```matlab
% This script is to perform Monte Carlo simulations for 1CellPK
% This script includes the following situations (for figure 4):
% Case# 1: AP->BL transport, pHa = 6.5, 0.4um-membrane, 5min
% Case# 2: AP->BL transport, pHa = 6.5,   3um-membrane, 5min
% Case# 3: AP->BL transport, pHa = 7.4, 0.4um-membrane, 5min
% Case# 4: AP->BL transport, pHa = 7.4,   3um-membrane, 5min

% Case# 5: BL->AP transport, pHb = 6.5, 0.4um-membrane, 5min
% Case# 6: BL->AP transport, pHb = 6.5,   3um-membrane, 5min
% Case# 7: BL->AP transport, pHb = 7.4, 0.4um-membrane, 5min
% Case# 8: BL->AP transport, pHb = 7.4,   3um-membrane, 5min

% ==========================Case#1: AP->BL transport, pHa = 6.5, 0.4um-
membrane,5min=======================================

clear ;                       % Clear the memory
z1 = 1 ;                      % ionization group 1 of CQ
z2 = 2 ;                      % ionization group 2 of CQ
i1 = sign(z1) ;
i2 = sign(z2) ;

T = 310.15 ;                  % temperature
R = 8.314 ;                   % universal gas constant
F = 96484.56 ;                % faraday constant
C_a = 1 ;                     % initial drug concentration (mM)

sim = 10000;                  % number of simulations
paraNo = 25;
outputNo = 7;                 % number of output parameters
Para = zeros(sim,paraNo);
Results = zeros(sim,outputNo);

dMdt_exp = 2.2E-6;            % +/- 7.18E-7, pmol/sec/cell, measured after
4hrs
Ppore_exp = 2.18E+02;        % +/- 34.4, 10^-6 cm/sec, measured after 4hrs
Peff_exp = 1.35;             % +/- 0.442, 10^-6 cm/sec, measured after 4hrs
IntraMass_exp = 0.00373;     % +/- 0.00014 pmol/cell , measured after 5min

for i = 1:sim

    % Drug information -- ChemAxon calculation including logPn, pKa1, and pKa2
    logPn = 3.93-0.5+rand();    % unif [3.43, 4.43] ;
    pKa1 = 9.96-0.5+rand();     % unif [9.46, 10.46] ;
    pKa2 = 7.47-0.5+rand();     % unif [6.97, 7.97] ;
    logPd1 = 0.43-0.5+rand();   % unif [-0.07, 0.93] ;
    logPd2 = -0.91-0.5+rand();  % unif [-1.41, 0.41] ;
    Pn = 10^(logPn-6.7);
    Pd1 = 10^(logPd1-6.7);
    Pd2 = 10^(logPd2-6.7);


    CellNo = 2*10^5*(1+rand());                              % cell
number/insert: unif [2*10^5, 4*10^5]
    PoreDens = 4*10^6*0.4*(2+rand());                        % pore
number/cm^2: unif [3.2*10^6, 4.8*10^6]
    A_insert = 1.12*10^(-4) ;                                % insert area:
1.12 cm^2
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```
    PoreNo_insert = PoreDens*A_insert*10^(4);                  % pore
number/insert
    PoreNo_cell = PoreNo_insert/CellNo ;                       % average pore
number/cell
    A_pore_insert = 3.14*((0.4/2)*10^(-6))^2*PoreNo_insert ;   % pore area /
insert (m^2)
    A_pore_cell = 3.14*((0.4/2)*10^(-6))^2*PoreNo_cell ;       % average pore
area / cell (m^2)

    A_a = 10^(-10)*(1+9*rand());                               % apical
membrane surface area: unif [10^(-10),10*(10)^(-10))] (m^2)
    A_aa = A_pore_cell;                                        % pore area/cell
(m^2)
    A_b = A_aa+(10^(-10)-A_aa)*rand();                         % basolateral
membrane surface area: unif [A_aa, 10^(-10))] (m^2)
    A_l = 100*3.14*10^(-12);                                   % lysosomal
membrane surface area (m^2)
    A_m = 100*3.14*10^(-12);                                   % mitochondrial
membrane surface area (m^2)
    V_c = 0.5*10^(-15)*(1+5*rand());                           % cytosolic
volume: unif [0.5*10^(-15), 3*10^(-15)] (m^3)
    V_l = 10^(-18)*(9.24+(23.8-9.24)*rand());                  % lysosomal
volume: unif [9.24*10^(-18), 23.8*10^(-18)] (m^3)
    V_m = 100*5.24*10^(-19)/5*(1+24*rand());                  % mitochondrial
volume: unif [10.48*10^(-18), 262*10^(-18)](m^3)
    V_b = 1.5*10^(-6);                                         % basolateral
volume: 1.5 mL

    % Membrane potential (unit in 'Voltage')
    E_a = -0.0093-0.005+0.01*rand();                           % apical
membrane potential: unif [-0.0143, -0.0043]
    E_l = 0.01-0.005+0.01*rand();                              % lysosomal
membrane potential: unif [0.005, 0.015]
    E_m = -0.16 ;                                              % mitochondrial
membrane potential
    E_b = 0.0119-0.005+0.01*rand();                           % basolateral
membrane potential: unif [0.0069, 0.0169]

    % pH values
    pH_a = 6.4+0.2*rand();                                     % pH in apical
compartment: unif [6.4, 6.6]
    pH_c = 7.0+0.4*rand();                                     % pH in cytosol:
unif [7.0, 7.4]
    pH_l = 4.8+0.4*rand();                                     % pH in
lysosomes: unif [4.8, 5.2]
    pH_m = 7.8+0.4*rand();                                     % pH in
mitochondria: unif[7.8, 8.2]
    pH_b = 7.4;                                                % pH in
basolateral compartment

    % Apical Compartment
    fn_a = 1 / (1 + 10^(i1*(pKa1-pH_a)) + 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a))) ;
    fd2_a = fn_a * 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a)) ;
    fd1_a = fn_a * 10^(i1*(pKa1-pH_a)) ;
    Nd2_a = z2*E_a*F/(R*T) ;
    Nd1_a = z1*E_a*F/(R*T) ;
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```
    % Cytoplasm
    L_c = 0.05+0.1*rand();                                      % lipid
fraction in cytosol: unif [0.05, 0.15]
    W_c = 1-L_c ;                                               % water
fraction in cytosol
    Is_c = 0.3 ;                                                % ion
strength in cytosol (mol)
    gamman_c = 10^(0.3*Is_c) ;                                  %
activity coefficient of neutral molecules in cytosol
    gammad1_c = 10^(-0.5*z1*z1*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of monovalent base in cytosol
    gammad2_c = 10^(-0.5*z2*z2*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of bivalent base in cytosol
    Kn_c = L_c*1.22*10^(logPn) ;
    Kd1_c = L_c*1.22*10^(logPd1) ;
    Kd2_c = L_c*1.22*10^(logPd2) ;
    an_c = 1 / (1 + 10^(i1*(pKa1-pH_c)) + 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c))) ;
    ad2_c = an_c * 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c)) ;
    ad1_c = an_c * 10^(i1*(pKa1-pH_c)) ;
    Dd2_c = ad2_c / an_c ;
    Dd1_c = ad1_c / an_c ;
    fn_c = 1 / (W_c/gamman_c + Kn_c/gamman_c + Dd2_c*W_c/gammad2_c +
Dd2_c*Kd2_c/gammad2_c ...
            + Dd1_c*W_c/gammad1_c + Dd1_c*Kd1_c/gammad1_c ) ;
    fd2_c = fn_c * Dd2_c ;
    fd1_c = fn_c * Dd1_c ;

    % Mitochondria
    L_m = 0.05+0.1*rand();                                      % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_m = 1-L_m ;                                               % water
fraction in mitochondria
    Is_m = 0.3 ;                                                % ion
strength in mitochondria (mol)
    Nd2_m = z2*E_m*F/(R*T) ;
    Nd1_m = z1*E_m*F/(R*T) ;
    gamman_m = 10^(0.3*Is_m) ;                                  %
activity coefficient of neutral molecules in mitochondria
    gammad1_m = 10^(-0.5*z1*z1*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of monovalent base in mitochondria
    gammad2_m = 10^(-0.5*z2*z2*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of bivalent base in mitochondria
    Kn_m = L_m*1.22*10^(logPn) ;
    Kd1_m = L_m*1.22*10^(logPd1) ;
    Kd2_m = L_m*1.22*10^(logPd2) ;
    an_m = 1 / (1 + 10^(i1*(pKa1-pH_m)) + 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m))) ;
    ad2_m = an_m * 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m)) ;
    ad1_m = an_m * 10^(i1*(pKa1-pH_m)) ;
    Dd2_m = ad2_m / an_m ;
    Dd1_m = ad1_m / an_m ;
    fn_m = 1 / (W_m/gamman_m + Kn_m/gamman_m + Dd2_m*W_m/gammad2_m +
Dd2_m*Kd2_m/gammad2_m ...
            + Dd1_m*W_m/gammad1_m + Dd1_m*Kd1_m/gammad1_m ) ;
    fd2_m = fn_m * Dd2_m ;
    fd1_m = fn_m * Dd1_m ;

    % Lysosomes
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```matlab
    L_l = 0.05+0.1*rand();                                        % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_l = 1-L_l ;                                                 % water
fraction in lysosomes
    Is_l = 0.3 ;                                                  % ion
strength in lysosomes (mol)
    Nd2_l = z2*E_l*F/(R*T) ;
    Nd1_l = z1*E_l*F/(R*T) ;
    gamman_l = 10^(0.3*Is_l) ;                                    %
activity coefficient of neutral molecules in lysosomes
    gammad1_l = 10^(-0.5*z1*z1*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of monovalent base in lysosomes
    gammad2_l = 10^(-0.5*z2*z2*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of bivalent base in lysosomes
    Kn_l = L_l*1.22*10^(logPn) ;
    Kd1_l = L_l*1.22*10^(logPd1) ;
    Kd2_l = L_l*1.22*10^(logPd2) ;
    an_l = 1 / (1 + 10^(i1*(pKa1-pH_l)) + 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l))) ;
    ad2_l = an_l * 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l)) ;
    ad1_l = an_l * 10^(i1*(pKa1-pH_l)) ;
    Dd2_l = ad2_l / an_l ;
    Dd1_l = ad1_l / an_l ;
    fn_l = 1 / (W_l/gamman_l + Kn_l/gamman_l + Dd2_l*W_l/gammad2_l +
Dd2_l*Kd2_l/gammad2_l ...
            + Dd1_l*W_l/gammad1_l + Dd1_l*Kd1_l/gammad1_l ) ;
    fd2_l = fn_l * Dd2_l ;
    fd1_l = fn_l * Dd1_l ;

    % Basolaterial Compartment
    fn_b = 1 / (1 + 10^(i1*(pKa1-pH_b)) + 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b))) ;
    fd2_b = fn_b * 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b)) ;
    fd1_b = fn_b * 10^(i1*(pKa1-pH_b)) ;
    Nd2_b = z2*(-E_b)*F/(R*T) ;
    Nd1_b = z1*(-E_b)*F/(R*T) ;

    % Solve the differential equation system:
    % Given a system of linear ODE's expressed in matrix form:
    % Y' = AY+G with initial conditions Y(0) = RR,
        k11 = -(A_a/V_c)*Pn*fn_c-
(A_a/V_c)*Pd1*Nd1_a*fd1_c*exp(Nd1_a)/(exp(Nd1_a)-1)...
            -(A_a/V_c)*Pd2*Nd2_a*fd2_c*exp(Nd2_a)/(exp(Nd2_a)-1)...
            -(A_m/V_c)*Pn*fn_c-(A_m/V_c)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
            -(A_m/V_c)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1)...
            -(A_l/V_c)*Pn*fn_c-(A_l/V_c)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
            -(A_l/V_c)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1)...
            -(A_b/V_c)*Pn*fn_c-(A_b/V_c)*Pd1*Nd1_b*fd1_c/(exp(Nd1_b)-1)...
            -(A_b/V_c)*Pd2*Nd2_b*fd2_c/(exp(Nd2_b)-1) ;
        k12 =
(A_m/V_c)*Pn*fn_m+(A_m/V_c)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
            +(A_m/V_c)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1);
        k13 =
(A_l/V_c)*Pn*fn_l+(A_l/V_c)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
            +(A_l/V_c)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1);
        k14 =
(A_b/V_c)*Pn*fn_b+(A_b/V_c)*Pd1*Nd1_b*fd1_b*exp(Nd1_b)/(exp(Nd1_b)-1)...
            +(A_b/V_c)*Pd2*Nd2_b*fd2_b*exp(Nd2_b)/(exp(Nd2_b)-1);
        S1 = (A_a/V_c)*C_a*(Pn*fn_a+Pd1*Nd1_a*fd1_a/(exp(Nd1_a)-1)...
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                +Pd2*Nd2_a*fd2_a/(exp(Nd2_a)-1))  ;

        k21 = (A_m/V_m)*Pn*fn_c+(A_m/V_m)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
                +(A_m/V_m)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1) ;
        k22 = -(A_m/V_m)*Pn*fn_m-
(A_m/V_m)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
                -(A_m/V_m)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1) ;
        k23 = 0;
        k24 = 0 ;
        S2 = 0;

        k31 = (A_l/V_l)*Pn*fn_c+(A_l/V_l)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
                +(A_l/V_l)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1) ;
        k32 = 0;
        k33 = -(A_l/V_l)*Pn*fn_l-
(A_l/V_l)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
                -(A_l/V_l)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1) ;

        k34 = 0 ;
        S3 = 0;

        k41 = (A_b/V_b)*Pn*fn_c+(A_b/V_b)*Pd1*Nd1_b*fd1_c/(exp(Nd1_b)-1)...
                +(A_b/V_b)*Pd2*Nd2_b*fd2_c/(exp(Nd2_b)-1) ;
        k42 = 0;
        k43 = 0;
        k44 = -(A_b/V_b)*Pn*fn_b-
(A_b/V_b)*Pd1*Nd1_b*fd1_b*exp(Nd1_b)/(exp(Nd1_b)-1)...
                -(A_b/V_b)*Pd2*Nd2_b*fd2_b*exp(Nd2_b)/(exp(Nd2_b)-1);
        S4 = 0;

        A = [k11, k12, k13, k14; k21, k22, k23, k24; k31, k32, k33, k34; k41,
k42, k43, k44];
        G = [S1, S2, S3, S4]';
        RR = [0,0,0,0]';
        t = 300 ;    % time in sec (5min)


        [V,E] = eig(A);
        E = diag(E);
        H = inv(V)*G;
        B = V \ RR;
        C = B + H./E;
        Z = -(H./E) + exp(t * E).*C ;
        Y = real(V * Z);
        Y = Y' ;

        Ppore = Y(4)*V_b /(t*A_aa*C_a)*10^(2)*10^6 ;                    %
Pcell, 10^(-6)cm/sec
        Peff = Y(4)*V_b*CellNo/(t*A_insert*C_a)*10^(2)*10^6;           %
Peff, 10^(-6)cm/sec, normalized by insert area, which is 1.12 cm^2
        Mass_cell = (Y(1)*V_c + Y(2)*V_m + Y(3)*V_l)*10^12 ;          %
cellular mass, pmol/cell
        dMdt = Y(4)*V_b/t*10^12;                                       %
transport rate: pmol/sec/cell
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```
    Para(i,:) = [A_a*10^12,PoreNo_cell,
A_l*10^12,A_m*10^12,A_b*10^12,V_c*10^18,V_l*10^18,V_m*10^18,V_b*10^6,E_a*1000,E_
l*1000,E_m*1000,E_b*1000,...
                  pH_a,pH_c,pH_l,pH_m,pH_b,CellNo,PoreDens,
pKa1,pKa2,logPn,logPd1, logPd2];
    Results(i,:)=[Y(1),Y(2),Y(3),Ppore, Peff, dMdt, Mass_cell];

end

comb = [Results(:,1:7),Para];
fid5 = fopen('AtoB_pH65_04um_5min.dat','w');
fprintf(fid5,'%12.4e %12.4e %12.4e %12.4e %12.4e  %12.4e %12.4e %12.2e %12.0f %1
2.4e %12.4e %12.4e  %12.4e %12.4e %12.4e %12.4e %12.4f %12.4f %12.4f %12.4f %12.
