DESIGN CHALLENGES FOR SPACE BIOREACTORS

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ABSTRACT

The design of bioreactors for operation under conditions of microgravity presents unique problems and challenges. Absence of a significant body force such as gravity can have profound consequences for interfacial phenomena including cohesion, adhesion and interphase heat and mass transport. Marangoni convection can no longer be overlooked. Many speculations on the advantages and benefits of microgravity can be found in the literature. Very few have been demonstrated by incontrovertible experimental evidence.

Initial bioreactor research considerations for space applications had little regard for the suitability of the designs for conditions of microgravity. Closed loop flow schemes were touted with oxygen sparging, CO_2 bubble coalescence and CO_2 venting as if microgravity made no difference in these operations. However, during this decade, the scientific community has become keenly interested in advancing the fundamental questions pertaining to operation of bioreactors under microgravity.

Bioreactors can be classified in terms of their function and type of operation. The complex interaction of parameters leading to optimal design and operation of a bioreactor is illustrated by the JSC mammalian cell culture system. The design of a bioreactor is strongly dependent upon its intended use as a production unit for cell mass and/or biologicals or as a research reactor for the study of cell growth and function. Therefore a variety of bioreactor configurations are presented in rapid summary. Following this, a rationale is presented for not attempting to derive key design parameters such as the oxygen transfer coefficient from ground-based data.

A set of themes/objectives for flight experiments to develop the expertise for design of space bioreactors is then proposed for discussion. These experiments, carried out systematically, will provide a database from which engineering tools for space bioreactor design will be derived.

1. INTRODUCTION

Enabling technologies for closed ecological life support systems(CELSS) are under various stages of development around the world. CELSS must provide a safe and healthy human habitat in extra-terrestrial locations. A major responsibility of CELSS is to meet the need for food and biologicals and thus ensure the health and survival of mankind in outer space. Bioreactors for the production of unconventional food sources, food supplements and pharmaceuticals as well as for the treatment of wastes (primarily lignocellulosics) have become a part of such developmental efforts.

The scientific research community in the field of cell biology is being challenged with questions concerning the behavior of various cells under microgravity and other environmental conditions prevailing in extra-terrestrial locations. The understanding of such cell function and behavior to be developed through carefully planned investigations will be of great value in realizing NASA's goals for extended human presence in space during the early 21st century.

It has been recognized that terrestrial bioreactors cannot be operated as such under microgravity. New designs appropriate for extra-terrestrial applications have to be developed. Such design effort cannot proceed without new design tools and methodology in the field of variable-gravity bioprocess engineering. This approach requires a well orchestrated experimental program which can provide reliable and quantitative answers to all the questions of the engineers charged with the challenge of designing, building and operating space bioreactors.

2. CONSEQUENCES OF THE ABSENCE OF GRAVITY

It is not clear whether the basic biochemical kinetic rates and even the basic phenomenon of molecular diffusion are functions of the gravitational body force. However, our knowledge of interactions between dissimilar fluid phases and of convection currents induced by thermal and concentration gradients within a fluid phase, lead us to deduce a significant dependence for mass and heat transport on the magnitude and direction of a body force such as gravity.

Under conditions of microgravity, natural convection induced by buoyancy forces is insignificantly small while Marangoni convection driven by surface tension gradients can produce dramatic effects. The dominance of buoyancy forces over viscous forces has been represented by a dimensionless group called the Grashof number. This group takes on two forms depending on whether the buoyancy is caused by thermal gradients or concentration gradients as shown below:

$$\text{Thermal Grashof Number, } Gr_t = \frac{D^3\rho^2 g\beta\Delta T}{\mu^2}$$

Concentration Grashof Number, $Gr_C = \dfrac{D^3\rho^2 g\zeta\Delta x}{\mu^2}$

Here $$\beta = -\frac{1}{\rho}\left(\frac{\partial\rho}{\partial T}\right)_{P,x}$$

$$\zeta = -\frac{1}{\rho}\left(\frac{\partial\rho}{\partial x}\right)_{P,T}$$

P = Pressure

T = Temperature

D = A typical dimension of the flow field

ρ = Density

g = Gravitational acceleration

ΔT = Temperature change along flow direction

μ = Dynamic viscosity

Δx = Concentration (mole fraction) change along flow direction

The relevance of these Grashof numbers is readily appreciated by considering the typical dependence of mass and heat transfer coefficients on them. A typical mass transfer coefficient, kx can be written as function of its corresponding Grashof number Gr as follows:

