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Professor Daniel I.C. Wang: A Legacy of Education, Innovation, Publication, and Leadership

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Biochemical engineering at MIT emerged in the 1950's with a focus on the use of fermentation technology for traditional food and beverage processing and the increasing demands of antibiotics production. New discoveries in natural products were creating a need for improvements in large-scale fermentation as an enabling technology. In this context, the biochemical engineering program became a collaboration between biology, chemical engineering and the newer department of nutrition and food science. Its curriculum embraced fundamentals from these three disciplines. With its multidisciplinary roots, the Department of Nutrition and Food Science, home to the Biochemical Engineering Program, reached out in 1965 to hire a young Ph.D. Chemical Engineer from the University of Pennsylvania, Daniel I. C. Wang. After completing his Ph.D. research with Prof. Arthur E. Humphrey on high-temperature short-time sterilization, the new Dr. Wang spent 2 years in the US Army doing bioprocess research at the Fort Dietrich Biological Research Laboratories. This postdoctoral experience significantly broadened Wang's experience into fermentation and the nascent technology of animal cell culture.

It was in a backdrop of rapidly emerging scientific discoveries in biology providing a technology push and an increasing appreciation within multiple industries creating a technology pull, that Daniel I. C. Wang joined the Department of Nutrition and Food Science at MIT as an Assistant Professor of Biochemical Engineering. During the next 40 years he would become the primary driver of innovation in both education and multidisciplinary research initiatives that have defined modern Biochemical Engineering. It is interesting to reflect on the evolution of our discipline over these past 40 years as it has changed substantially in many ways while being invariant in the vision of "engineering of biochemical systems and components over multiple scales".

1 | 1965–75—ESTABLISHING THE FOUNDATION FOR BIOCHEMICAL ENGINEERING IN FOOD AND FEED PRODUCTION

By the mid 1960's, when the young Dan Wang joined the Department, the price of corn and soy beans was rising rapidly while global food and feed resources were poorly distributed. The Green revolution was beginning to take effect but projections of food and feed shortages were calling for innovative solutions in production. The concept of single cell protein (SCP) or protein derived from microbial sources emerged as a promising solution to this global problem. Economic SCP production required low-cost, large-scale technologies and created an opportunity to move not only fermentation technology but also cell and protein recovery technology to a higher plane through improved understanding and innovation. During this period we saw research from Wang's lab on the airlift fermentor, the use of flocculation and membrane processes for cell and protein recovery, the fermentation of formose sugar syrups and hydrocarbons for SCP, and the elucidation of principles for cell disruption by high-pressure homogenization to name a few of the contributions. Keep in mind that while predictions of food prices were escalating rapidly, prices for energy resources such as gas and petroleum were declining, thus, making the conversion of methane, methanol, and n-alkanes to protein very attractive. This work established the platform on which many other researchers began to build the discipline. One could also see interesting excursions into areas that would later become critical to the field; for example, his early work on cell culture on centrifugation of animal cells in 1968 and the recovery of viruses with ultra filtration membranes in 1971 in collaboration with Anthony J. Sinskey.

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2 | 1975–85—THE ERA OF ENZYME TECHNOLOGY, COMPUTER CONTROL, AND CELLULOSIC BIOMASS CONVERSION

By 1975, the prices of corn and soybean had begun to stabilize and the Green Revolution was beginning to have positive impact on global supplies of corn and soybean. The need for SCP declined but the lessons learned from the drive to improve the fundamentals of fermentation and recovery technologies were of great benefit to the bioprocess industry at large. Furthermore, the education and training of a new cadre of leaders in the discipline of biochemical engineering had a broad confidence building effect on other applications of this technology. Some of Dan's early students—Charles Cooney, Larry Gasner, Henry Wang, and Richard Mudgett—had become academicians and were building on a multidisciplinary educational paradigm that Wang has established. Furthermore by this time, the Fermentation Technology summer course had moved into its second decade with its focus on fundamental principles with topical applications to industrial problems.

In this period, there was great fascination with the concept of building biochemical systems from purified enzymes. With Wang's leadership, a large multidisciplinary initiative on the use of enzymes for in vitro, non-ribosomal peptide synthesis was successfully taken to the National Science Foundation for funding. This was a significant accomplishment for several reasons. First, the proposal to NSF was large relative to the more common single investigator project and very risky because no one had set forth to synthesize a molecule as structurally complex as Gramicidin S, with its attendant need for multiple co-factor regeneration, before. NSF was ready for the risk and the scale of the problem. The project required multiple disciplines—chemical engineering, chemistry, and biology—working closely together; this established a close collaboration with George Whitesides, Charles Cooney, Anthony Sinskey, Arnold Demain, and Clark Colton and their students and post-docs. The success of this initiative was seen in the ability to meet the target of gram quantity synthesis of Gramicidin S, regeneration of both ATP and NADH, and the production and purification of large enzyme complexes.