2f %12.2f %12.2f %12.2f %12.2f %12.0f %12.0f %12.2f %12.2f %12.2f %12.2f %12.2f
\n', comb') ;
fclose(fid5);

figure(1) ; clf ; hold on ;
grid on;
hist (log10(comb(:,4)),1000);
line([log10(Ppore_exp), log10(Ppore_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{cell}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
xlim([0, 6]);
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of cell
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(2) ; clf ; hold on ;
grid on;
hist (log10(comb(:,5)),1000);
xlim([-3, 3]);
line([log10(Peff_exp), log10(Peff_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{app}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of apparent
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(3) ; clf ; hold on ;
grid on;
hist (log10(comb(:,6)),1000);
xlim([-8,-2]);
line([log10(dMdt_exp), log10(dMdt_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (dM/dt,
pmol/sec/cell)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
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title ('histogram of transport
rate','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(4) ; clf ; hold on ;
grid on;
hist (log10(comb(:,7)),1000);
xlim([-5,-0]);
line([log10(IntraMass_exp),
log10(IntraMass_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (intracellular mass, pmol/cell)
','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of intracellular
mass','FontSize',30,'FontWeight','Bold','FontName','Times') ;




% =========================Case# 2: AP->BL transport, pHa = 6.5,   3um-membrane,
5min=====================================

clear ;                    % Clear the memory
z1 = 1 ;                   % ionization group 1 of CQ
z2 = 2 ;                   % ionization group 2 of CQ
i1 = sign(z1) ;
i2 = sign(z2) ;

T = 310.15 ;               % temperature
R = 8.314 ;                % universal gas constant
F = 96484.56 ;             % faraday constant
C_a = 1 ;                  % initial drug concentration (mM)

sim = 10000;               % number of simulations
paraNo = 25;
outputNo = 7;              % number of output parameters
Para = zeros(sim,paraNo);
Results = zeros(sim,outputNo);

dMdt_exp = 5.19e-6;        % +/- 1.01e-6, pmol/sec/cell, measured after 4hrs
Ppore_exp = 1.40E+01;      % +/- 3.33, 10^(-6) cm/sec, measured after 4hrs
Peff_exp = 1.98E+00;       % +/- 0.471, 10^(-6) cm/sec, measured after 4hrs
IntraMass_exp = 0.00188;   % +/- 0.00054, pmol/cell, measured after 5min

for i = 1:sim

    % Drug information -- ChemAxon calculation including logPn, pKa1, and pKa2
    logPn = 3.93-0.5+rand();    % unif [3.43, 4.43] ;
    pKa1 = 9.96-0.5+rand();     % unif [9.46, 10.46] ;
    pKa2 = 7.47-0.5+rand();     % unif [6.97, 7.97] ;
    logPd1 = 0.43-0.5+rand();   % unif [-0.07, 0.93] ;
    logPd2 = -0.91-0.5+rand();  % unif [-1.41, 0.41] ;
    Pn = 10^(logPn-6.7);
    Pd1 = 10^(logPd1-6.7);
    Pd2 = 10^(logPd2-6.7);
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    CellNo = 2*10^5*(1+rand());                         % cell
number/insert: unif [2*10^5, 4*10^5]
    PoreDens = 2*10^6*0.4*(2+rand());                   % pore
number/cm^2: unif [1.6*10^6, 2.4*10^6]
    A_insert = 1.12*10^(-4) ;                           % insert area:
1.12 cm^2
    PoreNo_insert = PoreDens*A_insert*10^(4);           % pore
number/insert
    PoreNo_cell = PoreNo_insert/CellNo ;                % average pore
number/cell
    A_pore_insert = 3.14*((3/2)*10^(-6))^2*PoreNo_insert ;   % pore area /
insert (m^2)
    A_pore_cell = 3.14*((3/2)*10^(-6))^2*PoreNo_cell ;  % average pore
area / cell (m^2)

    A_a = 10^(-10)*(1+9*rand());                        % apical
membrane surface area: unif [10^(-10),10*(10)^(-10))] (m^2)
    A_aa = A_pore_cell;                                 % pore area/cell
(m^2)
    A_b = A_aa+(10^(-10)-A_aa)*rand();                  % basolateral
membrane surface area: unif [A_aa, 10^(-10))] (m^2)
    A_l = 100*3.14*10^(-12);                            % lysosomal
membrane surface area (m^2)
    A_m = 100*3.14*10^(-12);                            % mitochondrial
membrane surface area (m^2)
    V_c = 0.5*10^(-15)*(1+5*rand());                    % cytosolic
volume: unif [0.5*10^(-15), 3*10^(-15)] (m^3)
    V_l = 10^(-18)*(9.24+(23.8-9.24)*rand());           % lysosomal
volume: unif [9.24*10^(-18), 23.8*10^(-18)] (m^3)
    V_m = 100*5.24*10^(-19)/5*(1+24*rand());            % mitochondrial
volume: unif [10.48*10^(-18), 262*10^(-18)](m^3)
    V_b = 1.5*10^(-6);                                  % basolateral
volume: 1.5 mL

    % Membrane potential (unit in 'Voltage')
    E_a = -0.0093-0.005+0.01*rand();                    % apical
membrane potential: unif [-0.0143, -0.0043]
    E_l = 0.01-0.005+0.01*rand();                       % lysosomal
membrane potential: unif [0.005, 0.015]
    E_m = -0.16 ;                                       % mitochondrial
membrane potential
    E_b = 0.0119-0.005+0.01*rand();                     % basolateral
membrane potential: unif [0.0069, 0.0169]

    % pH values
    pH_a = 6.4+0.2*rand();                              % pH in apical
compartment: unif [6.4, 6.6]
    pH_c = 7.0+0.4*rand();                              % pH in cytosol:
unif [7.0, 7.4]
    pH_l = 4.8+0.4*rand();                              % pH in
lysosomes: unif [4.8, 5.2]
    pH_m = 7.8+0.4*rand();                              % pH in
mitochondria: unif[7.8, 8.2]
    pH_b = 7.4;                                         % pH in
basolateral compartment
```

```
    % Apical Compartment
    fn_a = 1 / (1 + 10^(i1*(pKa1-pH_a)) + 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a))) ;
    fd2_a = fn_a * 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a)) ;
    fd1_a = fn_a * 10^(i1*(pKa1-pH_a)) ;
    Nd2_a = z2*E_a*F/(R*T) ;
    Nd1_a = z1*E_a*F/(R*T) ;

    % Cytoplasm
    L_c = 0.05+0.1*rand();                                      % lipid
fraction in cytosol: unif [0.05, 0.15]
    W_c = 1-L_c ;                                               % water
fraction in cytosol
    Is_c = 0.3 ;                                                % ion
strength in cytosol (mol)
    gamman_c = 10^(0.3*Is_c) ;                                  %
activity coefficient of neutral molecules in cytosol
    gammad1_c = 10^(-0.5*z1*z1*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of monovalent base in cytosol
    gammad2_c = 10^(-0.5*z2*z2*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of bivalent base in cytosol
    Kn_c = L_c*1.22*10^(logPn) ;
    Kd1_c = L_c*1.22*10^(logPd1) ;
    Kd2_c = L_c*1.22*10^(logPd2) ;
    an_c = 1 / (1 + 10^(i1*(pKa1-pH_c)) + 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c))) ;
    ad2_c = an_c * 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c)) ;
    ad1_c = an_c * 10^(i1*(pKa1-pH_c)) ;
    Dd2_c = ad2_c / an_c ;
    Dd1_c = ad1_c / an_c ;
    fn_c = 1 / (W_c/gamman_c + Kn_c/gamman_c + Dd2_c*W_c/gammad2_c +
Dd2_c*Kd2_c/gammad2_c ...
            + Dd1_c*W_c/gammad1_c + Dd1_c*Kd1_c/gammad1_c ) ;
    fd2_c = fn_c * Dd2_c ;
    fd1_c = fn_c * Dd1_c ;

    % Mitochondria
    L_m = 0.05+0.1*rand();                                      % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_m = 1-L_m ;                                               % water
fraction in mitochondria
    Is_m = 0.3 ;                                                % ion
strength in mitochondria (mol)
    Nd2_m = z2*E_m*F/(R*T) ;
    Nd1_m = z1*E_m*F/(R*T) ;
    gamman_m = 10^(0.3*Is_m) ;                                  %
activity coefficient of neutral molecules in mitochondria
    gammad1_m = 10^(-0.5*z1*z1*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of monovalent base in mitochondria
    gammad2_m = 10^(-0.5*z2*z2*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of bivalent base in mitochondria
    Kn_m = L_m*1.22*10^(logPn) ;
    Kd1_m = L_m*1.22*10^(logPd1) ;
    Kd2_m = L_m*1.22*10^(logPd2) ;
    an_m = 1 / (1 + 10^(i1*(pKa1-pH_m)) + 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m))) ;
    ad2_m = an_m * 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m)) ;
    ad1_m = an_m * 10^(i1*(pKa1-pH_m)) ;
    Dd2_m = ad2_m / an_m ;
    Dd1_m = ad1_m / an_m ;
```

```
    fn_m = 1 / (W_m/gamman_m + Kn_m/gamman_m + Dd2_m*W_m/gammad2_m +
Dd2_m*Kd2_m/gammad2_m ...
            + Dd1_m*W_m/gammad1_m + Dd1_m*Kd1_m/gammad1_m ) ;
    fd2_m = fn_m * Dd2_m ;
    fd1_m = fn_m * Dd1_m ;

    % Lysosomes
    L_l = 0.05+0.1*rand();                                      % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_l = 1-L_l ;                                               % water
fraction in lysosomes
    Is_l = 0.3 ;                                                % ion
strength in lysosomes (mol)
    Nd2_l = z2*E_l*F/(R*T) ;
    Nd1_l = z1*E_l*F/(R*T) ;
    gamman_l = 10^(0.3*Is_l) ;                                  %
activity coefficient of neutral molecules in lysosomes
    gammad1_l = 10^(-0.5*z1*z1*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of monovalent base in lysosomes
    gammad2_l = 10^(-0.5*z2*z2*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of bivalent base in lysosomes
    Kn_l = L_l*1.22*10^(logPn) ;
    Kd1_l = L_l*1.22*10^(logPd1) ;
    Kd2_l = L_l*1.22*10^(logPd2) ;
    an_l = 1 / (1 + 10^(i1*(pKa1-pH_l)) + 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l))) ;
    ad2_l = an_l * 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l)) ;
    ad1_l = an_l * 10^(i1*(pKa1-pH_l)) ;
    Dd2_l = ad2_l / an_l ;
    Dd1_l = ad1_l / an_l ;
    fn_l = 1 / (W_l/gamman_l + Kn_l/gamman_l + Dd2_l*W_l/gammad2_l +
Dd2_l*Kd2_l/gammad2_l ...
            + Dd1_l*W_l/gammad1_l + Dd1_l*Kd1_l/gammad1_l ) ;
    fd2_l = fn_l * Dd2_l ;
    fd1_l = fn_l * Dd1_l ;

    % Basolaterial Compartment
    fn_b = 1 / (1 + 10^(i1*(pKa1-pH_b)) + 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b))) ;
    fd2_b = fn_b * 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b)) ;
    fd1_b = fn_b * 10^(i1*(pKa1-pH_b)) ;
    Nd2_b = z2*(-E_b)*F/(R*T) ;
    Nd1_b = z1*(-E_b)*F/(R*T) ;

    % Solve the differential equation system:
    % Given a system of linear ODE's expressed in matrix form:
    % Y' = AY+G with initial conditions Y(0) = RR,
        k11 = -(A_a/V_c)*Pn*fn_c-
(A_a/V_c)*Pd1*Nd1_a*fd1_c*exp(Nd1_a)/(exp(Nd1_a)-1)...
                -(A_a/V_c)*Pd2*Nd2_a*fd2_c*exp(Nd2_a)/(exp(Nd2_a)-1)...
                -(A_m/V_c)*Pn*fn_c-(A_m/V_c)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
                -(A_m/V_c)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1)...
                -(A_l/V_c)*Pn*fn_c-(A_l/V_c)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
                -(A_l/V_c)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1)...
                -(A_b/V_c)*Pn*fn_c-(A_b/V_c)*Pd1*Nd1_b*fd1_c/(exp(Nd1_b)-1)...
                -(A_b/V_c)*Pd2*Nd2_b*fd2_c/(exp(Nd2_b)-1) ;
        k12 =
(A_m/V_c)*Pn*fn_m+(A_m/V_c)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
                +(A_m/V_c)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1);
```

```matlab
        k13 =
(A_l/V_c)*Pn*fn_l+(A_l/V_c)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
            +(A_l/V_c)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1);
        k14 =
(A_b/V_c)*Pn*fn_b+(A_b/V_c)*Pd1*Nd1_b*fd1_b*exp(Nd1_b)/(exp(Nd1_b)-1)...
            +(A_b/V_c)*Pd2*Nd2_b*fd2_b*exp(Nd2_b)/(exp(Nd2_b)-1);
        S1 = (A_a/V_c)*C_a*(Pn*fn_a+Pd1*Nd1_a*fd1_a/(exp(Nd1_a)-1)...
            +Pd2*Nd2_a*fd2_a/(exp(Nd2_a)-1)) ;

        k21 = (A_m/V_m)*Pn*fn_c+(A_m/V_m)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
            +(A_m/V_m)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1) ;
        k22 = -(A_m/V_m)*Pn*fn_m-
(A_m/V_m)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
            -(A_m/V_m)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1) ;
        k23 = 0;
        k24 = 0 ;
        S2 = 0;

        k31 = (A_l/V_l)*Pn*fn_c+(A_l/V_l)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
            +(A_l/V_l)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1) ;
        k32 = 0;
        k33 = -(A_l/V_l)*Pn*fn_l-
(A_l/V_l)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
            -(A_l/V_l)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1) ;

        k34 = 0 ;
        S3 = 0;

        k41 = (A_b/V_b)*Pn*fn_c+(A_b/V_b)*Pd1*Nd1_b*fd1_c/(exp(Nd1_b)-1)...
            +(A_b/V_b)*Pd2*Nd2_b*fd2_c/(exp(Nd2_b)-1) ;
        k42 = 0;
        k43 = 0;
        k44 = -(A_b/V_b)*Pn*fn_b-
(A_b/V_b)*Pd1*Nd1_b*fd1_b*exp(Nd1_b)/(exp(Nd1_b)-1)...
