BIOPROCESSING

DESIGNING BIOREACTORS FOR SPACE FLIGHT

PHILADELPHIA—A bioreactor designed to operate in microgravity should be ready for its maiden voyage within the next year, according to Dennis Morrison, head of NASA's bioprocessing laboratory at Johnson Space Center (Houston, TX).

Morrison, speaking at a seminar on space bioprocessing hosted by the Bioprocessing and Pharmaceutical Research Center (BPRC) here in December, emphasized the range of practical considerations that enter into the design of a bioreactor to be operated on the space shuttle. For instance, all components of the apparatus, except the process controls and power supplies, must be autoclaved before launch, since the shuttle does not have this capability. This means that all valves, solenoids, and sensors must be sterilizable. Also, pressurization controls must be built-in to compensate for any sudden drop in cabin pressure. Moreover, because the onboard operators of the bioreactor will be astronauts, not bioengineers, the equipment should be easy to use.

Traditional ground-based reactors have a mechanism for stirring to keep cells suspended, a sparger for oxygen, a large head space because oxygen's solubility in an aqueous phase is low, sensors to detect changes in pH and dissolved oxygen and in carbon dioxide, and a way of removing the medium without removing cells. Morrison's first modification of this traditional design was to eliminate the head space. Unfortunately, this made getting oxygen to the cells difficult. Morrison's group solved this by circulating the medium at a very high flow rate through an external loop; a remote spin filter removes cell-free medium from a 500-milliliter reactor at a rate of 100 milliliters per minute.

Because there is no sedimentation in microgravity, unconventional means of controlling the mixing of cell-coated microcarrier beads now become attractive. The reactor can be operated at very low shear in the absence of bubble buoyancy; this eliminates foaming problems. The bioreactor has a spiral-vein mixing system that is driven separately and is not in the chamber; this effectively separates the mixing and spinning functions. All sensors are also removed from the chamber; they monitor the medium as it leaves and as it enters to detect any changes within the chamber.

Morrison's group has experimented with new methods for isolating sub-populations of cells from pancreas and kidney. These target cells are selected for their ability to secrete elevated levels of "desirable" proteins. The scientists have also been able to select cells that are hearty, predictable in their growth, and able to withstand the rigors of the electrophoretic techniques used to separate them into sub-populations.

Morrison envisions the bioreactor as an intermediate step in an overall bioprocess that will run on the space station—separating populations of cells to obtain high producers, growing the cells in bioreactors, maintaining the cells in serum-free medium while they secrete product, and then purifying the product in one or a very few steps.

Why would anyone want to grow cells in space? As Paul Todd, director of the BPRC, says, if a product's annual market value is at least 10 to 100 million dollars, and it can be purified from some reasonable starting volume, then you actually save money by isolating it in space. Morrison adds that there has even been some political realization that there may be worthwhile reasons—other than prestige—to build the space station. Top among these is the processing of biologicals, particularly because these products already have a market here on earth. **—Jennifer Van Brunt**

COMPUTER SIMULATION

THE VERY MODEL OF A MODERN MICROBE PROCESS

MONTREAL, Que.—By "flying" an innovative computer simulation, a group at McGill University here may have found a way to discover hitherto unsuspected, highly productive steady states for continuous microbial cultures.

Bohumil Volesky, an associate professor of chemical engineering, has applied to continuous cultures the kinds of techniques used to model catalytic crackers in the petroleum industry. Initial work on his group's model system—the acetone-butanol-ethanol (ABE) biosynthesis of *Clostridium acetobutylicum*—revealed what appears to be a potential steady culture state two or three times more productive than the usual.

Have these results been verified in the lab? "No," says Volesky, who refrains from making strong claims for this particular set of analyses. "These predictions are strictly based on model conditions. To do the experiments would require special control arrangements, and these have not been developed yet." Indeed, the McGill University project is aimed, ultimately, at producing models that will manage on-line computer control of continuous processes. Volesky says he knows of no system yet capable of controlling conditions precisely enough to "force" a culture into a more productive state. Thus, verification of the model depends on application of the model; progress will come in increments, as the fermenter hardware and modeling software progress together.

The key to Volesky's approach is a "physiological state marker." This is a function of some measurable condition—it may be NADH, ATP, or RNA—that tells the simulation how to adapt to aging, metabolic transitions, and abnormal stages.

"There is," says Volesky, "great potential in this single [mathematical] term. A whole bag of things are contained in this input." Unfortunately, it is not yet clear how to interpret—physically or mathematically—changes in the physiological marker.

The story of Volesky's association with computer modeling is, he says, a tale of conversion (as he noted in a presentation on the topic at Online's Biotech 85 USA): "Just five years ago, I was myself a firm non-believer.

"This is the second generation of modeling attempts. It is the product of accumulated knowledge of microbial biochemical pathways, the availability of methods for handling the mathematics (methods taken from chemical and electrical engineering), and the ready availability of sophisticated software and hardware."

Volesky's group works without industrial support (it is funded by the Canadian National Research Council) and he discounts the possibility of commercial interest in his ABE findings. "There isn't a chance in hell of it being commercialized on this continent," Volesky says. Competition from more conventional producers is just too keen. The lack of industrial interest doesn't surprise the researcher; batch processes, not continuous cultures, are the industrial norm.

—Douglas McCormick