$$k_x = \frac{cD_{AB}}{D} f_G\,(Gr\ Sc)$$

where c = bulk molar concentration

D_{AB} = Diffusivity of species A through B

Sc = Schmidt number, $\mu/\rho\, D_{AB}$

f_G = Correlating function

Similarly, a typical heat transfer coefficient can be written as

$$h = \frac{k}{D} f_G \text{ (Gr Pr)}$$

where k = Thermal conductivity

Pr = Prandtl number, $C_p\mu/k$

C_p = Specific heat at constant pressure

Under microgravity, buoyancy due to thermal and concentration gradients can be negligibly small and hence the corresponding Grashof numbers close to zero. This correlates with very small mass and heat transfer rates as shown in the above equations. However, we cannot categorically assert that spontaneous phase separation is impossible under conditions of microgravity. Even though there can be little buoyancy within a fluid phase in the absence of gravity, there can be significant convection currents originating at the interfaces of two or more fluid phases in contact. Such convection currents are induced by surface tension gradients associated with temperature and concentration differences along the interfaces. The relative magnitude of surface tension driven convection to viscous and molecular effects is represented by the dimensionless Marangoni groups which take on the following forms:

Thermal Marangoni number, $$Ma_t = - \frac{d\sigma}{dT} \frac{D\Delta T}{\mu k}$$

Concentration Marangoni number, $$Ma_c = \frac{d\sigma}{dx} \frac{D\,\Delta x}{\mu D_{AB}}$$

where σ = Surface tension

Through similarity, it may be possible to correlate the dependence of the Marangoni mass and heat transfer on the corresponding Marangoni numbers as follows:

Marangoni mass transfer coefficient, $$k_{Mx} = \frac{cD_{AB}}{D} f_M \text{ (Ma Sc)}$$

Marangoni heat transfer coefficient, $$h_M = \frac{k}{D} f_M \text{ (Ma Pr)}$$

where f_M = Correlating function.

Spontaneous phase separation by Marangoni convection can be expected when surface tension values are very sensitive to changes in temperature and/or concentration. If such fluid phases are found in a bioreactor, gas bubbles or liquid droplets can be found to move towards hotter regions of the interfacial surface or towards regions of higher concentration along the interfacial surface. Marangoni convection can be augmented or retarded by body forces such as gravity depending on the direction and magnitude of the body force with respect to the convection vector. The relative dominance of surface tension forces over gravity forces can be represented by a ratio of Marangoni and Grashof numbers which reduces to the following elegant form:

$$\frac{\text{Acceleration due to surface tension gradient}}{\text{Acceleration due to gravity}} = \frac{\left(\frac{\partial\sigma}{\partial\rho}\right)\left(\frac{1}{D^2}\right)}{g}$$

When significant Marangoni effects prevail, the interfaces cease to be quiescent and the resulting interfacial turbulence augment mass and heat transfer rates across interfaces (Skelland 1974). However, such effects cannot be predicted to any acceptable degree of accuracy because of the complex and interactive dependence of surface tension gradients on changes in species concentrations and temperature. For example, interfacial turbulence is promoted by the following factors:

1. Microgravity
2. Solute transfer out of a high viscosity phase
3. Solute transfer out of a low diffusivity phase
4. Large differences in kinematic viscosities or molecular diffusivities between contacting phases
5. Large concentration gradients near the interface
6. Large changes in surface tension for smallchanges in concentration or temperature
7. Low viscosity and diffusivity in both phases
8. Absence of surfactants
9. Large interfacial area

From the above discussion it is clear that microgravity can significantly enhance surface effects and interfacial phenomena (Day and Ray, 1985). As a

the absence of forced convection. Microgravity can alter such surface effects as cohesion and adhesion. Even if one of these effects can be anticipated in a space bioreactor, its performance can be expected to depart significantly and nonlinearly from terrestrial performance.

3. SPECULATIONS ON THE ADVANTAGES AND BENEFITS OF MICROGRAVITY

Tairbekov (1983) concluded without convincing evidence that "free-living unicellular organisms are indifferent to variations in the magnitude and direction of the gravitational field.

Jordon (1974), Mayeux (1977) and Kober(1970) variously attributed the following enhancements in bioreactor performance to microgravity, again without adequate evidence and well-controlled and scientifically sound experiments:

(a) Increase in cell growth rate

(b) Increase in cell population densities

(c) Increase in biological production (enzyme, vaccine,etc.) from microbial fermentation

(d) Higher levels of oxygen solubility in nutrient solution

(e) Greater control of convection/mixing to suit shear- sensitive mammalian cells

A report by Arthur D. Little Inc. (1978) speculated on a purely imaginary model of gas exchange through a membrane under microgravity where the gas was presumed to form a layer on the liquid side of the membrane as well and prevent the liquid from wetting the membrane.

