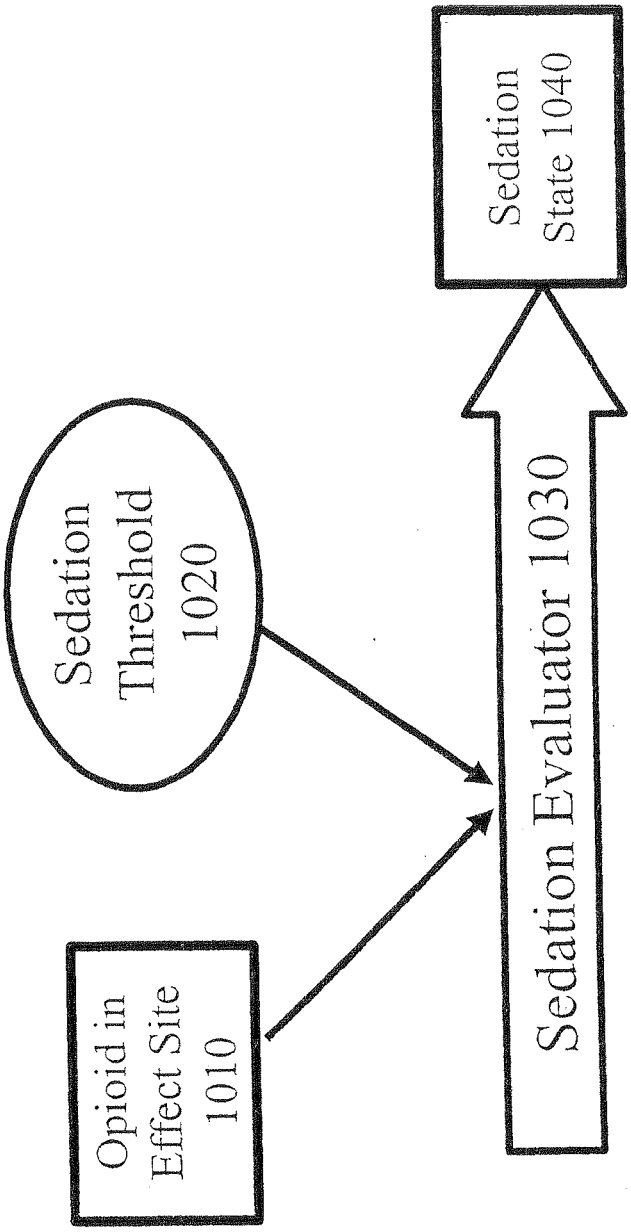
Figure 1: Sedation Model



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Figure 2: Ventilatory Depression Model

