Hannon J.R, Bakker A., Lynd L.R., Wyman C.E. (2007). Comparing the Scale-Up of Anaerobic and Aerobic Processes. Presented at the Annual Meeting of the American Institute of Chemical Engineers, Salt Lake City, Utah, November 8, 2007.

Comparing the Scale-Up of Anaerobic and Aerobic Processes

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Salt Lake City, Utah
November 8, 2007

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[2] University of California at Riverside

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Growth Of Anaerobic Processes

- Historically –scale up of aerobic processes
  - Fuel to Food processes – ICI, Ltd.
  - Scale-up was a significant engineering challenge
  - Challenges include heat and oxygen transfer
  - Scale-up techniques – combination of art & science
- Future –scale up of anaerobic processes
  - Current corn-to-ethanol plants (automotive fuel production)
  - Future cellulosic biomass-to-ethanol plants
  - Although anaerobic, scale is much larger than for typical aerobic systems
- Benefits of Cellulosic Biomass
  - Environmental, Economic, Energy Security
  - No commercial scale cellulose-to-ethanol process exists (yet)

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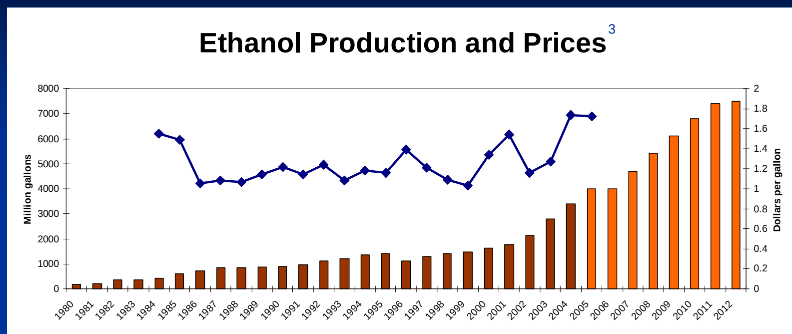
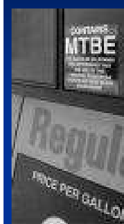
Ethanol Growth



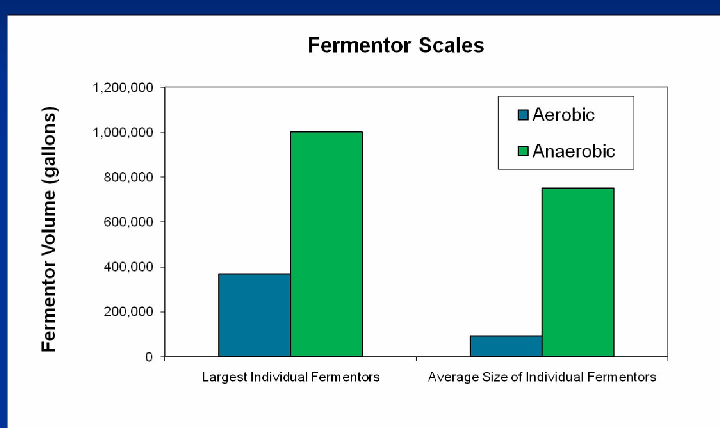


"Tonight, I ask Congress to join me in pursuing a great goal. Let us build on the work we've done and reduce gasoline usage in the United States by 20 percent in the next 10 years. When we do that we will have cut our total imports by the equivalent of three-quarters of all the oil we now import from the Middle East. **To reach this goal, we must increase the supply of alternative fuels, by setting a mandatory fuels standard to require 35 billion gallons of renewable and alternative fuels in 2017** -- and that is nearly five times the current target. "

- George Bush, State of Union Address, Jan 23 2007

3. USDA, 2006

Magnitude of Scale Differences for Anaerobic and Aerobic Processes



- Corn-to-ethanol plant typically contain 4-10 fermentors where aerobic plants have 1-2 making the differences even larger

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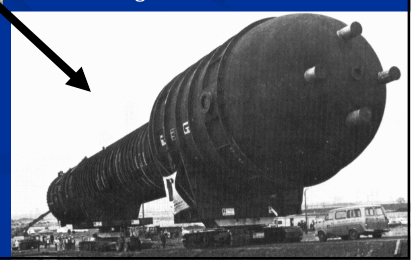
Objectives

- Examine the differences between scaling-up anaerobic and aerobic processes.
- Is one scale-up more challenging than the other and why?
- What additional scale-up challenges are presented with the larger overall volumes encountered with anaerobic fermentors?