During this same period, an energy crisis emerged and expectations for petroleum and gas prices reversed themselves as predictions of grave shortages of these much needed commodities generated rapid increases in prices. One solution was to ferment renewable resources as a means to convert solar power, converted into plant material, to liquid fuels. The social and political implications of converting food and feed resources, primarily sugar and starch, to fuel drove the thinking to focus on cellulosic biomass. Once again, under Wang's leadership, a multidisciplinary team was created to address this large-scale problem with innovative solutions. The concept of direct conversion of cellulosic biomass containing cellulose, hemicellulose, and lignin emerged as a unifying theme as we entered the early 1980s. The Department of Energy was receptive to funding this venture and a team was formed. Many lessons had been learned about large-scale fermentation, enzyme production and purification, and genetic manipulations from prior work in the laboratories of Wang and his collaborators at MIT. These lessons now needed to be applied to a new set of microorganisms growing under strict anaerobic conditions. The research focused not only on ethanol but also on chemicals such as acetic acid, butyric acid, butanol, and acetone. It was necessary to develop the means to genetically modify and improve the performance of obligate anaerobes for cellulose production and product tolerance. The cellulose system for lignocellulose degradation was poorly understood and fundamental research to elucidate the rate-limiting steps was needed. In the end, there was substantial success in demonstrating the direct fermentation of cellulosic biomass to ethanol and other chemical products. Application of the technology at scale was precluded by a decline in energy prices. Now 20 years later interest in this strategy has again emerged as fuel prices rise.

Fermentation emerged as the core technology able to address multiple industrial needs ranging from health care products such as antibiotics; food products such as protein, amino acids, and vitamins; liquid fuels and chemicals such as ethanol and acetic acid; and industrial enzymes. Research continued to address the needs of this core technology in the labs of Wang and his collaborators. Improvement in mass transfer for non-Newtonian mycelial fermentations; understanding the underlying principles of the air-lift fermentor; introduction of novel sensors to monitor performance; and the introduction of computer control to facilitate understanding and enhance process performance were amongst the contributions of this period.

By 1980, recombinant DNA technology was seen as a transformational event and the potential for production of many new human therapeutic products was becoming real. With humble beginnings in the production of heterologous human proteins in bacterial systems, the concept quickly advanced to animal cell culture. It is notable that Wang's interest in animal cell culture had continued to thrive in the background of major multidisciplinary programs on enzyme synthesis and cellulosic biomass conversion. In 1977, he published on the use of microcarriers for not only animal cell cultivation but also virus production as well as interferon synthesis. Clearly there were lessons to be learned by extending knowledge of traditional fermentation to cell culture and Wang's students and collaborators were building a platform for the future.

3 | 1985–95—ADVANCES IN ANIMAL CELL CULTURE, PROTEIN REFOLDING, AND THE BIOTECHNOLOGY PROCESS ENGINEERING CENTER (BPEC)

The events of the early 1980's were indeed transformational. The biochemical engineering program had become a joint program between the Departments of Chemical Engineering and Applied Biology (the new name for the former Department of Nutrition and Food Science); the Biotechnology Process Engineering Center (BPEC) was

formed with major funding as an Engineering Research Center from the National Science Foundation with significant support from industry; recombinant DNA technology led to creation of a new Biotechnology industry; multidisciplinary research initiatives became the normal strategy to address large important problems and students were thirsty for multidisciplinary education.

The early recombinant proteins made in Escherichia coli, were overexpressed in large quantity but often accumulated as insoluble and inactive aggregates of improperly folded proteins. Recognizing the need for an engineering solution to this problem, Wang and his collaborators, which included Alan Hatton and Jonathan King, investigated multiple alternatives to refolding proteins in vitro. It became clear that to address the real problems of manufacturing biotherapeutics, one needed increasingly powerful analytical techniques that could track molecular scale events associated with protein synthesis, folding and post-translational modification. The problems of protein folding with bacterial-derived recombinant proteins as well as the inability of bacteria to properly catalyze post-translational events such as glycosylation further emphasized the need to use animal cells as a manufacturing method for recombinant proteins.

