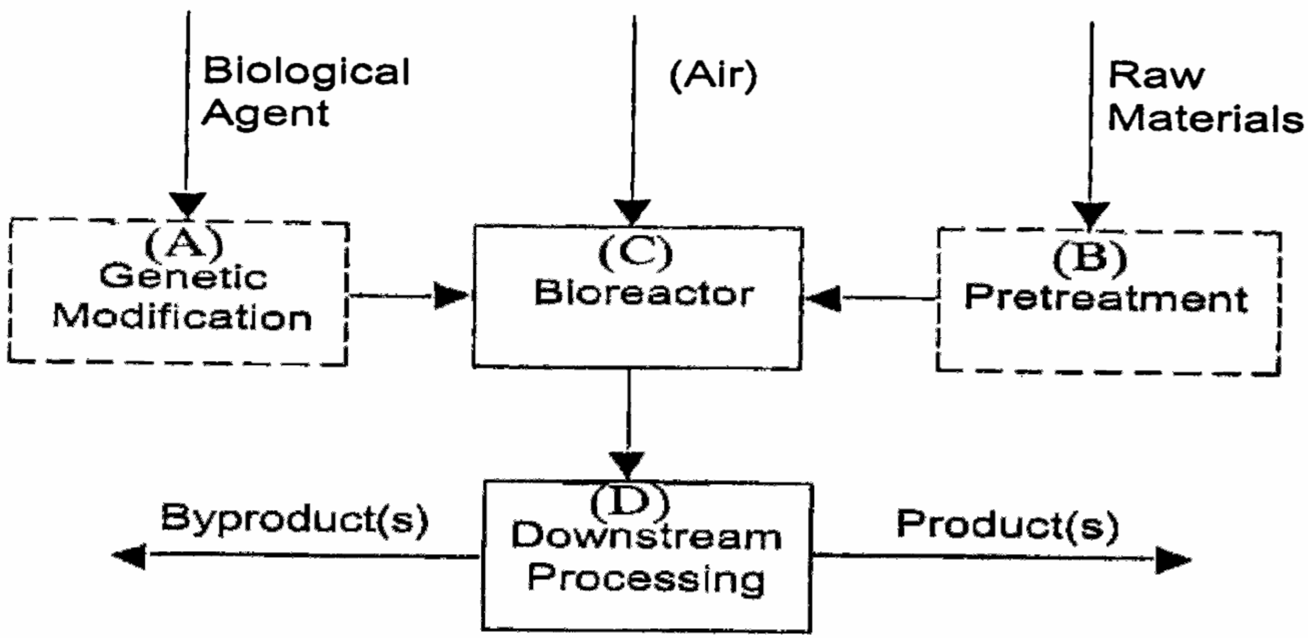
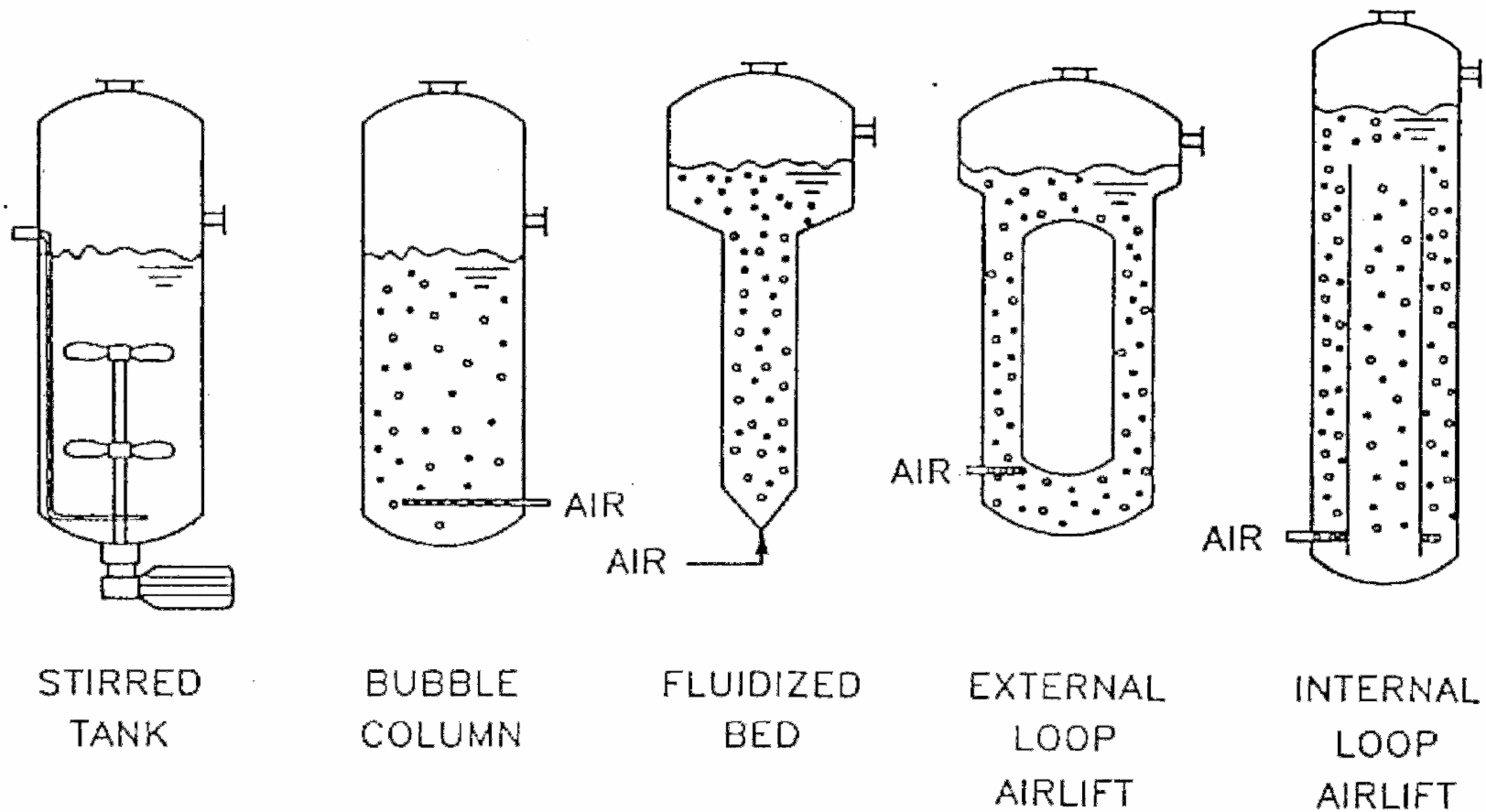
HEALTH, BIOTECHNOLOGY AND *Cellnet*

