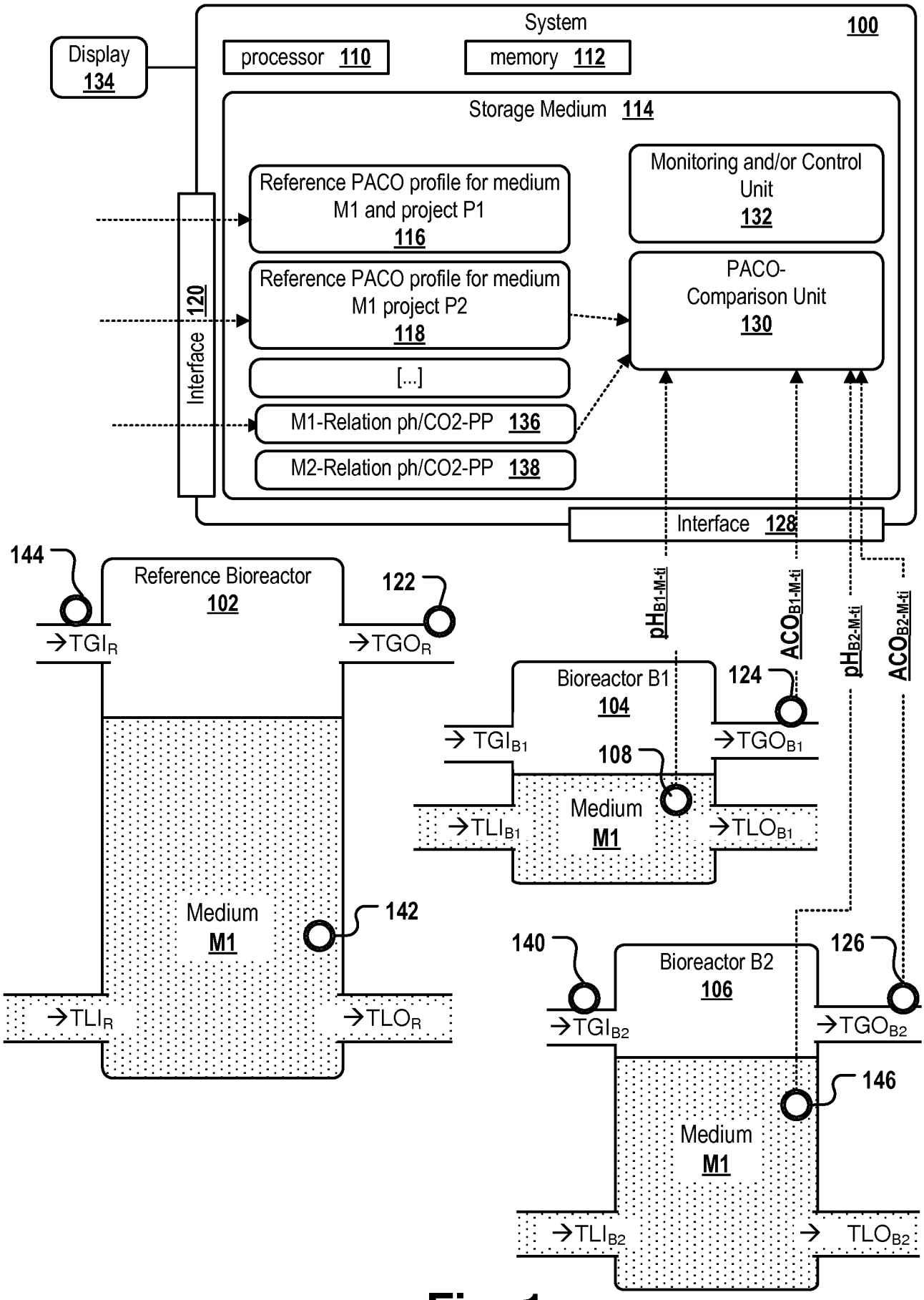
System
100
Display
134
processor 110
memory 112
Storage Medium 114
Reference PACO profile for medium M1 and project P1
116
Reference PACO profile for medium M1 project P2
118
[...]
M1-Relation ph/CO2-PP 136
M2-Relation ph/CO2-PP 138
Interface 120
Monitoring and/or Control Unit
132
PACO-Comparison Unit
130
Interface 128
144
Reference Bioreactor
102
122
→TGI$_R$
→TGO$_R$
Medium
M1
142
→TLI$_R$
→TLO$_R$
pH$_{B1-M-ti}$
ACO$_{B1-M-ti}$
pH$_{B2-M-ti}$
ACO$_{B2-M-ti}$
Bioreactor B1
104
124
→TGI$_{B1}$
→TGO$_{B1}$
108
Medium
M1
→TLI$_{B1}$
→TLO$_{B1}$
140
Bioreactor B2
106
126
→TGI$_{B2}$
→TGO$_{B2}$
146
Medium
M1
→TLI$_{B2}$
→ TLO$_{B2}$

