Instruction
m code for Figure 2 - D, E and F

There are five m files in this PDF file. Their locations were listed in the table below. Put all five m files as noted below into same folder, and run Main.m file to run the simulation.

m file name	Pages (starting – end page)
AW.m	2-13
AL.m	14-23
Lung.m	24-29
Lung_fun.m	30-30
Main.m	31-31

```
% 4/30/2009
% 1CellPK based lung-airways model starts here (Rats)
% 12 compartments:
% aEp (surface lining liquied), imEp (Macrophage),
% cEp(epithelial cells),cEpMito(mito of cEp), cEpLyso (lyso of cEp)
% int(Interstitium),imInt(immune cells), sm(smooth muscle),
% cEd(endothelial cells), cEdMito(mito of cEd),cEdLyso (lyso of cEd), p(plasma)
 function [M, G, M_v, Vp] = AW(pKa,logPN,x)
%molecular physiochemical property
logPD = logPN-3.7 ;
 % Constant
T = 273.15+37;
R = 8.314;
F = 96484.56;
z = 1;
 %lipid fraction
LaEp = 0.2;
LimEp = 0.05;
LcEp = 0.05 ;
Lint = 0;
Lsm = 0.05;
LimInt = 0.05;
LcEd = 0.05;
Lp = 0;

%volumetric water fraction=1-lipid fraction
WaEp = 1 - LaEp;
WimEp = 1 - LimEp;
WcEp = 1 - LcEp;
Wint = 1 - Lint;
Wsm = 1 - Lsm;
WimInt = 1 - LimInt;
WcEd = 1 - LcEd;
Wp = 1 - Lp;

%activity coefficient of species(N:neutral,D:desociated)
GaEpN = 1;
GaEpD = 1;
GimEpN = 1.23;
GimEpD = 0.74;
GcEpN = 1.23;
GcEpD = 0.74;
GintN = 1;
GintD = 1;
GsmN = 1.23;
GsmD = 0.74;
GimIntN = 1.23;
GimIntD = 0.74;
GcEdN = 1.23;
GcEdD = 0.74;
GpN = 1;
GpD = 1;

% By Jingyu Yu (used in publication J YU Pharm Res 2010, 27) parameters in airways
% Areas and volumes (m^2, m^3) for 7 membranes and corresponding compartments
AaEp = 108*10^(-4);%
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AbEp = 108*10^(-4);%assuming same with apical
AimEp = x*0;%No macrophage
AimInt = 0.01*AaEp;%estimate
Asm = AaEp*2; % two side, double the surface area of airway,T model
AbEd = AaEp/5;% estimated 1/5 surface of epithelium
AaEd = AaEp/5;% same as basical side
% volumes for 8 compartments(m3)
ASL = 15; % um literature
VaEp = AaEp*ASL*10^(-6); %15 um thickness
VimEp = x*10^(-30); %10^(-12)*VaEp; % Anynumber,No macrophage at surface
VcEp = 0.072*10^(-6); % estimated from yori model,basement membrane->surface area->thickness of each
generation
Vint = AaEp*1*10^(-6);%estimated
Vsm = 0.047*10^(-6);%% estimated from yori model,basement membrane->surface area->thickness of each
generation
VimInt = 0.01*Vint;%setimated
VcEd = AbEd*0.4*10^(-6); %estimated from literature,thickness of endothelium in AW
% Vp = 5; %total blood

R_org = 0.1;
% calculate constant
VcEpMito = R_org*VcEp;
VcEpLyso = R_org*VcEp;
VcEdMito = R_org*VcEd ;
VcEdLyso = R_org*VcEd ;
VsmMito = R_org*Vsm;
VsmLyso = R_org*Vsm;

AcEpMito = 5.9924e+006*VcEpMito ;
AcEpLyso = 5.9924e+006*VcEpLyso ;
AcEdMito = 5.9924e+006*VcEdMito ;
AcEdLyso = 5.9924e+006*VcEdLyso ;
AsmMito = 5.9924e+006*VsmMito ;
AsmLyso = 5.9924e+006*VsmMito ;
%#########################################################################

M_v = diag([VaEp,VimEp,VcEp,VcEpMito,VcEpLyso,Vint,Vsm, VsmMito, VsmLyso, VimInt, VcEd, VcEdMito,
VcEdLyso]);
V_LUN = trace(M_v)*10^6;
Vp = 340*10^(-9)*V_LUN;

% Membrane potential (V)
EaEp = -0.0093;
EbEp = 0.0119;
EimEp = -0.06;
Esm = -0.06;
EimInt = -0.06;
EbEd = -0.06;
EaEd = -0.06;
% pH values
pHaEp = 7.4;
pHimEp = 7.0;
pHcEp = 7.0;
pHint = 7.0;
pHsm = 7.0;
pHimInt = 7.0;
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pHcEd = 7.0;
pHp = 7.4;

%adjustment for logP
if ( abs(z-1) <= 10^(-6) )
   logP_nlipT = 0.33*logPN+2.2 ;
   logP_dlipT = 0.37*logPD+2 ;
end
if ( abs(z+1) <= 10^(-6) )
   logP_nlipT = 0.37*logPN+2.2 ;
   logP_dlipT = 0.33*logPD+2.6 ;
end
if ( abs(z-0) <= 10^(-5) )
   logP_nlipT = 0.33*logPN+2.2 ;
   logP_dlipT = 0.33*logPD+2.2 ;
end

% Get the first two decimals
logP_n = round(logP_nlipT*100)/100 ;
logP_d = round(logP_dlipT*100)/100 ;
%calculate the membrane permeability

Pn = 10^(logP_n-6.7)*60; % in 1/min
Pd = 10^(logP_d-6.7)*60; % in 1/min

i = -sign(z) ;
%calculate N for flux of ion happening at 7 membranes
C = z*F/(R*T);
NaEp = C*(-EaEp) ;
NbEp = C*EbEp ;
NimEp = C*EimEp ;
Nsm = C*Esm ;
NimInt = C*EimInt ;
NbEd = C*(-EbEd) ;
NaEd = C*EaEd ;
%calculate Kn and Kd for 8 compartments
N = 1.22*10^(logP_n);
D = 1.22*10^(logP_d);

%calculate Kn and Kd for 8 compartments

KaEpN = N*LaEp ;
KaEpD = D*LaEp ;
KimEpN = N*LimEp ;
KimEpD = D*LimEp ;
KcEpN = N*LcEp ;
KcEpD = D*LcEp ;
KintN = N*Lint ;
KintD = D*Lint ;
KsmN = N*Lsm ;
KsmD = D*Lsm ;
KimIntN = N*LimInt ;
KimIntD = D*LimInt ;
KcEdN = N*LcEd ;
KcEdD = D*LcEd ;
KpN = N*Lp ;
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KpD = D*Lp ;

%####################for mito and lyso compartments in cEp, sm
and %cEd####################################################
LcEpMito = 0.05 ;
LcEpLyso = 0.05 ;
LsmMito = 0.05 ;
LsmLyso = 0.05 ;
LcEdMito = 0.05 ;
LcEdLyso = 0.05 ;

WcEpMito = 1-LcEpMito ;
WcEpLyso = 1-LcEpLyso ;
WsmMito = 1-LsmMito ;
WsmLyso = 1-LsmLyso ;
WcEdMito = 1-LcEdMito ;
WcEdLyso = 1-LcEdLyso ;

GcEpMitoN = 1.23 ;
GcEpMitoD = 0.74 ;
GcEpLysoN = 1.23 ;
GcEpLysoD = 0.74 ;

GsmMitoN = 1.23 ;
GsmMitoD = 0.74 ;
GsmLysoN = 1.23 ;
GsmLysoD = 0.74 ;

GcEdMitoN = 1.23 ;
GcEdMitoD = 0.74 ;
GcEdLysoN = 1.23 ;
GcEdLysoD = 0.74 ;

EcEpMito = -0.16 ;
EcEpLyso = +0.01 ;
EsmMito = -0.16 ;
EsmLyso = +0.01 ;
EcEdMito = -0.16 ;
EcEdLyso = +0.01 ;

pHcEpMito = 8 ;
pHcEpLyso = 5 ;
pHsmMito = 8 ;
pHsmLyso = 5 ;
pHcEdMito = 8 ;
pHcEdLyso = 5 ;


NcEpMito = C*EcEpMito ;
NcEpLyso = C*EcEpLyso ;
NsmMito = C*EsmMito ;
NsmLyso = C*EsmLyso ;
NcEdMito = C*EcEdMito ;
NcEdLyso = C*EcEdLyso ;
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KcEpMitoN = N*LcEpMito ;
KcEpMitoD = D*LcEpMito ;
KcEpLysoN = N*LcEpLyso ;
KcEpLysoD = D*LcEpLyso ;

KsmMitoN = N*LsmMito ;
KsmMitoD = D*LsmMito ;
KsmLysoN = N*LsmLyso ;
KsmLysoD = D*LsmLyso ;

KcEdMitoN = N*LcEdMito ;
KcEdMitoD = D*LcEdMito ;
KcEdLysoN = N*LcEdLyso ;
KcEdLysoD = D*LcEdLyso ;



fcEpMitoN = 1/(WcEpMito/GcEpMitoN+KcEpMitoN/GcEpMitoN+WcEpMito*10^(i*(pHcEpMito-
pKa))/GcEpMitoD...
        +KcEpMitoD*10^(i*(pHcEpMito-pKa))/GcEpMitoD);
fcEpMitoD = fcEpMitoN*10^(i*(pHcEpMito-pKa));

fcEpLysoN = 1/(WcEpLyso/GcEpLysoN+KcEpLysoN/GcEpLysoN+WcEpLyso*10^(i*(pHcEpLyso-
pKa))/GcEpLysoD...
        +KcEpLysoD*10^(i*(pHcEpLyso-pKa))/GcEpLysoD);
fcEpLysoD = fcEpLysoN*10^(i*(pHcEpLyso-pKa));


fsmMitoN = 1/(WsmMito/GsmMitoN+KsmMitoN/GsmMitoN+WsmMito*10^(i*(pHsmMito-pKa))/GsmMitoD...
        +KsmMitoD*10^(i*(pHsmMito-pKa))/GsmMitoD);
fsmMitoD = fsmMitoN*10^(i*(pHsmMito-pKa));

fsmLysoN = 1/(WsmLyso/GsmLysoN+KsmLysoN/GsmLysoN+WsmLyso*10^(i*(pHsmLyso-pKa))/GsmLysoD...
        +KsmLysoD*10^(i*(pHsmLyso-pKa))/GsmLysoD);
fsmLysoD = fsmLysoN*10^(i*(pHsmLyso-pKa));


fcEdMitoN = 1/(WcEdMito/GcEdMitoN+KcEdMitoN/GcEdMitoN+WcEdMito*10^(i*(pHcEdMito-
pKa))/GcEdMitoD...
        +KcEdMitoD*10^(i*(pHcEdMito-pKa))/GcEdMitoD);
fcEdMitoD = fcEdMitoN*10^(i*(pHcEdMito-pKa));

fcEdLysoN = 1/(WcEdLyso/GcEdLysoN+KcEdLysoN/GcEdLysoN+WcEdLyso*10^(i*(pHcEdLyso-
pKa))/GcEdLysoD...
