Harnessing Biotechnology: A Practical Guide

Biotechnology is increasingly proving its ability to address chemical industry challenges. An engineering-focused approach — bioengineering — is vital to successful industrial application

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IN BRIEF

FIGURE 1. At Cargill's biorefinery in Blair, Neb., companies such as Corbion, Evonik and Natureworks produce bio-based products

For those undertaking overall process design and implementation for intermediate and specialty chemicals, the incorporation of biotechnology-based processes has become a viable option for the chemical process industries (CPI). Bioprocesses have the potential to deliver benefits in cost, quality and sustainability.

Many well-known chemicals are already produced biologically. For example, Cargill Inc. (Minneapolis, Minn.; www.cargill.com) produces lactic acid for polymer applications at petrochemical scale at its Blair, Neb. site (Figure 1) using a proprietary, low-pH, yeast-based fermentation process. DuPont Tate & Lyle Bioproducts Co. (Loudon, Tenn.; www.duponttateandlyle.com) produces 1,3-propanediol biologically, after DuPont determined that bio-based production would cost less than chemical routes to that product. BASF SE (Ludwigshafen, Germany; www.basf.com) produces vitamin B2 (riboflavin) biologically and has replaced its established chemical route. Lysine is another example of a large-volume chemical produced biologically. And 1,4-butanediol (BDO) is the next bio-based commercial process on the horizon: BASF and Novamont Sp.A. (Novara, Italy; www.novamont.com) have licensed technology from the author's company to produce BDO biologically.

This article is not intended as an introduction to biology, nor a recap of bioprocess advantages or case studies (see *Chem. Eng.*,

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November, 2015, p. 40). Rather, the article is intended as a practical guide for how to think about, plan for, and integrate bioprocess technologies into chemical production facilities. To do this, the article highlights similarities and differences between bioprocess and conventional chemical process designs, equipment and operations, while strongly emphasizing cost economics and overall process analysis.

Principle 1: Whole-process design

A well-known idiom states: "begin with the end in mind." This suggestion — in the current context, designing a process with the whole system in mind — is appropriate.

The first part of our framework recognizes a key idea: chemical engineers had it right all along. Chemical engineers have decades of experience in designing and optimizing integrated, large-scale processes to convert raw materials into useful products. In its best application, considerable effort is invested upfront, in the form of conceptual designs, even before the associated experimental program is launched.

By contrast, many of the headlines associated with the rise of biotechnology-based processes have focused on specific technologies, tools and advances. Among the favorite topics are the tools for designing microorganisms (sometimes referred to informally as "bugs"). For the purposes of this article, the specific biology is not important — these engineered microorganisms can be thought of as fancy, biology-based "super-catalysts" that can perform multiple unit operations, such as all the steps needed to convert sugar into a desired target chemical with high specificity and minimal byproducts. While the progress has been impressive in using new biological tools to shorten the timelines to engineer an organism suitable for a proof of concept, the reality is that commercializing a bio-based technology is not just about the bug.

Instead of thinking about bio-based process design as a linear sequence (first, design the bug, then figure out the unit operations to best separate and purify its output, and then loop back to tune the design of the microorganism), a better approach is to "co-develop" and "co-optimize" the microorganism in conjunction with the overall process. Table 1 illustrates the differences between these two approaches — the "bug-first" approach is designated as "bio-centric" in the table, and the co-optimization approach is designated as "whole-process."