Large Anaerobic Fermentors

Large Aerobic Fermentors



Investigation Pathway

Anaerobic Fermentation

$C_6H_{12}O_6$ --> $2C_2H_5OH + 2CO_2$ + $\boxed{\text{Heat}}$ + cells

Aerobic Fermentation

$C_6H_{12}O_6 + 6O_2$ --> $6CO_2 + 6H_2O$ + $\boxed{\text{Heat}}$ + cells

Targets

Seek to compare:

- Heat generation
- Reactant residence time
- Predictions for scale-up by CFD versus traditional methods

Investigation Pathway

Anaerobic Fermentation

$C_6H_{12}O_6$ --> $2C_2H_5OH + 2CO_2$
+ $\boxed{\text{Heat}}$ + cells

Aerobic Fermentation

$C_6H_{12}O_6 + 6O_2$ --> $6CO_2 + 6H_2O$
+ $\boxed{\text{Heat}}$ + cells

Targets

- Heat generation comparison
- Reactant residence time
- Scaling-up with CFD versus traditional methods

Heat Generation Comparison[4]

Anaerobic Cases								
Vessel Information			**Vessel Information**			**Vessel Information**		
H	0.169	m	H	1.69	m	H	16.9	m
D	0.169	m	D	1.69	m	D	16.9	m
SA	0.135	m^2	SA	13.45	m^2	SA	1345.2	m^2
Volume	1.00	gallons	Volume	1,000	gallons	Volume	1,000,000	gallons
SA / Volume	35.5		SA / Volume	3.55		SA / Volume	0.36	
Heat Generated			**Heat Generated**			**Heat Generated**		
Initial Glucose	100	g/L	Initial Glucose	100	g/L	Initial Glucose	100	g/L
Final Glucose	0	g/L	Final Glucose	0	g/L	Final Glucose	0	g/L
Time	10	hours	Time	10	hours	Time	10	hours
Δ Glucose	2.10	moles	Δ Glucose	2,100	moles	Δ Glucose	2,100,000	moles
Heat Release (1)	235	kJ/mole	Heat Release (1)	235	kJ/mole	Heat Release (1)	235	kJ/mole
Total Heat Rel	3.63	W/L	Total Heat Rel	3.6	W/L	Total Heat Rel	3.63	W/L
	13.7	Watts		13700	Watts		13,710,000	Watts
Cooling Requirements			**Cooling Requirements**			**Cooling Requirements**		
U (air/outside)	25	W/m^2C	U (air/outside)	25	W/m^2C	U (air/outside)	25	W/m^2C
Del T	3.91	C	Del T	20	C	Del T	20	C
Q (outside)	13.15	W/m^2	Q (outside)	6,726	W/m^2	Q (outside)	672,622	W/m^2
# Cooling tubes	0	#	# Cooling tubes	3	#	# Cooling tubes	249	#
Diameter	0.0065	m	Diameter	0.05	m	Diameter	0.11	m
Height	0.152	m	Height	1.52	m	Height	15.2	m
Surface Area	0.003	m^2	Surface Area	0.24	m^2	Surface Area	5.25	m^2
U (cooling coils)	500	W/m^2C	U (cooling coils)	500	W/m^2C	U (cooling coils)	500	W/m^2C
Q (coils)	0.00	Watts	Q (coils)	7,166	Watts	Q (coils)	13,084,720	Watts
Q (outside)	95.86	%	Q (outside)	49.10	%	Q (outside)	4.91	%
Q (inside coils)	0.00	%	Q (inside coils)	52.30	%	Q (inside coils)	95.44	%