            -(A_b/V_b)*Pd2*Nd2_b*fd2_b*exp(Nd2_b)/(exp(Nd2_b)-1);
        S4 = 0;

        A = [k11, k12, k13, k14; k21, k22, k23, k24; k31, k32, k33, k34; k41,
k42, k43, k44];
        G = [S1, S2, S3, S4]';
        RR = [0,0,0,0]';
        t = 300 ;    % time in sec (5min)


        [V,E] = eig(A);
        E = diag(E);
        H = inv(V)*G;
        B = V \ RR;
        C = B + H./E;
        Z = -(H./E) + exp(t * E).*C ;
        Y = real(V * Z);
        Y = Y' ;

        Ppore = Y(4)*V_b /(t*A_aa*C_a)*10^(2)*10^6 ;                  %
Pcell, 10^(-6)cm/sec
        Peff = Y(4)*V_b*CellNo/(t*A_insert*C_a)*10^(2)*10^6;          %
Peff, 10^(-6)cm/sec, normalized by insert area, which is 1.12 cm^2
```

```matlab
        Mass_cell = (Y(1)*V_c + Y(2)*V_m + Y(3)*V_l)*10^12 ;               %
cellular mass, pmol/cell
        dMdt = Y(4)*V_b/t*10^12;                                          %
transport rate: pmol/sec/cell


    Para(i,:) = [A_a*10^12,PoreNo_cell,
A_l*10^12,A_m*10^12,A_b*10^12,V_c*10^18,V_l*10^18,V_m*10^18,V_b*10^6,E_a*1000,E_
l*1000,E_m*1000,E_b*1000,...
                      pH_a,pH_c,pH_l,pH_m,pH_b,CellNo,PoreDens,
pKa1,pKa2,logPn,logPd1, logPd2];
    Results(i,:)=[Y(1),Y(2),Y(3),Ppore, Peff, dMdt, Mass_cell];

end

comb = [Results(:,1:7),Para];
fid5 = fopen('AtoB_pH65_3um_5min.dat','w');
fprintf(fid5,'%12.4e %12.4e %12.4e %12.4e %12.4e  %12.4e %12.4e %12.2e %12.0f %1
2.4e %12.4e %12.4e  %12.4e %12.4e %12.4e %12.4e %12.4f %12.4f %12.4f %12.4f %12.
2f %12.2f %12.2f %12.2f %12.2f %12.0f %12.0f %12.2f %12.2f %12.2f %12.2f %12.2f
\n', comb') ;
fclose(fid5);

figure(5) ; clf ; hold on ;
grid on;
hist (log10(comb(:,4)),1000);
line([log10(Ppore_exp), log10(Ppore_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{cell}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
xlim([0, 6]);
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of cell
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(6) ; clf ; hold on ;
grid on;
hist (log10(comb(:,5)),1000);
xlim([-3, 3]);
line([log10(Peff_exp), log10(Peff_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{app}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of apparent
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(7) ; clf ; hold on ;
grid on;
hist (log10(comb(:,6)),1000);
xlim([-8,-2]);
line([log10(dMdt_exp), log10(dMdt_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (dM/dt,
pmol/sec/cell)','FontSize',30,'FontWeight','Bold','FontName','Times');
```

```
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of transport
rate','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(8) ; clf ; hold on ;
grid on;
hist (log10(comb(:,7)),1000);
xlim([-5,-0]);
line([log10(IntraMass_exp),
log10(IntraMass_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (intracellular mass, pmol/cell)
','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of intracellular
mass','FontSize',30,'FontWeight','Bold','FontName','Times') ;




% =========================Case# 3: AP->BL transport, pHa = 7.4, 0.4um-membrane,
5min=======================================
clear ;                        % Clear the memory
z1 = 1 ;                       % ionization group 1 of CQ
z2 = 2 ;                       % ionization group 2 of CQ
i1 = sign(z1) ;
i2 = sign(z2) ;

T = 310.15 ;                   % temperature
R = 8.314 ;                    % universal gas constant
F = 96484.56 ;                 % faraday constant
C_a = 1 ;                      % initial drug concentration (mM)

sim = 10000;                   % number of simulations
paraNo = 25;
outputNo = 7;                  % number of output parameters
Para = zeros(sim,paraNo);
Results = zeros(sim,outputNo);

dMdt_exp = 2.28e-5;            % +/- 7.41e-7, pmol/sec/cell, measured after
4hrs
Ppore_exp = 1.56E+03;         % +/- 161, 10^-6 cm/sec, measured after 4hrs
Peff_exp = 7.85;              % +/- 0.81, 10^-6 cm/sec, measured after 4hrs
IntraMass_exp = 0.00872;      % +/- 0.00094 pmol/cell, measured after 5min

for i = 1:sim

    % Drug information -- ChemAxon calculation including logPn, pKa1, and pKa2
    logPn = 3.93-0.5+rand();    % unif [3.43, 4.43] ;
    pKa1 = 9.96-0.5+rand();     % unif [9.46, 10.46] ;
    pKa2 = 7.47-0.5+rand();     % unif [6.97, 7.97] ;
    logPd1 = 0.43-0.5+rand();   % unif [-0.07, 0.93] ;
    logPd2 = -0.91-0.5+rand();  % unif [-1.41, 0.41] ;
```

```matlab
    Pn = 10^(logPn-6.7);
    Pd1 = 10^(logPd1-6.7);
    Pd2 = 10^(logPd2-6.7);


    CellNo = 2*10^5*(1+rand());                         % cell
number/insert: unif [2*10^5, 4*10^5]
    PoreDens = 4*10^6*0.4*(2+rand());                   % pore
number/cm^2: unif [3.2*10^6, 4.8*10^6]
    A_insert = 1.12*10^(-4) ;                           % insert area:
1.12 cm^2
    PoreNo_insert = PoreDens*A_insert*10^(4);           % pore
number/insert
    PoreNo_cell = PoreNo_insert/CellNo ;                % average pore
number/cell
    A_pore_insert = 3.14*((0.4/2)*10^(-6))^2*PoreNo_insert ;   % pore area /
insert (m^2)
    A_pore_cell = 3.14*((0.4/2)*10^(-6))^2*PoreNo_cell ;   % average pore
area / cell (m^2)

    A_a = 10^(-10)*(1+9*rand());                        % apical
membrane surface area: unif [10^(-10),10*(10)^(-10))] (m^2)
    A_aa = A_pore_cell;                                 % pore area/cell
(m^2)
    A_b = A_aa+(10^(-10)-A_aa)*rand();                  % basolateral
membrane surface area: unif [A_aa, 10^(-10))] (m^2)
    A_l = 100*3.14*10^(-12);                            % lysosomal
membrane surface area (m^2)
    A_m = 100*3.14*10^(-12);                            % mitochondrial
membrane surface area (m^2)
    V_c = 0.5*10^(-15)*(1+5*rand());                    % cytosolic
volume: unif [0.5*10^(-15), 3*10^(-15)] (m^3)
    V_l = 10^(-18)*(9.24+(23.8-9.24)*rand());           % lysosomal
volume: unif [9.24*10^(-18), 23.8*10^(-18)] (m^3)
    V_m = 100*5.24*10^(-19)/5*(1+24*rand());            % mitochondrial
volume: unif [10.48*10^(-18), 262*10^(-18)](m^3)
    V_b = 1.5*10^(-6);                                  % basolateral
volume: 1.5 mL

    % Membrane potential (unit in 'Voltage')
    E_a = -0.0093-0.005+0.01*rand();                    % apical
membrane potential: unif [-0.0143, -0.0043]
    E_l = 0.01-0.005+0.01*rand();                       % lysosomal
membrane potential: unif [0.005, 0.015]
    E_m = -0.16 ;                                       % mitochondrial
membrane potential
    E_b = 0.0119-0.005+0.01*rand();                     % basolateral
membrane potential: unif [0.0069, 0.0169]

    % pH values
    pH_a = 7.0+0.4*rand();                              % pH in apical
compartment: unif [7.0, 7.4]
    pH_c = 7.0+0.4*rand();                              % pH in cytosol:
unif [7.0, 7.4]
    pH_l = 4.8+0.4*rand();                              % pH in
lysosomes: unif [4.8, 5.2]
```

```matlab
    pH_m = 7.8+0.4*rand();                                      % pH in
mitochondria: unif[7.8, 8.2]
    pH_b = 7.4;                                                 % pH in
basolateral compartment

    % Apical Compartment
    fn_a = 1 / (1 + 10^(i1*(pKa1-pH_a)) + 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a))) ;
    fd2_a = fn_a * 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a)) ;
    fd1_a = fn_a * 10^(i1*(pKa1-pH_a)) ;
    Nd2_a = z2*E_a*F/(R*T) ;
    Nd1_a = z1*E_a*F/(R*T) ;

    % Cytoplasm
    L_c = 0.05+0.1*rand();                                      % lipid
fraction in cytosol: unif [0.05, 0.15]
    W_c = 1-L_c ;                                               % water
fraction in cytosol
    Is_c = 0.3 ;                                                % ion
strength in cytosol (mol)
    gamman_c = 10^(0.3*Is_c) ;                                  %
activity coefficient of neutral molecules in cytosol
    gammad1_c = 10^(-0.5*z1*z1*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of monovalent base in cytosol
    gammad2_c = 10^(-0.5*z2*z2*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of bivalent base in cytosol
    Kn_c = L_c*1.22*10^(logPn) ;
    Kd1_c = L_c*1.22*10^(logPd1) ;
    Kd2_c = L_c*1.22*10^(logPd2) ;
    an_c = 1 / (1 + 10^(i1*(pKa1-pH_c)) + 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c))) ;
    ad2_c = an_c * 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c)) ;
    ad1_c = an_c * 10^(i1*(pKa1-pH_c)) ;
    Dd2_c = ad2_c / an_c ;
    Dd1_c = ad1_c / an_c ;
    fn_c = 1 / (W_c/gamman_c + Kn_c/gamman_c + Dd2_c*W_c/gammad2_c +
Dd2_c*Kd2_c/gammad2_c ...
          + Dd1_c*W_c/gammad1_c + Dd1_c*Kd1_c/gammad1_c ) ;
    fd2_c = fn_c * Dd2_c ;
    fd1_c = fn_c * Dd1_c ;

    % Mitochondria
    L_m = 0.05+0.1*rand();                                      % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_m = 1-L_m ;                                               % water
fraction in mitochondria
    Is_m = 0.3 ;                                                % ion
strength in mitochondria (mol)
    Nd2_m = z2*E_m*F/(R*T) ;
    Nd1_m = z1*E_m*F/(R*T) ;
    gamman_m = 10^(0.3*Is_m) ;                                  %
activity coefficient of neutral molecules in mitochondria
    gammad1_m = 10^(-0.5*z1*z1*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of monovalent base in mitochondria
    gammad2_m = 10^(-0.5*z2*z2*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of bivalent base in mitochondria
    Kn_m = L_m*1.22*10^(logPn) ;
    Kd1_m = L_m*1.22*10^(logPd1) ;
    Kd2_m = L_m*1.22*10^(logPd2) ;
```

```matlab
    an_m = 1 / (1 + 10^(i1*(pKa1-pH_m)) + 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m))) ;
    ad2_m = an_m * 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m)) ;
    ad1_m = an_m * 10^(i1*(pKa1-pH_m)) ;
    Dd2_m = ad2_m / an_m ;
    Dd1_m = ad1_m / an_m ;
    fn_m = 1 / (W_m/gamman_m + Kn_m/gamman_m + Dd2_m*W_m/gammad2_m +
Dd2_m*Kd2_m/gammad2_m ...
          + Dd1_m*W_m/gammad1_m + Dd1_m*Kd1_m/gammad1_m ) ;
    fd2_m = fn_m * Dd2_m ;
    fd1_m = fn_m * Dd1_m ;

    % Lysosomes
    L_l = 0.05+0.1*rand();                                       % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_l = 1-L_l ;                                                % water
fraction in lysosomes
    Is_l = 0.3 ;                                                 % ion
strength in lysosomes (mol)
    Nd2_l = z2*E_l*F/(R*T) ;
    Nd1_l = z1*E_l*F/(R*T) ;
    gamman_l = 10^(0.3*Is_l) ;                                   %
activity coefficient of neutral molecules in lysosomes
    gammad1_l = 10^(-0.5*z1*z1*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of monovalent base in lysosomes
    gammad2_l = 10^(-0.5*z2*z2*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of bivalent base in lysosomes
    Kn_l = L_l*1.22*10^(logPn) ;
    Kd1_l = L_l*1.22*10^(logPd1) ;
    Kd2_l = L_l*1.22*10^(logPd2) ;
    an_l = 1 / (1 + 10^(i1*(pKa1-pH_l)) + 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l))) ;
    ad2_l = an_l * 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l)) ;
    ad1_l = an_l * 10^(i1*(pKa1-pH_l)) ;
    Dd2_l = ad2_l / an_l ;
    Dd1_l = ad1_l / an_l ;
    fn_l = 1 / (W_l/gamman_l + Kn_l/gamman_l + Dd2_l*W_l/gammad2_l +
Dd2_l*Kd2_l/gammad2_l ...
          + Dd1_l*W_l/gammad1_l + Dd1_l*Kd1_l/gammad1_l ) ;
    fd2_l = fn_l * Dd2_l ;
    fd1_l = fn_l * Dd1_l ;

    % Basolaterial Compartment
    fn_b = 1 / (1 + 10^(i1*(pKa1-pH_b)) + 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b))) ;
    fd2_b = fn_b * 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b)) ;
    fd1_b = fn_b * 10^(i1*(pKa1-pH_b)) ;
    Nd2_b = z2*(-E_b)*F/(R*T) ;
    Nd1_b = z1*(-E_b)*F/(R*T) ;

    % Solve the differential equation system:
    % Given a system of linear ODE's expressed in matrix form:
    % Y' = AY+G with initial conditions Y(0) = RR,
        k11 = -(A_a/V_c)*Pn*fn_c-
(A_a/V_c)*Pd1*Nd1_a*fd1_c*exp(Nd1_a)/(exp(Nd1_a)-1)...
              -(A_a/V_c)*Pd2*Nd2_a*fd2_c*exp(Nd2_a)/(exp(Nd2_a)-1)...
              -(A_m/V_c)*Pn*fn_c-(A_m/V_c)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
              -(A_m/V_c)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1)...
              -(A_l/V_c)*Pn*fn_c-(A_l/V_c)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
              -(A_l/V_c)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1)...
```

```
                -(A_b/V_c)*Pn*fn_c-(A_b/V_c)*Pd1*Nd1_b*fd1_c/(exp(Nd1_b)-1)...
                -(A_b/V_c)*Pd2*Nd2_b*fd2_c/(exp(Nd2_b)-1) ;
        k12 =
(A_m/V_c)*Pn*fn_m+(A_m/V_c)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
                +(A_m/V_c)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1);
        k13 =
(A_l/V_c)*Pn*fn_l+(A_l/V_c)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
                +(A_l/V_c)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1);
        k14 =
(A_b/V_c)*Pn*fn_b+(A_b/V_c)*Pd1*Nd1_b*fd1_b*exp(Nd1_b)/(exp(Nd1_b)-1)...
                +(A_b/V_c)*Pd2*Nd2_b*fd2_b*exp(Nd2_b)/(exp(Nd2_b)-1);
        S1 = (A_a/V_c)*C_a*(Pn*fn_a+Pd1*Nd1_a*fd1_a/(exp(Nd1_a)-1)...
                +Pd2*Nd2_a*fd2_a/(exp(Nd2_a)-1)) ;

        k21 = (A_m/V_m)*Pn*fn_c+(A_m/V_m)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
                +(A_m/V_m)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1) ;
        k22 = -(A_m/V_m)*Pn*fn_m-
(A_m/V_m)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
                -(A_m/V_m)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1) ;
        k23 = 0;
        k24 = 0 ;
        S2 = 0;

        k31 = (A_l/V_l)*Pn*fn_c+(A_l/V_l)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
                +(A_l/V_l)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1) ;
        k32 = 0;
        k33 = -(A_l/V_l)*Pn*fn_l-
(A_l/V_l)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
                -(A_l/V_l)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1) ;

        k34 = 0 ;
        S3 = 0;

        k41 = (A_b/V_b)*Pn*fn_c+(A_b/V_b)*Pd1*Nd1_b*fd1_c/(exp(Nd1_b)-1)...
                +(A_b/V_b)*Pd2*Nd2_b*fd2_c/(exp(Nd2_b)-1) ;
        k42 = 0;
        k43 = 0;
        k44 = -(A_b/V_b)*Pn*fn_b-
(A_b/V_b)*Pd1*Nd1_b*fd1_b*exp(Nd1_b)/(exp(Nd1_b)-1)...
