ARTICLES

Biocommodity Engineering

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The application of biotechnology to the production of commodity products (fuels, chemicals, and materials) offering benefits in terms of sustainable resource supply and environmental quality is an emergent area of intellectual endeavor and industrial practice with great promise. Such "biocommodity engineering" is distinct from biotechnology motivated by health care at multiple levels, including economic driving forces, the importance of feedstocks and cost-motivated process engineering, and the scale of application. Plant biomass represents both the dominant foreseeable source of feedstocks for biotechnological processes as well as the only foreseeable sustainable source of organic fuels, chemicals, and materials. A variety of forms of biomass, notably many cellulosic feedstocks, are potentially available at a large scale and are cost-competitive with low-cost petroleum whether considered on a mass or energy basis, and in terms of price defined on a purchase or net basis for both current and projected mature technology, and on a transfer basis for mature technology. Thus the central, and we believe surmountable, impediment to more widespread application of biocommodity engineering is the general absence of low-cost processing technology. Technological and research challenges associated with converting plant biomass into commodity products are considered relative to overcoming the recalcitrance of cellulosic biomass (converting cellulosic biomass into reactive intermediates) and product diversification (converting reactive intermediates into useful products). Advances are needed in pretreatment technology to make cellulosic materials accessible to enzymatic hydrolysis, with increased attention to the fundamental chemistry operative in pretreatment processes likely to accelerate progress. Important biotechnological challenges related to the utilization of cellulosic biomass include developing cellulase enzymes and microorganisms to produce them, fermentation of xylose and other nonglucose sugars, and "consolidated bioprocessing" in which cellulase production, cellulose hydrolysis, and fermentation of soluble carbohydrates to desired products occur in a single process step. With respect to product diversification, a distinction is made between *replacement* of a fossil resource-derived chemical with a biomass-derived chemical of identical composition and *substitution* of a biomass-derived chemical with equivalent functional characteristics but distinct composition. The substitution strategy involves larger transition issues but is seen as more promising in the long term. Metabolic engineering pursuant to the production of biocommodity products requires host organisms with properties such as the ability to use low-cost substrates, high product yield, competitive fitness, and robustness in industrial environments. In many cases, it is likely to be more successful to engineer a desired pathway into an organism having useful industrial properties rather than trying to engineer such often multi-gene properties into host organisms that do not have them naturally. Identification of host organisms with useful industrial properties and development of genetic systems for these organisms is a research challenge distinctive to biocommodity engineering. Chemical catalysis and separations technologies have important roles to play in downstream processing of biocommodity products and involve a distinctive set of challenges relative to petrochemical processing. At its current nascent state of development, the definition and advancement of the biocommodity field can benefit from integration at multiple levels. These include technical issues associated with integrating unit operations with each other, integrating production of individual products into a multi-product biorefinery, and integrating biorefineries into the broader resource, economic, and environmental systems in which they function. We anticipate that coproduction of multiple products, for example, production of fuels, chemicals, power, and/or feed, is likely to be essential for economic viability. Lifecycle analysis is necessary to verify the sustainability and environmental quality benefits of a particular biocommodity product or process. We see biocommodity engineering as a legitimate focus for graduate study, which is responsive to an established personnel demand in an industry that is expected to grow in the future. Graduate study in biocommodity engineering is supported by a distinctive blend of intellectual elements, including biotechnology, process engineering, and resource and environmental systems.

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I. Introduction

Among the major trends expected to impact human society in the 21st century, two of the most important are: (1) a transition toward a modern society based on sustainable resources and (2) a technological revolution resulting from advances in understanding and capability related to living systems. Squarely at the intersection of these trends is the use of biological systems to produce large-scale commodity products such as fuels, bulk chemicals, and materials, an emergent field of intellectual endeavor and industrial practice for which we propose the term Biocommodity Engineering.

Whereas health care has been the dominant motivation underlying the biotechnology field to date, biocommodity engineering aims to be responsive to societal needs for sustainable resource utilization and improved environmental quality. This potential arises from the use of plant biomass as feedstocks combined with the use of biotechnology to carry out chemical transformations. Plant biomass is the only foreseeable sustainable source of organic fuels, chemicals, and materials. As the primary component of the biosphere, biomass is also an industrial raw material uniquely compatible with human and other life forms. Because of the CO_2-consuming character of plant growth, biomass-based processes and products can be incorporated into nature's photosynthesis-driven carbon cycle with lifecycle greenhouse gas emissions approaching zero in some cases (*1*, *2*, *3*). Biological processing in aqueous (as opposed to hydrocarbon) processing environments typically gives rise to process effluents easily rendered harmless for discharge. Moreover, the products of biomass processing are typically biodegradable and nontoxic. Sustainability and environmental benefits are in general strongly related to scale of production; hence very large-scale products such as fuels and monomers for synthesis of plastics are particularly important to consider in this context and will be the primary focus of this article.

Signs of the emergence of the biocommodity engineering field are increasingly evident. Morris and Ahmed (*4*) forecast increasing production of chemicals and industrial materials from plant matter as society moves toward a "Carbohydrate Economy". A National Science and Technology Council study (*5*) speaks of a "second wave" of biotechnology applied to fields other than health care. A National Research Council study (*6*) projects that 50% of organic chemicals and materials will be produced from plant material by 2020 with biologically based processes playing a central role. The chemical industry is restructuring itself in the wake of the biotechnology revolution (*7*), including hundreds of millions of dollars in investment, formation of joint ventures, and formation of life science-oriented spinoffs of a size comparable to their parent companies (*8*). Shell LTD's preferred scenario for world energy supply and economic development entails utilization of plant biomass on a scale exceeding that of oil in 2060 (*9*). Biomass-based fuels were identified by auto industry representatives of a Presidential Advisory Committee as one of two "technological homeruns" for reducing transportation sector greenhouse gas emissions (*10*). Groundbreaking for the first commercial facility producing fuel ethanol from cellulosic biomass has recently been announced (*11*), and the long-term societal benefits of such biologically based fuel production have been praised in an article entitled "The New Petroleum" (*12*) by Senator Richard Lugar and former Director of Central Intelligence R. James Woolsey.

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Driven by the dominant imperative of industrialization and enabled by transformative advances in the field of organic chemistry, petroleum refining became a major source of energy and materials in the first half of the 20th century. This development was directly responsible for the emergence of chemical engineering as an academic discipline. We think it possible and appropriate that biocommodity engineering will develop along similar lines in the first half of the 21st century, with the dominant imperative being sustainability and the enabling factor being transformative advances in biotechnology. In this paper, we take a long-term view of biocommodity engineering in terms of the forces that will shape it, the intellectual activity that will enable it, and the technology that will result from it.

II. Evolution and Distinctiveness of the Biocommodity Engineering Field

When the modern era of biotechnology began following the development of recombinant DNA technology in the 1970s, the academic biochemical engineering community responded by focusing on efficient manufacturing at the process level. Over time, though, the focus of health care-motivated biochemical engineering has shifted "away from biochemical equipment design and operations, toward the understanding at the cellular level of biochemical and biological systems" (*13*). This shift includes an emphasis on product production at the cellular rather than process scale. It appears to also include a de-emphasis on products of any kind in favor of the quantitative description of cellular and bodily phenomena. For example, in outlining the annual meeting of the AIChE, the 1997 Newsletter of the Food, Pharmaceutical, and Bioengineering grouped 17 of 35 session topics under "Biomedical Engineering/Engineering Fundamentals in the Life Sciences".

A significant factor underlying this shift is the realization that low cost manufacturing is usually not an important factor in the process development path for high-value pharmaceuticals. As recently discussed by Basu (*14*), production of material for clinical and safety studies typically begins very early in pharmaceutical process development, after which there is strong incentive to make as few process changes as possible in order to avoid delays in obtaining regulatory approval. As a result, pharmaceutical manufacturing tends to rely on standardized equipment that can be brought on line quickly and will reliably achieve high process consistency. By contrast, process development for commodity products emphasizes low-cost manufacturing often using improved technology specific to the process of interest. Whereas the dominant driving forces in pharmaceutical process development are being first to market and achieving high product quality, the dominant forces for commodity products are efficient manufacturing and utilization of low cost feedstocks. Thus high yields, volumetric productivity, and product concentration as well as realization of value from coproducts are primary objectives for biocommodity process development and typically not for biopharmaceutical process development.