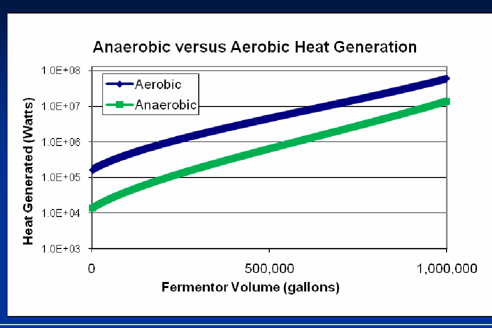
http://www.msu.edu/course/mmg/301/lec19.pdf

Heat Generation Comparison[5]

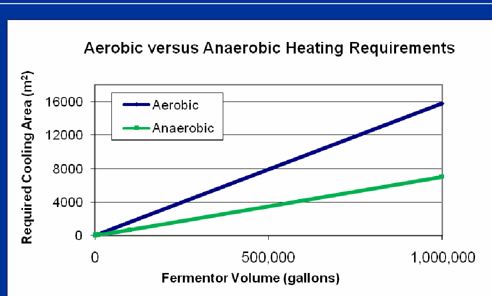
Aerobic Scale-Up Scenarios								
Vessel Information			**Vessel Information**			**Vessel Information**		
H	0.27	m	H	2.7	m	H	27	m
D	0.135	m	D	1.35	m	D	13.5	m
Surf. Area (SA)	0.143	m^2	Surf. Area (SA)	14.31	m^2	Surf. Area (SA)	1431.4	m^2
Volume	1.00	gallons	Volume	1,000	gallons	Volume	1,020,000	gallons
SA / Volume	37.04		SA / Volume	3.70		SA / Volume	0.37	
Heat Generated			**Heat Generated**			**Heat Generated**		
Initial Glucose	100	g/L	Initial Glucose	100	g/L	Initial Glucose	100	g/L
Final Glucose	0	g/L	Final Glucose	0	g/L	Final Glucose	0	g/L
Time	10	hours	Time	10	hours	Time	10	hours
Δ Glucose	2.1	moles	Δ Glucose	2,100	moles	Δ Glucose	2,142,000	moles
Heat Release	2840	kJ/mole	Heat Release	2840	kJ/mole	Heat Release	2840	kJ/mole
Total Heat Rel	43.83	W/L	Total Heat Rel	43.83	W/L	Total Heat Rel	43.8	W/L
	166	Watts		165,667	Watts		168,980,000	Watts
Cooling Requirements			**Cooling Requirements**			**Cooling Requirements**		
U (air/outside)	25	W/m^2C	U (air/outside)	25	W/m^2C	U (air/outside)	25	W/m^2C
Del T	20	C	Del T	20	C	Del T	20	C
Q (outside)	71.6	W/m^2	Q (outside)	7,157	W/m^2	Q (outside)	715,694	W/m^2
# Cooling tubes	2	#	# Cooling tubes	42	#	# Cooling tubes	2004	#
Diameter	0.0065	m	Diameter	0.05	m	Diameter	0.11	m
Height	0.243	m	Height	2.43	m	Height	24.3	m
Surface Area	0.0050	m^2	Surface Area	0.3817	m^2	Surface Area	8.3975	m^2
U (cooling coils)	500	W/m^2C	U (cooling coils)	500	W/m^2C	U (cooling coils)	500	W/m^2C
Q (coils)	100	Watts	Q (coils)	160,320	Watts	Q (coils)	168,285,000	Watts
Q (outside)	43.2	%	Q (outside)	4.3	%	Q (outside)	0.4	%
Q (inside coils)	60.4	%	Q (inside coils)	96.8	%	Q (inside coils)	99.6	%

 www.cbu.edu/~esalgado/BIOL111/chapter09.doc

Heat Generation Comparison

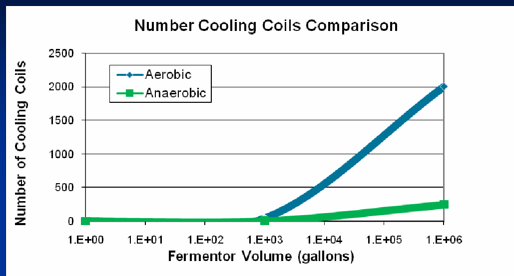


- Heat generation is higher in aerobic versus anaerobic case making this aspect of scale-up more challenging