                 -(A_b/V_b)*Pd2*Nd2_b*fd2_b*exp(Nd2_b)/(exp(Nd2_b)-1);
        S4 = 0;

        A = [k11, k12, k13, k14; k21, k22, k23, k24; k31, k32, k33, k34; k41,
k42, k43, k44];
        G = [S1, S2, S3, S4]';
        RR = [0,0,0,0]';
        t = 300 ;   % time in sec (5min)


        [V,E] = eig(A);
        E = diag(E);
        H = inv(V)*G;
        B = V \ RR;
        C = B + H./E;
        Z = -(H./E) + exp(t * E).*C ;
        Y = real(V * Z);
        Y = Y' ;
```

```matlab
        Ppore = Y(4)*V_b /(t*A_aa*C_a)*10^(2)*10^6 ;                  %
Pcell, 10^(-6)cm/sec
        Peff = Y(4)*V_b*CellNo/(t*A_insert*C_a)*10^(2)*10^6;          %
Peff, 10^(-6)cm/sec, normalized by insert area, which is 1.12 cm^2
        Mass_cell = (Y(1)*V_c + Y(2)*V_m + Y(3)*V_l)*10^12 ;         %
cellular mass, pmol/cell
        dMdt = Y(4)*V_b/t*10^12;                                     %
transport rate: pmol/sec/cell

    Para(i,:) = [A_a*10^12,PoreNo_cell,
A_l*10^12,A_m*10^12,A_b*10^12,V_c*10^18,V_l*10^18,V_m*10^18,V_b*10^6,E_a*1000,E_
l*1000,E_m*1000,E_b*1000,...
                    pH_a,pH_c,pH_l,pH_m,pH_b,CellNo,PoreDens,
pKa1,pKa2,logPn,logPd1, logPd2];
    Results(i,:)=[Y(1),Y(2),Y(3),Ppore, Peff, dMdt, Mass_cell];

end

comb = [Results(:,1:7),Para];
fid5 = fopen('AtoB_pH74_04um_5min.dat','w');
fprintf(fid5,'%12.4e %12.4e %12.4e %12.4e %12.4e  %12.4e %12.4e %12.2e %12.0f %1
2.4e %12.4e %12.4e  %12.4e %12.4e %12.4e %12.4e %12.4f %12.4f %12.4f %12.4f %12.
2f %12.2f %12.2f %12.2f %12.2f %12.0f %12.0f %12.2f %12.2f %12.2f %12.2f %12.2f
\n', comb') ;
fclose(fid5);

figure(9) ; clf ; hold on ;
grid on;
hist (log10(comb(:,4)),1000);
line([log10(Ppore_exp), log10(Ppore_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{cell}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
xlim([0, 6]);
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of cell
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(10) ; clf ; hold on ;
grid on;
hist (log10(comb(:,5)),1000);
xlim([-3, 3]);
line([log10(Peff_exp), log10(Peff_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{app}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of apparent
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(11) ; clf ; hold on ;
grid on;
```

```matlab
hist (log10(comb(:,6)),1000);
xlim([-8,-2]);
line([log10(dMdt_exp), log10(dMdt_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (dM/dt,
pmol/sec/cell)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of transport
rate','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(12) ; clf ; hold on ;
grid on;
hist (log10(comb(:,7)),1000);
xlim([-5,-0]);
line([log10(IntraMass_exp),
log10(IntraMass_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (intracellular mass, pmol/cell)
','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of intracellular
mass','FontSize',30,'FontWeight','Bold','FontName','Times') ;




% =========================Case# 4: AP->BL transport, pHa = 7.4,   3um-membrane,
5min=====================================

clear ;                      % Clear the memory
z1 = 1 ;                     % ionization group 1 of CQ
z2 = 2 ;                     % ionization group 2 of CQ
i1 = sign(z1) ;
i2 = sign(z2) ;

T = 310.15 ;                 % temperature
R = 8.314 ;                  % universal gas constant
F = 96484.56 ;               % faraday constant
C_a = 1 ;                    % initial drug concentration (mM)

sim = 10000;                 % number of simulations
paraNo = 25;
outputNo = 7;                % number of output parameters
Para = zeros(sim,paraNo);
Results = zeros(sim,outputNo);

dMdt_exp = 4.66e-5;          % +/- 6.28e-6, pmol/sec/cell, measured after 4hrs
Ppore_exp = 8.59E+01;        % +/- 15.6, 10^(-6) cm/sec, measured after 4hrs
Peff_exp = 1.21E+01;         % +/- 2.21, 10^(-6) cm/sec, measured after 4hrs
IntraMass_exp = 0.00890;     % +/- 0.00026, pmol/cell, measured after 5min

for i = 1:sim

    % Drug information -- ChemAxon calculation including logPn, pKa1, and pKa2
```

```
    logPn = 3.93-0.5+rand();     % unif [3.43, 4.43] ;
    pKa1 = 9.96-0.5+rand();      % unif [9.46, 10.46] ;
    pKa2 = 7.47-0.5+rand();      % unif [6.97, 7.97] ;
    logPd1 = 0.43-0.5+rand();    % unif [-0.07, 0.93] ;
    logPd2 = -0.91-0.5+rand();   % unif [-1.41, 0.41] ;
    Pn = 10^(logPn-6.7);
    Pd1 = 10^(logPd1-6.7);
    Pd2 = 10^(logPd2-6.7);


    CellNo = 2*10^5*(1+rand());                      % cell
number/insert: unif [2*10^5, 4*10^5]
    PoreDens = 2*10^6*0.4*(2+rand());                % pore
number/cm^2: unif [1.6*10^6, 2.4*10^6]
    A_insert = 1.12*10^(-4) ;                        % insert area:
1.12 cm^2
    PoreNo_insert = PoreDens*A_insert*10^(4);        % pore
number/insert
    PoreNo_cell = PoreNo_insert/CellNo ;             % average pore
number/cell
    A_pore_insert = 3.14*((3/2)*10^(-6))^2*PoreNo_insert ;   % pore area /
insert (m^2)
    A_pore_cell = 3.14*((3/2)*10^(-6))^2*PoreNo_cell ;       % average pore
area / cell (m^2)

    A_a = 10^(-10)*(1+9*rand());                     % apical
membrane surface area: unif [10^(-10),10*(10)^(-10))] (m^2)
    A_aa = A_pore_cell;                              % pore area/cell
(m^2)
    A_b = A_aa+(10^(-10)-A_aa)*rand();               % basolateral
membrane surface area: unif [A_aa, 10^(-10))] (m^2)
    A_l = 100*3.14*10^(-12);                         % lysosomal
membrane surface area (m^2)
    A_m = 100*3.14*10^(-12);                         % mitochondrial
membrane surface area (m^2)
    V_c = 0.5*10^(-15)*(1+5*rand());                 % cytosolic
volume: unif [0.5*10^(-15), 3*10^(-15)] (m^3)
    V_l = 10^(-18)*(9.24+(23.8-9.24)*rand());        % lysosomal
volume: unif [9.24*10^(-18), 23.8*10^(-18)] (m^3)
    V_m = 100*5.24*10^(-19)/5*(1+24*rand());         % mitochondrial
volume: unif [10.48*10^(-18), 262*10^(-18)](m^3)
    V_b = 1.5*10^(-6);                               % basolateral
volume: 1.5 mL

    % Membrane potential (unit in 'Voltage')
    E_a = -0.0093-0.005+0.01*rand();                 % apical
membrane potential: unif [-0.0143, -0.0043]
    E_l = 0.01-0.005+0.01*rand();                    % lysosomal
membrane potential: unif [0.005, 0.015]
    E_m = -0.16 ;                                    % mitochondrial
membrane potential
    E_b = 0.0119-0.005+0.01*rand();                  % basolateral
membrane potential: unif [0.0069, 0.0169]

    % pH values
    pH_a = 7.0+0.4*rand();                           % pH in apical
compartment: unif [7.0, 7.4]
```

```
    pH_c = 7.0+0.4*rand();                                          % pH in cytosol:
unif [7.0, 7.4]
    pH_l = 4.8+0.4*rand();                                          % pH in
lysosomes: unif [4.8, 5.2]
    pH_m = 7.8+0.4*rand();                                          % pH in
mitochondria: unif[7.8, 8.2]
    pH_b = 7.4;                                                     % pH in
basolateral compartment

    % Apical Compartment
    fn_a = 1 / (1 + 10^(i1*(pKa1-pH_a)) + 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a))) ;
    fd2_a = fn_a * 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a)) ;
    fd1_a = fn_a * 10^(i1*(pKa1-pH_a)) ;
    Nd2_a = z2*E_a*F/(R*T) ;
    Nd1_a = z1*E_a*F/(R*T) ;

    % Cytoplasm
    L_c = 0.05+0.1*rand();                                         % lipid
fraction in cytosol: unif [0.05, 0.15]
    W_c = 1-L_c ;                                                  % water
fraction in cytosol
    Is_c = 0.3 ;                                                   % ion
strength in cytosol (mol)
    gamman_c = 10^(0.3*Is_c) ;                                     %
activity coefficient of neutral molecules in cytosol
    gammad1_c = 10^(-0.5*z1*z1*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of monovalent base in cytosol
    gammad2_c = 10^(-0.5*z2*z2*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of bivalent base in cytosol
    Kn_c = L_c*1.22*10^(logPn) ;
    Kd1_c = L_c*1.22*10^(logPd1) ;
    Kd2_c = L_c*1.22*10^(logPd2) ;
    an_c = 1 / (1 + 10^(i1*(pKa1-pH_c)) + 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c))) ;
    ad2_c = an_c * 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c)) ;
    ad1_c = an_c * 10^(i1*(pKa1-pH_c)) ;
    Dd2_c = ad2_c / an_c ;
    Dd1_c = ad1_c / an_c ;
    fn_c = 1 / (W_c/gamman_c + Kn_c/gamman_c + Dd2_c*W_c/gammad2_c +
Dd2_c*Kd2_c/gammad2_c ...
          + Dd1_c*W_c/gammad1_c + Dd1_c*Kd1_c/gammad1_c ) ;
    fd2_c = fn_c * Dd2_c ;
    fd1_c = fn_c * Dd1_c ;

    % Mitochondria
    L_m = 0.05+0.1*rand();                                         % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_m = 1-L_m ;                                                  % water
fraction in mitochondria
    Is_m = 0.3 ;                                                   % ion
strength in mitochondria (mol)
    Nd2_m = z2*E_m*F/(R*T) ;
    Nd1_m = z1*E_m*F/(R*T) ;
    gamman_m = 10^(0.3*Is_m) ;                                     %
activity coefficient of neutral molecules in mitochondria
    gammad1_m = 10^(-0.5*z1*z1*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of monovalent base in mitochondria
```

```matlab
    gammad2_m = 10^(-0.5*z2*z2*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of bivalent base in mitochondria
    Kn_m = L_m*1.22*10^(logPn) ;
    Kd1_m = L_m*1.22*10^(logPd1) ;
    Kd2_m = L_m*1.22*10^(logPd2) ;
    an_m = 1 / (1 + 10^(i1*(pKa1-pH_m)) + 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m))) ;
    ad2_m = an_m * 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m)) ;
    ad1_m = an_m * 10^(i1*(pKa1-pH_m)) ;
    Dd2_m = ad2_m / an_m ;
    Dd1_m = ad1_m / an_m ;
    fn_m = 1 / (W_m/gamman_m + Kn_m/gamman_m + Dd2_m*W_m/gammad2_m +
Dd2_m*Kd2_m/gammad2_m ...
            + Dd1_m*W_m/gammad1_m + Dd1_m*Kd1_m/gammad1_m ) ;
    fd2_m = fn_m * Dd2_m ;
    fd1_m = fn_m * Dd1_m ;

    % Lysosomes
    L_l = 0.05+0.1*rand();                                    % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_l = 1-L_l ;                                             % water
fraction in lysosomes
    Is_l = 0.3 ;                                             % ion
strength in lysosomes (mol)
    Nd2_l = z2*E_l*F/(R*T) ;
    Nd1_l = z1*E_l*F/(R*T) ;
    gamman_l = 10^(0.3*Is_l) ;                               %
activity coefficient of neutral molecules in lysosomes
    gammad1_l = 10^(-0.5*z1*z1*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of monovalent base in lysosomes
    gammad2_l = 10^(-0.5*z2*z2*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of bivalent base in lysosomes
    Kn_l = L_l*1.22*10^(logPn) ;
    Kd1_l = L_l*1.22*10^(logPd1) ;
    Kd2_l = L_l*1.22*10^(logPd2) ;
    an_l = 1 / (1 + 10^(i1*(pKa1-pH_l)) + 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l))) ;
    ad2_l = an_l * 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l)) ;
    ad1_l = an_l * 10^(i1*(pKa1-pH_l)) ;
    Dd2_l = ad2_l / an_l ;
    Dd1_l = ad1_l / an_l ;
    fn_l = 1 / (W_l/gamman_l + Kn_l/gamman_l + Dd2_l*W_l/gammad2_l +
Dd2_l*Kd2_l/gammad2_l ...
            + Dd1_l*W_l/gammad1_l + Dd1_l*Kd1_l/gammad1_l ) ;
    fd2_l = fn_l * Dd2_l ;
    fd1_l = fn_l * Dd1_l ;

    % Basolaterial Compartment
    fn_b = 1 / (1 + 10^(i1*(pKa1-pH_b)) + 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b))) ;
    fd2_b = fn_b * 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b)) ;
    fd1_b = fn_b * 10^(i1*(pKa1-pH_b)) ;
    Nd2_b = z2*(-E_b)*F/(R*T) ;
    Nd1_b = z1*(-E_b)*F/(R*T) ;

    % Solve the differential equation system:
    % Given a system of linear ODE's expressed in matrix form:
    % Y' = AY+G with initial conditions Y(0) = RR,
        k11 = -(A_a/V_c)*Pn*fn_c-
(A_a/V_c)*Pd1*Nd1_a*fd1_c*exp(Nd1_a)/(exp(Nd1_a)-1)...
```

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            -(A_a/V_c)*Pd2*Nd2_a*fd2_c*exp(Nd2_a)/(exp(Nd2_a)-1)...
            -(A_m/V_c)*Pn*fn_c-(A_m/V_c)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
            -(A_m/V_c)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1)...
            -(A_l/V_c)*Pn*fn_c-(A_l/V_c)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
            -(A_l/V_c)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1)...
            -(A_b/V_c)*Pn*fn_c-(A_b/V_c)*Pd1*Nd1_b*fd1_c/(exp(Nd1_b)-1)...
            -(A_b/V_c)*Pd2*Nd2_b*fd2_c/(exp(Nd2_b)-1) ;
        k12 =
(A_m/V_c)*Pn*fn_m+(A_m/V_c)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
            +(A_m/V_c)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1);
        k13 =
(A_l/V_c)*Pn*fn_l+(A_l/V_c)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
            +(A_l/V_c)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1);
        k14 =
(A_b/V_c)*Pn*fn_b+(A_b/V_c)*Pd1*Nd1_b*fd1_b*exp(Nd1_b)/(exp(Nd1_b)-1)...
            +(A_b/V_c)*Pd2*Nd2_b*fd2_b*exp(Nd2_b)/(exp(Nd2_b)-1);
        S1 = (A_a/V_c)*C_a*(Pn*fn_a+Pd1*Nd1_a*fd1_a/(exp(Nd1_a)-1)...