Biocommodity engineering builds directly on the same molecular biology foundation that enables technology for production of high-value products and will benefit from continued maturation of this technology. Beyond this common foundation, the differences between the production of high- and low-value bioproducts are much more numerous than the similarities (Table 1). The value of pharmaceuticals on a mass basis differs tremendously

Table 1. Comparison of Commodity and High-Value Bioproducts[a]

feature	high-value product(s) (e.g. biopharmaceuticals)	commodity product(s) (e.g. ethanol)
product value		
$/g	$\geq 10^4$	10^{-4}
$/L unseparated broth	10 to 100	10^{-5}
contribution to selling price (%)		
raw materials	0.1 to 1	up to 75%
cost of production	<30[b]	>90
potential markets (for individual products, assuming mature technology)		
$billion/year[c]	1−10 s	potentially 10 s
Kg/year	usually <1	potentially $>10^{11}$

[a] Values given are approximate, with order of magnitude variation possible and even likely in some cases. High-value product data are based on personal communication of David DeLucia (formerly of Verax Inc., Lebanon, NH) except where otherwise noted and are representative of mammalian cell production systems in the biopharmaceutical industry. Commodity product values are the author's estimates based on mature technology such as that envisioned in ref *15*. [b] From Angus Macdonald (Macdonald & Associates, Providence RI). Includes costs for capital and capital-related costs (insurance, maintenance, taxes) and operating costs including labor and raw materials. Excludes fees associated with licensing, clinical trials, obtaining FDA approval, and recovery of R&D costs. [c] The largest markets for individual biopharmaceutical products are just over $1 billion currently (*16*). Biocommodity market sizes are consistent with projected markets for biologically produced transportation fuels (*17*) and bulk plastics (*18*).

from that of biocommodity products, with 8 orders of magnitude being a representative ratio. Although commodity products are usually present in higher concentrations prior to separation as compared to pharmaceuticals, product value per volume of unseparated broth is still much greater for biopharmaceuticals, typically by over 5 orders of magnitude. Raw materials usually account for a very small fraction of the selling price of pharmaceuticals, whereas raw materials are large and are often dominant factors in determining the price of commodity products. The cost of production including capital recovery is usually by far the dominant factor determining the price of commodity products, whereas the cost of production is not nearly so important for pharmaceuticals. Measured in dollars, markets for individual biopharmaceutical and biocommodity products are of relatively similar magnitude and very large. However, tremendous differences exist with respect to market size on a mass basis, with the largest commodity markets exceeding pharmaceutical markets by approximately 11 orders of magnitude. The production of high-volume/low-value biocommodity products has an absolute requirement for high-volume/low-value feedstocks and must be responsive to the availability and characteristics of feedstocks, whereas no such requirement exists for the production of pharmaceuticals.

It was natural that the nascent biotechnology field focused first on high-value products, since such products have less stringent requirements for low-cost processing technology as compared to commodity products, and since they have the potential to be produced profitably on a relatively small scale. We anticipate continued rapid advances in biotechnology related to health care. In addition, we anticipate the emergence of biocommodity engineering as a significant area of endeavor that will become increasingly distinctive over time. The evolution of technology toward lower unit value and larger production volume has been observed many times, with oil and utility industries offering prominent examples (*9*, *19*). Indeed, even production of pharmaceuticals must follow this evolution at least to some degree as patents on early generation products expire, product development costs are recovered, and competition increases.

III. Feedstocks

Feedstocks for biocommodity processes have a large and often dominant impact on process economics, siting of commercial facilities, environmental benefits and impacts, and process development. A diversity of potential feedstocks are available in the form of residues from the forest products, agricultural, and other established industries as well as from dedicated crops for the purpose of providing feedstocks for biocommodity processes. Feedstocks with both large-scale availability and amenability to biological processing generally fall into the categories of sugar-rich crops such as sugar cane and sweet sorghum, oils of plant or animal origin, corn or other starch-rich grains, and cellulose-rich materials in either woody or herbaceous form. Because of their high degree of reductance compared to carbohydrates, oils offer some interesting and unique biological processing possibilities. The question of whether oils can be cost-effective feedstocks for biocommodity processes is impacted strongly by the extent to which value can be found for the nonoil portions of oil-producing plants. a situation not unlike the use of transgenic plants (Section IV-C). Materials rich in soluble sugars suffer from seasonal availability and higher price as compared to other sources of carbohydrate and thus have limited potential as biocommodity feedstocks in most locations.

Because of low cost, plentiful supply, and amenability to biotechnology, carbohydrates appear likely to be the dominant source of feedstocks for biocommodity processing. Starch-rich and cellulosic materials each have important advantages in this context, and we expect that both have important, although probably distinct, roles to play. Advantages to grains include an established feedstock production and processing infrastructure and the presence of carbohydrate in a form that is both more homogeneous and more reactive than that found in cellulosic materials. Because of these advantages, corn is by far the dominant feedstock for biological production of commodity products today. Advantages to cellulosic materials include much larger ultimate supply, lower purchase cost and lower anticipated transfer cost (see Section IV), less erosivity (*20*), and lower inputs of chemicals and energy required for production (*17*, *20*). These features make cellulosic materials the preferred long-term feedstock for large-scale biocommodity products provided that cost-effective and environmentally benign technologies for overcoming the recalcitrance of cellulosic biomass can be developed (Section V-A). Corn has an important transition role to play as an established feedstock for biocommodity processes while cellulose-based technology matures. Furthermore, the corn plant is a potentially significant source of cellulosic feedstocks in the form of crop residues (*6*). A likely permanent advantage of corn as compared to cellulosic materials is that carbohydrate-rich process streams of sufficient purity to accommodate production of food, food additives, and pharmaceutical products for human consumption are more easily obtained.

Although carbohydrate represents from $^2/_3$ to $^3/_4$ of the dry weight of most plant materials, substantial diversity is exhibited among different types of biomass with respect to individual carbohydrate components (Table 2). For

Table 2. Composition of Representative Biomass Feedstocks[a]

	carbohydrate	noncarbohydrate
seeds		
starch-rich		
corn	starch (72%), hemicellulose (6%), cellulose (3%)	protein (10%), oil (10%) ash and lignin (2%)
oil and protein-rich		
soybeans	fiber (8%)	protein (61%), oil (24%) ash, lignin & other (%)
cellulosic materials		
agricultural residues		
corn stover	glucan (36.4%), xylan (18%), arabinan (3%), galactan (1%), mannan (0.6%)	lignin (16.6%), ash (9.7%), extractives (7.3%)
wheat straw	glucan (38.2%), xylans (21.2%), arabinan (2.5%) galactan (0.7%), mannan (0.3%)	lignin (23.4%), extractives (13.0%), ash (10.3%)
woody		
hardwoods	glucan (50%), xylan (17.4%), mannan (2.5%), galactan (0.8%), arabinan (0.5%)	lignin (21%), extractives & ash (~3%)
softwoods	glucan (46%), mannan (11.2%), xylan (5.7%), galactan (1.4%), arabinan (1.0%)	lignin (29%), extractives & ash (~3%)
herbaceous		
switchgrass (early cut)	cellulose (40.7%), hemicellulose (35.1%)	protein (11%), ash (5.8%), lignin (5.5%)
switchgrass (late cut)	cellulose (44.9%), hemicellulose (31.4%)	lignin (12%), ash (4.6%), protein (4.5%)

[a] Percent values shown are based on dry weight. Theoretical yields of soluble sugars are higher than the values shown by 1.11 for hexan and 1.14 for pentan due to the water of hydrolysis. Fiber incluces cellulose and hemicellulose. The diversity of compositional categories used reflects that in the literature. Corn composition from ref *21*. Soybeans from ref *22*. Corn stover and wheat straw from ref *23*. Hardwood data are from ref *24* except for ash and extractives, which are from ref *23*. Switch data are from ref *25* except for protein which is from Bruce Dale (personal communication).

corn kernels, most of the carbohydrate fraction is made up of D-glucose molecules joined by alpha linkages to form starch, whereas the carbohydrate fraction in cellulosic biomass consists of cellulose and hemicellulose. Cellulose is a homopolymer of β-linked glucose usually present in a highly ordered crystalline structure that impedes hydrolysis. Hemicellulose, also found in cellulosic materials, is an amorphous polymer and typically contains five different sugars: L-arabinose, D-galactose, D-glucose, D-mannose, and D-xylose. Hemicellulose often also contains smaller amounts of nonsugar components such as acetyl groups. The fiber fractions of both corn and oil crops are composed of cellulose and hemicellulose.

Whereas the noncarbohydrate fraction of corn kernels contains protein and oils, the noncarbohydrate portion of cellulosic materials is comprised of mostly lignin with lesser amounts of ash and soluble substances termed extractives. Lignin is a complex phenyl propene material, while the ash consists of inorganics such as silica, potassium, and sodium. Early-cut herbaceous materials can contain a significant amount of protein.

Careful attention to the utilization of all feedstock components is important in terms of process technology, economic, and environmental considerations. In the case of corn, oil can be recovered in the wet milling process and the presence of protein adds value to byproducts such as corn gluten meal, and corn gluten feed. In the case of cellulosic materials, development of microorganisms capable of converting hemicellulose-derived pentose sugars (Section V-A) has resulted in significant cost benefits. Lignin-rich process residues provide a potential source of aromatic chemicals at low production volumes and an attractive fuel for power generation at high volume. For appropriately harvested herbaceous cellulosic materials, protein can potentially be recovered and sold as animal feed. Economic impacts of coproduct production are explored in Sections IV-A and VI.

Both feedstock production and process coproducts can have profound impacts with respect to resource and environmental metrics (see Section VI-C). For example, the presence of lignin in many cellulosic materials can lead to the export of power and the elimination of external inputs of processing energy, which in turn has a large beneficial impact on net greenhouse gas emissions (*2*). The coproduction of animal feed protein and feedstocks for bioprocessing potentially offers large benefits in terms of land-use efficiency.

U.S. production of primary building blocks for the synthesis of organic chemicals (ethylene, propylene, benzene, methanol, toluene, xylene, butadiene) totaled about 64 million tons in 1997 (*26*). This may be compared to the current rate of biomass consumption by the corn refining industry (52 million tons/year, ref *27*) and the pulp and paper industry (100 million tons/year, ref *28*). Annual availability of collectable waste cellulosic biomass, with allowance for maintaining soil fertility, at a price $\leq$\$45/ton has been estimated at 140 million tons/year (*2*); many estimates for the potential availability of dedicated cellulosic crops are substantially larger than this value (see refs *2*, *17*). These observations support the conclusion that the magnitude of the sustainably harvestable biomass resource is sufficient to meet the demand for all petrochemicals produced in the United States. The possible sufficiency of the biomass resource to meet much larger fuel needs is an important and contentious issue. We believe that there are responsible scenarios in which biomass-derived fuels can meet U.S. mobility demands but defer analysis of this complex question to a future paper.

