

Unsolved Problems in Chemical Engineering

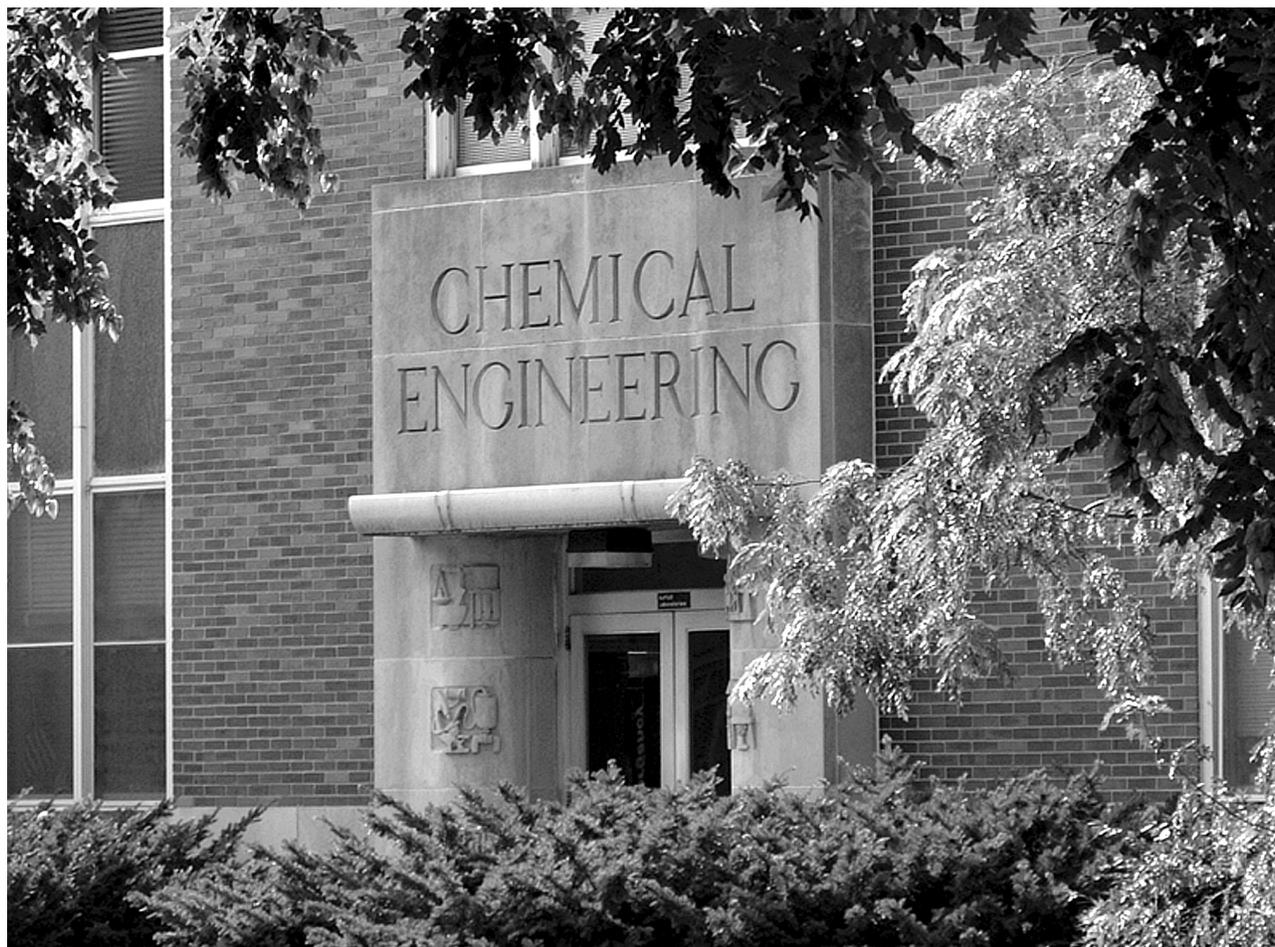
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A Short History of the Chemical Engineering Department



Chemical Engineering at The Ohio State University traces its roots back over 100 years. Offered initially as a “B.S. in Chemistry from the College of Engineering,” the first degree was awarded to Samuel Vernon Peppel in 1899. In the 1902-1903 University Bulletin, *The Outline of the Course in Chemical Engineering* was listed for the first time, although the degree conferred remained a “B.S. in Chemistry from the College of Engineering”. In 1904 the name of the degree changed to “Bachelor of Science in Chemical Engineering.” Its first two recipients were Arno Fieldner and Lewis Benjamin Case in 1906. The first M.Sc. was issued in 1910 to Orlando Sweeney, the first Ph.D.s in 1918 to Herbert Spencer Coith and James Howard Young.

From 1902 to 1924, chemical engineering was a division of the chemistry department, a common practice among universities at that time. (The beginning of chemical engineering education in the United States is usually attributed to M.I.T. where the first degrees in chemical engineering were awarded in 1881.) Dr. James Withrow headed the Division until 1924 when it became the Department of Chemical Engineering. He was Department Chair until 1948. In 1925, the degree program was one of the first 10 to be accredited by the American Institute of Chemical Engineers.

Groundbreaking for the current chemical engineering building took place in 1958; it was later named to honor Dr. Joseph Koffolt, the Department Chair from 1948-1968. Plans are currently under way to initiate construction of a new facility within the next 10 years, as the department enters its second century of service to its students, to the University, and to the profession.



Qualitative Chemistry Lab, ca. 1900



Dr. Robert Brodkey, Professor Emeritus (center, with camera) and Dr. Joseph Koffolt (right, with shovel) at the 1958 groundbreaking ceremony.

In 1968, Dr. Aldrich Syverson succeeded Joe Koffolt as Chair. When his health failed in 1976, Dr. Edwin Haering served as Acting Chair until Dr. Jacques Zakin took over in 1977 and held the position until 1994 when Dr. Liang-Shih Fan became Chair. The current Chair, Dr. Stuart Cooper, joined the faculty in January 2004. The faculty, all of whom came to Ohio State since 1977, is relatively young and has both increased the intensity and broadened the scope of research in the Department, while retaining close personal contact with students, a long-standing tradition.

On April 24-25, 2003, a two-day program celebrated the Centennial of the Department's founding. The event was divided into two parts:

1. One day was devoted to a look backward at the chemical engineering profession and at the history of the Department, including reminiscences by alumni from the '30s to the '70s and by faculty of the last 25 years. A video power-point presentation depicting the 100-year development of the department was presented by Geoffrey Hulse. Professor L.E. (Skip) Scriven described the development of reaction engineering in his talk, "When Chemical Reactors Were Admitted and Earlier Roots of Chemical Engineering."

2. A symposium was held in which four distinguished chemical engineers addressed the future in their areas of research under the general title "Unsolved Problems in Chemical Engineering." These written presentations, and that of Professor Scriven, are provided here for the benefit of the chemical engineering community. Their live presentations can be found at www.che.eng.ohio-state.edu. The topics are:



Arthur Westerberg, Howard Brenner, Michael Shuler and Matthew Tirrell (April 24, 2003)

Howard Brenner – Massachusetts Institute of Technology

“Unsolved Problems in Fluid Mechanics: On the Historical Misconception of Fluid Velocity as Mass Motion, Rather than Volume Motion”

Michael L. Shuler – Cornell University

“Unsolved Problems in Biomolecular Engineering”

Arthur W. Westerberg – Carnegie Mellon University

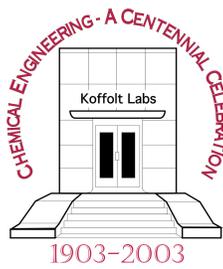
“Unsolved Problems in Process/Product Systems Engineering”

Matthew Tirrell – University of California at Santa Barbara

“Unsolved Problems in Nanotechnology: Chemical Processing by Self-Assembly”

The Department looks forward to continuing its contributions to the education of students at the undergraduate and graduate level, expanded research on both theoretical and technological problems, and serving the University, our community, the nation, and the chemical engineering profession in the years ahead.

Liang-Shih Fan
Martin Feinberg
Geoffrey Hulse
Thomas L. Sweeney
Jacques L. Zakin



THE OHIO STATE UNIVERSITY

When Chemical Reactors Were Admitted And Earlier Roots of Chemical Engineering



Biographical sketch of L. E. 'Skip' Scriven

L. E. 'Skip' Scriven is Regents' Professor and holder of the L E Scriven Chair of Chemical Engineering & Materials Science at the University of Minnesota. He is a Fellow of the Minnesota Supercomputer Institute, founded the Coating Process Fundamentals Program, and now co-leads it with Professor Lorraine F. Francis. He is distinguished for pioneering researches in several areas of fluid mechanics, interfacial phenomena, porous media and surfactant technologies, and the recently emerged field of coating science and engineering. He promoted close interactions with industry by showing how good theory, incisive experimental techniques, and modern computer-aided mathematics can be combined to solve industrial processing problems. He graduated from the University of California, Berkeley, received a Ph.D. from the University of Delaware, and was a research engineer with Shell Development Company for four years before joining the University of Minnesota. He received the AIChE Allan P. Colburn Award four decades ago, the William H. Walker Award two decades ago, the Tallmadge Award in 1992, and the Founders Award in 1997. He has also been honored by the University of Minnesota and the American Society for Engineering Education for outstanding teaching. He has co-advised or advised many undergraduate, graduate and postdoctoral research students, including over 100 Ph.D.'s. Elected to the National Academy of Engineering in 1978, he has served on several U.S. national committees setting priorities for chemical engineering and materials science research. In 1990-92 he co-chaired the National Research Council's Board on Chemical Sciences and Technology, and in 1994-97 he served on the governing Commission on Physical Sciences, Mathematics, and Applications.

When Chemical Reactors Were Admitted and Earlier Roots of Chemical Engineering

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In the Beginning

The Industrial Revolution's first major innovations in chemical manufacture were the chamber process for sulfuric acid in the mid-18th century in England and the Leblanc process for sodium carbonate. The latter originated in France in the early 19th century and soon diffused to England and throughout the Continent. Both stimulated other technological developments, some stemming from what would today be called their environmental impact. Both drew competition: the one from vapor-phase catalytic processes for sulfuric acid (invented by Phillips in 1831 but not commercialized for more than 50 years), which finally replaced it early in the 20th century; the other from the marvelously inventive Solvay process, which more rapidly replaced the earlier Leblanc technology. Both of the newer technologies, heavily metamorphosed, are



Ernest Solvay

in the industrial background today: chemical engineers at large pay them little heed, though sulfuric acid and sodium carbonate are indispensable.

Ernest Solvay's 1872 Ammonia-Soda process was a breakthrough. He divided the process into distinct operations of gas-liquid contacting, *reaction* with cooling, and separations; he invented new types of equipment for carrying them all out continuously on a large scale; and he himself dealt with the chemistry, the materials handling, the process engineering, and the equipment design. In short, the Belgian with no university education performed as what would come to be called a chemical engineer. Though this was not evident to his contemporaries, his performance did catch some attention in England, and it surely impressed the aggressive Americans. They soon licensed the process, integrating it and its principles into a fast-developing inorganic chemicals industry that would be invading European markets around the turn of the century.

In these two heavy-chemical fields are the roots of chemical engineering. They brought need for chemists and for engineers in chemical manufacture, and then for individuals versed in chemistry *and* engineering. They gave rise to George E. Davis, the British inventor of chemical engineering.

Davis left the Royal School of Mines — not a University — around 1868, at 18 or 19 years of age. Starting in the Midlands as an analyst of benzene in coal gas, he conceived of a benzene recovery plant, contrived to finance and build one, then cashed out when the price of benzene quartered. He invented and sold an ammonia still. He started a company to sell ammonium sulfate to farmers and instruct them in using it. And so on. He was a dynamic, competent young chemical entrepreneur and inventor. He was noticed by some of Manchester's intellectual and scientific elite, among them Angus Smith, a University-educated chemist dedicated to the cure of nuisances — by which he meant chemical pollution.

Chemical plants, crudely conceived, poorly built, and often badly managed, had become dreadful polluters.

Hydrogen chloride emissions brought Parliament's first "Alkali Works Act" in 1863. Angus Smith was appointed Chief Inspector. It took him several years to organize the Alkali Inspectorate, for which he chose four professionals more competent in analytical and industrial chemistry than most of the manufacturers. The Inspectors could get compliance by supplying money-saving or even money-making advice. Indeed, the Inspectors became welcome visitors to most works. Smith chose George Davis for the plum district: Lancashire, Yorkshire, and Cheshire, heartland of the chemical industrial revolution.

Davis, the leading light among the four Inspectors, came to know "everything that went on in everybody's works" in the 1870's. That was a time when everyone kept proprietary secrets but most of the secrets were well known. Davis, it soon transpired, saw much more than "secrets" and thought penetratingly and creatively about all of his experiences. He also began his lifelong striving to find ways to abate pollution.

An Idea Takes Root

By 1880 Davis was back in business for himself as consultant and entrepreneur. He was talking with a few like-minded colleagues about a new idea: the idea of chemical engineering and chemical engineers, which they thought fit themselves. Their vision was clear: "a chemical engineer is a person possessing knowledge of chemistry, physics, and mechanics and who employed that knowledge for the utilization of chemical reactions on the large scale" (as Davis recalled in 1901). Formation of a national society of technical chemists, or industrial chemists, to parallel the young, academically oriented Chemical Society, was being widely discussed. When Davis and his colleagues as attendees at an organizing meeting in Manchester proposed a Society of Chemical Engineers, they were turned down: most of the rest of the attendees did not think of themselves as chemical engineers or did not know what a chemical engineer should be. Some were leading industrialists, founders of companies that eventually merged into Imperial Chemical Industries, or ICI. Others were prominent chemistry professors with consulting practices. They called the society they formed in 1881 the Society of Chemical Industry, and that is its name to this day. Of its first 297 members, 14 described themselves as *chemical engineers*.

George Davis, thirty-one years of age, was elected first General Secretary. At the Annual Meetings and local section meetings he gave technical papers based on his experience in trouble-shooting and what later would be called process development, pilot-planting, and design, all in the course of a thriving partnership with a brother. He called himself Chemical Engineer and began



George E. Davis

building his case. He was elected Vice Chairman of the Manchester Section. The Chairman was his five-year older friend and client, Ivan Levinstein, the influential proprietor of the largest dyestuff works in Britain, later President of the Society of Chemical Industry, prime driver in reform of English patent law, and Du Pont's instructor in dye manufacture after the First World War broke out.

Levinstein, born in Germany, by age 20 had studied chemistry at Berlin Technical University, emigrated to Manchester, and begun manufacture of dyes from coal tar aniline. He prospered. His interests were wide. He became a mover and shaker. He spoke and wrote on challenges facing the chemical industry. In an 1886 article on the international competitiveness of the British chemical industries, he defined chemical engineering as the conversion of laboratory processes into industrial ones, called Ernest Solvay a chemical engineer, and proclaimed that professors who combined scientific attainments, practical knowledge, and industrial contacts were needed to train such men so that Britain could, among other things, meet the rising German competition in coal tar dyes. Levinstein was particularly interested in education. He was a governor of the University of Manchester's forerunner. He backed the Manchester Technical School, which he later helped upgrade into the Manchester Institute of Science and Technology of today. Then it was chiefly an evening school. Levinstein suggested to Davis that

he develop his ideas on chemical engineering into a course of lectures.

The Invention of Chemical Engineering

In 1887 Davis delivered his course at the Technical School. Many of his lectures appeared one-by-one over the next six years in *Chemical Trade Journal*, a weekly newsmagazine he founded the same year. He collected additional material and published some of it — even useful formulas like one for head loss in pipe flow. He had advised Professor Henry Edward Armstrong on setting up a diploma course called “chemical engineering” at the City and Guilds College in London, a combination of chemistry and engineering instruction that enrolled 11 sophomores in 1886 but had its name changed to chemistry the next year. He became aware of a similar combination of industrial chemistry and mechanical engineering courses, including a new one on “chemical machinery from an engineering point of view,” set up as a chemical engineering curriculum in 1888 at Massachusetts Institute of Technology by Lewis Mills Norton (an MIT graduate and 1879 Göttingen Ph.D. in chemistry). Norton died young two years later and the new curriculum languished, though it kept its name. In the United States chemistry and chemical manufacture were seen as frontiers. The idea of chemical engineering was vague yet attractive to chemistry professors. For example, at Minnesota the first curriculum in chemistry, established in 1891, was named chemical engineering, and the first four graduates (in 1897) received the degree Chemical Engineer, but that designation was not repeated for a decade. The University of Pennsylvania in 1892 was apparently second in establishing permanently a curriculum called chemical engineering, Tulane in 1894 third, and Michigan in 1898 fourth.

Davis in 1901 transformed his lectures into the first book on the discipline of chemical engineering. His preface highlighted the mounting competition from America (the British viewed the United States then rather as the Americans viewed Japan in recent times) in heavy chemicals and the “wonderful developments in Germany of commercial organic chemistry.” An expanded, two-volume second edition of *A Handbook of Chemical Engineering* was published in 1904. It departed radically from the earlier textbooks and handbooks on industrial chemistry, which covered each chemical industry separately. Davis had recognized that the basic problems were reaction management and engineering issues.

Reaction management he does not name but illustrates by examples of choosing reaction feeds and conditions to reduce reactor volume or shorten reaction time, reduce by-products, facilitate product purification, and

make the entire process profitable. He recognizes mass action effects on reaction equilibrium and rate. His principle for dealing with reaction problems is a Technical Laboratory for scaling up from the chemist’s gram-scale benchtop procedures to the chemical engineer’s development scale of a few kilos and apparatus more like that used in manufacture. He implies that further ton-scale trials may be needed — what came to be known as semi-works or pilot plant operations. He states that new chemical processes often require new combinations of apparatus and newly devised “appliances.” He notes that in developing a new process “privacy is often of the greatest importance,” and that privacy is afforded by a secure purpose-built Technical Laboratory. Davis and his brother had such a laboratory, where they did process development for clients and themselves.

The principles for dealing with engineering problems Davis recognized could be organized around *basic operations common to many*: fluid flow, solids treating, heat or cold transfer, extraction, absorption, distillation, and so on. These were covered chapter by chapter in his book, the forerunner of the unit operations texts on which chemical engineers cut their eye teeth from 1923 onwards. There was also an important chapter on materials of fabrication. And, as W. K. “Doc” Lewis noted in 1952 in an eloquent, long overdue acknowledgment of Davis’s impact on the pioneers at Massachusetts Institute of Technology, the development was as quantitative as the resources of the end-of-century had allowed.

Very few people were ready to act on George Davis’ vision of a discipline of chemical engineering, either in 1887, or in 1901, or in 1904. It fit no university curriculum of that time. Davis had no close ties with technical schools, much less universities in the United Kingdom, though he certainly knew George Lunge, an international authority in industrial chemistry with similar views of the basic operations, who was a professor at the Swiss Federal Institute of Technology (ETH) in Zurich. But the vision did not go unnoticed in the United States, where there were others who were calling themselves chemical engineers and there were university curricula called chemical engineering. Just how that term gained currency is not clear, but it is likely that the *Chemical Trade Journal* crossed the Atlantic and it is certain that the *Journal of the Society of Chemical Industry* had avid readers here. Davis died in 1907 at 57, deprived of seeing his invention, once it was reduced to practice by Walker, Lewis, and colleagues, grow into a flourishing profession and discipline, first in the U.S. Perhaps he would have fanned to flame their smoldering growth in Britain ignited by wartime pressure on that nation’s chemical industry.

Organic Chemicals and Industrial Chemistry

The second round of innovations in chemical manufacture were *batch* processes for small-volume production of high value-added dyes and other coal tar derivatives. These began with Perkins' mauve in England. Apart from Levinstein's firm in England this field was very soon dominated by German research prowess in organic chemistry. The rise of that prowess was aided by university-industry research cooperation, an innovation triggered by British example; and it was integrated into a German industrial juggernaut that before long controlled international markets. Early pharmaceuticals followed the same route. Here, though, the research chemist's laboratory methods were turned over to mechanical engineers to scale up directly, and many of them became skilled enough that in 1886 Levinstein thought some to be scientific chemical engineers. Still, this was no harbinger of chemical engineering as a discipline, nor did it lead the way to continuous processing and the economies that *that* could bring when markets expanded and competition demanded.

Meanwhile the sugar industries, distillation industries, and many others were evolving in Europe. Process engineering and industrial chemistry curricula were being installed in the technical universities (Technische Hochschule) that had appeared in Germany, Switzerland, Austria, and even Hungary. A few of the professors and their counterparts, the chief engineers in certain companies, highly educated in science and mathematics, took to analyzing common, constituent operations like heat transfer (Peclét in France), vaporization, condensation and drying (Hausbrand in Germany), and distillation (by Hausbrand and by Sorel in France). Peclét's seminal monograph went through several editions earlier in the century; monographs by the rest of these authors were published between 1890 and 1899. These too were important forerunners of the discipline of chemical engineering. So also were atlases of chemical manufacturing equipment organized by basic operations rather than industries. Consulting professors wrote about technologies of specific chemical industries. German-British-Swiss George Lunge's successive editions on sulfuric acid were magisterial. These fed into the discipline emerging in the U.S., as did the compendious texts on industrial chemistry — purely qualitative descriptions of industry upon industry — that began appearing. Examples were Samuel Sadtler's *Industrial Organic Chemistry* (1891, 1895, 1900, 1912, 1923) from the University of Pennsylvania and Philadelphia College of Pharmacy (in 1908 Sadtler was elected the first president of the American Institute of Chemical Engineers); Frank Thorp's *Industrial Chemistry* (1898, 1908), from M.I.T. in Boston, a textbook for students

which was dedicated to the memory of Lewis Mills Norton, late Professor of Industrial Chemistry; Allan Roger's *Industrial Chemistry* (1902, 1912, 1915, 1920, 1925, 1931; 1942 edited by C. C. Furnas); and Emil Riegel's *Industrial Chemistry* (1928, 1933, 1937) from University of Buffalo (the last edition of which was one of the writer's burdens as an undergraduate student a few years before the admission of reaction engineering). Until 1923 such texts were the only ones unique to chemical engineering curricula.

Electrochemicals, Niagara, and Outgrowths

The third round of innovation was electrochemical processing, which rose in England, Germany, and France in the decades before 1900 but diffused to America, where cheap electricity generated from cheap coal, and mass production in the new tradition of the iron, steel, copper, nickel, and tin industries, enabled the Americans to compete successfully, even invading international markets — for example, with electrolytic caustic soda and chlorine. Though not much American *science* came up to European standards of the era, “Yankee ingenuity,” especially in improving on European inventions and technologies, was very much in evidence. Charles Hall invented in 1886 the most successful process for producing aluminum. Such innovations and commercializations were plentiful before a U.S. scientist had received a Nobel Prize.

In 1895 came the stupendous hydroelectric development at Niagara Falls; by 1910 that was the location of “the world's greatest center of electrochemical activity,” not only of production but also of process research and product development. Outstanding was Frederick Becket and his Niagara Research Laboratories, where he invented processes for making carbon-free chromium, tungsten, molybdenum, and vanadium by direct reduction of their oxides, and other important processes as well. This was one of the very first industrial research labs in America, and it and Becket were soon bought up by Union Carbide to be theirs.

Electrochemistry was the glamour science and emerging technology of the era. The Electrochemical Society was the meeting ground for leaders of the new science of physical chemistry like Ostwald, Nernst, Bancroft of Cornell, and Whitney — who moved from Arthur Noyes' circle at the Massachusetts Institute of Technology to Schenectady to head General Electric's brand-new research laboratory, the country's first corporate research establishment. It was the meeting ground for educated inventor-entrepreneurs like Elmer Sperry, then of National Battery, and Herbert Dow of Midland; and for prominent industrial chemists and chemical engineers like Samuel Sadtler of Philadelphia,

William Walker of the partnership of Little & Walker in Boston, and Fritz Haber of Karlsruhe Technical University in Germany.

Emergence of the Discipline

With the mention of William Walker, who led the implementation of George Davis's invention, it is appropriate to go back to the scene in America's colleges and universities in the 1880's. Industrialization of the country was accelerating, and with it the need for engineers and, to a lesser extent, chemists. From decades earlier there was popular demand for *relevant* college education, and this had been answered by the appearance of engineering schools like Rensselaer Polytechnic Institute in Troy, New York, Brooklyn Polytechnic, and the Massachusetts Institute of Technology; by scientific schools at Yale, Harvard, Dartmouth, Columbia, and so on; and by the Morrill Act of 1862, which enabled the states to establish land-grant colleges, one purpose of which was education in "the mechanic arts," which turned out to be engineering — civil, mining, and mechanical; then electrical, metallurgical, and finally chemical.