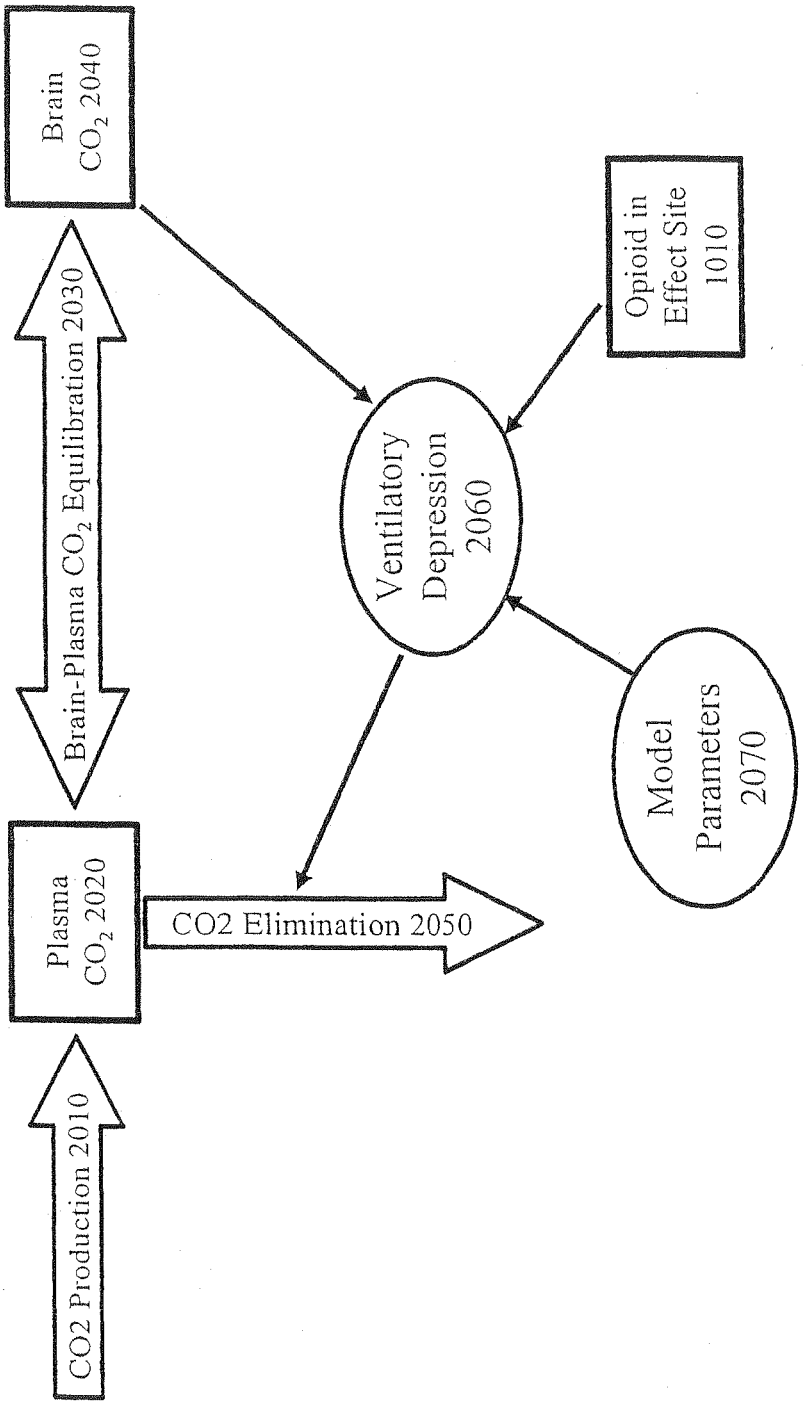


Figure 3: Device Model

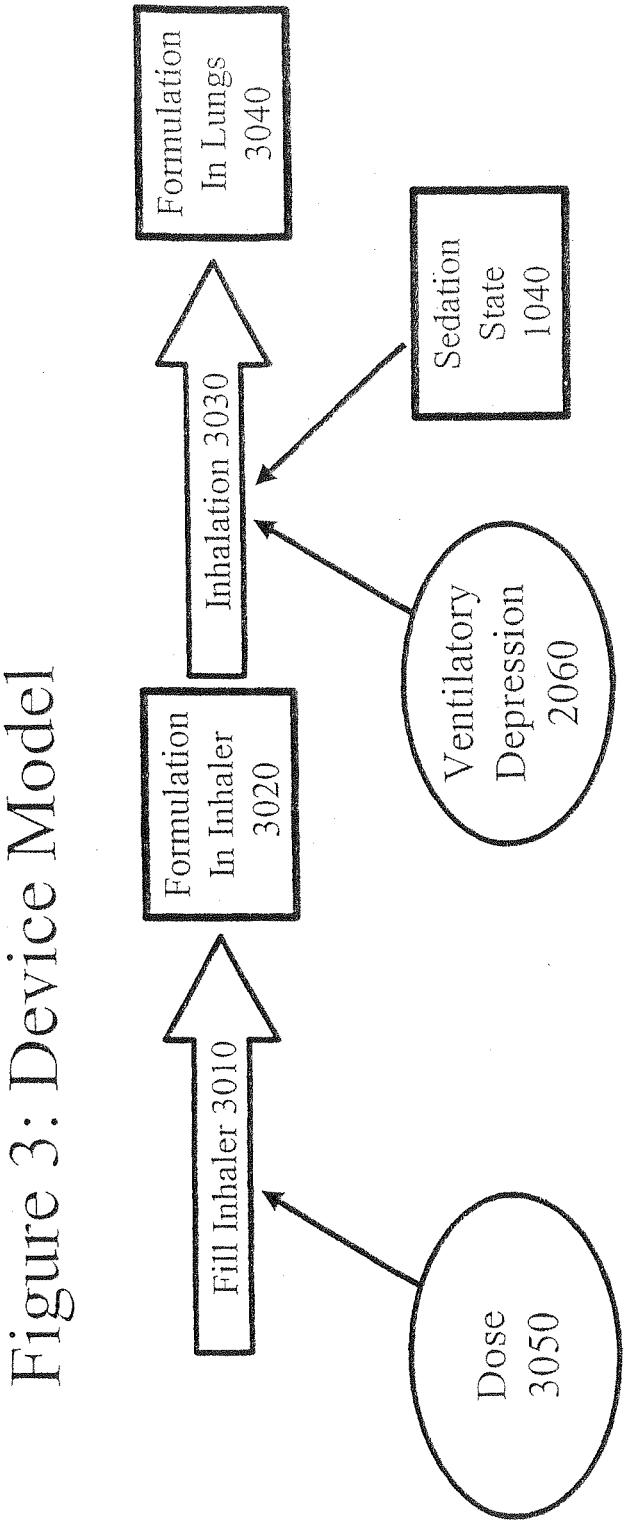


Figure 4: Pharmacokinetic Model

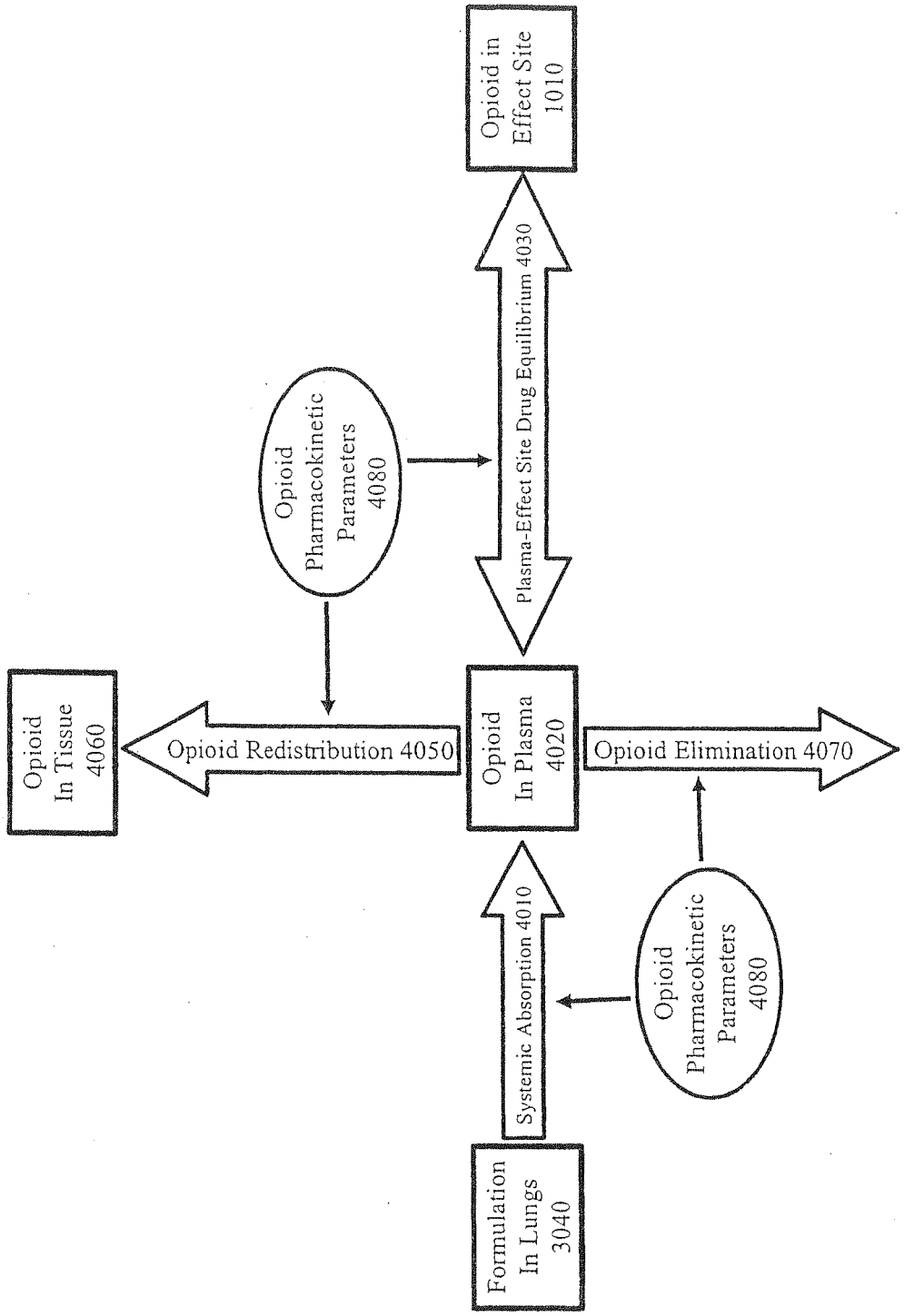


Figure 5A

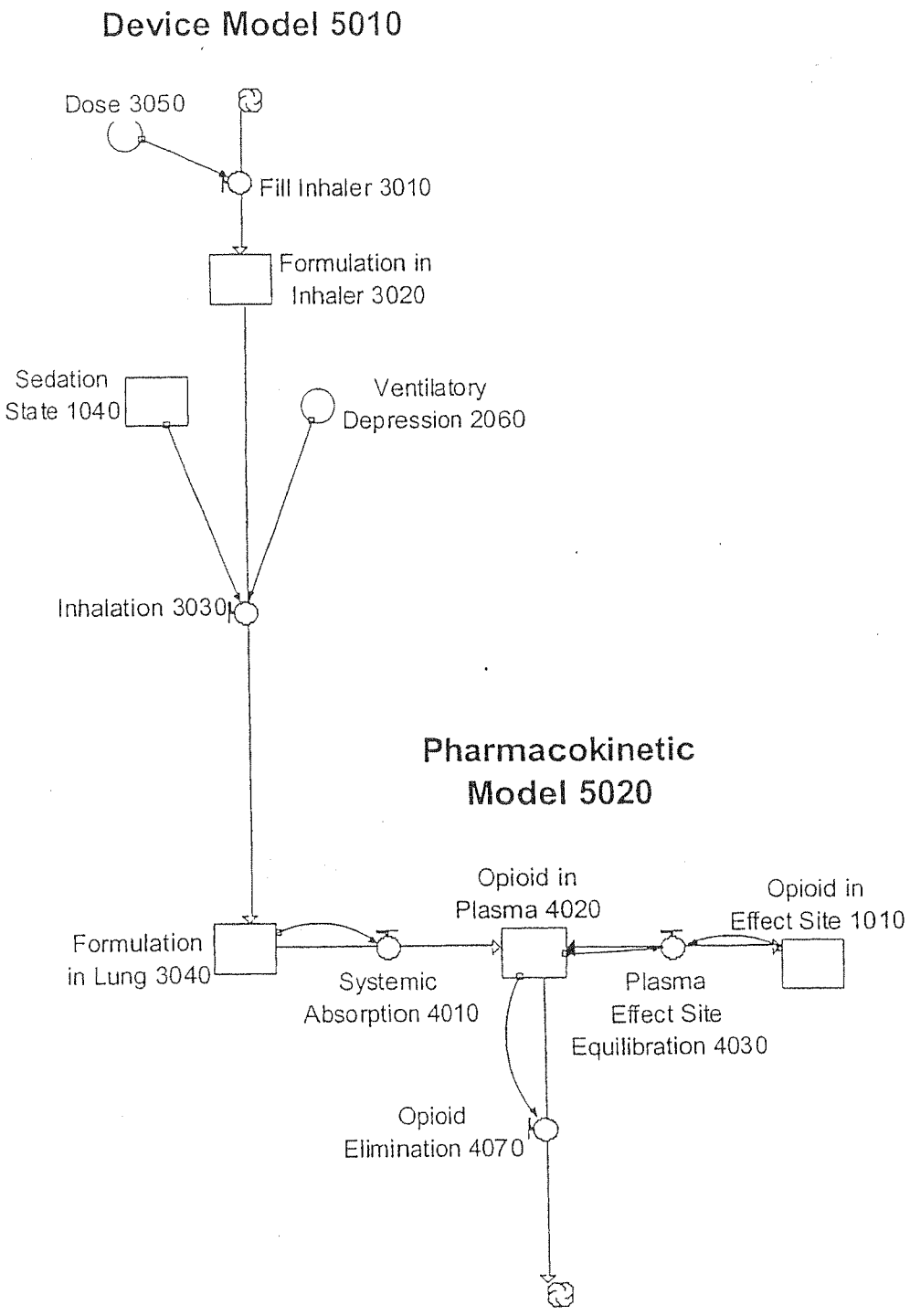

Device Model 5010
Dose 3050
Fill Inhaler 3010
Formulation in Inhaler 3020
Sedation State 1040
Ventilatory Depression 2060
Inhalation 3030
Pharmacokinetic Model 5020
Opioid in Plasma 4020
Opioid in Effect Site 1010
Formulation in Lung 3040
Systemic Absorption 4010
Plasma Effect Site Equilibration 4030
Opioid Elimination 4070

Figure 5B

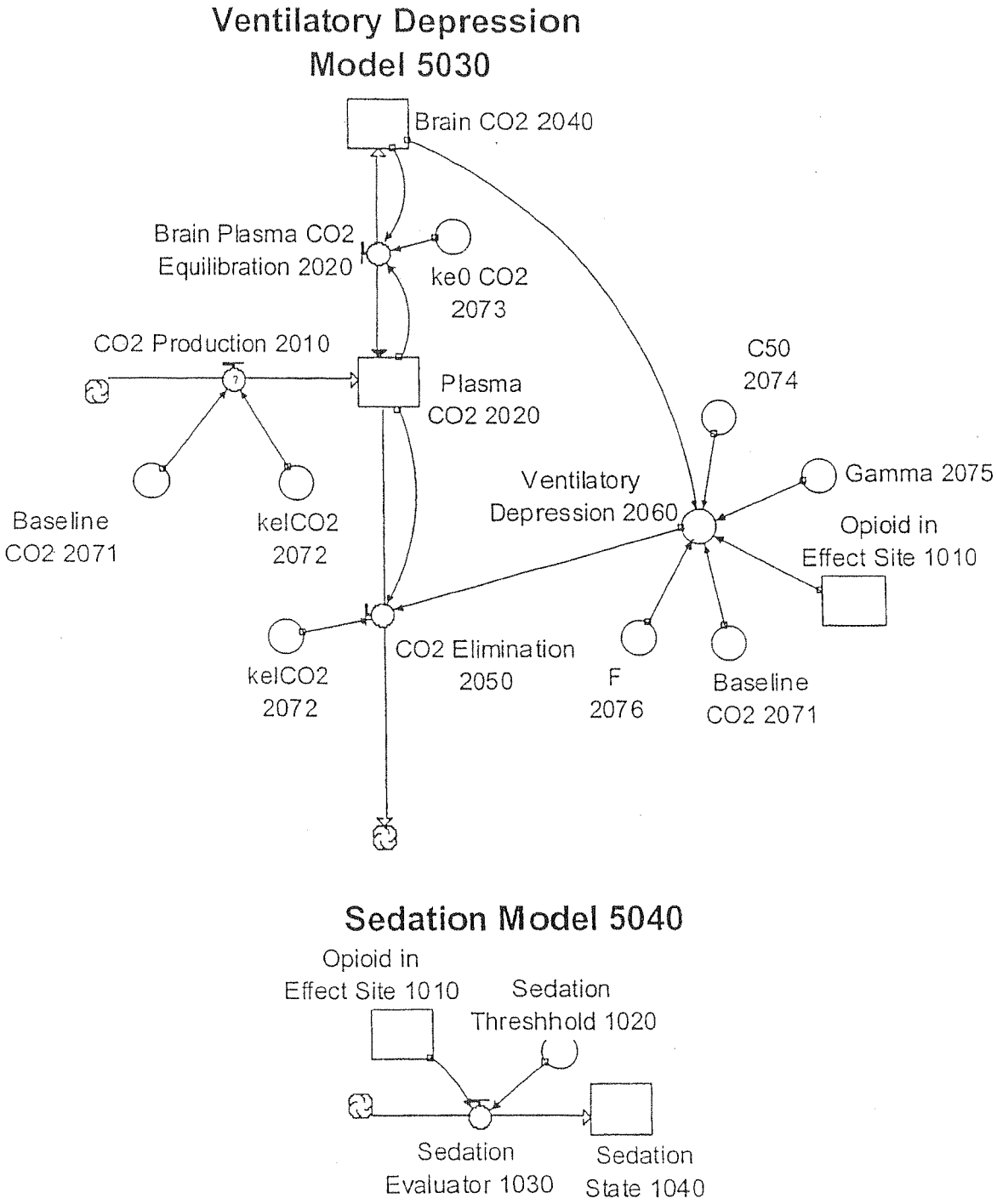

Ventilatory Depression
Model 5030
Brain CO2 2040
Brain Plasma CO2
Equilibration 2020
ke0 CO2
2073
CO2 Production 2010
Plasma
CO2 2020
C50
2074
Gamma 2075
Ventilatory
Depression 2060
Opioid in
Effect Site 1010
Baseline
CO2 2071
kelCO2
2072
CO2 Elimination
2050
kelCO2
2072
F
2076
Baseline
CO2 2071
Sedation Model 5040
Opioid in
Effect Site 1010
Sedation
Threshhold 1020
Sedation
Evaluator 1030
Sedation
State 1040

Figure 6

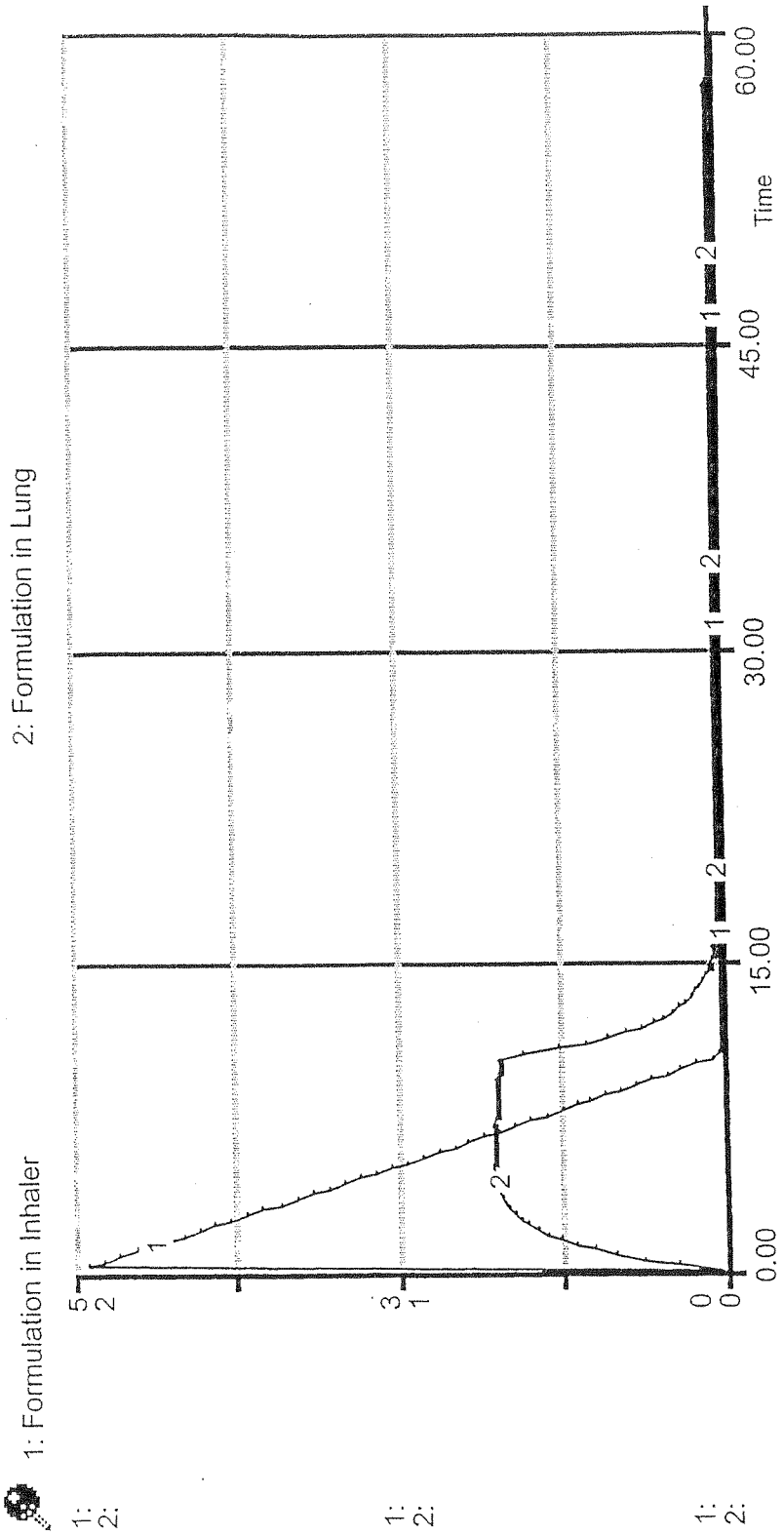

1: Formulation in Inhaler
2: Formulation in Lung
1:
2:
1:
2:
1:
2:
5
2
3
1
0
0
0.00
15.00
30.00
45.00
60.00
Time

