APPENDIX I

$$P_{m,O2}$$

$$P_{i,O2}$$

$$V_{tidal} f_{breath}$$

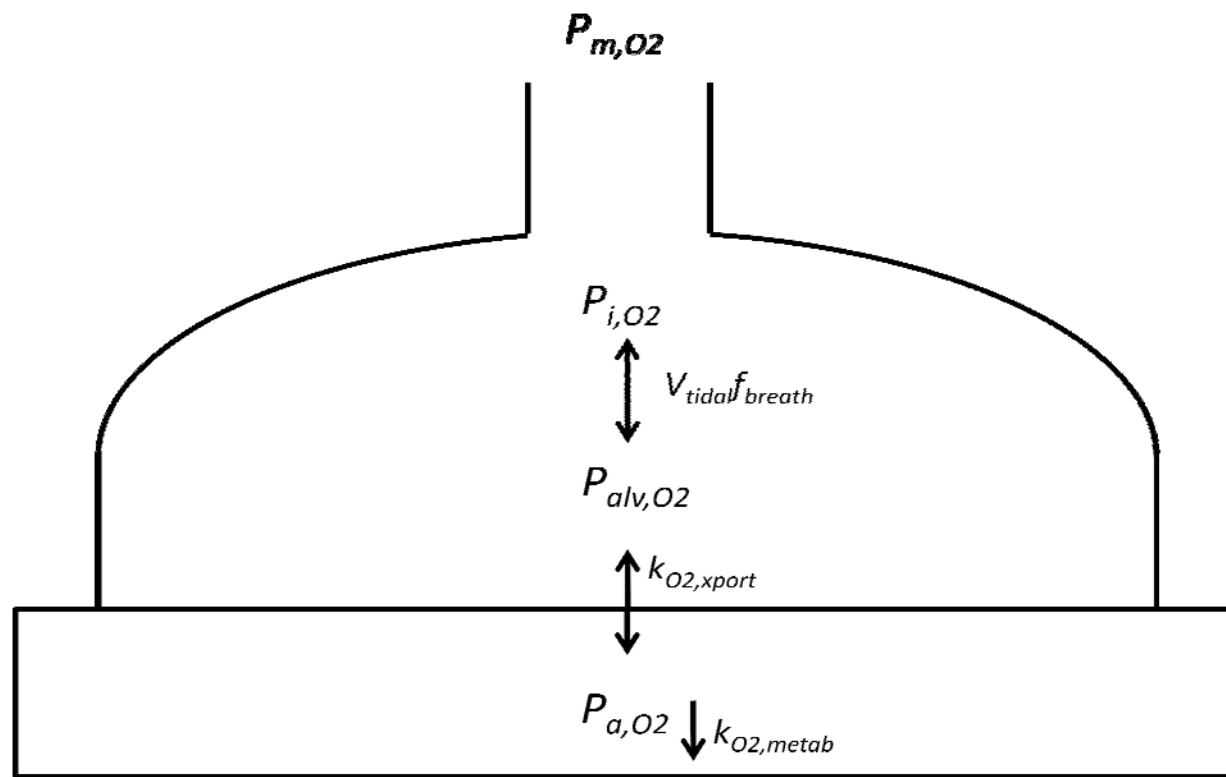$$P_{alv,O2}$$

$$k_{O2,xport}$$

$$P_{a,O2} \quad k_{O2,metab}$$

Schematic of gas transfer model

Steady State Lung Mechanics

$$V_{dead} = 0.2 V_{tidal}$$

$$V_{alv} = V_{tidal} - V_{dead}$$

$$P_{i,O_2}{}^0 = \frac{P_{m,O_2}(V_{tidal} - V_{dead}) + P_{alv,O_2}{}^0 V_{dead}}{V_{tidal}}$$

$$\dot{V} = V_{tidal} f_{breath}$$

$$k_{O_2,xport}{}^0 = \dot{V} \frac{\left(P_{i,O_2}{}^0 - P_{alv,O_2}{}^0\right)}{\left(P_{alv,O_2}{}^0 - P_{a,O_2}{}^0\right)}$$

$$k_{O_2,metab} = k_{O_2,xport}{}^0 \frac{\left(P_{alv,O_2}{}^0 - P_{a,O_2}{}^0\right)}{P_{a,O_2}{}^0}$$

Dynamic Lung Mechanics

$$k_{O_2,xport} = 2 \frac{ECR^{h_{EC}}}{1 + ECR^{h_{EC}}} k_{O_2,xport}{}^0$$

$$P_{i,O_2} = \frac{P_{m,O_2}(V_{tidal} - V_{dead}) + P_{alv,O_2} V_{dead}}{V_{tidal}}$$