By the 1880's, strong curricula in science and engineering had sprung up in many land-grant schools, among them Pennsylvania State College. There young William Hultz Walker enrolled in 1886 and graduated in chemistry in 1890. Having been a good student, he set off for graduate study in Germany — as did some 1,000 other top graduates in chemistry between 1850 and World War I and perhaps 9,000 more in other fields. Germany then was the center of freedom of learning, freedom of teaching, academic research, and chemistry. Returning from Göttingen with a Ph.D. in 1892, Walker taught for a couple of years at Penn State, moved to M.I.T., then resigned in 1900 to join M.I.T. - chemistry graduate Arthur Dehon Little in an industrial chemistry consulting partnership. (Little had lost his original partner Griffin in a laboratory explosion.

In 1902 William Walker not only became a charter member of the American Electrochemical Society; he also accepted an appointment in the Chemistry Department at M.I.T. to take charge of the curriculum called chemical engineering, though he continued his partnership with Arthur Little until 1905. To his new position he brought his recollections of Norton's ideas from 1888-1890; whatever he had picked up from such writings as Ivan Levinstein's published lecture in the *Journal of the Society of Chemical Industry* in 1886 and George Lunge's influential one in the *Journal of the American Chemical Society* in 1893; his own annotated copy of George Davis's magnum opus on *Chemical Engineering*; and his ideas for transforming



William H. Walker

the chemical engineering curriculum. Those ideas can be glimpsed in his still diffuse 1905 article, "What Constitutes a Chemical Engineer," in Richard Meade's partisan magazine, *The Chemical Engineer*, which was addressed to "technical chemists and engineers in the laboratories and supervision of the operations of the great chemical and metallurgical industries" of the United States. From what happened it's plain that Walker's program was to incorporate the new sciences of physical chemistry and thermodynamics, the new engineering sciences — as they could have been called — of heat transfer, distillation, evaporation, and fluid mechanics that had emerged in Europe, and his own specialty, corrosion; to organize a chemical engineering course including laboratories around Davis's (and his colleague George Lunge's) conception of what would come to be known as "the unit operations"; and to develop research through student theses and industrial interactions. As it happened, in the same department his chemist colleague Arthur Amos Noyes, an 1890 Ph.D. with Ostwald in Leipzig, had just developed a course in physical chemistry that emphasized, among other things, problem solving. Noyes urged, and William Walker insisted, that every chemical engineering student take it.

The success of Walker's program was assured when he arranged for a 1905 graduate, Warren Kendall Lewis, to go to Germany for a Ph.D. in chemistry at Breslau. For upon returning in 1908, Lewis joined Walker and, besides teaching, embarked on a series of analyses of distillation, filtration, fluid flow, countercurrent contacting, heat transfer, and so on. Most of them involved bachelor's and master's theses and many were

published in the young *Journal of Industrial and Engineering Chemistry*, which in 1909 the American Chemical Society started along with the Division of Industrial Chemistry and Chemical Engineers, as an in-your-face counter to the A.I.Ch.E.!. These researches developed principles of the physical side of chemical engineering, which were expounded in mimeographed notes for classes and then in the famous 1923 book, *Principles of Chemical Engineering*, by Walker, Lewis, and the younger McAdams, who joined them in 1919.

This book, *the first textbook of chemical engineering*, was organized along the lines of Davis's 1904 magnum opus, but omitted the managing of chemical reactions and overall view of a chemical process. The first chapter was on simple industrial stoichiometry. A later one opened with manometers, then dealt with pipe flow — both straightline (laminar), citing Lamb's *Hydrodynamics*, and turbulent, laying out the engineers' version of Bernoulli's equation and Fanning's correlation of viscous losses with the newly accepted Reynolds modulus. Another chapter put forward a crude bundle-of-capillary-tubes model of filter cake, developed equations of constant-pressure-difference and constant-rate filtration from Poiseuille's equation, and sketched how to optimize a batch filtration. A short chapter told about putative stagnant fluid films next to solid surfaces and their posited role in heat transfer, citing Langmuir's work on hot wires (as in recently developed light bulbs) but omitting the relevance of gases' viscosity rising with absolute temperature. It also described colleague W. G. Whitman's brand-new hypothesis of stagnant films next to liquid surfaces — the embryonic “two-film theory.” A later chapter returned to this as the basis of interphase transfer coefficients in equations to correlate performance of dehumidifiers and cooling towers. Another chapter treated drying simply in terms of an evaporation coefficient. The wet bulb thermometer was analyzed by postulating that heat and humidity must diffuse across the same stagnant film at its surface. A chapter covered rudimentary heat conduction and radiation, then drew on mechanical engineering papers and McAdams's recent data from M.I.T. undergraduate theses to treat convective transfer to flowing fluid, condensing vapor, and boiling liquid in and on tubes. A companion chapter dealt with evaporation — even basic analysis of a four-effect multiple evaporator. The distillation chapter, after a lot of qualitative descriptions, got to relative volatility, Rayleigh's 1904 equation for simple batch distillation of binary solutions, Sorel's 1893 equations for binary distillation in a column of ideal plates that are equilibrium stages, and the critical design choices: a reflux ratio greater than would require an infinite number of plates, a column diameter large enough that the rising vapor flow does not splash and entrain downflowing liquid excessively, and liquid depth on each plate great enough to accommodate the liquid flow across it.

Whether plates actually behave as equilibrium stages was not broached. Current versions of all of these things are embedded in the basic education of every chemical engineer.

The other chapters, on fuels and power, combustion, furnaces and kilns, gas producers, crushing and grinding, and mechanical sizing, were as purely descriptive as George Davis's book or anything else of the era. There was nothing, not even rules of thumb, about capacities, dimensions, or shapes. And not a word about reaction kettles, converters, or other sorts of reactors. But in many places the text pointed to needs for experimental data, correlations, and quantitative design procedures. From the M.I.T. faculty other textbooks preceded slightly or followed: Robinson's on *Elements of Fractional Distillation* (1922), Lewis and Radasch's on *Industrial Stoichiometry* (1926), Haslam and Russell's on *Fuels and Their Combustion* (1926), McAdams' on *Heat Transmission* (1933), and later Sherwood's on *Absorption and Extraction* (1937). Fluid flow textbooks were left to civil and mechanical engineers; mechanical comminution and separations, to mining and mechanical engineers. Chemical engineering authorities from other institutions contributed books to the campaign which was orchestrated, for a time exclusively, by the New York publisher McGraw-Hill. Then John Wiley launched a series with a new kind of introductory text, a combination of stoichiometry, applicable physical chemistry and thermodynamics: Olaf Hougen's and Ken Watson's *Industrial Chemical Calculations* (1931) from the University of Wisconsin.

The first textbook, *Principles of Chemical Engineering*, a fine one for its day (apart from sparse references to the literature, finally rectified by the third and last edition in 1937), shaped the discipline and helped mold the profession. Follow-on textbooks, beginning with Badger and McCabe's 1931 *Elements of Chemical Engineering*, were organized along the same lines — to the exclusion of the chemical reactors that are the heart of a chemical process and dictate the needs for the unit operations, as Davis had pointed out.

Incidentally Warren McCabe as one of the earliest Ph.D. candidates at M.I.T. had teamed with fellow graduate student Ernest Thiele around 1925 to devise the neat McCabe-Thiele diagram for graphically analyzing the simplest sort of binary separation by distillation in a column of distillation plates. The diagram has of course been a staple of chemical engineering since the 1927 second edition of the *Principles* and the 1931 first edition of the *Elements*.

From around 1910 Walker and Lewis, along with Columbia University's Milton C. Whitaker, a Coloradan who alternated between industrial and academic careers, were the vanguard of those

developing the laboratory course for the emerging discipline. What they wrought was virtually devoid of chemical reaction and came to be known later as the “unit operations laboratory,” the cornerstone of chemical engineering education.

Founding of the Profession and Naming of Unit

Operations

Walker’s program was further reinforced by his former partner, the well-connected consulting industrial chemist Arthur D. Little. In 1908 they together took part in an *ad hoc* meeting provoked by Richard Meade, a young industrial chemist with a cause, and his four-year-old magazine *The Chemical Engineer* for a pulpit. The outcome was a recommendation for organizing an American Institute of Chemical Engineers, which was done in Philadelphia that year. It appears that no one with a degree in chemical engineering was among the established practitioners and professors trained as industrial chemists and mechanical engineers who founded the A.I.Ch.E.

Surprisingly, neither Walker nor Little were founders. They became instead the Chairman and Secretary of the Division of Industrial Chemistry and Chemical Engineering formed that year by the American Chemical Society in direct opposition to the A.I.Ch.E. When attitudes tempered, the new division took its present name, Division of Industrial and Engineering Chemistry. It catered particularly to those concerned with industrial applications of chemical reactions. It developed vigorous technical sessions at A.C.S. meetings and a quality journal for industrial chemists and chemical engineers.

The A.I.Ch.E. in its meetings, transactions, and curriculum accreditation activities seems tacitly to have backed away from the reaction operations in chemical manufacture. (Although chemical engineering benefited greatly, on balance, by developing in close connection with chemistry, the association was not a uniformly positive one.) Some chemical engineers joined both organizations. Both Walker and Little joined the A.I.Ch.E. within a few years and Little, A.C.S. president from 1912 to 1914, was elected A.I.Ch.E. president for 1919. (He was also president of the British-based binational Society of Chemical Industry for 1928-1929.) From 1908, Arthur Little took increasing interest in chemical engineering education and by 1915 was the chairman of a Visiting Committee for Chemical Engineering at M.I.T. Little was famous as a fine speaker and writer (though windy by today’s standards) and was particularly eloquent regarding the need for industrial research in America. In that year’s report to the M.I.T. administration and

board of governors (the Corporation), he coined a name that stuck. The name was “unit operations” for those basic physical operations in chemical manufacture that Davis had written about decades earlier (Little nowhere mentions being aware of Davis’s writings though he must have been reading the *Journal of the Society of Chemical Industry* before the turn of the century). George Lunge too had spotlighted them in an influential 1893 speech to the World’s Congress of Chemists at America’s first great international exposition, the Columbian Exposition in Chicago, and his speech had appeared in the fledgling *Journal of the American Chemical Society*. Some professors and other members of the newly organized profession were talking and writing about those operations. Many in the chemical and metallurgical industries were of course practicing them in the course of their work.

What nobody got around to identifying were the basic kinds of *chemical* operations in chemical manufacture, although by 1905 Walker, like Davis before him, had epitomized the chemical engineer as one “who can devise, construct, and operate industrial plants based on *chemical reactions*,” and in Germany the rudiments of chemical reaction engineering were being uncovered by Knietsch, Haber, Bosch, and others. In Germany, there was neither a discipline nor an organized profession to follow up (only in the 1930s did Eucken and Damköhler take up the line — in a research university). In the United States a young metallurgical engineer (Columbia University) turned physical chemist (1906 Ph.D. with Nernst at Göttingen) named Irving Langmuir, who was teaching at Stevens Institute of Technology in New Jersey, authored a pregnant paper in 1908. It was an astute theoretical analysis of the continuous flow reactors that had come into vogue in Germany for studies of reaction rates in gases — and for Knietsch’s commercialization at BASF of Phillips’ old invention of vapor-phase oxidation of sulfur dioxide to make sulfuric acid. Mixing by convection and diffusion was the key issue and it led Langmuir to equations and solutions for what later was called a continuous flow stirred tank reactor, the completely stirred limit, and for the latter-day plug flow reactor, the totally unstirred limit. The next year appeared a clear, thorough, equation-grounded exposition of chemical kinetics basic to reaction engineering: opposing reactions, side reactions (concurrent reactions), sequential reactions (consecutive reactions), catalysis, effects of temperature and pressure; the book was J. W. Mellor’s *Chemical Statics and Dynamics* (1909). An indication that these events were not entirely missed at M.I.T. is that W. K. Lewis and E. D. Ries later published on temperature-controlled sulfur dioxide converter design based on their analysis of Knietsch’s tubular reactor data. Would reactors have been admitted to the emerging discipline had Langmuir, unhappy at Stevens, gone not to General Electric’s research laboratory but to M.I.T.’s department of

chemistry and chemical engineering, there to fall in with Lewis as both were starting their careers ?

Alas, there was no nascent subdiscipline of reactor analysis and design, only the tradition of descriptive industrial chemistry, to inform the A.I.Ch.E.'s 12-year-long efforts to *define* chemical engineering more fully, prescribe a basic curriculum, and establish an accrediting scheme—the first in engineering—all of which succeeded ultimately. Arthur Little himself led the later stages of the effort to establish the curriculum, the core of the discipline. The principles embodied in that curriculum, having later made room for chemical reactor engineering, have prevailed ever since.

Relationships with Petroleum and Chemical

Industries

By the turn of the century, major American industries were being consolidated through mergers and acquisitions, partly because of the stress of international competition. Frank A. Vanderlip observed in *Scribner's Magazine* in 1905 that “as combinations are made in the industrial field, the possibility of employing highly trained technical experts rapidly increases. Technical training is therefore becoming of vastly more importance than ever before, and those nations which are offering the best technical training to their youths are making the most rapid industrial progress . . . the relative efficiency of nations was never before so largely influenced by the character of their educational facilities”. The transformation of chemical engineering that William Walker launched was remarkably successful, and he is widely regarded as the father of the discipline. Testimony to the success were the impacts of graduates, ideas, approaches, and research results on the chemical and petroleum industries of the United States. That country had come out of World War I the world's most powerful economy.

The relationship with petroleum refining was particularly significant. Refining, which had developed outside the mainstream of chemical processing, was a growth industry of the motor age, a large and expanding area of opportunity for chemical engineering. W. M. Burton's process of thermal cracking, a crude kind of batch reaction processing, had been innovated at Standard Oil of Indiana in 1912; J. A. and C. P. Dubbs' competing patents led to *continuous* thermal cracking — and the Universal Oil Products Company, a nursery of reaction engineering. Catalytic cracking was a couple of decades in the future. Distillation separations, incredible as it may seem today, were a *batch* process in refineries until

continuous flow pipe stills replaced shell stills and fractionators came in after World War I. Mixer-settler trains for treating gasoline gave way to continuous countercurrent extraction in towers of perforated plates. Abruptly, there was high demand for analysis and design of distillation and extraction equipment as well as cracking furnaces. Petroleum refining became the frontier. When Jersey Standard moved to set up a research and development department to apply chemistry, physics, and chemical engineering to the oil industry, it retained as advisors chemist Ira Remson, president emeritus of John Hopkins, physicist Robert Millikan of Caltech, and Warren Lewis.

At M.I.T., Lewis pushed combustion, the only sort of reaction to draw concerted investigation by chemical engineers of that era, and launched Robert Haslam and Robert Russell, whose researches were capped by their 1927 volume on *Fuels and Their Combustion*. Haslam subsequently became development manager at Standard Oil Development Co. and later vice president and a director of Jersey Standard. Clark Robinson, who had graduated in 1909, spent five years in industry, and returned to do a master's and join the staff, answered demand in 1922 with the first physical chemistry-based text on *The Elements of Fractional Distillation*, a best-seller that went through several editions, later with younger Edwin Gilliland as coauthor. In the same year Robinson also published a book on *The Recovery of Volatile Solvents*. In the next year, he coauthored a seminal little textbook with Professor Frank Hitchcock of the mathematics department based on a course they had begun in 1919. A remarkable outburst!

The little book, *Differential Equations in Applied Chemistry*, had only isolated impact, though all through an era when few engineers truly understood calculus it showed off powerful mathematical tools, among them (in the 1936 second edition) numerical solution methods. Not only did it connect with chemist J. W. Mellor's 1902 *Higher Mathematics for Students of Chemistry and Physics—with Special Reference to Practical Work*; it also displayed analyses of reaction rate in simple reaction systems from Mellor's *Chemical Statics and Dynamics* (1909). It did inspire at least a few scientifically-minded young chemical engineers to develop more accurate mathematical descriptions of some of the basic physical and chemical operations that they encountered. Perhaps more influential were textbooks in applied mathematics for engineers that began appearing in the 1930's (e.g. Sokolnikoff & Sokolnikoff's in 1934, Reddick & Miller's in 1938, von Kármán & Biot's in 1940) to which small numbers of chemical engineers were exposed in elective academic courses and rump study groups in industrial R & D organizations. The argument can be raised that *chemical reaction engineering* and *systematic process engineering*, including

comprehensive methods of addressing *control* and *design optimization*, could not develop until adequate mathematical tools had been assimilated into the discipline, which took decades.

Petroleum refining was but one of the arenas of innovation in that era that came to need chemical engineering. Courses were strengthened or installed in universities across the United States, and war veterans swelled enrollments in the young discipline to 6000. The country's output of B.S. chemical engineers rose through the 1920's. Ph.D. programs, an inheritance from the chemistry side — not the mechanical engineering side of the early conglomerate curricula — began to take hold. Apparently the first doctorates in chemical engineering were awarded at the University of Wisconsin starting in 1905. By 1920, thirty had been granted nationwide: the flow of chemistry graduates, pure and industrial, to Germany for postgraduate study had been staunch. The total of U.S. Ph.D.'s and Sc.D.'s in the following decade was 120. Many went to industry, others — the split is not clear — to chemical engineering faculties, which continued growing and which A.I.Ch.E. accreditation standards expected to be engaged in research.

Petroleum refining consumed a lot of university outputs, but so did the American chemistry industry, already in aggregate the world's largest and still growing lustily. Among new large volume processes were those for carbon tetrachloride and chloroform, which required accurate temperature control and precise fractional distillation; for the intermediates phenol, monochlorobenzene, phthalic acid, and diphenyl; for the alcohols from methanol to hexanols and the cellosolves; for acetone and acetates; for high-strength hydrogen peroxide, for magnesium; and for a variety of plastics precursors like styrene, vinyl esters, polybasic acids, polyhydric alcohols, and acrylates. Smaller volume batch processes appeared for a host of synthetic dye stuffs, medicinals, and germicides as well as other specialty chemicals, organic and inorganic.

As had been true in Davis's time and before, design and performance of the reactors in these processes were closely held by the companies that developed them. Any information was kept secret that related key performance factors — conversion of the limiting reactant, yield of the product, and by-product distribution — to the operating parameters: proportions of reactants and diluents in the feed; unrecovered products, by-products, and diluents in recycle; volume and holding time in a batch reactor or dimensions and nominal residence time (the reciprocal of what was called the "space velocity," which was *not* a velocity) in a flow reactor; and pressure and temperature program in time or profile along the length. Patents were vague, professional papers and technical articles generally silent on these things, which are of

course the vitals of a *chemical* process: they dictate what the separations and other unit operations must do in the rest of a plant.

Only for mature processes like sulphuric acid manufacture had rules of thumb of design and operation passed into the possession of consultants and authors like George Lunge and George Davis. Davis, for example, gave such figures for continuous sulfuric acid manufacture as 16 cubic feet of lead-lined chamber for sulfur dioxide oxidation and absorption per pound of sulfur burned per 24 hours — a rough stand-in for residence time or space velocity. (Two decades later Riegel noted that higher-temperature operation and the use of circulating fans had brought the figure down to 12 cubic feet.) Otherwise the design and operation rules had to be learned by engineers after they joined the plant, and then on a need-to-know basis. Generally, the batch furnaces, ovens, kilns, autoclaves, kettles and pots, the continuous converters and coiled tubes were chosen on the basis of experience and the ease of adding another to the "battery;" they were operated with proprietary recipes derived from chemists' benchtop trial-and-error and successive scale-up experiments. Processing small-volume batches of dyes, medicinals and the like might be adjusted on the production scale by the chemists themselves, as in Germany. For larger volume processes Davis seems to have advocated scale-up from bench to "technical experiment" to see what happens in plant-type equipment, to explore and improve operating conditions, to assess impacts of impurities and by-products, to test materials of construction, and so forth; then to semi-works scale for more of the same plus salable product; then to full scale — three steps of scale-up, four levels. Writing in 1930 (in an Introduction to Badger and Banchero's book), Arthur D. Little states that in his practice he has found it advisable, for an important process which may ultimately require heavy investment, to have five or six steps between bench-top operations and final plant design: "Thus the validity of the *proposed reactions* [emphasis added] is confirmed, difficulties are disclosed and overcome [presumably he included matters of recycling unreacted reactants and purging them of troublesome constituents], yields gradually improved, and any defects in materials of construction or limitations of units of equipment revealed. Not until the operation of a plant of semiworks size has verified the estimates of costs of production and the product has been sold at a satisfactory price . . . can one feel that he has reached the goal of the long road of process development". A quest expensive in money and time! It's no wonder that reactor design, operation, and performance were closely held within companies. It's also no wonder that investigators in universities could rarely afford to study realistic reactors.

Unit Processes Cul-de-Sac

What the academics along with journal editors went after instead were qualitative process flow sheets, which eventually became a fashionable form of public relations with such audiences as the readerships of *Industrial and Engineering Chemistry* and *Chemical and Metallurgical Engineering*. From the journals the sheets went to a new variety of industrial chemistry book. The idea of unit processes was put forward in 1928 in *Chemical and Metallurgical Engineering* by P. H. Groggins, an industrial chemist in aniline and dyes, in a paper on “Nitration — A Unit Process of Chemical Engineering.” What he meant by a unit process was a chemical conversion in contrast to the physical transport and transformations called unit operations. “Unit processes deal principally with chemical reactions, whereas unit operations relate largely to physical phenomena,” he wrote in the 1935 book he edited and wrote a large part of: *Unit Processes in Organic Synthesis*, a description of nitration, halogenization, sulfonation, oxidation, alkylation, etc., etc. with flow sheets. There were only casual mentions of reaction conditions and losses and scarcely any information on reactor design and performance. It was updated industrial chemistry and it filled needs. Generations of chemical engineering undergraduates memorized portions of its contents in the industrial chemistry courses that still survived. Only for its fifth edition 23 years later did Groggins commission Thomas Corrigan (1949 Ph.D. with Kenneth Watson at Wisconsin) of Olin Mathieson Chemical Corporation and John McKetta of University of Texas to write short chapters on Chemical Kinetics and Chemical-Process Kinetics, i.e. reaction engineering.

The unit processes idea was indefatigably promoted by Norris Shreve, an organic technology professor in the chemical engineering department — so large it was called a School — at Purdue University in Indiana. Dissatisfied with the absence of chemical reaction from the unit operations paradigm, Shreve by 1933 organized lecture courses (“Flowsheets 101” to the irreverent) and lab courses (“Pots and Pans 102”), the latter taking gram-scale syntheses and separations to 100 gram-scale, that were fairly widely emulated in university curricula. From 1937 he organized an annual symposium on unit processes for the Division of Industrial and Engineering Chemistry at American Chemical Society meetings; the symposia drew papers and attendees engaged in industrial applied kinetics and nascent reaction engineering. His 1945 textbook, *The Chemical Process Industries*, was organized around more than 100 flow sheets that had been published in *Chemical and Metallurgical Engineering* and that illustrated, he emphasized, the coordinated sequences of unit processes and unit operations that constitute chemical processes. That the “operations” transcend specific reactions, chemicals, and industries whereas



Carl Bosch

the “processes” do not, he never grasped, although he did sense that the reaction engineering emerging around him from industry and taking root in academia was the future. That did not diminish the largely stultifying effect of the book wherever it was inflicted on undergraduate chemical engineers. As one distinguished chemical engineer in management wrote in that era, “The modern employer does not engage a graduating student because the student can describe for his employer how his product is made”.

Ascendancy of Continuous, Catalytic, and High-

Pressure Reactors

In the decade before World War One, Fritz Haber, Walther Nernst, and others in Germany had taken up gas-phase reactions — Haber published his instructive book on the thermodynamics of such reactions in 1906 — and were soon pursuing nitrogen fixation by ammonia synthesis, a goal of tremendous economic and geopolitical significance. Haber got the breakthrough by discovering a catalyst in 1908. A leading German corporation, Badische Anilin-und-Sodafabrik (BASF) took on the development, assigning to it a self-made chemical engineer, Carl Bosch, a mechanical engineering graduate of Leipzig University with a Ph.D. in industrial chemistry, and to a methodical chemist, Alwin Mittasch, who reportedly oversaw 20,000 trials with different catalyst formulations to find the best (the irreverent assert that though techniques of combinatorial chemistry have

speeded up catalyst design lately, the approach hasn't changed in nearly a century). Before 1900, Rudolf Knietsch of BASF had, by scientifically informed experimentation, systematically analyzed and designed reactors for vapor-phase oxidation of sulfur dioxide. Building on this earlier pioneering, his colleague Bosch designed the first high-pressure, continuous flow tubular reactor—actually a tube—and the rest of the plant. By 1913, they had the Haber-Bosch process for synthetic ammonia in operation, a signal accomplishment like Solvay's 50 years earlier.