Figure 7

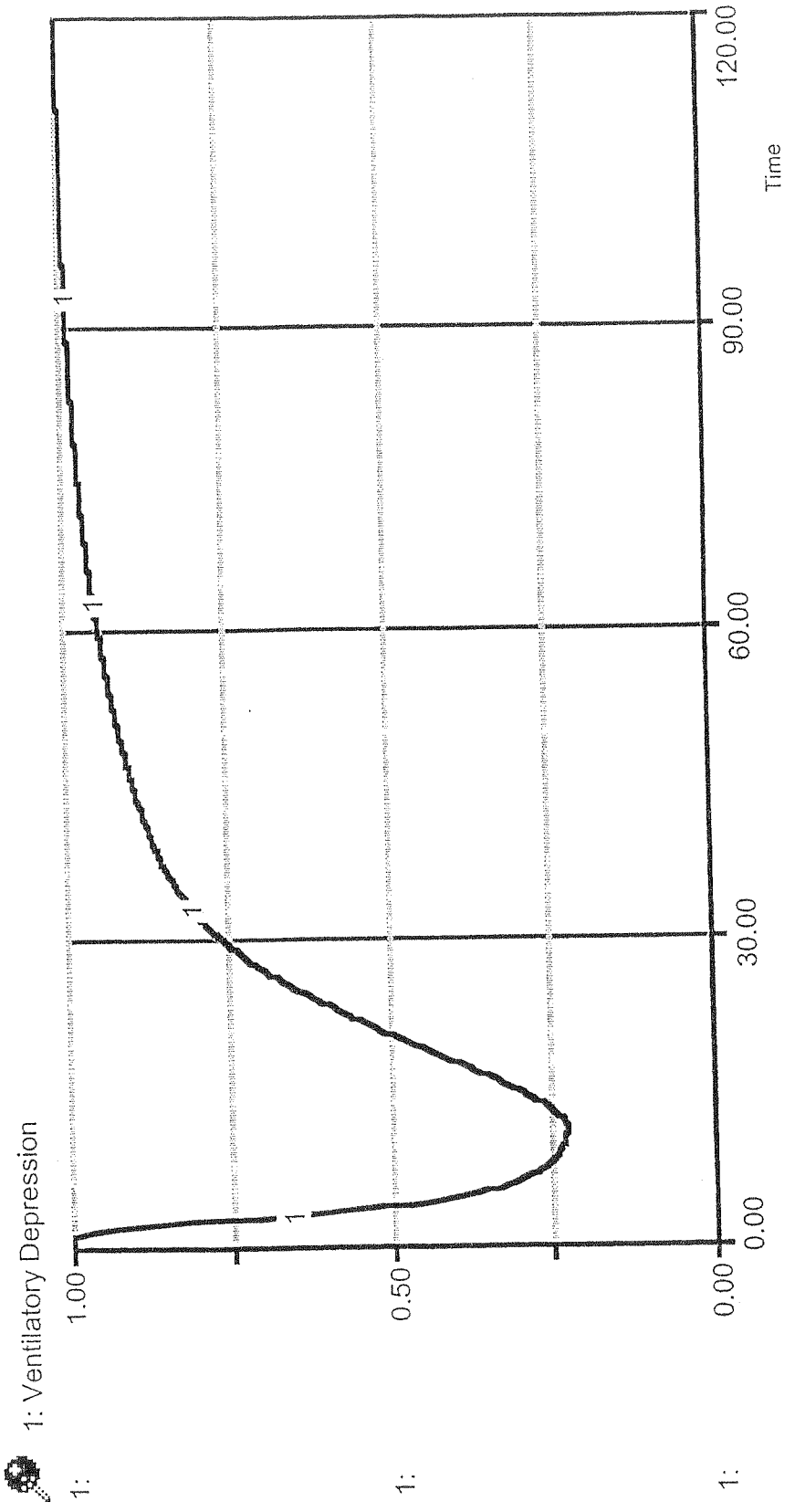

1: Ventilatory Depression
1.00
0.50
0.00
0.00
30.00
60.00
90.00
120.00
Time

Figure 8

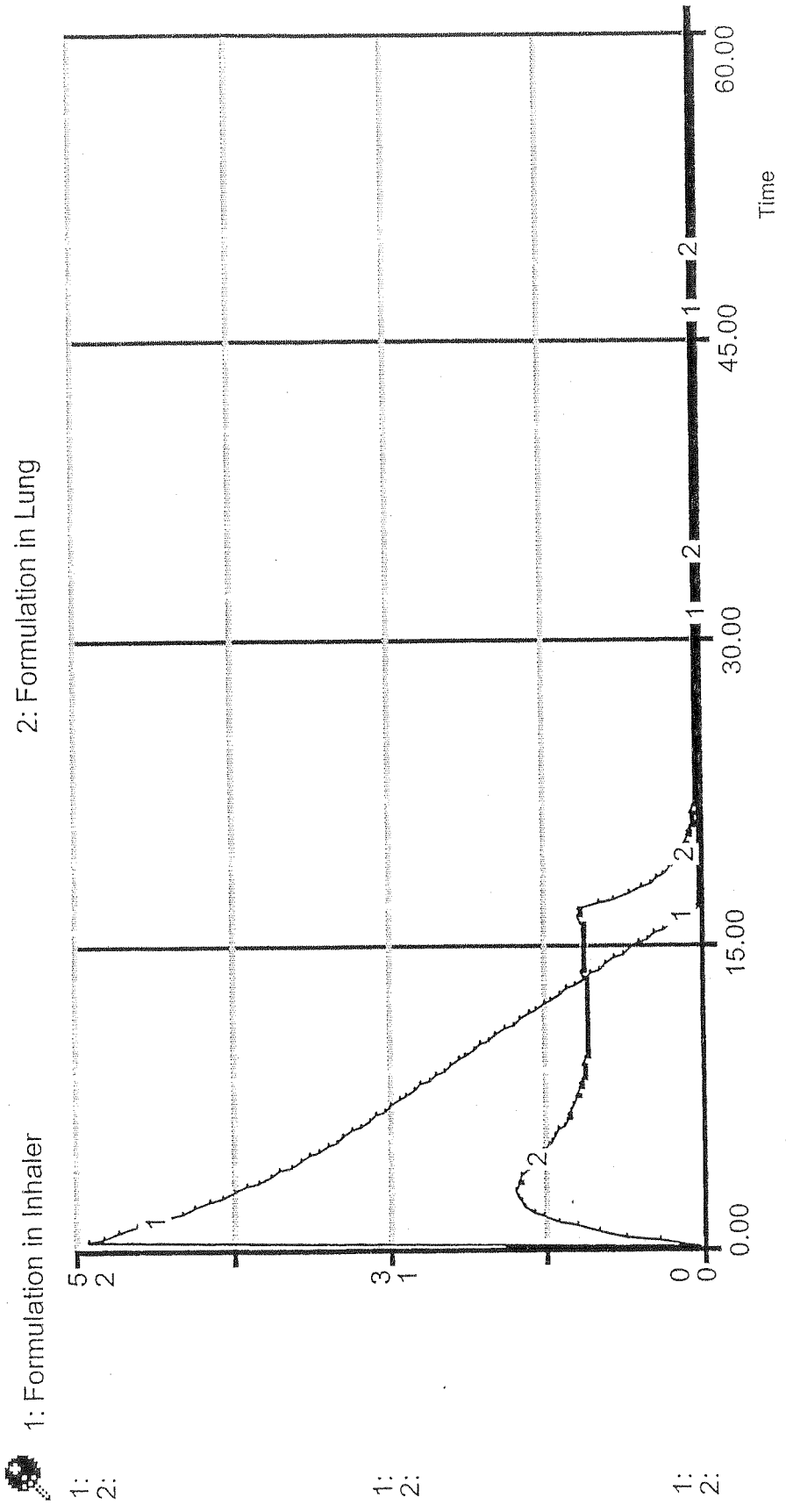

1: Formulation in Inhaler
2: Formulation in Lung
Time
0.00
15.00
30.00
45.00
60.00