IV. Economic Framework

To contribute significantly to sustainable resource supply and improved environmental quality, biocommodity processes must be attractive from economic as well as environmental viewpoints. Economic analysis is also important in targeting opportunities for R&D-driven cost reductions and anticipating the direction of future technology. Aspects of the economic framework for biocommodity engineering are considered in this section with

Table 3. Representative Prices for Selected Biomass and Fossil Resources[a]

	$/dry metric ton	$/GJ
fossil		
oil		
@ $17.5/barrel	129	3.1
@ $12.7/barrel	94	2.3
@ $6/barrel	44	1.2
natural gas (@ $2.50/1000 scf)	122	2.3
coal	33	1.0
biomass		
corn		
kernels (@ $2.5/bushel)	98	5.0
stover	19	1.0
cellulosic		
short rotation poplar, switchgrass	44	2.3

[a] Prices for fossil resources from ref *29*. Corn stover price from ref *6*. Cellulosic price from refs *30, 31*. Heating values from ref *32*.

respect to feedstocks, overall processing, and plant-based production systems.

A. Cost Competitive Raw Materials. It is logical to benchmark the cost of plant biomass against the cost of oil, the dominant source of organic fuels and chemicals currently, as well as other prominent fossil resources, natural gas and coal (Table 3). Relative to oil at $17.5/barrel, a representative value during the 1990s (*29*), the price of corn at $2.50/bushel (also representative) is competitive on a mass basis but not on an energy basis. Cellulosic materials such as short-rotation poplar and switchgrass are expected to be very widely available at $40/delivered dry ton (*30, 31*), a price calculated on the basis of fully compensating farmers for producing cellulosic crops as opposed to more traditional crops. Waste cellulosic materials such as corn stover, sugar cane bagasse, waste paper sludge, and municipal solid waste are available at many locations for substantially lower prices. Even at $40/ton, the price of cellulosic biomass is substantially less than that of oil at $17.5/barrel on both a mass and energy basis. The break-even oil price relative to cellulosic biomass at $40/ton is $12.7/barrel on an energy basis and $6/barrel on a mass basis. Relative to natural gas, at $2.50/1000 scf, cellulosic biomass is price-competitive on an energy basis and has a substantial price advantage on a mass basis. The purchase price of dedicated biomass crops approaches being cost competitive with coal on a mass basis but not on an energy basis. Both corn and cellulosic materials compare more favorably on a mass basis than an energy basis because of the more reduced and oxygen-poor character of fossil resources. It may be noted that the prices of oil, corn, and pulpwood all have varied by more than 2-fold during the 1990s.

Today's corn and oil refineries convert these chemically diverse raw materials into an array of saleable products. We believe this will also be true of cellulose refineries of the future. Beyond the simple purchase price, other feedstock cost metrics can be defined to reflect the fact that coproducts produced from noncarbohydrate portions of biomass feedstocks can impact the effective cost of carbohydrate for biological processing. Alternative price metrics relevant in this context are listed in Table 4. The purchase price of carbohydrate, P_c, is the purchase price on a dry mass basis divided by the potential soluble sugar content of the feedstock expressed as a mass fraction. The net price of cabohydrate, N_c, represents the purchase price less the value of coproducts. The transfer price of carbohydrate, T_c, represents the net price adjusted for coproduct revenues and for operating and annualized

Table 4. Alternative Feedstock Price Metrics

purchase price (P)	¢/kg feedstock
purchase price of carbohydrate, P_c	$P_c = \frac{P}{F_c}$
net price of carbohydrate, N_c	$N_c = P_c = \sum_i V_{Pi}$
transfer price of carbohydrate, T_c	$T_c = \frac{N + o + c}{\epsilon}$
% product value, F	$F = \frac{P}{\sum_j V_{Pj} Y_{Pj}}$

where:
P_c = ¢/kg feedstock
F_c = kg PSS[a]/kg feedstock
N_c = net price of carbohydrate (¢/kg PSS)
V_{Pi} = product value (¢/unit product)[b]
Y_{Pi} = product yield, carbohydrate basis (unit product/kg PSS)
i = coproduct index, excluding the primary product
j = index of all products, including the primary product
o = operating cost[c] (¢/kg PSS)
c = annualized capital cost[c] (¢/kg PSS)
ϵ = carbohydrate conversion efficiency (actual soluble sugar/PSS)

[a] PSS = potential soluble sugar. [b] Fermentable carbohydrate valued at its transfer cost in computing F. [c] For production of carbohydrate and all coproducts.

capital costs for all process steps up to and including the production of fermentable carbohydrates and coproducts (including waste treatment) and also adjusted for the carbohydrate conversion efficiency. In essence, the transfer price is the price of carbohydrate that a company would have to charge itself to recover its cost at a given return on investment. The transfer price is exclusive of costs associated with conversion of soluble sugars to products of interest. The percent of product value, F, provides an indication of the impact of feedstock costs on overall process economics.

Table 5 compares feedstock price metrics and other data relevant to refining of corn (via wet milling; Ron Landucci, ProForma Systems, Inc., personal communication), cellulose processing via current technology, and cellulose processing via projected mature technology. Costs for cellulose processing via current and mature technology are based on the base-case and, most likely, advanced case scenarios for ethanol production from poplar defined by Lynd et al. (*15*). We expect that the cost of processing cellulosic biomass would be similar for herbaceous cellulosic feedstocks such as switchgrass. The data in Table 5 illustrate the potential of cellulosic feedstocks as low-cost sources of carbohydrate for biological processing, as the purchase and net price is substantially lower for both cellulose scenarios as compared to corn. The carbohydrate-transfer price is similar for the corn wet mill and current cellulosic biomass scenarios but is substantially lower for the mature cellulosic scenario. For the corn wet mill scenario, comparison of the net and transfer prices indicates that, although substantial coproduct value is realized, the costs associated with this realization are comparably large. For the current cellulosic scenario, the transfer price is more than twice the purchase price, reflecting primarily the high cost of overcoming the recalcitrance of cellulosic biomass using current technology (see Section V. A.). Realization of the transfer price for the current cellulosic scenario will require that risk and the cost of capital be lowered

Table 5. Cost of Sugar for Processing Corn and Cellulosic Biomass[a]

	sugar yields (mass basis)	coproducts	price of feedstock (¢/kg soluble sugars)			*F*, feedstock price as a % of product value
			purchase	net	transfer	
corn wet mill						
corn @$2.5/bu	0.80	gluten feed, germ, gluten meal	14.3	6.6	14.1	66
cellulosic (poplar)						
current ($44/tonne)	0.58	power	5.7	4.6	13.5	52
mature ($42.5/tonne)	0.66	power	5.3	3.5	7.6	66

[a] Costs are for sugars as intermediates in the refining process rather than as purified products suitable for sale. Corn wet mill values from Ron Landucci (ProForma Systems Inc). Purchase, net, and transfer costs are defined as in Table 4. Cellulosic values are from Lynd et al. (*15*). Costs are calculated from the base case and most likely advanced scenarios for ethanol production, with costs for product recovery subtracted and associated steam used to generate power. The current/base case scenario involves dilute acid hydrolysis and SSF. Cellulosic sugar yields are for both hexoses and pentoses and reflect losses due to incomplete hydrolysis, pentose degradation during pretreatment, and cellulase production. The mature scenario involves liquid hot water pretreatment and consolidated bioprocessing. For both the current and mature cases, power is derived via burning lignin-rich process residues in a Rankine cycle. A consistent costing framework is used for both corn and cellulosic plants as specified by Landucci. Features of this framework include 20 year plant life, 3 year construction period, 20% discounted cash flow rate of return, 37% combined federal and state taxes, 3% inflation, MACRS depreciation, 10 year equipment life, 31 year building service life, 25% owner equity financing, 10% effective loan rate.

to values characteristic of corn processing, which is not currently the case. In addition, the transfer price for cellulosic biomass implicitly assumes ability to process both pentose and hexose sugars at high yields, which has been realized to date for some but not all products (see Section V. A.). Realization of the transfer price for mature cellulosic technology will require R&D-driven advances associated with overcoming the recalcitrance of cellulosic biomass (see ref *15* and subsequent discussion herein). It is likely that a more complete slate of coproducts, such as those produced from an oil refinery, would lower the transfer price of carbohydrate in the mature cellulosic scenario somewhat further.

Comparison of values for the percent product value represented by feedstock, *F*, suggests that corn wet-milling technology is relatively mature. That is, the conversion processes are developed to the point that the price of feedstock represents the largest share of total product value and processing cost margins are relatively small. In particular, *F* values for both corn wet milling ($F = 0.66$, Table 5) and oil refining ($F = 0.67$, based on the average value for U.S. refining industry for the period 1990−1997; refs *29*, *33*, *34*) are about $^2/_3$, which we take to be indicative of mature technologies for production of commodity products. The realism of the mature cellulosic biomass scenario is supported by its similar *F* value ($F = 0.66$). The far lower value for the current cellulosic scenario (0.52) is a strong indication of the relative immaturity of this technology.