At the war's end the Allies took German technology as a war prize. The war had also stimulated the U.S. chemical industry: explosives to be sure, but most notably dyestuffs by Dow and Du Pont and nitrogen fixation and nitric acid manufacture by government-financed plants at Muscle Shoals, Alabama. Gasoline demand for proliferating motorcars provoked improvements in thermal cracking. Easily refined petroleum deposits began to seem quite limited. There were also wartime profits to invest in upgraded and new technologies. So it was that in America in the decade after World War I, process innovation turned to high pressure and often high temperature, capitalizing on German advances in vapor-phase catalytic reaction processes and on advances in metallurgy and fabrication — enormously important advances!

A few months after the war's end, the U.S. government organized the Fixed Nitrogen Research Laboratory, which pioneered high-pressure property and process research and ammonia catalyst development for the nation's needs. Led in succession by Dr. A. B. Lamb, Prof. R. C. Tolman, and Dr. F. G. Cottrell, outstanding and practical scientists all, it recruited talented chemists and engineers who were periodically raided by companies assembling cadres for industrial research and development—a classical mode of technology transfer. Moreover, in 1925 and 1926, industry's Chemical Foundation started financing high-pressure laboratories in the chemical engineering departments of Massachusetts Institute of Technology (Prof. W. G. Whitman), Yale University (Prof. B. F. Dodge), and University of Illinois (Prof. N. W. Krase) — each laboratory a beautifully small center of engineering research!

Among recipients of the research and personnel was Du Pont, which had been growing fast and diversifying since its reorganization in 1902, the year it created its corporate engineering department and first ventured into corporate research as well. Du Pont actually purchased ammonia synthesis technology from French and Italian interests. It launched a program of nitric acid from ammonia in its Research Department in 1924. Staffed by Guy B. Taylor, a 1913 physical chemistry Ph.D. from Princeton, Fred C. Zeisberg, a chemist turned chemical engineer expert in acid manufacture,

and Thomas C. Chilton, a Columbia University chemical engineering graduate with three years of prior research experience, the program was a roaring success. It led to Du Pont's high-pressure nitric acid process, which was scaled up, commercialized, and licensed to other chemical companies within four years, testimony to the astuteness of Vanderlip's 1905 observation in *Scribner's Magazine*. The great impact within Du Pont was heightened by contributions the seven or eight other chemical engineers (half of them postwar graduates from M.I.T.) in the Research Department made to process technology for producing ammonia, methanol, and other products. The research director, Charles M. A. Stine, already a respected advocate of fundamental research and spokesman for chemical engineering, responded by organizing half his chemical engineers into a group with the goal of getting their discipline onto a sound scientific footing and simultaneously serving as internal consultants. He put young Tom Chilton in charge, who soon hired Alan Colburn, a fresh Wisconsin Ph.D. — thus the famous Chilton & Colburn contributions to the discipline.

Preceding Du Pont's cheaper nitric acid, the first products from the high-pressure high technology of the mid- and late- 1920s were methanol and other commercial solvents, setting the stage for what Arthur D. Little in 1928 foresaw: the coming era of chemicals —“new solvents and organic chemicals in great variety” —from petroleum feedstocks. In particular there were the refinery off-gases that were being burned as fuel, rising amounts of ethylene and other olefins among them. More and more petroleum was being thermally cracked to increase gasoline yield, and olefins were by-products. The economic environment was ready for the next high technologies to evolve.

And evolve they did. Union Carbide went from light hydrocarbons to liquefying them (liquefied petroleum gas, LPG) to ethylene oxidation to Cellosolve solvent, a glycol ether marketed in 1926; then “permanent antifreeze” in 1928 and synthetic ethyl alcohol in 1930. The international Shell Group set up its development Company in 1928 near Berkeley, California under the direction of Dr. E. Clifford Williams, who had just before established a chemical engineering curriculum at the University of London. Shell Development became the leading pioneer of petrochemical process development—alcohols, ketones, and glycerin, and aviation gasoline to boot.

On the other hand, the Shell Group as well as Standard Oil of New Jersey (which became part of Exxon) and Anglo-Iranian Oil declined in 1930 to back Eugene J. Houdry, a French mechanical engineer pursuing his vision of catalytic rather than thermal cracking of heavy crudes. Losing French government financing despite good progress in developing his process, Houdry managed to interest Vacuum Oil Company

(which became part of Mobil) and then Sun Oil Company in pilot plant work, moved his efforts to Paulsboro, New Jersey, and together with his partners achieved in 1937 the first commercial cat cracker, a fixed-bed, regenerative unit. This development spawned a lot of U.S. corporate research. Applicable *scientific* research on catalytic cracking was led in Russia by petroleum chemists, but from 1930 the Universal Oil Products Company, stoked by Russian émigré Vladimir N. Ipatieff, had pulled ahead, first with what was called olefin polymerization. Universal Oil Products was owned by seven major U.S. oil companies at that time.

Standard of New Jersey itself had been slowly developing German technology for hydrogenation of heavy crudes, to which it had access through agreements that Robert Haslam helped negotiate with I. G. Farbenindustrie, the cartel forged by Carl Bosch, who was by 1925 the top executive in BASF. The Houdry process and Kellogg Engineering Company's concept of a moving-bed cracker spurred formation of another development combine, Catalytic Research Associates, a multinational one that included I. G. Farben, notwithstanding the rising war clouds. The combine had competition from Socony-Vacuum (Mobil), which was first to commercialize a moving-bed cracker. Moreover, it was upstaged by Standard of New Jersey's own Standard Oil Development Company, still advised by Warren Lewis and larded with former students from M.I.T. There the concept of gas lift was borrowed from grain transport practice, and the concept of fluidized beds was adapted from Fritz Winkler's 1921 development in Germany of high-pressure coal gasification to create fluidized bed catalytic cracking, a momentous innovation.

Like nitrogen fixation on the eve of World War I, catalytic cracking had tremendous economic and geopolitical significance. Through 1943, Houdry units and after that fluidized bed units accounted for most of the aviation gasoline available to the United States and its allies in World War Two.

Between the wars, the growing numbers of continuous catalytic processes — in other manufactures as well as petroleum refining and petrochemicals — absorbed more and more chemical engineers. They brought incentives to focus as much on selective reactions of flowing fluids and suspensions as on the separations and particulate solids-processing methods that constituted the unit operations. They also became nuclei of all sorts of opportunities for the chemical engineering profession.

The Profession Begins Metamorphosing

The profession itself altered its image. The early American Institute of Chemical Engineers had been small, elite, and prudent in dealing with other societies that also catered to chemical engineers, in particular those of chemistry, electrochemistry, mining and metallurgy, and mechanical engineering. Most of those had superior journals that attracted chemical engineering research. The older American Society of Mechanical Engineers in 1930 took aim on creating a new Process Industry Division that would appeal to chemical engineers. This threat and Depression-generated deficits propelled the 900-member A.I.Ch.E. to liberalize its stringent membership requirements, hire a half-time executive secretary, campaign to recruit young graduates, strengthen ties to its Student Chapters in universities, and improve its meeting programming and *Transactions* publication. The latter had begun to draw some of the quality technical papers and research reports that had gone to the A.C.S.'s *Journal of Industrial and Engineering Chemistry* and elsewhere. But as late as 1943 the A.I.Ch.E. was still "placing major stress on the unit operations and declining to publish articles on reaction rates and reactor engineering".

The most significant event of all was publication, a year later, in 1934, of the *Chemical Engineer's Handbook*, the prime reference work in the McGraw-Hill series that had begun with Walker, Lewis, and McAdams' textbook. Seven years in the making, the project had been entrusted to John H. Perry of Du Pont as editor-in-chief of 62 specialists drawn from industry and academia (over one-quarter of them from Du Pont and no more than a handful from or associated with the petroleum and gas industry). The *Handbook's* 2600 small pages were addressed to students as well as practicing engineers (the latter were no doubt the targets of the section on patent law and of the 10 pages on arithmetic). It codified the discipline.

Thus Charles Stine's goal at Du Pont of getting chemical engineering onto a sound scientific footing led first to codification. Simultaneously, the center of mass of unit-operations research shifted southwestward from New England toward Wilmington, Delaware, where the exceptional research engineer, Allan P. Colburn, Olaf Hougen's prize student at Wisconsin, had joined the others in Tom Chilton's team. The remarkable output of incisive papers that followed was, according to Chilton, a by-product of improving the company's existing technologies and engineering new ones, with a premium on *fast and accurate process design and scale-up*. Younger talent attracted to the team heightened its impact on the blending of unit operations and chemical processing that had already started in the high-pressure process for nitric acid; with that blending, a discipline better based in science, mathematical modeling, and rigorous computational methods emerged — to be codified, too slowly perhaps,

and with too little attention to chemical reactions, in succeeding editions of the *Chemical Engineer's Handbook*.

Though it was a bellwether, Chilton's team was, needless to add, far from alone. Competition came not only from other companies in the United States, but also from Germany, where *scientific* engineering was already especially well established in some universities and had the attention of at least a few companies. Colburn, for example, had built extensively on researches by Prandtl, Nusselt, von Kármán (when he was in Germany), Schmidt, and Jakob (still in Germany at that time). Just how well Colburn and his American colleagues kept up with developments in Germany is not clear. A chemical engineering discipline was being compiled there too.

Chemische Ingenieur-Technik, a 2200-page treatise intended as something between a textbook and a reference work, appeared in 1935. Its 24 authors were drawn mostly from industry, a handful from technical universities, and a couple from the more prestigious universities. It is certainly more scholarly than Perry's *Handbook*, and it avoids ancillary areas like patent law, accounting and cost finding, safety and fire protection, and report writing. Its editor, Ernst Berl, studied with George Lunge at ETH and became professor of technical chemistry and electrochemistry at the Darmstadt Technical University. Leaving Germany like so many others, he had become professor at Carnegie Institute of Technology, Pittsburgh, U.S.A. No champion remained: German chemical engineering research proceeded chiefly in engineering and Technischen Chemie.

An encyclopedia about physical operations in chemical and related process industries, *Der Chemie-Ingenieur*, was far more imposing. Twelve volumes were published between 1932 and 1940 under the editorship of Professor Arnold Eucken of Göttingen and, initially, Professor Max Jakob of Berlin, who soon departed for the United States. Eight volumes treated unit operations on a scientific footing, with abundant citations of sources, frequent use of mathematical tools, and sophisticated accounts of the best practice. Then came the add-on volumes, which treated physicochemical and economic aspects of chemical *reaction* operations, i.e., chemical process principles; the chapters include one by Gerhard Damköhler that is now celebrated in chemical reaction engineering. The encyclopedia's title apparently was inspired by Walker, Lewis, and McAdams' text, yet Eucken was a physical chemist who, with I. G. Farben support, championed Verfahrenstechnik as a field of engineering science. Indeed, it was he who in 1934 steered Damköhler into the study of flow reactors.

So it was that although chemical engineering was *practiced* very well within segments of German industry, and the *discipline* had been compiled in fine scientific form, it could not propagate without an academic base, nor could a *profession* emerge without an industry that wanted it, or journals for its voice, or a society for its organization.

Industry Drives Reaction Engineering

Profitability of a reaction process hinges on the conversions of reactants, the yields of products, the distribution of by-products, the mixings of the input and separations of the outputs, the recyclings of unconverted reactants. These depend on the rates of all the reactions — and rare is the industrial reaction that proceeds virtually alone. Rarer, too, are the reactions that proceed without liberating or absorbing heat, and the reaction rates, which depend on temperature as well as concentrations, set the rate of heating or cooling needed. A reactor is a volume where reactants react, and reaction rates determine its size and its design for heat transfer by conduction, convection, and radiation. They also determine the requirements for mixing, separation, and transport. Catalysis is all about rates of reaction: catalysts that preferentially speed up desirable reactions (or slow down undesirable ones) can improve profitability enormously. But catalysis at solid surfaces — heterogeneous catalysis — calls for high-surface solids, porous or finely divided, at which reaction is typically slowed down by diffusional resistance to arriving reactants and departing products. Moreover, gas-phase reaction processes have, from the first, cried out to be continuous. They have also invited pressure, which generally enhances reaction rates of gases and lowers reactor volume needed; it can shift equilibria advantageously; and it can lower compression and pumping costs.

From the 1920's through the heyday of petroleum refining and chemical manufacture from petroleum and natural gas feedstocks, process developers sought reliable ways of thinking about all of these things, of analyzing benchtop and pilot-plant data, and of designing plants. At stake were financial resources to commercialize newly developed processes for creating new markets or advancing in established ones. No doubt the advances came first in large companies that had Research & Development arms, like Du Pont, Mathieson, Union Carbide, Dow, Imperial Chemical Industries, Standard Oils of New Jersey, Indiana, and California, Shell, Dutch Staatsminen — and in the unique process invention and development firm, Universal Oil Products, located near Chicago.

While industrial chemists were searching indefatigably for new and better catalysts, academic chemists were taking a broader view. In the first edition (1926) of their influential book, *Catalysis in Theory and Practice*, E. K. Rideal (Cambridge University) and H. S. Taylor (Princeton U.) touched on catalyzed gas reactions, mentioning the reactor concepts of space velocity and space time yield. They noted that “No satisfactory data have been published on the design of converters [reactors].” A. F. Benton’s (U. Virginia) seminal *Kinetics of [adsorption] catalyzed gas reactions in flow systems* appeared in 1927 (Ind. Eng’g. Chem. **19** 494-7). G. M. Schwab’s (U. Munich) *Catalysis from the Standpoint of Chemical Kinetics*, the 1936 translation of his 1931 work, explicitly discussed competing reactions. In their 1932 *Catalytic Oxidation of Organic Compounds* L. F. Marck (M.I.T.) and D. A. Hohn (Mt. Holyoke) summarized the few reactor designs and heat removal schemes that had appeared in patents; they also showed representative flow sheets, some of which had integral recycle streams. Such were the early public glimmerings of reaction engineering.

In 1930 N. W. Krause, an alumnus of the Fixed Nitrogen Research Laboratory who had moved to Chemical Engineering at the University of Illinois, published a keynote article on high pressure, high temperature technology (Chem. Met. Eng’g. **37** 529-24). Two years later appeared the magnum opus from the Laboratory, *Fixed Nitrogen* edited by H. A. Curtis; it covered conversion and yield versus space velocity in ammonia synthesis and ammonia oxidation — and much more. In 1934 appeared *Pressure synthesis possibility for sulfuric acid manufacture* (Chem. Met. Eng’g. **41** 571-5) by the distinguished emigré Ernst Berl, who had taken his Ph.D. with George Lunge. In 1936 from a U. Michigan chemical engineering thesis project sponsored by UOP came *Laboratory cracking data as a basis for plant design* by R. L. Huntington and George Granger Brown. (Ind. Eng’g. Chem. **27** 699-707). The same year saw *Catalytic Reactions at High Pressures and Temperatures*, the magisterial book by the pioneer of high pressure catalysis, Vladimir Ipatieff, whom UOP had induced to emigrate from the Soviet Union. For the company he had discovered *inter alia* olefin polymerization (“catalytic condensation”) and alkylation reactions that were commercialized. The next year (1937) brought *Pressure pyrolysis of gaseous paraffin hydrocarbons* (Ind. Eng’g. Chem. **28** 324-32) by Hans Tropsch, a pioneer whom UOP had attracted from Germany, C. L. Thomas, and Gus Egloff, a UOP mainstay (Tropsch shortly died prematurely). UOP supported a project at Armour Research Institute (later I. I. T.) by another prominent emigré from Germany, Eucken’s co-editor Max Jakob; in his paper on *Measurements of the true temperature and heat exchange in a catalytic reaction* (Trans. A.I.Ch.E. **35** 563-86) Jakob called attention to Damköhler’s researches. Earlier in *Catalytic vapor*



Kenneth M. Watson

phase nitration of benzene (Ind. Eng’g. Chem. **28** 662-7 1936) R. H. McKee and Richard H. Wilhelm at Columbia U. had followed up on a tantalizing German patent in what proved to be the launch of Wilhelm, a leading researcher in reaction engineering — a researcher well acquainted with Damköhler’s work.

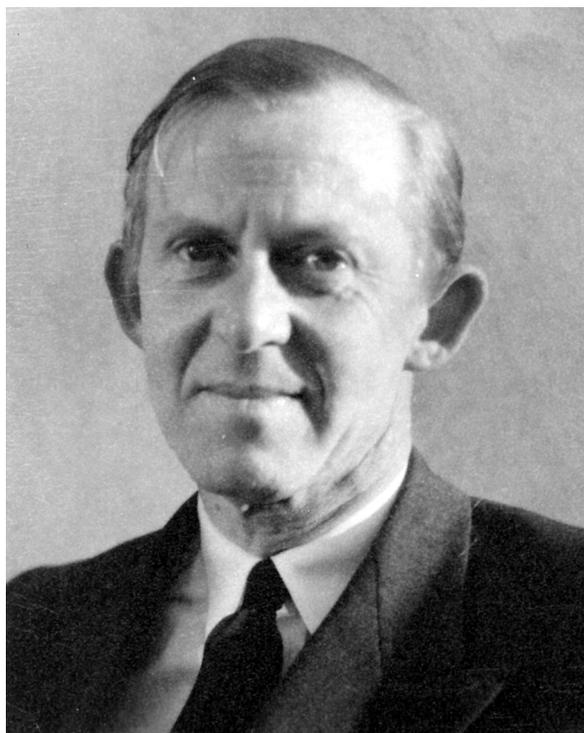
A singular achievement in 1935 was *The theory of short-circuiting in continuous flow mixing vessels in series and the kinetics of chemical reactions in such systems* by R. B. MacMullin and M. Weber of Mathieson Alkali Works at Niagara Falls (Trans. A.I.Ch.E. **34** 409-58). They thoroughly worked out continuous flow stirred tank reactors five years ahead of Kirillov, nine years ahead of Denbigh, but their impact was not visible in the literature until the 1940’s.

Ernst W. Thiele’s celebrated *Relation between catalytic activity and size of particle* — lucid and thorough on diffusional limitation of reaction on internal surface — gave the world the effectiveness factor and Thiele modulus. Thiele’s paper had been stimulated by that of Dutch consultant F. G. Laupichler the year before: *Catalytic water-gas reaction: mass transfer and catalyst activity* (Ind. Eng’g. Chem. **30** 578-86 1938).

Signs of reactor design at UOP began to appear in the literature. L. S. Kassel’s *Application of reaction kinetics to process design*, which contained theoretical

analysis indicating superiority of two reactors over one and three in a certain case, was printed in 1939 (Ind. Eng'g. Chem. **31** 276-7). An unpublished paper by UOP's K. M. Watson presented before the Chemical Engineering Division of the Society for the Promotion of Engineering Education at Pennsylvania State College in 1939 was liberally cited in Section 5 of the Second Edition of the *Chemical Engineers' Handbook* in 1941. Watson also called attention to the lack of information and training in applied kinetics and reactor design, Olaf Hougen recorded later (Ind. Eng'g. Chem. **40** 556-65 1948). From the Karpov Institute in Moscow came another sign: *Kinetics of ammonia synthesis on promoted iron catalysts* [in English] (Acta Physicochim U.R.S.S. **12** 327-356 1940) in which M. Temkin and V. Pyzhev succeeded in matching theoretical analysis with experimental data on the Haber-Bosch process. And from Monsanto Chemical Corporation's R. R. Wenner came probably the first textbook treatment of design of tubular flow reactors, a chapter on "Converter Design" in his 1941 *Thermochemical Calculations*.

Industrial Reaction Rates, a Symposium of the Industrial Engineering Division of the American Chemical Society in December 1942, signaled the future admission of chemical reactors to the chemical engineering canon. The papers, most of them published in 1943 in Volume **35** of *Industrial & Engineering Chemistry*, included *Solid catalysts and reaction rates* by O. A. Hougen and K. M. Watson (U. Wisconsin); *Principles of reactor design* by D. M. Hurd (Du Pont?); *Conduction, convection, and heat release in catalytic converters* [with references to Damköhler] by R. H. Wilhelm, W. C. Johnson, and F. S. Acton (Princeton U.). The chair of the organizers, Olaf Hougen, wrote that "despite the interest of chemical engineers in the release of industrial data on the applications of reaction rate principles to reactor design, the committee soon found that contributions were not readily forthcoming . . . [There were also] last-minute withdrawals . . . In an early postwar year another symposium on the same subject should be timely . . . Many of the customary repeated and extensive pilot plant investigations might be eliminated by more complete understanding of the principles involved." A few slightly earlier industrial papers had released bits of data, for example two in 1940: *Catalytic alkylation of isobutane with gaseous olefins* (Ind. Eng'g. Chem. **32** 328-30) by F. H. Blunck and D. R. Carmody (Standard Oil Co. of Indiana) recorded some data on conversion and distribution of products, and *Hydrogenation of petroleum* (Ind. Eng'g. Chem. **32** 1203-12) by E. V. Murphree, C. L. Brown, and E. J. Gohr (Standard Oil Development Co. of New Jersey and Louisiana) listed some data on yields and quality. War production stimulated a 1944 masterpiece by K. G. Denbigh in England (Ministry of Supply and Southampton U.), in which he analyzed batch and



K. G. Denbigh

flow reactors, tubular and multiple stage continuous flow stirred tanks (quite unaware of MacMullin and Weber's 1935 paper), and advantages and disadvantages of each in cases of competing reactions: *Velocity [rate] and yield in continuous systems* (Trans. Faraday, Soc. **40** 352-73). Similar in origin was the original and definitive treatment of conditions for multiple steady states in continuous flow stirred tank reactors with exothermic reaction, by Carl Wagner in Germany (Technische Hochschule Darmstadt) in 1945: *On the temperature control in highest performance catalytic reactors* [in German] (Die Chemische Technik **18** 28-34). More academic in origin was H. M. Hulburt's pair of 1945 papers (from Princeton U.) establishing general equations and their dimensional analysis for tubular reactors in general and for highly idealized instances of catalytic reaction — and due appreciation of Damköhler and Thiele: *Chemical reactions in continuous flow systems. Reaction kinetics. Heterogeneous reactions* (Ind. Eng'g. Chem. **36** 1012-7 and **37** 1063-9).

Industrial papers of the sort sought by Hougen's committee finally appeared in 1948, notably *Reactor design for manufacture of toluene by catalytic reforming* (Chem. Eng'g. Progress [A. I. Ch. E.] **44** 195-200) by A. A. Burton et. al. (California Research Corp. — Standard Oil Co. of California) and *Catalytic dehydrogenation of ethylbenzene* (Chem. Eng'g. Prog. **44** 275-86). Both were unprecedentedly full reports of pilot plant data, one including scale-up issues and

commercial plant data, the other discussing the method of designing a commercial plant. Both drew interesting published discussion. Both probably reported work done some years before. As it happened, they were preceded by seminal publications on reactor design.

In 1946 a series of four articles, *Principles of reactor design*, authored by K. M. Watson (U. Wisconsin) and, respectively, C. O. Reiser, P. S. Myers, R. H. Dodd, and L. N. Johnson, that had appeared in the National Petroleum News Technical Section, was reprinted and circulated. It was soon quoted by Hougen & Watson for their book and later by J. M. Smith for his, and so had a strong influence. An industrial paper on design of tubular flow reactors, or “coils,” with substantial pressure drop was authored by J. H. Hirsch and collaborators at Gulf Research & Development Corporation: *Projection of laboratory reaction velocity [rate] data into commercial designs* (Ind. Eng’g. Chem. **38** 885-90). In 1947 from Imperial Chemical Industries in the U. K. came K. G. Denbigh’s *Continuous reactions. Part II. The kinetics of steady state polymerization* (Trans. Faraday Soc. **43** 648-60), which opened up the area of polymerization reactor analysis and design. And from O. A. Hougen and K. M. Watson at the University of Wisconsin came Part III of their *Chemical Process Principles* volumes, namely *Kinetics and Catalysis*, the first textbook to systematize analysis and design of plug-flow tubular reactors. Though they totally missed continuous flow stirred tank reactors, their book was without peer for instruction in applied kinetics and tubular reactor design for nearly a decade, until 1956.