Figure 9

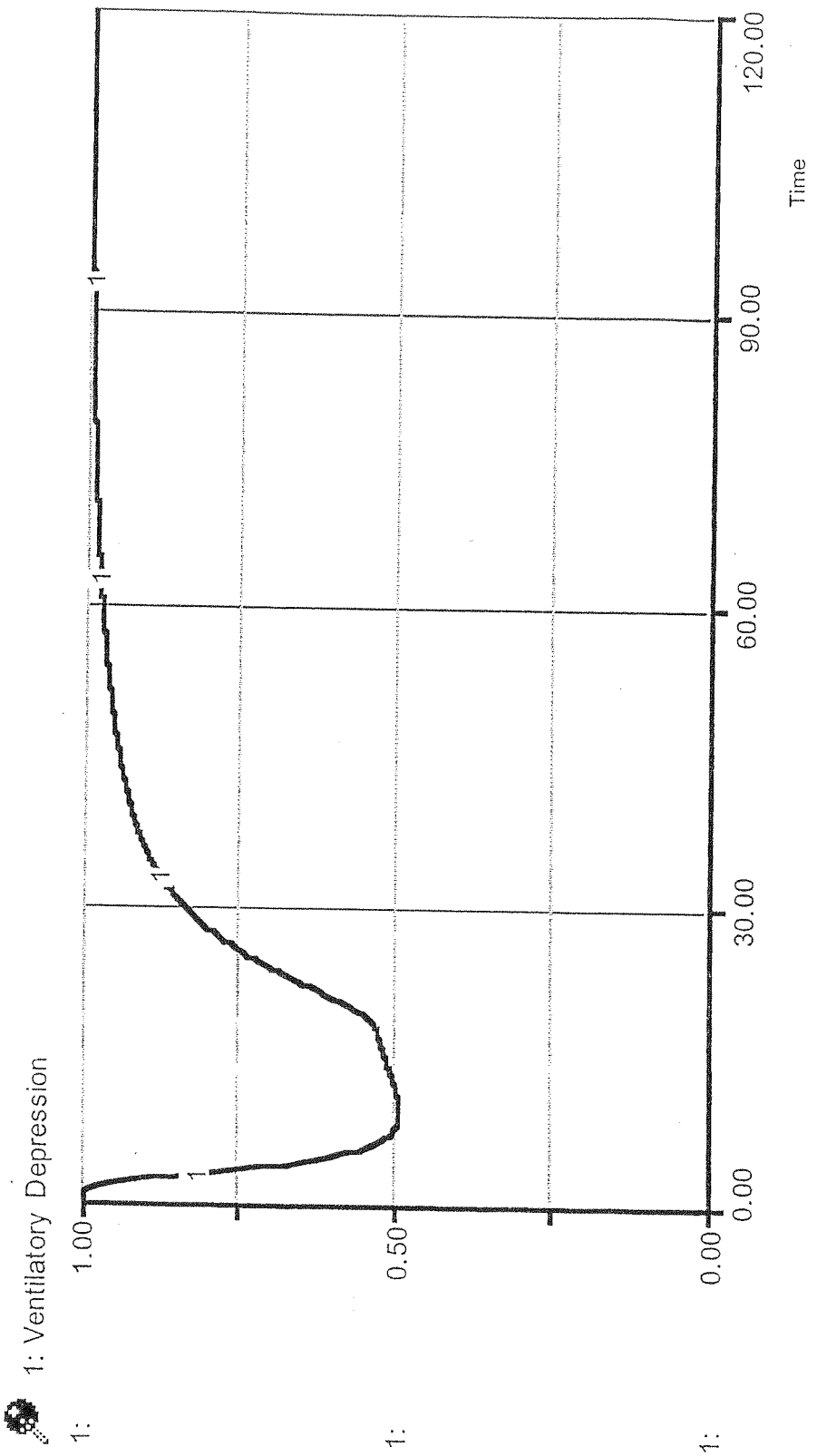

1: Ventilatory Depression
1.00
0.50
0.00
0.00
30.00
60.00
90.00
120.00
Time

Figure 10

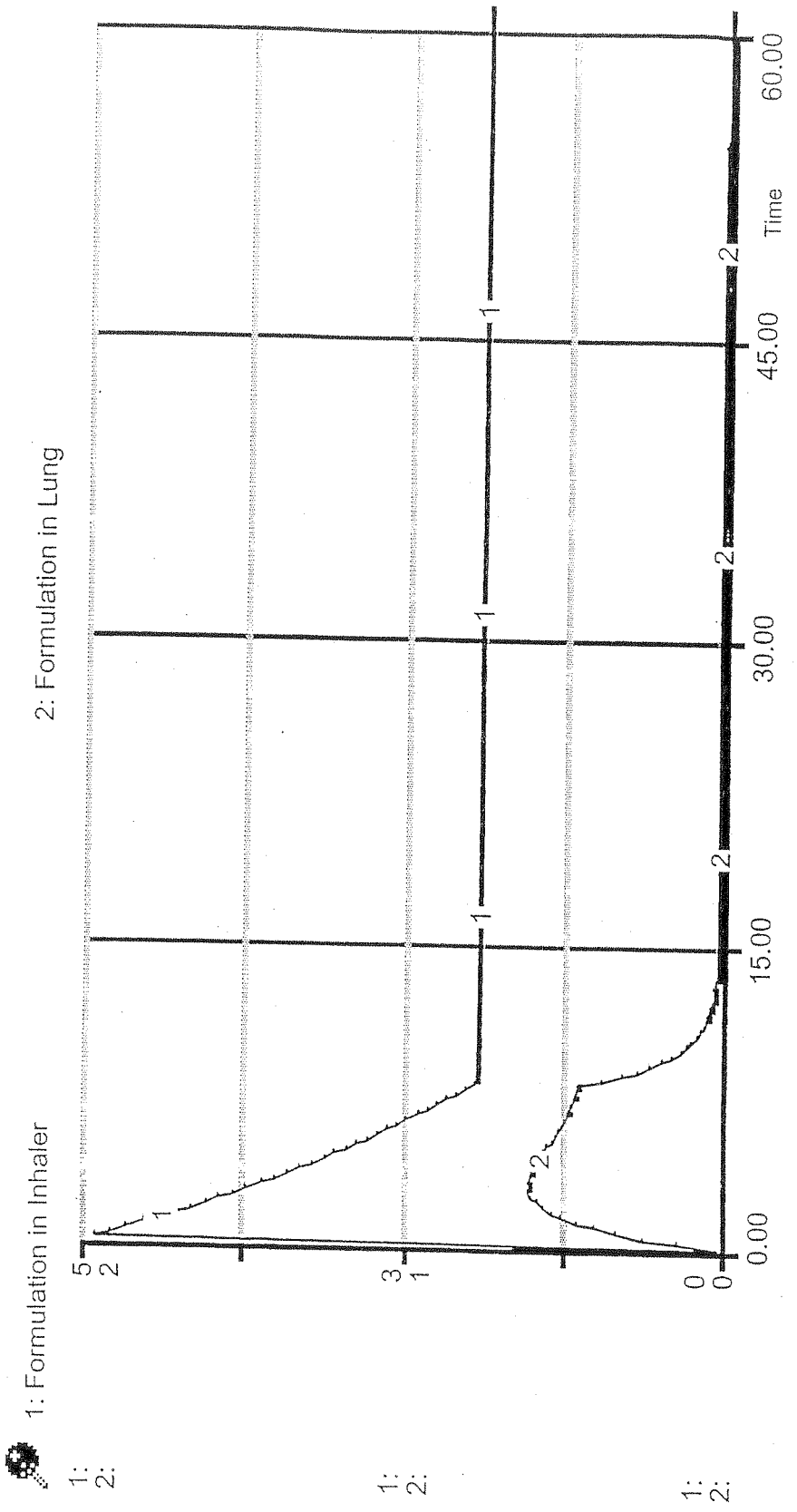

1: Formulation in Inhaler
2: Formulation in Lung
1:
2:
5
2
3
1
0
0
0.00
15.00
30.00
45.00
60.00
Time