The platform that Daniel Wang began in the late 1960's on biochemical engineering of animal cell culture became a platform for manufacturing many of the important biologics in use today. From the mid 1980's onward, Wang's laboratory became a hotbed of innovation in cell culture technology. There was a focus on improving cell cultivation with microcarrier technology, growth medium design, process monitoring, and control and novel bioreactor design. An understanding of mass transfer needs and effects of mechanical shear led to significant improvement in operation. The wide array of approaches and the in depth understanding that evolved from these studies are seen in the numerous publications form this period. An important consequence of this work was the training of many students, not only in animal cell technology, but also in how to bring multidisciplinary and innovative solutions to important problems. The impact these students have had on the nascent biotechnology industry has been very important to the delivery of healthcare globally.

4 | 1995–PRESENT—MULTISCALE APPROACHES TO MANUFACTURING BIOTHERAPEUTICS

By 1995, the stage had been set for new paradigms in biochemical engineering research and education. Throughout his 40-year career, Wang with his students and collaborators strove to take a broad view of biochemical engineering that embraced the engineering of biochemical systems and components. Moving into the mid 1990's, our understanding of biology and the introduction of new analytical tools allowed us to move to the molecular scale to both seek understanding and develop new solutions to important problems. Fundamental approaches to engineering of biochemical systems moved from the reactor to the cell to the metabolic pathway to the proteins themselves. This is seen in the work to evolve from Wang's laboratory that addresses elucidation of how process operation affects post-translational modification of proteins and cellular behavior. This is done with the goal of improving manufacturing and thus delivery of important products to improve global health care. The work with collaborators, which included Philip Sharp, Greg Stephanopoulos, Bernhardt Trout, Harvey Lodish, Daniel Blankstein, and Paul Libinis added to those already mentioned speaks to how he reached out to embrace multidisciplinary approaches to complex problems. This has set an example for an untold number of students that not only says reach beyond your areas of scientific comfort but also teach to others what you know and understand.

The story does not end here. As we speak, Prof. Daniel Wang's laboratory continues to embrace important problems, especially in animal cell culture for biotherapeutics production. As energy prices rise, there is new interest in direct conversion of cellulosic biomass, albeit with the introduction of new molecular-scale understanding and technology that will enable major improvement in the potential for this technology. The lessons learned in biochemical engineering have become the fundamentals of the discipline on which we all continue to build. The students trained have become the next generation of teachers and the industrial leaders. For all this we are grateful and we look forward to more to come.

5 | PUBLICATION HISTORY

Professor D.I.C. Wang is one of the pioneers and greatest contributors within the field of biochemical engineering. In addition to numerous books and patents, he has co-authored 230 research papers between 1964 through 2005 (Afeyan & Wang, 1986; Archer, Ragnarsson, Tannenbaum, & Wang, 1973; Archer, Tannenbaum, & Wang, 1974; Augenstein, Sinskey, & Wang, 1971; Augenstein, Thrasher, Sinskey, & Wang, 1974; Aunins & Wang, 1989, 1990; Aunins, Croughan, Wang, & Goldstein, 1986; Aunins, Woodson, Hale, & Wang, 1989; Avgerinos & Wang, 1980a, b, 1983; Avgerinos, Fang, Biocic, & Wang, 1981; Baratti, Couderc, Cooney, & Wang, 1978; Baynes, Wang, & Trout, 2005; Bommarius, Holzworth, Wang, & Hatton, 1990a, b, 1995; Bravo & Wang, 1981; Butterworth & Wang, 1972; Butterworth, Wang, & Sinskey, 1970; Chahal & Wang, 1978; Chang & Wang, 1995a, b; Chang, Grodzinsky, & Wang, 1995; Cheftel, Ahern, Wang, & Tannenbaum, 1971; Chen, King, & Wang, 1995; Chen, Liu, Sharp, & Wang, 2001; Chiou, Murakami, & Wang, 1991; Chu, Yin, Wang, & Trout, 2004a, b, c; Cleland & Wang, 1990, 1991a, b, 1992, 1993a,b; Cooney & Wang, 1970, 1976; Cooney, Gordon, Jimenez, & Wang, 1978; Cooney, Wang, & Mateles, 1969, 1976; Cooney, Wang, & Wang, 1977; Coppella & Wang, 1990; Croughan and Wang, 1989, 1991; Croughan, Hamel, & Wang, 1987; Croughan, Hamel, & Wang, 1988; Croughan, Sayre, & Wang, 1989; Demain and Wang, 1976; Follstad, Wang, & Stephanopoulos, 2000; Follstad, Wang, & Stephanopoulos, 2002; Fox, Yap, & Wang, 2004; Fuchs and