        +KcEdLysoD*10^(i*(pHcEdLyso-pKa))/GcEdLysoD);
fcEdLysoD = fcEdLysoN*10^(i*(pHcEdLyso-pKa));

%##########################################################################

%compute the fn and fd for 8 compartments
faEpN = 1/(WaEp/GaEpN+KaEpN/GaEpN+WaEp*10^(i*(pHaEp-pKa))/GaEpD...
        +KaEpD*10^(i*(pHaEp-pKa))/GaEpD);
faEpD = faEpN*10^(i*(pHaEp-pKa));
fimEpN = 1/(WimEp/GimEpN+KimEpN/GimEpN+WimEp*10^(i*(pHimEp-pKa))/GimEpD...
        +KimEpD*10^(i*(pHimEp-pKa))/GimEpD);
fimEpD = fimEpN*10^(i*(pHimEp-pKa));
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fcEpN = 1/(WcEp/GcEpN+KcEpN/GcEpN+WcEp*10^(i*(pHcEp-pKa))/GcEpD...
        +KcEpD*10^(i*(pHcEp-pKa))/GcEpD);
fcEpD = fcEpN*10^(i*(pHcEp-pKa));
fintN = 1/(Wint/GintN+KintN/GintN+Wint*10^(i*(pHint-pKa))/GintD...
        +KintD*10^(i*(pHint-pKa))/GintD);
fintD = fintN*10^(i*(pHint-pKa));
fimIntN = 1/(WimInt/GimIntN+KimIntN/GimIntN+WimInt*10^(i*(pHimInt-pKa))/GimIntD...
        +KimIntD*10^(i*(pHimInt-pKa))/GimIntD);
fimIntD = fimIntN*10^(i*(pHimInt-pKa));
fsmN = 1/(Wsm/GsmN+KsmN/GsmN+Wsm*10^(i*(pHsm-pKa))/GsmD...
        +KsmD*10^(i*(pHsm-pKa))/GsmD);
fsmD = fsmN*10^(i*(pHsm-pKa));
fcEdN = 1/(WcEd/GcEdN+KcEdN/GcEdN+WcEd*10^(i*(pHcEd-pKa))/GcEdD...
        +KcEdD*10^(i*(pHcEd-pKa))/GcEdD);
fcEdD = fcEdN*10^(i*(pHcEd-pKa));
fpN = 1/(Wp/GpN+KpN/GpN+Wp*10^(i*(pHp-pKa))/GpD...
        +KpD*10^(i*(pHp-pKa))/GpD);
fpD = fpN*10^(i*(pHp-pKa));

%mucus clearance: optional
Ke = 0;

%compute the coefficient matrix for ODEs
% #1: Surface Lining Liquid (aEp)
KaEp_aEp = AaEp/VaEp*(Pn*(-faEpN)+Pd*NaEp/(exp(NaEp)-1)*(-faEpD)*exp(NaEp))...
       -AimEp/VaEp*(Pn*faEpN+Pd*NimEp/(exp(NimEp)-1)*faEpD)...
       -Ke;
KaEp_imEp = -AimEp/VaEp*(Pn*(-fimEpN)+Pd*NimEp/(exp(NimEp)-1)*(-fimEpD)*exp(NimEp));
KaEp_cEp = AaEp/VaEp*(Pn*(fcEpN)+Pd*NaEp/(exp(NaEp)-1)*(fcEpD));
KaEp_cEpMito = 0;
KaEp_cEpLyso = 0;
KaEp_int = 0;
KaEp_sm = 0;
KaEp_smMito = 0;
KaEp_smLyso = 0;
KaEp_imInt = 0;
KaEp_cEd = 0;
KaEp_cEdMito = 0;
KaEp_cEdLyso = 0;
KaEp_p = 0;
SaEp = 0;

% #2: Macrophage (imEp)
KimEp_aEp = AimEp/VimEp*(Pn*faEpN+Pd*NimEp/(exp(NimEp)-1)*faEpD);
KimEp_imEp = AimEp/VimEp*(Pn*(-fimEpN)+Pd*NimEp/(exp(NimEp)-1)*(-fimEpD)*exp(NimEp));
KimEp_cEp = 0;
KimEp_cEpMito = 0 ;
KimEp_cEpLyso = 0 ;
KimEp_int = 0;
KimEp_sm = 0;
KimEp_smMito = 0;
KimEp_smLyso = 0;
KimEp_imInt = 0;
KimEp_cEd = 0;
KimEp_cEdMito = 0 ;
KimEp_cEdLyso = 0 ;
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KimEp_p = 0;
SimEp = 0;

% #3: Epithelial Cells (cEp)
KcEp_aEp = -AaEp/VcEp*(Pn*(-faEpN)+Pd*NaEp/(exp(NaEp)-1)*(-faEpD)*exp(NaEp));
KcEp_imEp = 0;
KcEp_cEp = -AaEp/VcEp*(Pn*(fcEpN)+Pd*NaEp/(exp(NaEp)-1)*(fcEpD))...
        -AcEpMito/VcEp*(Pn*fcEpN+Pd*NcEpMito/(exp(NcEpMito)-1)*fcEpD)...
        -AcEpLyso/VcEp*(Pn*fcEpN+Pd*NcEpLyso/(exp(NcEpLyso)-1)*fcEpD)...
        +AbEp/VcEp*(Pn*(-fcEpN)+Pd*NbEp/(exp(NbEp)-1)*(-fcEpD)*exp(NbEp));
KcEp_cEpMito = -AcEpMito/VcEp*(Pn*(-fcEpMitoN)+Pd*NcEpMito/(exp(NcEpMito)-1)*(-
fcEpMitoD)*exp(NcEpMito)) ;
KcEp_cEpLyso = -AcEpLyso/VcEp*(Pn*(-fcEpLysoN)+Pd*NcEpLyso/(exp(NcEpLyso)-1)*(-
fcEpLysoD)*exp(NcEpLyso)) ;
KcEp_int = AbEp/VcEp*(Pn*(fintN)+Pd*NbEp/(exp(NbEp)-1)*(fintD));
KcEp_sm = 0;
KcEP_smMito = 0;
KcEp_smLyso = 0;
KcEp_imInt = 0;
KcEp_cEd = 0;
KcEp_cEdMito = 0 ;
KcEp_cEdLyso = 0 ;
KcEp_p = 0;
ScEp = 0;

% #4: : Epithelial Cells (cEpMito)
KcEpMito_aEp = 0;
KcEpMito_imEp = 0;
KcEpMito_cEp = AcEpMito/VcEpMito*(Pn*(fcEpN)+Pd*NcEpMito/(exp(NcEpMito)-1)*(fcEpD));
KcEpMito_cEpMito = AcEpMito/VcEpMito*(Pn*(-fcEpMitoN)+Pd*NcEpMito/(exp(NcEpMito)-1)*(-
fcEpMitoD)*exp(NcEpMito));
KcEpMito_cEpLyso = 0 ;
KcEpMito_int = 0 ;
KcEpMito_sm = 0;
KcEpMito_smMito = 0;
KcEpMito_smLyso = 0;
KcEpMito_imInt = 0;
KcEpMito_cEd = 0;
KcEpMito_cEdMito = 0 ;
KcEpMito_cEdLyso = 0 ;
KcEpMito_p = 0;
ScEpMito = 0;

% #5: : Epithelial Cells (cEpLyso)
KcEpLyso_aEp = 0;
KcEpLyso_imEp = 0;
KcEpLyso_cEp = AcEpLyso/VcEpLyso*(Pn*(fcEpN)+Pd*NcEpLyso/(exp(NcEpLyso)-1)*(fcEpD));
KcEpLyso_cEpMito = 0 ;
KcEpLyso_cEpLyso = AcEpLyso/VcEpLyso*(Pn*(-fcEpLysoN)+Pd*NcEpLyso/(exp(NcEpLyso)-1)*(-
fcEpLysoD)*exp(NcEpLyso));
KcEpLyso_int = 0 ;
KcEpLyso_sm = 0;
KcEpLyso_smMito = 0;
KcEpLyso_smLyso = 0;
KcEpLyso_imInt = 0;
KcEpLyso_cEd = 0;
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KcEpLyso_cEdMito = 0 ;
KcEpLyso_cEdLyso = 0 ;
KcEpLyso_p = 0;
ScEpLyso = 0;

% #6: : Interstitium (int)
Kint_aEp = 0;
Kint_imEp = 0;
Kint_cEp = -AbEp/Vint*(Pn*(-fcEpN)+Pd*NbEp/(exp(NbEp)-1)*(-fcEpD)*exp(NbEp));
Kint_cEpMito = 0 ;
Kint_cEpLyso = 0 ;
Kint_int = -AbEp/Vint*(Pn*(fintN)+Pd*NbEp/(exp(NbEp)-1)*(fintD))...
        -Asm/Vint*(Pn*fintN+Pd*Nsm/(exp(Nsm)-1)*fintD)...
        -AimInt/Vint*(Pn*fintN+Pd*NimInt/(exp(NimInt)-1)*fintD)...
        +AbEd/Vint*(Pn*(-fintN)+Pd*NbEd/(exp(NbEd)-1)*(-fintD)*exp(NbEd));
Kint_sm = -Asm/Vint*(Pn*(-fsmN)+Pd*Nsm/(exp(Nsm)-1)*(-fsmD)*exp(Nsm));
Kint_smMito = 0;
Kint_smLyso = 0;
Kint_imInt = -AimInt/Vint*(Pn*(-fimIntN)+Pd*NimInt/(exp(NimInt)-1)*(-fimIntD)*exp(NimInt));
Kint_cEd = AbEd/Vint*(Pn*(fcEdN)+Pd*NbEd/(exp(NbEd)-1)*(fcEdD));
Kint_cEdMito = 0 ;
Kint_cEdLyso = 0 ;
Kint_p = 0;
Sint = 0;


% #7: Smooth Muscle (sm)
Ksm_aEp = 0;
Ksm_imEp = 0;
Ksm_cEp = 0;
Ksm_cEpMito = 0 ;
Ksm_cEpLyso = 0 ;
Ksm_int = Asm/Vsm*(Pn*fintN+Pd*Nsm/(exp(Nsm)-1)*fintD);
Ksm_sm = Asm/Vsm*(Pn*(-fsmN)+Pd*Nsm/(exp(Nsm)-1)*(-fsmD)*exp(Nsm))...
       -AsmMito/Vsm*(Pn*fsmN+Pd*NsmMito/(exp(NsmMito)-1)*fsmD)...