Figure 11

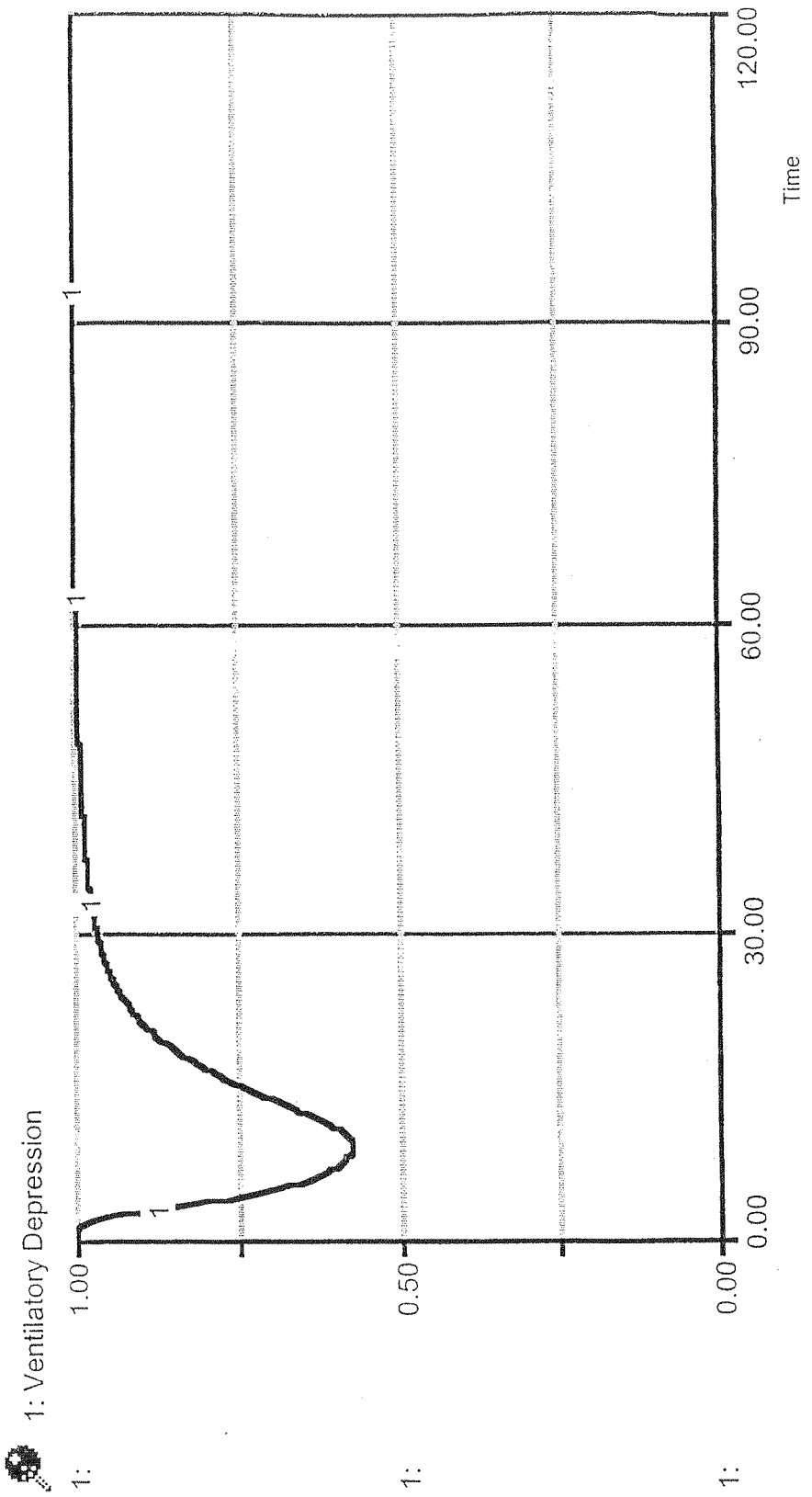

1: Ventilatory Depression
1:
1.00
0.50
0.00
0.00
30.00
60.00
90.00
120.00
Time

Figure 12: Two Opioid Model

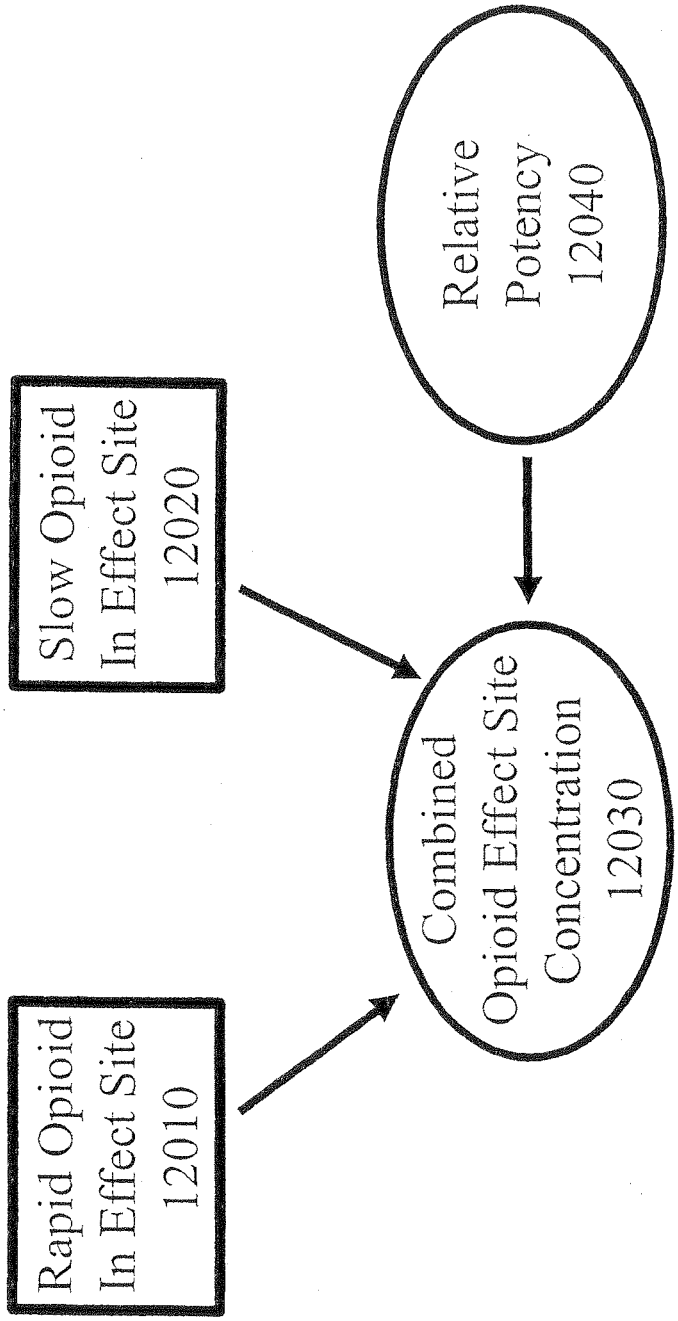
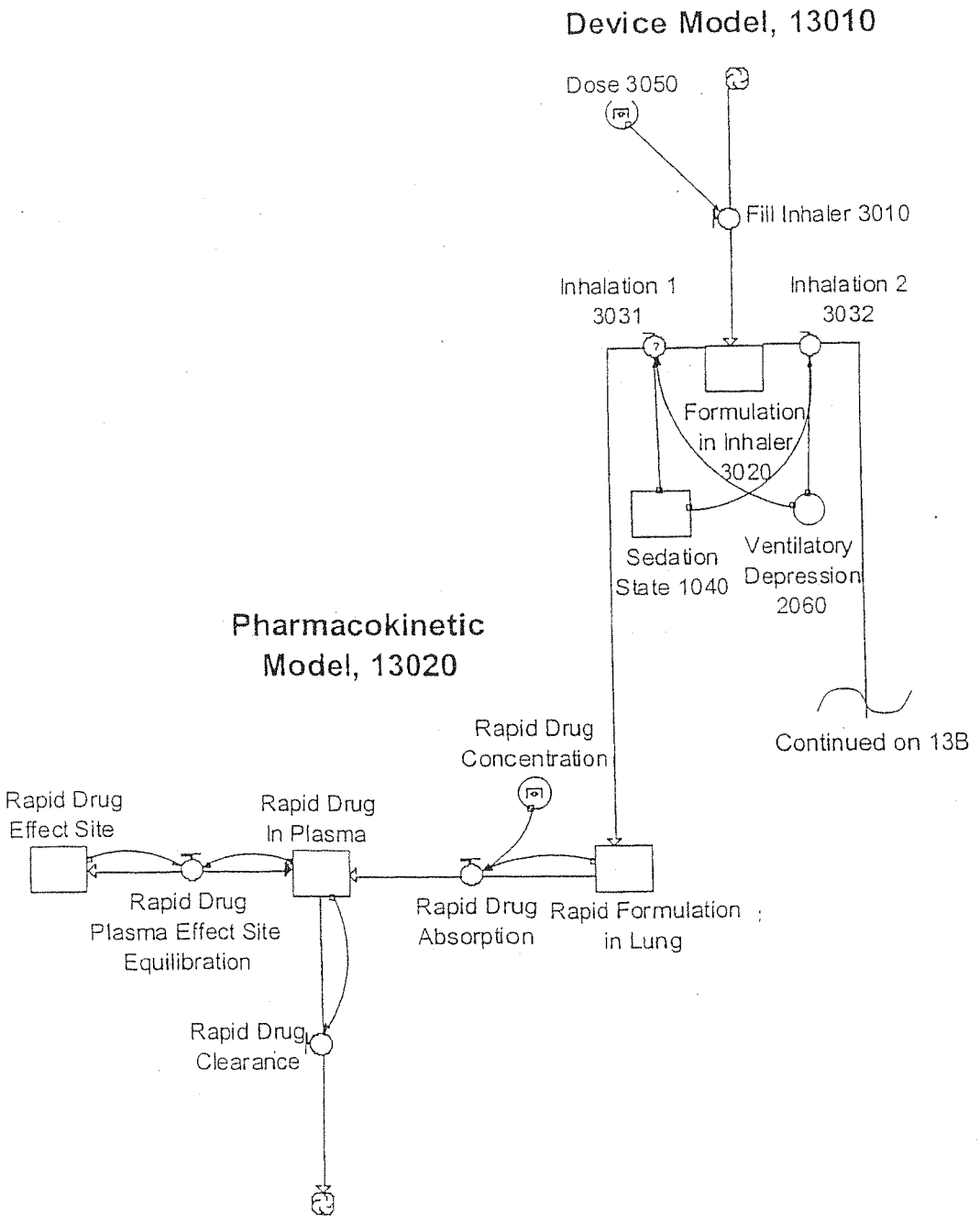


Figure 13A: The elements of the invention, wherein two opioids are administered through inhalation.



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Figure 13B The elements of the invention, wherein two opioids are administered through inhalation.

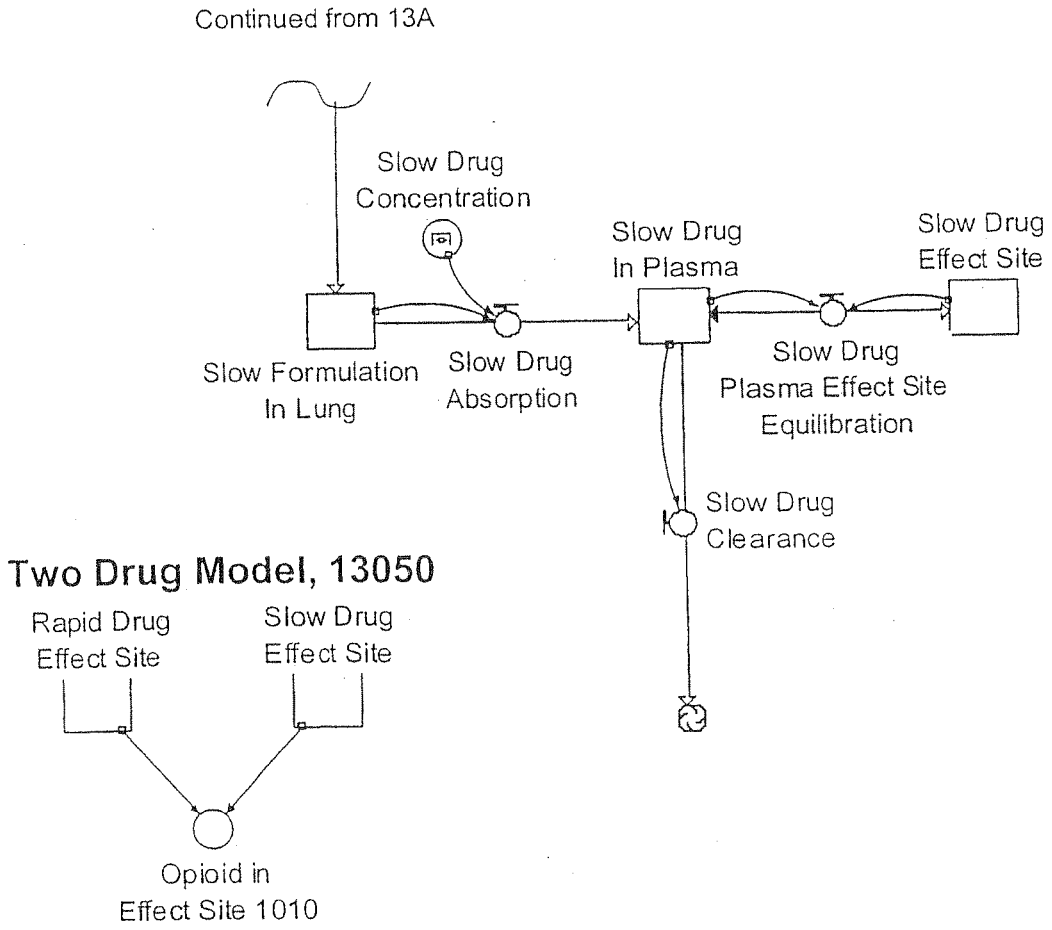
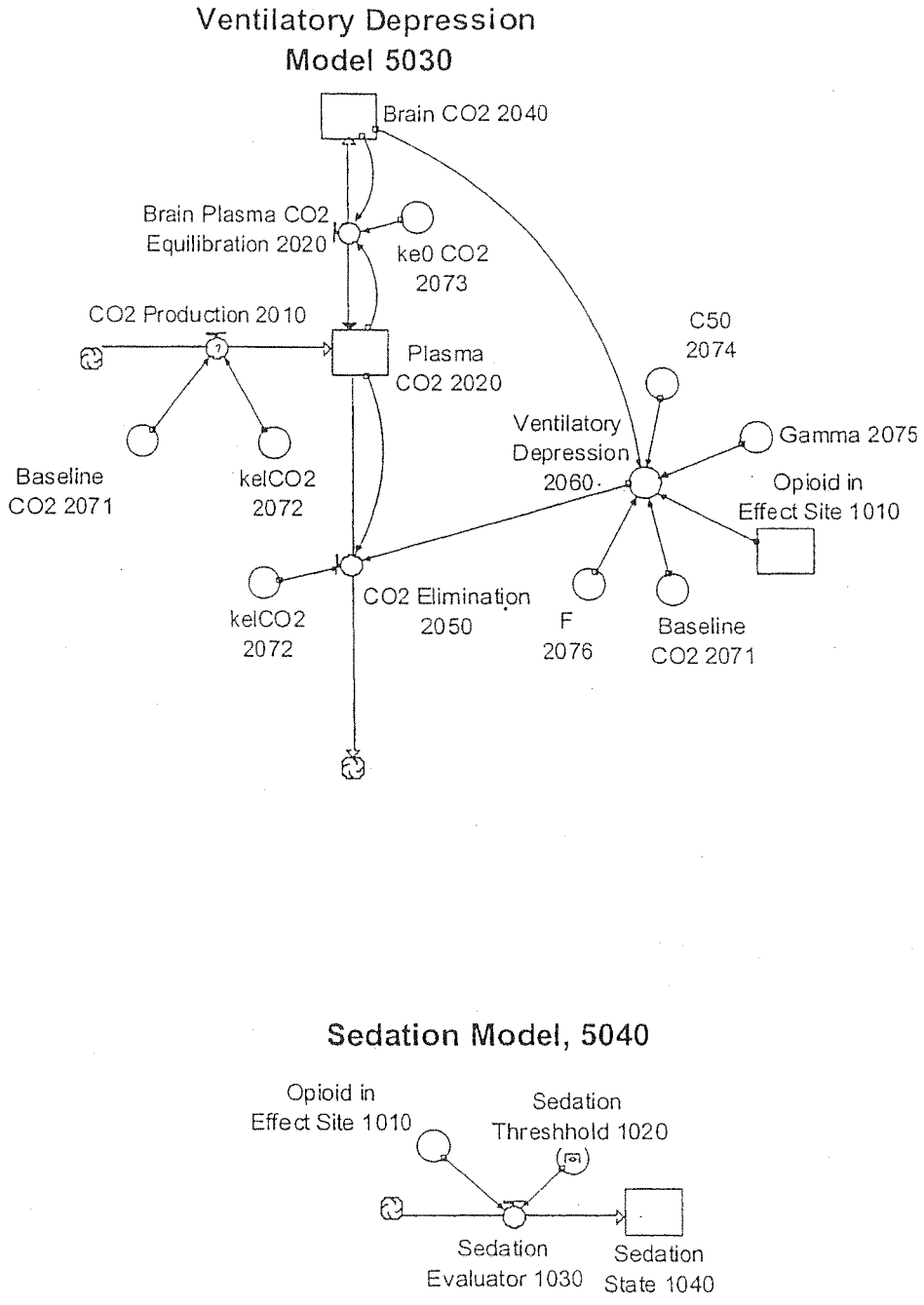


Figure 13C The elements of the invention, wherein two opioids are administered through inhalation.