Fig. 1

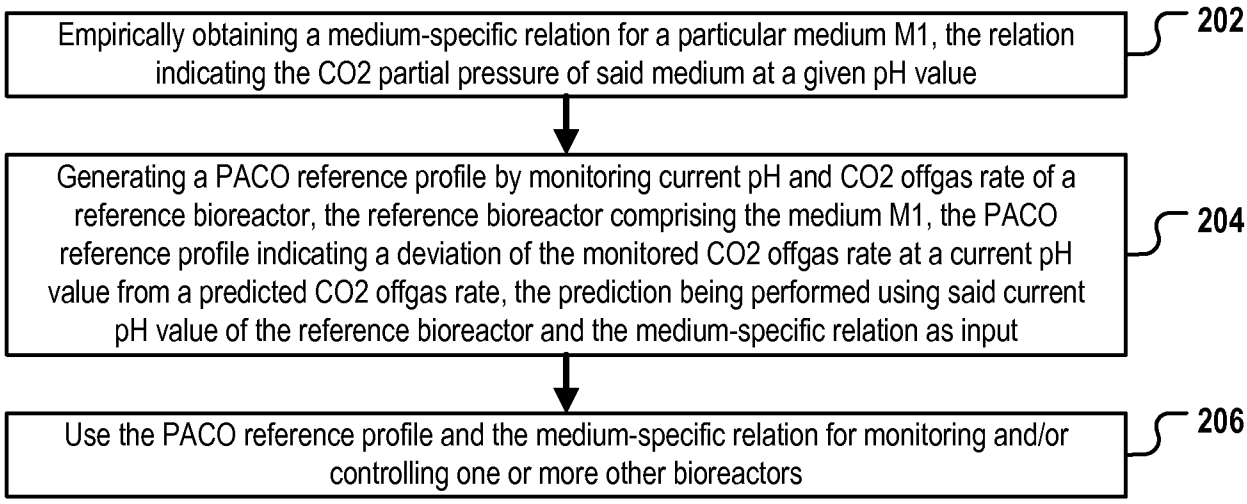
Empirically obtaining a medium-specific relation for a particular medium M1, the relation indicating the CO2 partial pressure of said medium at a given pH value
202
Generating a PACO reference profile by monitoring current pH and CO2 offgas rate of a reference bioreactor, the reference bioreactor comprising the medium M1, the PACO reference profile indicating a deviation of the monitored CO2 offgas rate at a current pH value from a predicted CO2 offgas rate, the prediction being performed using said current pH value of the reference bioreactor and the medium-specific relation as input
204
Use the PACO reference profile and the medium-specific relation for monitoring and/or controlling one or more other bioreactors
206

Fig. 2a

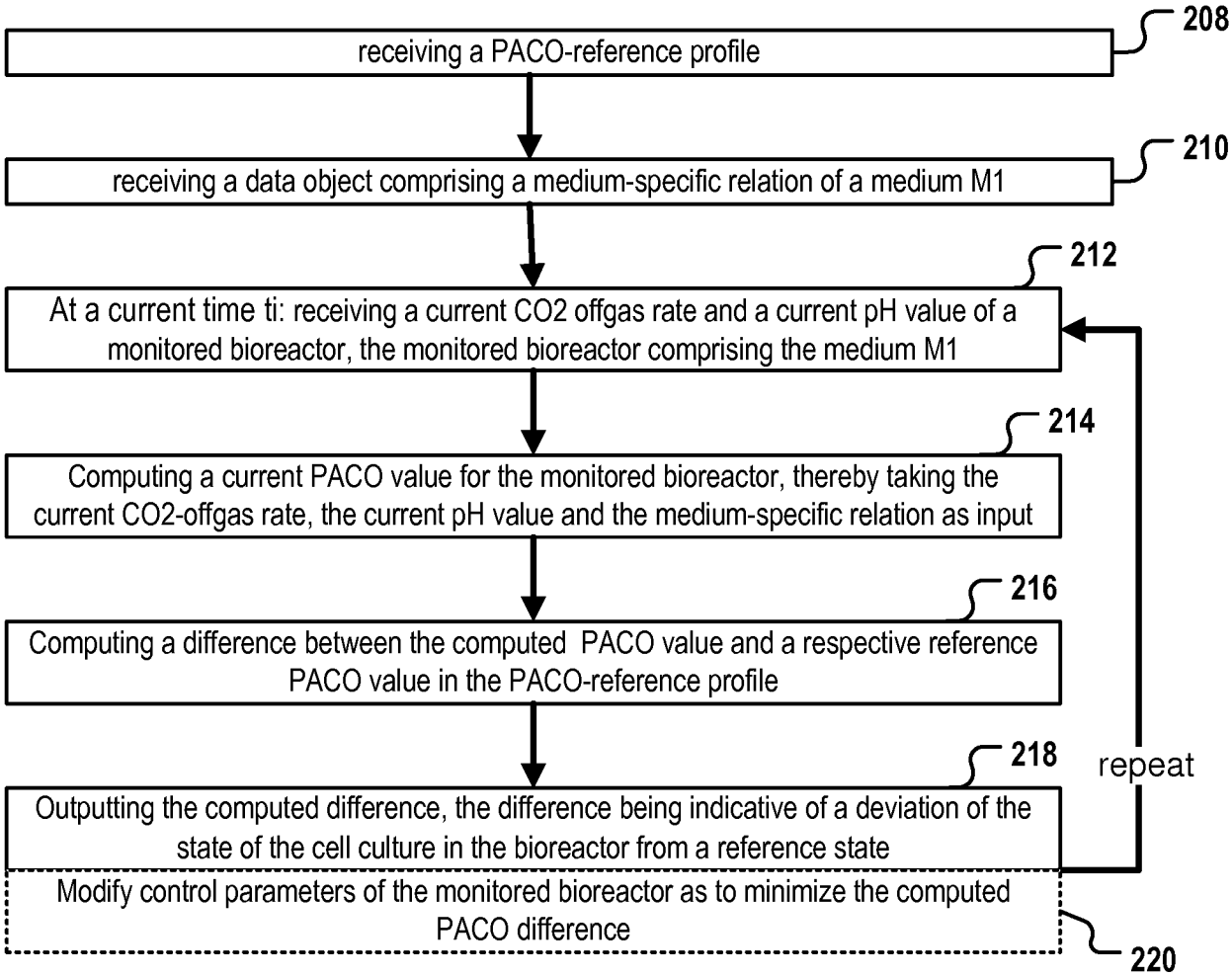
receiving a PACO-reference profile
208
receiving a data object comprising a medium-specific relation of a medium M1
210
At a current time ti: receiving a current CO2 offgas rate and a current pH value of a monitored bioreactor, the monitored bioreactor comprising the medium M1
212
Computing a current PACO value for the monitored bioreactor, thereby taking the current CO2-offgas rate, the current pH value and the medium-specific relation as input
214
Computing a difference between the computed PACO value and a respective reference PACO value in the PACO-reference profile
216
Outputting the computed difference, the difference being indicative of a deviation of the state of the cell culture in the bioreactor from a reference state
218
repeat
Modify control parameters of the monitored bioreactor as to minimize the computed PACO difference
220