The Biosatellite II Project was commissioned to evaluate the effect of weightlessness on bacterial growth. It was found that the density of Salmonella typhimurium cells grown under microgravity was higher than that for terrestrial culture of the same bacterium. This led to a number of "off-the-cuff" speculations. Mattoni (1963) attributed the increased cell density to enhanced efficiency of nutrient transfer to and waste product removal from the cells. Nyiri (1976) attributed the same to better oxygen transfer under microgravity.

None of the above speculations was followed up by any serious scientific effort to verify and validate them. This volume of the proceedings of the Cells II conference contains a number of interesting papers on the effect of microgravity, viz.,the production of growth hormone in rat pituitary cells, inhibition of blastogenic response, and response of carrot cells. However, fundamental questions such as the dependence of biokinetic rate, marangoni driven convection, basic molecular diffusivity, viscosity, thermal conductivity, thickness of laminar sublayer, the turbulent boundary layer etc. on microgravity remain unanswered today.

4. COMPLEX PARAMETRIC INTERDEPENDENCE IN A SPACE BIOREACTOR

A serious attempt at designing and operating a bioreactor under microgravity is in progress at NASA-JSC (Cherry, 1985).

The bioreactor employs mammalian cells cultured on microcarrier beads. Oxygenation of the nutrient liquid and cell growth are carried out in two separate chambers. Unlike earlier concepts (Charles, 1979 and Gitelzon, 1975) where oxygen sparging and carbon dioxide venting were not examined for feasibility of operation under microgravity, the JSC design is well thought out for its intended application. The cell growth chamber is a continuously stirred tank reactor where the agitation rate is optimized to reduce damage to the shear-sensitive cells while providing adequate homogeneity of oxygen and nutrient concentration throughout the reactor volume.

This reactor is designed for low rates of oxygen delivery and a great concern for minimizing cell damage due to bead-bead and bead-impeller collisions. The primary design objective of minimizing cell damage can be accomplished in one or more of the following three ways:

(a) Increase in turbulent eddy size

(b) Decrease of bead-bead collision frequency

(c) Decrease of bead-impeller collision frequency

Turbulent eddy size could be increased by

(a) increasing the kinematic viscosity of the nutrient solution,

(b) decreasing the impeller diameter, and/or

(c) decreasing the impeller speed.

On the contrary, any of these measures would reduce the homogeneity of the reactant mixture and thus tend to decrease production.

Bead-bead collision frequency could be decreased by

(a) decreasing the volume fraction of beads and/or

(b) increasing bead diameter.

Again, to the contrary, decreasing the volume fraction of beads would entail production cutback and increasing bead diameter would result in more violent collisions leading to increased cell damage.

Bead-impeller collision frequency could be decreased by

(a) decreasing bead size,

(b) decreasing impeller speed,

(c) decreasing impeller diameter, and/or

(d) decreasing the number of impeller blades.

Decreasing the bead size could increase the bead-bead collision frequency but the collisions will be less energetic. However, reduction in impeller characteristics (speed, diameter and number of blades) could compromise homogeneity and hence production.

In addition to the recognition of all the above design trade-off issues, it was also determined that coating the impeller blades with an elastic material could soften the bead-impeller collision and reduce cell damage therefrom. It was estimated that laminar boundary layer could cause very little damage to the mammalian cells.

The above example was presented here to illustrate the complexity of the decision process in designing the bioreactor for just one criterion, viz., minimal cell damage.

5. SPACE BIOREACTOR CONFIGURATIONS

A space bioreactor could be designed in a variety of configurations to meet a corresponding variety of operational needs and constraints.

If production is the objective, the configuration chosen should accommodate the conditions of cell culture at the required production rate for the least reactor volume. Shear-hardy yeast cells grown as an alternate food source in space habitats will require a fermenter which can take advantage of high agitation rates and rapid oxygen supply rates for maximum cell growth rate. On the other hand, biological production (enzymes, vaccines, etc.) using highly shear-sensitive mammalian cells will require gentler operation and appropriate hardware configuration such as the JSC bioreactor. Again, the hardware and operation will vary depending on the need for photosynthetic, aerobic and other requirements of any candidate cell culture.