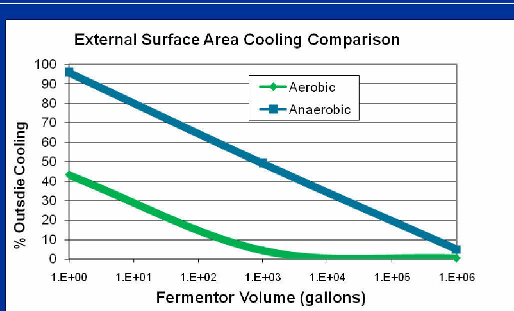


- Surface area for cooling typically done internally for aerobic processes due to constant oxygen demand, anaerobic can be external or internal

Cooling Requirements



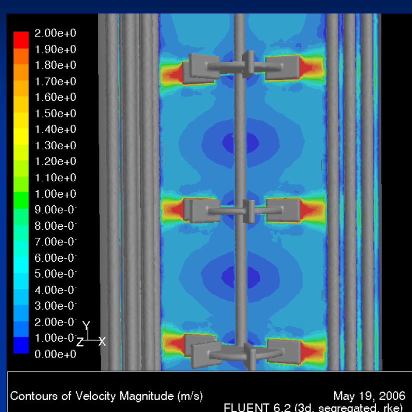
- Internal cooling coils may disrupt flow paths, decreasing heat transfer and pose contamination / cleaning issues
- Anaerobic fermentors can be cooled externally minimizing the above issues



- More relative cooling can be accomplished in anaerobic versus aerobic processes
- Significant cooling is accomplished for both at the small scale via outside walls and surface
- Additional cooling not required until pilot & certainly large scale fermentation

Aerobic Scale-Up

Trade-offs with different impeller geometries

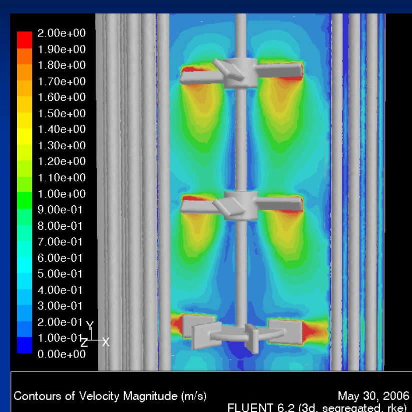


Bulk Velocity = 0.43 m/s

Stationary Zone = 0.39 m/s

Mixing Time = 60 sec

- More heat transfer but larger oxygen gradients using 3 Ruston impellers. Also Power consumption 2x.



Bulk Velocity = 0.41 m/s

Stationary Zone = 0.31 m/s

Mixing Time = 28 sec

- Less heat transfer but smaller oxygen gradients using 2 PBT, 1 Rushton impellers

Investigation Pathway

Anaerobic Fermentation

$C_6H_{12}O_6$ --> $2C_2H_5OH + 2CO_2$ + $\boxed{\text{Heat}}$ + cells

Aerobic Fermentation

$C_6H_{12}O_6 + 6O_2$ --> $6CO_2 + 6H_2O$ + $\boxed{\text{Heat}}$ + cells

Targets

- Heat generation comparison
- Reactant residence time
- Scaling-up with CFD versus traditional methods

Residence Time Comparison

Large Anaerobic Fermentors (ICM)

240 g Glu/L*hr feed rate

for 48 hour reaction time

Residence time of Glucose

= (2.4 g/L)/(5 g/L*hr) ~ 1700 sec

Mixing Time ~ 300 sec

Mixing time is fast compared to residence time

Large Aerobic Fermentors

OTR ~ 150 mM/L*hr, 10 % Sat.