B. Cost-Competitive Processes. We believe that the higher current cost of biologically processing biomass as compared to nonbiological processing of petroleum is due to the fact that modern society has invested vastly less effort in the former as compared to the latter. Furthermore, we anticipate that R&D-driven improvements in technology for biologically based conversion of plant biomass can, over the long term and given sufficient effort, result in commodity products priced competitively with products from petroleum at oil prices in the range seen in the 1990s. In addition to the data presented in Table 5, this view is further supported by the following observations:

•In light of the dominance of feedstock cost for commodity products (Table 5), selling price tends to be relatively insensitive to small differences in processing costs. Said another way, the cost of biomass processing would have to be substantially higher than the cost of processing petroleum in order to have much impact on product prices for mature technology.

•Because of their significant level of oxygen substitution, biomass and most biomass-derived products are more amenable to subsequent reactive transformations than largely aliphatic petroleum.

•Modern biotechnology, arguably the most powerful new development in processing technology, is much more readily applicable to processing plant biomass than petroleum. In particular, biotechnology can be applied to production of commodity products from biomass not once but twice: first in development of plants amenable to subsequent processing and second in developing improved biological catalysts for producing products of interest.

•Oil refineries are unlikely to have significant economies of scale advantages relative to mature biomass refineries. This expectation is supported by the fact that the largest existing corn wet mills process a material flow (∼11000 tonnes/day) in the range typical of an oil refinery (*34*) and further by the tremendous amount of plant material that can be produced within a reasonable (e.g., 50 mile) radius of a processing plant (*15*). These advantages are counterbalanced to some extent by the greater difficulty of handling solid-phase biomass as opposed to liquid-phase petroleum, but we think this unlikely to be a dominant economic factor in the long run. This expectation is based in part on the availability of different processing paradigms suitable for processing solid materials, considered in Section V.

C. Plant-Based Production Systems. Consistent with the perspective expressed in recent reviews (*35*−*37*), we believe that the prospect of "fermentorless" biosynthesis in transgenic plants is an exciting development that is likely to be the preferred production mode for some products. We also offer two cautionary comments relevant to plant-based production systems for commodity products as compared to fermentor-based production from whole plants.

For commodity products, potential savings due to elimination of process steps via use of transgenic plants can be offset by even small fractional increases in feedstock costs. Consider, for example, fermenting the entire carbohydrate fraction of a plant to lactic acid or ethanol, for which respective fermentation yields of 65% and 35% based on overall plant dry matter are possible. We think it exceedingly unlikely that such yields can be realized in a transgenic plant and that overall plant productivity will be severely compromised if attaining these yields does prove possible. Lower plant productivity, *P* (tons dry matter acre^{-1} year^{-1}), will raise the

effective feedstock cost for transgenic plants as compared to nontransgenic plants that can subsequently be processed by fermentation. For the common case of a fixed opportunity cost for land, O ($ acre^{-1} year^{-1}, determined by the revenue that could be realized growing some conventional crop), the feedstock price required to offset the opportunity cost of land, C ($/ton), is given by

$$C = O/P$$

For a commodity product resulting from mature conversion technology for which processing represents $^1/_3$ the of total product value (Table 5), savings realized as a result of eliminating processing costs through transgenic plant production will be canceled entirely by increased feedstock costs accompanying a plant productivity decrease of 33%. Moreover, this calculation is based on an upper limit of the savings possible by realization of plant-based production since in reality some processing will still be necessary.

Our second cautionary comment is that satisfying a significant fraction of the demand for fuels and plastic monomers via processes that produce these compounds at the low fractional mass yields likely to be realized by plant-based production requires careful identification of very large-scale coproducts, which will usually be an important factor in overall process economics. Consider, for example, transgenic production of monomers for thermoplastic polymer synthesis from biomass at the current U.S. production of over 60 billion pounds (*26*) and a 15% mass yield on plant dry matter. The 400 billion pounds of plant residues would exceed, for example, the total production of wood pulp in the U.S. It is yet more difficult to identify suitably high-volume coproducts for transgenic production of fuels at low mass yield.

For products well-suited to production in plants at modest yields (e.g., $\leq$15% of plant dry matter), economic and environmental imperatives strongly favor producing an additional useful product from the residue remaining after the transgenic product is recovered. Microbial conversion in a fermentor is one of the most attractive options for processing these residues. It is quite possible that sequential application of plant-based and fermentor-based biotechnology could, in some cases, provide a viable means by which to get the maximum product value from an acre of land. In such a scenario, the relationship between these two production routes becomes complementary. However, we think that the most natural complementation is for specialty products to be produced in plants at low mass yield with commodity products produced from residues. This has the effect of matching relative production to demand, which becomes increasingly necessary as biological production becomes a larger fraction of overall commodity product consumption.

V. Process Technology and Related Research Challenges

Plant biomass, the dominant foreseeable source of feedstocks for biological processing of any kind, is a cost-competitive raw material with low-cost petroleum whether considered on a mass or energy basis (Table 3) or in terms of purchase or transfer price (Table 5). This indicates that the dominant factor impeding biological production of commodity products is the high cost of current processing technology rather than the cost of raw materials.

Technological and research challenges associated with converting plant biomass into commodity products can usefully be grouped into two categories: (1) overcoming the recalcitrance of cellulosic biomass (that is, converting cellulosic biomass into reactive intermediates); and (2) product diversification (that is, converting reactive intermediates into useful products). Before considering these challenges, two general observations are offered. First, processing paradigms most advantageous for solid biomass feedstocks may well differ from those most advantageous for liquid petroleum. For example, processing of fluid-phase petroleum is based on conveyance of fluids between time-invariant spacially discreet processing environments. By contrast, a sequencing batch operating mode featuring dynamic variation of the process environment with little or no conveyence of feedstock between processing environments may be preferred for upstream unit operations associated with refining solid-phase biomass feedstocks (e.g., pretreatment). Approaches to bioreactor productivity enhancement provide a second example of different processing paradigms for biomass as compared to soluble substrates. Whereas retention/recycle of cells or enzymes is a standard approach to increasing productivity for soluble substrates, differential retention of substrates is more easily implemented and more likely to be effective for biological processing of solid substrates.

Our second general observation is that processes and biocatalysts for production of biocommodity products are typically developed and designed on the basis of feedstock characteristics. This may be contrasted to high-value bioproducts, for which carbon sources are usually selected on the basis of requirements of the process and biocatalyst. Consistent with these observations, by far the major focus of biopharmaceutical manufacturing R&D is how to make and recover a product of interest. For biocommodity products, such product-focused activity is also important but no more so than R&D directed toward the matter of how to utilize a feedstock of interest. Indeed, a significant fraction of biocommodity research frontiers are defined by feedstock characteristics, including overcoming the recalcitrance of cellulosic biomass, utilization of all sugars present in the feedstock, and value recovery from noncarbohydrate feedstock fractions.

A. Overcoming the Recalcitrance of Cellulosic Biomass. The recalcitrance of cellulosic biomass is a generic obstacle impeding the cost-effective production of both fuels and chemicals from cellulose-rich materials, as well as realizing value from residues associated with production of starch-rich grains. Approaches for overcoming the recalcitrance of cellulosic biomass include gasification, acid hydrolysis, and pretreatment/enzymatic hydrolysis. Process design studies have indicated that, for all of these approaches, steps associated with overcoming the recalcitrance of cellulosic biomass are typically the most costly (*15*, *38*, *39*).

Gasification and enzymatic hydrolysis were found to have roughly equal costs in a comparative study reported by Wyman et al. in 1993 (*38*). Enzymatic and acid hydrolysis have been seen as being competitive in the emergent biomass ethanol industry in terms of both process design studies and commercial activity. Thus gasification, acid hydrolysis, and enzymatic hydrolysis have been thought to be roughly cost-competitive in the 1990s. The economics of these alternatives differ, however, with respect to their potential for future improvement. Enzymatic hydrolysis has been considered in the context of modern molecular biology for only a decade or so, and order-of magnitude reductions in the cost of biological processing in a pretreatment/enzymatic hydrolysis scenario have been forecast (*15*). By contrast, gasification and acid hydrolysis have been practiced and understood to a substantial degree for a half century or

more, and analyses of R&D-driven improvements project more modest cost impacts. We focus on pretreatment/enzymatic hydrolysis here because of its potential for future research-driven improvements. We note that biomass gasification has a potentially important role to play in energy-efficient production of electricity from biomass and that gasification-based power generation from lignin-rich residues may well provide an attractive way to realize value from the residues of processes featuring enzymatic hydrolysis.

Biomass Pretreatment. For most types of biomass, the enzymatic digestibility of the cellulose is very low (<20%) without some type of pretreatment to open up the structure and make it accessible to attack by enzymes (*40*−*43*). Removal of either hemicellulose or lignin is thought to create pores that allow the enzyme to penetrate into the biomass structure (*44*), but elimination of one barrier to hydrolysis can accentuate the importance of another. For example, removal of hemicellulose can increase the yields of cellulose hydrolysis via enzymatic digestion to over 90% (*45*, *46*), but the rate and yield of cellulose hydrolysis will increase further with removal of lignin (*47*−*49*). In addition, mitigating one barrier may actually alter another and mask its original impact. For instance, when hemicellulose is hydrolyzed at high temperatures, the nature of lignin is undoubtedly changed even though it remains on the solid substrate, impacting digestibility (*45*−*49*).