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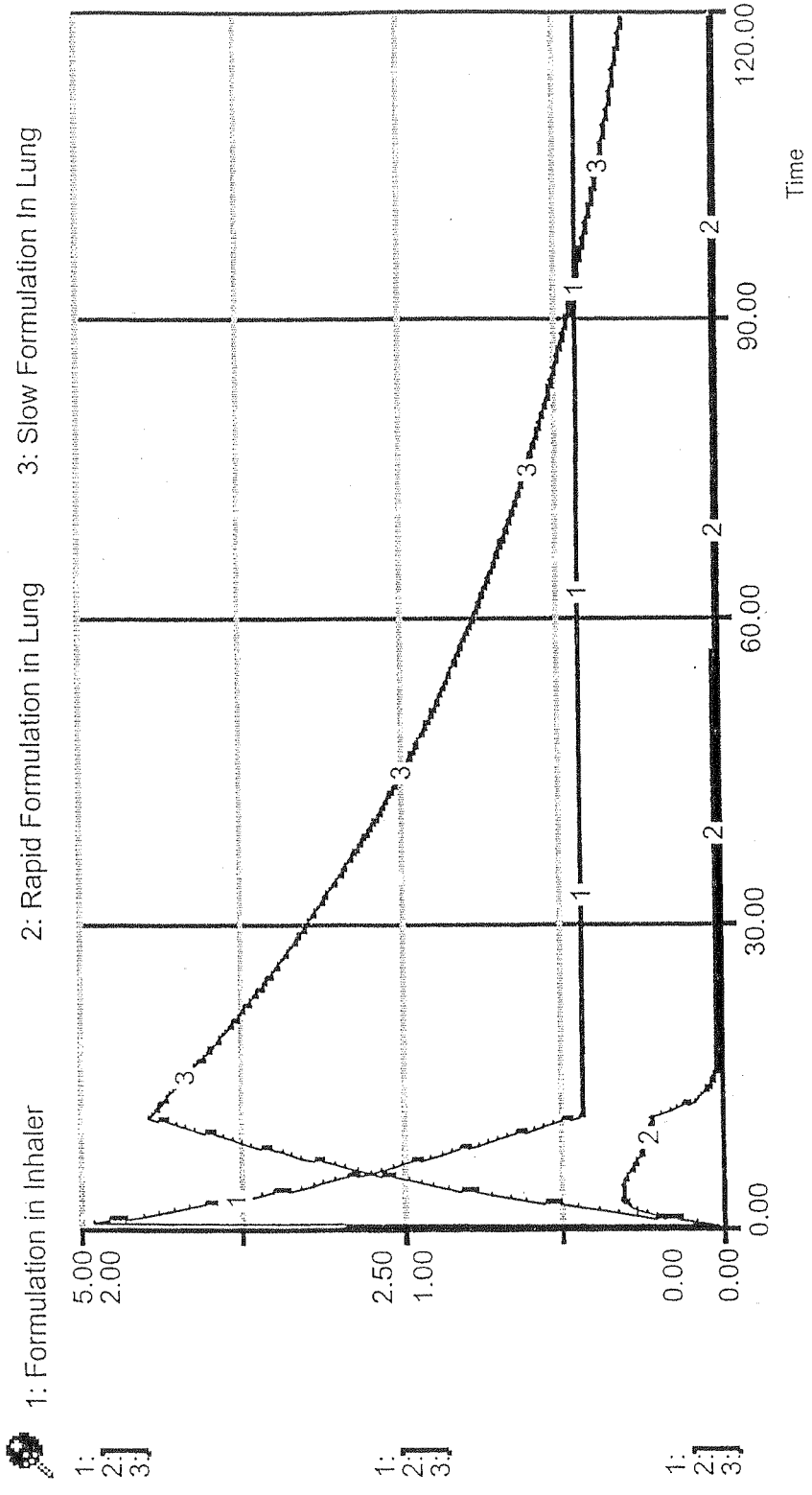


Figure 14: Drug in inhaler and lung in the presence of opioid-induced ventilatory depression and sedation for the two opioid model.

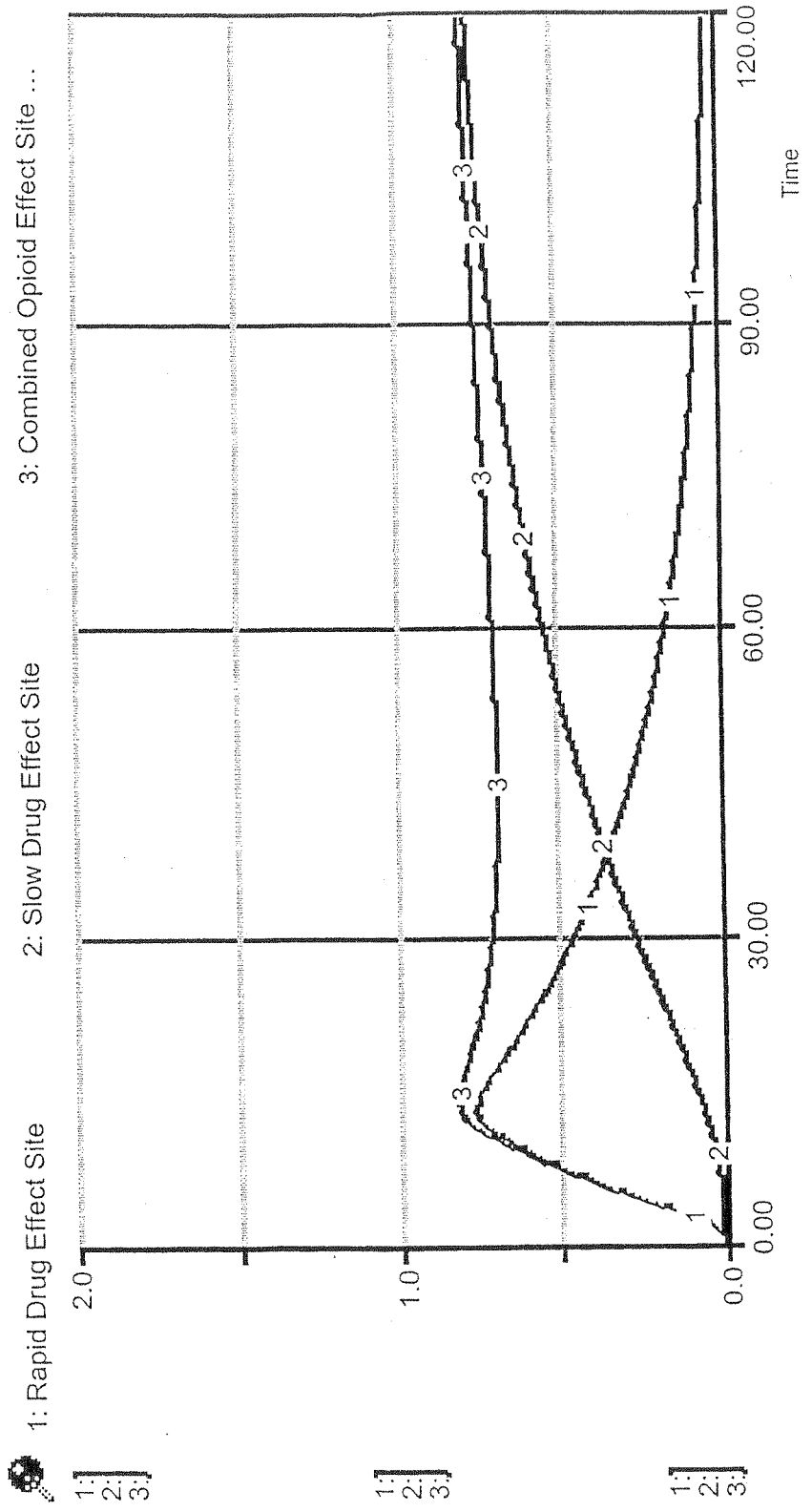


Figure 15: The rapidly acting opioid concentration in the effect site, the slowly acting opioid concentration in the effect site, and the combined concentration of opioid at the effect site, during two opioid administration with the device.

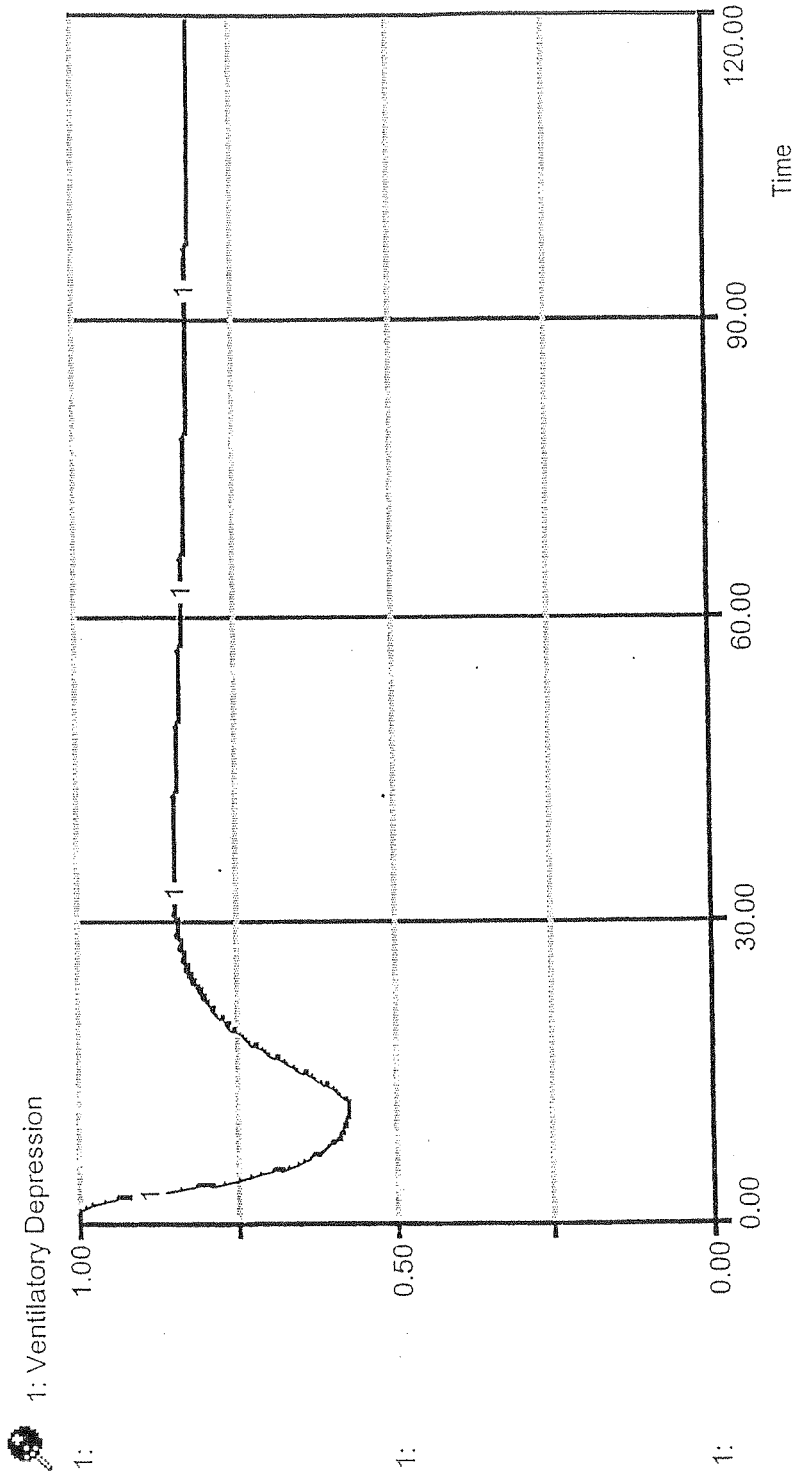


Figure 16: Ventilatory depression in the presence of self-limitation of opioid delivery from ventilatory depression and sedation with the two-opioid delivery system.