            +Pd2*Nd2_a*fd2_a/(exp(Nd2_a)-1)) ;

        k21 = (A_m/V_m)*Pn*fn_c+(A_m/V_m)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
            +(A_m/V_m)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1) ;
        k22 = -(A_m/V_m)*Pn*fn_m-
(A_m/V_m)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
            -(A_m/V_m)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1) ;
        k23 = 0;
        k24 = 0 ;
        S2 = 0;

        k31 = (A_l/V_l)*Pn*fn_c+(A_l/V_l)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
            +(A_l/V_l)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1) ;
        k32 = 0;
        k33 = -(A_l/V_l)*Pn*fn_l-
(A_l/V_l)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
            -(A_l/V_l)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1) ;

        k34 = 0 ;
        S3 = 0;

        k41 = (A_b/V_b)*Pn*fn_c+(A_b/V_b)*Pd1*Nd1_b*fd1_c/(exp(Nd1_b)-1)...
            +(A_b/V_b)*Pd2*Nd2_b*fd2_c/(exp(Nd2_b)-1) ;
        k42 = 0;
        k43 = 0;
        k44 = -(A_b/V_b)*Pn*fn_b-
(A_b/V_b)*Pd1*Nd1_b*fd1_b*exp(Nd1_b)/(exp(Nd1_b)-1)...
             -(A_b/V_b)*Pd2*Nd2_b*fd2_b*exp(Nd2_b)/(exp(Nd2_b)-1);
        S4 = 0;

        A = [k11, k12, k13, k14; k21, k22, k23, k24; k31, k32, k33, k34; k41,
k42, k43, k44];
        G = [S1, S2, S3, S4]';
        RR = [0,0,0,0]';
        t = 300 ;   % time in sec (5min)


        [V,E] = eig(A);
        E = diag(E);
        H = inv(V)*G;
```

```
        B = V \ RR;
        C = B + H./E;
        Z = -(H./E) + exp(t * E).*C ;
        Y = real(V * Z);
        Y = Y' ;

        Ppore = Y(4)*V_b /(t*A_aa*C_a)*10^(2)*10^6 ;                    %
Pcell, 10^(-6)cm/sec
        Peff = Y(4)*V_b*CellNo/(t*A_insert*C_a)*10^(2)*10^6;           %
Peff, 10^(-6)cm/sec, normalized by insert area, which is 1.12 cm^2
        Mass_cell = (Y(1)*V_c + Y(2)*V_m + Y(3)*V_l)*10^12 ;          %
cellular mass, pmol/cell
        dMdt = Y(4)*V_b/t*10^12;                                      %
transport rate: pmol/sec/cell

    Para(i,:) = [A_a*10^12,PoreNo_cell,
A_l*10^12,A_m*10^12,A_b*10^12,V_c*10^18,V_l*10^18,V_m*10^18,V_b*10^6,E_a*1000,E_
l*1000,E_m*1000,E_b*1000,...
                    pH_a,pH_c,pH_l,pH_m,pH_b,CellNo,PoreDens,
pKa1,pKa2,logPn,logPd1, logPd2];
    Results(i,:)=[Y(1),Y(2),Y(3),Ppore, Peff, dMdt, Mass_cell];

end

comb = [Results(:,1:7),Para];
fid5 = fopen('AtoB_pH74_3um_5min.dat','w');
fprintf(fid5,'%12.4e %12.4e %12.4e %12.4e %12.4e  %12.4e %12.4e %12.2e %12.0f %1
2.4e %12.4e %12.4e  %12.4e %12.4e %12.4e %12.4e %12.4f %12.4f %12.4f %12.4f %12.
2f %12.2f %12.2f %12.2f %12.2f %12.0f %12.0f %12.2f %12.2f %12.2f %12.2f %12.2f
\n', comb') ;
fclose(fid5);

figure(13) ; clf ; hold on ;
grid on;
hist (log10(comb(:,4)),1000);
line([log10(Ppore_exp), log10(Ppore_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{cell}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
xlim([0, 6]);
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of cell
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(14) ; clf ; hold on ;
grid on;
hist (log10(comb(:,5)),1000);
xlim([-3, 3]);
line([log10(Peff_exp), log10(Peff_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{app}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
```

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title ('histogram of apparent
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(15) ; clf ; hold on ;
grid on;
hist (log10(comb(:,6)),1000);
xlim([-8,-2]);
line([log10(dMdt_exp), log10(dMdt_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (dM/dt,
pmol/sec/cell)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of transport
rate','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(16) ; clf ; hold on ;
grid on;
hist (log10(comb(:,7)),1000);
xlim([-5,-0]);
line([log10(IntraMass_exp),
log10(IntraMass_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (intracellular mass, pmol/cell)
','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of intracellular
mass','FontSize',30,'FontWeight','Bold','FontName','Times') ;


% ==========================Case# 5: BL->AP transport, pHb = 6.5, 0.4um-membrane,
5min=======================================

clear ;                       % Clear the memory
z1 = 1 ;                      % ionization group 1 of CQ
z2 = 2 ;                      % ionization group 2 of CQ
i1 = sign(z1) ;
i2 = sign(z2) ;

T = 310.15 ;                  % temperature
R = 8.314 ;                   % universal gas constant
F = 96484.56 ;                % faraday constant
C_b = 1 ;                     % initial drug concentration (mM)

sim = 10000;                  % number of simulations
paraNo = 25;
outputNo = 7;                 % number of output parameters
Para = zeros(sim,paraNo);
Results = zeros(sim,outputNo);

dMdt_exp = 5.25e-6;           % +/- 1.24e-6, pmol/sec/cell, measured after
4hrs
Ppore_exp = 3.82E+02;         % +/- 81.7, 10^-6 cm/sec, measured after 4hrs
Peff_exp = 1.92;              % +/- 0.411, 10^-6 cm/sec, measured after 4hrs
```

```
IntraMass_exp = 0.00352;          % +/- 0.00093 pmol/cell, measured after 5min

for i = 1:sim

    % Drug information -- ChemAxon calculation including logPn, pKa1, and pKa2
    logPn = 3.93-0.5+rand();     % unif [3.43, 4.43] ;
    pKa1 = 9.96-0.5+rand();      % unif [9.46, 10.46] ;
    pKa2 = 7.47-0.5+rand();      % unif [6.97, 7.97] ;
    logPd1 = 0.43-0.5+rand();    % unif [-0.07, 0.93] ;
    logPd2 = -0.91-0.5+rand();   % unif [-1.41, 0.41] ;
    Pn = 10^(logPn-6.7);
    Pd1 = 10^(logPd1-6.7);
    Pd2 = 10^(logPd2-6.7);


    CellNo = 2*10^5*(1+rand());                        % cell
number/insert: unif [2*10^5, 4*10^5]
    PoreDens = 4*10^6*0.4*(2+rand());                  % pore
number/cm^2: unif [3.2*10^6, 4.8*10^6]
    A_insert = 1.12*10^(-4) ;                          % insert area:
1.12 cm^2
    PoreNo_insert = PoreDens*A_insert*10^(4);          % pore
number/insert
    PoreNo_cell = PoreNo_insert/CellNo ;               % average pore
number/cell
    A_pore_insert = 3.14*((0.4/2)*10^(-6))^2*PoreNo_insert ;   % pore area /
insert (m^2)
    A_pore_cell = 3.14*((0.4/2)*10^(-6))^2*PoreNo_cell ;      % average pore
area / cell (m^2)

    A_a = 10^(-10)*(1+9*rand());                       % apical
membrane surface area: unif [10^(-10),10*(10)^(-10))] (m^2)
    A_aa = A_pore_cell;                                % pore area/cell
(m^2)
    A_b = A_aa+(10^(-10)-A_aa)*rand();                 % basolateral
membrane surface area: unif [A_aa, 10^(-10)] (m^2)
    A_l = 100*3.14*10^(-12);                           % lysosomal
membrane surface area (m^2)
    A_m = 100*3.14*10^(-12);                           % mitochondrial
membrane surface area (m^2)
    V_c = 0.5*10^(-15)*(1+5*rand());                   % cytosolic
volume: unif [0.5*10^(-15), 3*10^(-15)] (m^3)
    V_l = 10^(-18)*(9.24+(23.8-9.24)*rand());          % lysosomal
volume: unif [9.24*10^(-18), 23.8*10^(-18)] (m^3)
    V_m = 100*5.24*10^(-19)/5*(1+24*rand());           % mitochondrial
volume: unif [10.48*10^(-18), 262*10^(-18)](m^3)
    V_a = 0.5*10^(-6);                                 % apical volume:
0.5 mL

    % Membrane potential (unit in 'Voltage')
    E_a = 0.0093-0.005+0.01*rand();                    % apical
membrane potential: unif [0.0043, 0.0143]
    E_l = 0.01-0.005+0.01*rand();                      % lysosomal
membrane potential: unif [0.005, 0.015]
    E_m = -0.16 ;                                      % mitochondrial
membrane potential
```

```matlab
    E_b = -0.0119-0.005+0.01*rand();                            % basolateral
membrane potential: unif [-0.0169, -0.0069]

    % pH values
    pH_a = 7.4;                                                 % pH in apical
compartment
    pH_c = 7.0+0.4*rand();                                      % pH in cytosol:
unif [7.0, 7.4]
    pH_l = 4.8+0.4*rand();                                      % pH in
lysosomes: unif [4.8, 5.2]
    pH_m = 7.8+0.4*rand();                                      % pH in
mitochondria: unif[7.8, 8.2]
    pH_b = 6.4+0.2*rand();                                      % pH in
basolateral compartment: unif [6.4, 6.6]

    % BL Compartment (donor)
    fn_b = 1 / (1 + 10^(i1*(pKa1-pH_b)) + 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b))) ;
    fd2_b = fn_b * 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b)) ;
    fd1_b = fn_b * 10^(i1*(pKa1-pH_b)) ;
    Nd2_b = z2*E_b*F/(R*T) ;
    Nd1_b = z1*E_b*F/(R*T) ;

    % Cytoplasm
    L_c = 0.05+0.1*rand();                                      % lipid
fraction in cytosol: unif [0.05, 0.15]
    W_c = 1-L_c ;                                               % water
fraction in cytosol
    Is_c = 0.3 ;                                               % ion
strength in cytosol (mol)
    gamman_c = 10^(0.3*Is_c) ;                                  %
activity coefficient of neutral molecules in cytosol
    gammad1_c = 10^(-0.5*z1*z1*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of monovalent base in cytosol
    gammad2_c = 10^(-0.5*z2*z2*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of bivalent base in cytosol
    Kn_c = L_c*1.22*10^(logPn) ;
    Kd1_c = L_c*1.22*10^(logPd1) ;
    Kd2_c = L_c*1.22*10^(logPd2) ;
    an_c = 1 / (1 + 10^(i1*(pKa1-pH_c)) + 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c))) ;
    ad2_c = an_c * 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c)) ;
    ad1_c = an_c * 10^(i1*(pKa1-pH_c)) ;
    Dd2_c = ad2_c / an_c ;
    Dd1_c = ad1_c / an_c ;
    fn_c = 1 / (W_c/gamman_c + Kn_c/gamman_c + Dd2_c*W_c/gammad2_c +
Dd2_c*Kd2_c/gammad2_c ...
          + Dd1_c*W_c/gammad1_c + Dd1_c*Kd1_c/gammad1_c ) ;
    fd2_c = fn_c * Dd2_c ;
    fd1_c = fn_c * Dd1_c ;

    % Mitochondria
    L_m = 0.05+0.1*rand();                                      % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_m = 1-L_m ;                                               % water
fraction in mitochondria
    Is_m = 0.3 ;                                               % ion
strength in mitochondria (mol)
    Nd2_m = z2*E_m*F/(R*T) ;
```

```
    Nd1_m = z1*E_m*F/(R*T) ;
    gamman_m = 10^(0.3*Is_m) ;                                              %
activity coefficient of neutral molecules in mitochondria
    gammad1_m = 10^(-0.5*z1*z1*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of monovalent base in mitochondria
    gammad2_m = 10^(-0.5*z2*z2*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of bivalent base in mitochondria
    Kn_m = L_m*1.22*10^(logPn) ;
    Kd1_m = L_m*1.22*10^(logPd1) ;
    Kd2_m = L_m*1.22*10^(logPd2) ;
    an_m = 1 / (1 + 10^(i1*(pKa1-pH_m)) + 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m))) ;
    ad2_m = an_m * 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m)) ;
    ad1_m = an_m * 10^(i1*(pKa1-pH_m)) ;
    Dd2_m = ad2_m / an_m ;
    Dd1_m = ad1_m / an_m ;
    fn_m = 1 / (W_m/gamman_m + Kn_m/gamman_m + Dd2_m*W_m/gammad2_m +
Dd2_m*Kd2_m/gammad2_m ...
          + Dd1_m*W_m/gammad1_m + Dd1_m*Kd1_m/gammad1_m ) ;
    fd2_m = fn_m * Dd2_m ;
    fd1_m = fn_m * Dd1_m ;

    % Lysosomes
    L_l = 0.05+0.1*rand();                                         % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_l = 1-L_l ;                                                  % water
fraction in lysosomes
    Is_l = 0.3 ;                                                   % ion
strength in lysosomes (mol)
    Nd2_l = z2*E_l*F/(R*T) ;
    Nd1_l = z1*E_l*F/(R*T) ;
    gamman_l = 10^(0.3*Is_l) ;                                     %
activity coefficient of neutral molecules in lysosomes
    gammad1_l = 10^(-0.5*z1*z1*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of monovalent base in lysosomes
    gammad2_l = 10^(-0.5*z2*z2*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of bivalent base in lysosomes
    Kn_l = L_l*1.22*10^(logPn) ;
    Kd1_l = L_l*1.22*10^(logPd1) ;
    Kd2_l = L_l*1.22*10^(logPd2) ;
    an_l = 1 / (1 + 10^(i1*(pKa1-pH_l)) + 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l))) ;
    ad2_l = an_l * 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l)) ;
    ad1_l = an_l * 10^(i1*(pKa1-pH_l)) ;
    Dd2_l = ad2_l / an_l ;
    Dd1_l = ad1_l / an_l ;
    fn_l = 1 / (W_l/gamman_l + Kn_l/gamman_l + Dd2_l*W_l/gammad2_l +
Dd2_l*Kd2_l/gammad2_l ...
          + Dd1_l*W_l/gammad1_l + Dd1_l*Kd1_l/gammad1_l ) ;
    fd2_l = fn_l * Dd2_l ;
    fd1_l = fn_l * Dd1_l ;

    % AP Compartment (receiver compartment)
    fn_a = 1 / (1 + 10^(i1*(pKa1-pH_a)) + 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a))) ;
    fd2_a = fn_a * 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a)) ;
    fd1_a = fn_a * 10^(i1*(pKa1-pH_a)) ;
    Nd2_a = z2*(-E_a)*F/(R*T) ;
    Nd1_a = z1*(-E_a)*F/(R*T) ;
```

```
% Solve the differential equation system for each drug:
% Given a system of linear ODE's expressed in matrix form:
% Y' = AY+G with initial conditions Y(0) = RR,
    % Ccyto = Y(1)
    k11 = -(A_b/V_c)*Pn*fn_c-
(A_b/V_c)*Pd1*Nd1_b*fd1_c*exp(Nd1_b)/(exp(Nd1_b)-1)-
(A_b/V_c)*Pd2*Nd2_b*fd2_c*exp(Nd2_b)/(exp(Nd2_b)-1)...
            -(A_m/V_c)*Pn*fn_c-(A_m/V_c)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)-
(A_m/V_c)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1)...
            -(A_l/V_c)*Pn*fn_c-(A_l/V_c)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)-
(A_l/V_c)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1)...