In that interval the principles of reaction engineering were better and better understood, as exemplified by a remarkable monograph and four papers. The monograph was D. A. Frank-Kamenetzki’s 1947 *Diffusion and Heat Exchange in Chemical Kinetics* from the Academy of Sciences in Moscow, finally translated into English in 1955 at R. H. Wilhelm’s instigation. Focused on combustion, flames, and explosions, it covered basics of parallel and consecutive reactions, oscillating reactions, temperature rise and runaway in reactors, and reactions at combustible and catalytic surfaces. Wilhelm et al. (Princeton U.) published analog computer solutions of governing equations and results of experiments, in *Reaction rate, heat transfer, and temperature distribution in fixed-bed catalytic converters* (Chem. Eng’g. Prog. **44** 105-16 1948). R. B. MacMullin (Consultant) echoed the 1935 paper with one on consecutive reactions in multi-stage CFSTR’s: *Distribution of reaction products in benzene chlorination: batch vs. continuous process procedures* (Chem. Eng’g. Prog. **44** 183-8 1948). Dirk W. van Krevelen, P. J. Hoftyzer and C. J. van Hooren (Netherlands State Mines) addressed, by experiment and theory, gas absorption with chemical reaction in



Joseph Mauk Smith

Kinetics of gas-liquid reactions (Recueil des travaux chimiques des Pays-Bas **67** 563-99 1948). D. R. Mason and Edgar L. Piret (U. Minnesota) with DuPont support inquired into transient behavior, in *Continuous stirred tank reactor systems . . . transient equations, applications, and experimental confirmation* (Ind. Eng’g. Chem. **43** 1210-19 1951). C. van Heerden (Netherlands State Mines), apparently unaware of Wagner’s 1945 treatment, analyzed multiple steady states in steady flow reactors with exothermic reactions, in what became a celebrated paper: *Autothermic processes: properties and reactor design* (Ind. Eng’g. Chem. **45** 1242-7 1953). Another significant thing was the appearance of A. A. Frost and R. G. Pearson’s (Northwestern U.) textbook, *Kinetics and Mechanism* (1953), which covered only homogeneous chemical reactions but had a chapter on complex reactions and flow methods that appealed to some influential chemical engineers of the day.

In 1956 *Chemical Engineering Kinetics*, with chapters on reactor design, was published by Joe M. Smith, a young professor at Purdue University. The focus of Smith’s research and teaching had shifted from chemical engineering thermodynamics, in which he had coauthored a long-lived textbook, to reaction engineering, in which he had industrial experience at Monsanto, Chevron, and Texaco going back to before 1945. His teaching impelled him to a comprehensive view of the subject. His was the first textbook of chemical reaction engineering. It emphasized reactor

design. It was widely adopted for undergraduate courses in “applied kinetics,” “reactor design,” or “reaction engineering.” It arose in the same department that housed R. Norris Shreve, who was stuck on “unit processes” — a striking coincidence.

That the concept Smith developed was taking hold elsewhere was made plain by *Chemical Reaction Engineering: First European Symposium on Chemical Engineering*, held in Amsterdam in 1957. It was a well-staged event with papers from the Netherlands, Germany, England, and France that were afterward printed as a special supplement to the initially Eurocentric young journal *Chemical Engineering Science*. The Symposium and its sequels in 1960 and 1964 established chemical reaction engineering in Europe and helped solidify it in the United States.

As just recounted, chemical reactors and reaction engineering took a couple of decades to work their way on stage as applied chemical kinetics and practical catalysis, and thence toward the front and center of technology, the discipline, and the profession. It is worth noting that the ratio of significant publications by industrial authors to those by academic ones seems about as in the foregoing selection. That the proportion of outright chemists fell, and of chemical engineers rose with time is surely accurate. So is the indication of shift of publication from the A.C.S. to the A.I.Ch.E. journals. In 1942 the A.I.Ch.E. actually declined to hold the Industrial Reaction Rates Symposium that proceeded instead under A.C.S. auspices. (MacMullin and Weber’s 1935 article in *Trans. A.I.Ch.E.* was an anomaly.) Many of the academic authors had already served in process development trenches of industry. Some were actively encouraged by industrial people. Most notable of the lot was Ken Watson, who in 1932 had left the University of Wisconsin for UOP, there pioneered tubular reactor analysis, design, and scale-up, and — after his 1939 challenge to academics to take these things up — in 1942 returned part-time to Wisconsin for his wartime service in designing and constructing plants for the U.S. government-driven synthetic rubber production. In those plants and many others that were built under enormous time pressure for war production, chemical and petroleum companies had to go from sparse laboratory data to full-scale plants without the usual progression of pilot-plant and semi-works stages. Reactors had to be designed. A by-product, as anticipated by Olaf Hougen, partly on Watson’s experience, was greater willingness among companies to publish results of kinetic studies and pilot-plant trials — and to promote the new subdiscipline.

Admission of Chemical Reactors to the Canon

What signaled admission of chemical reactors and chemical reaction engineering to the canon of chemical engineering? They became prominent in the Symposia and recognition awards of the American Institute of Chemical Engineers and the European Federation of Chemical Engineering, which was formed after 1950. They appeared in required courses of the chemical engineering curricula of more and more universities, until finally the Accreditation Standards caught up and demanded them. They were integrated with applicable chemical kinetics, explained in quantitative terms, and applied to realistic problems of design and operation in course-derived textbooks beginning with Olaf Hougen’s and Kenneth Watson’s seminal *Chemical Process Principles. III. Kinetics and Catalysis* from Wisconsin (and UOP) in 1947. Then came the landmark: Joe Smith’s *Chemical Engineering Kinetics* from Purdue in 1956. It was followed by Walter Brötz’s *Fundamentals of Chemical Reaction Engineering* (in German, later translated into English) from Ruhrchemie AG and Technische Hochschule Aachen in 1958, and Stanley Walas’s *Reaction Kinetics for Chemical Engineers* from Nofsinger Co. and University of Kansas in 1959. A transatlantic flood ensued in the 1960’s — texts by Kramers, Denbigh, Aris, Levenspiel, et al. The number of these books that grew out of an author’s grappling with analysis and design of *industrial* reactors is noteworthy.

By the end of the 1960’s chemical engineering fully accorded with George Davis’s eighty-year-old vision of application of chemistry, physics, and mechanics to the utilization of chemical reactions on a large scale. Moreover the reactions’ reactors and their associated recycles and purges had come to be clearly viewed as a chemical process’s hub on which turn all the separations and other unit operations.

The ultimate imprimatur was the upgrading of reactors and reaction engineering to the status of *full section* in the Fourth Edition of the *Chemical Engineers’ Handbook*, published in 1963. They shared the section with not unrelated Thermodynamics, but they got top billing. One of the authors of their part was Robert H. Perry, coeditor of the Fourth Edition and son of Du Pont’s John H. Perry, editor of the first three editions. In the very first edition, in 1934, the older Perry had himself coauthored a short subsection on Reaction Rates, including a paragraph on gas-phase flow reaction and a couple on the prevalence of simultaneous and sequential reactions in practice. Perry had been certain that at least a peek at the heart of chemical engineering had to appear in a handbook dominated by the body of unit operations.

The fluidized bed catalytic cracker was invented and developed at Standard Oil of New Jersey sites early in

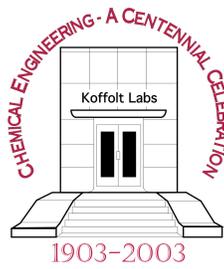
World War Two. Already in the pages of the *Handbook's* Third Edition, in 1950, it had appeared not as the magnificent reactor that it is, but as a relative of continuously fed process furnaces and an example of gas-solids contacting. In fact it epitomized the modern chemical reactor. Neal Amundson on receiving the National Academy of Engineering's Founder's Award a decade ago pointed out that such a chemical reactor "may be an extremely complicated device, substantially more complex than a nuclear reactor . . . The size of some . . . is awesome." Indeed in 2003 there are fluidized bed cat crackers processing 100,000 or more barrels per day, and circulating particulate catalyst between reactor and regenerator at rates of 3000 to 4000 tons per hour. The understanding, design and operation of processes based on such reactors is a major success of our discipline, profession, and industries.

Acknowledgements

This text is drawn partly from my article, "On the Emergence and Evolution of Chemical Engineering," pp. 1-40 in *Perspectives in Chemical Engineering*, edited by C. K. Colton, Academic Press, New York, 1991 (*Advances in Chemical Engineering*, Volume 16) and partly from subsequent study and reflection. I am indebted to Maribeth R. Mrozek (then a senior in chemical engineering, since a development engineer, and now a law student) for discerning assistance in locating and assessing sources; and to John T. Lund (currently a senior) for unstinting help in tracking down materials.

Note:

What I see as the basic questions about what constitutes the discipline of chemical engineering, what maintains the associated profession, and how both relate to the industries and technologies served are stated in the closing of the 1991 article cited above.



THE OHIO STATE UNIVERSITY

Unsolved Problems in Fluid Mechanics



Biographical sketch of Howard Brenner

Born and raised in New York City, Howard Brenner received his Bachelor's degree in Chemical Engineering from Pratt Institute in 1950 and D.Eng.Sci. from New York University in 1957. His 48-year career as a chemical engineering faculty member includes New York University (1955-1966), Carnegie-Mellon University (1966-1977), the University of Rochester --- as Departmental Chair (1977-1981) and, since 1981, MIT, where he is currently W.H. Dow Professor. Brenner has co-authored three fluid dynamics and transport phenomena books, namely "Low Reynolds Number Hydrodynamics (1965)," "Interfacial Transport Processes and Rheology (1991)," and "Macrotransport Processes (1993)." Honors include the American Institute of Chemical Engineer's "Lewis," "Walker," and "Alpha Chi Sigma" Awards, the American Society for Engineering Education's "Senior Research Gold Medal Award," the American Chemical Society's Kendall Award in "Colloid and Interface Science," the "Bingham Medal" of the Society of Rheology, and the American Physical Society's "Fluid Dynamics Prize." Brenner holds membership in the National Academy of Sciences, the National Academy of Engineering, and the American Academy of Arts & Sciences. Lifelong research interests focus on hydrodynamics and transport processes in fluid-particle systems --- addressing both fundamentals and applications. He has published about 250 papers in these fields. Most recently, his work has shown that the classical notions of fluid-mechanical transport processes in systems involving mass density gradients, dating back to the founders of the subject, including Euler, Navier, Stokes and Fourier, are patently wrong on principle. Concomitantly, Brenner's discovery and quantification of the notion that volume can be transported diffusively, i.e. molecularly (above and beyond the purely convective transport of volume accompanying the movement of mass) has been used to modify the basic momentum and energy transport equations in fluid continua, thereby correcting the works of the above-cited authors. He is currently working on a transport phenomena/continuum mechanics monograph encompassing these modifications.

Unsolved Problems in Fluid Mechanics: On the Historical Misconception of Fluid Velocity as Mass Motion, Rather than Volume Motion

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Abstract

Existing experimental data on the thermophoretic velocity of a small, rigid, non-Brownian particle through an otherwise quiescent gaseous continuum, when re-interpreted as representing the motion of a passive tracer entrained in a moving fluid, reveals that macroscopic fluid movement (*motion*) can occur purely diffusively, by the movement of volume, without a concomitant (convective) movement of mass^{1,2}. This experimental fact negates Euler's 250-year old generic, mass-based definition³ of the velocity field in fluid continua, undermining thereby the heretofore seemingly rational foundations^{4,5} of fluid mechanics and derivative subjects. This, in turn, requires a fundamental reformulation of the basic equations of fluid mechanics^{6,7} as well as of molecular theories^{8,9} of transport processes^{10,11} in fluid continua. This detailed re-fashioning, which is effected elsewhere¹, is based upon recognizing that volume can be transported purely diffusively¹², representing, *inter alia*, a previously unrecognized mechanism for momentum and energy transport in fluids.

Let me begin by congratulating the Ohio State Chemical Engineering Department on the occasion of its 100th anniversary. I am flattered to have been asked to participate in the celebratory exercises surrounding this happy occasion. May the Department continue to successfully serve the needs of its students, its faculty, the University, the chemical engineering profession, and the community of scholars at large.

Like several other invitees on this occasion, I was asked to emote on the subject of "Unsolved Problems in Chemical Engineering," specifically in the general area of Fluid Mechanics. However, having succeeded in identifying a problem crying out for solution, how is an indefatigable researcher expected to prevent his mind from attempting to solve the very problem or problems that he/she has identified as being unsolved? And woe to the speaker who actually succeeds in solving these. For this very action will render him incapable of presenting his lecture entitled "Unsolved Problems in Chemical Engineering," leaving him with the unpleasant alternative of identifying and writing about yet another unsolved problem, and so on, *ad infinitum*, *ad nauseum*. This is a logical conundrum, one that I strongly suspect the planners of this lecture series failed to anticipate. Obviously, they failed to reckon with Heisenberg's *uncertainty principle*, whereby the mere act of observing a system alters the state of that system --- the system here being the "unsolved problem" that one was asked to identify and discourse upon.

As a consequence of this unanticipated phenomenon, coupled with my own tenacity and sheer brilliance (not

to mention an obvious lack of modesty), I stand before you today as a failure, a man unable to honestly present a talk entitled: "Unsolved Problems in Chemical Engineering." I will, therefore, instead, present a lecture entitled: "A Previously Unsolved Problem in Chemical Engineering," more pretentiously subtitled: "On the Historical Misconception of Fluid Velocity as Mass Motion, Rather than Volume Motion." The formal lecture notes pertaining to this topic follow subsequently, after the overview of the general topic given immediately below.

Overview of the Problem

According to all standard works and research publications on fluid mechanics, the velocity \mathbf{v} at a point of a fluid continuum is governed by the movement of mass through a hypothetical surface fixed in space, as witness the first appearance of the symbol \mathbf{v} for velocity in the well-known continuity equation of fluid mechanics, $\partial\rho/\partial t + \nabla \cdot (\rho\mathbf{v}_m) = 0$. On the other hand, the velocity of a material object is measured experimentally by tracking its temporal movement through space. (Anyone who has ever thrown a ball to a catcher will recognize that this is, indeed, the way to measure velocity.) Adapting this scheme to the measurement of fluid velocity, an object (a "tracer") --- which is sufficiently small such as to not disturb the pre-existing fluid motion into which it is introduced --- can be visually tracked in time so as to monitor the undisturbed fluid movement serving to convect the

passive tracer through space; that is, the tracer merely renders visible the otherwise invisible continuum fluid motion existing in its absence, without itself affecting that very movement! But where is the experimental and/or theoretical proof that the tracer and mass velocities are indeed the same?

This is (or rather was) the "unsolved problem" with which I began to prepare my talk. Based upon seemingly unequivocal experimental and theoretical grounds, I arrived at the surprising conclusion that these two velocities are, in well-defined circumstances, generally unequal. Indeed, in certain circumstances, namely in the case of phoretic phenomena (e.g. thermophoresis), involving the motion of a small, non-Brownian particle through a bounded, single-component fluid under the influence of a temperature gradient (in the absence of gravity effects), no continuum mass motion whatsoever exists at any point of the fluid, as is easily verified from the Navier-Stokes, continuity, and energy equations, together with the thermal equation of state for the fluid. Nevertheless, a thermophoretic particle, one animated by an externally-imposed fluid temperature gradient, is observed to move through the fluid from high to low temperature. And this particle qualifies as a "tracer," since its velocity is (observed experimentally to be) independent of its size, thereby enabling us to regard it as an effectively point-size object! This constitutes a physically authenticated situation in which the mass and tracer velocities of the fluid differ. The standard explanation for the phenomenon of thermophoretic motion (at least in gases), dating back constitutively to Maxwell in 1879, and consistent with the particle's size-independence, argues that the phenomenon arises from non-continuum fluid-mechanical effects existing near the surface of the particle, and involving a violation of the no-slip velocity condition at the particle surface. This, despite the fact that the Knudsen numbers (mean-free path to particle size) characterizing the fluid motion were vanishingly small during those experiments for which particle-size independence of the thermophoretic velocity was observed.

We offer here an alternative, strictly continuum, non-slip explanation of phoretic phenomena, albeit one based upon a major modification of the Navier-Stokes equations governing the fluid's convective and diffusive momentum transport processes in continua, wherein it is claimed that the mass velocity appearing in the continuity equation is not, in fact, the velocity of the fluid continuum (as measured by a tracer)! The consequences of the proposed general velocity inequality are profound, in that they undermine the basic fluid-mechanical and chemical engineering transport principles that we all learned in school,



James Clerk Maxwell

principles currently assumed to govern all fluid-mechanical transport phenomena.

Has Fundamental Research in Transport Phenomena Been Ossified By Its Own Success

During the roughly 30-year period beginning in the mid-1950's, chemical engineering research moved heavily into the area of engineering science. This effort was largely characterized by an intense focus on transport phenomena, including mass, species, energy, and momentum transport processes. Much of the codification of knowledge in the field at the beginning of that era was embodied in the classic 1960 textbook by Bird, Stewart and Lightfoot, which, after a lapse of 40 years, was brought up to date by the recent publication of a second, thoroughly revised edition¹⁰, co-authored by these same authors, a very singular accomplishment given the time lapse. The seemingly classical status of this the subject would lead one to believe that no outstanding problems of a truly fundamental nature remain to be resolved in this field. Undoubtedly, much is yet to be accomplished in terms of actually solving the pertinent transport equations in the context of specific applications, an activity largely delegated nowadays to computers. Even in the realm of

establishing the phenomenological coefficients entering into relevant constitutive equations, the action has largely moved from experiment towards purely statistical-mechanical computation of these parameters. The prevailing view is that, in terms of fundamentals, basic research in transport phenomena, at both the continuum and molecular levels, belongs to the ages. This lecture aims to negate this impression by identifying major problems in the field, as well as providing a prescription for their resolution.

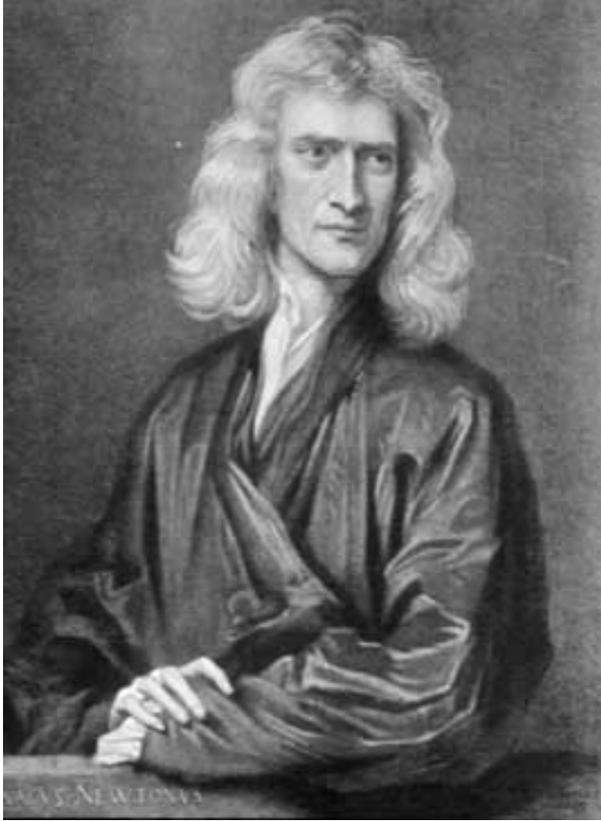
Specifically, a recent publication¹ casts doubt upon the comfortable perspective of a field ossified by its own success. In particular, it appears to me, as well as to several others with whom I have shared my concerns, that a major flaw exists in the fundamental conceptions underlying transport phenomena, traceable back to the physical interpretation to be placed upon the velocity, \mathbf{v} , existing at a point of the fluid continuum. Given that this velocity serves to distinguish convective transport from diffusive transport, any problems connected with the proper identification of \mathbf{v} automatically spill over from the continuum into the molecular realm. Even more generally, to the extent that a problem exists in the transport phenomena field, comparable issues necessarily obtain in the related fields of continuum and statistical mechanics, including such subfields as rheology and irreversible thermodynamics. The sole publication¹ claiming to undermine the foundations of transport processes is too new to have been widely studied, much less accepted by the engineering and scientific research communities. Nevertheless, irrespective of its present status, its arguments point up non-trivial questions of a fundamental nature. Explicitly, the currently unresolved issues facing the transport and fluid-mechanical communities are two-fold: (i) Is the proposed new theory correct; and (ii) if so, what are the limitations of its validity, given that it incorporates several idealizations? Irrespective of the answer(s) to these questions, the exercise of attempting to provide rational answers thereto is bound to be informative, certainly to its discussants, and hopefully to a wider audience as well.

On the assumption that the first question is answered in the affirmative, in the sense of recognizing the existence of a basic flaw in our present understanding of the continuum fluid velocity \mathbf{v} , these written notes — which are designed to supplement the main verbal lecture, which is more technical in scope — serve to identify what would appear to be the historical source of the misconception. The latter deals essentially with understanding the intellectual background that gave rise to the error in the first place, and which, subsequently, prevented recognition of the logical flaw during the past



Leonhard Euler

250 years following its introduction by Euler in 1755. At the same time, the lecture reinforces the general need for performing critical experiments in the transport phenomena field, or indeed in any field of research, an issue which in today's computer age would surely appear of little import to most young researchers (although obviously still relevant in areas explicitly recognized as a being in a state of flux). In any event, a quick study of the new theory would almost create the impression that such mid-course "corrections" to one's understanding of transport phenomena are important only in specialized circumstances, such as arise, for example, in connection with phoretic phenomena, e.g. thermophoresis or diffusiophoresis, where the pertinent Reynolds number is quite small owing largely to the relatively small sizes of the aerosol and hydrosol particles involved. However, given the current focus on small-scale technological processes, including nanotechnology, microfluidics, and cellular biological transport phenomena, entailing low Reynolds number flows resulting from the small particle and/or conduit sizes encountered, we believe that this newly-altered view of transport processes will ultimately result in novel applications to pertinent physical and biological phenomena. It is with these and related fields in mind that we formally address the following topic.



Isaac Newton

The primitive notion of the (vector) velocity of a material body, namely the directed distance traveled through space divided by the time required to traverse that distance, is one of the most important concepts in our arsenal of theoretical tools required for a quantitative description of physical phenomena. For example, in the case of rigid bodies moving through empty space, the temporal rate of change of this velocity, namely the body's acceleration, plays a fundamental role in determining the forces acting upon the body, and conversely. As such, a clear understanding of how velocity is to be measured experimentally is central to any dynamical description of the behavior of physical systems, rigid or otherwise. In the simplest case, involving the motion of a rigid body moving *in vacuo*, any potential ambiguities regarding the definition of its velocity were removed at the outset by Newton (actually by Euler), who began by initially focusing attention on the motion of a hypothetical mass point, an abstraction. Subsequently, rigid bodies of finite extent were addressed by regarding them as being composed of a finite collection of such idealized point masses, permanently joined together, with its members interacting through

centrally-symmetric forces¹³. In such circumstances, and for strictly dynamical reasons arising from the fact that, in the case of point masses, momentum is simply mass times velocity, the velocity of choice for characterizing the motion of a rigid body came to be specified in terms of the movement of its center of mass, a point within the body at which its entire mass is regarded as effectively concentrated.

Thus began the intimate association of velocity with mass, a fraternization subsequently adopted by Euler³, the "father"^{4,5} of continuum fluid mechanics, when, in 1755, he derived the so-called continuity equation^{6,7,10,11}, a purely *kinematical* field relation, expressing the law of conservation of mass at a point within a fluid continuum in terms of the "velocity," \mathbf{v}_m , of the fluid's mass movement. Fluids are, however, deformable rather than rigid. As such, the physical identification of fluid velocity with the movement of mass, so central to rigid-body mechanics, loses its dynamical *raison de etre* in the case of fluids, retaining only a kinematical, purely mass-conservation, rationale for its appearance therein. Failure to appreciate this fundamentally altered role played by mass movement in fluids compared with its role in rigid-body dynamics, along with the failure to recognize that the fluid's Lagrangian or tracer velocity, \mathbf{v}_l , may differ from its Eulerian or mass-based velocity, \mathbf{v}_m , has led to a *dynamical* and *energetic* misinterpretation of fluid-mechanical phenomena¹. Demonstration, by experiment, of a difference between \mathbf{v}_m and \mathbf{v}_l constitutes the focus of this lecture, with details provided elsewhere¹ of the impact of this finding upon the correct equations of fluid mechanics and derivative subjects. In the latter scheme, \mathbf{v}_l rather than \mathbf{v}_m is found to constitute the fundamentally correct continuum fluid velocity, not only in terms of the primitive notion of "motion," a purely *kinematical* conception, but also, more importantly, in terms of the fluid's specific momentum density, kinetic energy, and other attributes associated with the literal movement of corporeal bodies through space, representing *dynamical* and *energetic* notions.