       -AsmLyso/Vsm*(Pn*fsmN+Pd*NsmLyso/(exp(NsmLyso)-1)*fsmD);
Ksm_smMito = -AsmMito/Vsm*(Pn*(-fsmMitoN)+Pd*NsmMito/(exp(NsmMito)-1)*(-
fsmMitoD)*exp(NsmMito)) ;
Ksm_smLyso = -AsmLyso/Vsm*(Pn*(-fsmLysoN)+Pd*NsmLyso/(exp(NsmLyso)-1)*(-
fsmLysoD)*exp(NsmLyso)) ;
Ksm_imInt = 0;
Ksm_cEd = 0;
Ksm_cEdMito = 0 ;
Ksm_cEdLyso = 0 ;
Ksm_p = 0;
Ssm = 0;

% #8: Smooth Muscle (smMito)
KsmMito_aEp = 0;
KsmMito_imEp = 0;
KsmMito_cEp = 0;
KsmMito_cEpMito = 0;
KsmMito_cEpLyso = 0 ;
KsmMito_int = 0 ;
KsmMito_sm = AsmMito/VsmMito*(Pn*(fsmN)+Pd*NsmMito/(exp(NsmMito)-1)*(fsmD));
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KsmMito_smMito = AsmMito/VsmMito*(Pn*(-fsmMitoN)+Pd*NsmMito/(exp(NsmMito)-1)*(-
fsmMitoD)*exp(NsmMito));
KsmMito_smLyso = 0;
KsmMito_imInt = 0;
KsmMito_cEd = 0;
KsmMito_cEdMito = 0 ;
KsmMito_cEdLyso = 0 ;
KsmMito_p = 0;
SsmMito = 0;

% #9: Smooth Muscle (smLyso)
KsmLyso_aEp = 0;
KsmLyso_imEp = 0;
KsmLyso_cEp = 0;
KsmLyso_cEpMito = 0 ;
KsmLyso_cEpLyso = 0;
KsmLyso_int = 0 ;
KsmLyso_sm = AsmLyso/VsmLyso*(Pn*(fsmN)+Pd*NsmLyso/(exp(NsmLyso)-1)*(fsmD));
KsmLyso_smMito = 0;
KsmLyso_smLyso = AsmLyso/VsmLyso*(Pn*(-fsmLysoN)+Pd*NsmLyso/(exp(NsmLyso)-1)*(-
fsmLysoD)*exp(NsmLyso));
KsmLyso_imInt = 0;
KsmLyso_cEd = 0;
KsmLyso_cEdMito = 0 ;
KsmLyso_cEdLyso = 0 ;
KsmLyso_p = 0;
SsmLyso = 0;

% #10: Immune Cells (imInt)
KimInt_aEp = 0;
KimInt_imEp = 0;
KimInt_cEp = 0;
KimInt_cEpMito = 0;
KimInt_cEpLyso = 0;
KimInt_int = AimInt/VimInt*(Pn*fintN+Pd*NimInt/(exp(NimInt)-1)*fintD);
KimInt_sm = 0;
KimInt_smMito = 0;
KimInt_smLyso = 0;
KimInt_imInt = AimInt/VimInt*(Pn*(-fimIntN)+Pd*NimInt/(exp(NimInt)-1)*(-fimIntD)*exp(NimInt));
KimInt_cEd = 0;
KimInt_cEdMito = 0;
KimInt_cEdLyso = 0;
KimInt_p = 0;
SimInt = 0;

% #11: Endothelial celss (cEd)
KcEd_aEp = 0;
KcEd_imEp = 0;
KcEd_cEp = 0;
KcEd_cEpMito = 0;
KcEd_cEpLyso = 0;
KcEd_int = -AbEd/VcEd*(Pn*(-fintN)+Pd*NbEd/(exp(NbEd)-1)*(-fintD)*exp(NbEd));
KcEd_sm = 0;
KcEd_smMito = 0;
KcEd_smLyso = 0;
KcEd_imInt = 0;
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KcEd_cEd = -AbEd/VcEd*(Pn*(fcEdN)+Pd*NbEd/(exp(NbEd)-1)*(fcEdD))...
          -AcEdMito/VcEd*(Pn*fcEdN+Pd*NcEdMito/(exp(NcEdMito)-1)*fcEdD)...
          -AcEdLyso/VcEd*(Pn*fcEdN+Pd*NcEdLyso/(exp(NcEdLyso)-1)*fcEdD)...
          +AaEd/VcEd*(Pn*(-fcEdN)+Pd*NaEd/(exp(NaEd)-1)*(-fcEdD)*exp(NaEd));
KcEd_cEdMito = -AcEdMito/VcEd*(Pn*(-fcEdMitoN)+Pd*NcEdMito/(exp(NcEdMito)-1)*(-
fcEdMitoD)*exp(NcEdMito));
KcEd_cEdLyso = -AcEdLyso/VcEd*(Pn*(-fcEdLysoN)+Pd*NcEdLyso/(exp(NcEdLyso)-1)*(-
fcEdLysoD)*exp(NcEdLyso));
KcEd_p = AaEd/VcEd*(Pn*(fpN)+Pd*NaEd/(exp(NaEd)-1)*(fpD));
ScEd = 0;

% #12: Endothelial celss (cEd) Mito
KcEdMito_aEp = 0;
KcEdMito_imEp = 0;
KcEdMito_cEp = 0;
KcEdMito_cEpMito = 0;
KcEdMito_cEpLyso = 0;
KcEdMito_int = 0;
KcEdMito_sm = 0;
KcEdMito_smMito = 0;
KcEdMito_smLyso = 0;
KcEdMito_imInt = 0;
KcEdMito_cEd = AcEdMito/VcEdMito*(Pn*(fcEdN)+Pd*NcEdMito/(exp(NcEdMito)-1)*(fcEdD)) ;
KcEdMito_cEdMito = AcEdMito/VcEdMito*(Pn*(-fcEdMitoN)+Pd*NcEdMito/(exp(NcEdMito)-1)*(-
fcEdMitoD)*exp(NcEdMito));
KcEdMito_cEdLyso = 0;
KcEdMito_p = 0 ;
ScEdMito = 0;

% #13: Endothelial celss (cEd) Lyso
KcEdLyso_aEp = 0;
KcEdLyso_imEp = 0;
KcEdLyso_cEp = 0;
KcEdLyso_cEpMito = 0;
KcEdLyso_cEpLyso = 0;
KcEdLyso_int = 0 ;
KcEdLyso_sm = 0;
KcEdLyso_smMito = 0;
KcEdLyso_smLyso = 0;
KcEdLyso_imInt = 0;
KcEdLyso_cEd = AcEdLyso/VcEdLyso*(Pn*(fcEdN)+Pd*NcEdLyso/(exp(NcEdLyso)-1)*(fcEdD)) ;
KcEdLyso_cEdMito = 0;
KcEdLyso_cEdLyso = AcEdLyso/VcEdLyso*(Pn*(-fcEdLysoN)+Pd*NcEdLyso/(exp(NcEdLyso)-1)*(-
fcEdLysoD)*exp(NcEdLyso));
KcEdLyso_p = 0;
ScEdLyso = 0;

% #14: plasma(p)
Kp_aEp = 0;
Kp_imEp = 0;
Kp_cEp = 0;
Kp_cEpMito = 0;
Kp_cEpLyso = 0;
Kp_int = 0;
Kp_sm = 0;
Kp_smMito = 0;
```

```
Kp_smLyso = 0;
Kp_imInt = 0;
Kp_cEd = -AaEd/Vp*(Pn*(-fcEdN)+Pd*NaEd/(exp(NaEd)-1)*(-fcEdD)*exp(NaEd));
Kp_cEdMito = 0;
Kp_cEdLyso = 0;
Kp_p = -AaEd/Vp*(Pn*(fpN)+Pd*NaEd/(exp(NaEd)-1)*(fpD));
Sp = 0;

M =
[KaEp_aEp,KaEp_imEp,KaEp_cEp,KaEp_cEpMito,KaEp_cEpLyso,KaEp_int,KaEp_sm,KaEp_smMito,KaEp_smL
yso,KaEp_imInt,KaEp_cEd,KaEp_cEdMito,KaEp_cEdLyso,KaEp_p;...

KimEp_aEp,KimEp_imEp,KimEp_cEp,KimEp_cEpMito,KimEp_cEpLyso,KimEp_int,KimEp_sm,KimEp_smMito,
KimEp_smLyso,KimEp_imInt,KimEp_cEd,KimEp_cEdMito,KimEp_cEdLyso,KimEp_p;...

KcEp_aEp,KcEp_imEp,KcEp_cEp,KcEp_cEpMito,KcEp_cEpLyso,KcEp_int,KcEp_sm,KcEP_smMito,KcEp_smL
yso,KcEp_imInt,KcEp_cEd,KcEp_cEdMito,KcEp_cEdLyso,KcEp_p;...

KcEpMito_aEp,KcEpMito_imEp,KcEpMito_cEp,KcEpMito_cEpMito,KcEpMito_cEpLyso,KcEpMito_int,KcEpMi
to_sm,KcEpMito_smMito,KcEpMito_smLyso,KcEpMito_imInt,KcEpMito_cEd,KcEpMito_cEdMito,KcEpMito_c
EdLyso,KcEpMito_p;...

KcEpLyso_aEp,KcEpLyso_imEp,KcEpLyso_cEp,KcEpLyso_cEpMito,KcEpLyso_cEpLyso,KcEpLyso_int,KcEpL
yso_sm,KcEpLyso_smMito,KcEpLyso_smLyso,KcEpLyso_imInt,KcEpLyso_cEd,KcEpLyso_cEdMito,KcEpLyso_
cEdLyso,KcEpLyso_p;...

Kint_aEp,Kint_imEp,Kint_cEp,Kint_cEpMito,Kint_cEpLyso,Kint_int,Kint_sm,Kint_smMito,Kint_smLyso,Kint_i
mInt,Kint_cEd,Kint_cEdMito,Kint_cEdLyso,Kint_p;...

Ksm_aEp,Ksm_imEp,Ksm_cEp,Ksm_cEpMito,Ksm_cEpLyso,Ksm_int,Ksm_sm,Ksm_smMito,Ksm_smLyso,Ksm
_imInt,Ksm_cEd,Ksm_cEdMito,Ksm_cEdLyso,Ksm_p;...

KsmMito_aEp,KsmMito_imEp,KsmMito_cEp,KsmMito_cEpMito,KsmMito_cEpLyso,KsmMito_int,KsmMito_sm,
KsmMito_smMito,KsmMito_smLyso,KsmMito_imInt,KsmMito_cEd,KsmMito_cEdMito,KsmMito_cEdLyso,Ksm
Mito_p;...

KsmLyso_aEp,KsmLyso_imEp,KsmLyso_cEp,KsmLyso_cEpMito,KsmLyso_cEpLyso,KsmLyso_int,KsmLyso_sm
,KsmLyso_smMito,KsmLyso_smLyso,KsmLyso_imInt,KsmLyso_cEd,KsmLyso_cEdMito,KsmLyso_cEdLyso,Ks
mLyso_p;...

KimInt_aEp,KimInt_imEp,KimInt_cEp,KimInt_cEpMito,KimInt_cEpLyso,KimInt_int,KimInt_sm,KimInt_smMito,
KimInt_smLyso,KimInt_imInt,KimInt_cEd,KimInt_cEdMito,KimInt_cEdLyso,KimInt_p;...

KcEd_aEp,KcEd_imEp,KcEd_cEp,KcEd_cEpMito,KcEd_cEpLyso,KcEd_int,KcEd_sm,KcEd_smMito,KcEd_smL
yso,KcEd_imInt,KcEd_cEd,KcEd_cEdMito,KcEd_cEdLyso,KcEd_p;...