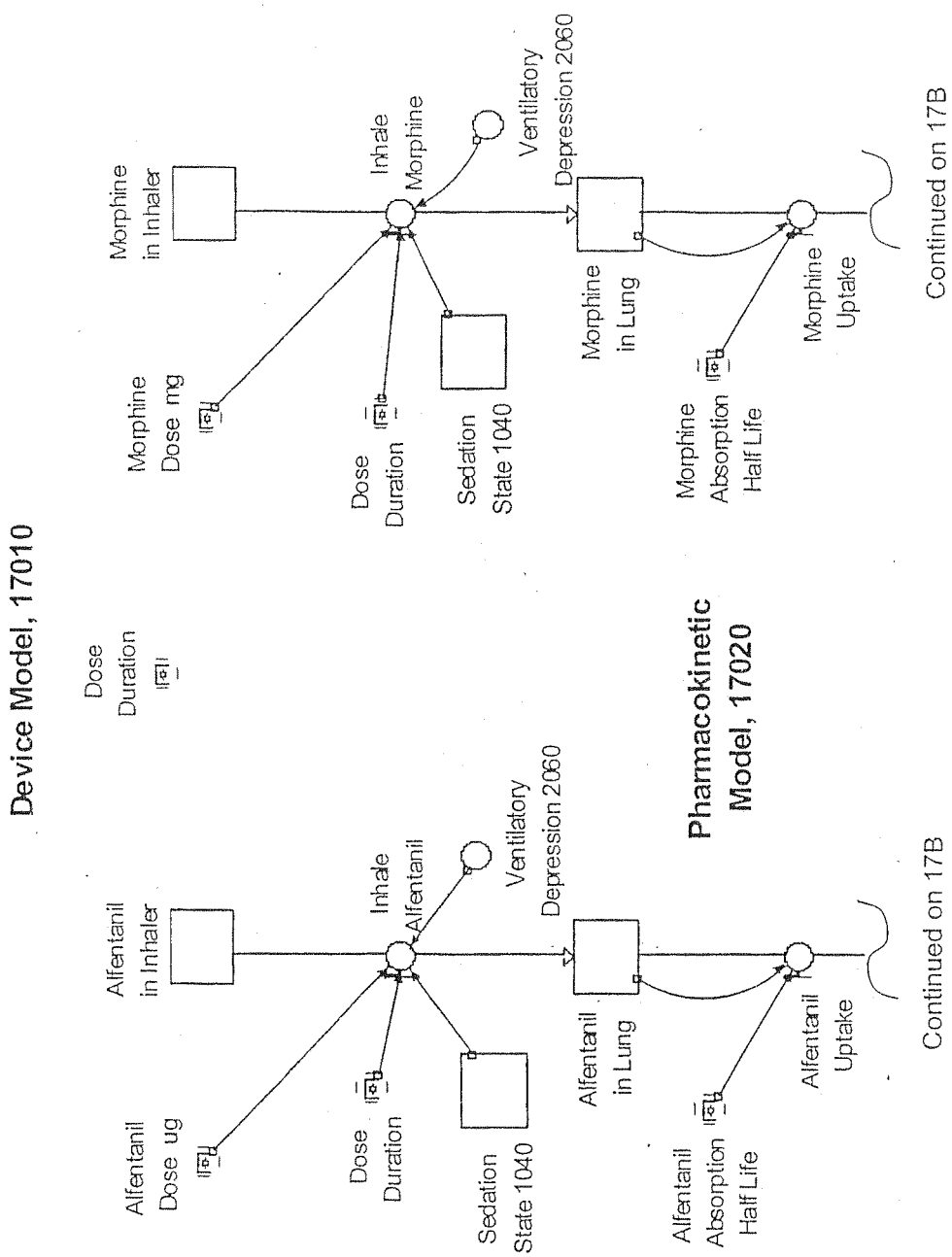


Figure 17A: The elements of the invention, wherein two opioids are administered through inhalation, and the rapidly acting opioid is alfentanil, and the slowly acting opioid is morphine.

Figure 17B: The elements of the invention, wherein two opioids are administered through inhalation, and the rapidly acting opioid is morphine.

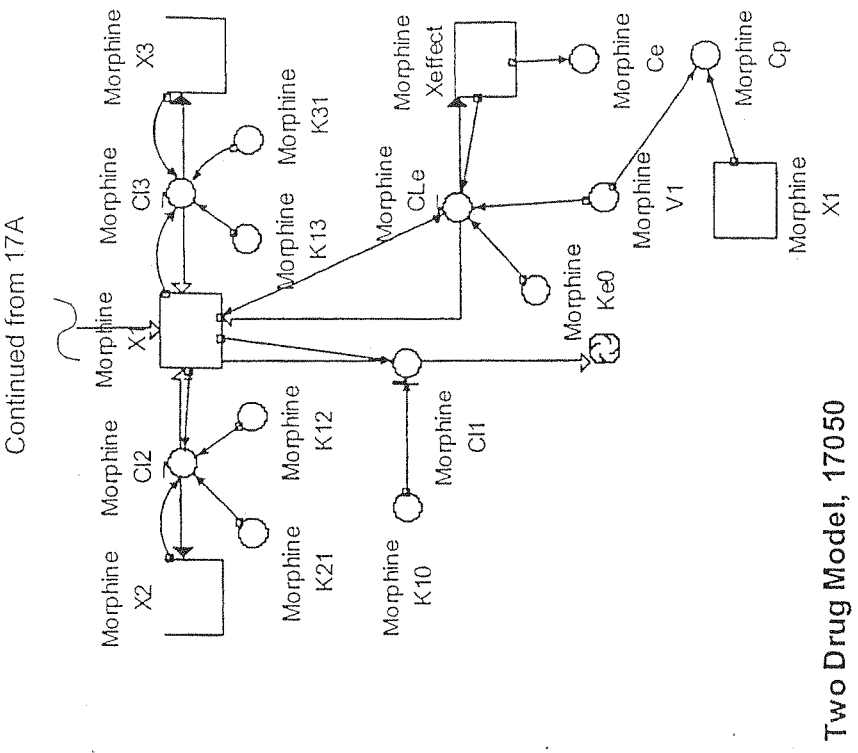
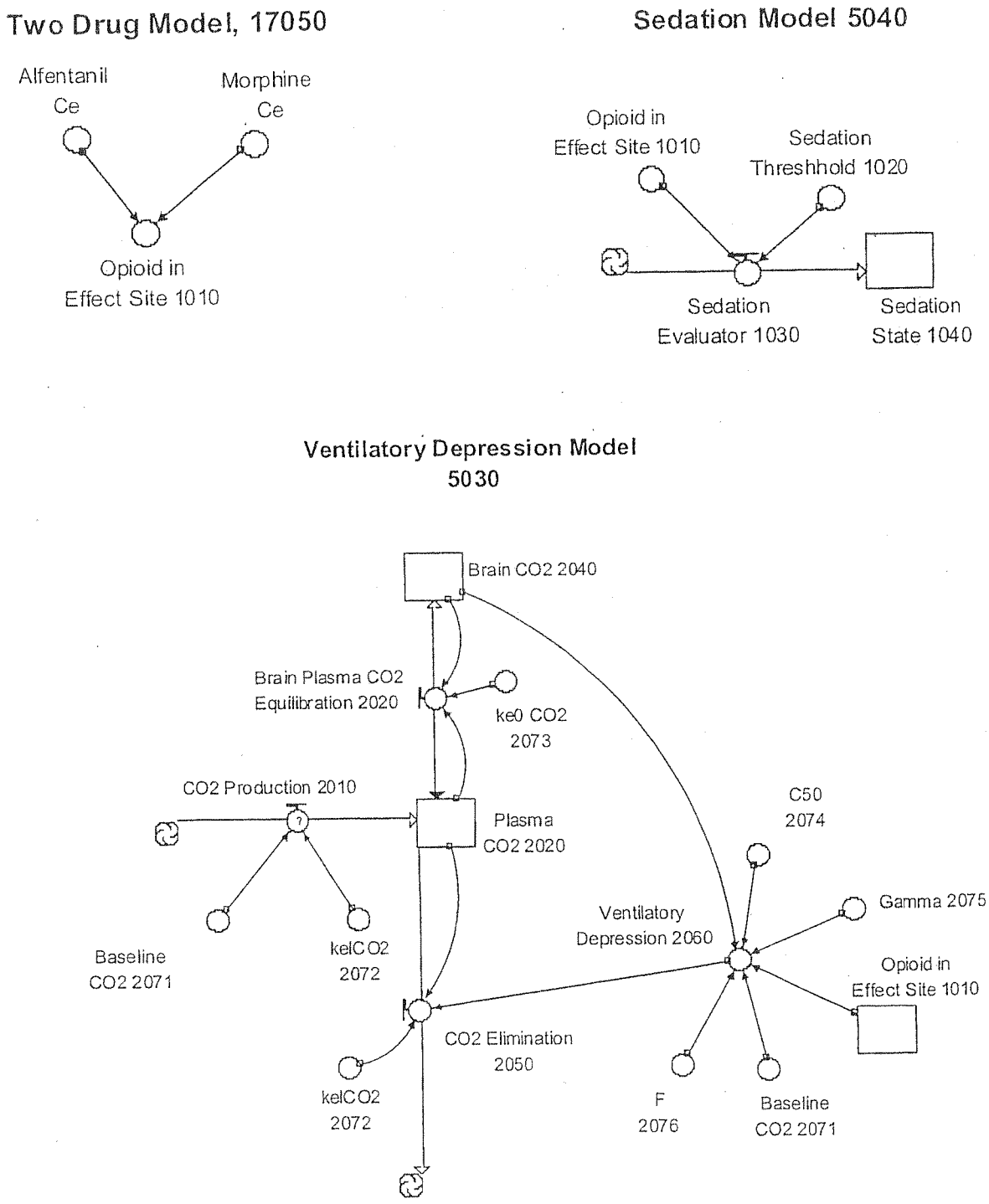


Figure 17C: The elements of the invention, wherein two opioids are administered through inhalation, and the rapidly acting opioid is alfentanil, and the slowly acting opioid is morphine.



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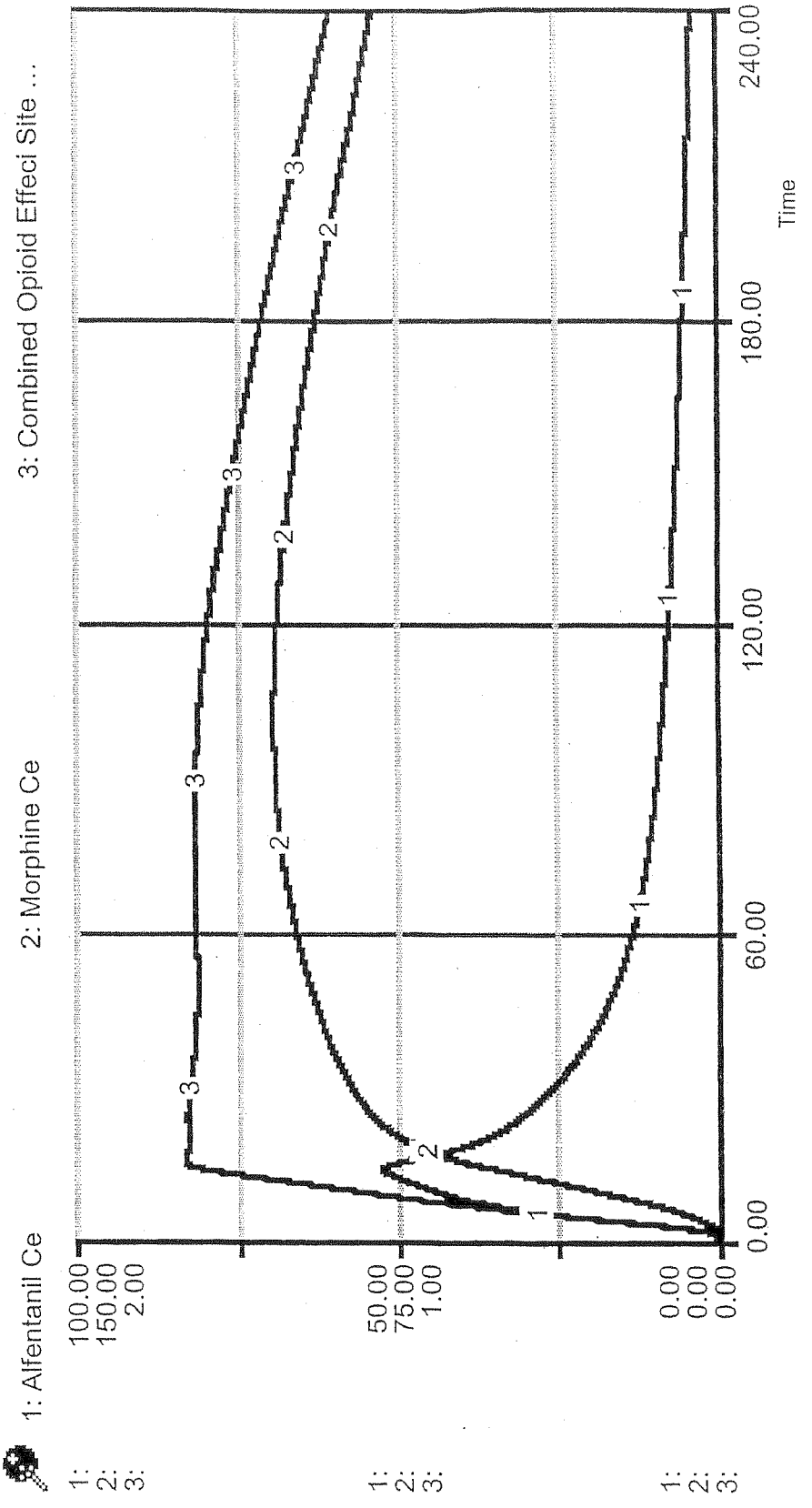


Figure 18: Alfentanil, morphine, and combined opioid effect site concentrations.