Wang, 1974; Gasner and Wang, 1971 Cleland et al., 1992a,b; Ditsch, Lindermann, Laibinis, Wang, & Hatton, 2005a, b; Fox et al. 2005a, b; Gbewonyo and Wang, 1981, 1983a, b, 1987; Giard, Fleischaker, Sinskey, & Wang, 1981; Giard, Loeb, Thilly, Wang, & Levine, 1979; Giard, Thilly, Wang, & Levine, 1977; Gold, Mohagheghi, Cooney, & Wang, 1981; Goldblith and Wang, 1967; Goldblith, Tannenbaum, & Wang, 1968; Goswami, Sinskey, Steller, Stephanopoulos, & Wang, 1999; Gu and Wang, 1998; Gu, Harmon, & Wang, 1997a, b, 1998; Hagen, Hatton, & Wang, 1990a, b; Hamilton, Montgomery, & Wang, 1974; Harmon, Gu, & Wang, 1996; Ho, Baddour, & Wang, 1984; Hu and Wang, 1985, 1986, 1987; Hu, Meier, & Wang, 1984; Hu, Meier, & Wang, 1986; Itoh, Thien, Hatton, & Wang, 1990a, b; Junker, Wang, & Hatton, 1988; Junker, Hatton, & Wang, 1990a, b, 1993; Kamei et al., 2002a,b,c,d; Kelley, Wang, & Hatton, 1993a, b, c; Kennedy, Wang, & Stephanopoulos, 1992a, b; Kusunose and Wang, 2004a, b, 2005; Lam, Kavoos, Haynes, Wang, & Blankschtein, 2005; Lasko and Wang, 1993, 1996; Leung and Wang, 1981; Levine, Wang, Wang, & Thilly, 1977; Levine, Wang, & Thilly, 1979a, b; Liu, Kamei, King, Wang, & Blankschtein, 1998; Loh and Wang, 1996; Manfredini and Wang, 1972; McMillan and Wang, 1987, 1992; Meier, Hatton, & Wang, 1999; Mudgett, Smith, Wang, & Goldblith, 1971; Mudgett, Wang, & Goldblith, 1974; Murakami, Chiou, & Wang, 1991; Nadler, Paliwal, Regnier, Singhvi, & Wang, 1994; Nestaas and Wang, 1981a, b, 1983a,b; Nestaas, Wang, Suzuki, & Evans, 1981; Nyberg, Balcarcel, Follstad, Stephanopolous, & Wang, 1998a, b; Paliwal, Nadler, Wang, & Regnier, 1993; Park, Wang, & Yarmush, 1992; Perry and Wang, 1989; Rangel-Yagui et al., 2003; Robinson and Wang, 1987, 1988; Schilling, Alvarez, Wang, & Cooney, 2002; Shabtai and Wang, 1990; Singhvi, Stephanopoulos, & Wang, 1992; Singhvi, Stephanopoulos, & Wang, 1994a, b, 1996; Sinskey, Chu, & Wang, 1971; Sinskey, Fleischaker, Tyo, Giard, & Wang, 1981; Smiley, Hu, & Wang, 1989; Speed, Wang, & King, 1995; Speed, Wang, & King, 1996; Speed, King, & Wang, 1997a, b; Stramando, Avgerinos, Costa, Colton, & Wang, 1981, 1978; Thien, Hatton, & Wang, 1987a,b, 1989; Tyo and Wang, 1981; Tzeng, Thrasher, Montgomery, Hamilton, & Wang, 1975; Van Dyke, Wang, & Goldblith, 1969; Wang, 1968a, b, 1969a,b, 1982, 1984, 1985a,b, 1986, 1987a,b,c, 1988, 1991, 1992a,b, 1993a,b, Wang and Chiou, 1990; Wang and Cleland, 1992; Wang and Fewkes, 1977; Wang and Gbewonyo, 1982; Wang and Goldstein, 1989; Wang and Hagen, 1990; Wang and Hamilton, 1977; Wang and Hatch, 1972; Wang and Humphrey, 1969; Wang and Ochoa, 1972; Wang and Sinskey, 1970; Wang and Wang, 1984, 1989a, b, 1990; Wang, Scharer, & Humphrey, 1964a,b, 1968a,b, 1969a,b, 1971, 1977a,b, 1978, 1979a,b,c,d, 1983, 1984, 1997; Wilcox, Evans, & Wang, 1978; Wise, Wang, & Mateles, 1969; Wise, Wang, & Racicot, 1971; Xie and Wang, 1994a, b, 1995, 1996a,b,c, 1997; Yabannavar and Wang, 1987, 1991a, b,c; Yin, Bonner, & Wang, 2002; Yin, Lin, Li, & Wang, 2003; Yin et al. 2004a, b, c; Yuk and Wang, 2002a, b, c; Yuk, Wildt, Wang, Jolicoeur, & Stephanopoulos, 2002; Zhang and Wang, 1998). These papers can be lumped into six categories of topics. In order of historical sequence from earliest publication forward, these are:. Food Processing Technologies/Single Cell Proteins. Downstream Processing/Bioseparations. Fermentation/Biochemical Engineering. Bioconversion/Enzyme Technology. Cell Culture Technology. Protein Analysis/Product Characterization