TABLE 1. BETTER PROCESS PERFORMANCE THROUGH WHOLE-PROCESS THINKING

"Bio-centric" approach	"Whole-process" approach
Focus: Maximize microorganism performance (for example, titer, rate and yield)	*Focus*: Design microorganism and overall process to minimize total production cost, meet all specifications and maximize operational robustness
Priority: Laboratory-scale strain and fermentation development is prioritized, supported by computational tools and iterative strain design, testing and metric optimization	*Priority:* Choose microorganisms and metabolic pathways that are compatible with the lowest-cost operating conditions (for example, pH, temperature, aerobic versus anaerobic, co-product value). Design the microorganism for the process, not the other way around
Process design: Process is designed subsequently to fit the needs, capabilities and limitations of the microorganism	*Process design:* Pay close attention to managing process impurities (raw material residuals, metabolic byproducts, chemical reaction products) that could otherwise increase capital and operating costs, or compromise product quality
Process performance: Performance in the laboratory may not be realized at large scale due to overlooked, scale-dependent parameters. Or, high performance at large scale may require special (expensive) operating conditions, be more sensitive to process upsets (less robust), more subject to contamination by foreign microbes (plant shutdown), or incur higher downstream processing costs	*Process performance:* Develop the microorganism and process at laboratory scale under anticipated large-scale conditions (time and temperature profiles, mixing times, pressures, recycles). Characterize key process sensitivities. Demonstrate the whole process at an appropriate scale to document its performance with engineering data. Use those data as the basis of detailed plant design
Downstream processing: Downstream processing is not addressed until the late stages of development (when the microorganism and fermentation are nearly finished). It is the responsibility of downstream processing to identify and solve any problems that have arisen upstream. This invariably adds cost.	*Downstream processing:* Microorganism is designed for the process, to enable least expensive operating conditions (includes pH, aerobic versus anaerobic, fermentation time and so on)
Plant: Large-scale plant is designed and built to accommodate the laboratory-scale process	*Plant:* The whole-process approach translates directly to design of large-scale plant, minimizing changes and added costs

We refer to this whole-process discipline as *bioengineering*. This approach better captures the intimate intertwining of, and co-optimization across, multiple disciplines.

While everyone can surely appreciate — and even marvel at — the continued advances in specific parts of the biology toolkit, the best practice is to take a whole-process view when exploring how to harness bio-based processes as a component of a plant construction project. Product customers may also marvel at the science underlying a particular microorganism, but ultimately, they are really looking for ways to lower costs, raise product quality and improve the sustainability profile.

Principle 2: Extend TEA

The second principle in evaluating and deploying biotechnology is to apply one of the most favored tools from conventional process technology: techno-economic analysis (TEA).

TABLE 2. CAPITAL COSTS PER TON OF PRODUCT FOR CONVENTIONAL AND BIO-BASED PLANTS (EXAMPLES)

	Conventional	Bio-based	Comparison
100,000-ton/yr plant	$300 million total $3,000 per ton	$230 million total $2,300 per ton	Bio is 23% lower
50,000-ton/yr plant	$200 million total $4,000 per ton	$140 million total $2,800 per ton	Bio is 30% lower

Source: Genomatica estimates, based on industry analyst data, company data and discussions with chemical producers. Assumes scaling exponent of 0.6 for conventional and 0.7 for bio-based at these ranges of capacity

Many readers are likely already familiar with TEA, and may use it to better understand the overall economics of potential process designs for conventional chemistry-based processing. The idea is to apply the same concepts of TEA to bio-based processes (see sidebar, p. 41). Some of the individual line items of the TEA will be different, but the overall goal remains the same — to generate an all-inclusive picture of the total capital investment and production costs for a potential process.

An important recommendation at this point is to create a management dashboard to facilitate internal discussion and decisions (Figure 2). If biotechnology is a new area for your organization, then this kind of dashboard will help your team become more comfortable with how process economics change under varying conditions (for example, historical data, forecasts, competitive processes, alternative feedstocks and geography).

Similarly, you can expect questions about the competitiveness of bio-based processes, especially given the current low prices of crude petroleum in 2016. A helpful way to approach this is by creating indifference curves (essentially, sensitivity analyses), which provide an unbiased perspective on overall process economics. For example, as shown in Figure 3, the x-axis corresponds to the feedstock price for a conventional process and the y-axis is the feedstock price for a bio-based process. The first line to draw is where total production costs are equal for the two competing process technologies. The region on one side of that line shows all the feedstock price combinations where one process technology is lower cost; and the other side of that line shows the price combinations where the other process is favored. Next, map historical data points, and see which process technology would have delivered lower costs given actual feedstock prices over time (as shown by the Xs and circles in Figure 3). Lastly, draw additional lines to highlight the relative feedstock pricing when one process delivers, for example, a 25% cost advantage. By doing so, you can get a feel for how processes compare over time, even when using different feedstocks.

Interestingly, some bio-based processes may offer lower total process costs even with the current low prices of fossil-based feedstocks. And many analysts believe that petroleum-based feedstocks will eventually return to higher, more traditional prices, which may provide a truer point of comparison for when a new plant begins operation.