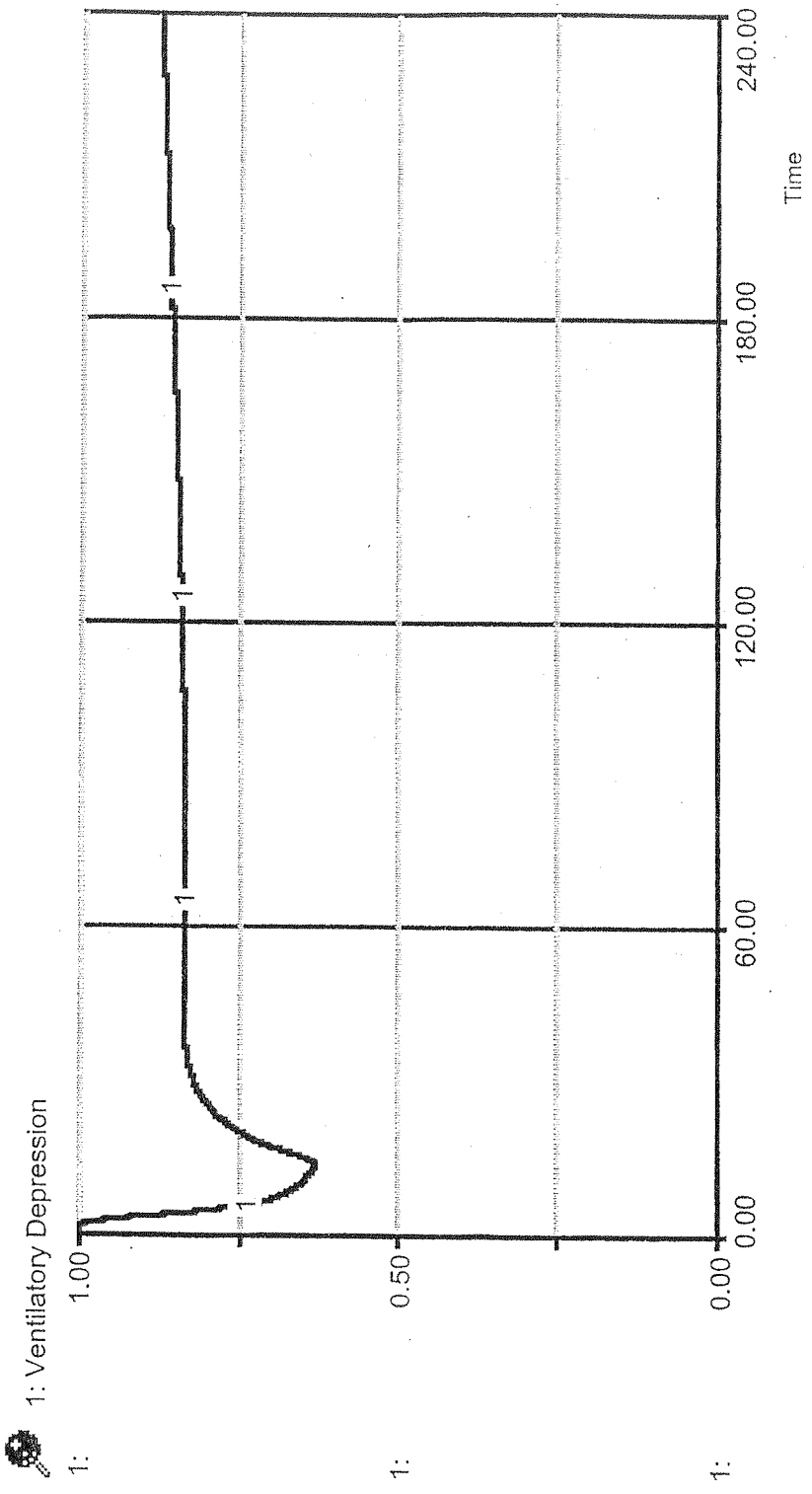

1: Ventilatory Depression
1:
1.00
0.50
0.00
1:
0.00
60.00
120.00
180.00
240.00
Time

Figure 19

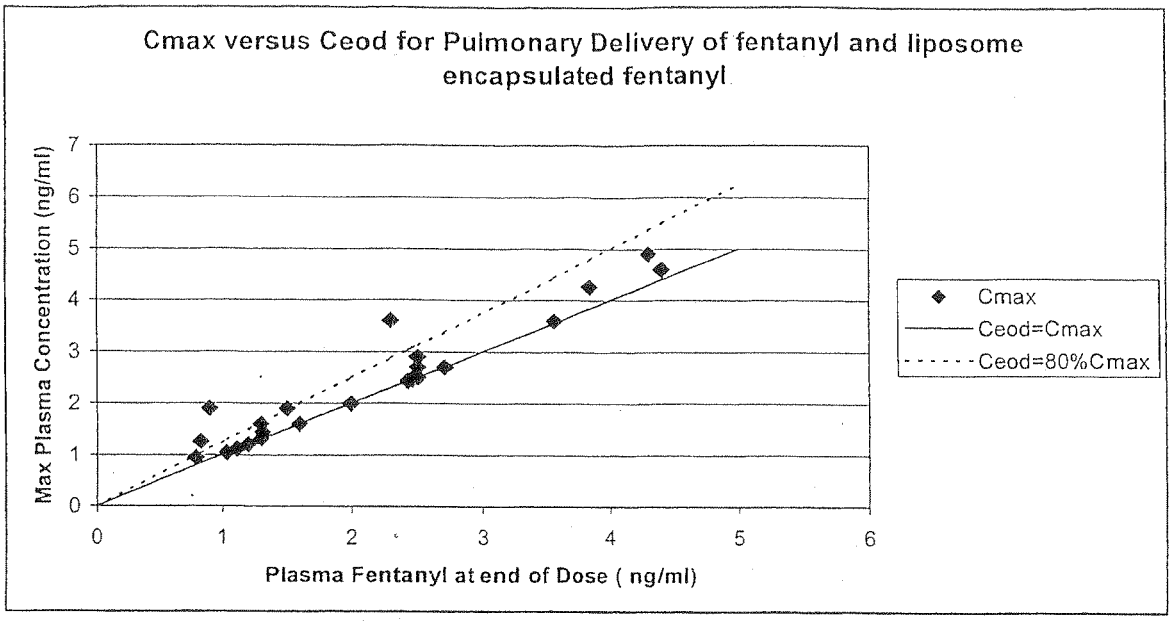


Figure 20A

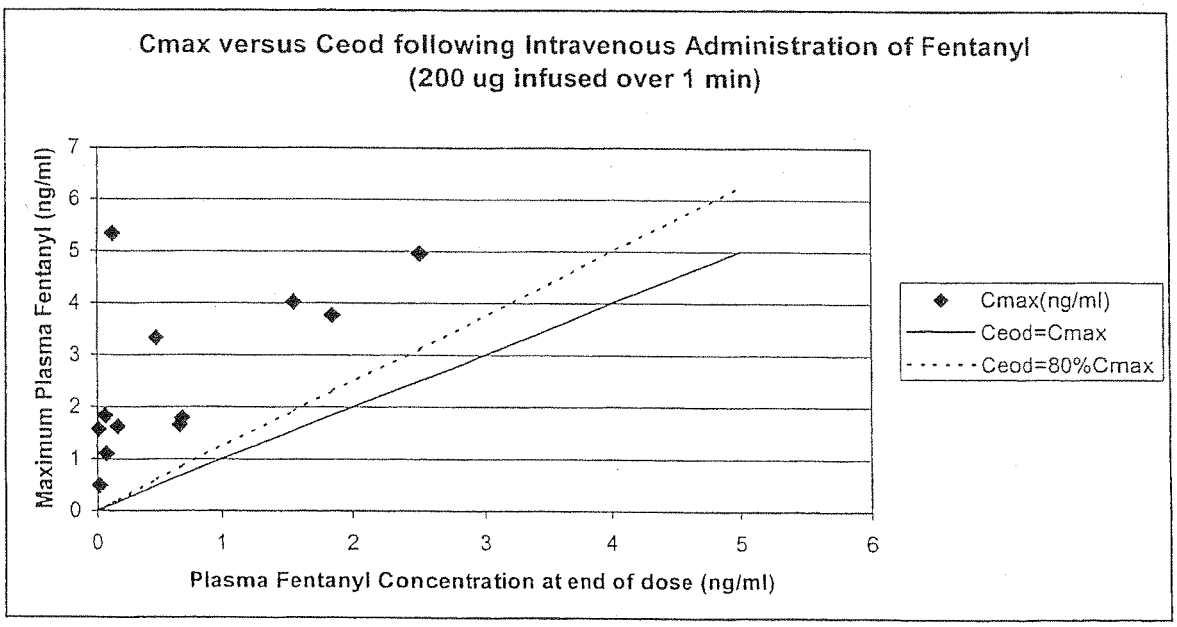


Figure 20B

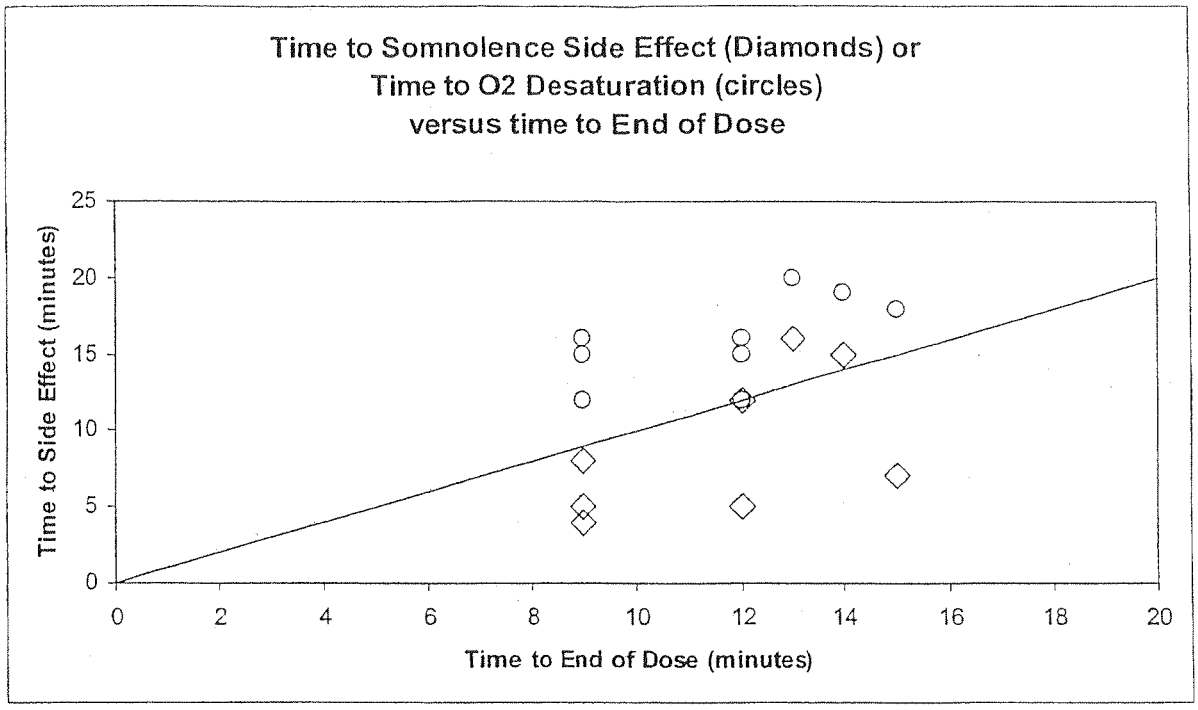

Time to Somnolence Side Effect (Diamonds) or
Time to O2 Desaturation (circles)
versus time to End of Dose
Time to Side Effect (minutes)
0
5
10
15
20
25
0
2
4
6
8
10
12
14
16
18
20
Time to End of Dose (minutes)

Figure 21

Figure 22: Correlation of side effect to toxic event

No side effect		Side effect	
N	26	24	
No hypoxia	22	14	36
Hypoxia	4	10	14
Null effect			
No hypoxia	18.72	17.28	36
Hypoxia	7.28	6.72	14
P value	0.038653124		

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