Bioprocesses for Drugs, Food and the Environment

Outline of a Typical Bioprocess



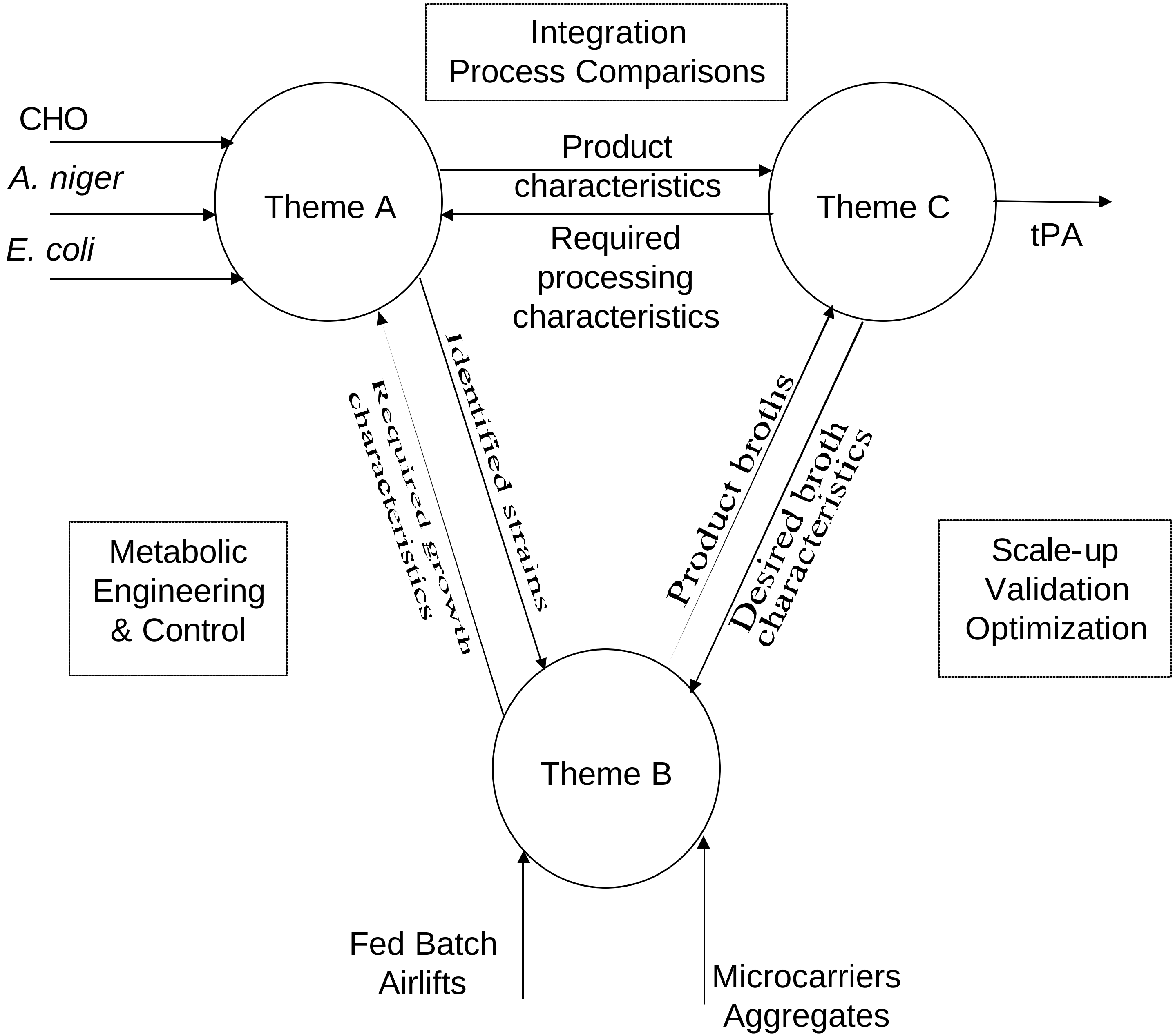
Common Configurations of Bioreactors



Biotechnology Background

- The Multidisciplinary Arena
- Science-Push *vs* Market-Pull
- Ongoing Challenges

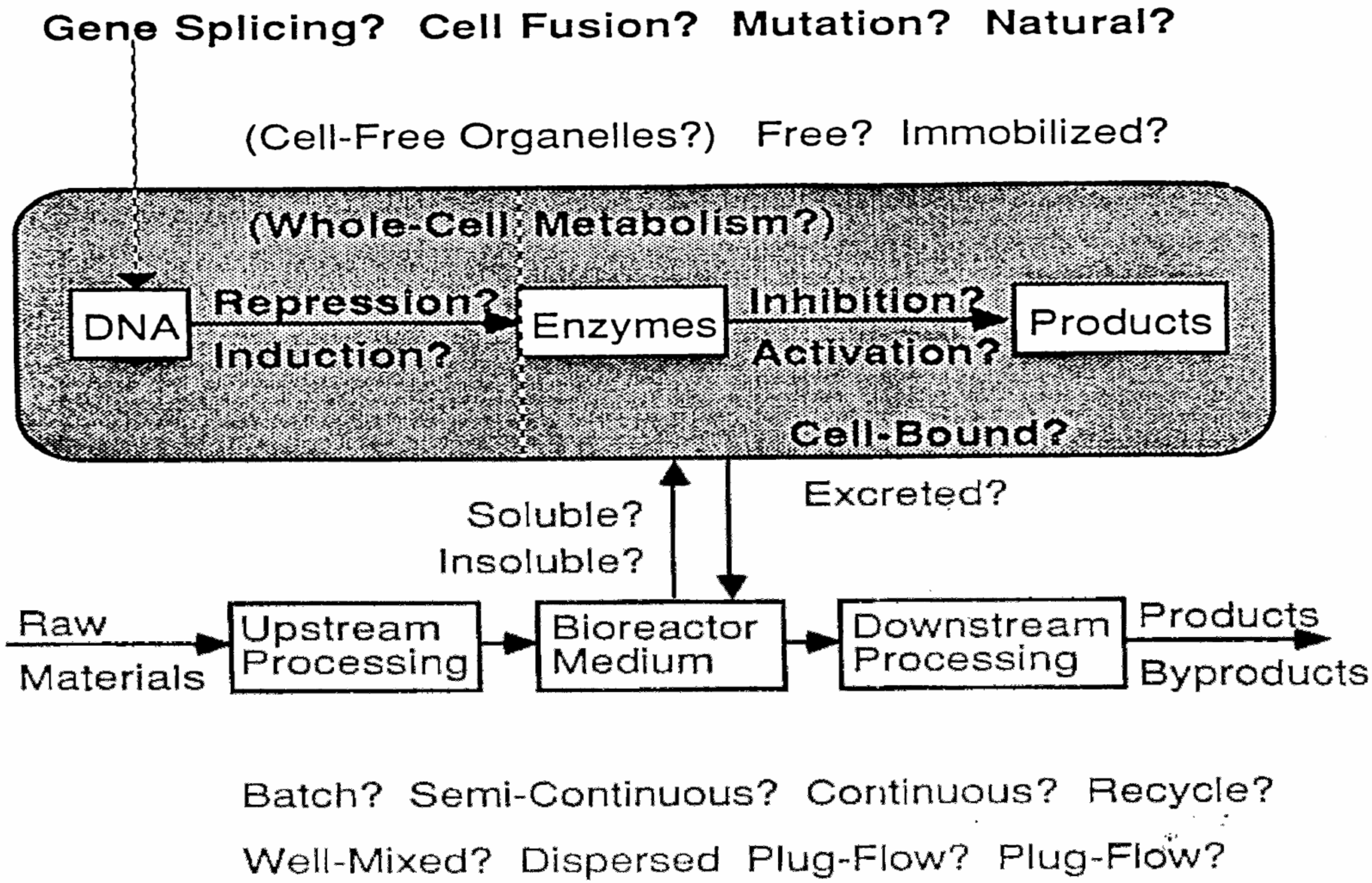
Outline of the Network integrated case studies in cell-factory biomanufacturing

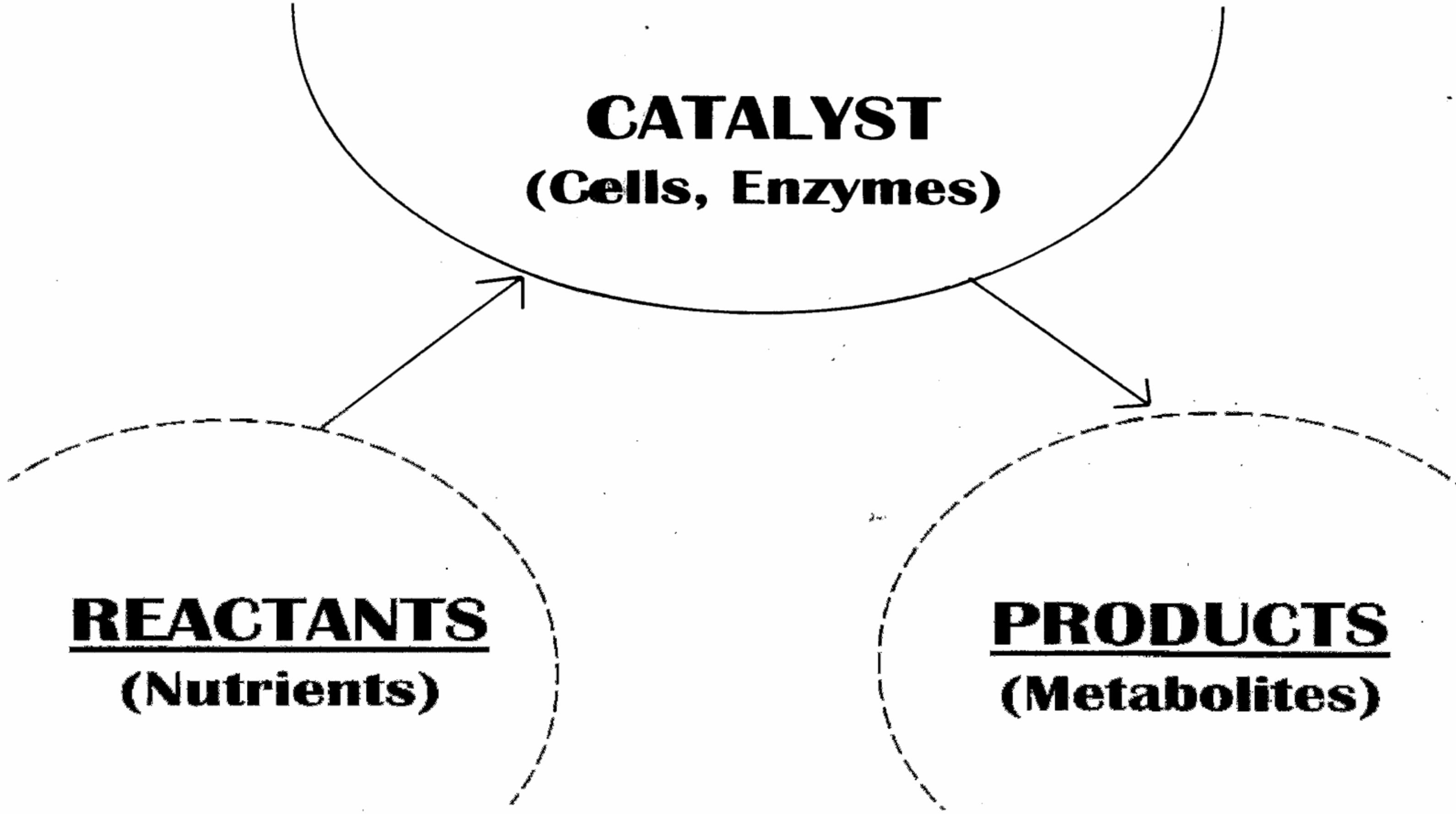


ONGOING CHALLENGES

- Host genetic instability
- Protease co-production
- Intracellular product formation
- Phenotypic stress intolerance
- Media complexity
- Operational variations
- Oxygen limitation
- Cooling restrictions
- Biocatalytic inefficiency
- Product impurities