In creating the subject of continuum fluid mechanics using rigid-body mechanics as a model, Euler^{3,4} introduced the notion of mass *per unit volume*, namely the mass density *field*, $\rho \equiv \rho(\mathbf{x}, t)$, at each point $\mathbf{x} \equiv (x, y, z)$ of the fluid continuum and at each instant of time t , an experimentally measurable fluid property. Additionally, he adapted to fluid continua the center-of-mass velocity concept associated with rigid bodies, by defining the fluid velocity field, $\mathbf{v} \equiv \mathbf{v}(\mathbf{x}, t)$ (our \mathbf{v}_m), such that $\mathbf{v} := \mathbf{n}_m / \rho$, where the mass flux density (or current), \mathbf{n}_m , represents the experimentally measured

mass of fluid per unit time instantaneously crossing a space-fixed unit area centered at \mathbf{x} at time t . (In fact, it would appear that \mathbf{n}_m cannot actually be measured directly, although the truth of this statement does not impact upon the issues addressed here.) This definition of velocity, which involves experimentally monitoring the movement of mass at a point (and concomitantly measuring the fluid density at that point), appears, superficially, to be similar to, if not identical with, the Newtonian center-of-mass definition of the velocity of a moving body — the "material body"^{4,5} in this case being the (differential) element of mass that one is tracking as it crosses the (differential) area centered at \mathbf{x} . This experimental protocol differs from the usual scheme for measuring the velocity of a material object, whereby one simply tracks the latter by monitoring its trajectory through space, *without regard to the mass of the object being tracked*. (Optically "tracking" the statistically-averaged movement of, say, a small group of photochromically-labeled or otherwise tagged molecules of the fluid does not qualify as being isomorphic with a tracer velocity measurement. Explicitly, a collection of molecules is not equipollent with a material tracer, the latter being a single, rigid, corporeal entity.)

It is with Euler's mass-based definition of fluid velocity that we take issue. In particular, a differential mass element (explicitly a so-called differential *material fluid particle*) is neither isomorphic to nor equipollent with a corporeal tracer, in the sense that individual molecules, each possessing its own individual properties (namely mass and velocity), are free to enter and leave the mass element as the latter moves deterministically through space. As such, whereas the *total* amount of mass contained therein remains fixed during the material fluid particle's movement through space, this mass does not consist permanently of the same molecules (i.e., the same "matter"). Accordingly, despite the constancy of its total mass, this differential material "particle" differs fundamentally from the mass point of Newton's rigid-body mechanics. Moreover, in an energetic sense, a material fluid particle constitutes a molecularly "open" (rather than "closed") system as a result of the ability of individual molecules to freely cross its boundaries in either direction. As such, the First and Second laws of thermodynamics are not directly applicable to this system without modification¹⁴.

Despite the fact that the mass-based definition of velocity, \mathbf{v}_m , differs from the primitive physical notion of velocity, as embodied in the fluid's tracer velocity, \mathbf{v}_l , Euler nevertheless implicitly assumed these two velocities to be one and the same entity (in, say, much the same spirit as Newton earlier hypothesized

gravitational and inertial mass to be one and the same entity). To the best of the author's knowledge, this view has gone unchallenged for the past 250 years. Indeed, so pervasive is the universal acceptance of this equality that but a single symbol, typically \mathbf{v} , is employed to denote both velocities. Nevertheless, on the basis of both theory and experiment, this assumption was recently shown¹ to be invalid in circumstances where density gradients, $\nabla\rho$, exist within the fluid as a consequence of either composition gradients in multicomponent fluid mixtures undergoing mass transfer or temperature gradients in single-component fluids undergoing heat transfer — that is, in compressible, molecularly inhomogeneous gases and liquids.

Internally consistent, tripartite evidence exists¹ for the general velocity inequality, $\mathbf{v}_m \neq \mathbf{v}_l$, based separately and collectively upon quantitative arguments involving: (i) existing thermophoretic² and diffusiophoretic¹⁵ experimental data; (ii) a revised version of the current continuum theory of mass, heat, and momentum transport in fluids^{10,11}, the revision thereto originating with the recognition that volume can be transported diffusively¹², independently of the movement of mass; and (iii) molecular theory results available in the literature, based upon the well-known Burnett non-continuum additions to the original Chapman-Enskog continuum solutions of the Boltzmann equation⁹. In support of the velocity inequality hypothesis we confine attention in this lecture exclusively to the experimental evidence furnished in connection with item (i).

Thermophoresis is a phenomenon whereby a small, unrestrained, essentially weightless and otherwise force-free particle suspended in a single-component isobaric fluid (usually a gas), within which a steady, essentially homogeneous, temperature gradient exists, is observed to move from regions of high to low temperature¹⁶⁻¹⁹. Equivalently, a tethered particle experiences a force²⁰ tending to move it towards the low temperature region. Thermophoretic forces exerted on aerosol particles were first recognized by Tyndall²¹ in 1870 when he observed the presence of dust-free regions proximate to hot surfaces in a dust-filled room. A non-continuum "explanation" of the basic physics underlying thermophoretic phenomena, one still invoked today, was provided by Maxwell²² in 1879 (and, independently, by Reynolds²³ in that same year) when he offered an analysis of the workings of Crookes' radiometer²⁴, the latter device first exhibited publicly in 1873. Maxwell's molecularly-based explanation invokes the hypothesis of a thin, non-continuum, Knudsen boundary layer (only later so-named) existing in the immediate neighborhood of a solid body bathed by a gas of non-uniform temperature.

(This Knudsen layer is assumed to exist even when the particle size-based Knudsen number is sufficiently small such as to expect purely continuum behavior.) This non-continuum behavior is presumed to result in tangential "slip" of the fluid "velocity" \mathbf{v} (i.e., \mathbf{v}_m) along the surface of the non-isothermal body in a direction opposite to that of the surface temperature gradient, giving rise to thermal stresses of hydrodynamic origin exerted on the body, urging the latter towards regions of diminishing bulk fluid temperature.

Maxwell's "thermal stress," cum slip, explanation of the general phenomenon underlies all contemporary theories of thermophoresis in gases²⁵. Elsewhere^{1,2}, however, we argue against this supposed non-continuum, Knudsen slip-layer explanation, suggesting instead an alternative, purely continuum, "no-slip" velocity condition imposed upon \mathbf{v}_l , accompanied by appropriate modifications of the basic equations of continuum fluid mechanics, wherein \mathbf{v}_l replaces \mathbf{v}_m in all instances involving the explicit dynamical notion of physical motion through space (as, for example, in the case of the fluid's momentum density or kinetic energy). On the other hand, the mass "velocity," \mathbf{v}_m , is retained in those circumstances where the issue is purely kinematical, for example when following the contents of a mass element (i.e., a material fluid particle) as it moves through space.

Irrespective of the correct theoretical explanation of the mechanism underlying thermophoretic motion, the existing correlation¹⁶⁻¹⁸ of empirical experimental data remains viable, and, as such, will be seen to provide an objective test of Euler's $\mathbf{v}_m / \mathbf{v}_l$ velocity equality hypothesis. The main attribute of these data impacting upon the issue of the fluid's velocity (namely the velocity of the undisturbed, particle-free, fluid) lies in the experimentally-observed effect of particle size on thermophoretic velocity in the case where the spherical particle is sufficiently large such as to exhibit no sensible Brownian movement, and yet is sufficiently small such that the temperature varies only imperceptibly over its surface. Experiments¹⁶⁻¹⁸ performed under circumstances where the undisturbed fluid motion in the particle's absence is everywhere identically zero ($\mathbf{v}_m = \mathbf{0}$) reveal that the particle's thermophoretic velocity, \mathbf{U} , say, is independent of particle size in the continuum region, where the gas's mean-free path is small compared with the particle's radius (corresponding to an effectively zero Knudsen number, continuum phenomenon).

Explicitly, in the hypothetical (extrapolated) limit of "zero" particle size, a (non-Brownian) spherical

thermophoretic particle immersed in the fluid continuum is observed to move with velocity¹⁶⁻¹⁸

$$\mathbf{U} = -\frac{C_s}{1+(k_s/2k)} \nu \nabla \ln T, \quad (1)$$

where ν and k , are, respectively, the fluid's kinematic viscosity and thermal conductivity, and T is the absolute temperature of the gas; C_s , which is of $O(1)$, is Maxwell's (dimensionless) thermal stress slip coefficient, whose "best fit"²⁶ experimental value is about 1.2 (slightly larger than Maxwell's original molecular theory-based estimate of 3/4); k_s is the particle's thermal conductivity²⁷. In this limit, *such a zero-size particle serves as a "tracer" of the undisturbed, particle-free fluid* movement through space (at least in circumstances where the particle's thermal conductivity is small compared with that of the gas, $k_s/k \ll 1$, corresponding to an effectively thermally insulated particle, the latter property rendering the tracer "inert"¹ with respect to its physicochemical interaction with the fluid). Explicitly, the tracer velocity, \mathbf{v}_l , of the undisturbed non-isothermal fluid is simply equal to \mathbf{U} . Inasmuch as $\mathbf{v}_m = \mathbf{0}$ and $\mathbf{v}_l = \mathbf{U} \neq \mathbf{0}$, it follows, *ipso facto*, that $\mathbf{v}_m \neq \mathbf{v}_l$. That the intrinsic source of the fluid "motion" \mathbf{v}_l arises from a temperature gradient is irrelevant to the objective experimental measurement of the fluid's velocity. In fact, it is actually the density gradient rather than the temperature gradient that constitutes the animating force underlying such motion, as confirmed by comparable diffusiphoretic experiments¹⁵, as well as by the general theory of phoretic phenomena¹.

Written in a more objective, observer-invariant form, the experimental tracer velocity, and hence the undisturbed fluid velocity, in the case of gases is thus found from eq. (1) to be

$$\mathbf{v}_l - \mathbf{v}_m = -C_s \nu \nabla \ln T, \quad (2)$$

with \mathbf{v}_l and \mathbf{v}_m each measured relative to the same reference frame. By way of comparison with the experimental result (2), our theoretical expression^{1,2} for this velocity disparity, valid for both gases and liquids, is

$$\mathbf{v}_l - \mathbf{v}_m = -\alpha \beta \nabla T, \quad (3)$$

where $\alpha = k / \rho \hat{c}_p$ and $\beta = \hat{v}^{-1} (\partial \hat{v} / \partial T)_p$ are, respectively, the fluid's thermometric diffusivity and isobaric thermal expansivity, with \hat{c}_p the specific-heat capacity at constant pressure and $\hat{v} = 1/\rho$ the specific

volume. In the case of ideal gases^{8,10}, $\beta = 1/T$ and $\alpha = (1/4)(9 - 5\gamma^{-1})\nu$, where $\gamma = \hat{c}_p/\hat{c}_v$ is the specific heat ratio (possessing the value 5/3 for monatomic gases and 7/5 for diatomic gases). Upon introducing these values into (3), the resulting expression is seen to agree, both constitutively and phenomenologically, with the experimentally-observed undisturbed fluid velocity result cited in (2). In addition to this accord for the gaseous case, the theoretical formula (3) also agrees satisfactorily^{1,2} with the limited experimental thermophoretic particle data available for *liquids*²⁸.

Whereas traditional continuum transport equations¹⁰ governing steady-state heat transfer indicate the particle-free fluid to be at rest, in the sense of the absence of mass motion ($\mathbf{v}_m = \mathbf{0}$), the fact remains that the undisturbed fluid is in motion ($\mathbf{v}_l \neq \mathbf{0}$), as physically evidenced by the movement of a passive tracer inserted into the fluid to monitor the latter's motion through space! How can it be that the fluid is both at rest and yet physically moving? The answer to the paradox lies in the fact while there is no mass motion of the fluid, there nevertheless exists a volumetric fluid motion driven by the fluid's thermal expansivity β acting in concert with the mass density gradient (engendered by the temperature gradient). However, since $\mathbf{v}_m = \mathbf{0}$, this volumetric motion is entirely non-convective, being purely diffusive in nature. Moreover, in the general case, without restriction to purely phoretic-type undisturbed fluid motions, the fluid's Lagrangian velocity, \mathbf{v}_l , is identical¹ to its volume velocity, \mathbf{v}_v , the latter representing the flux density of volume (volume per unit time per unit area crossing a space-fixed surface), with the diffusive flux density of volume, \mathbf{j}_v , defined generically by the expression¹ $\mathbf{j}_v = \mathbf{v}_v - \mathbf{v}_m$. In the single-component heat transfer case, the constitutive equation for this volume current is^{1,12} $\mathbf{j}_v = \alpha \nabla \ln \rho$. In the case of steady-state heat transfer through a confined single-component fluid the preceding expression leads eventually^{1,2} to the velocity disparity quantified by eq. (3). With an appropriate transposition of symbols, a comparable theoretical result also applies to the case of binary convective-diffusive mass transfer phenomena occurring in isothermal, isobaric fluid mixtures (the latter obeying the "law" of additive volumes), the resulting expression being in accord with experimental diffusiphoretic particle data¹⁵.

The initial strangeness of the notion of a purely diffusive, non-convective mechanism for volume transport represents a failure of one's intuition, arising from a psychological predisposition to associate volume with mass through the intermediary of the fluid's

density ρ , especially in the case of liquids. However, like energy, momentum, or entropy, volume is not a material property that can, itself, be directly visualized. Rather, volume is abstract rather than corporeal, and therein lies the difficulty of conceptualizing its movement through space.

From a transport point of view, individual molecules carry with them such extensive properties as mass, momentum, and (kinetic) energy, as they move about through space. But they do not themselves, as individual entities, convey more abstract extensive properties, such as volume (and, say, entropy), since such extensive properties are *collective* in nature, rather than being associated with individual molecules. Addressing this distinction, by extending existing molecular theories^{8,9} so as to explicitly recognize and hence take account of the diffusive transport of volume, is clearly prerequisite to any comprehensive continuum theory of transport processes that purports to derive rationally from subcontinuum models of the phenomenon.

The pragmatic consequences of our remarks will likely be of interest only to practicing fluid mechanics and molecular theorists. However, since fluid mechanics often constitutes the first example^{6,7} of a non-trivial field theory^{4,5} (i.e., a *continuum* theory) to which applied scientists and engineers are exposed as neophytes, the issues raised herein provide a classic textbook example of the more generic philosophical need for such novitiates to appreciate the intimate relation existing between theory and experiment. Explicitly, how is a given physical entity (appearing in a mathematical description of the phenomenon to which the student is being exposed) to be measured experimentally. This lesson is especially needed in the computer age, where, for example, molecular dynamic simulations are often regarded as being isomorphic with the performance of actual physical experiments. That view notwithstanding, in order for the consequences of such theoretical computations to be physically interpreted, the statistical predictions emanating therefrom need to be expressed in terms of their macroscale experimental counterparts. And if such equivalences are subject to possible ambiguities, such as those resulting from an incomplete appreciation of the experimental protocol underlying their definitions, fundamental physical misconceptions can result. Such a misinterpretation has arisen (at least in our view), for example, during attempts to understand the role of literal, molecular-level "boundary conditions" prevailing at solid surfaces, in whose neighborhood the macroscale continuum physics — described by the very equations to which such boundary conditions are meant to apply — is not itself applicable owing to obvious inadequacies in such macroscale models of the

phenomenon at molecular distances from the surface²⁹. Apart from its fluid-mechanical implications, this lecture aims to emphasize, to a broader audience, the general importance of experiments in the theoretical sciences.

In this context of the preceding remarks, it is informative to recite an anecdotal story related by the late, pioneering rheologist, Karl Weissenberg (1893-1976) to a continuum-mechanical audience assembled at Carnegie-Mellon University in the early 1970's, which lecture I had the good fortune to attend. Prefacing his remarks (on Osborne Reynolds theory of dilatation in sand-water mixtures, during which he demonstrated a wonderfully simple illustrative experiment), Weissenberg noted that just prior to World War I he had served as a young applied mathematician at the Kaiser Wilhelm Institute of Physics in Germany, which Einstein visited periodically as part of the his "administrative" responsibilities as Director. On one of these visits, Weissenberg collared Einstein, telling him how much he admired his work, and seeking the latter's advice and counsel regarding an appropriate course of self-study that would permit his metamorphosis from applied mathematician to theoretical physicist. Without a moment's hesitation, Einstein suggested that his questioner learn how to design scientific instruments. Not understanding this response, Weissenberg posited that perhaps Einstein had misunderstood his original query, since his wish was to become a *theoretical* physicist, not an *experimental* one. Einstein assured him that he had not misunderstood the original question, and went on to elaborate that the only mechanism by which one could truly and deeply understand the fundamental meaning of a physical entity appearing in the guise of a mathematical symbol in a theoretical equation was by going through the mental exercise of systematically and methodically identifying the sequence of steps prerequisite to an unambiguous experimental determination of that entity. (Presumably underlying Einstein's response was the decisive role played in his 1905 special theory of relativity by his *gedanken* experiment involving the measurement of time, as well as by his then current efforts to understand the theoretical implications of the seemingly empirical equality of inertial and gravitational mass, an unequivocal experimental fact established earlier by Eötvös³⁰ in 1889.)

In any event, the fact that the relationship between the experimental measurement of fluid velocity and the symbol \mathbf{v} appearing in fluid-mechanical equations, posited by Euler some two-and-a-half centuries ago, has, until now, never been properly subjected to rational inquiry and subsequent critical experimental test (most simply, in *compressible* fluids at rest), points up the

sagacity of Einstein's advice. This object lesson is particularly striking when viewed in the context of the large number of students and professionals, scientists and engineers, prominent and otherwise (including, of course, myself at an earlier, more naive stage of life), who, despite their often extensive exposure to fluid mechanics, failed to question Euler's implicit assumption positing equality of the fluid's Eulerian and Lagrangian velocities.

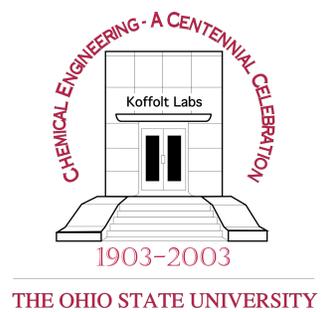
In summary, the work briefly reported upon here, if, independently substantiated by others, negates the foundations of 250 years of fluid mechanics, as well as derivative subjects, including continuum mechanics, transport processes, molecular theories of gases and liquids, irreversible thermodynamics, and rheology.

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Unsolved Problems in Biomolecular Engineering



Biographical sketch of Michael L. Shuler

Michael L. Shuler is the Samuel B. Eckert Professor of Chemical Engineering, Director of the School of Chemical Engineering, and Director, Bioengineering Program at Cornell University. He joined the faculty at Cornell in 1974 after receiving his doctorate in Chemical Engineering from the University of Minnesota. He holds a B.S. in Chemical Engineering from the University of Notre Dame. Shuler has held visiting appointments at ETH (Zurich, Switzerland, 1995), Boyce Thompson Institute (1995/96), University of Wisconsin (1988/89), and the University of Washington (1980/81). He has held short-term distinguished visiting professorships at the University of Florida, Osaka University, and the University of Newcastle upon Tyne. Shuler was the Director of the School of Chemical and Biomolecular Engineering from 1998 to 2002.

Shuler has current research interests in several aspects of bioengineering, particularly bioreactors. These interests include production of secondary metabolites from plant cell cultures (e.g. Taxol), structured mathematical models of cells (e.g. a "minimal" cell model to relate genomic structure to cell function), microfabricated, heterologous protein expression systems, and *in vitro* toxicology using cell culture analogs and physiologically-based pharmacokinetic models. He authored or co-authored over 200 refereed papers, and 7 books, including a textbook, "Bioprocess Engineering: Basic Concepts", now in its second edition.

He was elected to the National Academy of Engineering in 1989, an Inaugural Fellow for the American Institute of Medical & Biological Engineers in 1992, and American Academy of Arts and Sciences (1996). He has served on numerous taskforces and committees for the National Research Council, including the committee responsible for "Beyond the Molecular Frontier, Challenges for Chemistry, and Chemical Engineering". He also has been an active member of the ACS, American Society for Microbiology, American Society of Pharmacognosy, and AIChE (Fellow, 1997). He is currently a member of AIChE's board of directors and headed a recent taskforce on how to better integrate bioengineering into AIChE.

Unsolved Problems in Biomolecular Engineering

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Abstract:

The growing interface of biology with that of chemical engineering principles is a major challenge in chemical engineering education (esp. curriculum) and research. The “problem” for the chemical engineering profession is how do we best exploit these emerging opportunities. The most critical driver of change is the advent of molecular biology, genomics, and related technology. Biology is evolving from a data poor to a data rich science where the underlying molecular mechanisms of life are becoming clearer. Traditional strengths of chemical engineers are their ability to think across length and time scales and integrate descriptions of molecular level phenomena into an understanding of macroscopic systems. Chemical engineers are well positioned to contribute to biological discovery because of their skills in systems integration across length scales. Chemical engineers will be major players in the emerging field of systems biology. Further, chemical engineers are key contributors to the tools necessary for rapid, accurate and cost effective analysis of biomolecules. Finally, chemical engineers will increasingly convert the basic insights from the emerging understanding of biology into useful processes, diagnostics, therapies, and devices that will be of broad benefit to human kind. Some key examples are improved, lower cost cell culture processes to make therapeutic proteins that are more authentic, devices that allow rapid and more accurate assessment of disease, methods to evaluate pharmaceuticals for toxicity to reduce the cost of drug approvals, and more accurate ways to deliver drugs and genes to specific target tissues.

These intellectual drivers are also changing the nature of chemical engineering education. While the core chemical engineering principles will remain intact, biology (esp. biochemistry) will become a foundational science for all chemical engineers. Examples from biomolecular engineering as well as other emerging areas such as electronics and materials need to permeate the core courses supplementing examples from petrochemicals. Ultimately, I predict that within chemical engineering departments there will emerge an identifiable track for those students who wish to focus on biomolecular engineering.

Introduction

The grand challenge for the chemical engineering community is how to best exploit the emerging opportunities at the interface of biology and chemical engineering principles.

The “Problem” or “Challenge”

Biology is undergoing a revolution. The emergence of molecular biology followed by high throughput analytical techniques is generating data at rates that were inconceivable 15 years ago. Biology is evolving from data poor to a data rich science. This abundance of data will drive biology towards formulation of theoretical constructs to summarize these data efficiently and to form general principles and models. Biology is moving from an observational, descriptive science towards a mechanistic and quantitative science.

As it does so, the opportunities for chemical engineering science to be relevant to biology and biology to chemical engineering increase significantly. Biomolecular engineering emerges from this interface. Biomolecular engineering was defined by National Institute’s of Health for a December 1992 meeting as “...research at the interface of chemical engineering and biology with an emphasis at the molecular level.”

Why Are Chemical Engineering Principles Key to Biology?

Life obeys all the rules of chemistry and physics. Living cells are complex chemical plants. While mechanical and electrical forces (and their transformation into chemical signals) are important, the dominant science in cells is chemistry. Biology, especially at the molecular and cellular level, is primarily the study of chemical systems. Cellular regulation – information sensing and control of the corresponding chemical reactions – is typically done

using chemical signals and signal transduction pathways.

Analysis of cell function calls upon all of the principle components in a chemical engineering education: mass and energy balances, thermodynamics, reaction kinetics, transport processes (esp. mass transfer), separations (esp. natural membranes), and process control. The chemical engineering education is also unique in its emphasis on integrating from molecular to the macro scale as in the design of a chemical plant. These principles and the ability to work quantitatively across both length and time scales places chemical engineers in an unique situation to contribute to both using biology to create devices or developing useful therapeutic strategies and to discover more clearly how living organisms function.

Basic Biological Concepts

While some readers will have an in depth knowledge of biology, others may not. Consequently I cover some elementary concepts and vocabulary to insure that the remainder of the discussion is readily accessible. (Greater detail is available in Shuler & Kargi, 2002)

Molecular biology is principally concerned with the storage, replication, and use of information. A living cell must process information from the external world and act upon it to ensure survival and replication of the organism. The primary challenge to an intact cell is the flow and control of information. The primary tenant of molecular biology is known as the Central Dogma. The information necessary for a cell is encoded in the double helix of DNA (deoxyribonucleic acid). DNA acts as template for its own *replication*. Segments of DNA that encode information for the primary structure (i.e., sequence of amino acids) in a protein are called genes. The information for production of the protein is first transcribed from DNA through synthesis of a messenger RNA (ribonucleic acid) molecule by the process of *transcription*. Regulatory elements on the DNA determine when and how often a particular gene is transcribed. The information on the messenger RNA is converted to a protein through a process known as *translation*. If the physiological conditions in the cell are correct, the nascent protein folds into its proper 3-dimensional shape. Proteins act as catalysts, transporters, receptors of information, regulators, and structural elements in the cell.

The language of biology consists of four letters (A, T, C, and G corresponding to four different nucleotides) in DNA and three letter words. Each three letter word specifies a particular amino acid (or start or stop translation). Other combinations of DNA letters (of

various lengths) combine with proteins in the cell to block or encourage transcription of genes; these combinations of letters constitute regulatory elements. The language of the processes in the Central Dogma is universal; the same language applies to humans, plants, and microbes. The universality of this language is essential to modern biotechnology.