A number of biological, chemical, and physical pretreatment techniques have been investigated (*42*, *43*). Physical approaches such as irradiation and comminution tend to be slow, energy-intensive, and too costly. Biological methods based on lignin-solubilizing organisms are conceptually inviting because of their simplicity and low-energy demands, but they are slow and they consume cellulose and hemicellulose in addition to lignin. Steam heating hydrolyzes hemicellulose with natural acids released during the reaction, but reported sugar yields from hemicellulose are less than about 65% of theoretical (*50*−*52*). Pretreatment with liquid hot water appears to exhibit different and more promising behavior relative to steam pretreatment; however the mechanistic basis of these differences is not understood and it is not clear to what extent they are limited to low solid concentrations (*49*, *53*−*56*).

Various chemicals have been incorporated into pretreatment processes to improve the enzymatic digestibility of cellulosic materials (*42*, *43*). Solvents such as ethanol and methanol or bases such as sodium hydroxide dissolve lignin, but costs are so high that these methods are not considered competitive for manufacture of high-volume, low-value commodity products. Ammonia has been employed in combination with explosive decompression to enhance the digestibility of certain types of some grasses and agricultural residues with some success (*57*). Ammonia is relatively easy to recycle, few fermentation inhibitors are formed, the energy use and capital costs are projected to be reasonable, and opportunities have been defined to improve the economics. However, it is not clear whether the process is effective for woody materials or waste paper. Dilute acid pretreatment, and particularly dilute sulfuric acid pretreatment, has been studied extensively and is considered by many to be the leading pretreatment option at this time (*58*−*63*). However, dilute sulfuric acid pretreatment requires very expensive materials of construction, additional costs for neutralization chemicals, and handling and disposal of large amounts of gypsum or other salts formed in neutralization (*15*, *62*, *63*). Use of sulfur dioxide (*64*, *65*) and of carbon dioxide (*66*) has also been considered to reduce chemical and materials of construction costs. Sulfur dioxide has been found to be effective, although at higher cost than for sulfuric acid (*67*).

A number of attributes are very important for effective pretreatment (*2*, *15*, *42*, *43*, *62*, *63*, *68*). It is vital that high yields of sugars are realized from the hemicellulose fraction and that the cellulose fiber left be very digestible by enzymes; yields on the order of 90% and preferably closer to 100% are important from each hydrolysis reaction. A low corrosivity environment is advantageous to keep materials of construction costs reasonable. Because energy demands for mechanical size reduction of biomass prior to pretreatment can be one of the largest in the plant, pretreatment technologies that minimize this requirement are obviously desirable. Chemicals released as direct products from the hemicellulose hydrolysis reaction (e.g., acetic acid) and by biomass degradation during pretreatment (e.g., furfural) can be toxic to downstream biological steps, and it is advantageous to develop technologies that reduce or eliminate conditioning steps, avoiding use of costly chemicals and production of problematic residues. It is also important that pretreatment involve minimal water addition to reduce energy demands and produce an acceptable sugar and consequently final product concentration. These targets for pretreatment technology have major implications on not only the direct cost of pretreatment itself but also that for upstream and downstream operations (*15*, *62*, *63*).

Although a large literature exists addressing pretreatment on a phenomenological basis, few studies have examined the chemistry underlying pretreatment processes from a fundamental perspective. At this point, gaining more insight into pretreatment fundamentals is a particularly important frontier in terms of enabling further applied advances. The knowledge gained will provide vital directions for technology advancement by clarifying cause-and-effect relationships and guiding selection of process configurations and conditions. It also supports scale-up of pretreatment technologies by providing a rational basis for plant designs that engineers can apply with less need for expensive and time-consuming pilot and demonstration plant studies. Establishing solid fundamentals and resultant process concepts for improvement and scale-up of pretreatment technologies is an important opportunity to enable production of commodity products from plant biomass in much the same way that chemical engineering enabled petroleum refining to realize the impact we see today.

Biotechnology for Utilization of Cellulosic Materials. Four biologically mediated events typically occur in the course of biological processing of cellulosic biomass using enzymatic hydrolysis: cellulase production, cellulose hydrolysis, hexose fermentation, and pentose fermentation. Process configurations proposed for the biological steps differ in the degree to which these events are integrated. As presented in Figure 1, separate hydrolysis and fermentation (SHF) involves four discrete process steps. Simultaneous saccharification and fermentation (SSF) consolidate hydrolysis and hexose fermentation. Simultaneous saccharification and cofermentation (SSCF) combine hydrolysis, hexose fermentation, and pentose fermentation. Consolidated bioprocessing (CBP) accomplishes cellulase production, hydrolysis, and fermentation simultaneously in a single step. [The term "consolidated bioprocessing" is synonymous with the term "direct microbial conversion" (of DMC) used in earlier literature. See ref *2* for a discussion of nomenclature.]

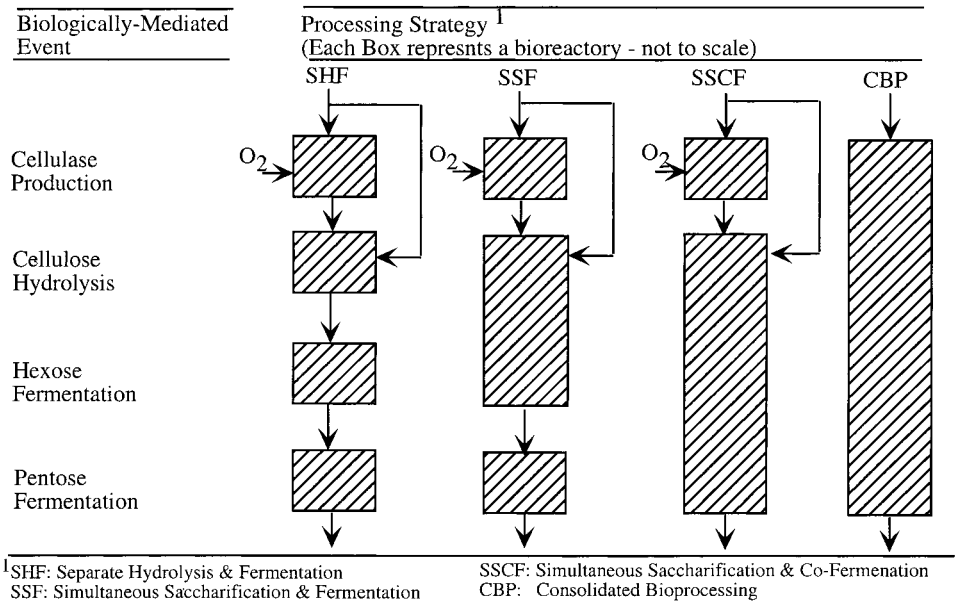

Figure 1. Evolution of biomass processing configurations featuring enzymatic hydrolysis.

As reviewed elsewhere (*2*, *68*), detailed process analyses of ethanol production from cellulosic biomass using the extensive process design framework of the National Renewable Energy Laboratory (NREL) support the potential for substantially lower processing costs for SSF as compared to SHF (*69*) and for CBP as compared to SSF or SSCF (*15*). We think it very likely that the trend of decreasing potential processing cost with increasing consolidation is applicable to most products. However, the magnitude of R&D advances required to realize this potential is higher for the more highly consolidated strategies and for CBP in particular.

SHF, SSF, and SSCF all rely on the production of cellulase in a dedicated unit operation separate from the unit operation(s) used for producing a desired product. Key research challenges common to these configurations include developing microorganisms that can utilize biomass-derived soluble sugars in addition to glucose under industrially relevant conditions and lowering the cost of cellulase production.

Engineering of microorganisms that can utilize xylose and other nonglucose sugars has received substantial attention over the past decade and represents one of the more extensively studied applications of metabolic engineering. Pursued to date largely in the context of ethanol production, such organism development has been based on one of two strategies (Figure 2). The "native substrate utilization" strategy involves beginning with a microorganism that already utilizes the substrate of interest and improving selectivity and other desired product-related features. The "recombinant substrate utilization" strategy involves beginning with an organism that already has high product selectivity and other product-related features and conferring the ability to utilize substrates of interest. The work of Ingram and co-workers with *Escherichia coli* and *Klebsiella oxytoca* (*70*, *71*) exemplifies the former strategy, whereas the work of both Ho and co-workers with *Saccharomyces cerevisiae* (*72*) and Zhang and co-workers with *Zymomonas mobilis* (*73*, *74*) exemplifies the latter. Current research frontiers address improving the industrial robustness (e.g., decreased sensitivity to inhibitors generated during pretreatment) of recombinant strains, increasing the range of sugars utilized, and increasing the range of products produced.