            -(A_a/V_c)*Pn*fn_c-(A_a/V_c)*Pd1*Nd1_a*fd1_c/(exp(Nd1_a)-1)-
(A_a/V_c)*Pd2*Nd2_a*fd2_c/(exp(Nd2_a)-1) ;
    k12 =
(A_m/V_c)*Pn*fn_m+(A_m/V_c)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-
1)+(A_m/V_c)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1);
    k13 =
(A_l/V_c)*Pn*fn_l+(A_l/V_c)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-
1)+(A_l/V_c)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1);
    k14 =
(A_a/V_c)*Pn*fn_a+(A_a/V_c)*Pd1*Nd1_a*fd1_a*exp(Nd1_a)/(exp(Nd1_a)-
1)+(A_a/V_c)*Pd2*Nd2_a*fd2_a*exp(Nd2_a)/(exp(Nd2_a)-1);
    S1 = (A_b/V_c)*C_b*(Pn*fn_b+Pd1*Nd1_b*fd1_b/(exp(Nd1_b)-
1)+Pd2*Nd2_b*fd2_b/(exp(Nd2_b)-1)) ;


    % Cmito = Y(2)
    k21 = (A_m/V_m)*Pn*fn_c+(A_m/V_m)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
            +(A_m/V_m)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1) ;
    k22 = -(A_m/V_m)*Pn*fn_m-
(A_m/V_m)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
            -(A_m/V_m)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1) ;
    k23 = 0;
    k24 = 0 ;
    S2 = 0;

    % Clyso = Y(3)
    k31 = (A_l/V_l)*Pn*fn_c+(A_l/V_l)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
            +(A_l/V_l)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1) ;
    k32 = 0;
    k33 = -(A_l/V_l)*Pn*fn_l-
(A_l/V_l)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
            -(A_l/V_l)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1) ;

    k34 = 0 ;
    S3 = 0;


    % Cap = Y(4)
    k41 = (A_a/V_a)*Pn*fn_c+(A_a/V_a)*Pd1*Nd1_a*fd1_c/(exp(Nd1_a)-1)...
            +(A_a/V_a)*Pd2*Nd2_a*fd2_c/(exp(Nd2_a)-1) ;
    k42 = 0;
    k43 = 0;
    k44 = -(A_a/V_a)*Pn*fn_a-
(A_a/V_a)*Pd1*Nd1_a*fd1_a*exp(Nd1_a)/(exp(Nd1_a)-1)...
            -(A_a/V_a)*Pd2*Nd2_a*fd2_a*exp(Nd2_a)/(exp(Nd2_a)-1);
    S4 = 0;
```

```matlab
        A = [k11, k12, k13, k14; k21, k22, k23, k24; k31, k32, k33, k34; k41,
k42, k43, k44];
        G = [S1, S2, S3, S4]';
        RR = [0,0,0,0]';
        t = 300;

        [V,E] = eig(A);
        E = diag(E);
        H = inv(V)*G;
        B = V \ RR;
        C = B + H./E;
        Z = -(H./E) + exp(t * E).*C ;
        Y = real(V * Z);
        Y = Y' ;

        Ppore = Y(4)*V_a /(t*A_aa*C_b)*10^(2)*10^6 ;                  %
Pcell, 10^(-6)cm/sec
        Peff = Y(4)*V_a*CellNo/(t*A_insert*C_b)*10^(2)*10^6;         %
Peff, 10^(-6)cm/sec, normalized by insert area, which is 1.12 cm^2
        Mass_cell = (Y(1)*V_c + Y(2)*V_m + Y(3)*V_l)*10^12 ;          %
cellular mass, pmol/cell
        dMdt = Y(4)*V_a/t*10^12;                                       %
transport rate: pmol/sec/cell

    Para(i,:) = [A_a*10^12,PoreNo_cell,
A_l*10^12,A_m*10^12,A_b*10^12,V_c*10^18,V_l*10^18,V_m*10^18,V_a*10^6,E_a*1000,E_
l*1000,E_m*1000,E_b*1000,...
                    pH_a,pH_c,pH_l,pH_m,pH_b,CellNo,PoreDens,
pKa1,pKa2,logPn,logPd1, logPd2];
    Results(i,:)=[Y(1),Y(2),Y(3),Ppore, Peff, dMdt, Mass_cell];

end

comb = [Results(:,1:7),Para];
fid5 = fopen('BtoA_pH65_04um_5min.dat','w');
fprintf(fid5,'%12.4e %12.4e %12.4e %12.4e %12.4e  %12.4e %12.4e %12.2e %12.0f %1
2.4e %12.4e %12.4e  %12.4e %12.4e %12.4e %12.4e %12.4f %12.4f %12.4f %12.4f %12.
2f %12.2f %12.2f %12.2f %12.2f %12.0f %12.0f %12.2f %12.2f %12.2f %12.2f %12.2f
\n', comb') ;
fclose(fid5);

figure(17) ; clf ; hold on ;
grid on;
hist (log10(comb(:,4)),1000);
line([log10(Ppore_exp), log10(Ppore_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{cell}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
xlim([0, 6]);
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of cell
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(18) ; clf ; hold on ;
grid on;
```

```matlab
hist (log10(comb(:,5)),1000);
xlim([-3, 3]);
line([log10(Peff_exp), log10(Peff_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{app}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of apparent
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(19) ; clf ; hold on ;
grid on;
hist (log10(comb(:,6)),1000);
xlim([-8,-2]);
line([log10(dMdt_exp), log10(dMdt_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (dM/dt,
pmol/sec/cell)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of transport
rate','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(20) ; clf ; hold on ;
grid on;
hist (log10(comb(:,7)),1000);
xlim([-5,-0]);
line([log10(IntraMass_exp),
log10(IntraMass_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (intracellular mass, pmol/cell)
','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of intracellular
mass','FontSize',30,'FontWeight','Bold','FontName','Times') ;




% ============================Case# 6: BL->AP transport, pHb = 6.5,   3um-membrane,
5min=========================================

clear ;                    % Clear the memory
z1 = 1 ;                   % ionization group 1 of CQ
z2 = 2 ;                   % ionization group 2 of CQ
i1 = sign(z1) ;
i2 = sign(z2) ;

T = 310.15 ;               % temperature
R = 8.314 ;                % universal gas constant
F = 96484.56 ;             % faraday constant
C_b = 1 ;                  % initial drug concentration (mM)
```

```matlab
sim = 10000;                    % number of simulations
paraNo = 25;
outputNo = 7;                   % number of output parameters
Para = zeros(sim,paraNo);
Results = zeros(sim,outputNo);

dMdt_exp = 7.12e-6;             % +/- 4.73e-7, pmol/sec/cell, measured after 4hrs
Ppore_exp = 1.58E+01;           % +/- 2.45, 10^(-6) cm/sec, measured after 4hrs
Peff_exp = 2.24;                % +/- 0.346, 10^(-6) cm/sec, measured after 4hrs
IntraMass_exp = 0.00494;        % +/- 0.00106, pmol/cell, measured after 5min


for i = 1:sim

    % Drug information -- ChemAxon calculation including logPn, pKa1, and pKa2
    logPn = 3.93-0.5+rand();    % unif [3.43, 4.43] ;
    pKa1 = 9.96-0.5+rand();     % unif [9.46, 10.46] ;
    pKa2 = 7.47-0.5+rand();     % unif [6.97, 7.97] ;
    logPd1 = 0.43-0.5+rand();   % unif [-0.07, 0.93] ;
    logPd2 = -0.91-0.5+rand();  % unif [-1.41, 0.41] ;
    Pn = 10^(logPn-6.7);
    Pd1 = 10^(logPd1-6.7);
    Pd2 = 10^(logPd2-6.7);


    CellNo = 2*10^5*(1+rand());                         % cell
number/insert: unif [2*10^5, 4*10^5]
    PoreDens = 2*10^6*0.4*(2+rand());                   % pore
number/cm^2: unif [1.6*10^6, 2.4*10^6]
    A_insert = 1.12*10^(-4) ;                           % insert area:
1.12 cm^2
    PoreNo_insert = PoreDens*A_insert*10^(4);           % pore
number/insert
    PoreNo_cell = PoreNo_insert/CellNo ;                % average pore
number/cell
    A_pore_insert = 3.14*((3/2)*10^(-6))^2*PoreNo_insert ;     % pore area /
insert (m^2)
    A_pore_cell = 3.14*((3/2)*10^(-6))^2*PoreNo_cell ;        % average pore
area / cell (m^2)

    A_a = 10^(-10)*(1+9*rand());                        % apical
membrane surface area: unif [10^(-10),10*(10)^(-10))] (m^2)
    A_aa = A_pore_cell;                                 % pore area/cell
(m^2)
    A_b = A_aa+(10^(-10)-A_aa)*rand();                  % basolateral
membrane surface area: unif [A_aa, 10^(-10)] (m^2)
    A_l = 100*3.14*10^(-12);                            % lysosomal
membrane surface area (m^2)
    A_m = 100*3.14*10^(-12);                            % mitochondrial
membrane surface area (m^2)
    V_c = 0.5*10^(-15)*(1+5*rand());                    % cytosolic
volume: unif [0.5*10^(-15), 3*10^(-15)] (m^3)
    V_l = 10^(-18)*(9.24+(23.8-9.24)*rand());           % lysosomal
volume: unif [9.24*10^(-18), 23.8*10^(-18)] (m^3)
    V_m = 100*5.24*10^(-19)/5*(1+24*rand());            % mitochondrial
volume: unif [10.48*10^(-18), 262*10^(-18)](m^3)
    V_a = 0.5*10^(-6);                                  % apical volume:
0.5 mL
```

```matlab
    % Membrane potential (unit in 'Voltage')
    E_a = 0.0093-0.005+0.01*rand();                         % apical
membrane potential: unif [0.0043, 0.0143]
    E_l = 0.01-0.005+0.01*rand();                           % lysosomal
membrane potential: unif [0.005, 0.015]
    E_m = -0.16 ;                                           % mitochondrial
membrane potential
    E_b = -0.0119-0.005+0.01*rand();                        % basolateral
membrane potential: unif [-0.0169, -0.0069]

    % pH values
    pH_a = 7.4;                                             % pH in apical
compartment
    pH_c = 7.0+0.4*rand();                                  % pH in cytosol:
unif [7.0, 7.4]
    pH_l = 4.8+0.4*rand();                                  % pH in
lysosomes: unif [4.8, 5.2]
    pH_m = 7.8+0.4*rand();                                  % pH in
mitochondria: unif[7.8, 8.2]
    pH_b = 6.4+0.2*rand();                                  % pH in
basolateral compartment: unif [6.4, 6.6]

    % BL Compartment (donor)
    fn_b = 1 / (1 + 10^(i1*(pKa1-pH_b)) + 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b))) ;
    fd2_b = fn_b * 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b)) ;
    fd1_b = fn_b * 10^(i1*(pKa1-pH_b)) ;
    Nd2_b = z2*E_b*F/(R*T) ;
    Nd1_b = z1*E_b*F/(R*T) ;

    % Cytoplasm
    L_c = 0.05+0.1*rand();                                  % lipid
fraction in cytosol: unif [0.05, 0.15]
    W_c = 1-L_c ;                                           % water
fraction in cytosol
    Is_c = 0.3 ;                                            % ion
strength in cytosol (mol)
    gamman_c = 10^(0.3*Is_c) ;                              %
activity coefficient of neutral molecules in cytosol
    gammad1_c = 10^(-0.5*z1*z1*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of monovalent base in cytosol
    gammad2_c = 10^(-0.5*z2*z2*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of bivalent base in cytosol
    Kn_c = L_c*1.22*10^(logPn) ;
    Kd1_c = L_c*1.22*10^(logPd1) ;
    Kd2_c = L_c*1.22*10^(logPd2) ;
    an_c = 1 / (1 + 10^(i1*(pKa1-pH_c)) + 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c))) ;
    ad2_c = an_c * 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c)) ;
    ad1_c = an_c * 10^(i1*(pKa1-pH_c)) ;
    Dd2_c = ad2_c / an_c ;
    Dd1_c = ad1_c / an_c ;
    fn_c = 1 / (W_c/gamman_c + Kn_c/gamman_c + Dd2_c*W_c/gammad2_c +
Dd2_c*Kd2_c/gammad2_c ...
          + Dd1_c*W_c/gammad1_c + Dd1_c*Kd1_c/gammad1_c ) ;
    fd2_c = fn_c * Dd2_c ;
    fd1_c = fn_c * Dd1_c ;
```

```matlab
    % Mitochondria
    L_m = 0.05+0.1*rand();                                              % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_m = 1-L_m ;                                                       % water
fraction in mitochondria
    Is_m = 0.3 ;                                                        % ion
strength in mitochondria (mol)
    Nd2_m = z2*E_m*F/(R*T) ;
    Nd1_m = z1*E_m*F/(R*T) ;
    gamman_m = 10^(0.3*Is_m) ;                                          %
activity coefficient of neutral molecules in mitochondria
    gammad1_m = 10^(-0.5*z1*z1*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of monovalent base in mitochondria
    gammad2_m = 10^(-0.5*z2*z2*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of bivalent base in mitochondria
    Kn_m = L_m*1.22*10^(logPn) ;
    Kd1_m = L_m*1.22*10^(logPd1) ;
    Kd2_m = L_m*1.22*10^(logPd2) ;
    an_m = 1 / (1 + 10^(i1*(pKa1-pH_m)) + 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m))) ;
    ad2_m = an_m * 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m)) ;
    ad1_m = an_m * 10^(i1*(pKa1-pH_m)) ;
    Dd2_m = ad2_m / an_m ;
    Dd1_m = ad1_m / an_m ;
    fn_m = 1 / (W_m/gamman_m + Kn_m/gamman_m + Dd2_m*W_m/gammad2_m +
Dd2_m*Kd2_m/gammad2_m ...
            + Dd1_m*W_m/gammad1_m + Dd1_m*Kd1_m/gammad1_m ) ;
    fd2_m = fn_m * Dd2_m ;
    fd1_m = fn_m * Dd1_m ;


    % Lysosomes
    L_l = 0.05+0.1*rand();                                             % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_l = 1-L_l ;                                                       % water
fraction in lysosomes
    Is_l = 0.3 ;                                                        % ion
strength in lysosomes (mol)
    Nd2_l = z2*E_l*F/(R*T) ;
    Nd1_l = z1*E_l*F/(R*T) ;
    gamman_l = 10^(0.3*Is_l) ;                                          %
activity coefficient of neutral molecules in lysosomes
    gammad1_l = 10^(-0.5*z1*z1*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of monovalent base in lysosomes
    gammad2_l = 10^(-0.5*z2*z2*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of bivalent base in lysosomes
    Kn_l = L_l*1.22*10^(logPn) ;
    Kd1_l = L_l*1.22*10^(logPd1) ;
    Kd2_l = L_l*1.22*10^(logPd2) ;
    an_l = 1 / (1 + 10^(i1*(pKa1-pH_l)) + 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l))) ;
    ad2_l = an_l * 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l)) ;
    ad1_l = an_l * 10^(i1*(pKa1-pH_l)) ;
    Dd2_l = ad2_l / an_l ;
    Dd1_l = ad1_l / an_l ;
    fn_l = 1 / (W_l/gamman_l + Kn_l/gamman_l + Dd2_l*W_l/gammad2_l +
Dd2_l*Kd2_l/gammad2_l ...
            + Dd1_l*W_l/gammad1_l + Dd1_l*Kd1_l/gammad1_l ) ;
    fd2_l = fn_l * Dd2_l ;
    fd1_l = fn_l * Dd1_l ;
```

```matlab
    % AP Compartment (receiver compartment)
    fn_a = 1 / (1 + 10^(i1*(pKa1-pH_a)) + 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a))) ;
    fd2_a = fn_a * 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a)) ;
    fd1_a = fn_a * 10^(i1*(pKa1-pH_a)) ;
    Nd2_a = z2*(-E_a)*F/(R*T) ;
    Nd1_a = z1*(-E_a)*F/(R*T) ;

    % Solve the differential equation system for each drug:
    % Given a system of linear ODE's expressed in matrix form:
    % Y' = AY+G with initial conditions Y(0) = RR,
        % Ccyto = Y(1)
        k11 = -(A_b/V_c)*Pn*fn_c-
(A_b/V_c)*Pd1*Nd1_b*fd1_c*exp(Nd1_b)/(exp(Nd1_b)-1)-
(A_b/V_c)*Pd2*Nd2_b*fd2_c*exp(Nd2_b)/(exp(Nd2_b)-1)...