Simple bacterial cells (or procaryotes) are small (ca. 1 μ m) and have no internal organelles. A single, double stranded DNA (or chromosome) encodes the organism's genetic blueprint. In higher organisms (e.g. humans, plants, insects, even yeast) cells are larger (ca. 10 μ m) and have distinct organelles. The nucleus is one such organelle. Multiple double-stranded DNA molecules, or chromosomes, are present and maintained within a nuclear membrane. The minimal cell to be discussed later is a simple bacterial cell while eucaryotic cells are used in the "animal-on-a-chip" described at the end of this article.

Genomics and Systems Biology

The major advances in biology have led first to understanding the molecular basis of life, then to molecular techniques to manipulate cells (e.g. recombinant DNA technology) in a predictable manner and now to genomics. "**Genomics**" is the set of experimental and computational tools which allow the genetic blueprints of life to be read. By this statement we mean that we know the sequence of all the letters in genome or the total inheritable DNA in an organism. We have full genomic sequences for over 100 organisms. While most of these are for bacteria with only a single chromosome, full genomic sequences are available for representations of higher and more complex organisms (e.g. insects, plants, mammals and humans). As the technology for sequencing DNA improves, many additional species will be sequenced.

The emerging challenge is to understand this sequence data in terms of how an organism works. The term "**functional genomics**" is often used to suggest the range of activities necessary to relate genetic blueprints (genomic sequence) to the structure and behavior of organisms.

To fully understand regulation and physiology, DNA information is insufficient. Interactions among the expression of different genes requires complete knowledge of DNA sequence, mRNA expression, and protein content. Microarrays for determining time and situation dependent expression of mRNAs have been developed. A microarray is a high-density oligonucleotide array. Each oligonucleotide hybridizes with a corresponding m-RNA. For each known gene (eg

from sequence analysis) an oligonucleotide (eg 40 bases in length) can be synthesized that binds uniquely the mRNA from that gene. Using the techniques of photolithography, arrays for about 10,000 genes can be made that are less than 2 cm² in area. Binding with a mRNA can alter a fluorescent signal allowing the array to be read optically.

A study of the total protein content (proteome) of biological systems provides a unique protein fingerprint for a system and permits an elucidation of the key genes involved in a phenotype (eg functional features displayed by a cell). Hatzimanikatis et al. (1999) have shown that an understanding of the regulatory structure/response requires simultaneous data on DNA, RNA, and protein. Proteome analysis is slow, difficult, and expensive. Consequently, DNA and RNA are often obtained in the absence of protein information resulting in an incomplete understanding of the relation of genes and cellular regulation.

Even with complete knowledge of DNA, RNA, and protein, the full analysis of cellular function requires a knowledge of the small molecules in a cell or tissue, the physical structure of the cell, and the structure of metabolic pathways. The nature of a living cell is also dynamic (time-dependent) and requires a knowledge of current environmental state and past history to fully describe.

It is also critical to understand how these components work together. As an example, Bhalla and Iyengar (1999) have shown that when individual well-defined biochemical signaling pathways share common elements to form a network, new properties emerge when the network is analyzed. As this example illustrates the full properties of a cell or organism are more than a sum of identifiable components, but result from the complex non-linear interactions of the components. Understanding biology will mean understanding both which components are involved and the non-linear dynamics of how they interact. It is with respect to systems integration and analysis that engineering approaches may prove critical to biological discovery.

These considerations lead to the concept of “systems biology.” A goal of systems biology is the integration of genomics, high throughput, organism-wide data on cell composition and observations of physiology/function into a comprehensive mathematical model. Such a model of a living organism can predict the behavior of the organism in response to internal and external perturbations.

Why Is This Important?

The interface of chemical engineering with biology provides the best basis to develop “systems biology.” One of the most fundamental questions asked by humans is: “What is life?” What is the essence of being alive? Systems biology cannot ignore this question; a natural consequence of building a systems model is to ask what are the essential functions for life. Those biomolecular engineers engaged in developing systems biology will be leaders in this aspect of scientific discovery.

Biomolecular engineers will also create the devices and therapeutic strategies that arise from the “new” biology. One aspect of creation will simply be the tools necessary to more efficiently sequence DNA, to build microfabricated array systems to more effectively determine mRNA expression, or to better separate, purify and analyze all the proteins in a tissue or cell. The more critical aspect will be to couple engineering analysis and systems biology to create for example: cells that more effectively produce therapeutic proteins in large scales; to devise not only new vectors for gene delivery, but the overall predictive analysis to make gene therapy an useful clinical tool; to build new methods to separate different cells on a large scale to diagnosis and treat cancer; to grow artificial organs that can replace living tissues; and so forth.

Perhaps this point is a good place to ask what separates biomolecular engineering from biology. A key feature of biomolecular engineering is the emphasis on design: the ability to predict the output from controllable inputs. Another is to do the design in a macroscopic system using explicit links of the molecular scale to the macroscopic system. While engineering design, especially in the area of systems biology, may lead to biological discovery, the essential role of the biomolecular engineer is to create what has never been (e.g. a device, a computer model, or a therapeutic procedure). Scientists are primarily interested in discovering what exists (e.g. a new organism or novel protein).

What Is Known?

The origins of biomolecular engineering arise from the development of large-scale processes to produce antibiotics during World War II. Companies began to pair chemical engineers and microbiologists to gain the integrated knowledge of process engineering and microbiology necessary to produce these new compounds. The rise of processes to produce antibiotics induced students to seek combined training

in chemical engineering and microbiology. These students became the parents of biochemical engineering.

Somewhat in parallel, chemical engineers sought to apply the basic principles of chemical engineering to human health (e.g. development of the artificial kidney). This second group worked as biomedical engineers. From the 1950s to the 1980s these activities were thought to be rather separate. In the 1980s and beyond it became increasingly apparent that common principles from molecular and cellular bioengineering were foundational to both activities. For example, in both medical and non-medical applications it became important to understand how cells responded to different surface chemistries, or how they would respond to alterations in gene number or deletion, or how fluid shear would alter cell physiology, etc. By 1990 biochemical engineering had come to mean bioprocess engineering and seemed to exclude biomedical engineering. There was a need for a new word that would recognize that common principles supporting both medical and non-medical applications at the chemical engineering and biology interface. In 1992 (as described earlier) the term biomolecular engineering was coined to include all activities at the chemical engineering and biological interface with special emphasis on the emergence of molecular and cellular biology as the common linkage independent of area of application.

Biomolecular engineering is perhaps best defined by what biomolecular engineers do. There are four activities in which those with a chemical engineering background dominate:

- Bioprocesses (biochemical reaction engineering; bioreactors with associated bioseparations). Bioprocesses produce pharmaceuticals, chemical commodities and energy products and are an integral part of waste treatment.
- Bioseparations support bioprocesses and have important medical applications such as cell separations (e.g., stem cell recovery) and proteomics (e.g., total analysis of protein content in a cell).
- Metabolic engineering is the analysis and redirection or enhancement of the metabolic activities of a cell. Chemical engineers are currently playing a leading role in this area, often for the purposes of supporting bioprocess development for more efficient production of pharmaceuticals or chemicals.

- Biocatalysis concerns the generation of protein catalysts (enzymes) with novel or enhanced activities often in unusual environments, such as at high temperature or in organic solvents. These enzymes can be used to synthesize novel chemicals.

In addition biomolecular engineers are key contributors to research activities such as:

- Drug delivery is an area in which chemical engineers have had a major impact, particularly for controlled delivery of pharmaceuticals to specific target sites (e.g., a tumor).
- Gene therapy is really metabolic engineering combined with drug delivery. The right genes need to be delivered to the desired tissues, and proteins from that gene need to be made at the right time in the right amount. The lack of success with gene therapy is, at least in part, due to the inability of medical scientists to deal with these issues of well-controlled gene delivery and gene expression. The solution lies in a quantitative analysis of the entire system.
- Biomaterials (particularly for controlled release of bioactive compounds or surface modifications to become biologically compatible or to actively direct biological activities).
- Cell and tissue engineering combines biomaterials and broad concepts from metabolic engineering and analysis of chemical signaling. The issues for manufacturing (e.g., artificial skin) are very similar to those for bioprocesses.
- Systems biology, especially to computer models of cells and to rapid separation, purification and measurement of cell components such as proteins.
- Nanobiotechnology (e.g., “lab-on-a-chip” type devices; chemical engineers have played key roles in development of these devices which are basically small-scale chemical plants).

If the reader is interested in another listing of challenges to be solved by biomolecular engineers, they are referred to the new book just released by the National

Research Council (2003) on “Beyond the Molecular Frontier: Challenges for Chemistry and Chemical Engineering”

The next section details two programs our research group has undertaken that illustrate our response to the challenges arising from the new biology-chemical engineering interface.

Examples of Biomolecular Engineering

The Minimal Cell Model

We are constructing a mathematical model of a "minimal cell" to provide a platform to better understand the "design logic" of cellular regulation. The model, which contains kinetic and thermodynamic constraints as well as stoichiometric constraints, will be used as a tool to identify the organizing principles which relate the static linear sequence information of the genome to the dynamic non-linear functioning of the cell. A minimal cell will be a prokaryote with the minimum number of genes necessary for growth and replication in an "ideal" environment (i.e. a rich medium with preformed precursors, constant temperature and pH, and at a sufficiently low cell concentration that no metabolic by-product becomes inhibitory). Kooin (2000) provides a review of the minimal cell concept.

The success of whole organism genome sequencing and high-throughput measurements provides an opportunity for system-level analysis of whole organisms or what has been termed "systems biology" e.g. (Ideker, T., et al 2001). The emphasis in our project is on modeling the complete functionality of a cell and its explicit response to perturbations in its environment (Browning & Shuler, 2001). Our attempt to generate a "complete" model that predicts time-dependent responses in a cell differentiates this project from others.

The model we are developing focuses on essential functions while finding examples of gene products that can perform those functions. While the set of minimal genes we postulate may change (for example if a new multifunctional protein is found), we believe we can find a set of truly essential functions. Further, the technical difficulties associated with generating an experimental minimal cell and the ambiguities in interpretation of comparative genomic data argue for the establishment of a theoretical computer model of a minimal cell that is explicit in regard to minimal function and includes a realistic set of gene products to accomplish these functions. This is, in essence, the primary objective of the project.

We have previously developed a “complete” cell model of *E. coli* that contains all of the functional elements for the cell to grow, divide, and respond to a wide variety of environmental perturbations. This model serves as the basis for a minimal cell model, but does not qualify as a minimal cell model for two reasons. First, it is specific to a particular species (*E. coli*). Second, chemical species are lumped into a single model component so that the dynamic function of the cell cannot be mapped directly back to the genome. Basically, the model is a good summary of the functionality required for a minimal cell, but it does not capture explicitly the physical chemistry that supports those functions. We described our first mathematical model of a single *E. coli* cell in 1979 (Shuler, et al, 1979); at the time of its publication, it was the only model of an individual cell which did not include artificially-imposed constraints on aspects such as mode of growth, timing of cell division (e.g. growth rate), and cell size. Also, it was unique in its ability to respond explicitly to concentrations of nutrients in the environment (Bailey, 1998). This base model (Domach, et al 1984) has been embellished with additional biological details to allow prediction of a wide-range of microbial responses to environmental and genetic manipulations (Shuler, 1999). The initial model included only 18 components, and most components represented large groups of related chemical species; the mathematical description of cellular function, which is the core of the model, is based on time-variant mass balances for each component. Each mass balance takes into account the component's synthesis (as a function of availability of precursors and energy, and in some cases, relevant enzymes), utilization, and degradation. Stoichiometric coefficients for relating components through mass balances were derived primarily from published research, and in some cases, from our own experiments. It is important to note that the model was not developed by using adjustable parameters to fit model predictions to experimental results, nor did the stoichiometric mass balances assume a steady state (i.e., the amount of each component was allowed to vary with time). Despite the simplifications that were made in describing cell composition and relationships, the model can accurately predict changes in cell composition, cell size, cell shape, and the timing of chromosome synthesis as a function of changes in external glucose and ammonium concentration.

While the minimal cell model differs from the *E. coli* model (primarily in that each component in the minimal cell model will be directly related to an actual component in a living cell), the *E. coli* model has been an excellent starting point from which to construct a minimal cell model. The *E. coli* model is “complete” in terms of function and is “modular”. By modular we mean that we can “delump” a pseudochemical species

into individual components while still maintaining the essential connectivity to other functions in the cell. This allows us to add detail in parallel efforts on different “modules” and then have confidence that they can be recombined into a functional and functioning whole.

We have tested the hypothesis that it is not the exact values of parameters in the model that determine function, but that the relative values to one and another is critical. We tested this hypothesis by varying all kinetic rates by a scaling factor (or kinetic ratio). The growth rate scales directly with the kinetic ratio over about two orders of magnitude. At low values of growth rate the terms for maintenance due to membrane energization become important, and these factors are not directly influenced by the kinetic ratio and the linearity is lost. Cell composition (e.g. protein/cell, RNA/cell, etc.) remains constant for a wide range of kinetic ratios. Further, relative growth rate changes for models with different kinetic ratios are essentially the same for a wide variety of perturbations to cell function. All together these findings suggest that “...a minimal cell based on a hypothetical set of properties using dimensionless parameters should provide realistic insight into cellular regulation” (Browning & Shuler, 2001).

A particularly important aspect of the original Cornell *E. coli* model was a model that mechanistically coupled cell growth, chromosome replication, and cell division. We have updated the model for control of chromosome replication based on new experimental evidence over the last 25 years. While the revised model is significantly different in terms of biological mechanism (positive vs. negative control), the mathematical characteristics are quite similar. Indeed it may be that any functional mechanism for control of replication must satisfy similar mathematical characteristics.

We have nearly completed our model for nucleotide metabolism and have demonstrated that a functional system can be achieved with significantly fewer gene-encoded functions (13) than estimated previously. This “module” has been integrated into the whole cell minimal model and the resulting cell functions in a biologically realistic manner confirming the modularity of the model. We are currently extending the model to describe other “modules” with genetic level detail.

While this project focuses on the cellular level, it is possible to build useful models of complex, multicellular organisms, including humans.

An “Animal-on-a-chip”

Our ultimate goal is construction and validation of an *in vitro* device (cell culture analog or CCA) that realistically and inexpensively mimics uptake, distribution, metabolism, and biological response of humans to exposure to various chemicals and drugs (Ghanem & Shuler, 2000). A cell culture analog (CCA) is a device that is a direct physical replica of a physiologically based pharmacokinetic (PBPK) model. A PBPK model is a mathematical model that represents the body as interconnected compartments representing the functions of selected organs or tissues. The CCA uses living cells in “organ/tissue” compartments to represent some aspects of metabolism in that organ. Coupling of a CCA and corresponding PBPK can provide insight into molecular mechanisms of toxicity. This device will impact biomedical research by providing a cost-effective, pre-clinical system to estimate human response to a wide range of drug leads and assist in risk assessment for environmental exposure to chemicals while reducing dependence on animal studies.

While our initial experiments were on macroscale systems, there are a number of advantages to greatly reducing the size of the CCA device to microscale. Our design calculations for a prototype chip system have shown that we can achieve physiologically realistic organ residence times and ratio of fluid to tissue in an “organ” compartment, and maintain fluid flow rates at values that create only physiologic values of shear stress on cells. Only by going to the dimensions of a microsystem can we attain a physiologic design. Further, the microscale reduces the cost of the device and makes effective use of expensive reagents or difficult cell cultures.

We have constructed prototype microCCAs in silicon with 3 (liver-lung-other tissue) compartments. The constraints placed on the design were: (1) it should fit on a 2cm X 2cm silicon chip; (2) the ratio of the organ compartment sizes and the liquid residence times in each compartment should be physiologically realistic; (3) each compartment should have a minimum of 10,000 cells to facilitate analysis of chemicals and enzyme activity; and (4) the hydrodynamic shear stress on the cells must be within physiologic values (2dynes/cm² for body cells and 6-14 dyne/cm² for endothelial cells). We have also extended this technology to a 4-compartment system (liver-lung-fat-other tissues). Initial studies have been done with naphthalene as the model toxicant. These studies have used two-dimensional cell cultures (i.e., monolayers) of established cell lines. The models demonstrate the production of reactive, relatively stable metabolites in the liver compartment that circulate to the lung compartment and cause preferential cell death in the

lung compartment. When a fat compartment is present the level of toxicity is reduced due to adsorption of hydrophobic compounds into the fat compartment. Further we have identified naphthaquinone as the toxic metabolite.

We are currently adapting this approach to evaluate chemicals for the potential usefulness as compounds to suppress multidrug resistance in cancer cells. If successful we may find chemical mixtures, including chemotherapeutic agents, that will allow treatment of cancers that currently do not respond to chemotherapy.

These two examples of work at the chemical engineering biology interface demonstrate the need for biomolecular engineers to be expert in chemical engineering with significant biological knowledge. In the next section we discuss some implications for chemical engineering education.

Implications for Chemical Engineering Education

I believe that all chemical engineers (indeed all educated citizens) should have a basic college level understanding of biology and biochemistry. Without a basic understanding of biology, chemical engineers will be excluded from certain types of jobs, particularly in the pharmaceutical and biotechnology sectors. More importantly they will be unable to understand the basis for environmental and health regulations while they are responsible to meet those standards in the operation or design of any chemical facility, whether it is biologically based or not. Further, many of the great debates in our society will arise from advances in biology (e.g. stem cell therapies). It is also important for the unity of the discipline that all chemical engineers have biology as one of the supporting sciences.

It must be recognized that learning biology is not simply a matter of new vocabulary, but also understanding a different culture. What constitutes “proof” of a concept in biology is different than the typical approach in engineering. In particular, biologists have had to make progress in the absence of a quantitative theoretical framework. Thus biologists are particularly sensitive to the use of appropriate experimental controls; a concept not stressed in traditional engineering education where experiments are usually evaluated by comparison to theoretical expectations. I believe chemical engineers will become better chemical engineers as they broaden their perspective to incorporate both approaches to testing hypotheses.

As biomolecular engineering emerges all chemical engineering departments are faced with two problems:

how to offer specialized education in biomolecular engineering and how to integrate biomolecular engineering into traditional courses that teach the basic principles of chemical engineering.

For those students who wish to focus on biomolecular engineering, they need not only basic biology courses, but also courses in molecular and cellular principles of biomolecular engineering, quantitative analysis of physiological systems and bioprocess engineering (metabolic engineering, bioreactors, bioseparations). I believe the biggest unmet need is course material for molecular and cellular bioengineering. No textbooks are yet available to support such courses. It is material at this level that will define the intellectual foundations for biomolecular engineering.

Even students who do not intend to work in biotechnology or health are looking for inclusion of biomolecular engineering into the curriculum. The absence of biological based examples and context in textbooks is a barrier to the true integration of biology into chemical engineering. All of the chemical engineering principles can be developed in the context of biological systems. In addition to the need for modified textbooks, many chemical engineering faculty are uncomfortable with the intersection of chemical engineering and biology. While good textbooks would relieve some of the faculty anxiety, short courses specifically targeted to this issue would be helpful. Chemical Engineering as a sustainable unified discipline will require a professorate that are comfortable with biology as a core science of chemical engineering.

Chemical engineering education has undergone many changes over the last fifty years. Evolution to incorporate biology and biomolecular engineering into chemical engineering education should be a natural process. I believe that this evolution will be accomplished within less than a decade.

Concluding Thoughts

I believe that it is important to recognize that the intellectual revolution in biology provides a basis for fostering biomolecular engineering. Chemical engineers who embrace the basic concepts in biomolecular engineering are well prepared to become leaders in the field of systems biology.

In addition biomolecular engineers will continue to be leaders in bioprocess and bioreactor engineering, bioseparations, and metabolic engineering. Further biomolecular engineers will be critical in the development of the molecular and cellular aspects of

biomedical engineering. Particularly important will be opportunities in controlled drug delivery, gene therapy, tissue engineering, diagnostics (based on separations technology), and nanobiotechnology.

For the health of the chemical engineering profession, biology must be integrated into the curriculum. Chemical engineering principles should be developed throughout the curriculum in the context of biology as well as in the context of more traditional areas. Finally the academic enterprise should provide opportunities for specialization in biomolecular engineering which will require development of new courses which integrate biology and engineering in the same way chemistry and engineering were integrated at the beginning of the profession.

The opportunities and challenges to chemical engineering that arise from the biological revolution will invigorate the profession and attract students who otherwise might not select chemical engineering. Many of humankind's oldest problems may be solved by combining chemical engineering principles with opportunities emerging from the new biology.

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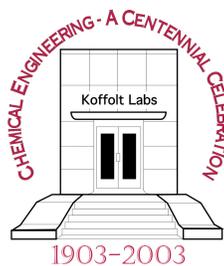
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THE OHIO STATE UNIVERSITY

Unsolved Problems in Process/Product Systems Engineering



Biographical sketch of Arthur W. Westerberg

Arthur W. Westerberg is currently the Swearingen University Professor of Chemical Engineering at Carnegie Mellon. He received his BS from Minnesota '60, MS from Princeton '61 and PhD from Imperial College, University of London '64, all in chemical engineering. He spent two years at Control Data Corporation and nine years as a faculty member at the University of Florida before joining Carnegie Mellon University in 1976. He has served as Director of the Design Research Center (78-80), Chemical Engineering Department Head (80-83), and founding Director of the Engineering Design Research Center, an NSF funded Engineering Research Center (86-89).

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Unsolved Problems in Process/Product Systems Engineering

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Abstract

We examine the process/product systems engineering (PSE) area of chemical engineering. A brief history of some of the accomplishments of the past four decades follows and notes the strong coupling of PSE with developments in computing. “Driving forces” in place today suggest where PSE research and development might move. The paper ends with a discussion of some major outstanding problems in PSE.

Introduction

Today the Chemical Engineering Department of Ohio State University is celebrating its 100th year, a very proud accomplishment. As a part of that celebration the department has invited several faculty from throughout the country to prepare papers and presentations, each of whose theme is to be the unsolved problems in one of the research areas in this discipline. Mine is to examine the relatively young area of process systems engineering. I will take the liberty of adding “product” to the title as we are more and more interested in delivering processes and products. While young, this area has been active, and, in the conventional process area, it is reaching maturity. Maturity means there are many others in the area, and all are competing to find and develop new ideas and to obtain research funds. With maturity comes the obligation to re-examine accomplishments and to think about where we should be heading. In this manner we are in the same situation that many believe chemical engineering as a discipline is in at this time. In spite of our maturity, some very difficult issues remain unresolved. We shall examine them in the final section of this paper.

What is process systems engineering?

Three years ago, Ignacio Grossmann and I prepared a “Perspectives in Chemical Engineering” article for the AIChE J on the process systems engineering area¹. Our first task was to define this area. We noted “companies must design and operate chemical processes effectively and efficiently so they may survive in today’s highly competitive world. Providing the methods, tools and people that allow industry to meet its needs by tying science to engineering is a compelling aspect of Process Systems Engineering (PSE).” I find it hard to improve on this view.

We elected to broaden the more conventional view that our domain was process design, control and operation. We start at the nano-scale with decisions

about what molecules to make. At the next scale, we often have to consider the aggregation and structuring of materials from these molecules. These first two types of decision are more in line with thinking about products rather than processes. We progress to our traditional scale, where we make decisions about production units and then whole processes. Companies worry about the proper designing and operating of multiple processes. Finally, at the meso-scale, companies, interlinked into supply chains, make decisions about how they fit into the whole of the manufacturing and delivery activity for an industry. Our move to the meso-scale is coming quickly. For example, in January of next year in Kunming, China, we have organized the seventh conference on PSE around the topic of business decision making (<http://pse2003.chemeng.tsinghua.edu.cn/>).

Our final definition for PSE became: “*Process Systems Engineering is concerned with the improvement of decision making processes for the creation and operation of the chemical supply chain. It deals with the discovery, design, manufacture and distribution of chemical products in the context of many conflicting goals.*”

What is different about PSE?

We noted in our perspectives paper that much of chemical engineering research is science-based. Its intellectual base is the study of nature, where the goal is to seek and understand the “truths” of nature. We perform as engineers when we use this understanding to create useful artifacts for the betterment of humanity. PSE resides within the activity of engineering, and its intellectual challenge is the discovery of concepts and models that will allow us to improve all levels of decision making processes. What we create does not have to be an exact representation but rather a useful one that leads us with least effort to correct decisions.

What are some accomplishments in PSE?