OTR =4.8 g/L*hr = 80 mg/L*min

OTR = $k_L a$ (C* - C_L)

C* = 9 mg/L, C_L = 0.9 mg/L

kLa = OTR/(C* - C_L)

= (80 mg/L*hr)/(8 mg/L) = 10 min $^{-1}$

Residence of O_2 in broth

= (1 mg/L)/(80 mg/L*min) ~ 1 sec

Mixing Time ~ 300 sec

Residence time is rapid compared to mixing time

Residence Time

Substrate Limitations

Anaerobic Fermentors	Aerobic Fermentors
Da = Mixing Time / Reaction Time	Da = Mixing Time / Reaction Time
Da = 15 s / 500 s ~ 0.03	Da = 15 s / 1 s ~ 15
Very well mixed for reaction	Not well mixed for reaction
	1 / kLa = Measure of Oxygen transfer
	Mass Transfer = 1/0.1 = 10 sec
Blend time (pilot scale) = 15 sec Blend time < Reaction Time (No glucose Gradients)	Blend time (pilot scale) = 15 sec Blend time ~ Mass Transfer (Small oxygen Gradients)
Blend time (large scale) = 60 sec Blend time < Reaction Time (No glucose Gradients)	Blend time (large scale) = 60 sec Blend time > Mass Transfer (Large oxygen Gradients)[6]

Ossterhuis, N.M.G.; Koosen, N.W.F. "Oxygen Transfer in a Production Scale Bioreactor" Chem. Eng. Res. Des., 61, 308 (1983)

Aerobic Scale-Up

Literature Article[7]

Vessel Information

T = 0.4 m

Z = 1.2 m

D = 0.16 m

Cell Count = 500,000

Where

T = Tank Diameter

Z = Liquid Height

D = Impeller Diameter

Small Scale Operation

RPM = 216

Po = 5.0

P/V = 500 W/m^3

Volume = 39 gallons

Gas Hold-up = 8%

S. Gas Velocity = 1.5 cm/s (0.77 vvm)

Large Scale Operation

RPM = 46.5

Po = 5.0

P/V = 500 W/m^3

Volume = 39,000 gallons

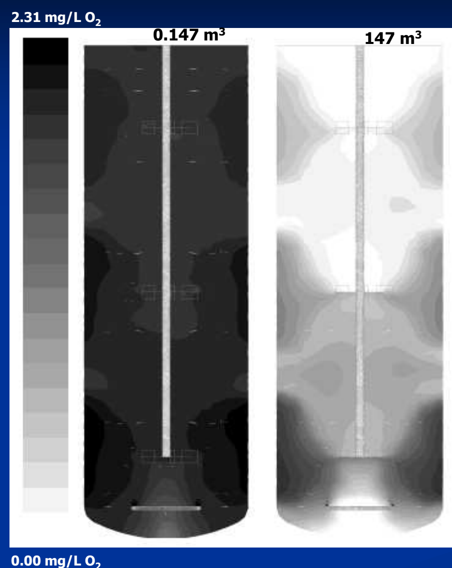
Gas Hold-up = 8%

S. Gas Velocity = 1.5 cm/s (0.077 vvm)

- **Bubble velocity & size increases w/ less pressure**

Schutze, J.; Hengstler, J. "Assessing Aerated Bioreactor Performance using CFD" 12th European Conference on Mixing, Bologna, 27-30 June 2006

Aerobic Scale-Up



- Small-scale (40 gallon) results

  Gradients (up to 0.40 mg/L)

  (~ 18 % of Reactant conc.)

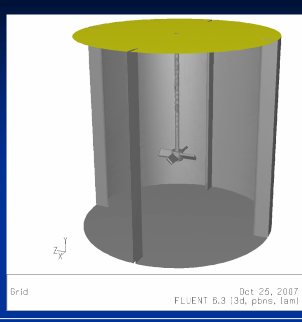
- Larger-scale (40,000 gallon) results

  Gradients (up to 2.2 g/L)

  (~ 90 % of Reactant conc.)

- **Large oxygen gradients recognized upon scale-up**

Anaerobic Scale-Up



Vessel Information

T = H = Z = 1.7 m
D/T = 0.285
C = 0.3 T
Volume = 1,000 gallons

Where

T = Tank Diameter
H = Tank Height
Z = Liquid Height
D = Impeller Diameter
C = Off bottom clearance

Pilot Scale

T = H = 1.7 m
Volume = 3.85 m^3
Volume = 1,000 gallons
Tip Speed = 3.0 m/s
RPM = 100
Power = 300 W
Re = 540,000