Dynamic Lung Mechanics - O_2 Partial Pressures

$$V_{alv} \frac{dP_{alv,O_2}}{dt} = \dot{V}\left(P_{i,O_2} - P_{alv,O_2}\right) - k_{O_2 xport}\left(P_{alv,O_2} - P_{a,O_2}\right)$$

$$V_{blood} \frac{dP_{a,O_2}}{dt} = k_{O_2 xport}\left(P_{alv,O_2} - P_{a,O_2}\right) - k_{O_2 metab} P_{a,O_2}$$

Steady State Blood Volume

$$V_{blood} = 0.070 \, {}^{L}/_{kg} * weight$$

<u>Dynamic Immune Cell Movement</u>

$$k_{B,L,MA/NA} = k_{B,L,MA/NA}{}^{0} * MA/NA * ECA$$

<u>Clinical Interventions</u>

Fluids

$$B_{inc,fluid} = \sum_{i=1}^{n\,infusions} \frac{\alpha_{B,fluid}}{infusion\,duration_{fluids}} \quad where\;t = [t_{Fon,i}, t_{Foff,i}]$$

Ventilators

$$P_{m,O_2} = 760mmHg * F_{i,O_2}$$

F_{i,O_2} is determined by the ventilator setting

Mean Arterial Pressure

$$\frac{dB}{dt} = B_{inc,fluid}(1 - B) + k_B \left(\frac{1}{1 + k_{B,NO}(NO - x_{B,NO})} - B \right)$$

$$f_B(B) = (1 - B)^4$$

Damage

$$\frac{dD}{dt} = \left(d_{D,B} f_B(B) + k_{D,6} \frac{IL6^{h_{D,6}}}{IL6^{h_{D,6}} + x_{D,6}^{h_{D,6}}} + k_{D,PaO2} \left(1 - \frac{1}{1 + e^{-h_{D,PaO2}(PaO2 - \beta_{PaO2})}} - \frac{1}{1 + e^{-h_{D,PaO2}(-\beta_{PaO2})}} \right) \right) \left(\frac{x_{D,NO}^2}{NO^2 + x_{D,NO}^2} \right) - d_D D$$

P/F Ratio

$$PF\ Ratio = \frac{P_{a,O_2}}{F_{i,O_2}}$$

NO and Precursors

$$\frac{diNOSd}{dt} = k_{iNOS,n} NA + k_{iNOS.m} MA + k_{iNOS,ec} \left(\frac{TNF^2 x_{iNOS,TNF}^2}{TNF^2 + x_{iNOS,TNF}^2} + k_{iNOS,6} \frac{IL6^2 x_{iNOS,6}^2}{IL6^2 + x_{iNOS,6}^2} \right) \left(\frac{x_{iNOS,10}^2}{IL10^2 + x_{iNOS,10}^2} \right) \left(\frac{x_{iNOS,NO}^{h_{iNOS,NO}}}{IL10^{h_{iNOS,NO}} + x_{iNOS,NO}^{h_{iNOS,NO}}} \right) - d_{iNOSd} iNOSd$$

$$\frac{diNOS}{dt} = k_{iNOS}(iNOSd - iNOS)$$

$$\frac{deNOS}{dt} = k_{eNOS,ec} \left(\frac{x_{eNOS,TNF}}{TNF + x_{eNOS,TNF}} \right) \left(\frac{x_{eNOS,LPS}}{LPS + x_{eNOS,LPS}} \right) - d_{eNOS} eNOS$$

$$\frac{dNO_3}{dt} = k_{NO_3}(NO - NO_3)$$

$$NO = iNOS \left(1 + k_{NO,ma}(MA + NA) \right) + eNOS$$

Endotoxin

$$\frac{dLPS}{dt} = \frac{load_{LPS}}{infusion\ duration_{LPS}} - d_{LPS}LPS$$

Macrophages

$$\frac{dMR}{dt} = -\left(\left(k_{M,LPS}\frac{LPS^2 x_{M,LPS}^2}{LPS^2 + x_{M,LPS}^2} + k_{M,D}\frac{D^{h_{M,D}}}{D^{h_{M,D}} + x_{M,D}^{h_{M,D}}}\right)\left(\frac{TNF^2}{TNF^2 + x_{M,TNF}^2} + k_{M,6}\frac{IL6^2}{IL6^2 + x_{M,6}^2}\right) + k_{M,B}f_B(B)\right)\frac{x_{M,10}^2}{IL10^2 + x_{M,10}^2}MR - d_{MR}(MR - S_M)$$