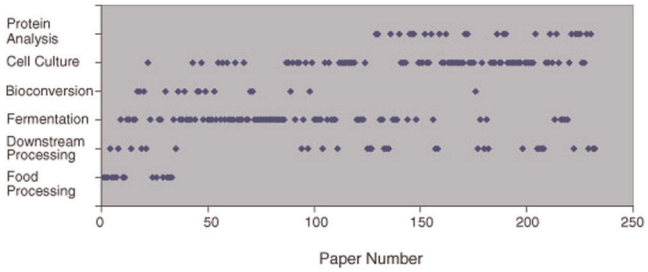

FIGURE 1 Prof. D. I C. Wang's publications between 1964 and 2005 shown in chronological order and according to subject matter

A hallmark of Prof. Wang's research philosophy is quantitative analysis and precision. In honor of this approach we analyzed his publication record. Figure 1 shows the distribution of co-authored papers by Prof. Wang within each topic from 1964 to the present. While the publication density varies between categories and also with time, it is noteworthy that a significant number of papers have been contributed within each topic area. Technologies related to fermentation and cell culture represent the majority of Prof. Wang's publications while Downstream Processing is the category within which he has been publishing for the longest time. His early interests in food processing technologies, the production of single cell proteins, and enzymatic bioconversions have been replaced later in his career by a new area of interest in protein analysis and characterization.

Figure 2 is a plot of publication number against time. The data shows a linear correlation between these variables with a regression coefficient R^2 of 0.98 and a slope of 6.37 coauthored papers per year. This steady-state rate of publication represents an output rate of one per 57.3 days. While the measured growth rate is not exponential as is the case with the living organisms that are the objects of much of Prof. Wang's research, the linear growth is analogous to the turnover

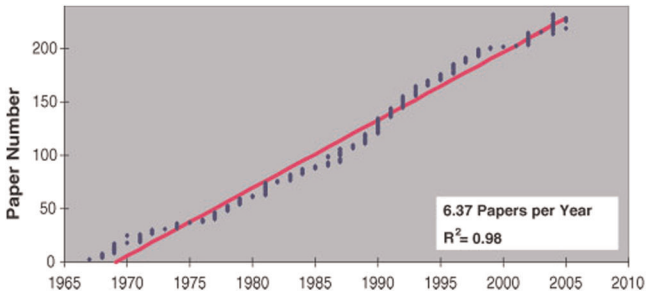

FIGURE 2 Prof. Wang's publications are plotted in chronological order against the year of publication. The best-fit linear regression line is shown with a slope of 6.37 papers per year and R^2 coefficient of 0.98.

rate of enzymes. This analogy is at best qualitative as the turnover rate of enzymes can be as high as 10^6 per second.

In order to further assess the consistency and predictability of Prof. Wang's publication record, we considered the distribution of his published articles across various journals. Of his 230 co-authored papers between 1964 and 2005, 94 were published in Biotechnology and Bioengineering. The next closest frequency was found in two journals with six papers in each. Prof. Wang has remarkably published in nearly 100 different publications.

6 | TREE OF DESCENT FROM PROF. WANG

Since joining MIT in 1965, Prof. Wang has supervised over 70 graduate student theses. While most graduates have pursued careers as biochemical engineers in industry, several have continued in Academia and have in turn supervised many additional graduate students. As a result, in aggregate over 300 graduates can trace their academic descent to a common ancestor. Figure 3 is an artist's rendering showing a tree of descent from Prof. Wang. Under the supervision of Prof. Wei-Shou Hu from University of Minnesota, this drawing was prepared for a reunion of Prof. Wang's students and colleagues that took place on April 21, 2006 on the occasion of his 70th birthday.