P/V Constant

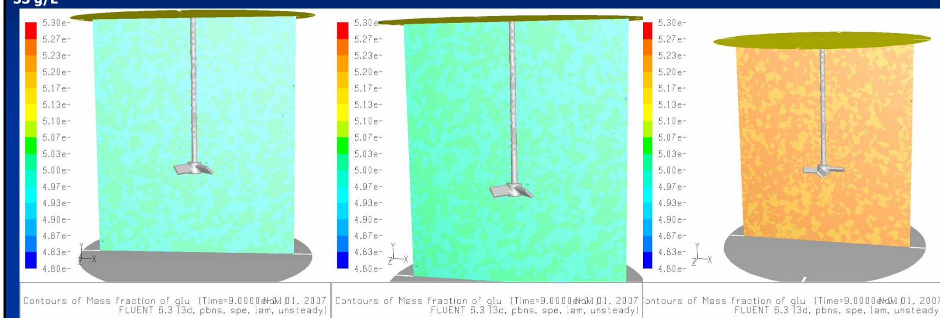
Large Scale

T = H = 17 m
Volume = 3,858 m^3
Volume = 1,000,000 gallons
Tip Speed = 6.5 m/s
RPM = 22
Power = 300,000 W
Re = 11,900,000

Anaerobic Scale-Up

- Small Scale = Volume=1 gallon
- Pilot Scale = 1,000 gallons
- Large Scale = 1,000,000 gallons

53 g/L



48 g/L

Small Scale	Pilot Scale	Large Scale
Gradients (up to 1 g/L)	Gradients (up to 1 g/L)	Gradients (up to 1.5 g/L)
(~ 2 % of Reactant conc.)	(~ 2 % of Reactant conc.)	(~ 3 % of Reactant conc.)

- **Small glucose gradients noticed for nearly all scales**

Investigation Pathway

Anaerobic Fermentation

$C_6H_{12}O_6$ --> $2C_2H_5OH + 2CO_2$ + $\boxed{\text{Heat}}$ + cells

Aerobic Fermentation

$C_6H_{12}O_6 + 6O_2$ --> $6CO_2 + 6H_2O$ + $\boxed{\text{Heat}}$ + cells

Targets

- Heat generation comparison
- Reactant residence time
- Scaling-up with CFD versus traditional methods

What Scale-up correlations cannot explain

Anaerobic Fermentation

- Constant Power/Volume [8]
- Mixing Pattern differences upon scale-up
- All fluid volume circulates through the impeller region
- Flow Field inside fermentor to locate "dead-zones"

Aerobic Fermentation

- Constant $k_L a$ [9]
- O_2(L) dispersion in small scale vessel
- O_2(L) dispersion in large scale vessel upon Scale-Up
- Flow Field inside fermentor (also with different vvm)

- Scale-up correlations are not all inclusive especially for large (1e6 gal) scale mixing tanks when you have case specific geometries, fluid behavior, heating, etc.
- CFD simulations can provide verification and additional information correlations cannot provide.

8 Ranade et al, Chem. Eng. Sci. 52 (24) (1997) 4473-4484
9 Bartholomew, W. H. (1960) Adv. Appl. Microbiol. 2:289

Anaerobic Scale-up Challenges

- **Larger fermentor volumes in anaerobic systems present new scale-up challenges**
  - Pressure effects on organism growth rates
  - Thorough mixing to minimize temperature gradients
  - Adequate mixing for solid suspensions to maximize mass transfer
- **These challenges can be carefully examined with a combination of using CFD, correlations and literature articles.**

Carbon Dioxide Effects

- Carbon dioxide pressure effects on cell growth[10]

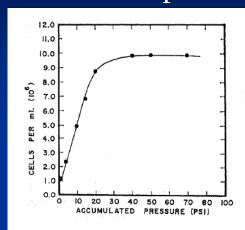
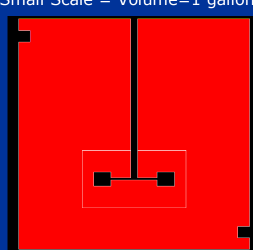


Table 2
Effects of Added N_2 or CO_2 Pressure on Growth of Saccharomyces cerevisiae *7752*