Computing

PSE as an active research area started in the late 1950s, at the same time that engineers could access computers that were more than adding machines. The first computer I used was a Univac 1101. It was a room full of tubes (valves in UK English) that would have, had the air conditioning failed, led to the burning down of the building in which it was housed. It had 1000 words of memory and a computer language that was one to one with machine instructions – and it was little more than programming in 0s and 1s. By 1960, I was using a dual drum IBM 650 at the Forrestal Research Center at Princeton with twice 2048 words of rotating drum memory and by the next spring a CDC 1604, a transistor-based machine with 32K words (at this time words were of the order of four bytes). The first supercomputer was likely the CDC 6600 that appeared in the early 1960s. In 1977 we saw the CRAY 1, a super-supercomputer that, according to the folklore I have heard, had about the capability of a 100 megahertz Pentium. The IBM personal computer appeared in 1983 – I had two. It had 640K words of fast memory and a 10 megabyte disk and cost about \$4400. 1995 was the year of the internet explosion. Today we have giga-everything on our desk. My latest computer is dual multithreaded xeon rated at 2.66 gigahertz each, with 2 gigabytes of fast memory and a dual, auto backup, 200 gigabyte disk. My new Ethernet card has a gigabit performance label.

Analysis and optimization

With this development in computing, PSE continually attacked larger and larger problems. Three data points are the solving of 19 equations in 19 unknowns in about as many hours in the late 1950s, to the bragging about solving 650 equations in the mid-1960s, to the solving of a million equations today in a few tens of minutes.

In the late 1960s, we could optimize a flowsheet, while using the computer time required to perform about 2000 flowsheet simulations. It took the entire weekend and often failed to get to the answer. People became skilled at saving intermediate results every hour so they would not have to start over when the inevitable failure occurred. With the advent of the generalized reduced gradient algorithm, optimizing a flowsheet used the equivalent in time of 100 converged flowsheet calculations. In the late 1970s, we participated in the development of the sequential quadratic programming algorithm, which uses a Newton-based scheme to solve the model equations and the necessary equations for optimality together. We demonstrated that we could optimize in about the time we took simply to solve the flowsheet equations alone. We believe it cannot get

much better. There has been a lot of later work to improve one's ability to converge to solutions under adverse numerical conditions, and throughout the 80s and 90s, we participated in the creation of systems to aid engineers in writing and debugging process models.

Discrete decision-making

In the early 1980s, Ignacio Grossmann added binary variables to our models. His first work showed how to set up and solve mixed integer linear programming (MILP) problems. Binary variables allow one to choose among discrete alternatives while optimizing, such as choosing between using a single- or a two-stage compressor or the choosing of the number of trays in a column. The solving algorithms involve the use of decision trees and bounds rather than just gradients, and they take a lot longer. He and his students subsequently developed the DICOPT algorithm, which became a part of the commercially available modeling system GAMS and thus accessible to all of us to solve mixed integer nonlinear programming (MINLP) problems. Many in PSE have now contributed to the literature that abounds with many, many tricks in formulating and strategizing about classes of problems so one can solve them. Industry often attests to using this type of method and saving millions of dollars annually. One example is to plan where and when to place oil rigs in the Caribbean. Another is to plan the investments for annual plant modifications while simultaneously making monthly production decisions to control inventories when one can only guess future demand and technology improvement. These techniques are routinely used to schedule batch/semi-continuous, multi-purpose plants.

Synthesis

Another area in which PSE researchers contributed is in developing so-called "process synthesis" methods to aid engineers to be creative when designing new processes. A very early paper on distillation by Lockhart in 1947 gave guidelines on whether to separate an ideal ternary mixture by separating the most or the least volatile component first. In the late 1960s, Dale Rudd and his students really started others to look at this area. They asked if one could automate the selection of equipment and its configuration first for heat exchanger networks and then for a complete flowsheet. In 1971 Ed Hohmann, a student of Lockhart, showed in his PhD thesis that one could compute the least amount of hot and cold utilities required for a process WITHOUT knowing the heat exchanger network that could accomplish it. He tried to publish twice, and peer review rejected his papers. He also showed how one could estimate the heat exchange area required. Linnhoff in 1977 independently discovered the same

ideas using a different formulation and brought these ideas into engineering practice. With these tools, synthesis reached the goal of outperforming what engineers could do without them.

In the 1970s, Gary Powers and many in chemistry looked at doing what I remember doing as a student in organic chemistry in the late 1950s: invent different ways to synthesize a particular organic molecule. This automation showed that there were literally millions of pathways, most of which unaided humans would never think to explore.

In addition, the early 1970s produced many papers on how to find the best sequence of distillation columns when separating relatively ideal mixtures. The real fun was the work on designing distillation and decanter systems for separating highly non-ideal mixtures, where azeotropes and liquid/liquid behavior abound. This latter work appeared first in the late 60s in the ex-Soviet literature (they had to be smart on paper because they did not have computers – see a soon-to-appear book by Petlyuk) and then with the work of Doherty and Perkins and then Doherty and his students.

In the early 1980s, Tennessee Eastman (now Eastman Chemicals) built a plant to manufacture methyl acetate that required about one sixth (yes, 85% less) the investment and operating expenditures of previous plants. Their design had one extractive, reactive distillation column in it, and it started many research efforts into understanding reactive distillation. Again, among the first were Doherty and his students. Several of the simulation companies added reaction to their column simulation packages. However, simulation and much of the analysis did not suggest to anyone if one should use reaction and, if so, where to place it in a column. Work still progresses in this area, and we now have a number of insights that can help engineers be creative in the design of these systems.

Other areas

Most of the above discussion relates to the design of conventional chemical processes. Major activities in PSE also cover the control and operation of chemical processes. Process control has moved from the using of frequency response methods and simple PID controllers in the late 50s, to computer supported optimal control in the 60s, to heavily computer supported model predictive control in the last two decades and lately to less complex but guaranteed stable control based on passivity theory. Better analysis methods include creating more accurate dynamic simulators, creating very fast simulators for training, showing how to analyze, optimize and control dynamic and distributed systems, and providing methods to determine the stability of a controlled process. Synthesis methods

include aiding engineers to decide what to measure, how to structure the control system, and how to alter the design to improve one's ability to control a process.

We also see work, often based on artificial intelligence approaches, for creating computer support systems to help operators, and now computers, determine what just went wrong and how to take safe corrective action in the running of a process.

Control systems involve the interaction of operators, computer programs, PLC circuits, control elements, and the process units. There is much opportunity in such a complex structure for there to be errors, many of which could be hidden catastrophes in the making. Can one hope to “verify” the correctness of such systems? Gary Powers, continuing his earlier work on safety, introduced the use of methods to verify the correctness of computer chips (e.g, a Pentium computer chip) to checking such systems. He is talking about 10^{50} pathways, which makes Avogadro's number looks small in comparison.

So what is next?

PSE has had a rich and exciting history. The academic community has also grown from only a handful of us in the 1960s to hundreds today (with a large percentage -- often stated to be about half of the academics -- on the Roger Sargent family tree). Engineers now routinely use our tools and methods to improve how they design, control, and operate processes.

Our domain for the last four decades has been chemical processes, with an emphasis on commodity chemical processes. While far from a fully explored problem area, it is becoming increasingly difficult to use problems from this domain to raise research funds. If we mention the word “distillation,” support agencies decline our proposals almost out of hand. So are we becoming a research topic without a problem domain? I will suggest that the future of PSE is going to be in many, very diverse research areas that the about-to-be-discussed drivers suggest. This moving of PSE research into other domains is already happening. We cannot just move, however; we must become domain experts in these new areas to feel comfortable in contributing to them. I see an analogy to many in computer science who have proposed and developed excellent new approaches to problem solving but have lacked interesting problems on which to apply them. To me it has been much more comfortable to be an engineer who then learns computer science than the reverse.

But what will be the domains into which we should migrate or areas out of which future PSE researchers will migrate into PSE? Let us explore the answer by first looking at the world today to identify the “drivers”

that will push or pull us into what we will do. The following are my thoughts.

Drivers for research

Let us assume (though the last two years could make this a dubious assumption) that people have increasing amounts of “extra” funds, that is, funds over and above the amount they deem necessary to survive. On what will we spend our extra funds without questioning the price? I would suggest two: on our **health** and on our **leisure**. On most other things, we tend to question price, but, on these two, we seem to accept the price charged. If so, these two areas may be where business will put its money in the future. We should at least review what we propose against this contention.

We are increasingly **socially aware**. We worry a lot more about harming the environment, about sustainability and about the total life cycle costs of decisions. This worry must increase as we continue to harm our planet more and more. Thus, it will have to be a driver for the future.

We are learning how to manufacture very small things, with the dimensions of molecules. NSF has programs almost requiring us to say the word “**nano**” in the title (with the consequence that a number of proposals now discuss 1300 nanometer sized objects). Materials where we can maneuver atoms into desirable positions have truly remarkable properties. They are often remarkably stronger, or they are able to detect and handle minute amounts of material, and so forth. We will be able to do for pennies what now cost hundreds of dollars – and we can now make these nano-objects. We are only scratching the surface. So “tiny” is a driving force of the future. Related to this nano area and by using thinner and thinner lines, computers are still following Moore’s law. They will ultimately run into the limits of physics, but not yet. Perhaps we have another decade. What can we hope to do with major computing that is tiny, fast and virtually without cost for the hardware?

But in computing, it is the **network** that is likely the real contributor to our future. We are fast becoming a wired planet of people. There are two implications: information is unbelievably available, and we can work with people around the globe almost as easily as with someone in the next office. For information, how many of us hesitate now to look up any topic using Google, and with amazing success? One can even use it to check the spelling of a word (unless it is commonly misspelled). When we want to know about a company – we type in www.companyname.com and find everything we would ever want to know. We want to buy a digital camera, we find reviews everywhere and get back lists of vendors sorted by price.

Networking is creating another driver: **globalization**. Companies now operate around the globe. We can no longer operate in isolation. Globalization gives us more markets, but it also gives us more competitors.

Another driver is our progress in **biology**. Our ability to know, to interpret and to modify gene sequences is changing such things as medicine, our understanding of biology, and how we will grow our food.

To support life as we know it, governments build or regulate the building of **infrastructures** such as transportation systems, power generation and distribution systems, gas pipeline systems, road systems, phone systems, water distribution systems, waste recovery systems and so forth. Many of the tools we use in PSE are directly applicable for the design and operation of infrastructures. Deregulating many of our infrastructures has caused turmoil; this will continue as we explore more and more how best to manage these large, often monopolistic systems. New technology is constantly altering the rules for how to construct them also, as with cellular phone systems and power generation and distribution systems. Integrating them, such as where the transportation system uses the phone system to effect control, is impacting these systems.

These systems are becoming more integrated and much more complex. So handling **complexity** is a driver, too.

And yes, there are still new algorithms to discover and tools to build

For about four decades now, we have seen enormous improvements in the speed of computer hardware. There have been equally impressive improvements in algorithms, many of which we just discussed and that we in PSE have contributed, such as when solving the difficult problems we like to pose.

The improvements typically come from tailoring algorithms to fit the particular features of the problem. The first method to solve simultaneous nonlinear equations involved gridding the space and writing embedded DO loops. The approach found the best point in the grid and around it regridged with a finer mesh. Next, we used iterative methods, such as successive substitution, in our flowsheet systems. We added accelerators like Wegstein’s method and Broyden’s method. Then we implemented full Gauss elimination algorithms as the inner loop of Newton-Raphson methods, but we could only deal with a few tens of equations. Sparse matrix methods developed in modeling electrical circuits migrated into chemical engineering in the 1970s and dramatically improved

computation times for the linear equation solving inner loop of Newton-Raphson based methods. We also learned how and when to use iterative methods for solving linear equations for extra large problems. Optimization went from pattern search to GRG to SQP, as noted earlier. We have contributed codes for solving mixed integer nonlinear programming problems that are widely used. We have also explored parallel computing whereby we decompose problems into parts that we solve in parallel.

It is evident in all this progress that many of us have been tool builders. Can we continue to be tool builders? Actually, I like the analogy to a tree falling in the forest. If no one is there to hear it, was there a sound? If no one uses our methods, was there a method? Yes, we will have to continue to build tools, but fewer of us will get credit for their novelty.

Is there anything new out there that will change the effectiveness of computing? Let us assume that we can have unlimited amounts of high speed networked computers for solving our problems. Can we find effective ways to exploit such a resource to solve very large hard problems? Parallel computing is a possibility. Unfortunately, in virtually all decompositions to parallelize algorithms, one finds a coordination step for which all the parallel steps must wait before carrying out the next iteration. If coordination takes ten percent of the time, then Amdahl's law states we are limited to a 10 fold decrease in "clock" time, even if we have hundreds of computers.

Agent-based systems: Another approach is the research of John Sirola, who is currently doing his PhD under the direction of Steinar Hauan and me. His topic is the use of agent-based computing to solve hard problems. This type of approach has been in the literature for about two decades, but we have not been exploiting it in chemical engineering. People have generally only used the method without examining quantitatively its effectiveness.

We can use the following metaphor to appreciate the ideas here. Suppose you were to direct a new research program at the NSF and were given a budget of \$10 million per year. You could choose to fund the one best, perhaps best by far, researcher in the US, or you could choose to fund the top two dozen. Most of us would agree that the latter approach is better. Now hold back 5% of the budget and insist that these researchers meet twice a year and share results.

There are two features of this last approach that appeal. We should like the diversity of having two dozen research programs looking at the topic. Second, the collaboration should aid researchers to see in the results of others better ways to proceed in their own

program. Agent-based software systems have both these features. John has measured the impact of both diversity and collaboration, and both dramatically improve performance on a contrived but very difficult optimization problem. With five degrees of freedom, his problem has 10^8 local optima and with ten over 10^{17} (10^{17} microseconds equals 3200 years). He has also investigated having two competing objectives where his goal is to find the trade-off curve (Pareto surface) for them. Single agents seldom find the global optimum; diverse agent systems typically do, and they find better answers remarkably faster. In parallel computing ten computers might allow problem solution to be four times faster than for one computer; in agent-based systems the time reduction could be by a factor of 100.

We see in this approach the opportunity to alter how we solve hard problems. It is a "softer" approach. There are a few elusive proofs already available, but when tested this approach really works. It has a "social" model underlying it, and we know this cannot be science – right? But it could open some new research areas or allow us to revisit some old ones we could not tackle before.

Unsolved problems

I will illustrate the kinds of problems that seem to me to be unsolved in the process systems area. The first example will take care of problems being too large. Then we will consider problems that we do not know how to solve yet, although many people have worked at solving small examples of them.

I cannot solve a problem with 10,000 binary variables – yet

A trivial answer for noting an unsolved problem is to say that we always want to solve modeling, optimization, control and operating problems that are larger than our computers will allow us to solve at this time. The implicit solution is that we need only wait, and larger computers will solve the problem. History predicts we will solve problems about 10,000 times larger in the next decade, and there are 10,000 seconds in a week. However, we should question if it is only the need for larger computers.

This simple three column flowsheet will not converge

In analysis and optimization, we all often fail to converge our problems. Much work in convergence has to do with improving the numerical schemes. For example, there are modified Newton schemes that take bounded steps between a steepest descent and a Newton direction. These really do make a difference, but I am a firm believer that we need physical insights to converge most of our problems. For example, we may well place

a specification on a separation device that device cannot deliver. In azeotropic separation, we may initialize a column in the wrong “distillation region” from which it will fail to converge, while initializing in the right region, even if done poorly, will generally succeed. In a “four sided” distillation region, we can find our distillation problem to be so sensitive to the numbers (changing the least significant bit of a double precision number) that the solution will jump from one behavior to a very different one. It is still an unsolved problem as to how we can provide feedback that tells an engineer why his problem is not converging and how he can overcome any such problem. We have made inroads on this problem in our ASCEND system, but we can only provide “clues” that the engineer still must decipher. I believe the approach will be to find hidden embedded near singularities and bifurcations and to trace their meaning through the problem. Connecting such a trace to its physical meaning will be an enormous benefit, but it will be very difficult.

I need a good solvent

A “cute” way to think of a reverse problem is that it is one in which we supply the answer and ask for the question. Reverse questions are at the heart of product and process design, and thus especially of process systems engineering. Assume our tools are models and not experiments, a good assumption for PSE. Given what we know and can model, what answers can we find that will aid us in engineering a solution to a problem? The flowsheet synthesis problem is a reverse problem of discovering a flowsheet that can manufacture a desired product. Another is to find a good catalyst using computational methods. Reverse questions always have many, many candidate solutions.

There are a few simple reverse questions that we keep thinking we should be able to solve, and we still cannot do them very well. One is to find components, mixtures of components and/or structures of components that have some desired physical properties. This type of problem is at the heart of designing a chemical product. For example, we use the Wilson method to predict the vapor-liquid behavior of many common organic mixtures. Suppose that we supply the physical behavior we want – e.g., we want a new solvent for our process. What solvent should we use? There is a considerable literature on this simple problem. Most of the time a paper on this topic will suggest stating the activity coefficient one wants and then seeking the groups (as in group contribution methods) that will give such a coefficient. The problem is then one of constructing molecules from those groups, and these papers typically find there to be many, including some good surprises. Unfortunately, only a few of the components we wish to consider have group

contribution methods available. Also what makes a good solvent is a lot more than an activity coefficient. How much it costs, its toxicity, how easy it is to handle, can we recover it, and so forth are all part of the evaluation. Also, when one thinks of “order of magnitude,” the number of components in our libraries for which group contribution methods work is not that much larger than the number of groups. With gigahertz computers, we can search over a lot of components directly. So we can often try all pure component possibilities rather easily. Mixtures and structures are another story. There will be mixed integer programs formulated to solve these problems. What we suffer from more than anything though is a lack of good models for predicting the properties we want. That puts this problem in part outside the PSE area.

Should I buy this tanker of crude oil?

I pick this problem as it is a very large and very critical one for an oil company, and it illustrates the complexity of making business decisions. Buying a wrong tanker of crude can have a serious economic impact on a company, much more than solving its design, control, and operating problems optimally. The problem is many faceted. First, how does the company estimate with any accuracy what is in the tanker? Can its refineries process it? Oil companies use information on the oil field from which it comes as a first indicator. Several measurements the suppliers made on the crude oil aid the oil company to estimate what it is it might be purchasing. However, getting representative samples on which to make the measurements is a difficult problem. The simple question as to how much oil is actually in the tanker is also surprisingly difficult to answer, even if one monitors the delivery. Suppose the company has a good estimate of what is in the tanker. It next needs to account for its forecasts as to what it needs to deliver as products for the next few months. What is currently in its storage tanks? What products can it make from these inventories when it considers having this tanker of crude and when it does not? It will have to anticipate what crude it can buy in the near future, also. Where are available tanks located into which it can unload this tanker? What is in them? Will it mix or not? Should it? Is there a “slot” available at the unloading facilities? Perhaps the company should wait for the next tanker of crude? How will currency fluctuations affect this decision? Should it buy the tanker with the intention to trade it in a day or so?

Can we hope to create and maintain the models needed to respond to all these questions? One will need to represent many of the variables probabilistically. Can we solve such an immense problem? What is the right problem to solve? Are we interested in the low

risk solution more than the high profit one? How will our decision affect our competitor's position?

Problem formulation – the oil tanker problem, second chapter

We already have many tools for analysis and optimization. As the above problem should have made clear, we now suffer from not knowing what problems we need to solve. Formulation is more important than solving. If we formulate the wrong problems, we get answers experienced engineers will reject out of hand. While it may sound trite, it is better to solve the right problem approximately than the wrong one optimally.

To understand how formulation is critical, what are the main selling points for portable computers today? Computer speed is not everything. Rather customers are also very interested in battery life, reliability, weight, screen resolution, security, connectivity, ruggedness, and service. If one overlooks an important customer need, one could doom his product.

Can there be strategies we can uncover to aid in formulation? Can there be tools we can develop to do the same?

How can I get my company to be one that survives? (subtitled: “Designing as a research topic”) – and the saga started above continues

I also believe that designing is an important research domain but designing in a much broader sense than we have generally defined it to date. There is no doubt that the tools we discussed above are enablers for a company to be good at designing. Companies interested in low cost have to be skilled at modeling and optimizing. Companies should not ignore the available synthesis tools whose positive impact many have now well documented.

These tools enable a company to be good, but they do not make a company great. We suggest that only the great companies are likely to be here in the future. What makes a company great? Is there research open to chemical engineers that speaks to this question? I suggest that the great companies are those that understand what they are about, are creative, and understand what their customers want.

In commodity chemicals, price is likely the major issue. But is it? An anecdote will illustrate. A to-be unnamed, but real, chemical company delivered a commodity chemical to one of its customers. This supplier company discovered it could deliver a product that went from being 98% pure to being 99% pure while decreasing its costs. Of course, a purer feed should please its customer. Well, it did not. The customer had tuned its process to use the less pure feedstock. Its product became slightly discolored. It almost switched

suppliers until the supplier company reverted to its old way of running its process.

Another anecdote is more personal. In 1986 we won NSF funding for our Engineering Design Research Center. Our goal was to improve the competitiveness of US industry by improving how it did its designing. We argued that by bringing many engineering and other disciplines together, we would greatly accelerate the sharing of methods and tools. We envisioned supplying much improved computer-based analysis and optimization tools.

Westinghouse brought us one of our first projects. We were to watch them design a new control system for a 2000 megawatt coal fired power plant, one in which the improved control would reduce emissions while not impacting overall efficiencies of the plant. We quickly discovered that they seldom were running computer simulations and optimizations. Other researchers doing ethnographic studies of such activities have estimated, as did we, that the designers used these tools for only about 15% of the time they spent on the design. Rather the design team members were in meetings sharing information, discussing how to make decisions, what decisions they had made and so forth. We started very quickly to question how we were to improve how they would do design if we only considered supplying improved analysis and optimization tools.

Since the spring of 1999, I have been directing the teaching of a course on product design at CMU. It is open to all juniors, seniors and graduate students at CMU. Company sponsors supply us with problems and expertise, as well as funding, to run the course. We have discovered that diversity on these teams (having a computer scientist, a chemical engineer, an industrial designer, a mechanical engineer and a business major on the same team) dramatically improves what they will create, something the students always find very surprising and enjoyable.

A main theme of a very interesting book by Bucciarelli² is that designing is a social as well as a technical process. Design teams carry out designs, and the design it selects, of the many possible, is a strong function of the personal values of its members. He argues that design is social because of the process by which one carries it out and social by the impact that personal values have on its outcome. To quote Bucciarelli: “The realization that design is a social process, that alternative designs are possible, and that a design’s quality is as much a question of culture and context as it is of a thing in itself or of the dictates of science or market forces -- all this is a prerequisite to moving beyond simplistic images and myths about technology and doing better as designers, as corporate

strategists, as government regulators, as consumers, and as citizens.”

This topic is fraught with problems. The most significant is that humans and their behavior are a major part of what we must understand. Chemical engineering researchers are usually not very interested in such a soft problem. However, how can we really aid designers if we ignore these issues? Only companies that deal with these issues will be great at designing.

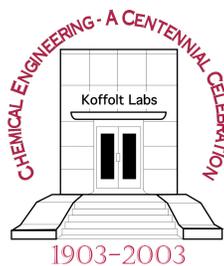
We have found our research niche in this area by developing tools to support information management and to support collaboration. This area is far from understood. Can chemical engineering researchers

contribute to it? Should they? Obviously I have thought so and still do. I do not see how we can forsake understanding what it takes to make companies great rather than just good.

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² Bucciarelli, L, Designing Engineers, MIT Press (1994).



THE OHIO STATE UNIVERSITY

Unsolved Problems in Nanotechnology



Biographical sketch of Matthew Tirrell

Matthew Tirrell received his undergraduate education in Chemical Engineering at Northwestern University and his Ph.D. in 1977 in Polymer Science from the University of Massachusetts. He is currently Dean of the College of Engineering at the University of California, Santa Barbara. From 1977 to 1999 he was on the faculty of Chemical Engineering and Materials Science at the University of Minnesota, where he served as head of the department from 1995 to 1999. His research has been in polymer surface properties including adsorption, adhesion, surface treatment, friction, lubrication and biocompatibility. He has co-authored about 250 papers and one book and has supervised about 60 Ph.D. students. Professor Tirrell has been a Sloan and a Guggenheim Fellow, a recipient of the Camille and Henry Dreyfus Teacher-Scholar Award and has received the Allan P. Colburn, Charles Stine and the Professional Progress Awards from AIChE. He was elected to the National Academy of Engineering in 1997, became a Fellow of the American Institute of Medical and Biological Engineers in 1998, was elected Fellow of the American Association for the Advancement of Science in 2000 and was named Institute Lecturer for the American Institute of Chemical Engineers in 2001.