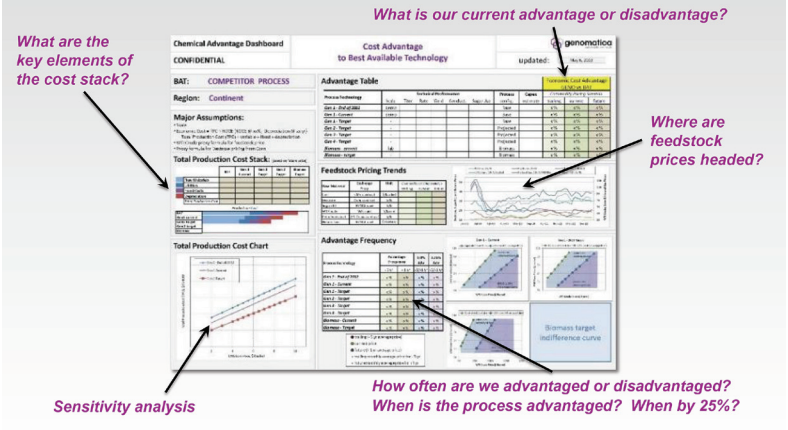

FIGURE 2. Management dashboards, such as the one shown here, can facilitate internal discussions of techno-economic analyses

Principle 3: Rethink economics

Economics is not just about total production cost (or even the economic cost of goods sold, which includes consideration for a return on capital employed (ROCE)). Bio-based processes can bring additional potential economic advantages, including deployment flexibility, greater price stability and lower safety and operations risks.

Let's start by looking at the forces acting on capital expenditures. First, the capital cost per ton may be significantly lower (sometimes 20–40%) for bio-based process technologies than for conventional chemical processes using fossil feedstocks — especially for mid-sized plants (Table 2). This is because a single bio-based unit operation (fermentation) frequently replaces multiple conventional unit operations. Additionally, capital equipment for that process may be less expensive (for example, with bio-based operations running at near-ambient temperature and pressure and near-neutral pH, versus the more challenging conditions often required in a conventional chemical process). Generally, only the largest conventional plants will not be disadvantaged in capital cost per ton. Second, the plant-scaling exponent is higher for bio-based processes, and this *increases* the cost-per-ton advantage for bio-based processes as

TECHNO-ECONOMIC ANALYSIS FOR BIO-BASED PROCESSES: NEW EXAMPLES

The use of techno-economic analysis (TEA) is all about understanding tradeoffs — the interplay between process design decisions and both capital and operating expenses.

TEA can be used when implementing a bio-based process in the same way it would be used for a conventional process. In the bio-based process, however, some new types of unit operations and equipment are in play, and they have different trade-offs compared to conventional processes. TEA can be used the same way, just with some substitutions.

As an example, consider fermentation. At first blush, it seems to be just a big tank, but in fact, process design — and tank design — can have a significant impact on capital and operating costs. Is it better to use a smaller number of large fermentation tanks (for instance, 1,000 m^3) or a larger number of smaller tanks (100 m^3)?

Other questions also must be answered, including whether the process will use aerobic or anaerobic microorganisms; whether a bubble column or stirred-tank reactor should be used; whether to control temperature with a cooling jacket, internal coil or external loop; and whether the process will be run as a batch or continuous process.

For separation and purification, considerations include feedstock quality (for example, more impurities at the start likely mean more effort and cost later); handling of solids both upstream (for example, biomass pretreatment and sucrose handling) and downstream (crystallization and drying); and the properties of the target chemical (such as solubility, volatility, permeability, target purity).

The net effect of these factors can be significant. For example, designing a bio-based process for lysine will tend to have higher capital costs per ton of annual production capacity (about $3,000 per annual ton), as compared to a process design for ethanol (approximately $600). Successful lysine processes have been aerobic; aseptic; use jacketed fermenters with chilled water; use semi-refined feedstocks; and need extensive downstream separations. Ethanol processes work well with large fermenters; are anaerobic and sanitary, and use external cooling loops and unrefined feedstocks. Ethanol processes also have easier separations due to its higher volatility.

These factors can also shift the balance of capital and operating expenses, with one type of process design being better at larger scale and another at smaller scale.

smaller plants are built.