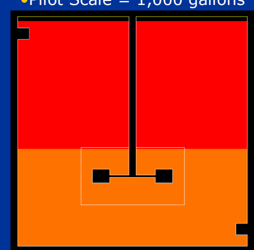
Treatment [a]	Growth rate (cell divisions/day)	Daughter cell buds [b] (% cells with a bud)	Dry weight [b] ($\mu g/ml \times 10^5$)	Metabolic Pressure [b] (psi)
Sealed control—no pressure added	6.22	12.9	65.0	16
40 psi N_2	6.16	12.7	66.0	15
40 psi CO_2	2.70	5.2	56.0	8

- Yeast growth ceases at 20 psig (~240,000 Pa)

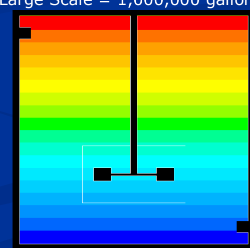
- Small Scale = Volume=1 gallon

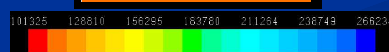


- Pilot Scale = 1,000 gallons



- Large Scale = 1,000,000 gallons



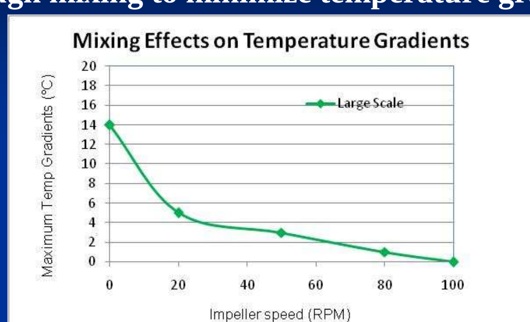


Pressures in Pascals (Pa)

Norton, Jane S.; Krauss, Robert W. *Plant & Cell Physiol.* 13: 139-149 (1972).

Anaerobic Scale-up Considerations

- **Thorough mixing to minimize temperature gradients**



- **Minimum mixing speed to ensure solid suspensions**
  - Zweitering Correlation

$$N_{js} = S\nu^{0.1}\left[\frac{g_c(\rho_s - \rho_l)}{\rho_l}\right]^{0.45} X^{0.13} d_p^{0.2} D^{-0.85}$$

  - For corn-to-ethanol: 8 RPM (large scale)
  - For cellulosic-to-ethanol: 4 RPM (large scale)

Discussion

- **Heat generation and substrate consumption is slower in anaerobic versus aerobic cases**
  - Because anaerobic fermentation broths can be cooled externally, external flat plate heat exchangers with a recirculation loop can be used to both cool and mix fermentors inexpensively
  - Lower substrate consumption rates in anaerobic fermentors allow for less intense mixing though must still suspend solids and minimize temp. gradients
- **Large(r) scale anaerobic fermentors**
  - Current maximum fluid height is nearly identical where dissolved carbon dioxide effects yeast growth rates.
  - Larger anaerobic vessels (>1 million gallons) are conceivable though carbon dioxide inhibition must be incorporated into kinetics along with contamination risks, structural strength, mixing.
  - CFD provides a very unique methodology to investigate mixing, heat transfer, and pressure effects that correlations and kinetics alone cannot answer.

Industrial Scale-up Survey

- **Conducted survey of 11 industrial scale-up experts**
  - Objective: To gain insight into issues that arise in large-scale fermentations that are not covered in academic publications which focus on smaller scales.
  - All industrial contacts are scale-up experts in aerobic processes, anaerobic processes, or both
- **Primary Questions asked**

1a)	How well established are scale-up methodologies for aerobic processes?
1b)	How well established are scale-up methodologies for anaerobic processes?
2a)	Is there a maximum volume for aerobic fermentors?
2b)	Is there a maximum volume for anaerobic fermentors?
3a)	What are reasonable scaling factors for aerobic scale-ups?
3b)	What are reasonable scaling factors for anaerobic scale-ups?
4)	Do you consider the difficulty of scaling up anaerobic to differ from aerobic?
5)	Are there any unresolved issues in scale-up?