            -(A_m/V_c)*Pn*fn_c-(A_m/V_c)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)-
(A_m/V_c)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1)...
            -(A_l/V_c)*Pn*fn_c-(A_l/V_c)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)-
(A_l/V_c)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1)...
            -(A_a/V_c)*Pn*fn_c-(A_a/V_c)*Pd1*Nd1_a*fd1_c/(exp(Nd1_a)-1)-
(A_a/V_c)*Pd2*Nd2_a*fd2_c/(exp(Nd2_a)-1) ;
        k12 =
(A_m/V_c)*Pn*fn_m+(A_m/V_c)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-
1)+(A_m/V_c)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1);
        k13 =
(A_l/V_c)*Pn*fn_l+(A_l/V_c)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-
1)+(A_l/V_c)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1);
        k14 =
(A_a/V_c)*Pn*fn_a+(A_a/V_c)*Pd1*Nd1_a*fd1_a*exp(Nd1_a)/(exp(Nd1_a)-
1)+(A_a/V_c)*Pd2*Nd2_a*fd2_a*exp(Nd2_a)/(exp(Nd2_a)-1);
        S1 = (A_b/V_c)*C_b*(Pn*fn_b+Pd1*Nd1_b*fd1_b/(exp(Nd1_b)-
1)+Pd2*Nd2_b*fd2_b/(exp(Nd2_b)-1)) ;

        % Cmito = Y(2)
        k21 = (A_m/V_m)*Pn*fn_c+(A_m/V_m)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
            +(A_m/V_m)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1) ;
        k22 = -(A_m/V_m)*Pn*fn_m-
(A_m/V_m)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
            -(A_m/V_m)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1) ;
        k23 = 0;
        k24 = 0 ;
        S2 = 0;

        % Clyso = Y(3)
        k31 = (A_l/V_l)*Pn*fn_c+(A_l/V_l)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
            +(A_l/V_l)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1) ;
        k32 = 0;
        k33 = -(A_l/V_l)*Pn*fn_l-
(A_l/V_l)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
            -(A_l/V_l)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1) ;
        k34 = 0 ;
        S3 = 0;


        % Cap = Y(4)
        k41 = (A_a/V_a)*Pn*fn_c+(A_a/V_a)*Pd1*Nd1_a*fd1_c/(exp(Nd1_a)-1)...
            +(A_a/V_a)*Pd2*Nd2_a*fd2_c/(exp(Nd2_a)-1) ;
```

```matlab
        k42 = 0;
        k43 = 0;
        k44 = -(A_a/V_a)*Pn*fn_a-
(A_a/V_a)*Pd1*Nd1_a*fd1_a*exp(Nd1_a)/(exp(Nd1_a)-1)...
               -(A_a/V_a)*Pd2*Nd2_a*fd2_a*exp(Nd2_a)/(exp(Nd2_a)-1);
        S4 = 0;

        A = [k11, k12, k13, k14; k21, k22, k23, k24; k31, k32, k33, k34; k41,
k42, k43, k44];
        G = [S1, S2, S3, S4]';
        RR = [0,0,0,0]';
        t = 300;

        [V,E] = eig(A);
        E = diag(E);
        H = inv(V)*G;
        B = V \ RR;
        C = B + H./E;
        Z = -(H./E) + exp(t * E).*C ;
        Y = real(V * Z);
        Y = Y' ;

        Ppore = Y(4)*V_a /(t*A_aa*C_b)*10^(2)*10^6 ;                      %
Pcell, 10^(-6)cm/sec
        Peff = Y(4)*V_a*CellNo/(t*A_insert*C_b)*10^(2)*10^6;             %
Peff, 10^(-6)cm/sec, normalized by insert area, which is 1.12 cm^2
        Mass_cell = (Y(1)*V_c + Y(2)*V_m + Y(3)*V_l)*10^12 ;            %
cellular mass, pmol/cell
        dMdt = Y(4)*V_a/t*10^12;                                        %
transport rate: pmol/sec/cell

    Para(i,:) = [A_a*10^12,PoreNo_cell,
A_l*10^12,A_m*10^12,A_b*10^12,V_c*10^18,V_l*10^18,V_m*10^18,V_a*10^6,E_a*1000,E_
l*1000,E_m*1000,E_b*1000,...
                     pH_a,pH_c,pH_l,pH_m,pH_b,CellNo,PoreDens,
pKa1,pKa2,logPn,logPd1, logPd2];
    Results(i,:)=[Y(1),Y(2),Y(3),Ppore, Peff, dMdt, Mass_cell];

end

comb = [Results(:,1:7),Para];
fid5 = fopen('BtoA_pH65_3um_5min.dat','w');
fprintf(fid5,'%12.4e %12.4e %12.4e %12.4e %12.4e  %12.4e %12.4e %12.2e %12.0f %1
2.4e %12.4e %12.4e  %12.4e %12.4e %12.4e %12.4e %12.4f %12.4f %12.4f %12.4f %12.
2f %12.2f %12.2f %12.2f %12.2f %12.0f %12.0f %12.2f %12.2f %12.2f %12.2f %12.2f
\n', comb') ;
fclose(fid5);

figure(21) ; clf ; hold on ;
grid on;
hist (log10(comb(:,4)),1000);
line([log10(Ppore_exp), log10(Ppore_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{cell}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
xlim([0, 6]);
ax1 = gca;
```

```matlab
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of cell
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(22) ; clf ; hold on ;
grid on;
hist (log10(comb(:,5)),1000);
xlim([-3, 3]);
line([log10(Peff_exp), log10(Peff_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{app}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of apparent
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(23) ; clf ; hold on ;
grid on;
hist (log10(comb(:,6)),1000);
xlim([-8,-2]);
line([log10(dMdt_exp), log10(dMdt_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (dM/dt,
pmol/sec/cell)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of transport
rate','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(24) ; clf ; hold on ;
grid on;
hist (log10(comb(:,7)),1000);
xlim([-5,-0]);
line([log10(IntraMass_exp),
log10(IntraMass_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (intracellular mass, pmol/cell)
','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of intracellular
mass','FontSize',30,'FontWeight','Bold','FontName','Times') ;




% ==========================Case# 7: BL->AP transport, pHb = 7.4, 0.4um-membrane,
5min=======================================
clear ;                         % Clear the memory
z1 = 1 ;                        % ionization group 1 of CQ
z2 = 2 ;                        % ionization group 2 of CQ
i1 = sign(z1) ;
```

```matlab
    i2 = sign(z2) ;

    T = 310.15 ;              % temperature
    R = 8.314 ;               % universal gas constant
    F = 96484.56 ;            % faraday constant
    C_b = 1 ;                 % initial drug concentration (mM)

    sim = 10000;              % number of simulations
    paraNo = 25;
    outputNo = 7;             % number of output parameters
    Para = zeros(sim,paraNo);
    Results = zeros(sim,outputNo);

    dMdt_exp = 2.94e-5;            % +/- 1.54e-6, pmol/sec/cell, measured after
    4hrs
    Ppore_exp = 2.00E+03;         % +/- 353, 10^-6 cm/sec, measured after 4hrs
    Peff_exp = 1.00E+01;          % +/- 1.77, 10^-6 cm/sec, measured after
    4hrs
    IntraMass_exp = 0.00828;      % +/- 0.00075 pmol/cell , measured after
    5min

    for i = 1:sim

        % Drug information -- ChemAxon calculation including logPn, pKa1, and pKa2
        logPn = 3.93-0.5+rand();    % unif [3.43, 4.43] ;
        pKa1 = 9.96-0.5+rand();     % unif [9.46, 10.46] ;
        pKa2 = 7.47-0.5+rand();     % unif [6.97, 7.97] ;
        logPd1 = 0.43-0.5+rand();   % unif [-0.07, 0.93] ;
        logPd2 = -0.91-0.5+rand();  % unif [-1.41, 0.41] ;
        Pn = 10^(logPn-6.7);
        Pd1 = 10^(logPd1-6.7);
        Pd2 = 10^(logPd2-6.7);


        CellNo = 2*10^5*(1+rand());                         % cell
    number/insert: unif [2*10^5, 4*10^5]
        PoreDens = 4*10^6*0.4*(2+rand());                   % pore
    number/cm^2: unif [3.2*10^6, 4.8*10^6]
        A_insert = 1.12*10^(-4) ;                           % insert area:
    1.12 cm^2
        PoreNo_insert = PoreDens*A_insert*10^(4);           % pore
    number/insert
        PoreNo_cell = PoreNo_insert/CellNo ;                % average pore
    number/cell
        A_pore_insert = 3.14*((0.4/2)*10^(-6))^2*PoreNo_insert ;   % pore area /
    insert (m^2)
        A_pore_cell = 3.14*((0.4/2)*10^(-6))^2*PoreNo_cell ;       % average pore
    area / cell (m^2)

        A_a = 10^(-10)*(1+9*rand());                        % apical
    membrane surface area: unif [10^(-10),10*(10)^(-10))] (m^2)
        A_aa = A_pore_cell;                                 % pore area/cell
    (m^2)
        A_b = A_aa+(10^(-10)-A_aa)*rand();                  % basolateral
    membrane surface area: unif [A_aa, 10^(-10)]) (m^2)
        A_l = 100*3.14*10^(-12);                            % lysosomal
    membrane surface area (m^2)
```

```matlab
    A_m = 100*3.14*10^(-12);                                % mitochondrial
membrane surface area (m^2)
    V_c = 0.5*10^(-15)*(1+5*rand());                        % cytosolic
volume: unif [0.5*10^(-15), 3*10^(-15)] (m^3)
    V_l = 10^(-18)*(9.24+(23.8-9.24)*rand());               % lysosomal
volume: unif [9.24*10^(-18), 23.8*10^(-18)] (m^3)
    V_m = 100*5.24*10^(-19)/5*(1+24*rand());                % mitochondrial
volume: unif [10.48*10^(-18), 262*10^(-18)](m^3)
    V_a = 0.5*10^(-6);                                      % apical volume:
0.5 mL

    % Membrane potential (unit in 'Voltage')
    E_a = 0.0093-0.005+0.01*rand();                         % apical
membrane potential: unif [0.0043, 0.0143]
    E_l = 0.01-0.005+0.01*rand();                           % lysosomal
membrane potential: unif [0.005, 0.015]
    E_m = -0.16 ;                                           % mitochondrial
membrane potential
    E_b = -0.0119-0.005+0.01*rand();                        % basolateral
membrane potential: unif [-0.0169, -0.0069]

    % pH values
    pH_a = 7.4;                                             % pH in apical
compartment
    pH_c = 7.0+0.4*rand();                                  % pH in cytosol:
unif [7.0, 7.4]
    pH_l = 4.8+0.4*rand();                                  % pH in
lysosomes: unif [4.8, 5.2]
    pH_m = 7.8+0.4*rand();                                  % pH in
mitochondria: unif[7.8, 8.2]
    pH_b = 7.0+0.4*rand();                                  % pH in
basolateral compartment: unif [7.0, 7.4]

    % BL Compartment (donor)
    fn_b = 1 / (1 + 10^(i1*(pKa1-pH_b)) + 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b))) ;
    fd2_b = fn_b * 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b)) ;
    fd1_b = fn_b * 10^(i1*(pKa1-pH_b)) ;
    Nd2_b = z2*E_b*F/(R*T) ;
    Nd1_b = z1*E_b*F/(R*T) ;

    % Cytoplasm
    L_c = 0.05+0.1*rand();                                  % lipid
fraction in cytosol: unif [0.05, 0.15]
    W_c = 1-L_c ;                                           % water
fraction in cytosol
    Is_c = 0.3 ;                                            % ion
strength in cytosol (mol)
    gamman_c = 10^(0.3*Is_c) ;                              %
activity coefficient of neutral molecules in cytosol
    gammad1_c = 10^(-0.5*z1*z1*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of monovalent base in cytosol
    gammad2_c = 10^(-0.5*z2*z2*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));   %
activity coefficient of bivalent base in cytosol
    Kn_c = L_c*1.22*10^(logPn) ;
    Kd1_c = L_c*1.22*10^(logPd1) ;
    Kd2_c = L_c*1.22*10^(logPd2) ;
    an_c = 1 / (1 + 10^(i1*(pKa1-pH_c)) + 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c))) ;
```

```
    ad2_c = an_c * 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c)) ;
    ad1_c = an_c * 10^(i1*(pKa1-pH_c)) ;
    Dd2_c = ad2_c / an_c ;
    Dd1_c = ad1_c / an_c ;
    fn_c = 1 / (W_c/gamman_c + Kn_c/gamman_c + Dd2_c*W_c/gammad2_c +
Dd2_c*Kd2_c/gammad2_c ...
            + Dd1_c*W_c/gammad1_c + Dd1_c*Kd1_c/gammad1_c ) ;
    fd2_c = fn_c * Dd2_c ;
    fd1_c = fn_c * Dd1_c ;

    % Mitochondria
    L_m = 0.05+0.1*rand();                                       % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_m = 1-L_m ;                                                % water
fraction in mitochondria
    Is_m = 0.3 ;                                                 % ion
strength in mitochondria (mol)
    Nd2_m = z2*E_m*F/(R*T) ;
    Nd1_m = z1*E_m*F/(R*T) ;
    gamman_m = 10^(0.3*Is_m) ;                                   %
activity coefficient of neutral molecules in mitochondria
    gammad1_m = 10^(-0.5*z1*z1*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of monovalent base in mitochondria
    gammad2_m = 10^(-0.5*z2*z2*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));   %
activity coefficient of bivalent base in mitochondria
    Kn_m = L_m*1.22*10^(logPn) ;
    Kd1_m = L_m*1.22*10^(logPd1) ;
    Kd2_m = L_m*1.22*10^(logPd2) ;
    an_m = 1 / (1 + 10^(i1*(pKa1-pH_m)) + 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m))) ;
    ad2_m = an_m * 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m)) ;
    ad1_m = an_m * 10^(i1*(pKa1-pH_m)) ;
    Dd2_m = ad2_m / an_m ;
    Dd1_m = ad1_m / an_m ;
    fn_m = 1 / (W_m/gamman_m + Kn_m/gamman_m + Dd2_m*W_m/gammad2_m +
Dd2_m*Kd2_m/gammad2_m ...
            + Dd1_m*W_m/gammad1_m + Dd1_m*Kd1_m/gammad1_m ) ;
    fd2_m = fn_m * Dd2_m ;
    fd1_m = fn_m * Dd1_m ;

    % Lysosomes
    L_l = 0.05+0.1*rand();                                       % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_l = 1-L_l ;                                                % water
fraction in lysosomes
    Is_l = 0.3 ;                                                 % ion
strength in lysosomes (mol)
    Nd2_l = z2*E_l*F/(R*T) ;
    Nd1_l = z1*E_l*F/(R*T) ;
    gamman_l = 10^(0.3*Is_l) ;                                   %
activity coefficient of neutral molecules in lysosomes
    gammad1_l = 10^(-0.5*z1*z1*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of monovalent base in lysosomes
    gammad2_l = 10^(-0.5*z2*z2*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of bivalent base in lysosomes
    Kn_l = L_l*1.22*10^(logPn) ;
    Kd1_l = L_l*1.22*10^(logPd1) ;
    Kd2_l = L_l*1.22*10^(logPd2) ;
```

```matlab
    an_l = 1 / (1 + 10^(i1*(pKa1-pH_l)) + 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l))) ;
    ad2_l = an_l * 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l)) ;
    ad1_l = an_l * 10^(i1*(pKa1-pH_l)) ;
    Dd2_l = ad2_l / an_l ;
    Dd1_l = ad1_l / an_l ;
    fn_l = 1 / (W_l/gamman_l + Kn_l/gamman_l + Dd2_l*W_l/gammad2_l +
Dd2_l*Kd2_l/gammad2_l ...