For decades, the chemical industry has moved in the direction of building ever-larger plants, in part to increase efficiency by reducing capital expenditure per ton. Now, with the capital advantages of bio-based processes, the industry can gain the option to go the other way — to economically deploy smaller, "right-sized" plants. This can allow entry into a local or regional market, and can allow capacity expansion without the large outlays needed for a mega-sized plant or the risk of disrupting the supply-and-demand market balance. It can also enable users of chemicals to backward-integrate and produce their own supplies, as Novamont is doing with bio-based 1,4-butanediol in Italy, with a planned start-up in the second half of 2016.

Readers should also consider the potential for better overall economic performance of a plant because of the greater sustainability of the chemical being produced and sold there. While this article's discussion so far has treated plant output as a direct substitute (that is, as a commodity), a bio-based plant may deliver a product with a smaller environmental footprint — and may be seen by customers as a more sustainable and desirable option. This is not the same as assuming a "green premium" based solely on sale price. Selling a more sustainable version of the same product may enable a supplier to gain longer-term customer commitments, or reduce the discounts it needs to offer to customers (especially during times of weak demand) — both of which improve the true economic performance, offering a more comprehensive view than a TEA.

Additional considerations in the broader economic picture are safety and operations-related risks. Accidents happen. And accidents at conventional plants, operating at high temperature and pressures and sometimes with toxic chemicals, can be very costly. By contrast, the less severe conditions of a bio-based process, combined with the aqueous-based environment of fermentations, reduce process-safety risk.

Lastly, the chemical industry has de-

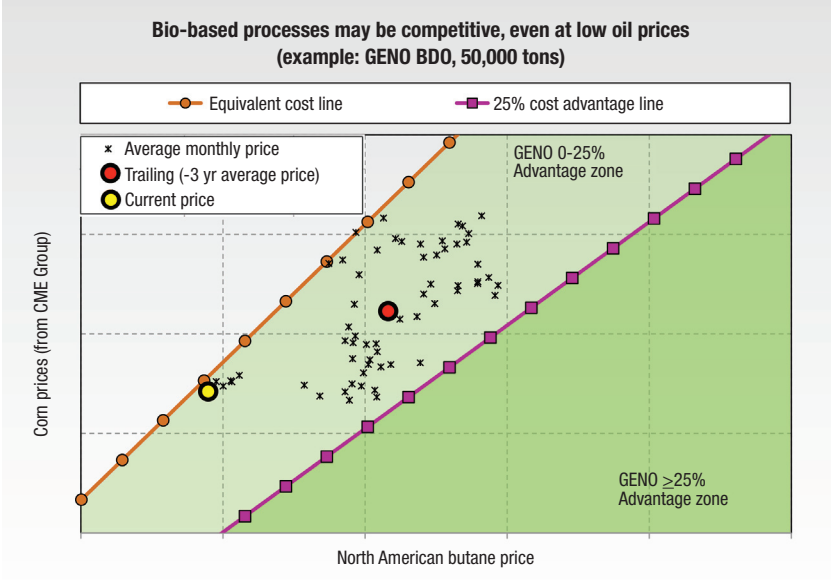

FIGURE 3. Indifference curves can help compare process economics of two alternative processing pathways

veloped strategies to manage many economic risks, including those tied to feedstock costs. Increasingly, similar tools are available to support bio-based projects. For example, Cargill, the global agricultural products and services firm, has among its core competencies the ability to manage the pricing and supply risks tied to agricultural commodities — which may be used as feedstock for bio-based production plants. In addition, Cargill is now offering a range of production-support services to companies interested in specific bio-based process technologies, including fully outsourced production, services and feedstock supplies.

Principle 4: Bioprocessing is different

While bioprocess engineering and conventional process engineering are disciplines that share a similar overall approach, there are important differences in the specifics of the two, as well as some specialized skills associated with bioprocessing. The following items represent some examples.

Downstream processing is different. Chemicals made from fossil feedstocks have characteristic impurities, while those made biologically have different impurity profiles, even if both types of process technologies offer end products at the same purity level. For example, the feedstock for bio-based processes is often carbohydrates. These can lead to product-quality issues, such as color and odor, if not addressed during process design. The bioprocess engineer must be familiar with carbohydrate chemistry and nitrogen (protein, amino acids) chemistry, as well as methods for separating color and odor-causing compounds. Similarly, separating the desired chemical product from the fermentation broth may require different techniques and equipment. Fermentation-based processes operate in an aqueous environment (required for microbial life to thrive). Effective handling and purification of aqueous streams often dictates specialized unit operations. Key concerns include energy-efficient techniques to remove water and the ability to recycle and reuse water.