Fig. 2b

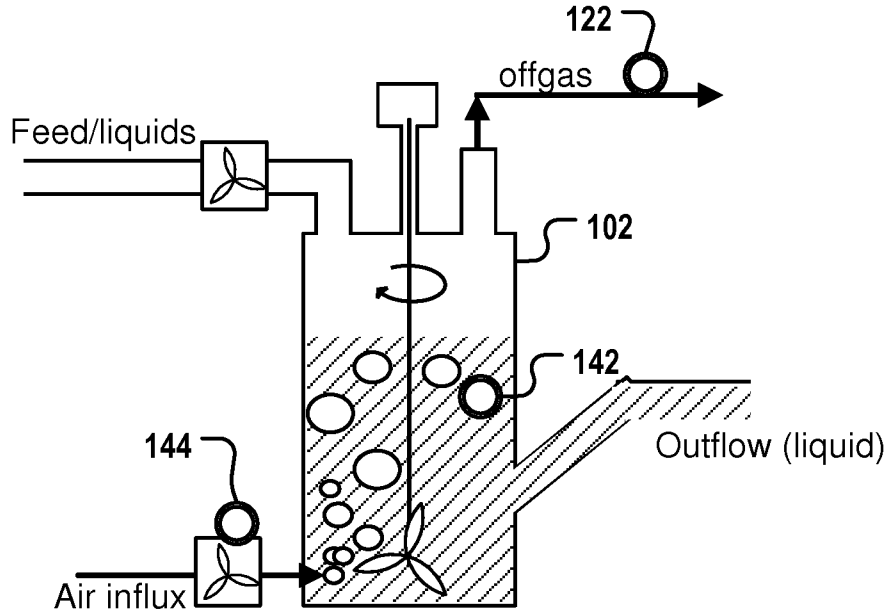
122
offgas
Feed/liquids
102
142
144
Outflow (liquid)
Air influx

Fig. 3

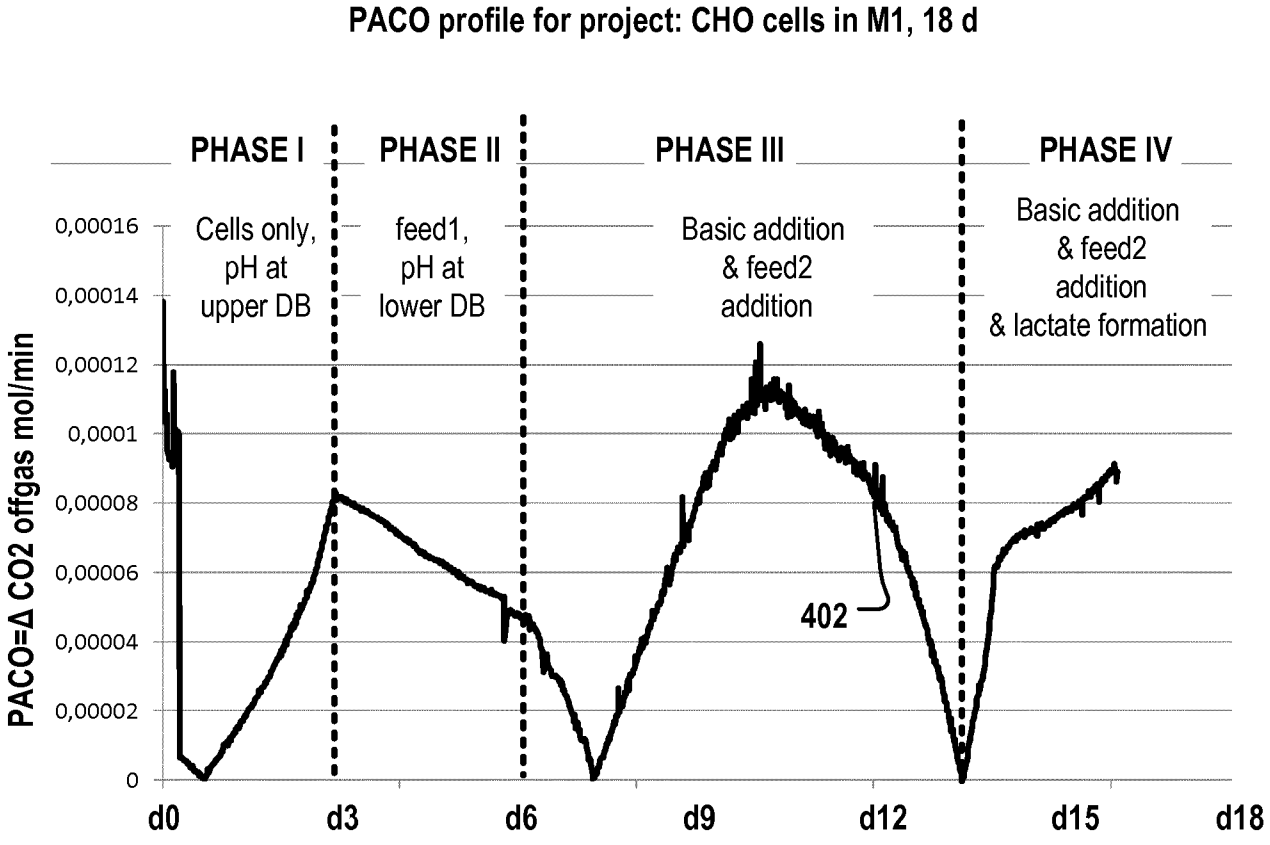
PACO profile for project: CHO cells in M1, 18 d
PHASE I
PHASE II
PHASE III
PHASE IV
Cells only, pH at upper DB
feed1, pH at lower DB
Basic addition & feed2 addition
Basic addition & feed2 addition & lactate formation
PACO=Δ CO2 offgas mol/min
0,00016
0,00014
0,00012
0,0001
0,00008
0,00006
0,00004
0,00002
0
402
d0
d3
d6
d9
d12
d15
d18