Industrial Scale-up Survey

Scale-Up Expert	Question 1a	Question 1b	Question 2a	Question 2b	Question 3a	Question 3b	Question 4	Question 5
1	Not well	not well established	No limit	No limit	1000x (volume)	1000x (volume)	No difference	role of microturbulence
2	well established	not well established	350,000 gallons	1,000,000 gallons	60x (volume)	2000x to 20,000x (volume)	anaerobic easier	quasi aerobic, anaerobic reactors
3	well established	well established	Limited to to heat transfer	No limit if you can mix well	10,000x	100,000x	anaerobic much simpler	quasi aerobic, anaerobic reactors
4	not well established for large scale	not well established for large scale	80,000 gallons	No limit	(only scale down experience)	(only scale down experience)	Not sure	using CFD to investigate temp gradients in reactor
5	fairly well established, need factors for large-scale	fairly well established, need factors for large-scale	100,000 gallons (but getting larger)	1,000,000 gallons (but getting larger)	Not sure	1,000x (volume)	Anaerobic seems trivial	No unresolved issues
6	well established	Not well established	100,000 gallons	5,000,000 gallons (no real limit)	1,000x (volume)	100,000x (volume)	Aerobic more difficult but better understood	Microaeration tricky and feeding at multiple locations
7	Fairly well established (semi-art, semi-science)	Not sure	200,000 gallons	Not sure	1,000x (volume)	Not sure	Heard anaerobic was easier	No unresolved issues for aerobic
8	Not well established (can't depend on it)	Not well established (can't depend on it)	No limit (currently 160,000 gallons)	No limit (currently 1,000,000 gallons)	1,000x (volume)	Not sure	Aerobic more difficult, corn to ethanol easy	what is the optimal scale for a reactor
9	fairly well established, need factors for large-scale	fairly well established, need factors for large-scale	400,000 gallons	750,000 gallons	(borrow existing designs)	(borrow existing designs)	Aerobic certainly more difficult	stress on organism
10	well established	Not sure	350,000 gallons	Not sure	10x (volume)	500x (volume)	Not sure on comparison	establishing accurate scale-down models
11	Not sure	Not sure	Not sure	750,000 gallons	100x (volume)	1000x (volume)	Aerobic 2 to 10x more difficult	Be able to monitor cell growth and death in fermentor

Industrial Scale-up Survey Results

- **Questions asked**

1a)	How well established are scale-up methodologies for aerobic processes?
1b)	How well established are scale-up methodologies for anaerobic processes?
2a)	Is there a maximum volume for aerobic fermentors?
2b)	Is there a maximum volume for anaerobic fermentors?
3a)	What are reasonable scaling factors for aerobic scale-ups?
3b)	What are reasonable scaling factors for anaerobic scale-ups?
4)	Do you consider the difficulty of scaling up anaerobic to differ from aerobic?
5)	Are there any unresolved issues in scale-up?

- **Summary of answers**

Scale-Up Expert	Question 1a	Question 1b	Question 2a	Question 2b	Question 3a	Question 3b	Question 4	Question 5
Overall	Well established (4), fairly well (3), Not well (3), Not sure (1)	Well established (1), farily well (2), Not well (5), Not sure (3)	No limit (2), 300,000 gallons (3), 100,000 (3), less than 100,000 (1), Not sure (2)	No limit (5), 750,000 gallons (4), Not sure (2)	1,000x (5), 100x (2), 10x(1), Not sure (3)	100,000x (2), 10,000x (1), 1,000x (3), Not sure (4)	Aerobic more difficult (8), no difference (1), Not sure (2)	microaeration (3), microturbulence (1), CFD (1), other (4), No unresolved issues (2)

Summary & Conclusions

- **Anaerobic scale-ups differ from aerobic scale-ups**
  - Less heat is generated per unit glucose consumed
  - Heat generation can be removed externally
  - Glucose residence time is significantly longer than oxygen (almost hours versus seconds), thus more homogeneous distribution of reactants
  - Industrial experts seem to agree that aerobic scale-ups are more difficult, scale-up factors and overall volumes larger for anaerobic
- **Larger volume fermentors in anaerobic processes require careful examination to ensure**
  - Adequate mixing for solid suspensions (mass transfer)
  - Heat transfer to maintain optimal fermentation temperature and minimize gradients
  - Pressure effects on cell growth are incorporated

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