KcEdMito_aEp,KcEdMito_imEp,KcEdMito_cEp,KcEdMito_cEpMito,KcEdMito_cEpLyso,KcEdMito_int,KcEdMi
to_sm,KcEdMito_smMito,KcEdMito_smLyso,KcEdMito_imInt,KcEdMito_cEd,KcEdMito_cEdMito,KcEdMito_c
EdLyso,KcEdMito_p;...

KcEdLyso_aEp,KcEdLyso_imEp,KcEdLyso_cEp,KcEdLyso_cEpMito,KcEdLyso_cEpLyso,KcEdLyso_int,KcEdL
yso_sm,KcEdLyso_smMito,KcEdLyso_smLyso,KcEdLyso_imInt,KcEdLyso_cEd,KcEdLyso_cEdMito,KcEdLyso_
cEdLyso,KcEdLyso_p;...

Kp_aEp,Kp_imEp,Kp_cEp,Kp_cEpMito,Kp_cEpLyso,Kp_int,Kp_sm,Kp_smMito,Kp_smLyso,Kp_imInt,Kp_cEd,
Kp_cEdMito,Kp_cEdLyso,Kp_p];
```

```
G = [SaEp,SimEp,ScEp,ScEpMito,ScEpLyso,Sint,Ssm,SsmMito,SsmLyso,SimInt,ScEd,ScEdMito,ScEdLyso,Sp]';
```

```
% 4/30/2010
% 1CellPK based lung:Alveoli model starts here (Rats)
% 12 compartments:
% aEp (surface lining liquied), imEp (Macrophage),
% cEp(epithelial cells),cEpMito(mito of cEp), cEpLyso (lyso of cEp)
% int(Interstitium),imInt(immune cells), sm(smooth muscle),
% cEd(endothelial cells), cEdMito(mito of cEd),cEdLyso (lyso of cEd), p(plasma)

function [M, G, M_v, Vp] = AL(pKa,logPN,x)

%molecular physiochemical property

logPD = logPN-3.7 ;
z = 1;

% Constant: See supplenmental information
T = 273.15+37;
R = 8.314;
F = 96484.56;

%lipid fraction
LaEp = 0.95;
LimEp = 0.05;
LcEp = 0.05 ;
Lint = 0;
LimInt = 0.05;
Lsm = 0;
LcEd = 0.05;
Lp = 0;

%volumetric water fraction=1-lipid fraction
WaEp = 1 - LaEp;
WimEp = 1 - LimEp;
WcEp = 1 - LcEp;
Wint = 1 - Lint;
WimInt = 1 - LimInt;
Wsm = 1 - Lsm;
WcEd = 1 - LcEd;
Wp = 1 - Lp;

%activity coefficient of species(N:neutral,D:desociated)
GaEpN = 1;
GaEpD = 1;
GimEpN = 1.23;
GimEpD = 0.74;
GcEpN = 1.23;
GcEpD = 0.74;
GintN = 1;
GintD = 1;
GimIntN = 1.23;
GimIntD = 0.74;
GsmN = 1.23;
GsmD = 0.74;
GcEdN = 1.23;
GcEdD = 0.74;
GpN = 1;
```

```
GpD = 1;

% Areas and volumes (m^2, m^3) for 7 membranes and corresponding cellular/subcellular compartments
% values are from literature, see J Yu,etal Pharm Res 2010, 27
AaEp = 0.387;%
AbEp = 0.387;%Assuming same with epical side
AimEp = 3.14*10^(-10)*0.89*10^(9)*3/100/2; % 10 um diameter, only half of surface gets contact with liquid,
since ASL = 5 um
AimInt = x*AimEp/10; % assuming number of immune cells is 1/10 of macrophage
Asm = 0;%No SM
AbEd = 0.452;%literature
AaEd = 0.452;%literature

%volumes for 8 compartments(m3)
ASL = 5; %literature um
VaEp = AaEp*ASL*10^(-6); %5 um thickness
VcEp = AaEp*0.384*10^(-6); % 0.384, literature
VimEp = x*0.89*10^(9)*3/100*1058*10^(-18);%number of macrophage(literature)*volume of macrophage
Vint = AaEp*0.693*10^(-6); % literature
VimInt = VimEp/10;% assuming number of immune cells is 1/10 of macrophage
Vsm = 10^(-30); % VcEp*10^(-12); % can be any number, surface is 0
VcEd = AbEd*0.358*10^(-6); %0.358 um thickness --literature


%##########################################################################
% Subcellular compartments in cEp (epithelial cells) and cEd(endothelial cells)
% calculate constant
R_org = 0.1;

VcEpMito = R_org*VcEp ; % 10^(-30); %
VcEpLyso = R_org*VcEp ; % 10^(-30); %
VcEdMito = R_org*VcEd ; % 10^(-30); %
VcEdLyso = R_org*VcEd ; % 10^(-30); %

AcEpMito = 5.9924e+006*VcEpMito; % 0 ;
AcEpLyso = 5.9924e+006*VcEpLyso; % 0 ;
AcEdMito = 5.9924e+006*VcEdMito; % 0 ;
AcEdLyso = 5.9924e+006*VcEdLyso; % 0 ;
%##########################################################################

M_v = diag([VaEp,VimEp,VcEp,VcEpMito,VcEpLyso,Vint,Vsm,VimInt,VcEd,VcEdMito,VcEdLyso]);
V_LUN = trace(M_v)*10^6;
Vp = 340*10^(-9)*V_LUN;

% Membrane potential (V)
EaEp = -0.0093;
EbEp = 0.0119;%0.0119;
EimEp = -0.06;
EimInt = -0.06;
Esm = -0.06;
EbEd = -0.06;
EaEd = -0.06;

% pH values
pHaEp = 7.4;
pHimEp = 7.0;
```

```
pHcEp = 7.0;
pHint = 7.0;
pHimInt = 7.0;
pHsm = 7.0;
pHcEd = 7.0;
pHp = 7.4;

%adjustment for logP
if ( abs(z-1) <= 10^(-6) )
   logP_nlipT = 0.33*logPN+2.2 ;
   logP_dlipT = 0.37*logPD+2 ;
end
if ( abs(z+1) <= 10^(-6) )
   logP_nlipT = 0.37*logPN+2.2 ;
   logP_dlipT = 0.33*logPD+2.6 ;
end
if ( abs(z-0) <= 10^(-5) )
   logP_nlipT = 0.33*logPN+2.2 ;
   logP_dlipT = 0.33*logPD+2.2 ;
end

% Get the first two decimals
logP_n = round(logP_nlipT*100)/100 ;
logP_d = round(logP_dlipT*100)/100 ;

%calculate the membrane permeability
Pn = 10^(logP_n-6.7)*60; % in 1/min
Pd = 10^(logP_d-6.7)*60; % in 1/min

i = -sign(z) ;
%calculate N for flux of ion happening at 7 membranes
C = z*F/(R*T);
NaEp = C*(-EaEp) ;
NbEp = C*EbEp ;
NimEp = C*EimEp ;
NimInt = C*EimInt ;
Nsm = C*Esm ;
NbEd = C*(-EbEd) ;
NaEd = C*(EaEd) ;

%calculate Kn and Kd for 8 compartments
N = 1.22*10^(logP_n);
D = 1.22*10^(logP_d);

%calculate Kn and Kd for 8 compartments

KaEpN = N*LaEp ;
KaEpD = D*LaEp ;
KimEpN = N*LimEp ;
KimEpD = D*LimEp ;
KcEpN = N*LcEp ;
KcEpD = D*LcEp ;
KintN = N*Lint ;
KintD = D*Lint ;
KimIntN = N*LimInt ;
KimIntD = D*LimInt;
```

```
KsmN = N*Lsm ;
KsmD = D*Lsm;
KcEdN = N*LcEd ;
KcEdD = D*LcEd ;
KpN = N*Lp ;
KpD = D*Lp ;


%#############################################################################
LcEpMito = 0.05 ;
LcEpLyso = 0.05 ;
LcEdMito = 0.05 ;
LcEdLyso = 0.05 ;

WcEpMito = 1-LcEpMito ;
WcEpLyso = 1-LcEpLyso ;
WcEdMito = 1-LcEdMito ;
WcEdLyso = 1-LcEdLyso ;

GcEpMitoN = 1.23 ;
GcEpMitoD = 0.74 ;
GcEpLysoN = 1.23 ;
GcEpLysoD = 0.74 ;
GcEdMitoN = 1.23 ;
GcEdMitoD = 0.74 ;
GcEdLysoN = 1.23 ;
GcEdLysoD = 0.74 ;

EcEpMito = -0.16 ;
EcEpLyso = +0.01 ;
EcEdMito = -0.16 ;
EcEdLyso = +0.01 ;

pHcEpMito = 8 ;
pHcEpLyso = 5 ;
pHcEdMito = 8 ;
pHcEdLyso = 5 ;


NcEpMito = C*EcEpMito ;
NcEpLyso = C*EcEpLyso ;
NcEdMito = C*EcEdMito ;
NcEdLyso = C*EcEdLyso ;



KcEpMitoN = N*LcEpMito ;
KcEpMitoD = D*LcEpMito ;
KcEpLysoN = N*LcEpLyso ;
KcEpLysoD = D*LcEpLyso ;

KcEdMitoN = N*LcEdMito ;
KcEdMitoD = D*LcEdMito ;
KcEdLysoN = N*LcEdLyso ;
KcEdLysoD = D*LcEdLyso ;
```

```
fcEpMitoN = 1/(WcEpMito/GcEpMitoN+KcEpMitoN/GcEpMitoN+WcEpMito*10^(i*(pHcEpMito-
pKa))/GcEpMitoD...
        +KcEpMitoD*10^(i*(pHcEpMito-pKa))/GcEpMitoD);
fcEpMitoD = fcEpMitoN*10^(i*(pHcEpMito-pKa));

fcEpLysoN = 1/(WcEpLyso/GcEpLysoN+KcEpLysoN/GcEpLysoN+WcEpLyso*10^(i*(pHcEpLyso-
pKa))/GcEpLysoD...
        +KcEpLysoD*10^(i*(pHcEpLyso-pKa))/GcEpLysoD);
fcEpLysoD = fcEpLysoN*10^(i*(pHcEpLyso-pKa));

fcEdMitoN = 1/(WcEdMito/GcEdMitoN+KcEdMitoN/GcEdMitoN+WcEdMito*10^(i*(pHcEdMito-
pKa))/GcEdMitoD...
        +KcEdMitoD*10^(i*(pHcEdMito-pKa))/GcEdMitoD);
fcEdMitoD = fcEdMitoN*10^(i*(pHcEdMito-pKa));

fcEdLysoN = 1/(WcEdLyso/GcEdLysoN+KcEdLysoN/GcEdLysoN+WcEdLyso*10^(i*(pHcEdLyso-
pKa))/GcEdLysoD...
        +KcEdLysoD*10^(i*(pHcEdLyso-pKa))/GcEdLysoD);
fcEdLysoD = fcEdLysoN*10^(i*(pHcEdLyso-pKa));

%###########################################################################

%compute the fn and fd for 8 compartments
faEpN = 1/(WaEp/GaEpN+KaEpN/GaEpN+WaEp*10^(i*(pHaEp-pKa))/GaEpD...