For the case of scientific investigations to examine the possible effects of microgravity on microbial cells, the design of bioreactors depends on the specific questions to be answered. Three broad categories of effects of microgravity on cells can be formulated as a starting basis for providing generic bioreactor hardware for scientific investigations:

1. Cell biology effects such as DNA replication, cell division and morphology

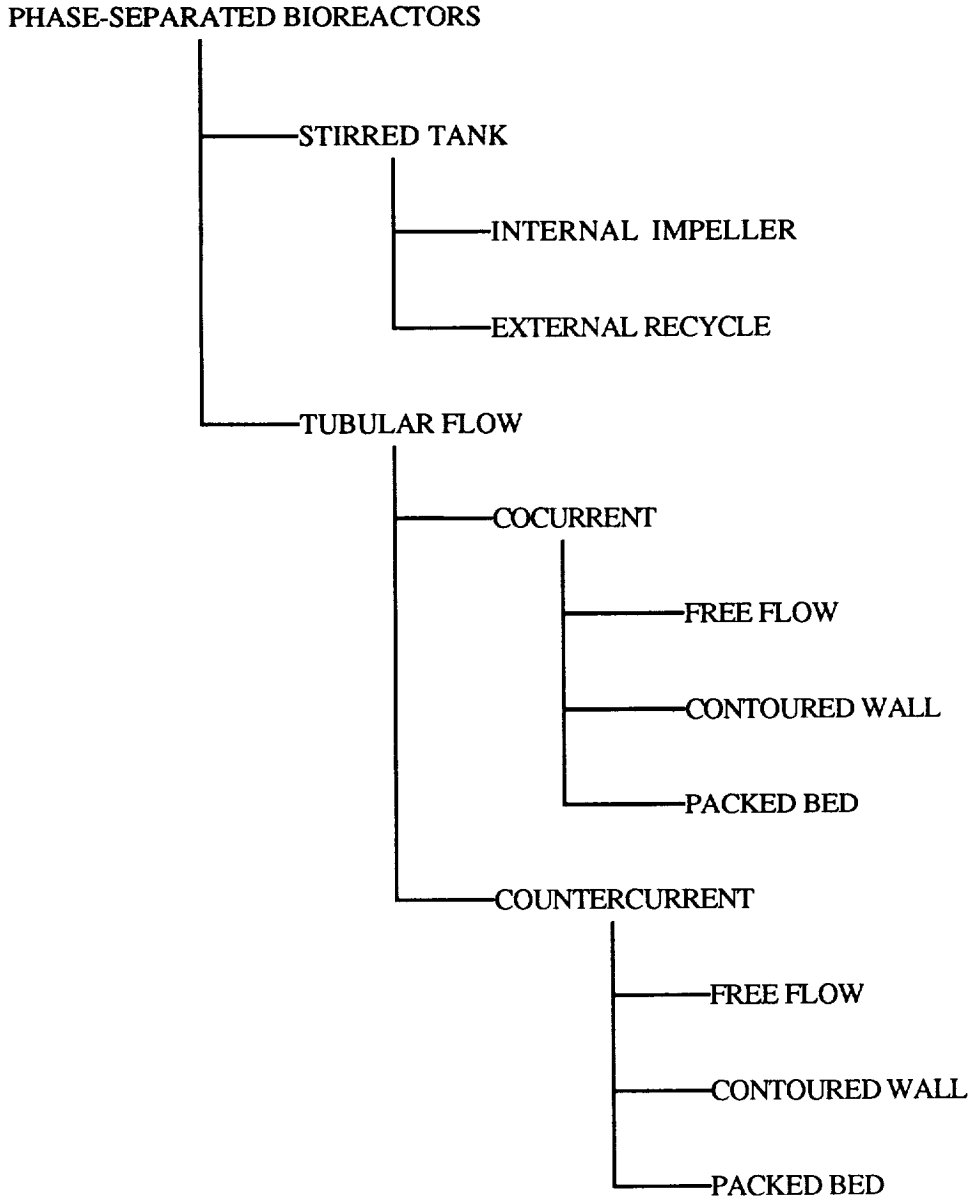
2. Intracellular metabolic effects

3. Microbial ecological effects such as the intercellular metabolic dependencies found in heterogeneous microbial populations

By carefully surveying all potential investigations in the above three categories, a set of design requirements for generic bioreactor hardware can be derived. A set of generic bioreactor hardware can then be designed, built,

and ground-tested by the potential investigators before committing the hardware for microgravity environments.

