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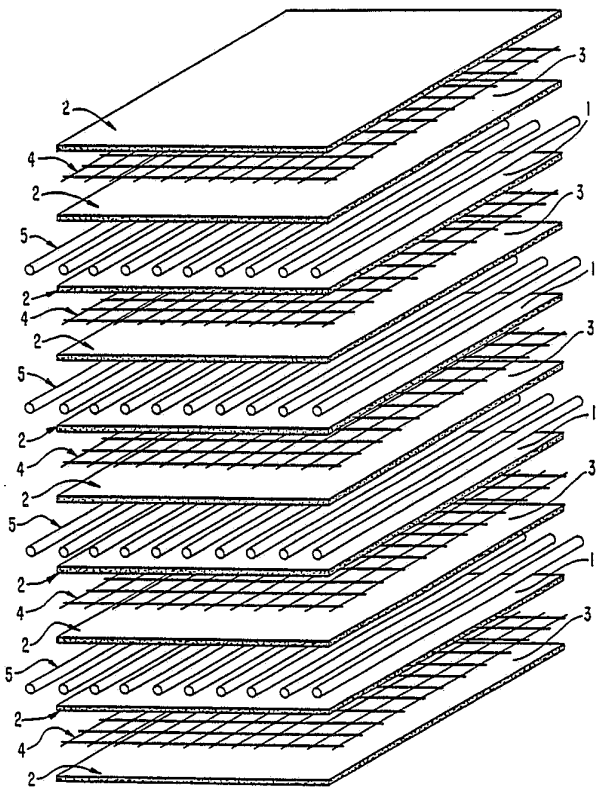
(54) Title: CELL GROWTH REACTOR WITH THREE COMPARTMENTS FORMED BY HYDROPHOBIC AND HYDROPHILIC MEMBRANES

(57) Abstract

A continuous, integrated membrane bioreactor system for the culture of hybridoma or mammalian cells which meets the nutritional and physical needs of hybridomas or mammalian cells, allows for the harvesting of products, and maintains sterile integrity of the system by combining several individual apparatus having separate functions into an integrated, functioning unit. Central to this bioreactor is the compact size of the cell enclosure which is made possible by the high cell densities achieved in the layered membrane design and the continuous feed and bleed nutrient medium system which minimizes the nutrient medium volume inside the bioreactor. Maximized product output per unit of volume minimizes the space necessary to house the bioreactor. Oxygen is passed through the bioreactor as air or another gas mixture, rather than dissolved in the nutrient medium.



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AMENDED CLAIMS

[received by the International Bureau on 21 December 1988 (21.12.88);
original claims 1-8 replaced by amended claims 1-8 (2 pages)]

1. In a cell reactor in which flexible membranes, in spaced-apart relation, are sealed and manifolded to form at least: one cell compartment for confining living cells for secretion of exocellular products; one nutrient compartment for feeding liquid nutrient to the cell compartment and for removal of the exocellular products therefrom; and one gas compartment for the supply of a free-oxygen-containing gas to the cell compartment,

the improvement for achieving economical usage of nutrients and gas, while maintaining the viability of significantly higher cell densities in said cell compartment, characterized by said cell compartment being formed by the opposing faces of a porous hydrophilic membrane and a hydrophobic membrane, which are maintained in said spaced-apart relation, at a distance not greater than 200 microns, by a spacer means.

2. The reactor of Claim 1, containing at least five compartments comprising: a gas compartment sandwiched between two cell compartments which are, in turn, sandwiched between two nutrient compartments,

whereby the gas compartment is formed by the inner faces of two hydrophobic membranes, each of the two bounding cell compartments is formed by the outer face of one of the hydrophobic membrane and an inner face of a hydrophilic membrane, and the outer faces of said hydrophilic membranes form a surface of each of the nutrient compartments.

3. The reactor of Claim 1, wherein the hydrophobic membranes are porous and have a pore size of 0.005 to 0.1 microns.

4. The reactor of Claim 2, wherein said spacer means are a plurality of hollow fiber porous membranes.

5. The reactor of Claim 1, wherein all said compartments are maintained in said spaced-apart relation by a spacer means.

6. The reactor of Claim 4, wherein said compartments are disposed in a spiral wound configuration.

7. The reactor of Claim 5, wherein the hydrophilic and hydrophobic membranes which form the cell compartment are spaced-apart a distance not greater than 100 microns.

8. The reactor of Claim 3, wherein said pore size is 0.01 to 0.05 microns.

STATEMENT UNDER ARTICLE 19

Amended claims 1-8 are filed in response to the references cited by the Examiner in the International Search Report mailed November 11, 1988. Applicant was not aware of U.S. Patent 4,225,671, which is clearly relevant to Applicant's invention. The claims were therefore amended to better distinguish over the '671 patent, which shows a series of parallel, flat membranes spaced widely apart, i.e., 2 mm.

Applicant's invention is based on the finding that, for a given membrane surface area, significantly higher cell densities (and therefore much higher production efficiencies) can be achieved if the spacing in the cell compartment is very narrowly spaced, such that no cells will be beyond oxygen diffusion distance from the gas compartment. Rather than stating this feature functionally as in original Claim 1, amended Claim 1 prescribes this limitation in quantitative terms, i.e., not greater than 200 microns. There is no recognition of this critical spacing requirement in the '671 reference patent. Moreover, since the membranes in that reference are supported along the perimeter solely by tensioning the membranes, maintaining a critical spacing could not be achieved by such tensioning. The amended claims further define how this critical spacing is maintained, i.e., by a spacer means.