        +KaEpD*10^(i*(pHaEp-pKa))/GaEpD);
faEpD = faEpN*10^(i*(pHaEp-pKa));
fimEpN = 1/(WimEp/GimEpN+KimEpN/GimEpN+WimEp*10^(i*(pHimEp-pKa))/GimEpD...
        +KimEpD*10^(i*(pHimEp-pKa))/GimEpD);
fimEpD = fimEpN*10^(i*(pHimEp-pKa));
fcEpN = 1/(WcEp/GcEpN+KcEpN/GcEpN+WcEp*10^(i*(pHcEp-pKa))/GcEpD...
        +KcEpD*10^(i*(pHcEp-pKa))/GcEpD);
fcEpD = fcEpN*10^(i*(pHcEp-pKa));
fintN = 1/(Wint/GintN+KintN/GintN+Wint*10^(i*(pHint-pKa))/GintD...
        +KintD*10^(i*(pHint-pKa))/GintD);
fintD = fintN*10^(i*(pHint-pKa));
fimIntN = 1/(WimInt/GimIntN+KimIntN/GimIntN+WimInt*10^(i*(pHimInt-pKa))/GimIntD...
        +KimIntD*10^(i*(pHimInt-pKa))/GimIntD);
fimIntD = fimIntN*10^(i*(pHimInt-pKa));
fsmN = 1/(Wsm/GsmN+KsmN/GsmN+Wsm*10^(i*(pHsm-pKa))/GsmD...
        +KsmD*10^(i*(pHsm-pKa))/GsmD);
fsmD = fsmN*10^(i*(pHsm-pKa));
fcEdN = 1/(WcEd/GcEdN+KcEdN/GcEdN+WcEd*10^(i*(pHcEd-pKa))/GcEdD...
        +KcEdD*10^(i*(pHcEd-pKa))/GcEdD);
fcEdD = fcEdN*10^(i*(pHcEd-pKa));
fpN = 1/(Wp/GpN+KpN/GpN+Wp*10^(i*(pHp-pKa))/GpD...
        +KpD*10^(i*(pHp-pKa))/GpD);
fpD = fpN*10^(i*(pHp-pKa));

%mucus clearance: optional
Ke = 0;

%compute the coefficient matrix for ODEs
% #1: Surface Lining Liquid (aEp)
KaEp_aEp = AaEp/VaEp*(Pn*(-faEpN)+Pd*NaEp/(exp(NaEp)-1)*(-faEpD)*exp(NaEp))...
       -AimEp/VaEp*(Pn*faEpN+Pd*NimEp/(exp(NimEp)-1)*faEpD)...
       -Ke;
```

```
KaEp_imEp = -AimEp/VaEp*(Pn*(-fimEpN)+Pd*NimEp/(exp(NimEp)-1)*(-fimEpD)*exp(NimEp));
KaEp_cEp = AaEp/VaEp*(Pn*(fcEpN)+Pd*NaEp/(exp(NaEp)-1)*(fcEpD));
KaEp_cEpMito = 0;
KaEp_cEpLyso = 0;
KaEp_int = 0;
KaEp_sm = 0;
KaEp_imInt = 0;
KaEp_cEd = 0;
KaEp_cEdMito = 0;
KaEp_cEdLyso = 0;
KaEp_p = 0;
SaEp = 0;

% #2: Macrophage (imEp)
KimEp_aEp = AimEp/VimEp*(Pn*faEpN+Pd*NimEp/(exp(NimEp)-1)*faEpD);
KimEp_imEp = AimEp/VimEp*(Pn*(-fimEpN)+Pd*NimEp/(exp(NimEp)-1)*(-fimEpD)*exp(NimEp));
KimEp_cEp = 0;
KimEp_cEpMito = 0 ;
KimEp_cEpLyso = 0 ;
KimEp_int = 0;
KimEp_sm = 0;
KimEp_imInt = 0;
KimEp_cEd = 0;
KimEp_cEdMito = 0 ;
KimEp_cEdLyso = 0 ;
KimEp_p = 0;
SimEp = 0;

% #3: Epithelial Cells (cEp)
KcEp_aEp = -AaEp/VcEp*(Pn*(-faEpN)+Pd*NaEp/(exp(NaEp)-1)*(-faEpD)*exp(NaEp));
KcEp_imEp = 0;
KcEp_cEp = -AaEp/VcEp*(Pn*(fcEpN)+Pd*NaEp/(exp(NaEp)-1)*(fcEpD))...
        -AcEpMito/VcEp*(Pn*fcEpN+Pd*NcEpMito/(exp(NcEpMito)-1)*fcEpD)...
        -AcEpLyso/VcEp*(Pn*fcEpN+Pd*NcEpLyso/(exp(NcEpLyso)-1)*fcEpD)...
        + AbEp/VcEp*(Pn*(-fcEpN)+Pd*NbEp/(exp(NbEp)-1)*(-fcEpD)*exp(NbEp));
KcEp_cEpMito = -AcEpMito/VcEp*(Pn*(-fcEpMitoN)+Pd*NcEpMito/(exp(NcEpMito)-1)*(-
fcEpMitoD)*exp(NcEpMito)) ;
KcEp_cEpLyso = -AcEpLyso/VcEp*(Pn*(-fcEpLysoN)+Pd*NcEpLyso/(exp(NcEpLyso)-1)*(-
fcEpLysoD)*exp(NcEpLyso)) ;
KcEp_int = AbEp/VcEp*(Pn*(fintN)+Pd*NbEp/(exp(NbEp)-1)*(fintD));
KcEp_sm = 0;
KcEp_imInt = 0;
KcEp_cEd = 0;
KcEp_cEdMito = 0 ;
KcEp_cEdLyso = 0 ;
KcEp_p = 0;
ScEp = 0;

% #4: : Epithelial Cells (cEpMito)
KcEpMito_aEp = 0;
KcEpMito_imEp = 0;
KcEpMito_cEp = AcEpMito/VcEpMito*(Pn*(fcEpN)+Pd*NcEpMito/(exp(NcEpMito)-1)*(fcEpD));
KcEpMito_cEpMito = AcEpMito/VcEpMito*(Pn*(-fcEpMitoN)+Pd*NcEpMito/(exp(NcEpMito)-1)*(-
fcEpMitoD)*exp(NcEpMito));
KcEpMito_cEpLyso = 0 ;
KcEpMito_int = 0 ;
```

```
KcEpMito_sm = 0;
KcEpMito_imInt = 0;
KcEpMito_cEd = 0;
KcEpMito_cEdMito = 0 ;
KcEpMito_cEdLyso = 0 ;
KcEpMito_p = 0;
ScEpMito = 0;

% #5: : Epithelial Cells (cEpLyso)
KcEpLyso_aEp = 0;
KcEpLyso_imEp = 0;
KcEpLyso_cEp = AcEpLyso/VcEpLyso*(Pn*(fcEpN)+Pd*NcEpLyso/(exp(NcEpLyso)-1)*(fcEpD));
KcEpLyso_cEpMito = 0 ;
KcEpLyso_cEpLyso = AcEpLyso/VcEpLyso*(Pn*(-fcEpLysoN)+Pd*NcEpLyso/(exp(NcEpLyso)-1)*(-
fcEpLysoD)*exp(NcEpLyso));
KcEpLyso_int = 0 ;
KcEpLyso_sm = 0;
KcEpLyso_imInt = 0;
KcEpLyso_cEd = 0;
KcEpLyso_cEdMito = 0 ;
KcEpLyso_cEdLyso = 0 ;
KcEpLyso_p = 0;
ScEpLyso = 0;


% #6: : Interstitium (int)
Kint_aEp = 0;
Kint_imEp = 0;
Kint_cEp = -AbEp/Vint*(Pn*(-fcEpN)+Pd*NbEp/(exp(NbEp)-1)*(-fcEpD)*exp(NbEp));
Kint_cEpMito = 0 ;
Kint_cEpLyso = 0 ;
Kint_int = -AbEp/Vint*(Pn*(fintN)+Pd*NbEp/(exp(NbEp)-1)*(fintD))...
        -Asm/Vint*(Pn*fintN+Pd*Nsm/(exp(Nsm)-1)*fintD)...
        -AimInt/Vint*(Pn*fintN+Pd*NimInt/(exp(NimInt)-1)*fintD)...
        +AbEd/Vint*(Pn*(-fintN)+Pd*NbEd/(exp(NbEd)-1)*(-fintD)*exp(NbEd));
Kint_sm = -Asm/Vint*(Pn*(-fsmN)+Pd*Nsm/(exp(Nsm)-1)*(-fsmD)*exp(Nsm));
Kint_imInt = -AimInt/Vint*(Pn*(-fimIntN)+Pd*NimInt/(exp(NimInt)-1)*(-fimIntD)*exp(NimInt));
Kint_cEd = AbEd/Vint*(Pn*(fcEdN)+Pd*NbEd/(exp(NbEd)-1)*(fcEdD));
Kint_cEdMito = 0 ;
Kint_cEdLyso = 0 ;
Kint_p = 0;
Sint = 0;

% #7: Smooth Muscle (sm)
Ksm_aEp = 0;
Ksm_imEp = 0;
Ksm_cEp = 0;
Ksm_cEpMito = 0 ;
Ksm_cEpLyso = 0 ;
Ksm_int = Asm/Vsm*(Pn*fintN+Pd*Nsm/(exp(Nsm)-1)*fintD);
Ksm_sm = Asm/Vsm*(Pn*(-fsmN)+Pd*Nsm/(exp(Nsm)-1)*(-fsmD)*exp(Nsm));
Ksm_imInt = 0;
Ksm_cEd = 0;
Ksm_cEdMito = 0 ;
Ksm_cEdLyso = 0 ;
Ksm_p = 0;
```

```
Ssm = 0;


% #8: Immune Cells (imInt)
KimInt_aEp = 0;
KimInt_imEp = 0;
KimInt_cEp = 0;
KimInt_cEpMito = 0;
KimInt_cEpLyso = 0;
KimInt_int = AimInt/VimInt*(Pn*fintN+Pd*NimInt/(exp(NimInt)-1)*fintD);
KimInt_sm = 0;
KimInt_imInt = AimInt/VimInt*(Pn*(-fimIntN)+Pd*NimInt/(exp(NimInt)-1)*(-fimIntD)*exp(NimInt));
KimInt_cEd = 0;
KimInt_cEdMito = 0;
KimInt_cEdLyso = 0;
KimInt_p = 0;
SimInt = 0;

% #9: Endothelial celss (cEd)
KcEd_aEp = 0;
KcEd_imEp = 0;
KcEd_cEp = 0;
KcEd_cEpMito = 0;
KcEd_cEpLyso = 0;
KcEd_int = -AbEd/VcEd*(Pn*(-fintN)+Pd*NbEd/(exp(NbEd)-1)*(-fintD)*exp(NbEd));
KcEd_sm = 0;
KcEd_imInt = 0;
KcEd_cEd = -AbEd/VcEd*(Pn*(fcEdN)+Pd*NbEd/(exp(NbEd)-1)*(fcEdD))...
        -AcEdMito/VcEd*(Pn*fcEdN+Pd*NcEdMito/(exp(NcEdMito)-1)*fcEdD)...