7 | LOOKING AHEAD

The Symposium to Honor Daniel I.C. Wang took place on April 22, 2006 at MIT (Figure 4 is from the symposium announcement). It brought together over 150 participants representing academia, large pharmaceutical, and chemical companies, mid-size biotech companies and start-ups. Attendees came from China, Japan, Singapore, Australia, New Zealand, Europe, South America, and North America. During this symposium, participants were invited to work together in groups identifying current challenges and offering predictions for the future within several sectors. Four groups were formed covering Cell

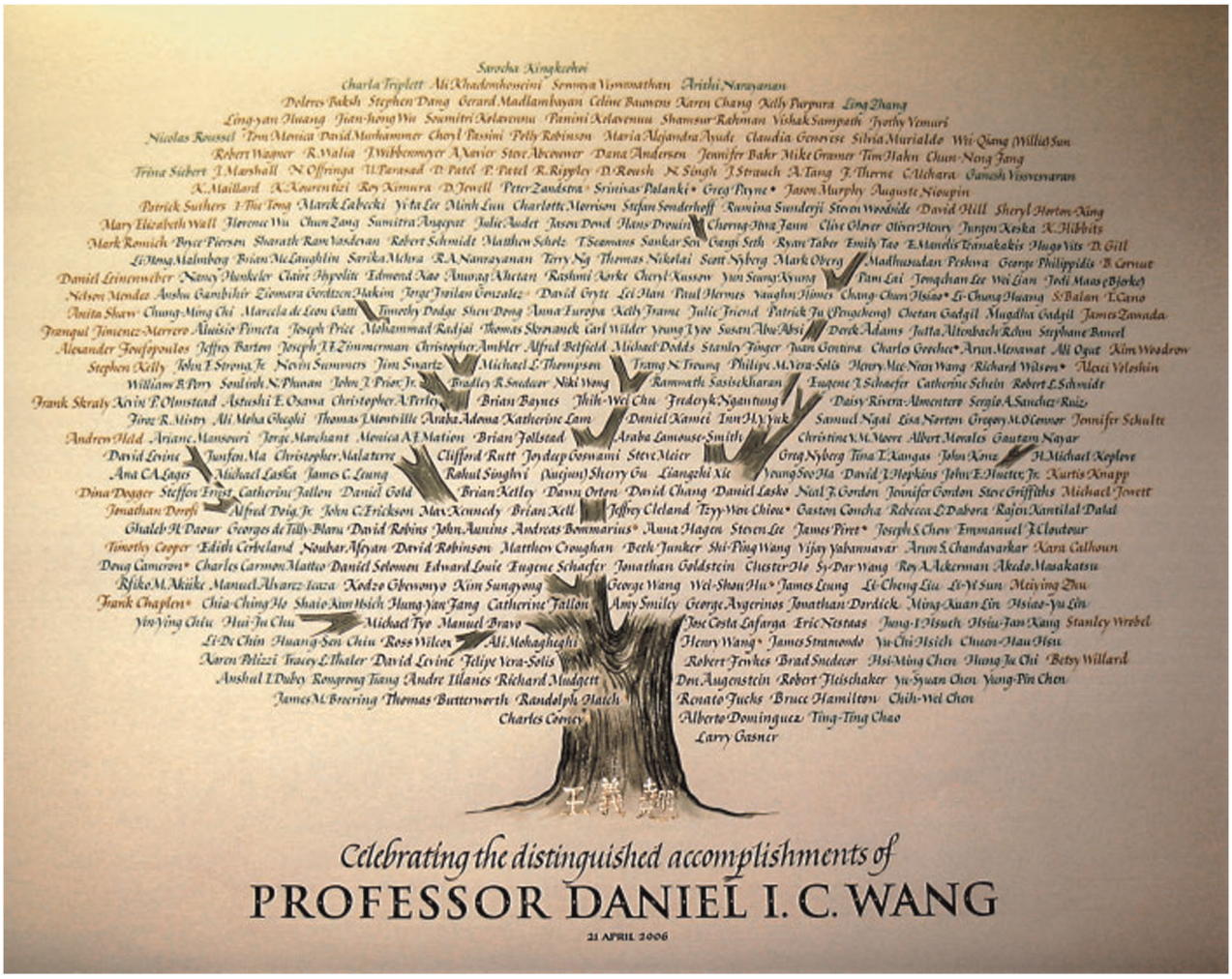

FIGURE 3 Tree of academic discent from Prof. Wang. (Created by Diane M. von Arx, artist and calligrapher, Minneapolis, MN. Used by kind permission of the artist.)