From a purely hardware point of view, a space bioreactor can operate in a phase-separated configuration or phase-mixing configuration. Operationally, each of these can be classified under "batch", "semi-batch", "fed-batch" and "continuous". The following diagram shows a logical arrangement of various phase- separated bioreactors:



Phase-separated designs utilize oxygen delivery to the culture medium through gas-permeable membranes. Stirred tank bioreactors are suited for moderate product concentrations. Temperature control is easily accomplished in these reactors. Figure 1 is a schematic of a phase-separated stirred tank bioreactor with internal impeller. This design permits fast cell growth rates

under conditions of vigorous agitation. For shear sensitive cells, soft impeller and slow stirring speeds are recommended. Oxygen is supplied by permeation through a bundle of tubes. Oxygen can be the carrier gas for carbon-dioxide venting or a separate interspersed tube bundle can be provided for carbon-dioxide removal. If photosynthesis is warranted, an interspersed bundle of light pipes (e.g., optical fibers) must be accommodated inside the tank. To maintain anaerobic conditions, the oxygen can be replaced by an inert carrier gas or a suitable absorbing medium for carbon dioxide.

A phase separated stirred tank with an external recycle pump replacing the impeller of the previous design is illustrated by Figure 2. This design is suitable for slow reactions and moderate product concentrations. The vigorous agitation obtained inthe previous design can be accomplished through very high pumping (recycle) rates. Channeling between pump input and output must be prevented by appropriate baffle arrangement. This design under mild agitation rates is suitable for slow reactions and moderate product concentrations. This design is not suited for shear-sensitive mammalian cells mounted on carrier-beads. However, a mild peristaltic pump may be appropriate for non-anchored shear-sensitive cell culture.

Tubular flow designs are not normally meant for batch, semi-batch and fed-batch modes of operation. However, these modes may be very appropriate for cell science research. For instance, in the various batch modes, introducing a small amount of culture inoculant at one end of a tube containing a rich nutrient medium will provide a continuous study of cell growth from early to late stages of cell development and lifetime. For production of cell mass at very high concentrations, a continuous tubular bioreactor will be appropriate. Figure 3 shows three design concepts for phase-separated tubular bioreactors with cocurrent flow of nutrients and oxygen/carrier gas. Cocurrent designs are not the most efficient for maximizing production rate of cell mass. However, this type of operation can maintain aerobic and anaerobic conditions at either end of the same reactor to meet the special needs of a scientific investigator. In the above designs, nutrient solution is shown in the annular flow and the oxygen/carrier medium in the central tubular flow. These two can be interchanged without serious consequences. Free flow concepts permit little radial uniformity of concentrations except under highly turbulent flow conditions. The presence of a contoured wall can improve radial uniformity with minimal shear penalty. The packed bed designs can provide the equivalent of intense agitation radially over an axial length equal several packing diameters. These designs can also accommodate photosynthetic organisms through suitable light piping. If high rates of oxygen and nutrient supply are required, oxygenation of the nutrient medium can be accomplished in a separate vessel and the oxygenated nutrient solution can be made to ooze rapidly into a largely porous tube instead of a gas-permeable membrane.

Tubular countercurrent designs shown in Figure 4 are especially suited for continuous cell culture with very high product cell densities. These designs supply the most oxygen where most needed, i.e., the product end of the tube. By maintaining laminar flow of the nutrient medium, mild hydrodynamic conditions can be provided for shear sensitive cultures. Again, as for the cocurrent designs, oxygenated rich nutrient solution can be made to ooze through porous tubing to sustain rapid high density cell cultures.

Countercurrent flow schemes provide the most economical reactor size for a given production rate. Free flow tubular bioreactors are for gentle slow culture. Contoured wall tubular bioreactors improve mixing efficiency without excessive turbulence. If contouring is implemented with soft elastomeric materials, this type of reactor can be compared with JSC stirred tank bioreactor for mammalian cells and trade-off studies can then provide a technology choice for mammalian cell culture in space. Even though packed tubular reactors can provide a high degree of radial mixing and hence favor rapid cell growth, the advantages gained must be offset against the bioreactor volume occupied by the packing. A trade-off study and a break-even plot will lead to the right combination of packing type, size, volume and flow rates to maximize cell mass production rate.

Phase-mixed reactors will not operate under microgravity since an efficient phase separation following mixing cannot be implemented in these reactors without introducing artificial body forces such as in centrifugation. So we can conceive of two types of phase mixed bioreactors as shown in Figure 5. In the rotating stirred tank bioreactor, gases are sparged through the liquid. Phase mixing is accomplished by countercurrent flow of gas and liquid and uniformity of concentration in the liquid phase is accomplished by a very high rate of recycle of the culture. The need for high recycle rates can be offset by providing packing material inside the bioreactor volume as shown for the rotating packed bed in Figure 5. The rotating packed bed designs can benefit from commercial Higee technology development by the Imperial Chemical Industries of England. By implementing carbon dioxide removal from the gas discharge, oxygen can also be recycled for economy of operation. Where high oxygen input rates are desired, an oxygenator must be inserted in the liquid recycle loop. These designs can also accommodate batch, semi-batch and fed-batch modes of operation of the bioreactor. In the phase- mixed designs, cocurrent arrangements are not feasible. Even though tubular flow rotating reactors can be conceived and built, the designs can provide no weight/volume advantages over those illustrated above.