$$\frac{dMA}{dt} = +\left(\left(k_{M,LPS}\frac{LPS^2 x_{M,LPS}^2}{LPS^2 + x_{M,LPS}^2} + k_{M,D}\frac{D^{h_{M,D}}}{D^{h_{M,D}} + x_{M,D}^{h_{M,D}}}\right)\left(\frac{TNF^2}{TNF^2 + x_{M,TNF}^2} + k_{M,6}\frac{IL6^2}{IL6^2 + x_{M,6}^2}\right) + k_{M,B}f_B(B)\right)\frac{x_{M,10}^2}{IL10^2 + x_{M,10}^2}MR - k_{B,L,MA}MA - d_{MA}MA$$

$$\frac{dMA_{Lung}}{dt} = k_{B,L,MA}MA - d_{MA}MA_{Lung}$$

Neutrophils

$$\frac{dNR}{dt} = -\left(k_{N,LPS}\frac{LPS\ x_{N,LPS}}{LPS + x_{N,LPS}} + k_{N,TNF}\frac{TNF^2 x_{N,TNF}^2}{TNF^2 + x_{N,TNF}^2} + k_{N,6}\frac{IL6^2 x_{N,6}^2}{IL6^2 + x_{N,6}^2} + k_{N,B}f_B(B) + k_{N,D}\frac{D^2 x_{N,D}^2}{D^2 + x_{N,D}^2}\right)\left(\frac{x_{N,10}^2}{IL10^2 + x_{N,10}^2}\right)NR - d_{NR}(NR - S_N)$$

$$\frac{dNA}{dt} = +\left(k_{N,LPS}\frac{LPS\ x_{N,LPS}}{LPS + x_{N,LPS}} + k_{N,TNF}\frac{TNF^2 x_{N,TNF}^2}{TNF^2 + x_{N,TNF}^2} + k_{N,6}\frac{IL6^2 x_{N,6}^2}{IL6^2 + x_{N,6}^2} + k_{N,B}f_B(B) + k_{N,D}\frac{D^2 x_{N,D}^2}{D^2 + x_{N,D}^2}\right)\left(\frac{x_{N,10}^2}{IL10^2 + x_{N,10}^2}\right)NR - k_{B,L,NA}NA - d_{NR}NA$$

$$\frac{dNA_{Lung}}{dt} = k_{B,L,NA}NA - d_{NA}NA_{Lung}$$

Lung Epithelial Cells

$$\frac{dECR}{dt} = -\left(k_{EC,LPS}\frac{LPS\ x_{EC,LPS}}{LPS + x_{EC,LPS}} + k_{EC,TNF}\frac{TNF^2 x_{EC,TNF}^2}{TNF^2 + x_{EC,TNF}^2} + k_{EC,6}\frac{IL6^2 x_{EC,6}^2}{IL6^2 + x_{EC,6}^2} + k_{EC,B}f_B(B) + k_{EC,D}\frac{D^2 x_{EC,D}^2}{D^2 + x_{EC,D}^2}\right)\left(\frac{x_{EC,10}^2}{IL10^2 + x_{EC,10}^2}\right)ECR - d_{ECR}(ECR - S_{EC})$$

$$\frac{dECA}{dt} = +\left(k_{EC,LPS}\frac{LPS\ x_{EC,LPS}}{LPS + x_{EC,LPS}} + k_{EC,TNF}\frac{TNF^2 x_{EC,TNF}^2}{TNF^2 + x_{EC,TNF}^2} + k_{EC,6}\frac{IL6^2 x_{EC,6}^2}{IL6^2 + x_{EC,6}^2} + k_{EC,B}f_B(B) + k_{EC,D}\frac{D^2 x_{EC,D}^2}{D^2 + x_{EC,D}^2}\right)\left(\frac{x_{EC,10}^2}{IL10^2 + x_{EC,10}^2}\right)ECR - d_{ECA}ECA$$