Production of cellulase has been the subject of extensive research, especially involving the aerobic fungus *Trichoderma reesei* (*75*, *76*), and is a substantial commercial activity serving the textile, food processing, and pulp and paper industries. Extensive fundamental literature also exists on the genetics, structure, and function of cellulase enzyme systems, which is summarized in recent comprehensive reviews (*77*−*80*). Notwithstanding, the cost of cellulase is a major impediment to cost-effectively processing cellulosic biomass via enzymatic hydrolysis. A recent comprehensive study by NREL (*81*) estimated cellulase costs at $3/gallon ethanol ($0.80/L) for commercial enzyme formulations and $0.50/gallon ethanol ($0.13/L) for less highly processed formulations. The latter value corresponds to about 5.1¢/kg biomass or about 8.6¢/kg carbohydrate (depending on the scenario assumed) and, thus, roughly doubles the feedstock cost on a purchase price basis for both the current and mature technology scenarios and on a transfer price basis for the mature scenario (Table 5). Although some members of the *Trichoderma* genus are prodigious producers of cellulase, other cellulases are thought to have substantially higher specific activities (*82*, *83*). Thus one strategy for reducing the cost of cellulase production involves the heterologous production of high-specific-activity cellulases. This will most likely involve aerobic processes and host organisms in light of the higher ATP yields and consequently higher potential protein yields of oxidative phosphorylation as opposed to anaerobic fermentation. Improvement of specific activity via protein engineering is another, potentially complementary option.

CBP is differentiated from the other processing strategies in Figure 1 in that both cellulase production and production of the desired product are carried out by a single microbial species or microbial community. This requires that cellulose hydrolysis be viewed as a microbial phenomenon and not only an enzymatic phenomenon, a perspective that has received relatively little attention in the literature. It will be desirable in many instances to implement the CBP strategy via anaerobic microorganisms producing C2 to C4 alcohols, ketones, and organic acids as catabolic products. While of particular interest, anaerobic CBP also poses a particular challenge: can high rates be supported given the low ATP gain of anaerobic metabolism in combination with the low substrate turnover number of hydrolytic enzymes?

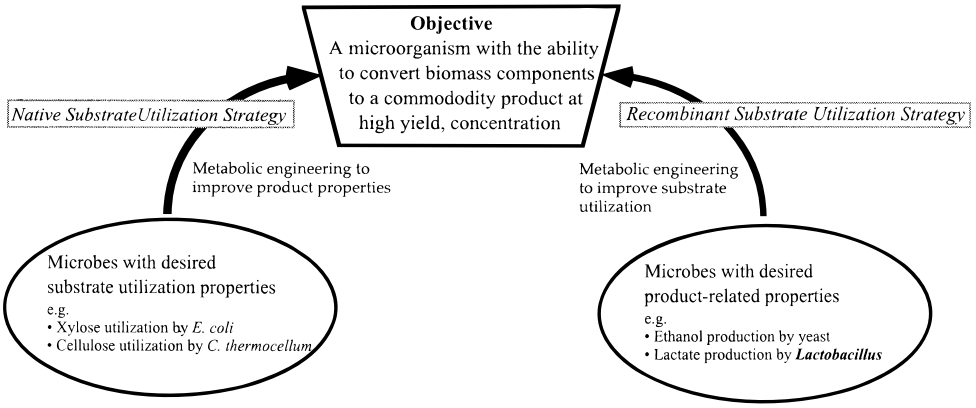

Figure 2. Alternative organism development strategies to obtain organisms useful in processing cellulosic feedstocks.

The kinetic and bioenergetic feasibility of anaerobic CBP is supported by the high rates of cellulose utilization exhibited by naturally hydrolytic anaerobes (*84*, *85*) and by quantitative models incorporating fermentative ATP generation, the ATP requirement for cellulase synthesis, and cellulase kinetics (*86*). As with xylose utilization, organism development for CBP can proceed via a native substrate utilization strategy or a recombinant substrate utilization strategy (Figure 2). The native substrate utilization strategy involves metabolic engineering of the end-product metabolism of cellulolytic microorganisms (e.g., *Clostridium thermocellum*). The recombinant substrate utilization strategy involves heterologous expression of cellulases in an organism whose product yield and tolerance credentials are well-established (e.g., yeast, *Lactobacillus*). Each strategy has its own advantages and challenges, and different strategies may well prove most advantageous for different products. A key research need for the native substrate utilization strategy is the development of gene-transfer systems, which are not available for most organisms of interest in this context. The recombinant hydrolytic strategy has been pursued most extensively in *Saccharomyces cerevisiea*, with simultaneous expression and secretion of several cellulase components and utilization of soluble cellulose recently reported (*87*, *88*). Utilization of insoluble cellulose is an important objective for the recombinant hydrolytic strategy.

B. Product Diversification. Most schemes envisioning a diversified biomass-based chemicals industry involve a small number of versatile, generally low molecular weight intermediates, most of which are derived via biological conversion (*4*, *89*−*95*), a scheme which closely resembles the structure of the existing petroleum-based petrochemicals industry (*96*). Each of these "platform" intermediates gives rise to a "family" of derivative chemicals, with synthesis of these derivatives involving either biological or, quite often, nonbiological conversion. In some cases, these chemicals directly *replace* a petroleum-based intermediate with identical composition. In other cases, envisioned biological platform chemicals have a distinct composition but *substitute* for their petrochemical counterparts by providing equivalent functional characteristics. Although the replacement route has the advantage of easy integration into the existing infrastructure, we think the substitution strategy will have more impact in the long run. Indeed, a reasonable argument could be made that it would be quite surprising if a given compositionally identical intermediate were the most advantageous for chemical synthesis involving both nonbiological processing of petroleum and biological processing of plant biomass. The replacement route typically targets oxygen-poor compounds for which theoretical yields from more highly oxygenated biomass feedstocks are low. By contrast, most of the attractive candidates for the substitution strategy have a degree of reduction comparable to that of their feedstocks, which makes high conversion yields possible.

These points are illustrated in Table 6 for production of polyethylene, the largest volume nonfuel organic material produced from petroleum. The market price of ethylene is substantially higher than any of the carbohydrate-transfer prices calculated in Table 5. For the direct replacement strategy, the stoichiometric yield of polyethylene from carbohydrate with an allowance for cell synthesis is 0.28, reflecting the mass losses in producing an oxygen-poor product from a more oxygen-rich reactant in both fermentation of carbohydrate to ethanol and dehydrogenation of ethanol to ethylene. At such low yields, the feedstock price advantage of biomass materials is lost for all but the mature cellulosic scenario. Polymers of lactic acid, polylactides, have relatively similar physical properties (e.g., strength, elongation to break) to polyethylene (*97*), and a wide range of properties can be obtained via copolymerization with relatively small amounts of other functional momomers (*18*). Thus polylactides represent a potential substitute for polyethylene. Because lactic acid is at the same oxidation state as carbohydrate and polymerization entails only a 20% yield loss due to dehydration, the stoichiometric yield from carbohydrate with an allowance for cell synthesis, 0.72, is much higher than that for the replacement strategy. At this high yield, the feedstock cost contribution (cents per kilogram of polymer) for all of the biological production scenarios is less than half that for polyethylene synthesis from petroleum, with the mature cellulosic scenario nearly 5-fold less than that of ethylene. The analysis presented in Table 6 does not consider the cost of processing downstream of production of fermentable carbohydrate; in particular, the cost of separation is not included. Nor does this analysis consider processing energy inputs, which are important in the context of lifecycle analysis. This example does, however, illustrate the potential advantages of a substitution-based strategy for biological production of organic chemicals. It also underscores the point made earlier (Section V) that the cost of processing, rather than feedstocks, is the primary impediment to cost-effective production of biocommodity products.

In general, there is not yet widespread consensus as to which biologically derived platform chemicals comprise viable substitutes for which current petroleum-derived chemicals. Developing such consensus is an important challenge related to the substitution strategy. Wide-

Table 6. Illustration of Replacement and Substitution Strategies for Synthesis of Commodity Plastics

processing scenario (feedstock/intermediate(s)/product)[a]	price of intermediate (¢/kg)[b]	yield (kg of polymer/ kg of intermediate)[c]	feedstock cost contribution (¢/kg polymer)[d]
petroleum processing			
oil/ethylene/pe	44	1	44
biological processing			
replacement strategy			
corn/fc/ethanol/ethylene/pe	14.1	0.28	50.4
cb/fc/ethanol/ethylene/pe (current)	13.5	0.28	48.2
cb/fc/ethanol/ethylene/pe (mature)	7.6	0.28	27.1
substitution strategy			
corn/fc/lactic acid/pl	14.1	0.72	19.6
cb/fc/lactic acid/pl (current)	13.5	0.72	18.8
cb/fc/lactic acid/pl (mature)	7.6	0.72	10.6

[a] FC = fermentable carbohydrate, PE = polyethylene, CB = cellulosic biomass, PL = polylactic acid. [b] Ethylene based on 1998 bulk pricing data (Chemical Marketing Reporter). For biological processing, based on transfer prices for fermentable carbohydrate (Table 5). [c] For biological processing, yields reflect stoichiometric fermentation yields times a 10% allowance for cell synthesis times the stoichiometric yield of secondary intermediate synthesis (where appropriate) times the stoichiometric polymerization yield. For FC → ethanol → ethylene-PE: (0.51)(0.9)(0.61)(1) = 0.28. For FC → lactic acid → PL: (1)(0.9)(0.8) = 0.72. [d] Equals (price of intermediate/polymer yield).

spread implementation of the substitution strategy will require R&D-driven advances associated with product diversification. Cost-effective production of substitute chemicals will also benefit from, and for some products require, advances associated with overcoming the recalcitrance of cellulosic biomass.

As pointed out by several substantial studies over the years (*4*, *89*−*95*), biomass can in principle provide substitutes for the vast majority of fuels, chemicals, and materials presently derived from petroleum. Development of cost-effective technology necessary to realizing this vision represents a technological challenge equally applicable to both starch-rich and cellulosic feedstocks. Pursuant advances will be required in the areas of metabolic engineering, chemical catalysis, and separations. Our consideration of metabolic engineering focuses on features distinctive to biocommodity processing, and only summary perspectives are offered on chemical catalysis and separations.