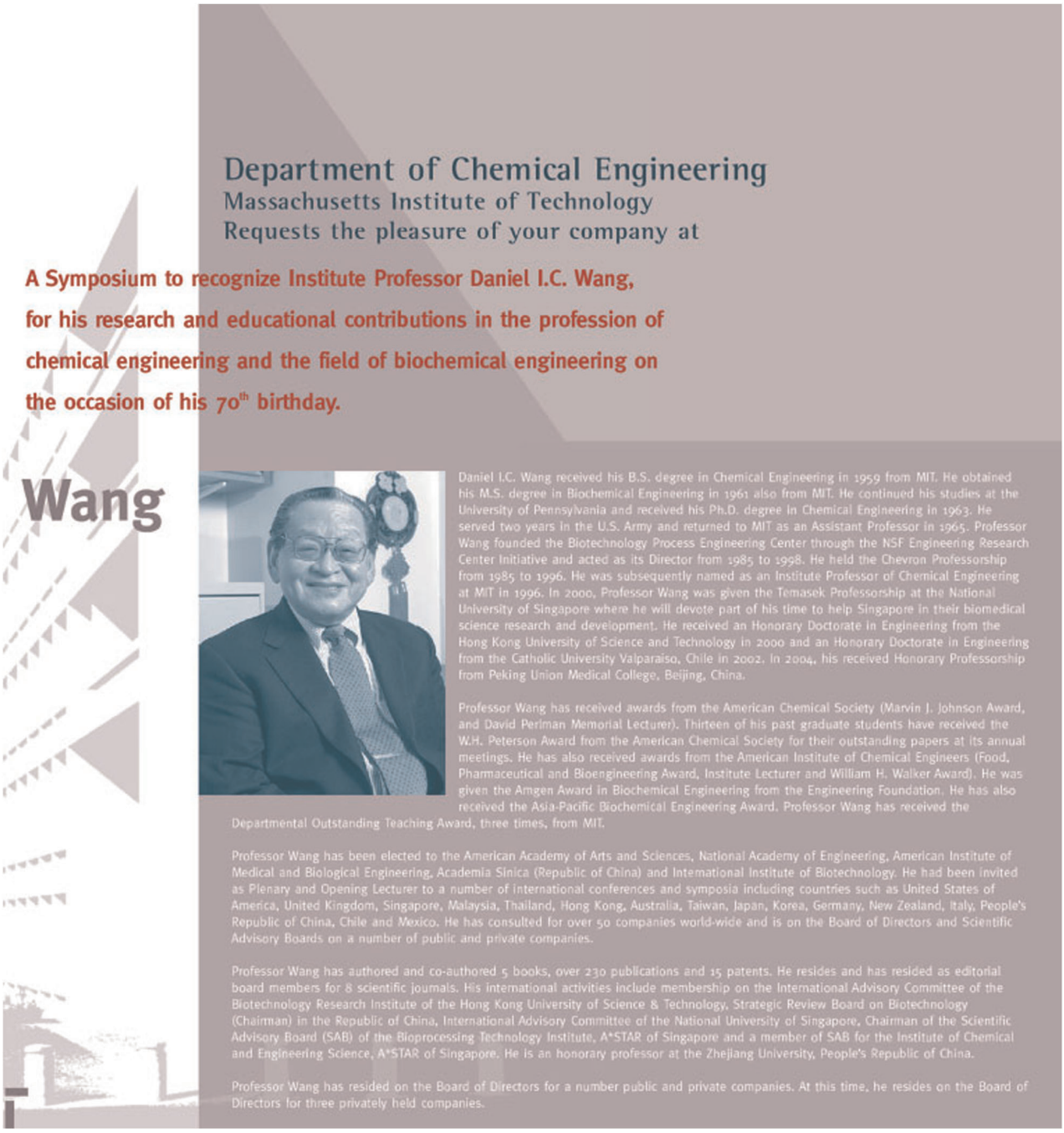

FIGURE 4 (Design by Wing Ngan of Ink Design, Boston, MA. Used by kind permission of the designer.)

Culture, Downstream Processing, Industrial and Enzyme Biotechnology, and Education. The following is a summary report from these working group sessions.

7.1 | Bioseparations

The challenges foreseen in the Downstream Processing arena included very large-scale production of biotherapeutics through cell culture. Without productivity increases in bioseparations, the upstream improvements in throughput will not to translate into overall gains. Another challenge identified by this working group is the one posed by rapid development cycles required to enter into clinical trials. Specifically, the industry anticipates requirements for a 6– 8 weeks development cycle for purification processes to produce clinical grade material for Phase I trials. The last challenge in this area was viewed to be the extreme conservatism towards adopting new technologies and innovations that exists in major biotechnology and pharmaceutical companies.