Unsolved Problems in Nanotechnology: Chemical Processing by Self-Assembly

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Abstract

The many impressive laboratory demonstrations of controllable self-assembly methods generate considerable hope and interest in self-assembly as a manufacturing method for nano-structured products. The practical realization of this hope will require several achievements in chemical engineering, including the precision manufacturing of precursors, expansion of our ideas of molecular chemistry to super-molecular chemistry from a bonding, kinetics and mechanistic point of view and a focus on self-assembly processes that can be scaled up to interesting levels. This leads to a rich array of research and process development issues for chemical engineers.

Chemical engineers are playing very significant roles in developing a new science base in phenomena, structures and potential applications where understanding at nanometer length scales is crucial. Synthesis and demonstration of new catalysts, new multi-component polymers and new biomaterials are all fine examples of areas to which chemical engineers are making major contributions to nanoscale science, in particular but not exclusively, via the self-assembly route that is the subject of this paper. Whether this new science base leads to important technological developments depends even more on chemical engineers. The thesis of this paper is that the opportunities for chemical engineers to advance nanotechnology demand an emphasis on developing suitably effective processing technologies. Treating self-assembly as a serious chemical process is rich with chemical engineering opportunities.

Self-assembly is a spontaneous process, guided by information content intrinsic to the assembling units, in which multiple levels of structural organization are built into a product (Kuhn and Ulman, 1995). Owing to the complexity of structures formed and the nominal ease of spontaneous organization, self-assembly is increasingly being examined as a practical chemical processing method. It is akin to crystallization except that the complexity of the structural elements involved is greater in self-assembly and length-scales beyond a single lattice constant emerge in the product. In some cases, self-assembly can result in intricate, interlocking, useful architectures of matter. The resultant structures are being actively explored as new materials, surface treatments, catalysts, membranes, photonic materials

and electronic devices, to name a few areas of current engineering exploration. Self-assembly is one of the key mechanisms by which nature builds products, from biological molecules such as proteins to larger structures such as cells and extracellular matrices, the spatial arrangement of atoms is determined, in large part, by information built into the assembling units. Complexity, in the sense of development of emergent properties of an assembly that cannot readily be envisioned from the constituents (Ottino, 2003), can arise spontaneously during self-assembly and often does, especially in biological systems. We are only beginning to develop sufficiently sophisticated synthetic assemblers to mimic biology in this way, as illustrated in Figure 1, from Simon, et al (2001).

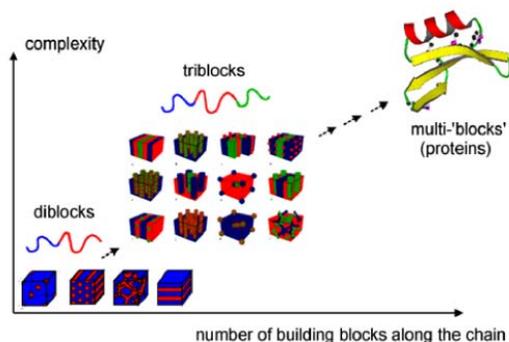


Figure 1. Schematic diagram showing how complexity of self-assembly may increase as the number of building blocks in a copolymer increases. (adapted from Simon, et al. 2001)

Indeed, other routes to self-organization, including those far from equilibrium (Ottino, 2003), may also be of interest for nanotechnology.

The ability to form structures spontaneously from the bottom up, using principles akin to biological assembly, has inspired considerable research among chemists, physicists and chemical engineers to develop useful products (Whitesides, et al. 1991). The high level of scientific activity in this field creates several kinds of major opportunities for chemical engineering research. The overall opportunity might be characterized as a shift from product to processing research in self-assembly. As self-assembly attempts to evolve from laboratory techniques and provocative demonstrations of structure, to practical, larger-scale, applied processing methods, a broad spectrum of important engineering research problems is being generated.

Opportunities for new chemical engineering research in self-assembly are the focus of this article. What this requires, among other matters, is taking self-assembly seriously as a processing method and asking, "What are the barriers to its development and widespread implementation in the commercial sector?" This review takes a processing perspective, appropriate to motivate this underdeveloped field of chemical engineering research. A recent review (Schreiber, 2000), from a surface science perspective, describes the current state of laboratory growth methods and structural characterization comprehensively, for the case of self-assembled monolayers. An up-to-date review on three-dimensional self-assembled structures has yet to be written. This article aims at processing two- and three-dimensional self-assembled structures.

An important characteristic of self-assembly processing, which changes both the chemistry and chemical engineering research perspective, is that the fundamental objects participating in the process are, more often than not, neither simple atoms nor simple molecules. Rather, they are modular, prefabricated, complex molecules or objects with internal structure and external size, shape and functionality. The structure, size, shape and functionality define the information content of the assembler. Colloidal crystallization of structured particles typifies the process of developing organized assembly of complex, multimolecular objects. The rules of chemical bonding (interaction potentials) and chemical kinetics for reactions among objects such as these to form stable, useful products remain to be thoroughly explored to form a good basis for process development.

Brief summary and critique of the state-of-the-art of self-assembly processing

Numerous processes for producing chemical products, surface layers or new materials by self-assembly have been developed. Table 1 gives a substantial but not exhaustive list. A short discussion of what is included, and what is omitted, and why, is warranted. Adsorption of polymers consisting of identical units, that is homopolymers (not on the list), is a widespread and effective practical method to modify materials surfaces. However, it is a random process without any particular guidance to the assembly coming from the molecular structure, and therefore it lacks an important ingredient (a trajectory guided by information content of the assemblers) in the definition of self-assembly. On the other hand, in the adsorption of multi-component polymers, such as block copolymers or hydrophobically modified polymers, some pieces of the molecule are driven by their chemical nature to stick to interfaces; others are not. The resulting molecular arrangement is directed by information (internal structure) in the adsorbing molecules. Amphiphilic molecules "know" which end is up when placed in a surface or interfacial region.

Table 1: Processes Incorporating self-assembly

Adsorption of multicomponent polymers
Cooperative supramolecular self-assembly of surfactant organic mesostructures
Grafting of polymers on interfaces
Langmuir-Blodgett deposition
Layer-by-layer deposition or sequential adsorption
Micellar control of reactions
Microcontact printing
Organizing colloids into arrays and crystals
Self-assembly of monolayers
Spin and dip coating of supramolecular solutions and dispersions
Surface directed ordering of molecules at interfaces (liquid crystals)
Surface modification by monolayer or multilayer deposition
Templating
Vesicle fusion

Some of the processes in Table 1 have been known for quite some time (e.g. Langmuir-Blodgett deposition); others have been developed in the last decade (e.g. microcontact printing). Note that by definition, in our parlance, a self-assembly process, while being largely controlled by the chemical architecture of the assemblers, may have elements that are neither spontaneous nor inherent in the assembling entities. That is, some of these are directed assembly processes,

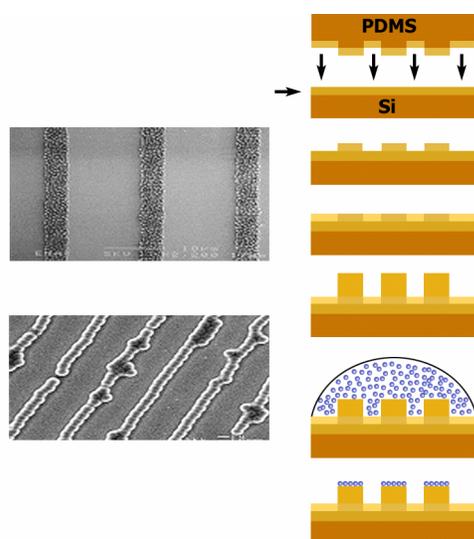


Figure 2. Extension from molecular to microscale systems. Selective self-organization of charged colloid particles using patterned multilayers as templates. Initial patterning done with microcontact printing, followed by layer-by-layer assembly, with the final step incorporating electrostatic assembly of nanoparticles. (adapted from Chen, et al. 2000)

which may incorporate non-thermodynamic influences (dipping, printing, spinning, quenching, etc) or effects of external influences (templates, surfaces, fields, etc.). In fact, the effective use of these influences will be one of the most important issues in developing practical self-assembly processes. This article does not make a sharp distinction between purely self-assembly processes and directed assembly processes. In both, the information content of the assembling objects plays a major role.

The practical history of Langmuir-Blodgett (LB) deposition as a processing method (Swalen, et al. 1987) offers a sharp focus, and a sobering shadow, on the future of self-assembly processing. LB processing has never been an important practical technology, despite its wide-spread utility and unique capability of controlling structure in laboratory-scale materials assembly, owing among other things to the difficulty in scaling-up the process via continuous, parallel or repetitive processing. As we shall see, continuous processing has been achieved in few examples of self-assembly processing.

One promising self-assembly method that seems to lend itself to scale-up and to continuous processing, and also possesses great versatility in the range of components that can be used in the process, is Layer-by-Layer growth (LbL), pioneered by Decher and co-workers, and now being much more broadly explored (Decher, 1997). LbL works by successive dipping cycles of substrates into solutions of molecules with some

interactive complementarity (usually of opposite charge). Möhwald and co-workers have generalized this method to LbL on particle surfaces (Caruso, et al. 1998; Caruso and Möhwald, 1999) developing the capability, after destruction of the templating particle (usually by dissolution), to make self-assembled capsules with controlled structure, contents and wall properties (mechanical and transport). Destruction of an organic template to leave a self-assembled inorganic material has proven a very effective route to new porous materials for catalysts, sorbents and membranes (Asefa, et al. 1999; Melde et al. 1999; Freemantle, 2000).

Microcontact printing (MCP) is another burgeoning laboratory-scale method incorporating self-assembly (Kumar, et al. 1994). In the basic application of this methodology, a stamp is “inked” with a self-assembled layer. The stamp is then used in MCP processing to transfer the self-assembled material to another surface. The possibilities for making MCP an efficient, versatile, even continuous, process seem very achievable, based as it is on classical printing technology. Clearly, many of the processes in Table 1, MCP included, are not purely self-assembly, or even directed assembly processes but involve the intervention of some other processing technique in concert with self-assembly. Self-assembly used as one method in a multi-step process is a very likely outcome of much of current nanoscale processing research. This would characterize methods such as micellar or microemulsion controlled reactions, as well as a range of “hybrid” self-assembly processes. Figure 2 (Chen, et al. 2000) shows the product of a hybrid LbL-MCP process, followed by the deposition of a layer of colloidal particles.

Other hybrid processes include ink-jet printing followed by a self-assembly process such as vesicle fusion

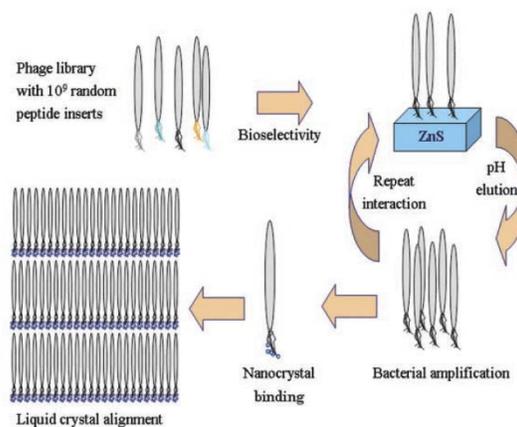


Figure 3. Schematic diagram of the process used to generate nano-crystal alignment by the phage display method. (Reprinted with permission from Science, Lee, et al. 296:892-895. Copyright 2002 AAAS.)

(Cremer and Boxer, 1999), and biological production of self-assembled products (Cha, et al. 2000; Belcher, et al. 2000; Seungju, et al. 2000; Wu, et al. 2002), one of which is illustrated in Figure 3.

Most of the current self-assembly processing methods function primarily to create surface and thin film structures (LB, LbL, multicomponent polymer adsorption.). This “two-dimensional” emphasis derives both from the many applications for surface modification and for the templating assistance that surfaces generally offer to self-assembly processes. Nevertheless, much more work is needed in the direction of three-dimensional self-assembly methods. As work in colloidal crystallization has shown, not only is three-dimensional assembly of pre-formed, supermolecular objects a route to materials with interesting new structures and properties (Velev, et al. 2000) but also, studying the crystallization of objects reveals considerable new insight into the inter-object potentials (Davis, et al. 1989).

Processes competitive with self-assembly

An issue that must be addressed is that of competing processes: What competitive processes are available to achieve similar targets? Structuring at the nanoscale is not available exclusively via self-assembly. While the “bottom-up”, additive approach embodied in self-assembly has much to recommend it, “top-down”, subtractive processes, such as nanolithography by x-ray, electron beam and UV also have considerable potential yet to be tapped. Furthermore, subtractive processes have a track record of past accomplishment. Direct-write processes, which are automated layer-by-layer depositions, including ink-jet printing (Sachs, et al. 1992), stereolithography or 3D printing (Griffith and Halloran, 1996), are also advancing rapidly, based in part on advances in robotics (Lewis, 2000). Nano-imprinting, a nano-scale throwback to the metal-stamping of, say, auto body parts or refrigerator housings, is also showing serious promise in electronic device fabrication. (Chou, et al. 2002) More conventional processes, such as lamination and multilayer extrusion (Cesarano and Calvert, 2000), are also achieving a greater degree of spatial control. Sol-gel processing and certain combustion/aerosol processes also are achieving some success in creating controlled nanostructured products.

Thus, there are serious competitors to self-assembly processing. Engineering research in self-assembly processing should be realistic about comparative advantages of alternative processes, and creative about

inventing combinations of new technologies for nanoscale processing.

New issues in self-assembly processing

There are several identifiable directions in which scientific and technological advances in the chemical sciences must be made in order for self-assembly processing to become an important, widely used processing tool. The directions discussed below are each important; a prioritized list is not possible in the current state of the field.

Precision synthesis of precursors.

The ability to form a desired state of organization spontaneously depends on the internal structure of the assemblers. It is then clear that information must be built into the assembling objects with some degree of fidelity. There are various avenues for achieving this. Size, shape (in rigid objects), conformation (in flexible objects), sequence (in multicomponent macromolecules), spatial relationships among subunits all can be “read” in molecular recognition interactions. In synthetic molecules, small amphiphiles such as surfactants or lipids are classes of molecules that can be synthesized with precision, that is, they can be made and isolated as pure compounds. The ability to make micellar and bilayer membrane structures by self-assembly is a direct consequence of the precise architectures of these molecules. Impurity in assembling molecular structure creates disorder or other degradation in quality in the self-assembled product.

Only biological systems currently achieve precise syntheses of molecules of more than a few hundred daltons. There are two broadly thought-provoking points in this realization for current self-assembly research. One is that precision synthesis and fidelity of information content is essential for effective self-assembly of intricate, functional systems. This should motivate a broad array of useful chemical synthesis and process research to produce the starting materials for non-biological self-assembly. Protein folding, the unimolecular self-assembly process by which proteins (multicomponent macromolecules with precise sequence distributions) take their functional forms, is far from fully understood. However, it is certain that the final state of a protein folding process is determined by the primary sequence of amino acids in the macromolecular backbone. Precision synthesis of the sequence controls the assembly. Folding processes of nucleic acids are also increasingly recognized to be functionally important, while information is built into polysaccharides by control of architectural features such as branching. Successful development of self-assembly

processes will place a premium on new chemical or directed biological routes to pure, precise macromolecular synthesis and production or particle formation. Furthermore, it will be fruitful to understand, in much more detail than we currently do, the sensitivity of various synthetic self-assembly processes to the lack of precision in the architecture of the assemblers.

A second lesson that may be extracted arising from consideration of biological self-assembly is understanding of how nature achieves precision synthesis. Biological systems do not synthesize perfectly; rather, considerable effort is expended in detecting and correcting errors en route to a pure product. The chemical processing analogs of this are on-line measurement, control and post-reaction separation processes. To achieve the necessary control over molecular architecture, it will be necessary to explore both chemical and biological synthesis routes with a realistic eye toward process efficiency.

Expanding the idea of the molecule.

Since self-assembly often, even usually, involves the spontaneous organization of objects considerably larger than molecules, it is useful to begin to think about larger assembling objects in self-assembly processes as we do about molecules in chemical reactions. The atomic and molecular notions of valence, bond strength, etc., have inexact but pragmatic counterparts when applied to interactions among structured macromolecules, nanotubes, particles and other important self-assembly constituents. Figure 4 (from Manoharan, et al. 2003) shows that composite, or structured, colloidal nanoparticles can be formed by the controlled consolidation of primary particles. The symmetry of these structured particles endows them with the potential for directional bonding, the molecular analog of the symmetry of electronic wavefunctions.

Another relevant example of an enlarged definition of

The minimal moment clusters

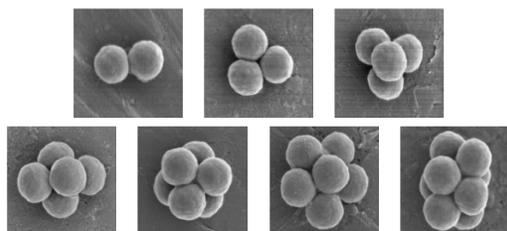


Figure 4. Composite particles formed by association of spheres confined within emulsion droplets. The precisely formed aggregates confer a selectable series of symmetries on the composite particles (adapted from Manoharan, et al. 2003)

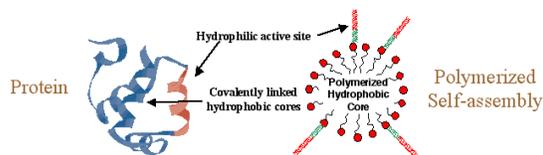


Figure 5. Micelles of peptide amphiphiles bear many similarities to protein macromolecules. They have hydrophobic cores, hydrophilic bio-active exteriors, globular shapes, and sizes in the tens if nanometer range. Connectivity can be introduced via polymerizable lipid tails.

the molecule is shown in Figure 5. In our group, we have been exploring the properties and applications of synthetic peptide-lipid conjugate molecules (Tirrell, et al. 2003). The idea of these molecules is to confer on unstructured, short, potentially biologically active peptide chains, some self-assembly character that will organize and present the functional peptide in an effective way. We have found that micelles formed from these peptide amphiphiles resemble proteins in several significant, and possible useful ways, enumerated in Figure 5. We now know (Yu, et al, 1998) how to use this self-assembly character to drive the peptide into ordered secondary structures as they are found in intact protein macromolecules. Protein analogous micelles are objects that can mimic protein molecules and, in this way, expand the notion of how to use protein functionality in self-assembly.

Scale-up of self-assembly processes.

As mentioned earlier in the context of Langmuir-Blodgett deposition, scale-up of self-assembly processes to technological significant scales has not been pursued to an appreciable degree. That is perhaps natural given the state of development of the field. Nevertheless, lack of ways to scale-up can be the demise of a promising processing route in a technological arena. Some of the most innovative developments in self-assembly processing to date have been achieved by chemists, where advances in assembly on non-planar surfaces have led to the ability to assemble macroscopic, three-dimensional structures spontaneously (Jacoby, 2000; Gracias, et al. 2000; Whitesides and Grzybowski, 2002). A great opportunity exists for some tools of process systems research to be applied to self-assembly processing, and nanoscale engineering in general. Success in enlarging the capacity of self-assembly processes by continuous, parallel or repetitive processing would be very valuable.

Kinetics and mechanisms of self-assembly processes.

Another important issue is the matter of kinetics. Self-assembly science is grounded in processes that tend

toward desirable equilibrium structures. Chemical processes generally should go as fast as possible, consistent with product quality. It is difficult to envision the processing research called for above proceeding fruitfully without data on the rates of self-assembly processes. Our view is that, for design and development purposes, we need to understand fully the trajectories, through time and structural intermediates, of self-assembly processes.

This need for research in self-assembly kinetics, and the related issue of mechanisms, has several facets. The acquisition of such data will stretch and eventually expand the tools we have to observe self-assembly in progress. Research on self-assembly kinetics requires data in real-time, pushing the field toward methods that are faster and more highly time-resolved. Accurate kinetic data are a necessary prelude to predictive models of the evolution of self-assembly processes. As the complexity and number of components in these processes increase, predictive models will become more important tools in process and product design. We believe it is fair to make the analogy between self-assembly and chemical reaction processes. Thorough understanding of chemical bonding, reaction mechanisms, pathways and kinetics are crucial to reactor design. Analogs in self-assembly are intermolecular or interparticle potentials, trajectories and rates of assembly.

As an example of work in this direction, we offer our group's work on vesicle fusion. The essential steps of this physico-chemical reaction are depicted in Figure 6a. Vesicle fusion, just as LB deposition, is an increasingly useful laboratory method to coat surfaces with monolayers of lipid molecules. We have been interested

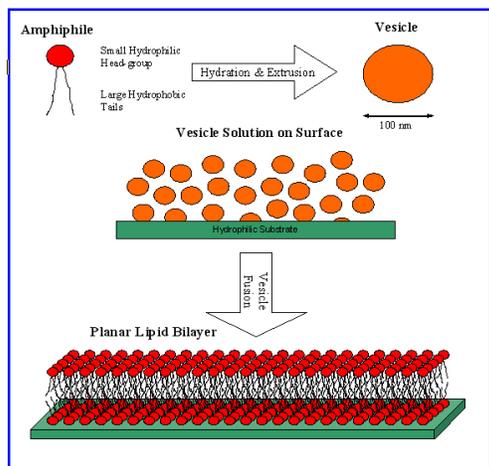


Figure 6(a) Schematic diagram of vesicle fusion. Attractive forces between vesicle and surface cause distortion of vesicle shape, eventual rupture of the vesicle and ultimately deposition of a nearly complete bilayer.

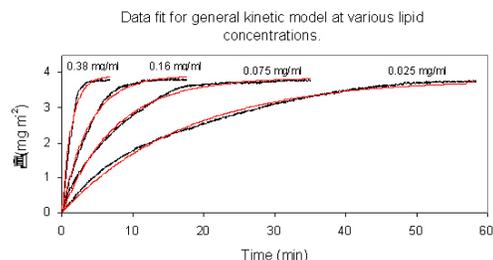


Figure 6(b) Kinetics of bilayer deposition via vesicle fusion as studied by ellipsometry. (A. Parra, D. Stroupoulis and M. Tirrell, unpublished data)

in its technological applications, particularly selective coating of the surfaces of microfabricated devices. For this we felt we needed kinetic data and a mechanistic interpretation so that we could extrapolate to new situations such as deposition on textured surfaces, in corners, etc. Phase-modulated ellipsometry has proven to be a useful tool in kinetic studies (Parra, et al. 2003). Figure 6b shows data on the accumulation of monolayers (we have proven that the plateau deposition is in fact a monolayer) fit to a model where we have considered both the diffusive rate of supply to the surface and surface reorganization as important potentially rate-controlling steps. Our unambiguous conclusion is that surface reorganization dominates in this case. These kinds of studies are very important to the advancement of this field.

Rates of self-assembly processes.

Chemical engineers are seldom satisfied with the rates of uncatalyzed chemical reactions for technological purposes. Biological self-assembly is, in some situations, promoted or directed by protein or templates. The fact that self-assembly proceeds down a free energy gradient to a thermodynamically determined endpoint is reassuring in some respects. However, metastable states of varying duration may intervene. Equilibration is unhurried; chemical manufacturing is not. It is challenging to think of how one might design a catalyst for a self-assembly process. Physical or chemical templating, for example, a type of epitaxial growth, is one possible route, which in self-assembly has been explored more for its effect on structure than on rate (Ball, 1997). External fields can profoundly affect the rates of self-assembly processes (Koppi, et al. 1993) and should be explored more extensively in this vein. Perhaps more than in simpler chemical reaction processes, the size and complexity of objects involved in self-assembly are such that diffusion limitations are more the rule than the exception, motivating a need for new research in transport phenomena applied to this field.

Characterization and process control.

Practical processes must be controlled to produce valuable products; in the case of self-assembly, these are products of intricate internal structure. Real-time structural analyses present instrumental challenges that must be addressed. Since self-assembly often produces structured products over several length- and time-scales, techniques capable of measuring, with resolution, over multiple length- and time-scales are needed. Informative, on-line measurement is a prerequisite for process control. Characterization of defects is particularly important for the applications envisioned. Furthermore, self-assembly processing of nanostructured products is a driver for new research in control of distributed processes (Christofides, 2001). Control of distributed systems such as self-assembly will also rely heavily on the development of tractable, predictive models.

Concluding remarks

It has been remarked that new directions in science are launched by new tools more often than by new concepts (Dyson, 1997). Self-assembly is a blend of concepts and tools; the field will advance more rapidly as we turn concepts into techniques. Research in the chemical sciences and technology over the next few years, pursued with a clear view to the barriers and competition facing self-assembly, is likely to produce important new progress, not only for self-assembly processing but for the optimum processing routes to nanostructured chemical products.

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