Cytokines

$$V_B \frac{dTNF}{dt} = \left(k_{N,TNF}NA + k_{M,TNF}MA\right)\left(\frac{x_{TNF,10}{}^{h_{TNF,10}}}{IL10^{h_{TNF,10}} + x_{TNF,10}{}^{h_{TNF,10}}}\right)\left(\frac{x_{TNF,6}{}^{h_{TNF,6}}}{IL6^{h_{TNF,6}} + x_{TNF,6}{}^{h_{TNF,6}}}\right) + Q_{lymph}TNF_{inter} - d_{TNF}TNF$$

$$V_B \frac{dIL1}{dt} = \left(k_{N,1}NA + k_{M,1}MA\right)\left(k_{1,TNF}\frac{TNF^{h_{1,TNF}}}{TNF^{h_{1,TNF}} + x_{1,TNF}{}^{h_{1,TNF}}} + k_{1,NO}\frac{NO^2}{NO^2 + x_{1,NO}{}^2} + k_{1,HM}\frac{HM^{h_{1,HM}}}{HM^{h_{1,HM}} + x_{1,HM}{}^{h_{1,HM}}}\right)\left(\frac{x_{1,10}{}^{h_{1,10}}}{IL10^{h_{1,10}} + x_{1,10}{}^{h_{1,10}}}\right)\left(\frac{x_{1,6}{}^{h_{1,6}}}{IL6^{h_{1,6}} + x_{1,6}{}^{h_{1,6}}}\right)$$
$$+ Q_{lymph}IL1_{inter} - d_{IL1}IL1$$

$$V_B \frac{dIL6}{dt} = \left(k_{6,N}NA + MA\right)\left(k_{6.M} + k_{6,TNF}\frac{TNF^{h_{6,TNF}}}{TNF^{h_{6,TNF}} + x_{6,TNF}{}^{h_{6,TNF}}} + \frac{IL1^{h_{6,1}}}{IL1^{h_{6,1}} + x_{6,1}{}^{h_{6,1}}} + k_{6,NO}\frac{NO^2}{NO^2 + x_{6,NO}{}^2} + k_{6,HM}\frac{HM^{h_{6,HM}}}{HM^{h_{6,HM}} + x_{6,HM}{}^{h_{6,HM}}}\right)$$
$$\left(\frac{x_{6,10}{}^{h_{6,10}}}{IL10^{h_{6,10}} + x_{6,10}{}^{h_{6,10}}}\right)\left(\frac{x_{6,6}{}^{h_{6,6}}}{IL6^{h_{6,6}} + x_{6,6}{}^{h_{6,6}}}\right) + Q_{lymph}IL6_{inter} - d_{IL6}IL6$$

$$V_B \frac{dIL10}{dt} = \left(k_{10,N}NA + MA\right)\left(k_{10.M} + k_{10,TNF}\frac{TNF^{h_{10,TNF}}}{TNF^{h_{10,TNF}} + x_{10,TNF}{}^{h_{10,TNF}}} + k_{10,6}\frac{IL6^{h_{10,6}}}{IL6^{h_{10,6}} + x_{10,6}{}^{h_{10,6}}} + k_{10,HM}\frac{HM^{h_{10,HM}}}{HM^{h_{10,HM}} + x_{10,HM}{}^{h_{10,HM}}}\right)$$
$$\left((1 - k_{10R})\frac{x_{10,12}{}^{h_{10,12}}}{IL12^{h_{10,12}} + x_{10,12}{}^{h_{10,12}}} + k_{10R}\right) + Q_{lymph}IL10_{inter} - d_{IL10}IL10$$

$$V_B \frac{dIL12}{dt} = \left(k_{12,M}MA\frac{x_{12,10}{}^2}{IL10^2 + x_{12,10}{}^2}\right) + Q_{lymph}IL12_{inter} - d_{IL12}IL12$$

$$V_B \frac{dHMGB1}{dt} = \left(k_{HM,N}NA + k_{HM,M}MA\right)\left(\frac{x_{HM,10}{}^{h_{HM,10}}}{IL10^{h_{HM,10}} + x_{HM,10}{}^{h_{HM,10}}}\right)\left(\frac{x_{HM,6}{}^{h_{HM,6}}}{IL6^{h_{HM,6}} + x_{HM,6}{}^{h_{HM,6}}}\right) + Q_{lymph}HMGB1_{inter} - d_{HM}HMGB1$$

$$V_{inter} \frac{dX_{inter}}{dt} = Q_{lymph}(X - X_{inter})$$
$$where\ X = \{TNF, IL1, IL6, IL10, IL12, HMGB1\}$$

Initial Conditions

Analyte	IC Value
B – Mean Arterial Pressure	1.0 (normalized)
D – Damage	0.0
PalvO2	104
PaO2	~95 (pig dependent)
Cytokines	0.0
LPS	0.0
Resting Cells	1.0 (normalized)
Active Cells	0.0
iNOS	0.0
iNOSd	0.0
eNOS	~0.015 (pig dependent)
NO3	~0.015 (pig dependent)