Bioreactor Heart of a Bioprocess





Possible Physical Barriers in Reactor Productivity

(A) Interparticle Resistances to Mass and Heat Transfer

(B) Intraparticle Resistances to Mass and Heat Transfer

Force Balance on Dispersed Phase

At dynamic equilibrium

$$We = \frac{\tau d}{\sigma}$$

Mass Balance on Dispersed Phase

Batch Processes

$$-\ln(1-E) = k_L a t$$

where

$$E = \frac{C_t - C_o}{C_\infty - C_o}$$

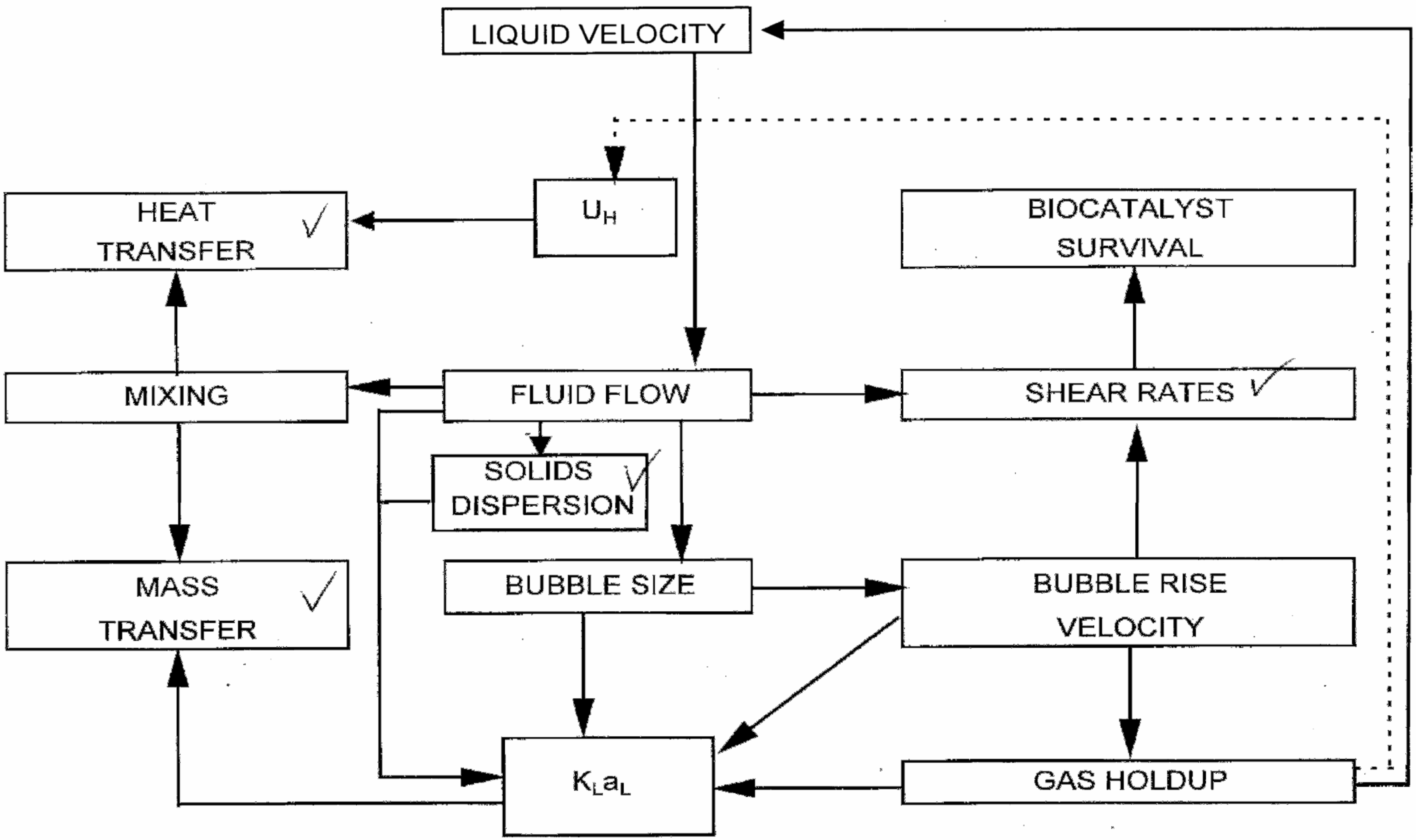
Continuous Processes

$$\frac{1}{1-E'} = \frac{k_L a}{D}$$

where

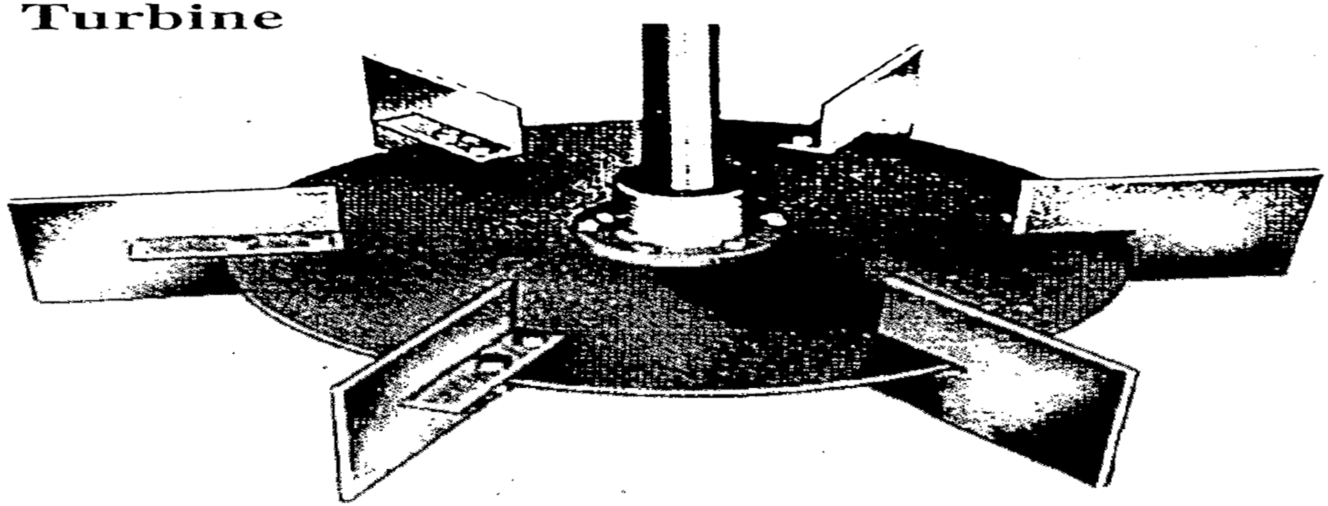
$$E' = \frac{C_{out} - C_{in}}{C_{\infty} - C_{in}}$$

Effects of Liquid Circulation on Bioreactor Design

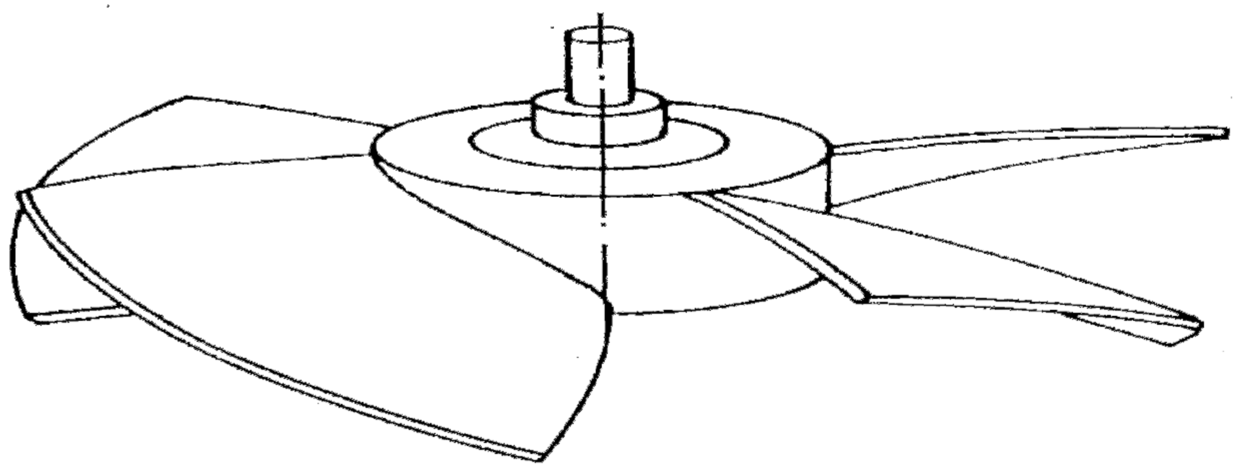


Agitators

Rushton Turbine



Prochem Maxflo Axial Flow Impeller



Gravity-induced interparticle transfer

$$k_L \, Sc^{2/3} = 0.31 \left(\frac{\Delta \varrho \, \mu g}{\varrho^2} \right)^{1/3}$$