Fig. 4

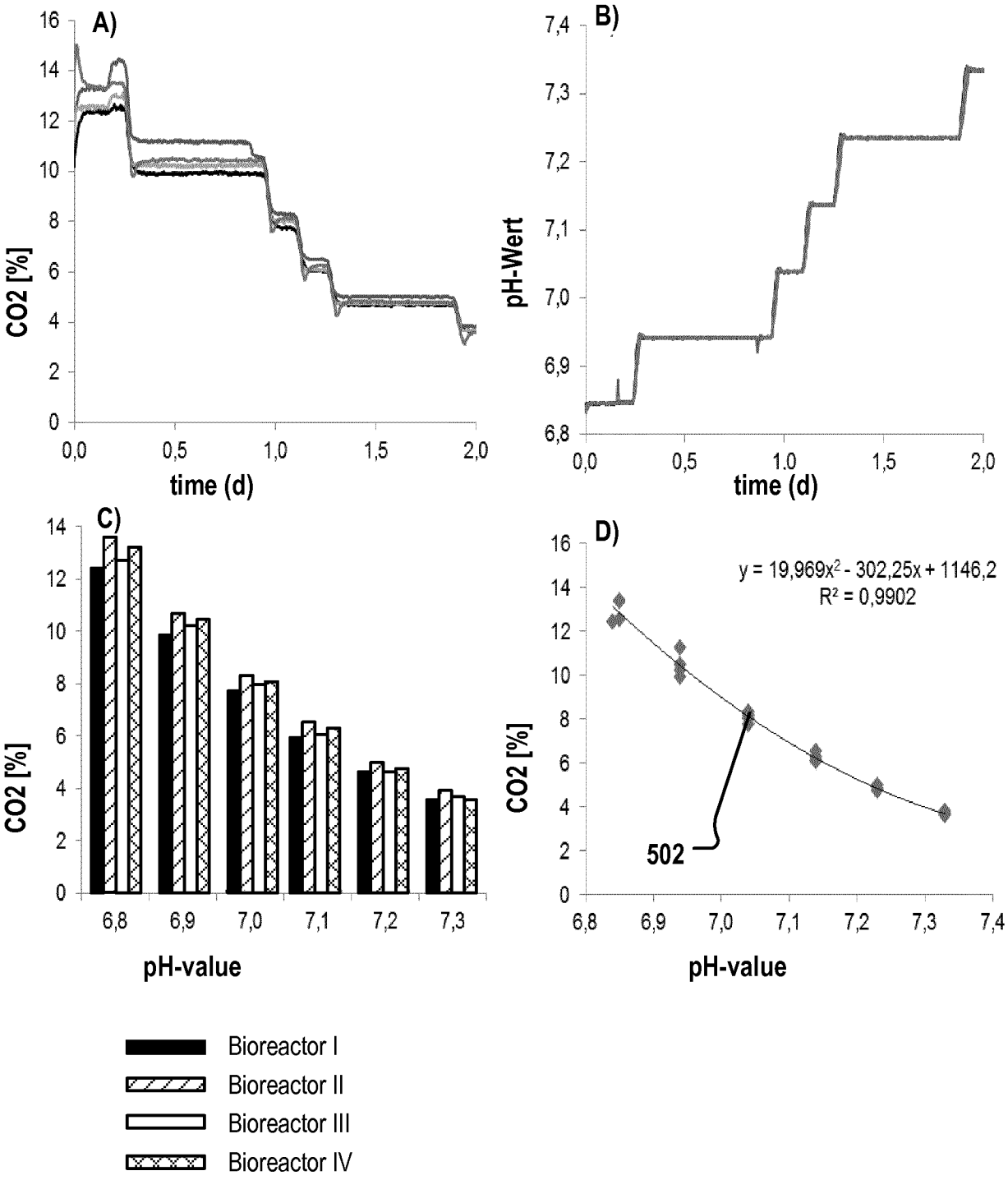
A)
CO2 [%]
time (d)
B)
pH-Wert
time (d)
C)
CO2 [%]
pH-value
D)
y = 19,969x² - 302,25x + 1146,2
R² = 0,9902
502
CO2 [%]
pH-value
Bioreactor I
Bioreactor II
Bioreactor III
Bioreactor IV