The tools to minimize byproducts are different. Removing byproducts is expensive, both in capital and operating costs. Bioengineering techniques generally allow the elimination of many byproducts from the outset, by designing a microorganism so that the byproducts are not produced in the first place. For example, initial strains of bacteria engineered by Genomatica to produce 1,4-butanediol also formed nitrogen-containing byproducts, such as 2-pyrrolidone. Strain modifications reduced this significantly, thereby reducing downstream processing costs. This ability to produce a targeted chemical with high selectivity can be a strong advantage.

Managing for variations in feedstock is different. Making a plant or process that is robust under varying inputs is a fundamental task for process engineers that impacts both capital and operating costs. The techniques for managing variations in feedstocks for bio-based processes are different than for conventional processes, and may include feedstock testing (to determine attributes), collaboration with feedstock suppliers to optimize consistency versus cost, rethinking the design of your microorganism to efficiently handle greater variation in feedstock properties, and adjusting fermentation or other operating parameters.

Requirements for sterility are different. Contamination is a concern in any production plant, but the manner in which it is realized for a bio-based process, and the rigor with which it must be maintained, are different. In particular, it is most often necessary to design, build, and operate a bio-based process to exclude viable foreign microbes. This is particularly demanding and critical in the fermenters and associated systems, and, depending on the product, can extend into downstream processing as well. The penalty for cutting corners on sterility can be severe.

Managing for the weather is different. For example, large-scale fermentations can be sensitive to the effect of outside temperatures on cooling-tower capacity. Insufficient cooling capacity can ruin a fermentation batch due to temperature run-up, with consequences that can extend into downstream processing. This risk can be addressed through operating procedures that adjust process parameters to slow down the fermentation rate to maintain temperature control of the fermentation process. Fermentation plants are often constructed with minimal enclosure and exposed piping. Given their lower operating temperatures and aqueous streams, it may be necessary to account for the possibility of freezing.

So what is the overall lesson here? Take advantage of people and firms that have bioprocess expertise as an integral part of your project planning and implementation. Missing this can be (and has been) a critical point of failure, just like trying to build your first-ever plant in a new part of the world without local

knowledge and resources. Coupled with Principle 1, this puts a premium on collaborating with partners that have proven experience in biotechnology, in bioengineering, and in taking a whole-process perspective.

The good news is that despite all these differences, large-scale commercial fermentation-based processes have been running for decades to make products like organic acids and amino acids. Recent advances in microorganism engineering have simply expanded the opportunities for employing bioengineering to develop cost-competitive, robust bioprocesses for a greater number of products and for a wider range of product types.

Principle 5: Evaluate services

If you have never bought a motorcycle before, it is important to learn the most important questions to ask and what tires to kick.

To successfully harness biotechnology in your projects, here are some key considerations in evaluating potential technology or project partners.

Design processes to operate at your targeted commercial scale. Technology should be demonstrated under large-scale conditions and piloted at a scale and to an extent necessary to mitigate scale-up risks. The best practice is to prioritize those technologies and partners that have "been there and done that" — they know what the end result should look like.

Invest in comprehensive integrated solutions. Do not take a piecemeal approach, where microorganism development, process development, TEA and large-scale plant design are disconnected activities.

Overprepare for technology transfer and take nothing for granted. It is easier to reduce resources later because technology transfer has gone smoothly, than to add resources to "fight fires." Prospective partners may offer validation of their technologies based on a plant that they have built, and now own and operate. Look for those that have successfully transferred their technology — ideally to multiple locations around the world — and possess documented, systematic approaches for doing so. If finding such a situation is difficult, look harder and persevere; they do exist.

Closing thoughts

Biotechnology brings increased options for many chemical-production businesses and offers more tools to harness where appropriate. There is a fast-expanding body of knowledge, experience, and best practices, from which all can benefit.

Our trade is tasked with planning for projects that start up three or more years from now. That means that now is the right time to learn how and where to integrate bioengineering and bring it into active consideration for your upcoming projects. ■

Edited by Scott Jenkins

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