Isotropic turbulence-driven dispersion

$$d_{Be} = 0.7 \frac{\sigma^{0.6}}{(P/V)^{0.4} \rho_L^{0.2}} \left(\frac{\mu_{app}}{\mu_g} \right)^{0.1} \qquad \text{in meters}$$

Prediction of Liquid Circulation Rate

$$U_{Lr} = \left[\frac{2 g h_D (\varepsilon_r - \varepsilon_d)}{\frac{K_T}{(1-\varepsilon_r)^2} + K_B \left(\frac{A_r}{A_d} \right)^2 \frac{1}{(1-\varepsilon_d)^2}} \right]^{0.5}.$$

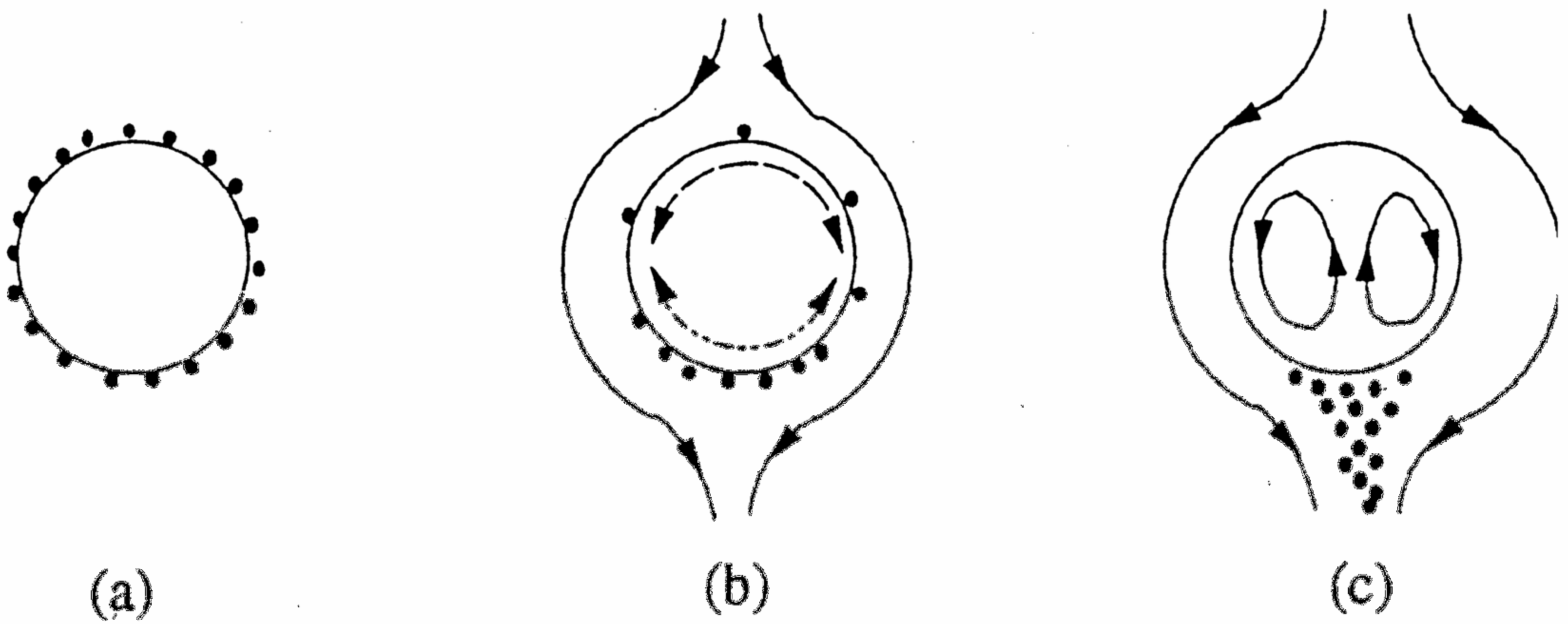
- Applies to

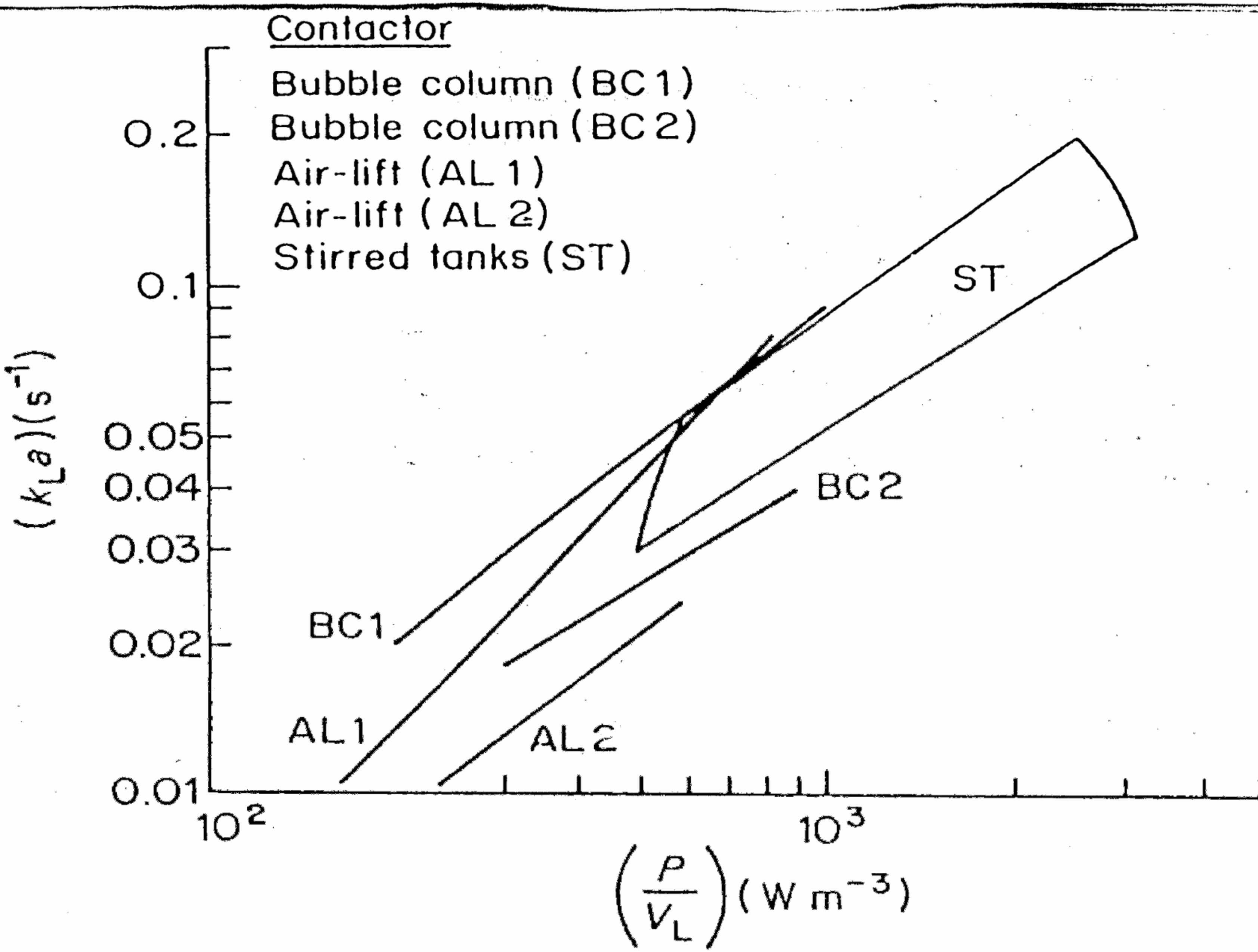
External-loop and
Internal-loop airlift bioreactors

Shear rate in mechanically-stirred tanks

$$\mu_{app} = K(\gamma)^{n-1} = \frac{K}{(BN)^{1-n}} \left(\frac{3n+1}{4n} \right)^n$$