Fig. 5

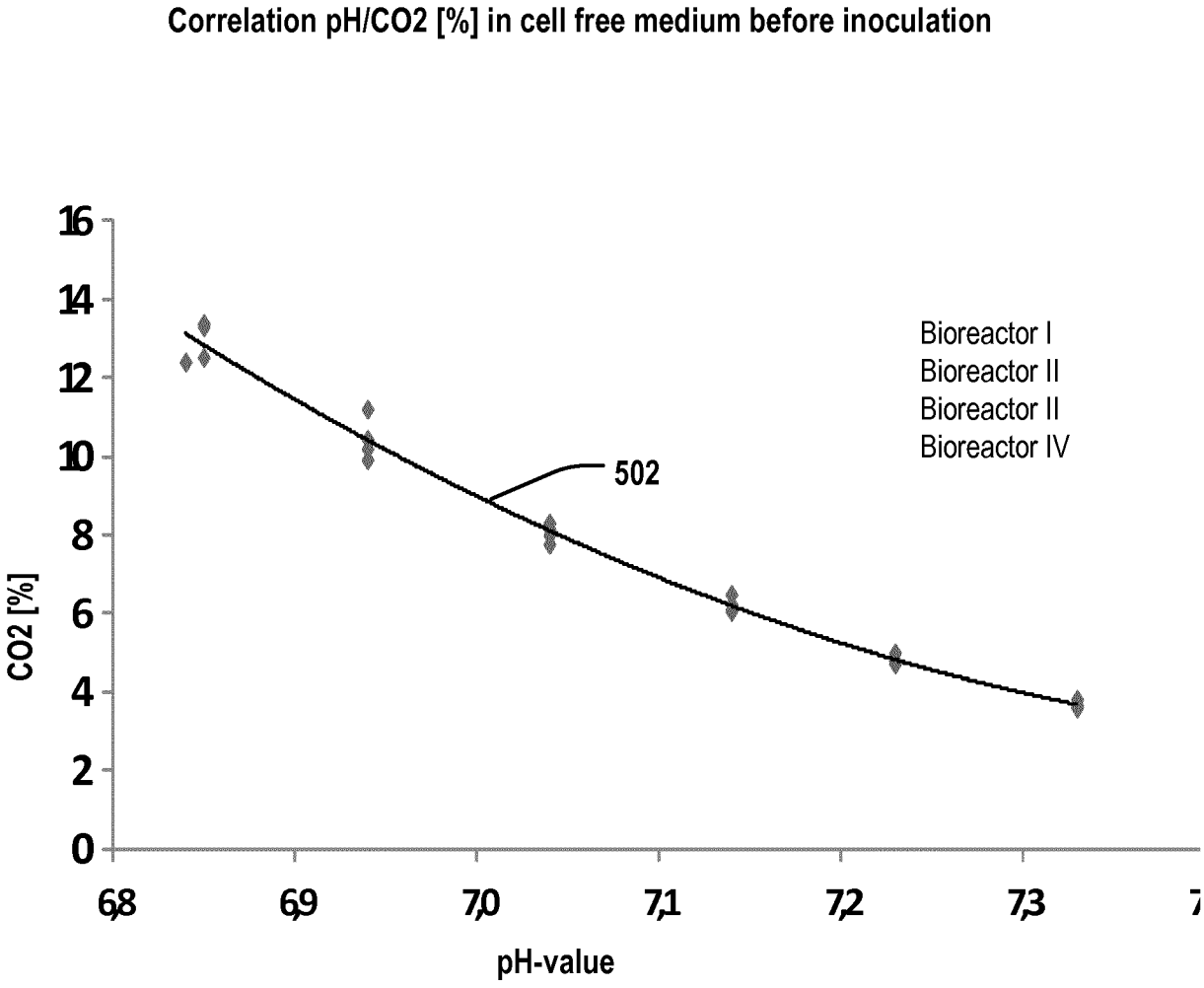
Correlation pH/CO2 [%] in cell free medium before inoculation
16
14
12
10
8
6
4
2
0
CO2 [%]
6,8
6,9
7,0
7,1
7,2
7,3
pH-value
Bioreactor I
Bioreactor II
Bioreactor II
Bioreactor IV
502

Fig. 6

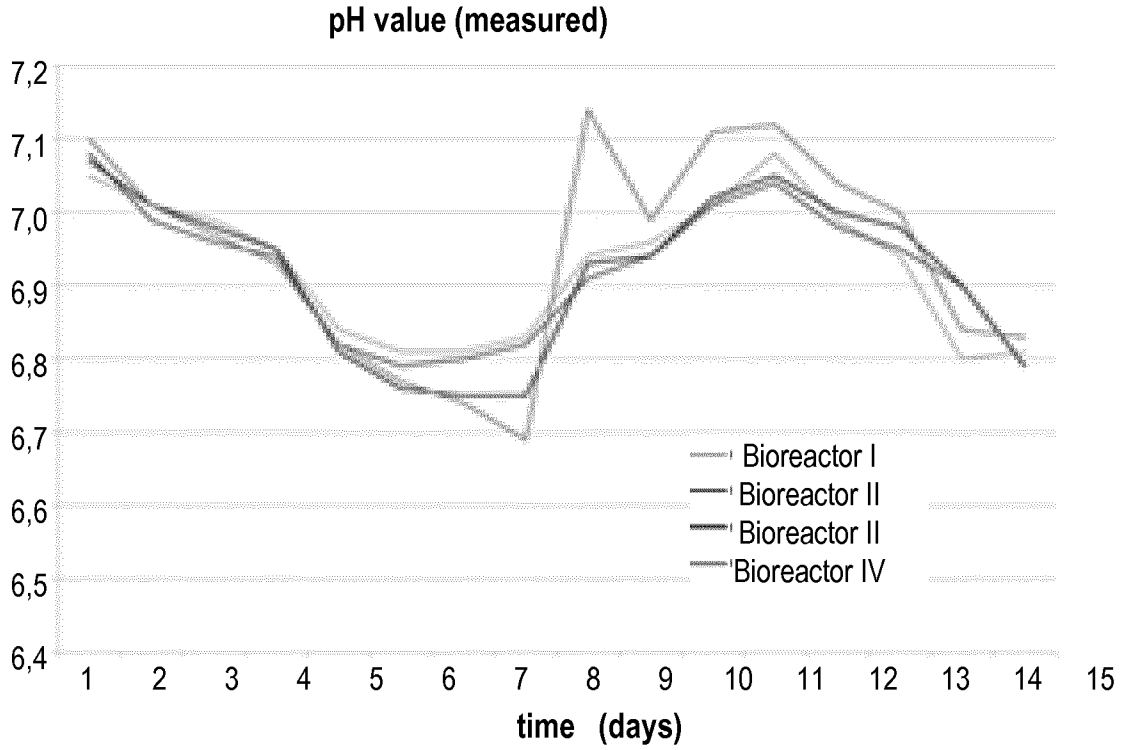
pH value (measured)
7,2
7,1
7,0
6,9
6,8
6,7
6,6
6,5
6,4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
time (days)
Bioreactor I
Bioreactor II
Bioreactor II
Bioreactor IV

