately reversed at higher nanoparticle volume fractions, where flocculation ensues because of entropic depletion forces, she says.

By tailoring the interactions between particles, the researchers were able to engineer the desired degree of colloidal stability into the mixture. “That means we can create designer colloidal fluids, gels and even crystals,” Lewis notes, and “this designer capability will assist us in developing improved materials.”