        -AcEdLyso/VcEd*(Pn*fcEdN+Pd*NcEdLyso/(exp(NcEdLyso)-1)*fcEdD)...
        +AaEd/VcEd*(Pn*(-fcEdN)+Pd*NaEd/(exp(NaEd)-1)*(-fcEdD)*exp(NaEd));
KcEd_cEdMito = -AcEdMito/VcEd*(Pn*(-fcEdMitoN)+Pd*NcEdMito/(exp(NcEdMito)-1)*(-
fcEdMitoD)*exp(NcEdMito));
KcEd_cEdLyso = -AcEdLyso/VcEd*(Pn*(-fcEdLysoN)+Pd*NcEdLyso/(exp(NcEdLyso)-1)*(-
fcEdLysoD)*exp(NcEdLyso));
KcEd_p = AaEd/VcEd*(Pn*(fpN)+Pd*NaEd/(exp(NaEd)-1)*(fpD));
ScEd = 0;


% #10: Endothelial celss (cEd) Mito
KcEdMito_aEp = 0;
KcEdMito_imEp = 0;
KcEdMito_cEp = 0;
KcEdMito_cEpMito = 0;
KcEdMito_cEpLyso = 0;
KcEdMito_int = 0;
KcEdMito_sm = 0;
KcEdMito_imInt = 0;
KcEdMito_cEd = AcEdMito/VcEdMito*(Pn*(fcEdN)+Pd*NcEdMito/(exp(NcEdMito)-1)*(fcEdD)) ;
KcEdMito_cEdMito = AcEdMito/VcEdMito*(Pn*(-fcEdMitoN)+Pd*NcEdMito/(exp(NcEdMito)-1)*(-
fcEdMitoD)*exp(NcEdMito));
KcEdMito_cEdLyso = 0;
KcEdMito_p = 0 ;
ScEdMito = 0;

% #11: Endothelial celss (cEd) Lyso
```

```
KcEdLyso_aEp = 0;
KcEdLyso_imEp = 0;
KcEdLyso_cEp = 0;
KcEdLyso_cEpMito = 0;
KcEdLyso_cEpLyso = 0;
KcEdLyso_int = 0 ;
KcEdLyso_sm = 0;
KcEdLyso_imInt = 0;
KcEdLyso_cEd = AcEdLyso/VcEdLyso*(Pn*(fcEdN)+Pd*NcEdLyso/(exp(NcEdLyso)-1)*(fcEdD)) ;
KcEdLyso_cEdMito = 0;
KcEdLyso_cEdLyso = AcEdLyso/VcEdLyso*(Pn*(-fcEdLysoN)+Pd*NcEdLyso/(exp(NcEdLyso)-1)*(-
fcEdLysoD)*exp(NcEdLyso));
KcEdLyso_p = 0;
ScEdLyso = 0;

% #12: plasma(p)
Kp_aEp = 0;
Kp_imEp = 0;
Kp_cEp = 0;
Kp_cEpMito = 0;
Kp_cEpLyso = 0;
Kp_int = 0;
Kp_sm = 0;
Kp_imInt = 0;
Kp_cEd = -AaEd/Vp*(Pn*(-fcEdN)+Pd*NaEd/(exp(NaEd)-1)*(-fcEdD)*exp(NaEd));
Kp_cEdMito = 0;
Kp_cEdLyso = 0;
Kp_p = -AaEd/Vp*(Pn*(fpN)+Pd*NaEd/(exp(NaEd)-1)*(fpD));
Sp = 0;

M =
[KaEp_aEp,KaEp_imEp,KaEp_cEp,KaEp_cEpMito,KaEp_cEpLyso,KaEp_int,KaEp_sm,KaEp_imInt,KaEp_cEd,K
aEp_cEdMito,KaEp_cEdLyso,KaEp_p;...

KimEp_aEp,KimEp_imEp,KimEp_cEp,KimEp_cEpMito,KimEp_cEpLyso,KimEp_int,KimEp_sm,KimEp_imInt,K
imEp_cEd,KimEp_cEdMito,KimEp_cEdLyso,KimEp_p;...

KcEp_aEp,KcEp_imEp,KcEp_cEp,KcEp_cEpMito,KcEp_cEpLyso,KcEp_int,KcEp_sm,KcEp_imInt,KcEp_cEd,Kc
Ep_cEdMito,KcEp_cEdLyso,KcEp_p;...

KcEpMito_aEp,KcEpMito_imEp,KcEpMito_cEp,KcEpMito_cEpMito,KcEpMito_cEpLyso,KcEpMito_int,KcEpMi
to_sm,KcEpMito_imInt,KcEpMito_cEd,KcEpMito_cEdMito,KcEpMito_cEdLyso,KcEpMito_p;...

KcEpLyso_aEp,KcEpLyso_imEp,KcEpLyso_cEp,KcEpLyso_cEpMito,KcEpLyso_cEpLyso,KcEpLyso_int,KcEpL
yso_sm,KcEpLyso_imInt,KcEpLyso_cEd,KcEpLyso_cEdMito,KcEpLyso_cEdLyso,KcEpLyso_p;...

Kint_aEp,Kint_imEp,Kint_cEp,Kint_cEpMito,Kint_cEpLyso,Kint_int,Kint_sm,Kint_imInt,Kint_cEd,Kint_cEdMit
o,Kint_cEdLyso,Kint_p;...

Ksm_aEp,Ksm_imEp,Ksm_cEp,Ksm_cEpMito,Ksm_cEpLyso,Ksm_int,Ksm_sm,Ksm_imInt,Ksm_cEd,Ksm_cEd
Mito,Ksm_cEdLyso,Ksm_p;...

KimInt_aEp,KimInt_imEp,KimInt_cEp,KimInt_cEpMito,KimInt_cEpLyso,KimInt_int,KimInt_sm,KimInt_imInt,K
imInt_cEd,KimInt_cEdMito,KimInt_cEdLyso,KimInt_p;...
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KcEd_aEp,KcEd_imEp,KcEd_cEp,KcEd_cEpMito,KcEd_cEpLyso,KcEd_int,KcEd_sm,KcEd_imInt,KcEd_cEd,Kc
Ed_cEdMito,KcEd_cEdLyso,KcEd_p;...

KcEdMito_aEp,KcEdMito_imEp,KcEdMito_cEp,KcEdMito_cEpMito,KcEdMito_cEpLyso,KcEdMito_int,KcEdMi
to_sm,KcEdMito_imInt,KcEdMito_cEd,KcEdMito_cEdMito,KcEdMito_cEdLyso,KcEdMito_p;...

KcEdLyso_aEp,KcEdLyso_imEp,KcEdLyso_cEp,KcEdLyso_cEpMito,KcEdLyso_cEpLyso,KcEdLyso_int,KcEdL
yso_sm,KcEdLyso_imInt,KcEdLyso_cEd,KcEdLyso_cEdMito,KcEdLyso_cEdLyso,KcEdLyso_p;...

Kp_aEp,Kp_imEp,Kp_cEp,Kp_cEpMito,Kp_cEpLyso,Kp_int,Kp_sm,Kp_imInt,Kp_cEd,Kp_cEdMito,Kp_cEdLyso
,Kp_p];

G = [SaEp,SimEp,ScEp,ScEpMito,ScEpLyso,Sint,Ssm,SimInt,ScEd,ScEdMito,ScEdLyso,Sp]';
```

```
% By J YU. @ 5/5/2010
% This is the generic PBPK model of rat
% Virtual Lung (with Mito and Lyso in cEp and cEd) - PBPK
% THIS IS A ISOLATED LUNG MODEL, SO the other organs are not relevant
% Six big compartment model: arterial blood, lung, venous blood, liver, brain, and rest

function [dConc] = Lung(t,Conc,pKa,logP,x)
global BW V_VEN fup B2P Vtot;
%call lung model
[LungM, LungG, M_v, Vp] = AL(pKa,logP,x); % get the coefficients for the Alveolar Region
[LungM_Airways, LungG_Airways, M_v_Airways, Vp_Airways] = AW(pKa,logP,x); % get the coefficients for the
airways


% From PATRICK POULIN, FRANK-PETER. THEILPrediction of Pharmacokinetics prior to In Vivo Studies.
% II. Generic Physiologically Based Pharmacokinetic Models of Drug Disposition
% Blood flow rate (mL/min)

Q_tot = 0.235*BW^0.75*1000 ; % Total cardiac output = 0.235 * body weight (kg)^0.75 (L/min)
Q_LUN = Q_tot ;
Q_BRA = 0.02*Q_tot ;
Q_LIV = 0.175*Q_tot ;
Q_Airways = 0.01*Q_tot;
Q_RES = Q_tot - Q_BRA - Q_LIV - Q_Airways;



% Volume of each organ (mL)= fraction of total body volume (L/kg)*BW*1000
V_ART = 0.0272*BW*1000 ;
V_LUN = trace(M_v)*10^6 ;
V_LUNp = Vp*10^(6) ; % plasma volume in the lung, obtained from 'LungRatReverse' (in m^3), converted to mL
V_LUNb = 519*10^(-3)*V_LUN ; % total blood volume in the lung = 519uL/g
V_LUN_Airways = trace(M_v_Airways)*10^6 ;
V_LUNp_Airways = Vp_Airways*10^(6) ;
V_LUNb_Airways = 519*10^(-3)*V_LUN_Airways ;
V_VEN = 0.0544*BW*1000 ;
V_BRA = 0.0057*BW*1000 ;
V_LIV = 0.0366*BW*1000 ;
V_RES = BW*1000 - V_ART - V_LUN - V_LUNp -V_LUNb - V_LUN_Airways -V_LUNp_Airways -
V_LUNb_Airways - V_VEN - V_BRA - V_LIV ;

% Tissue : Blood partition coefficient = K(Tissue:Plasma)/B2P
% From:  Trudy Rodgers and Malcolm Rowland, NOT RELEVANT IN THIS ISOLATED
% LUNG MODEL
Kp_BRA = 0.11 ;  % from exp.
Kp_LIV = 3.21 ;  % from exp.
Kp_LUN = 2.55 ;  % from exp.
Kp_RES = 1.2 ;  % arbitrary
Kiv = 0 ;

% Mass balance
% 1 - Arterial, ART
% 2 - Lung plasma free concentration, LUN,
   % Cellular compartments of the lung:
   % 7 - Surface lining liquid (aEp)
   % 8 - Macrophage (imEp)
```

```
   % 9 - Epithelial cells (cEp)
   % 10 - cEp-mito
   % 11 - cEp-lyso
   % 12 - Interstitium (int)
   % 13 - Smooth muscle (sm)
   % 14 - Immune cells (imInt)
   % 15 - Endothelial cells (cEd)
   % 16 - cEd - mito
   % 17 - cEd -lyso
% 3 - Venous, VEN
% 4 - Brain, BRA
% 5 - Liver, atenolol is mainly cleared by kidney
% 6 - Rest of the body, RES

dConc(1) = 0 ; % ART, arterial blood
dConc(2) = 0 ;  % 2 -Lung total blood concentration was fixed at 0, so it is a isolated lung model

   dConc(7) = LungM(1,1)*Conc(7) + LungM(1,2)*Conc(8) + LungM(1,3)*Conc(9) + LungM(1,4)*Conc(10) + 
LungM(1,5)*Conc(11)...