Metabolic Engineering. Metabolic engineering includes alteration of metabolic flux via cellular manipulation using recombinant DNA technology, development of quantitative tools and models to understand flux modification in complex biological systems, and development of laboratory techniques that allow fluxes and/or metabolite concentrations to be determined (*98*−*100*). As cloning and characterization of genes has become routine and sequence information for entire genomes is becoming increasingly available, modern science has access to an unprecedented numbers of enzymes capable of catalyzing a tremendous range of reactions. It is likely that metabolic engineers have only started to glimpse, much less realize, the potential to combine this array of catalysts into functional pathways.

Cameron and Tong (*99*) have catalogued over 100 examples of metabolic engineering applied to extending the range of substrates utilized, improved production of chemicals already made by the host organism, production of chemicals new to the host organism, modification of cell properties, and detoxification of toxic chemicals. All of these objectives are potentially relevant for biocommodity engineering. Examples of extended substrate range include developing *S. cerevisiae* and *Z. mobilis* strains that utilize nonglucose sugars (Section V-A). Examples among many of improved chemical production include high ethanol yields in *Escherichia coli* and *Klebsiella oxytoca* (Section V-A) and enhanced solvent production in *Clostridium acetobutylicum* (*101*). Examples of new chemical production include production in *E. coli* of 1,3-propanediol (*102*), production of novel polyhydroxyalkanoates in *Alcaligenes eutrophus* (*103*), and production of *cis*,*cis*-muconic acid, which can be catalytically converted into adipic acid, the precursor of nylon (*94*, *104*). Fewer examples exist of applying metabolic engineering to the modification of cell properties important in the context of biological processing, in part because the genetic basis of such properties is often difficult to determine (see below). Similarly, little effort has been devoted to detoxification associated with biocommodity applications, although this could be useful, for example, in the case of inhibitors generated during pretreatment.

Synthesis of proteins and secondary metabolites of interest for health care products is usually based on ATP-requiring anabolic metabolism. For most such products, aerobic production systems are likely to be preferred due to the much greater availability of ATP. By contrast, a substantial quantity of the small molecules of interest in the context of biocommodity engineering are available at potentially high yields from anaerobic catabolism. The absence of aeration and significantly lower-energy requirements for cooling characteristic of anaerobic processes can have substantial beneficial impacts in the context of lifecycle analysis (Section VI) and process economics. Important host organism characteristics for production of biocommodity products are listed in Table 7.

Bacteria and lower (generally unicellular) eukaryotes are typically the preferred host organisms for metabolic engineering directed toward biocommodity products. Such microorganisms are generally robust and fast-growing relative to higher eukaryotes (e.g., animal, plant, or insect cells). The chief incentive to use higher eukaryotes, post-translational modification of proteins to render them functional in humans, is unimportant for biocommodity products. At the same time, there is incentive to consider a broader range of microbial hosts for metabolic engineering of commodity products as compared to pharmaceuticals. This incentive arises because the properties in Table 6 are often determined by multiple genes and are thus difficult to access via genetic engineering. In many cases it is likely to be more successful to engineer a desired pathway into an organism having useful industrial properties, for example, competitive fitness, robustness in industrial environments, and perhaps the ability to utilize cellulose, rather than trying to engineer such multigene properties into hosts organisms that do not already have them. Figure 3 illustrates

Table 7. Important Host Organism Properties for Production of Biocommodity Products

ability to use low-cost substrates	Examples include cellulose and nonglucose sugars found in cellulosic biomass.
high product yield	Essential because of the dominance of feedstock costs.
stability and competitive fitness in relation to biological competition	Very limited measures can be undertaken to maintain a selectively negative phenotype in biocommodity processes. Thus host organisms with engineered properties need to be stable in relation to intra-strain competition with spontaneously arising mutants and/or special measures need to be taken to ensure that the frequency of such mutants is very low. The reality for bioreactors producing biocommodity products is that microbial contaminants are at best managed rather than entirely excluded. Thus host organisms also need to compete successfully with contaminant microorganisms. The ability to grow in "extreme" environments (e.g. low pH, high temperature) can be an important asset in this context.
robustness relative to nonbiological challenges characteristic of industrial processing environments	Such challenges include high product concentrations, inhibitors from upstream processing (e.g. pretreatment), and nutritionally lean growth media.

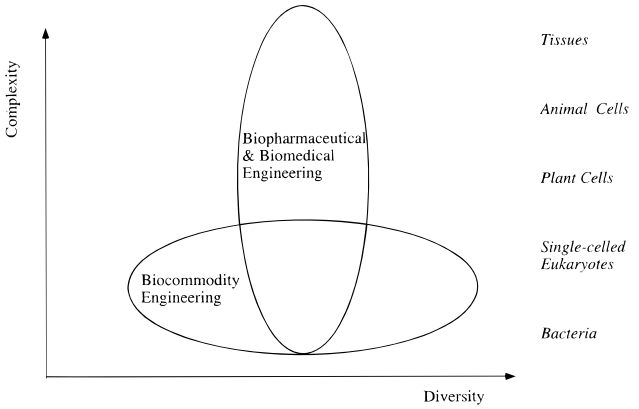

Figure 3. Largely different host organisms are of interest for production of commodity and medicinal products.

that biocommodity engineering is likely to utilize a largely distinct group of host organisms from those used in biopharmaceutical and biomedical engineering. Unfortunately, genetic systems are not well developed for many of the microorganisms that have attractive native features as hosts for biocommodity-focused metabolic engineering. Development of such systems is an important and distinctive research challenge associated with metabolic engineering for commodity products.

Chemical Catalysis and Separations. [Based on discussions with Dennis Miller (catalysis) and Kris Berglund (separations), both of Michigan State University.] The use of nonliving catalysts in biomass processing is in its infancy relative to petroleum processing and presents a different set of fundamental and applied challenges. In petroleum-based catalysis, most reactions are carried out in the vapor phase or in a liquid organic medium, and catalysts, supports, and reactors have been designed for these processing environments. By contrast, biocommodity products are typically available in aqueous solution or suspension. Whereas petroleum-based feedstocks are hydrocarbons or mildly oxygenated hydrocarbons, biologically produced products and intermediates are most often highly oxygenated and thus undergo significantly more complex reaction chemistry. Finally, these products and intermediates are less thermostable than their petroleum counterparts, so catalysis must be effective at lower temperatures and thermal degradation must be considered in reactor design. As with catalytic processing, fruitful approaches for separation of bioproducts involve a significant set of considerations distinct from separation in the petrochemical industry, many arising from the prevalence of water. In addition, biological products and intermediates themselves generally have distinctive properties relative to those of the petrochemical industry. For example, many are nonvolatile and thus not amenable to distillation, and many are present as salts. Because of these differences, separation processes compatible with biological processing are much less mature than processes associated with the petrochemical industry.

VI. Integration. Fields of academic endeavor and industrial practice emerge from the pieces of other fields as the interdependence and coherence of these pieces become apparent. At its current nascent stage of development, both the definition and advancement of the biocommodity engineering field can benefit substantially from further integration at multiple levels. These include technical issues associated with integrating unit operations with each other, integrating production of individual products into a multiproduct refinery, and integrating refineries into the broader systems, resource, environmental, and economic, in which they function. We also offer perspectives on the integration of multiple disciplines into a coherent area of study.

A. Integration of Unit Operations. Significant technological issues arise at most of the interfaces between the primary unit operations of biocommodity engineering: thermochemical processing and pretreatment, biological processing, catalytic processing, and separations (Figure 4). For example, many pretreatment processes give rise to inhibitory compounds that impede biological processing, and many biological processes require or produce compounds that complicate subsequent catalytic processing and/or separation. Consideration of these issues is only starting to receive significant attention and is expected to be essential to the maturation of biocommodity engineering.

B. "Biorefineries" with Integrated Production of Multiple Products. Biocommodity procesess and products are often treated as though one or at best a few of these products would be manufactured in a single plant. Although this approach may be necessary initially to keep the scope of marketing, financing, and technology development manageable for first-of-a-kind plants, a multiproduct biorefinery configuration is likely to be more cost-effective in the long term. Such an evolution would be similar to that experienced in the petroleum refining industry in which the initial focus on production of primarily kerosene with little revenue from the remaining fraction of oil ultimately gave way to integrated refineries that convert virtually all feedstock fractions into a wide range of valuable products. In fact, many of the latter products are chemicals that are far more