In the case of a slow culture, to obtain significant product output a large reactor volume will be required. If dense cell mass output is desired, a long tubular flow bioreactor design will be favored. The long tube can be accommodated by a spiral- wound or hairpin-bend type arrangements.

For high rates of oxygen delivery, the phase-separated stirred tank bioreactor can be configured as a combination of two stirred tanks, one large and one small as shown in Figure 6. In this scheme, the nutrient recycle rate can be as high as 100 times the product delivery rate. The filter shown above prevents cells from entering the oxygenation tank along with the nutrient recycle while building up high cell densities inside the bioreactor.

6. KEY DESIGN PARAMETERS

Measuring the values of molecular diffusivities, viscosities, thermal conductivities and interfacial tension under conditions of microgravity has a great scientific merit since comparison of these numbers to the corresponding terrestrial numbers will greatly enhance our fundamental understanding of the role of gravity.

However, when it comes to designing a space bioreactor, these basic numbers are not immediately useful. For engineering design we need typically one or more of the following for any particular reactor configuration:

(1) Individual Mass transfer coefficients, k_l or k_la and k_g or k_ga or overall mass transfer coefficient K_l or K_la or K_g or K_ga as a function of reactor throughput rate.

(2) Individual or overall heat transfer coefficient as a function of reactor throughput rate.

(3) Agitator or recycle pump power demand as a function of reactor throughput rate.

(4) Residence time distribution(RTD) as a function of reactor throughput rate. No bioreactor will operate as an ideal plug flow or a perfectly stirred tank reactor. Experimentally obtained RTD's can be used to correct idealized mathematical models for actual non-ideal effects. The non-ideal effects are caused by dead spots, partial segregation and partial micromixing within real bioreactors.

There are additional parameters of interest to the design engineer such as genetic mutation and radiation shielding which we shall not discuss here.

Using the above information, the design engineer will compute the reactor volume, gas transfer area, heat transfer area, impeller/recycle pump specifications etc. Through carefully planned flight experiments the above parameters must be obtained as a function of reactor size using sound scale-up procedures. There is no alternative to this approach.

To illustrate why mass transfer coefficients etc. must be measured under conditions of microgravity and cannot be derived from basic diffusivity etc. data let us consider the liquid film coefficient for oxygen transfer, k_la. This coefficient, though defined through an Ohm's law type relationship, is not a constant even with respect to the concentration differential. k_la is a complex composite parameter which includes the effects of all the following and more.

(1) Gas bubble size, membrane tube diameter and microbial cell dimensions

(2) Fluid density, viscosity and diffusivity

(3) Temperature, pressure and concentration distributions which depend on forced and Marangoni convection effects not easily modeled for a microgravity environment.

(4) Agitation intensity (recycle rate, impeller diameter, impeller blade size, shape and number, impeller speed)

(5) Fermenter and gas exchange geometry and arrangement of gas permeation tube bundle.

(6) Turbulent eddy dynamics with free cells or carrier-attached cells or both

(7) Counter diffusion of carbon dioxide and moisture into gas bubbles or gas stream

(8) Effect of microgravity on some or all of the above

The dependence of $k_l a$ or other mass transfer coefficients on all of the above is complex and non-linear. $k_l a$ does not scale in the same way as reactor size and agitation rate do (Oldshue, 1966).

Similar considerations apply for heat transfer coefficients if significant interfacial heat effects are involved.

In this context, it is interesting to observe how confusing and unreliable some of the research efforts have been in the area of estimating $k_l a$ values for bioreactors. To illustrate this, let us consider the claim in the literature (Charles, 1979) of an ingenious procedure to calculate oxygen transfer $k_l a$ from kinetic rates of oxidation of glucose to gluconic acid and hydrogen peroxide. Here, the glucose solution was sparged with air in a separate vessel. The air-sparged glucose solution was pumped to a reaction vessel and filled up without any head space and closed up. The enzyme glucose oxidase was then injected into the reaction vessel to the reaction started. The dissolved oxygen in the reaction vessel was traced against time and the rate of glucose oxidation was computed. It is then claimed that a big and unwieldy expression converts this glucose oxidation rate into the mass transfer coefficient in the air sparging vessel. No dissolved oxygen trace was reported to have been made for the air sparging operation. More details of how this feat was accomplished would indeed be interesting.