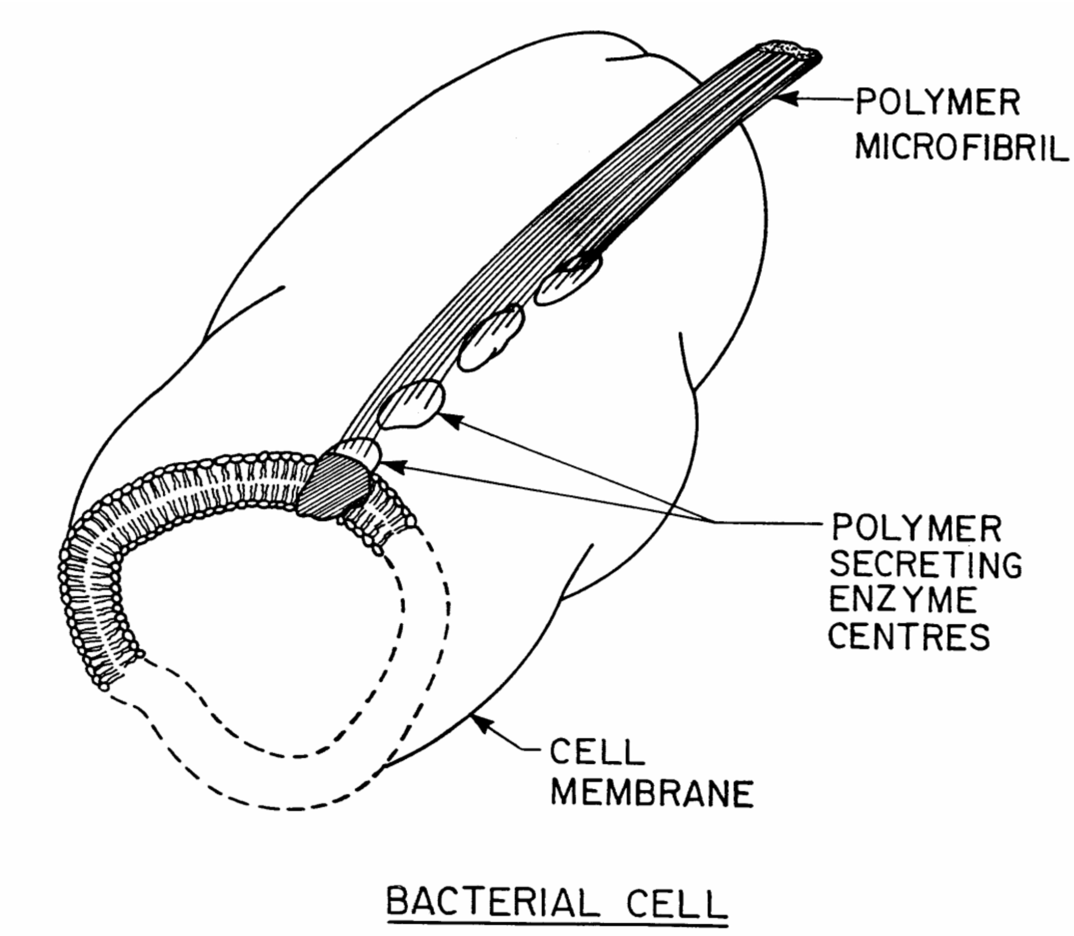
Bubble Interfacial Phenomena





Oxygen transfer coefficients (cell-free systems) for various bioreactors.

Morphology of *Cellulon* host



Cell growth and MAb production by Chitosan Occlusion invention compared to suspension culture (2L)

	Fibre Embodiment	Classical Suspension
Cell Density (cells/mL)	2.8×10^6	4.8×10^5
MAb Titre (ug/mL)	20	30
Productivity (ug/mL. hr)	0.71	0.19

Specific Protease Activities (*A. niger*)

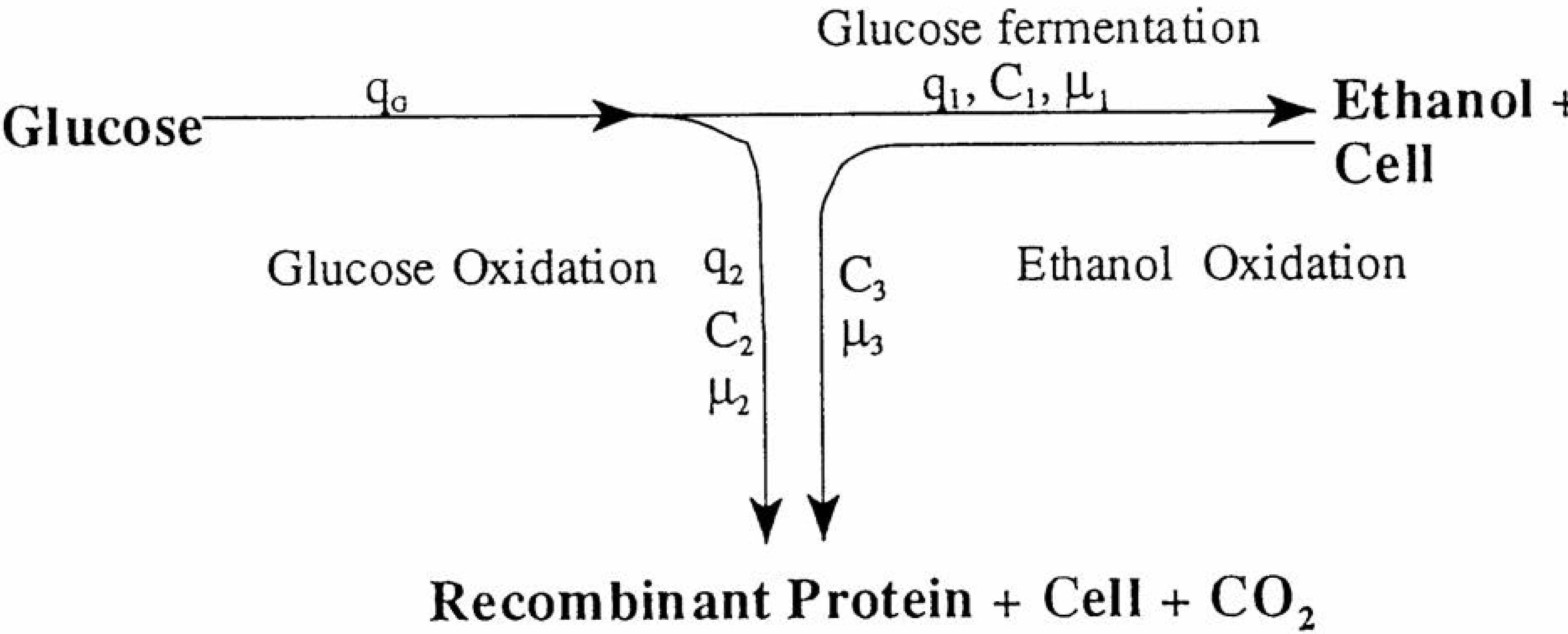
(a) in 15 L STR Bioreactor

Filamentous	355 u/g	(2.4)
Pulpy	284 u/g	(1.91)
Pellets	149 u/g	(1.0)

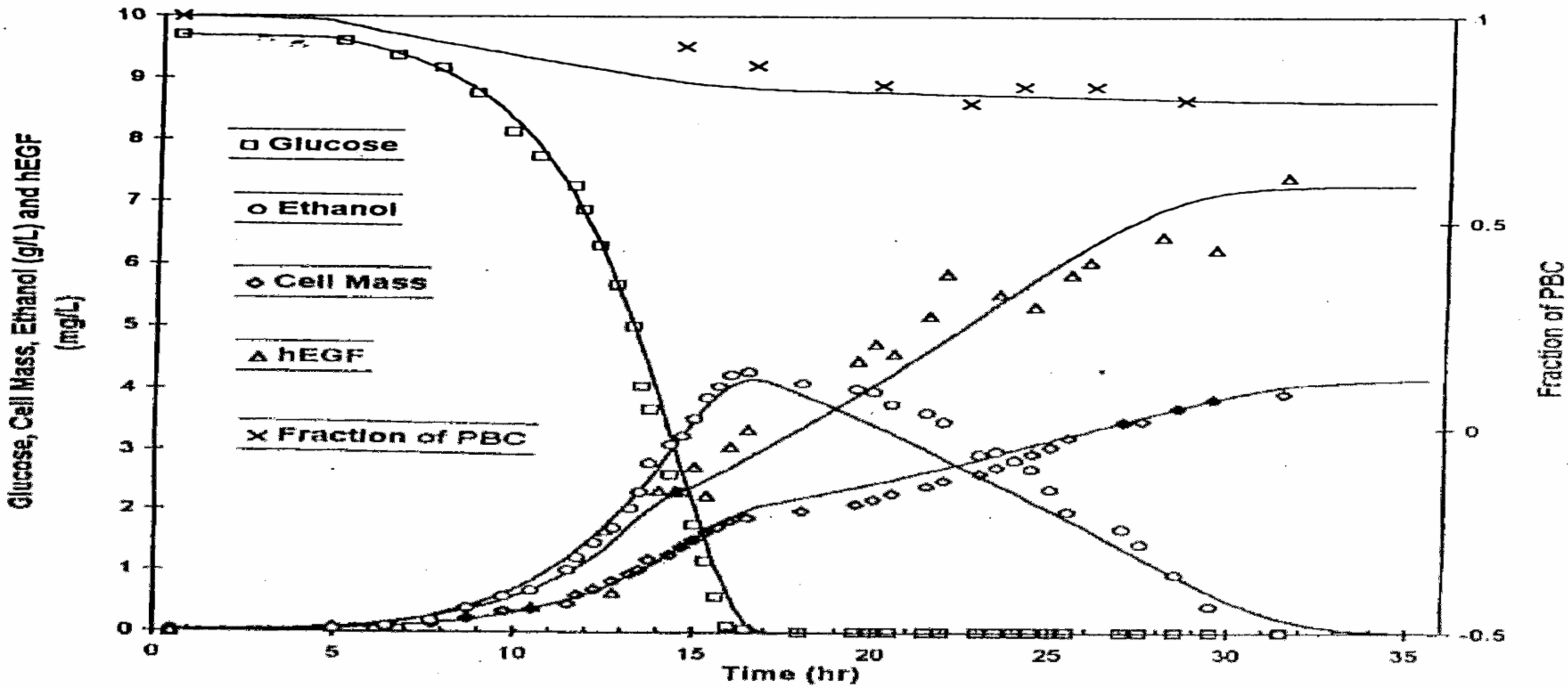
(b) in 3 L AL Bioreactor

Free Suspension		(5.9)
Immobilized SS Sheets		(1.0)