The Bioseparations working group predicted several solutions would emerge to address the current challenges. These include the development of very high-capacity chromatographic resins (e.g.,

Protein A resins with 150 g/L binding capacity), high-throughput screening of diverse chromatographic resins for rapid methods development, very large-scale separation methods such as liquid extraction or precipitation applied to proteins, magnetic nanoparticles, fast and precise analytical techniques, and highly specific affinity adsorbents.

7.2 | Cell Culture

The working group on cell culture technologies identified as the major challenges in their sector, capacity, cost, speed, and quality. As the production scale of certain biologic drugs has increased during the past decade, there is a need for more efficient and scaleable technologies. Given the regulatory environment, it is difficult to move lab innovations into a production setting without extensive validation trials with the attendant cost and time investments. Biogenerics and follow-on biologics are also expected to pose new challenges for cell culture processes. Post-translational modifications of biologics derived from cell culture continue to represent a significant challenge.

These challenges will represent opportunities for future generations of biochemical engineers. The tools available to them range from engineering cells to better control glycosilation or enabling non-mammalian production systems, to higher yield cell lines and better cell culture devices. In addition, with the advent of better and faster analytical techniques, the development of such processes will dramatically accelerate. There remains a significant need for training related to cell culture processes within industry and academia as well as within the FDA, as the number and complexity of glycosylated biotherapeutics increases rapidly.

7.3 | Industrial and Enzyme Biotechnology

Several challenges were identified within the area of industrial biotechnology. These include the relative lack of robustness of enzymes and microbial strains as compared to heterogeneous catalysts; the lack of reliable design capabilities for protein catalysts or cells with modified metabolic pathways; and challenges in fermentation of mixed sugars (e.g., pentose and hexose sugars derived from lignocellulosic biomass). Solutions to these challenges are expected to come from hybrid biological and chemical processes, engineered crops with superior properties for the intended use, and systems biology approaches applied to microbial systems to facilitate engineering of pathways.

The industrial biotechnology working group foresaw opportunities in integrating cellulosic feedstock into starchto-ethanol plants. In addition, significant reduction in process development times will be needed for this sector to meet the growing needs for biofuels and other specialty chemicals derived from agricultural products and waste. Also needed are significant improvements in pretreatment and ability to handle multiple feedstocks as well as in the waste treatment aspects of such bioprocesses. The group predicted that within 10 years designed enzymes and organisms would be in common use and molecules derived from renewable feedstocks such as carbohydrates and lipids would displace many petroleum-derived products in use today.

The industrial biotechnology area is one in which Prof. Wang made seminal contributions three decades ago. With the recent increase in the price of gasoline to exceed $70 per barrel, many of the technologies developed decades ago are now being rediscovered, improved upon, and applied at large scale. In addition to the renewed commercial attractiveness of such processes, molecular biology advances during the intervening period have made industrial biotechnology more predictable and productive than ever before.

A final note of caution was provided by the industrial biotechnology working group concerning the potential shortage of trained biochemical engineers who can work on engineering better enzymes, cells, and processes to capitalize on the emerging opportunities. The overwhelming majority of life sciences research funding in universities during the past decades has focused on health care applications. Without a significant re-emphasis on traditional biochemical engineering education, this shortage will be a major competitive disadvantage to the US.

7.4 | Education

The educational challenges within Biochemical Engineering were viewed by the working group to stem from the integration of "bio" within all components of engineering and science schools. As a result, undergraduates considering this field are often confused as are administrators within universities. In particular, incoming students often are not presented with sufficient information to distinguish biochemical engineering, biomedical engineering, biological engineering, and chemical engineering when choosing a major.

Instead of building a core curriculum that simply borrows courses from other disciplines, the group recommended that a core, integrated biochemical engineering curriculum based on shared principles, concepts and models be developed and taught. With the explosive increases in biological knowledge and innovative technologies available today, the textbooks, curriculum, and approaches to training experts in this field will need to be constantly updated. While doing this, it will be also important to maintain a clear set of core courses, including such foundational topics as fermentation and cell culture, which can be invariant even while new applications emerge over time. A strong educational foundation will be especially important to US educated personnel to be able to compete effectively within the current trend towards increasingly outsourcing the design and manufacture of biochemical products to China and India.

Educating students as well as academic and industrial colleagues is perhaps the most significant of the contributions made to the field by Prof. Wang. The challenge and responsibility of educating future generations of biochemical engineers lay on the shoulders of Prof. Wang's academic family and friends. The highest form of compliment

this community can pay to his legacy is a renewed commitment to excellence in educating the future, so-called "Danny Wangs", and following the path Prof. Wang has ably laid for us during the past four decades.

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