7. SUGGESTED THEMES FOR FLIGHT EXPERIMENTS

In addition to normal operation of candidate space bioreactors in microgravity and having obtained all the pertinent values of state and operating parameters, the following boundary values must be obtained in order to have a clear picture of operational bounds for the bioreactors in parametric space.

(a) Effect of microgravity on biokinetic rate.

By maintaining near-complete nutrient and oxygen availability for a low cell population, the cell growth rate shall be measured. The same must be studied under anaerobic conditions to understand product selectivities and changes, if any, in biochemical pathways under microgravity.

(b) Effect of microgravity on oxygen transfer rate.

By maintaining high cell population and oxygen availability just above the onset of anaerobic pathways within the cell, the cell growth rate or oxygen consumption rate shall be determined under microgravity. The same must be studied with minimal nutrient availability.

(c) Effect of microgravity on heat transfer.

By feeding preheated oxygen gas and cooling the reactor walls to maintain a uniform product outlet temperature, obtain the heat transfer rate and any associated change in oxygen mass transfer rates under both the kinetic and transport limited operations. By judiciously varying temperature profiles inside the bioreactor, onset of vigorous Marangoni turbulence must be studied.

(d) Effect of microgravity on residence time.

(e) Effect of microgravity on scale-up laws.

At least three different sizes of the same bioreactor configuration must be tested under identical microgravity environment to obtain all relevant data to derive scale-up laws to guide efficient future designs of space bioreactors.

Using standard pulse and step input methods, residence time distributions for candidate bioreactors must be obtained under microgravity.

In order to determine whether a direct correlation exists between terrestrial performance and microgravity performance of identical bioreactors, identical experiments shall also be conducted on earth and the data cross-plotted to derive such a correlation.

To improve our basic understanding of the effect of microgravity on fundamental physico-chemical and fluid dynamic parameters, standard testing procedures for measurement of diffusivity, solubility, viscosity, boundary layer properties, etc. must be carried out in microgravity and the results obtained must be correlated with terrestrial results to elicit the role of gravity on these basic parameters.

8. CONCLUSIONS

Until proven otherwise, current opinion in the scientific community that microgravity can significantly affect the performance of space bioreactors guides our strategy for design of flight experiments.

Operation of bioreactors involve complex parametric interdependences which are not readily modeled without experimental data under actual conditions of operation such as microgravity.

A variety of bioreactor configurations and operational modes are available for extra-terrestrial applications. It is possible to obtain a consensus among the CELLS research community and thus select one or more of the configurations for provision of generic bioreactor hardware facilities on board the space station and other extra-terrestrial locations.

Some of the bioreactor designs presented here are particularly suited for maximum cell mass/ biologicals production and should facilitate the effort towards alternate/unconventional food generation in controlled ecological life support systems.

In addition to flight experiments for developing basic understanding of cell growth and function under microgravity, the design of space bioreactors

will be handicapped without the benefit of flight experiments designed to derive key engineering design parameters applicable to microgravity operation. Of particular concern is the determination of scaling laws pertaining to any micro/variable gravity environments. Without such a thorough engineering design infrastructure, design of bioreactors for space applications will lead to considerable waste of effort through trial/error type redesign and considerable delays in accomplishing major manned missions under serious consideration by NASA.

9. ACKNOWLEDGEMENT

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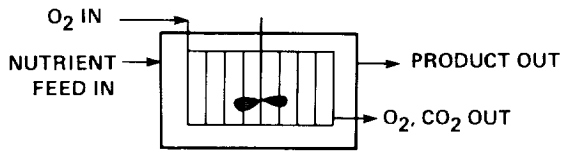

Figure 1. Phase-separated stirred tank with internal impeller.

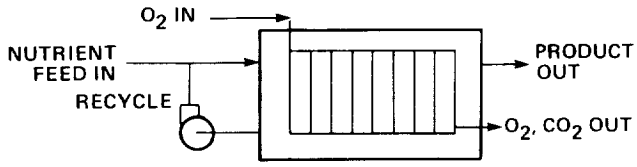

Figure 2. Phase-separated stirred tank with external recycle pump.