Simplified Yeast Metabolism



Application to Recombinant *S. cerevisiae* Producing Human Epidermal Growth Factor

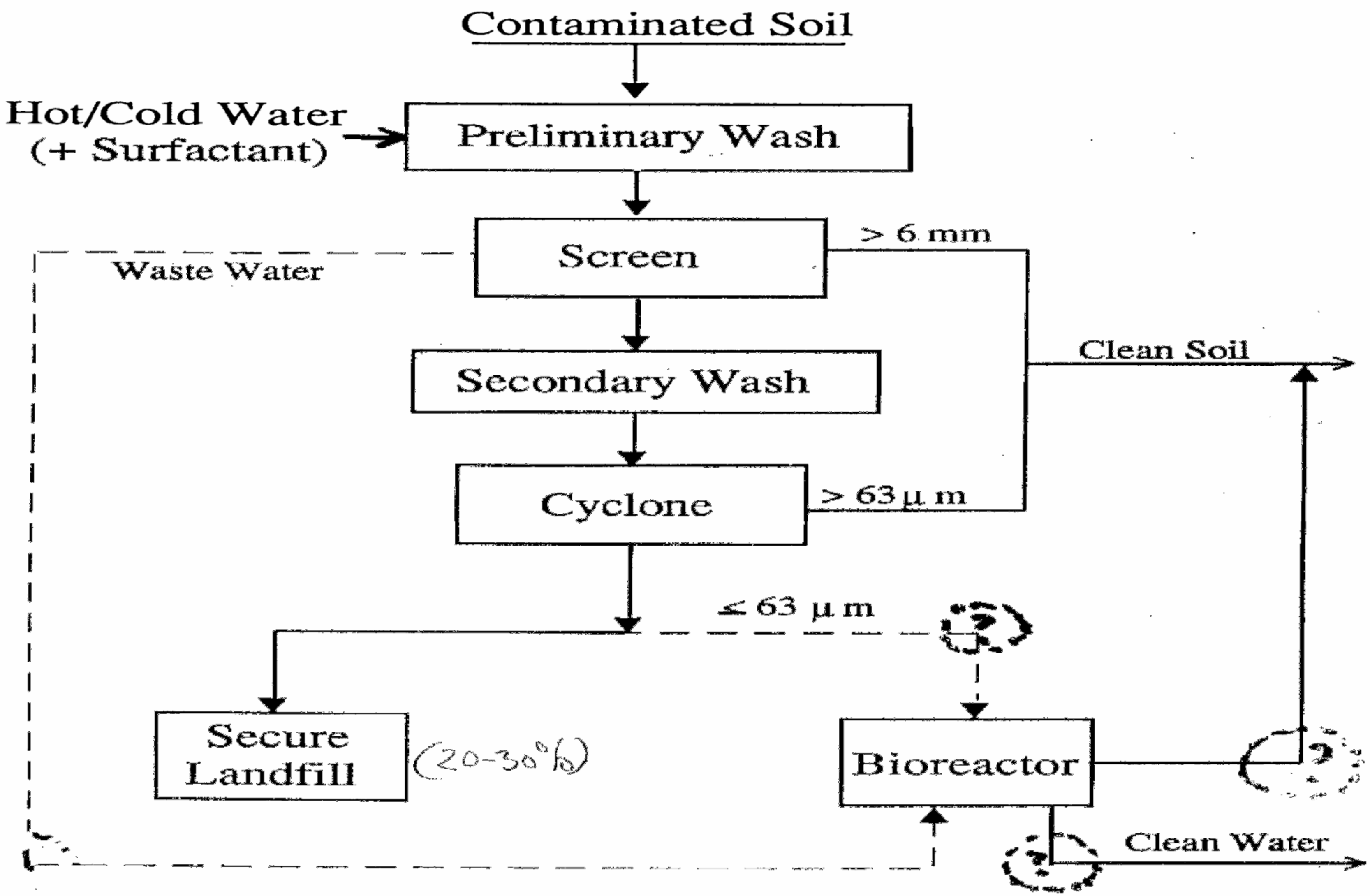


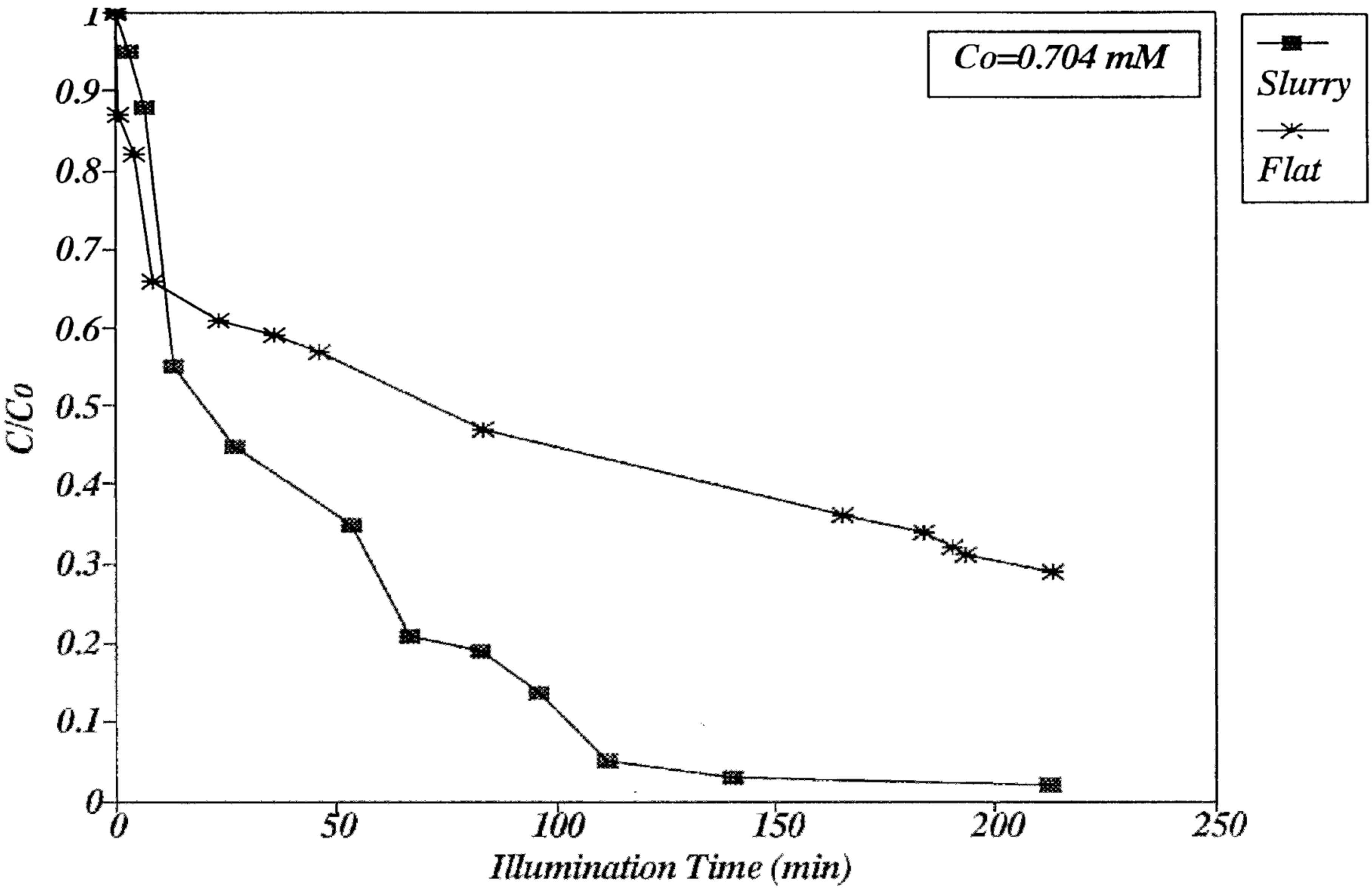
Coppella and Dhurjati, *Biotechnol. Bioeng.*, 35, 356 (1990)

Model Parameters

Coppella and Dhurjati model	48 (8 adjustable)
Our model	17 (4 adjustable)