Fig. 7a

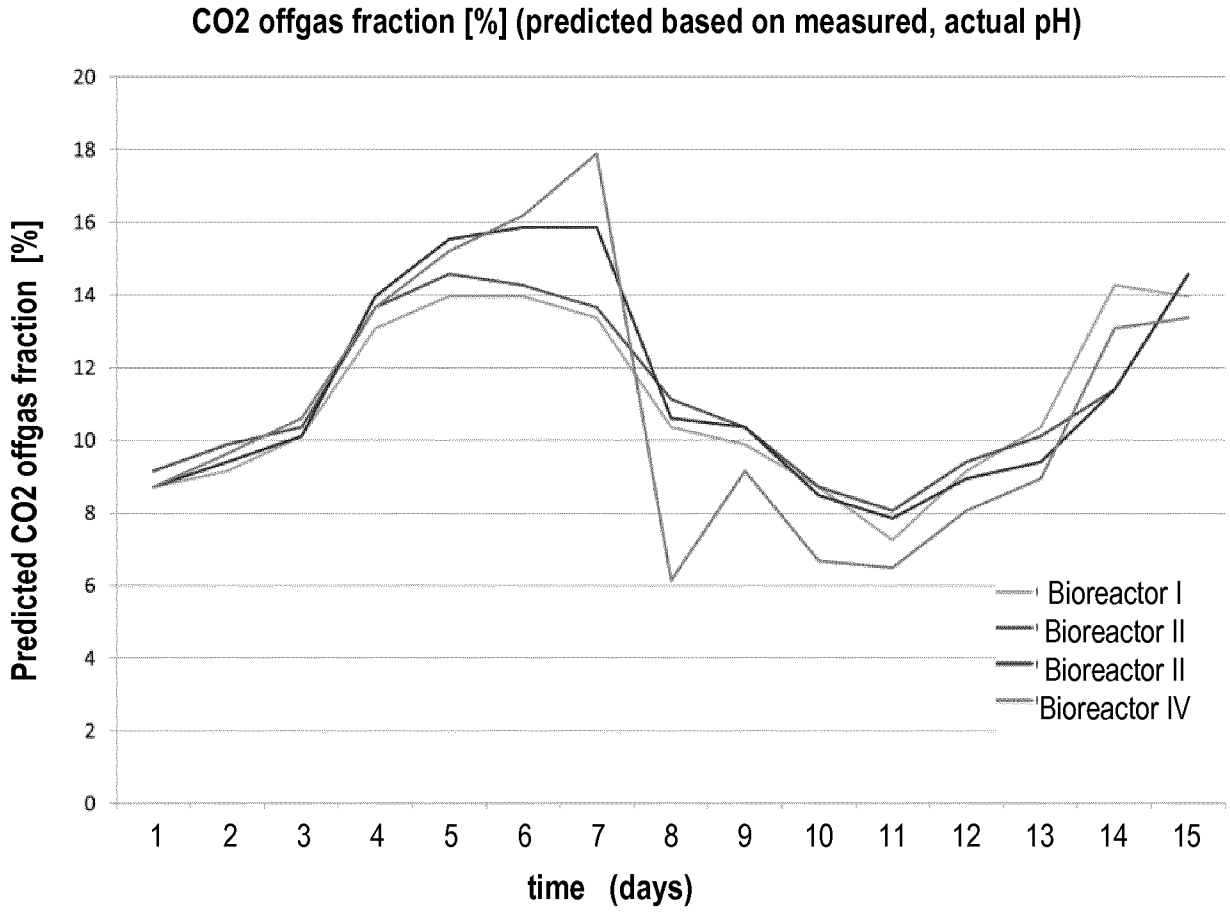
CO2 offgas fraction [%] (predicted based on measured, actual pH)
Predicted CO2 offgas fraction [%]
20
18
16
14
12
10
8
6
4
2
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
time (days)
Bioreactor I
Bioreactor II
Bioreactor II
Bioreactor IV

Fig. 7b

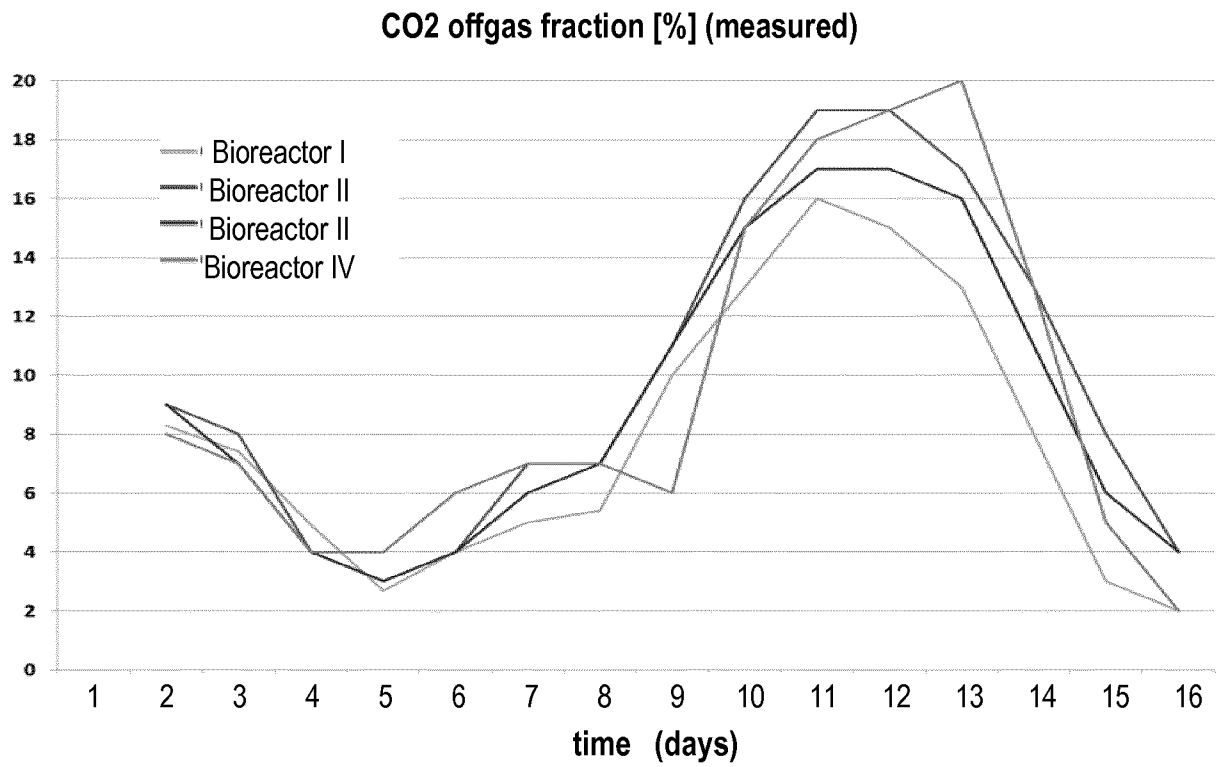
CO2 offgas fraction [%] (measured)
Bioreactor I
Bioreactor II
Bioreactor II
Bioreactor IV
20
18
16
14
12
10
8
6
4
2
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
time (days)