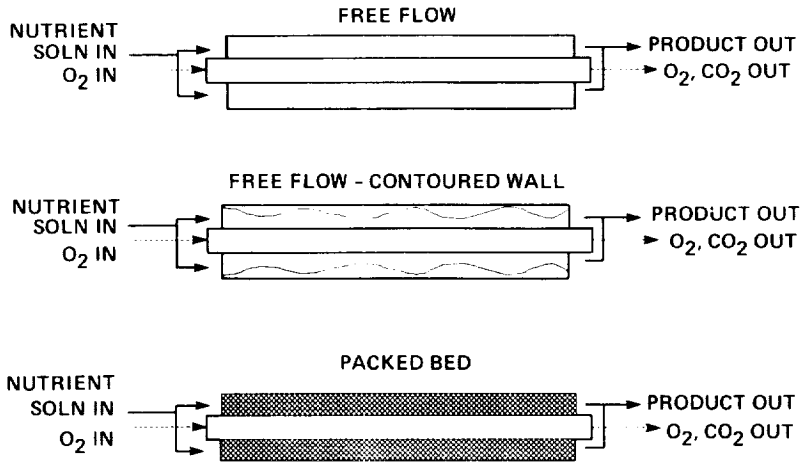

Figure 3. Phase-separated tubular cocurrent bioreactors.

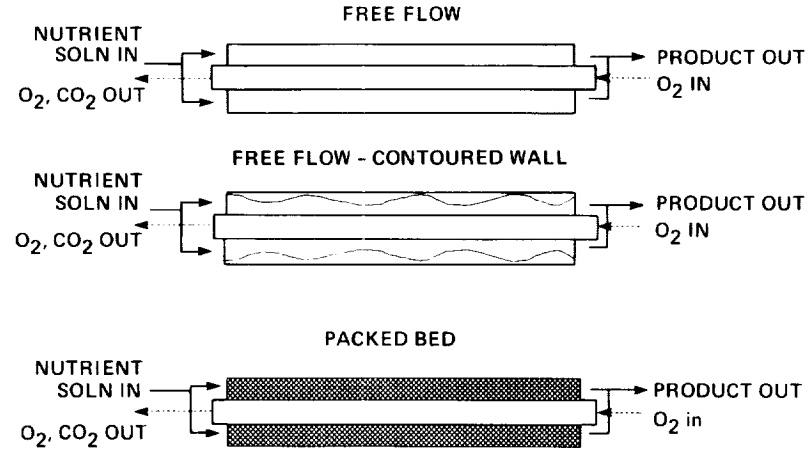

Figure 4. Phase-separated countercurrent tubular flow bioreactors.

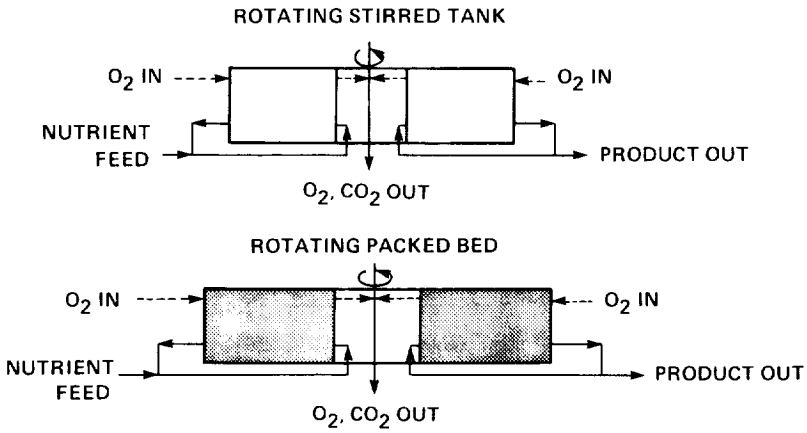

Figure 5. Phase-mixed rotating bioreactors.

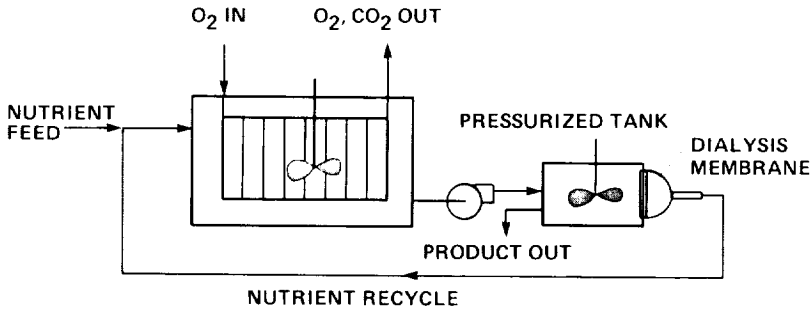

Figure 6. Phase-separated sirred tank bioreactor for high oxygen delivery rates.