Current Soil Washing Technology and Potential Improvements

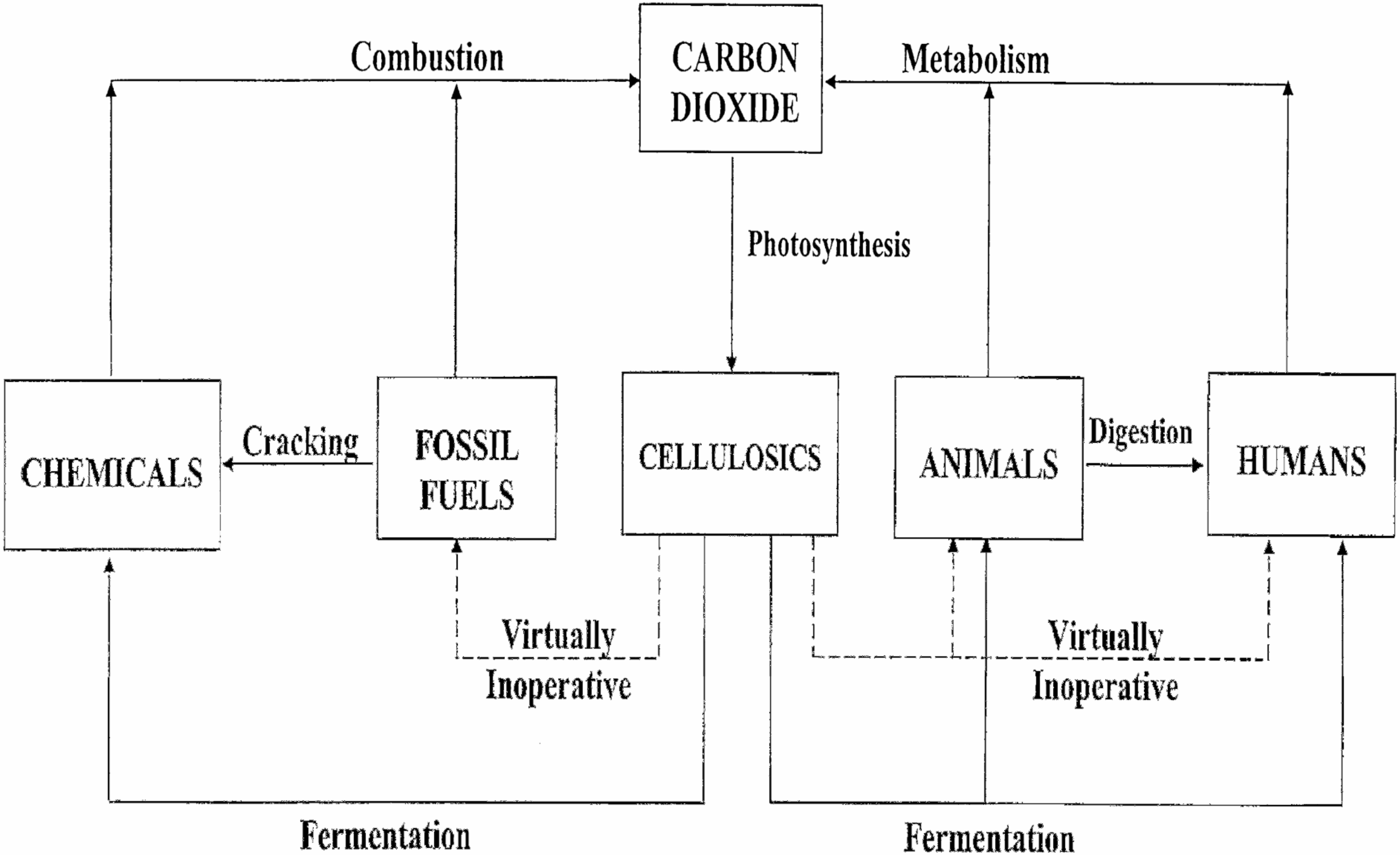




Photocatalytic Degradation of 1,4-dioxane (DIOX) in a small batch slurry photoreactor ([TiO2]=1 g/L) and Flat Plate Photoreactor

"The biggest single challenge of the 21st century will be ... to meet the food needs of the world population without damaging the environment"

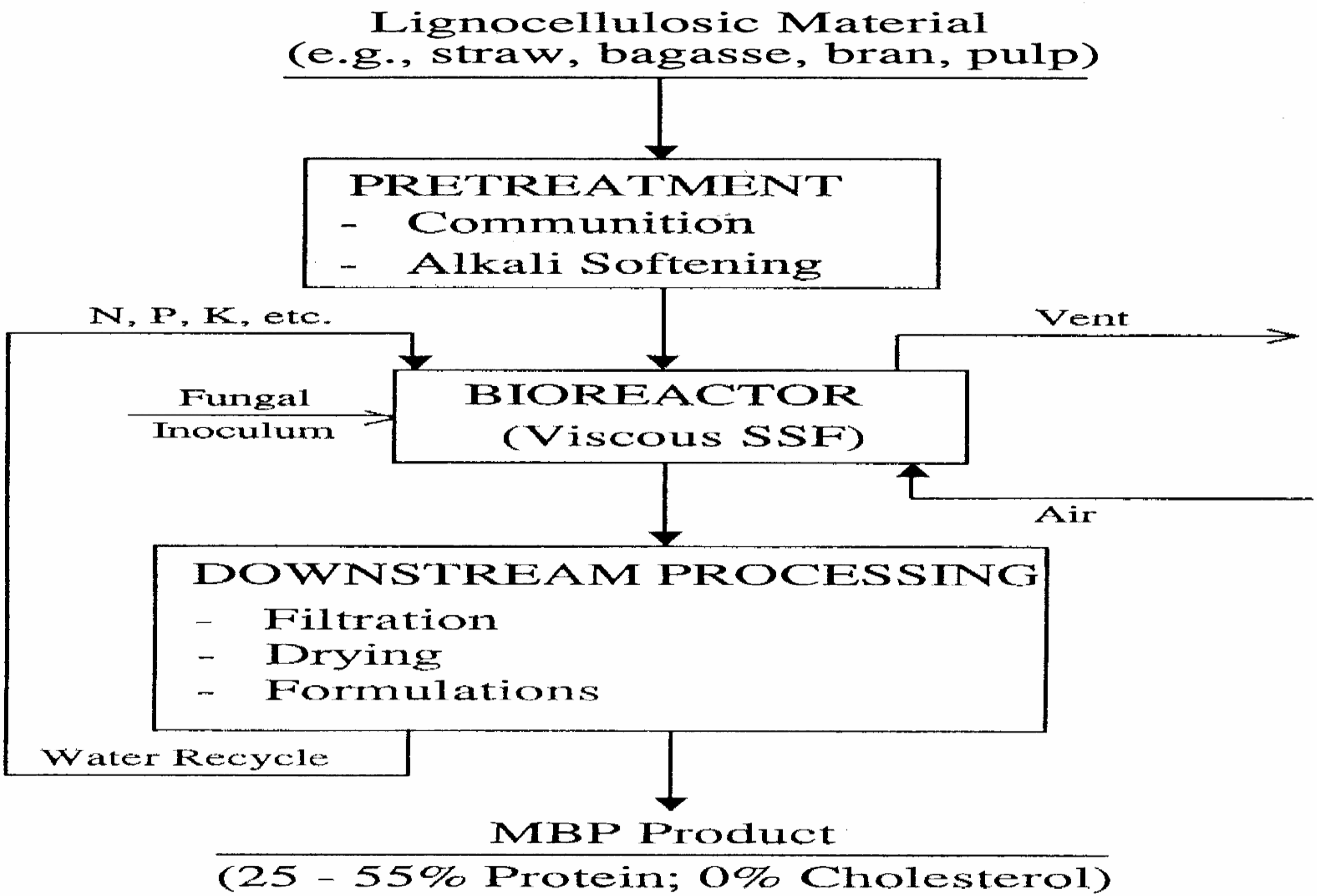
Genetic Engineering News (July/95)