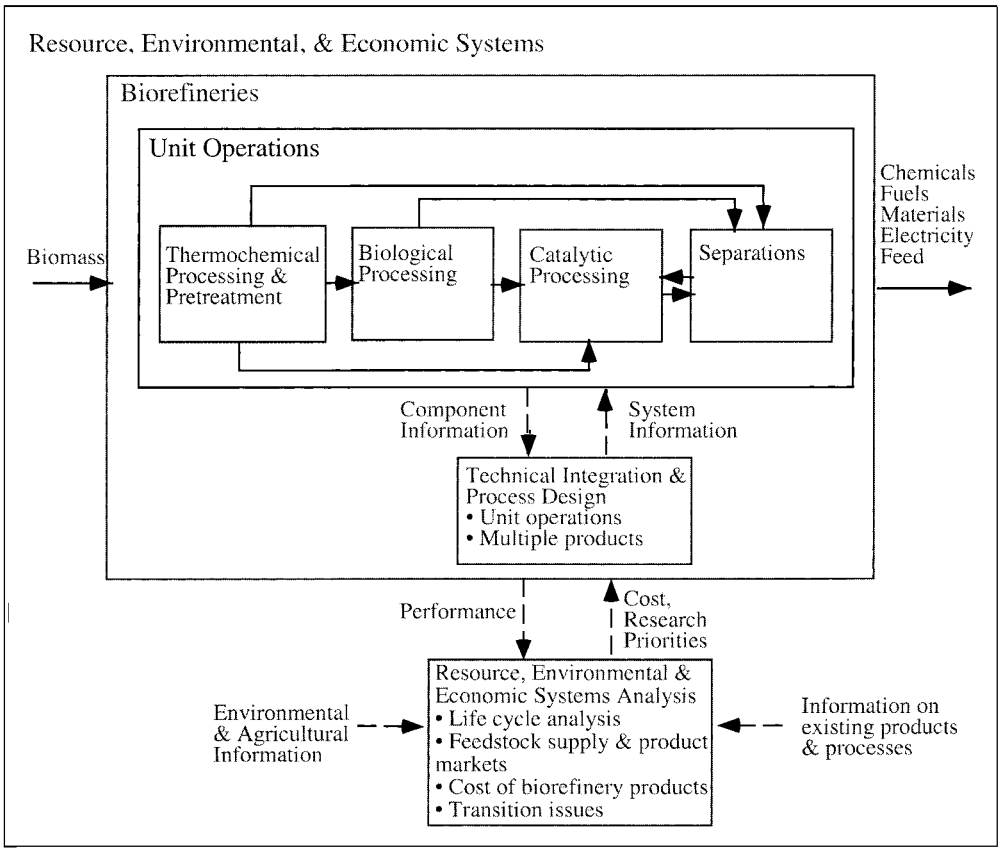

Figure 4. Biocommodity engineering overview.

profitable to manufacture than bulk materials such as gasoline. However, fuel production provides economies of scale that reduce the cost of making smaller-volume coproducts below levels that they could achieve on their own. In essence, coproduction allows fuels and smaller-volume products to be sold for lower prices than would be possible if either class of products was produced separately. Coproduction benefits are equally apparent and essential in the case of corn wet-milling, where the slate of products includes ethanol, high fructose corn syrup, corn oil, corn gluten meal, corn gluten feed, an increasing array of chemicals, and food-related products such as vitamins and amino acids.

We expect that similar synergies will support integration of processing technologies to produce a full slate of products from cellulosic feedstocks. The optimally sized plant for processing cellulosic biomass corresponds to the point at which the incremental savings in processing costs due to economies of scale are offset by the incremental increases in feedstock costs. For all but very low fractions of land harvested for feedstock production, the optimal plant size is quite large, comparable to the largest current corn wet mills. Only fuels and a small number of organic chemicals have markets sufficiently large to consume the dedicated output of one such plant; thus most chemicals will of necessity be coproducts of a mature biocommodity industry. The equipment required to produce fermentable carbohydrate from biomass is essentially identical whether such carbohydrate is converted to fuels, chemicals, or materials. Thus, a chemical plant that uses a side stream of fermentable carbohydrate from a larger process facility producing fuel or some other bulk product will be competitive at a lower price than a standalone plant, making the same volume of that chemical. The economics of producing bulk products (e.g., fuels) benefit equally from such coproduction, since the higher profit margin of chemical coproducts allows the bulk products to be more competitively priced.

Potential coproduction benefits extend beyond the synthesis of multiple organic products from fermentable carbohydrate. In the case of woody biomass, for example, about 25% of the dry weight and 40% of the energy in the feedstock is present as lignin, which is in general not viewed as a promising substrate for biological processing. In addition to relatively low-volume, but potentially high-value, markets for lignin-derived chemicals, power production represents a very high demand use for lignin-rich residues remaining after biological processing. Process designs anticipating advanced conversion technology for woody feedstocks have found that coproduction of power with biologically produced fuels or chemicals has the potential to be highly significant in terms of process economics, environmental benefits (in particular greenhouse gas related), and energy supply. Herbaceous cellulosic feedstocks (e.g., switchgrass, alfalfa) offer the potential for production of protein-rich animal feeds if harvested at a suitable point in their growth cycle. This possibility extends the coproduction concept yet further from the processing facility to the agricultural field. Growing a crop expressly for coproduction of animal feed and fermentable carbohydrate offers advantages not only in terms of maximizing product value but also in terms of maximizing land-use efficiency.

It is somewhat ironic that the relationship between production of fuels, chemicals, power, and feed (which commands the largest share of U.S. agricultural land) is often portrayed as competitive. In fact coproduction of most of these product classes in a single facility is expected to be beneficial and, in a majority of cases, is likely to be truly necessary for cost-competitiveness in the long run. The fundamental reasons for this are the economies of scale resulting from producing high-demand

Table 8. Major Components of Graduate Study in Biocommodity Engineering

biotechnology	Important themes include metabolic engineering applied to both substrate utilization and product formation, and the development and utilization of microbial hosts that are robust in industrial environments.
process engineering	Important themes include large-scale integrated processes in which cost of production is a dominant driving force.
resource and environmental systems	Important themes include understanding how such systems work, and lifecycle analysis applied to biocommodity products and processes.

products such as fuels and power, the higher product/feedstock price margins available from producing chemicals, the value maximization resulting from using all parts of the plant, and integration benefits (e.g., utilization of waste heat from power generation for process energy requirements).

Partially mature biocommodity processes with less than fully diversified product slates and less than fully developed infrastructures face significant challenges penetrating markets occupied by established petroleum-based processes. One useful strategy to address this dilemma is so-called "niche opportunities" consisting of low-cost feedstocks or established infrastructure elements (e.g., at a power plant, paper mill, or corn wet mill). A second useful strategy is to emphasize applications for which biological products have performance advantages and thus command higher prices. The cost benefits of niche opportunities and applications with performance advantages must often be balanced against the cost disadvantages of small-scale production. Over time, it is reasonable to expect larger-scale production, increasing use of substitution as compared to replacement, increasing competition based on price rather than performance, and an increasingly diverse range of coproducts such that value is extracted from all feedstock fractions and, to the extent possible, process effluents.

C. Process Design and Economic Analysis. Design of processes incorporating multiple integrated unit operations producing multiple products is an essential integrative activity associated with biocommodity engineering. Process design enables evaluation of the price-competitiveness of plant-derived products as compared to established products, identification of beneficial combinations of products and processes, and prioritization of opportunities for R&D-driven cost reductions. The gradual augmentation and eventual replacement of products of integrated petroleum refineries byproducts of integrated biomass refineries is a highly complex process that will benefit from economic analysis beyond the individual processing facility.

D. Resource and Environmental Analysis. Paraphrasing John Prausnitz: "If engineering is the application of science for human benefit, then the engineer must be a student both of the application of science and of human benefit as well" (*105*). For biocommodity engineering, the major dimension of human benefit evaluation beyond economic factors involves resources and the environment. For the reasons outlined in Section I, we believe that biocommodity engineering has legitimate potential to yield substantial resource and environmental benefits, a view which others have also supported (*94*, *106*). At the same time, we think it important to acknowledge that biocommodity engineering is a potential double-edged sword in this context as a result of competing uses for land and biomass feedstocks and the possibility of poor land use practices, the large volume of biocommodity products, and the energy and material inputs required for both feedstock production and processing. Guidance to realizing the positive potential of biocommodity engineering is available via application of lifecycle analysis and related tools within a mature understanding or resource and environmental systems.

As health care-motivated biotechnology has matured, increasing attention of educators, researchers, and practitioners is being afforded to the domain of health care-related products: the body. Similarly, as biocommodity engineering matures, we think it highly desirable that increasing attention be payed to its domain: the environment. Whereas efficacy validation for health care-related products is determined by clinical trials, efficacy evaluation for biocommodity products is determined by a lifecycle analysis.

E. Education. Academia has provided the tools of biotechnology, has played a major role in the development of the health care-motivated biotechnology industry, and is well-suited to play an equally important role in relation to biocommodity engineering. At the undergraduate level, we see biocommodity engineering as an appropriate topic for an elective course or a thesis but in general not as a major area of study in lieu of more traditional disciplines such as engineering, biology, and chemistry. Biocommodity engineering is, in our view, a legitimate focus for graduate study at both individual and programmatic levels.

As elaborated in Table 8, we see three major components of graduate study in biocommodity engineering: biotechnology, process engineering, and resource and environmental systems. In most cases, an individual student would develop primary competence in one of these areas, with secondary competence in the other two.

This mixture of disciplines and perspectives is much more likely to arise by design than coincidence and is unusual to find within a graduate degree program today. In particular, most existing biotechnology-focused programs emphasize product-focused genetic engineering for production of medicinal products and single-product relatively small-scale processes in which cost of production is not a driving force (Section I) without considering resource or environmental aspects.

For the near term at least, we see biocommodity engineering as a focus area spanning several departments, a model used increasingly by today's health care-oriented biotechnology programs and in other areas (e.g., microelectrical mechanical systems) as well. Our correspondence with representatives of industry suggests that significant hiring demands exist in biocommodity-related industries, that this demand is likely to grow over time, and that it is currently somewhat difficult to find degree recipients with the combination of skills most useful in a biocommodity context.

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