Fig. 7c

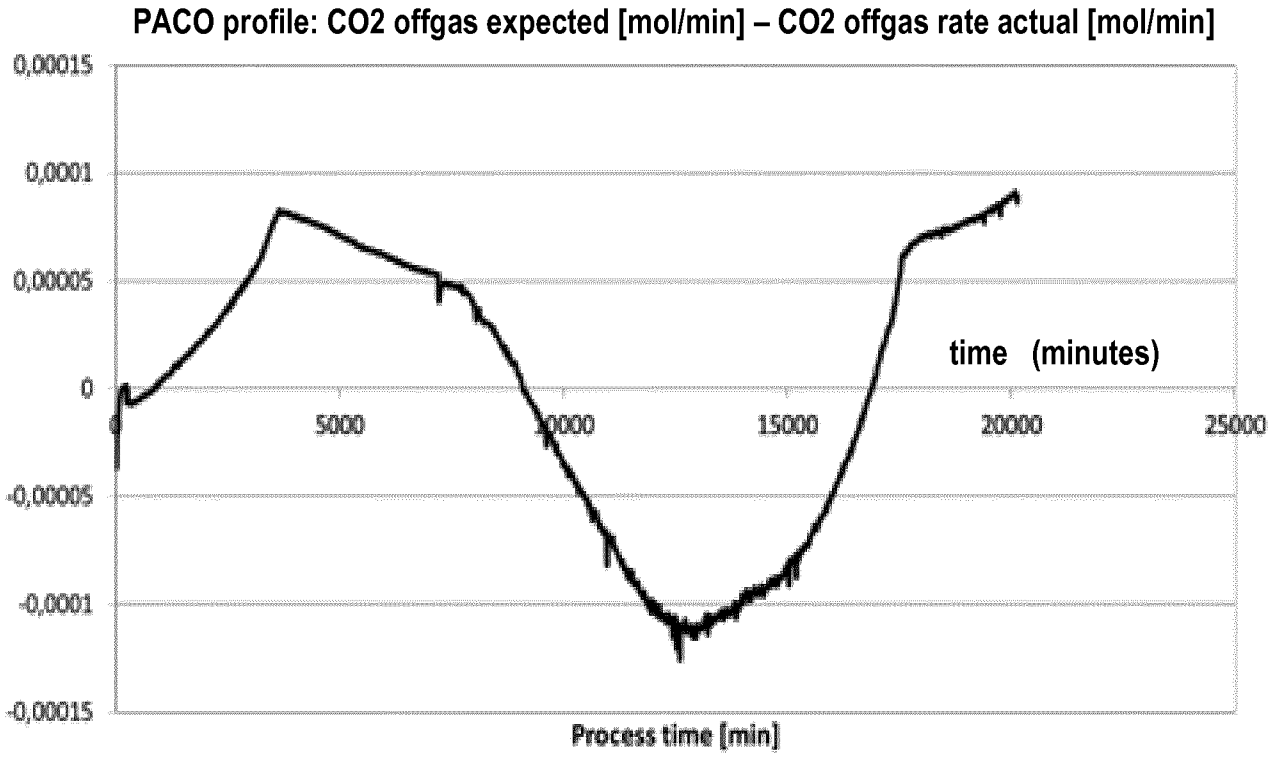
PACO profile: CO2 offgas expected [mol/min] – CO2 offgas rate actual [mol/min]
0,00015
0,0001
0,00005
0
-0,00005
-0,0001
-0,00015
5000
15000
20000
25000
time (minutes)
Process time [min]