          + LungM(1,6)*Conc(12) + LungM(1,7)*Conc(13) + LungM(1,8)*Conc(14) + LungM(1,9)*Conc(15) + 
LungM(1,10)*Conc(16)...
          + LungM(1,11)*Conc(17) + LungM(1,12)*Conc(2)*fup/B2P + LungG(1);                    % 14 - 
SurfaConce lining liquid (aEp)

   dConc(8) = LungM(2,1)*Conc(7) + LungM(2,2)*Conc(8) + LungM(2,3)*Conc(9) + LungM(2,4)*Conc(10) + 
LungM(2,5)*Conc(11)...
          + LungM(2,6)*Conc(12) + LungM(2,7)*Conc(13) + LungM(2,8)*Conc(14) + LungM(2,9)*Conc(15) + 
LungM(2,10)*Conc(16)...
          + LungM(2,11)*Conc(17) + LungM(2,12)*Conc(2)*fup/B2P + LungG(2);                    % 15 - 
Macrophage (imEp)

   dConc(9) = LungM(3,1)*Conc(7) + LungM(3,2)*Conc(8) + LungM(3,3)*Conc(9) + LungM(3,4)*Conc(10) + 
LungM(3,5)*Conc(11)...
          + LungM(3,6)*Conc(12) + LungM(3,7)*Conc(13) + LungM(3,8)*Conc(14) + LungM(3,9)*Conc(15) + 
LungM(3,10)*Conc(16)...
          + LungM(3,11)*Conc(17) +LungM(3,12)*Conc(2)*fup/B2P + LungG(3);                     % 16 - 
Epithelial cells (cEp)

   dConc(10) = LungM(4,1)*Conc(7) + LungM(4,2)*Conc(8) + LungM(4,3)*Conc(9) + LungM(4,4)*Conc(10) + 
LungM(4,5)*Conc(11)...
          + LungM(4,6)*Conc(12) + LungM(4,7)*Conc(13) + LungM(4,8)*Conc(14) + LungM(4,9)*Conc(15) + 
LungM(4,10)*Conc(16)...
          + LungM(4,11)*Conc(17) + LungM(4,12)*Conc(2)*fup/B2P + LungG(4);                    % 17 - 
Epithelial cells (cEpMito)

   dConc(11) = LungM(5,1)*Conc(7) + LungM(5,2)*Conc(8) + LungM(5,3)*Conc(9) + LungM(5,4)*Conc(10) + 
LungM(5,5)*Conc(11)...
          + LungM(5,6)*Conc(12) + LungM(5,7)*Conc(13) + LungM(5,8)*Conc(14) + LungM(5,9)*Conc(15) + 
LungM(5,10)*Conc(16)...
          + LungM(5,11)*Conc(17) + LungM(5,12)*Conc(2)*fup/B2P + LungG(5);                    % 18 - 
Epithelial cells (cEpLyso)

   dConc(12) = LungM(6,1)*Conc(7) + LungM(6,2)*Conc(8) + LungM(6,3)*Conc(9) + LungM(6,4)*Conc(10) + 
LungM(6,5)*Conc(11)...
          + LungM(6,6)*Conc(12) + LungM(6,7)*Conc(13) + LungM(6,8)*Conc(14) + LungM(6,9)*Conc(15) + 
LungM(6,10)*Conc(16)...
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            + LungM(6,11)*Conc(17) + LungM(6,12)*Conc(2)*fup/B2P + LungG(6);                    % 19 -
Interstitium (int)

    dConc(13) = LungM(7,1)*Conc(7) + LungM(7,2)*Conc(8) + LungM(7,3)*Conc(9) + LungM(7,4)*Conc(10) +
LungM(7,5)*Conc(11)...
            + LungM(7,6)*Conc(12) + LungM(7,7)*Conc(13) + LungM(7,8)*Conc(14) + LungM(7,9)*Conc(15) +
LungM(7,10)*Conc(16)...
            + LungM(7,11)*Conc(17) + LungM(7,12)*Conc(2)*fup/B2P + LungG(7);                    % 20 -
Smooth muscle (sm)


    dConc(14) = LungM(8,1)*Conc(7) + LungM(8,2)*Conc(8) + LungM(8,3)*Conc(9) + LungM(8,4)*Conc(10) +
LungM(8,5)*Conc(11)...
            + LungM(8,6)*Conc(12) + LungM(8,7)*Conc(13) + LungM(8,8)*Conc(14) + LungM(8,9)*Conc(15) +
LungM(8,10)*Conc(16)...
            + LungM(8,11)*Conc(17) + LungM(8,12)*Conc(2)*fup/B2P + LungG(8);                    % 21 -
Immune cells (imInt)

    dConc(15) = LungM(9,1)*Conc(7) + LungM(9,2)*Conc(8) + LungM(9,3)*Conc(9) + LungM(9,4)*Conc(10) +
LungM(9,5)*Conc(11)...
            + LungM(9,6)*Conc(12) + LungM(9,7)*Conc(13) + LungM(9,8)*Conc(14) + LungM(9,9)*Conc(15) +
LungM(9,10)*Conc(16)...
            + LungM(9,11)*Conc(17) + LungM(9,12)*Conc(2)*fup/B2P + LungG(9);                    % 22 -
Endothelial cells (cEd)

    dConc(16) = LungM(10,1)*Conc(7) + LungM(10,2)*Conc(8) + LungM(10,3)*Conc(9) + LungM(10,4)*Conc(10)
+ LungM(10,5)*Conc(11)...
            + LungM(10,6)*Conc(12) + LungM(10,7)*Conc(13) + LungM(10,8)*Conc(14) + LungM(10,9)*Conc(15)
+ LungM(10,10)*Conc(16)...
            + LungM(10,11)*Conc(17) + LungM(10,12)*Conc(2)*fup/B2P + LungG(10);                    % 23 -
Endothelial cells (cEdMito)

    dConc(17) = LungM(11,1)*Conc(7) + LungM(11,2)*Conc(8) + LungM(11,3)*Conc(9) + LungM(11,4)*Conc(10)
+ LungM(11,5)*Conc(11)...
            + LungM(11,6)*Conc(12) + LungM(11,7)*Conc(13) + LungM(11,8)*Conc(14) + LungM(11,9)*Conc(15)
+ LungM(11,10)*Conc(16)...
            + LungM(11,11)*Conc(17) + LungM(11,12)*Conc(2)*fup/B2P + LungG(11);                    % 24 -
Endothelial cells (cEdLyso)

CL = 0 ; % blood CL was fixed at 0, isolated lung model

dConc(3) = 0 ;      % Venous blood
dConc(4) = 0 ;                          % Brain
dConc(5) = 0 ;                          % Liver
dConc(6) = 0 ;

dConc(18) = 0;  % 18 -Lung total blood concentration was fixed at 0, so it is a isolated lung model



    dConc(19) = LungM_Airways(1,1)*Conc(19) + LungM_Airways(1,2)*Conc(20) +
LungM_Airways(1,3)*Conc(21) + LungM_Airways(1,4)*Conc(22) + LungM_Airways(1,5)*Conc(23)...
            + LungM_Airways(1,6)*Conc(24) + LungM_Airways(1,7)*Conc(25) + LungM_Airways(1,8)*Conc(26) +
LungM_Airways(1,9)*Conc(27) + LungM_Airways(1,10)*Conc(28)...
            + LungM_Airways(1,11)*Conc(29)+ LungM_Airways(1,12)*Conc(30)+
LungM_Airways(1,13)*Conc(31) ...
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        + LungM_Airways(1,14)*Conc(18)*fup/B2P + LungG_Airways(1);                        % 19 -
SurfaConce lining liquid (aEp)

   dConc(20) = LungM_Airways(2,1)*Conc(19) + LungM_Airways(2,2)*Conc(20) +
LungM_Airways(2,3)*Conc(21) + LungM_Airways(2,4)*Conc(22) + LungM_Airways(2,5)*Conc(23)...
        + LungM_Airways(2,6)*Conc(24) + LungM_Airways(2,7)*Conc(25) + LungM_Airways(2,8)*Conc(26) +
LungM_Airways(2,9)*Conc(27) + LungM_Airways(2,10)*Conc(28)...
        + LungM_Airways(2,11)*Conc(29)+ LungM_Airways(2,12)*Conc(30)+
LungM_Airways(2,13)*Conc(31) ...
        + LungM_Airways(2,14)*Conc(18)*fup/B2P + LungG_Airways(2);                        % 20 -
Macrophage (imEp)

   dConc(21) = LungM_Airways(3,1)*Conc(19) + LungM_Airways(3,2)*Conc(20) +
LungM_Airways(3,3)*Conc(21) + LungM_Airways(3,4)*Conc(22) + LungM_Airways(3,5)*Conc(23)...
        + LungM_Airways(3,6)*Conc(24) + LungM_Airways(3,7)*Conc(25) + LungM_Airways(3,8)*Conc(26) +
LungM_Airways(3,9)*Conc(27) + LungM_Airways(3,10)*Conc(28)...
        + LungM_Airways(3,11)*Conc(29)+ LungM_Airways(3,12)*Conc(30)+
LungM_Airways(3,13)*Conc(31) ...
        +LungM_Airways(3,14)*Conc(18)*fup/B2P + LungG_Airways(3);                        % 21 - Epithelial
cells (cEp)

   dConc(22) = LungM_Airways(4,1)*Conc(19) + LungM_Airways(4,2)*Conc(20) +
LungM_Airways(4,3)*Conc(21) + LungM_Airways(4,4)*Conc(22) + LungM_Airways(4,5)*Conc(23)...
        + LungM_Airways(4,6)*Conc(24) + LungM_Airways(4,7)*Conc(25) + LungM_Airways(4,8)*Conc(26) +
LungM_Airways(4,9)*Conc(27) + LungM_Airways(4,10)*Conc(28)...
        + LungM_Airways(4,11)*Conc(29)+ LungM_Airways(4,12)*Conc(30)+
LungM_Airways(4,13)*Conc(31) ...
        + LungM_Airways(4,14)*Conc(18)*fup/B2P + LungG_Airways(4);                        % 22 - Epithelial
cells (cEpMito)

   dConc(23) = LungM_Airways(5,1)*Conc(19) + LungM_Airways(5,2)*Conc(20) +
LungM_Airways(5,3)*Conc(21) + LungM_Airways(5,4)*Conc(22) + LungM_Airways(5,5)*Conc(23)...
        + LungM_Airways(5,6)*Conc(24) + LungM_Airways(5,7)*Conc(25) + LungM_Airways(5,8)*Conc(26) +
LungM_Airways(5,9)*Conc(27) + LungM_Airways(5,10)*Conc(28)...
        + LungM_Airways(5,11)*Conc(29)+ LungM_Airways(5,12)*Conc(30)+
LungM_Airways(5,13)*Conc(31) ...
        + LungM_Airways(5,14)*Conc(18)*fup/B2P + LungG_Airways(5);                        % 23 - Epithelial
cells (cEpLyso)

   dConc(24) = LungM_Airways(6,1)*Conc(19) + LungM_Airways(6,2)*Conc(20) +
LungM_Airways(6,3)*Conc(21) + LungM_Airways(6,4)*Conc(22) + LungM_Airways(6,5)*Conc(23)...