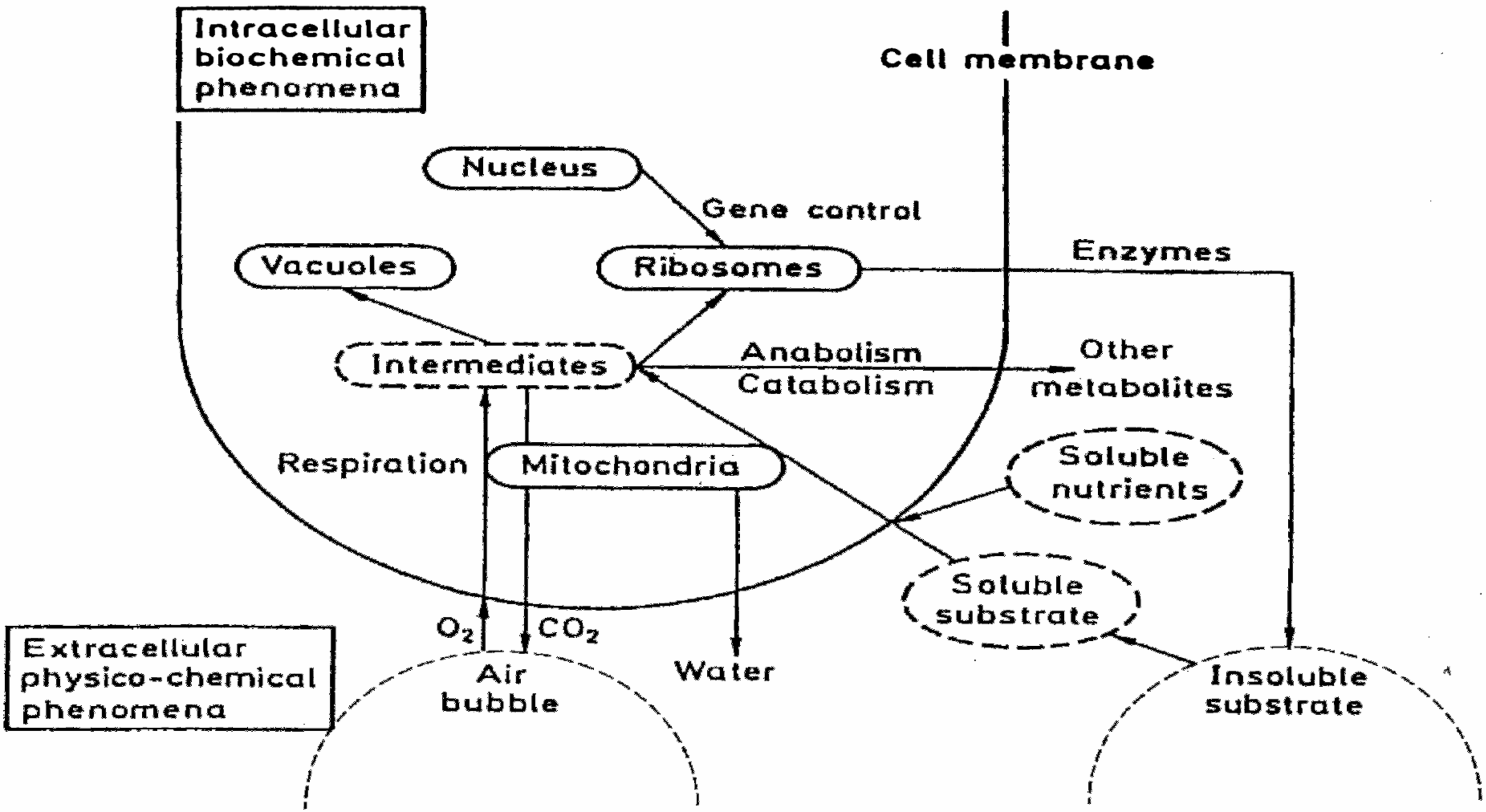
BIOMASS REFINERY SCHEMES TO RECYCLE RENEWABLE RESOURCES FOR FOOD AND FUEL PRODUCTION

THE MYCOPROTEIN PROCESS

(Coupled Bioremediation/Bioproduction)



Interactions Among Metabolic and Transport Pathways



NUTRITIONAL ANALYSIS per 100g

	Myco-Protein product	Pie Beef
kcals	100 kcals	245 kcals
kjoules	425 kjoules	1010 kjoules
Veg fats	4g	nil
Animal fats	nil	19g
Cholesterol	nil	20 mg
Protein	14g	18g
Dietary fibre	7g	nil

J Sainsbury plc Stamford Street London SE1 9LL

Science Push → **Potential Bottleneck** → **Market Pull**

1. Techno-economics

1.1 Inadequate market share
1.2 Process engineering constraints
1.3 Unskilled human resources

2. Socio-political

2.1 Lack of capital
2.2 Regulatory issues
2.3 Public apprehension

Barriers to Commercial Biotechnology

Health-Related Bioprocessing Research

- Biopharmaceuticals
- Contaminated Water
- Microbial Biomass Proteins

- Biotechnology Relevance
- Bioreactor Constraints
- Geopolitics

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The Multidisciplinary Nature and Scope of the Network

Name	Upstream				Bioreactor					Downstream			
	1	2	3	4	1	2	3	4	5	1	2	3	4
Anderson							X	X				X	
Butler	X		X				X						
Garnier			X		X	X		X					
Glick	X	X		X									
Guillemette		X		X							X		X
Haynes										X			X
Hayward								X	X				X
Jervis					X		X						
Jolicoeur		X				X		X				X	
Legge				X						X			X
Legros										X			
Moo-Young					X		X	X				X	
Moresoli											X		
Perrier									X			X	
Scharer						X		X	X	X			
Ward	X						X						
Amersham		X	X	X					X	X	X	X	X
Apotex	X			X			X			X			
Aventis		X	X		X	X		X	X		X	X	X
BRI-NRC	X	X	X		X	X	X	X	X	X	X	X	X
Cangene							X			X	X		
DSM Biologics	X	X		X	X			X		X	X		
NPS Pharma	X	X			X			X		X		X	

Systems Constraints

- Shear Sensitivity of Materials
- Protease Degradation of Products
- Genetic Instability of Host Organisms
- Pseudoplastic Hindrance of Mixing
- Substrate Recalcitrance

Bioreactor Optimization

- Immobilized-biocatalysts
- Slurry aeration compromise
- Fed-batch protocols
- Pretreatment enhancement

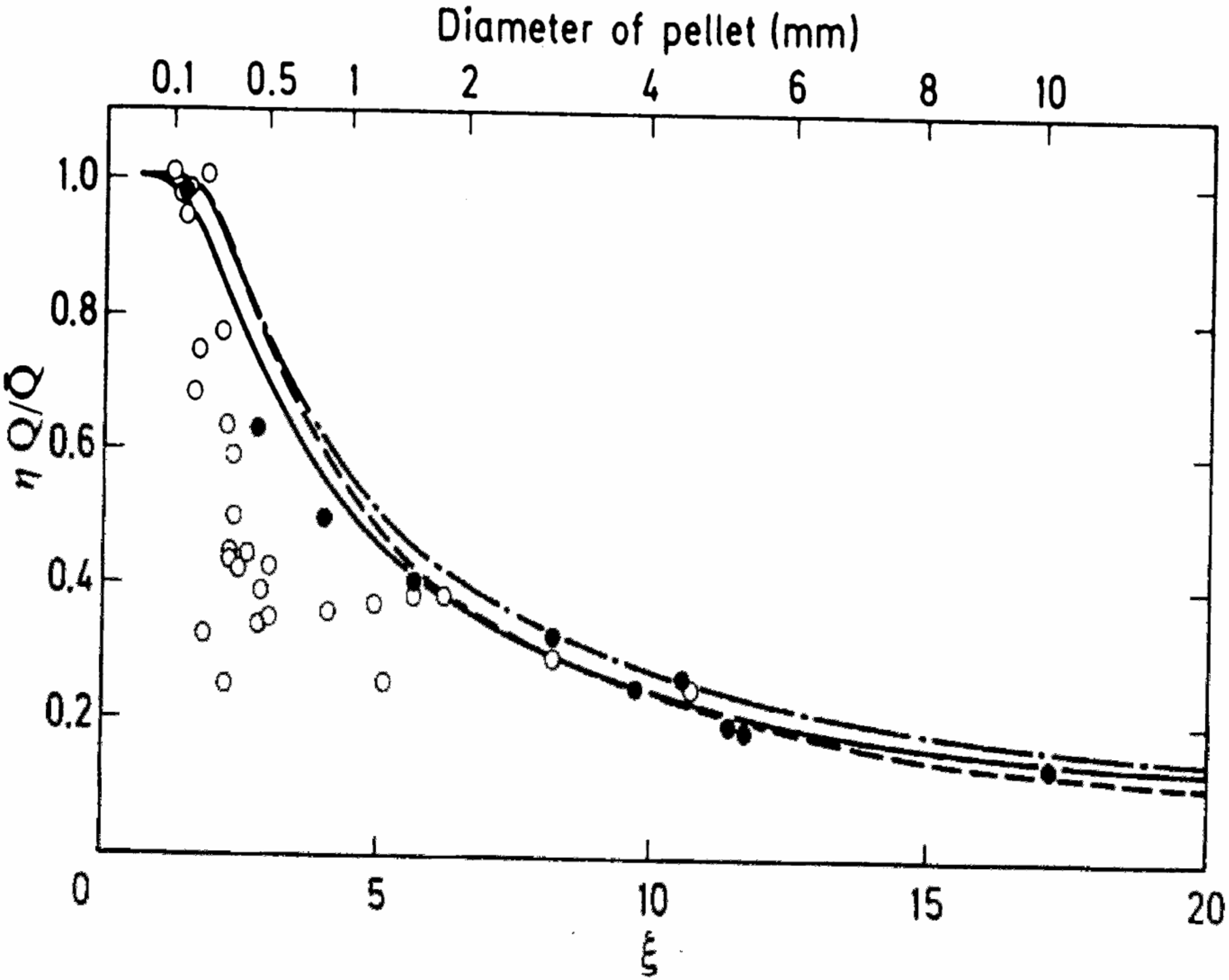

Fig. 12 Oxygen transfer in mold pellets. Comparison between theoretical curves relating η to ξ for cases a (·—·—·—), b (---------) and c (———). (○) Data of Yano et al.[179], (●) Data of Kobayashi et al.[85], $C = 1.9 \times 10^{-4}$ (μmol mm^{-3} O_2); $K_m = 3.0 \times 10^{-6}$ (μmol mg^{-1} min^{-2} O_2).

$\xi = R\sqrt{\varrho_m \bar{Q}/2D_r\bar{C}}$

BIOMANUFACTURING AND BIOREMEDIATION

Systems for drugs, food and the environment

Watfood Invention re-visited

DVD Video