Fig. 7d

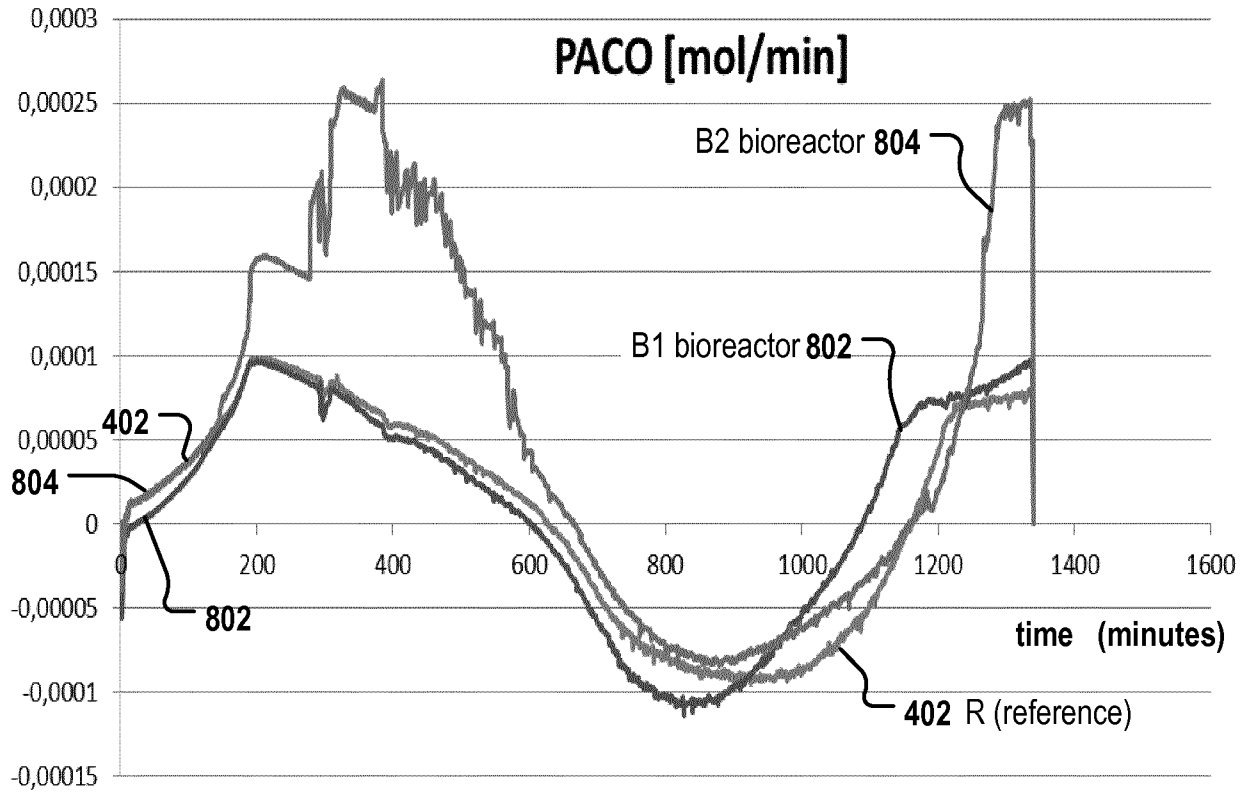
PACO [mol/min]
0,0003
0,00025
0,0002
0,00015
0,0001
0,00005
0
-0,00005
-0,0001
-0,00015
0
200
400
600
800
1000
1200
1400
1600
B2 bioreactor 804
B1 bioreactor 802
402
804
802
time (minutes)
402 R (reference)

Fig. 8a

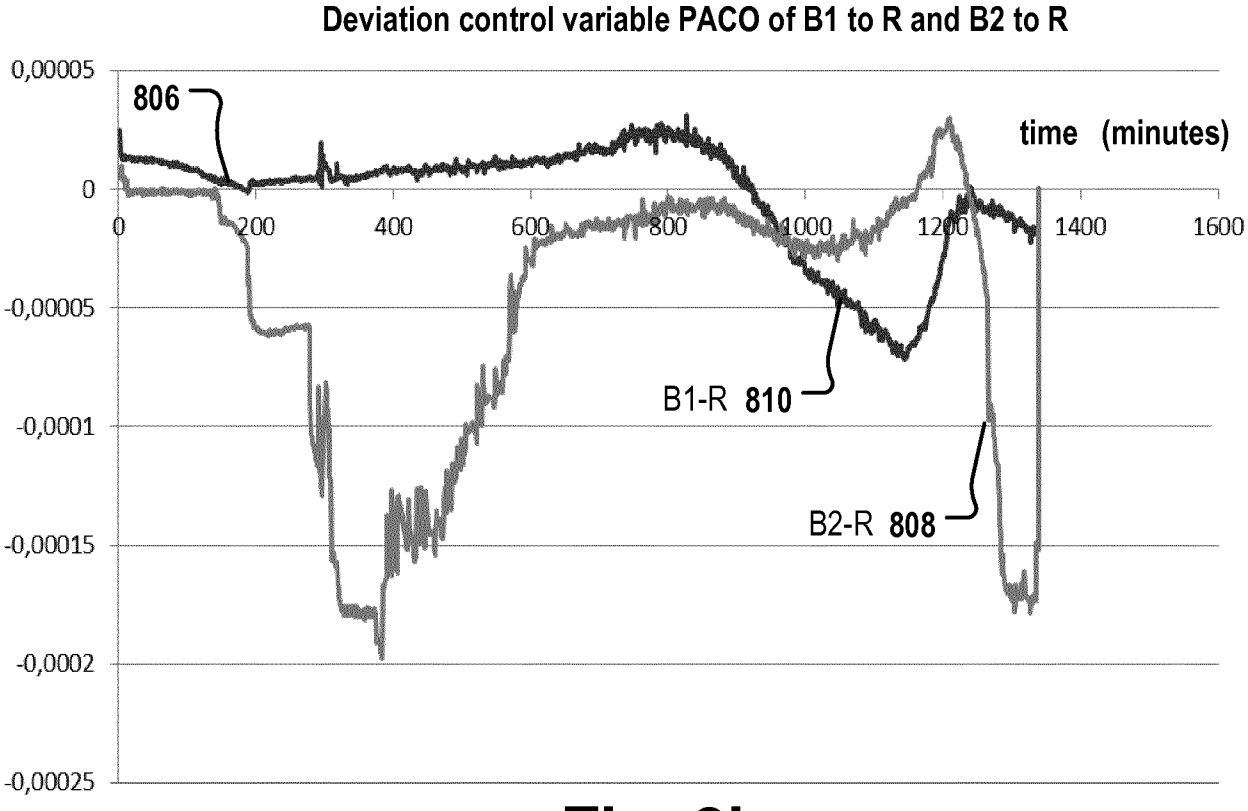
Deviation control variable PACO of B1 to R and B2 to R
0,00005
0
-0,00005
-0,0001
-0,00015
-0,0002
-0,00025
0
200
400
600
800
1000
1200
1400
1600
806
time (minutes)
B1-R 810
B2-R 808

Fig. 8b