        + LungM_Airways(6,6)*Conc(24) + LungM_Airways(6,7)*Conc(25) + LungM_Airways(6,8)*Conc(26) +
LungM_Airways(6,9)*Conc(27) + LungM_Airways(6,10)*Conc(28)...
        + LungM_Airways(6,11)*Conc(29)+ LungM_Airways(6,12)*Conc(30)+
LungM_Airways(6,13)*Conc(31) ...
        + LungM_Airways(6,14)*Conc(18)*fup/B2P + LungG_Airways(6);                        % 24 -
Interstitium (int)

   dConc(25) = LungM_Airways(7,1)*Conc(19) + LungM_Airways(7,2)*Conc(20) +
LungM_Airways(7,3)*Conc(21) + LungM_Airways(7,4)*Conc(22) + LungM_Airways(7,5)*Conc(23)...
        + LungM_Airways(7,6)*Conc(24) + LungM_Airways(7,7)*Conc(25) + LungM_Airways(7,8)*Conc(26) +
LungM_Airways(7,9)*Conc(27) + LungM_Airways(7,10)*Conc(28)...
        + LungM_Airways(7,14)*Conc(29)+ LungM_Airways(7,12)*Conc(30)+
LungM_Airways(7,13)*Conc(31) ...
        + LungM_Airways(7,12)*Conc(18)*fup/B2P + LungG_Airways(7);                        % 25 - Smooth
muscle (sm)
```

```
    dConc(26) = LungM_Airways(8,1)*Conc(19) + LungM_Airways(8,2)*Conc(20) +
LungM_Airways(8,3)*Conc(21) + LungM_Airways(8,4)*Conc(22) + LungM_Airways(8,5)*Conc(23)...
           + LungM_Airways(8,6)*Conc(24) + LungM_Airways(8,7)*Conc(25) + LungM_Airways(8,8)*Conc(26) +
LungM_Airways(8,9)*Conc(27) + LungM_Airways(8,10)*Conc(28)...
           + LungM_Airways(8,11)*Conc(29)+ LungM_Airways(8,12)*Conc(30)+
LungM_Airways(8,13)*Conc(31) ...
           + LungM_Airways(8,14)*Conc(18)*fup/B2P + LungG_Airways(8);                       % 26 - Smooth
muscle (smMito)

    dConc(27) = LungM_Airways(9,1)*Conc(19) + LungM_Airways(9,2)*Conc(20) +
LungM_Airways(9,3)*Conc(21) + LungM_Airways(9,4)*Conc(22) + LungM_Airways(9,5)*Conc(23)...
           + LungM_Airways(9,6)*Conc(24) + LungM_Airways(9,7)*Conc(25) + LungM_Airways(9,8)*Conc(26) +
LungM_Airways(9,9)*Conc(27) + LungM_Airways(9,10)*Conc(28)...
           + LungM_Airways(9,11)*Conc(29)+ LungM_Airways(9,12)*Conc(30)+
LungM_Airways(9,13)*Conc(31) ...
           + LungM_Airways(9,14)*Conc(18)*fup/B2P + LungG_Airways(9);                       % 27 - Smooth
muscle (smLyso)

    dConc(28) = LungM_Airways(10,1)*Conc(19) + LungM_Airways(10,2)*Conc(20) +
LungM_Airways(10,3)*Conc(21) + LungM_Airways(10,4)*Conc(22) + LungM_Airways(10,5)*Conc(23)...
           + LungM_Airways(10,6)*Conc(24) + LungM_Airways(10,7)*Conc(25) +
LungM_Airways(10,8)*Conc(26) + LungM_Airways(10,9)*Conc(27) + LungM_Airways(10,10)*Conc(28)...
           + LungM_Airways(10,11)*Conc(29)+ LungM_Airways(10,12)*Conc(30)+
LungM_Airways(10,13)*Conc(31) ...
           + LungM_Airways(10,14)*Conc(18)*fup/B2P + LungG_Airways(10);                     % 28 - Immune
cells (imInt)

    dConc(29) = LungM_Airways(11,1)*Conc(19) + LungM_Airways(11,2)*Conc(20) +
LungM_Airways(11,3)*Conc(21) + LungM_Airways(11,4)*Conc(22) + LungM_Airways(11,5)*Conc(23)...
           + LungM_Airways(11,6)*Conc(24) + LungM_Airways(11,7)*Conc(25) +
LungM_Airways(11,8)*Conc(26) + LungM_Airways(11,9)*Conc(27) + LungM_Airways(11,10)*Conc(28)...
           + LungM_Airways(11,11)*Conc(29)+ LungM_Airways(11,12)*Conc(30)+
LungM_Airways(11,13)*Conc(31)  ...
           + LungM_Airways(11,14)*Conc(18)*fup/B2P + LungG_Airways(11);                     % 29 -
Endothelial cells

    dConc(30) = LungM_Airways(12,1)*Conc(19) + LungM_Airways(12,2)*Conc(20) +
LungM_Airways(12,3)*Conc(21) + LungM_Airways(12,4)*Conc(22) + LungM_Airways(12,5)*Conc(23)...
           + LungM_Airways(12,6)*Conc(24) + LungM_Airways(12,7)*Conc(25) +
LungM_Airways(12,8)*Conc(26) + LungM_Airways(12,9)*Conc(27) + LungM_Airways(12,10)*Conc(28)...
           + LungM_Airways(12,11)*Conc(29)+ LungM_Airways(12,12)*Conc(30)+
LungM_Airways(12,13)*Conc(31) ...
           + LungM_Airways(12,14)*Conc(18)*fup/B2P + LungG_Airways(12);                     % 28 -
Endothelial cells (cEdMito)

    dConc(31) = LungM_Airways(13,1)*Conc(19) + LungM_Airways(13,2)*Conc(20) +
LungM_Airways(13,3)*Conc(21) + LungM_Airways(13,4)*Conc(22) + LungM_Airways(13,5)*Conc(23)...
           + LungM_Airways(13,6)*Conc(24) + LungM_Airways(13,7)*Conc(25) +
LungM_Airways(13,8)*Conc(26) + LungM_Airways(13,9)*Conc(27) + LungM_Airways(13,10)*Conc(28)...
           + LungM_Airways(13,11)*Conc(29)+ LungM_Airways(13,12)*Conc(30)+
LungM_Airways(13,13)*Conc(31) ...
           + LungM_Airways(13,14)*Conc(18)*fup/B2P + LungG_Airways(13);                     % 29 -
Endothelial cells (cEdLyso)
```

```
Vtot = diag([V_ART V_LUNb V_VEN V_BRA V_LIV V_RES diag(M_v)'*10^6 V_LUNb_Airways
diag(M_v_Airways)'*10^6]) ;

dConc = [dConc(1), dConc(2), dConc(3), dConc(4), dConc(5), dConc(6), dConc(7), dConc(8), dConc(9),
dConc(10),...
        dConc(11), dConc(12), dConc(13),  dConc(14), dConc(15), dConc(16), dConc(17),...
        dConc(18), dConc(19), dConc(20),  dConc(21), dConc(22), dConc(23), dConc(24),...
        dConc(25), dConc(26), dConc(27),  dConc(28), dConc(29), dConc(30), dConc(31)]' ;
```

```
% to caculate the AUC for airways and alveoli
function [T,Y,Conc_LUNSim,AUC_al,AUC_aw]= Lung_fun(pKa,logP,x)
global BW V_VEN fup B2P Vtot;
BW = 0.25 ; %kg from experiment
V_VEN = 0.0544*BW*1000 ;
B2P = 1.11 ;
fup = 0.96 ;

% calculate the concentration accumulated in the lung: airways and alveoli
[M, G, M_v, Vp] = AL(pKa,logP,x);
[M_Airways, G_Airways, M_v_Airways, Vp_Airways] = AW(pKa,logP,x);

Y0 = zeros(31,1) ;
dose = 1.0 ; %1mg, initial dose

Y0(7) = dose*BW/(M_v(1,1)*10^6) ;   % AL,mg/mL
Y0(19) = dose*BW/(M_v_Airways(1,1)*10^6) ;   % AW,mg/mL

Yopt = 1e-13 * ones(1,31) ;
options = odeset('RelTol',1e-13,'AbsTol',Yopt);

[T,Y] = ode15s(@Lung,[0 200*60],Y0,options,pKa,logP,x);
len = length(T) ;
% total lung mass and conc
Conc_LUNtemp = Y(:,7:17) ;%mg/ml
Mass_LUNtemp = Conc_LUNtemp*(M_v*10^6) ; %mg
% airways mass and conc
Conc_Airwaystemp = Y(:,19:31) ;%mg/ml
Mass_Airwaystemp = Conc_Airwaystemp*(M_v_Airways*10^6) ; %mg
% alveoli mass and conc
Mass_LUNSim = sum(Mass_LUNtemp, 2) + sum(Mass_Airwaystemp, 2) ;%mg
Conc_LUNSim = Mass_LUNSim*10^6 / ((trace(M_v)*10^6)+(trace(M_v_Airways)*10^6)); %ng/mL

Con_al = sum(Mass_LUNtemp, 2)*10^6/(trace(M_v)*10^6);%ng/ml
Con_aw = sum(Mass_Airwaystemp, 2)*10^6/(trace(M_v_Airways)*10^6);%ng/ml
% AUC at alveoli and airways
AUC_al = trapz(T,Con_al/10^6);
AUC_aw = trapz(T,Con_aw/10^6);

% lung:venous blood concentration ratio (Kp_LUN)
Kpulung = Conc_LUNSim(len)/(Y(len,3)*fup);
Kplung = Conc_LUNSim(len)/Y(len,3) ;
end
```

```
% main function
%logP and pKa with AUC at aw and al
% caculate the AUC and ratio, then plot
clear
close all
clc
i = 1;
for logP = [-2:0.4:4]
    j = 1;
    for pKa = [5:0.4:14,14]
    [T,Y,Conc_LUNSim,AUC_al,AUC_aw]= Lung_fun(pKa,logP,1);
    pKa_M(i,j) = pKa;
    logP_M(i,j) = logP;
    AUC_AL_M(i,j) = AUC_al;
    AUC_AW_M(i,j) = AUC_aw;
    j = j + 1;
    end
    i = i + 1;
end
R = AUC_AW_M./AUC_AL_M;
save('AUC_logP_pKa_200hr');
subplot(1,3,1);%T_al
v1=[0:20:100,200:200:1000];
[C1,H1]=contour(logP_M,pKa_M,AUC_AW_M,v1,'LineWidth',3,...
    'LineColor',[0 0 0]);
clabel(C1,H1,'manual','FontSize',20);

subplot(1,3,2)
v2=[0.1,0.2:0.2:2];
[C2,H2]=contour(logP_M,pKa_M,AUC_AL_M,v2,'LineWidth',3,...
    'LineColor',[0 0 0]);

clabel(C2,H2,'manual','FontSize',20);

subplot(1,3,3);
[C3,H3]=contour(logP_M,pKa_M,R,'LineWidth',3,...
    'LineColor',[0 0 0]);
clabel(C3,H3,'manual','FontSize',20);
```