         + Dd1_l*W_l/gammad1_l + Dd1_l*Kd1_l/gammad1_l ) ;
    fd2_l = fn_l * Dd2_l ;
    fd1_l = fn_l * Dd1_l ;

    % AP Compartment (receiver compartment)
    fn_a = 1 / (1 + 10^(i1*(pKa1-pH_a)) + 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a))) ;
    fd2_a = fn_a * 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a)) ;
    fd1_a = fn_a * 10^(i1*(pKa1-pH_a)) ;
    Nd2_a = z2*(-E_a)*F/(R*T) ;
    Nd1_a = z1*(-E_a)*F/(R*T) ;

    % Solve the differential equation system for each drug:
    % Given a system of linear ODE's expressed in matrix form:
    % Y' = AY+G with initial conditions Y(0) = RR,
        % Ccyto = Y(1)
        k11 = -(A_b/V_c)*Pn*fn_c-
(A_b/V_c)*Pd1*Nd1_b*fd1_c*exp(Nd1_b)/(exp(Nd1_b)-1)-
(A_b/V_c)*Pd2*Nd2_b*fd2_c*exp(Nd2_b)/(exp(Nd2_b)-1)...
                -(A_m/V_c)*Pn*fn_c-(A_m/V_c)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)-
(A_m/V_c)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1)...
                -(A_l/V_c)*Pn*fn_c-(A_l/V_c)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)-
(A_l/V_c)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1)...
                -(A_a/V_c)*Pn*fn_c-(A_a/V_c)*Pd1*Nd1_a*fd1_c/(exp(Nd1_a)-1)-
(A_a/V_c)*Pd2*Nd2_a*fd2_c/(exp(Nd2_a)-1) ;
        k12 =
(A_m/V_c)*Pn*fn_m+(A_m/V_c)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-
1)+(A_m/V_c)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1);
        k13 =
(A_l/V_c)*Pn*fn_l+(A_l/V_c)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-
1)+(A_l/V_c)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1);
        k14 =
(A_a/V_c)*Pn*fn_a+(A_a/V_c)*Pd1*Nd1_a*fd1_a*exp(Nd1_a)/(exp(Nd1_a)-
1)+(A_a/V_c)*Pd2*Nd2_a*fd2_a*exp(Nd2_a)/(exp(Nd2_a)-1);
        S1 = (A_b/V_c)*C_b*(Pn*fn_b+Pd1*Nd1_b*fd1_b/(exp(Nd1_b)-
1)+Pd2*Nd2_b*fd2_b/(exp(Nd2_b)-1)) ;

        % Cmito = Y(2)
        k21 = (A_m/V_m)*Pn*fn_c+(A_m/V_m)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
                +(A_m/V_m)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1) ;
        k22 = -(A_m/V_m)*Pn*fn_m-
(A_m/V_m)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
                -(A_m/V_m)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1) ;
        k23 = 0;
        k24 = 0 ;
        S2 = 0;

        % Clyso = Y(3)
        k31 = (A_l/V_l)*Pn*fn_c+(A_l/V_l)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
                +(A_l/V_l)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1) ;
        k32 = 0;
```

```
        k33 = -(A_l/V_l)*Pn*fn_l-
(A_l/V_l)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
            -(A_l/V_l)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1) ;
        k34 = 0 ;
        S3 = 0;


        % Cap = Y(4)
        k41 = (A_a/V_a)*Pn*fn_c+(A_a/V_a)*Pd1*Nd1_a*fd1_c/(exp(Nd1_a)-1)...
            +(A_a/V_a)*Pd2*Nd2_a*fd2_c/(exp(Nd2_a)-1) ;
        k42 = 0;
        k43 = 0;
        k44 = -(A_a/V_a)*Pn*fn_a-
(A_a/V_a)*Pd1*Nd1_a*fd1_a*exp(Nd1_a)/(exp(Nd1_a)-1)...
            -(A_a/V_a)*Pd2*Nd2_a*fd2_a*exp(Nd2_a)/(exp(Nd2_a)-1);
        S4 = 0;

        A = [k11, k12, k13, k14; k21, k22, k23, k24; k31, k32, k33, k34; k41,
k42, k43, k44];
        G = [S1, S2, S3, S4]';
        RR = [0,0,0,0]';
        t = 300;


        [V,E] = eig(A);
        E = diag(E);
        H = inv(V)*G;
        B = V \ RR;
        C = B + H./E;
        Z = -(H./E) + exp(t * E).*C ;
        Y = real(V * Z);
        Y = Y' ;

        Ppore = Y(4)*V_a /(t*A_aa*C_b)*10^(2)*10^6 ;                    %
Pcell, 10^(-6)cm/sec
        Peff = Y(4)*V_a*CellNo/(t*A_insert*C_b)*10^(2)*10^6;           %
Peff, 10^(-6)cm/sec, normalized by insert area, which is 1.12 cm^2
        Mass_cell = (Y(1)*V_c + Y(2)*V_m + Y(3)*V_l)*10^12 ;           %
cellular mass, pmol/cell
        dMdt = Y(4)*V_a/t*10^12;                                       %
transport rate: pmol/sec/cell

    Para(i,:) = [A_a*10^12,PoreNo_cell,
A_l*10^12,A_m*10^12,A_b*10^12,V_c*10^18,V_l*10^18,V_m*10^18,V_a*10^6,E_a*1000,E_
l*1000,E_m*1000,E_b*1000,...
                    pH_a,pH_c,pH_l,pH_m,pH_b,CellNo,PoreDens,
pKa1,pKa2,logPn,logPd1, logPd2];
    Results(i,:)=[Y(1),Y(2),Y(3),Ppore, Peff, dMdt, Mass_cell];

end

comb = [Results(:,1:7),Para];
fid5 = fopen('BtoA_pH74_04um_5min.dat','w');
fprintf(fid5,'%12.4e %12.4e %12.4e %12.4e %12.4e  %12.4e %12.4e %12.2e %12.0f %1
2.4e %12.4e %12.4e  %12.4e %12.4e %12.4e %12.4e %12.4f %12.4f %12.4f %12.4f %12.
2f %12.2f %12.2f %12.2f %12.2f %12.0f %12.0f %12.2f %12.2f %12.2f %12.2f %12.2f
\n', comb') ;
```

```matlab
fclose(fid5);

figure(25) ; clf ; hold on ;
grid on;
hist (log10(comb(:,4)),1000);
line([log10(Ppore_exp), log10(Ppore_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{cell}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
xlim([0, 6]);
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of cell
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(26) ; clf ; hold on ;
grid on;
hist (log10(comb(:,5)),1000);
xlim([-3, 3]);
line([log10(Peff_exp), log10(Peff_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{app}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of apparent
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(27) ; clf ; hold on ;
grid on;
hist (log10(comb(:,6)),1000);
xlim([-8,-2]);
line([log10(dMdt_exp), log10(dMdt_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (dM/dt,
pmol/sec/cell)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of transport
rate','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(28) ; clf ; hold on ;
grid on;
hist (log10(comb(:,7)),1000);
xlim([-5,-0]);
line([log10(IntraMass_exp),
log10(IntraMass_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (intracellular mass, pmol/cell)
','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
```

```matlab
title ('histogram of intracellular
mass','FontSize',30,'FontWeight','Bold','FontName','Times') ;




% ==========================Case# 8: BL->AP transport, pHb = 7.4,   3um-membrane,
5min========================================

clear ;                    % Clear the memory
z1 = 1 ;                   % ionization group 1 of CQ
z2 = 2 ;                   % ionization group 2 of CQ
i1 = sign(z1) ;
i2 = sign(z2) ;

T = 310.15 ;               % temperature
R = 8.314 ;                % universal gas constant
F = 96484.56 ;             % faraday constant
C_b = 1 ;                  % initial drug concentration (mM)

sim = 10000;               % number of simulations
paraNo = 25;
outputNo = 7;              % number of output parameters
Para = zeros(sim,paraNo);
Results = zeros(sim,outputNo);

dMdt_exp = 6.38e-5;           % +/- 1.59e-5, pmol/sec/cell, measured after 4hrs
Ppore_exp = 1.14E+02;         % +/- 19, 10^(-6) cm/sec, measured after 4hrs
Peff_exp = 1.62E+01;          % +/- 2.69, 10^(-6) cm/sec, measured after 4hrs
IntraMass_exp = 0.01177;      % +/- 0.00190, pmol/cell, measured after 5min

for i = 1:sim

    % Drug information -- ChemAxon calculation including logPn, pKa1, and pKa2
    logPn = 3.93-0.5+rand();    % unif [3.43, 4.43] ;
    pKa1 = 9.96-0.5+rand();     % unif [9.46, 10.46] ;
    pKa2 = 7.47-0.5+rand();     % unif [6.97, 7.97] ;
    logPd1 = 0.43-0.5+rand();   % unif [-0.07, 0.93] ;
    logPd2 = -0.91-0.5+rand();  % unif [-1.41, 0.41] ;
    Pn = 10^(logPn-6.7);
    Pd1 = 10^(logPd1-6.7);
    Pd2 = 10^(logPd2-6.7);


    CellNo = 2*10^5*(1+rand());                              % cell
number/insert: unif [2*10^5, 4*10^5]
    PoreDens = 2*10^6*0.4*(2+rand());                        % pore
number/cm^2: unif [1.6*10^6, 2.4*10^6]
    A_insert = 1.12*10^(-4) ;                                % insert area:
1.12 cm^2
    PoreNo_insert = PoreDens*A_insert*10^(4);                % pore
number/insert
    PoreNo_cell = PoreNo_insert/CellNo ;                     % average pore
number/cell
    A_pore_insert = 3.14*((3/2)*10^(-6))^2*PoreNo_insert ;   % pore area /
insert (m^2)
    A_pore_cell = 3.14*((3/2)*10^(-6))^2*PoreNo_cell ;       % average pore
area / cell (m^2)
```

```
    A_a = 10^(-10)*(1+9*rand());                              % apical
membrane surface area: unif [10^(-10),10*(10)^(-10))] (m^2)
    A_aa = A_pore_cell;                                       % pore area/cell
(m^2)
    A_b = A_aa+(10^(-10)-A_aa)*rand();                        % basolateral
membrane surface area: unif [A_aa, 10^(-10))] (m^2)
    A_l = 100*3.14*10^(-12);                                  % lysosomal
membrane surface area (m^2)
    A_m = 100*3.14*10^(-12);                                  % mitochondrial
membrane surface area (m^2)
    V_c = 0.5*10^(-15)*(1+5*rand());                          % cytosolic
volume: unif [0.5*10^(-15), 3*10^(-15)] (m^3)
    V_l = 10^(-18)*(9.24+(23.8-9.24)*rand());                % lysosomal
volume: unif [9.24*10^(-18), 23.8*10^(-18)] (m^3)
    V_m = 100*5.24*10^(-19)/5*(1+24*rand());                 % mitochondrial
volume: unif [10.48*10^(-18), 262*10^(-18)](m^3)
    V_a = 0.5*10^(-6);                                       % apical volume:
0.5 mL

    % Membrane potential (unit in 'Voltage')
    E_a = 0.0093-0.005+0.01*rand();                          % apical
membrane potential: unif [0.0043, 0.0143]
    E_l = 0.01-0.005+0.01*rand();                            % lysosomal
membrane potential: unif [0.005, 0.015]
    E_m = -0.16 ;                                            % mitochondrial
membrane potential
    E_b = -0.0119-0.005+0.01*rand();                         % basolateral
membrane potential: unif [-0.0169, -0.0069]

    % pH values
    pH_a = 7.4;                                              % pH in apical
compartment
    pH_c = 7.0+0.4*rand();                                   % pH in cytosol:
unif [7.0, 7.4]
    pH_l = 4.8+0.4*rand();                                   % pH in
lysosomes: unif [4.8, 5.2]
    pH_m = 7.8+0.4*rand();                                   % pH in
mitochondria: unif[7.8, 8.2]
    pH_b = 7.0+0.4*rand();                                   % pH in
basolateral compartment: unif [7.0, 7.4]

    % BL Compartment (donor)
    fn_b = 1 / (1 + 10^(i1*(pKa1-pH_b)) + 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b))) ;
    fd2_b = fn_b * 10^(i1*(pKa1-pH_b)+i2*(pKa2-pH_b)) ;
    fd1_b = fn_b * 10^(i1*(pKa1-pH_b)) ;
    Nd2_b = z2*E_b*F/(R*T) ;
    Nd1_b = z1*E_b*F/(R*T) ;

    % Cytoplasm
    L_c = 0.05+0.1*rand();                                              % lipid
fraction in cytosol: unif [0.05, 0.15]
    W_c = 1-L_c ;                                                       % water
fraction in cytosol
    Is_c = 0.3 ;                                                        % ion
strength in cytosol (mol)
```

```matlab
    gamman_c = 10^(0.3*Is_c) ;                                              %
activity coefficient of neutral molecules in cytosol
    gammad1_c = 10^(-0.5*z1*z1*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));    %
activity coefficient of monovalent base in cytosol
    gammad2_c = 10^(-0.5*z2*z2*(sqrt(Is_c)/(1+sqrt(Is_c))-0.3*Is_c));    %
activity coefficient of bivalent base in cytosol
    Kn_c = L_c*1.22*10^(logPn) ;
    Kd1_c = L_c*1.22*10^(logPd1) ;
    Kd2_c = L_c*1.22*10^(logPd2) ;
    an_c = 1 / (1 + 10^(i1*(pKa1-pH_c)) + 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c))) ;
    ad2_c = an_c * 10^(i1*(pKa1-pH_c)+i2*(pKa2-pH_c)) ;
    ad1_c = an_c * 10^(i1*(pKa1-pH_c)) ;
    Dd2_c = ad2_c / an_c ;
    Dd1_c = ad1_c / an_c ;
    fn_c = 1 / (W_c/gamman_c + Kn_c/gamman_c + Dd2_c*W_c/gammad2_c +
Dd2_c*Kd2_c/gammad2_c ...
            + Dd1_c*W_c/gammad1_c + Dd1_c*Kd1_c/gammad1_c ) ;
    fd2_c = fn_c * Dd2_c ;
    fd1_c = fn_c * Dd1_c ;

    % Mitochondria
    L_m = 0.05+0.1*rand();                                         % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_m = 1-L_m ;                                                   % water
fraction in mitochondria
    Is_m = 0.3 ;                                                    % ion
strength in mitochondria (mol)
    Nd2_m = z2*E_m*F/(R*T) ;
    Nd1_m = z1*E_m*F/(R*T) ;
    gamman_m = 10^(0.3*Is_m) ;                                      %
activity coefficient of neutral molecules in mitochondria
    gammad1_m = 10^(-0.5*z1*z1*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));    %
activity coefficient of monovalent base in mitochondria
    gammad2_m = 10^(-0.5*z2*z2*(sqrt(Is_m)/(1+sqrt(Is_m))-0.3*Is_m));    %
activity coefficient of bivalent base in mitochondria
    Kn_m = L_m*1.22*10^(logPn) ;
    Kd1_m = L_m*1.22*10^(logPd1) ;
    Kd2_m = L_m*1.22*10^(logPd2) ;
    an_m = 1 / (1 + 10^(i1*(pKa1-pH_m)) + 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m))) ;
    ad2_m = an_m * 10^(i1*(pKa1-pH_m)+i2*(pKa2-pH_m)) ;
    ad1_m = an_m * 10^(i1*(pKa1-pH_m)) ;
    Dd2_m = ad2_m / an_m ;
    Dd1_m = ad1_m / an_m ;
    fn_m = 1 / (W_m/gamman_m + Kn_m/gamman_m + Dd2_m*W_m/gammad2_m +
Dd2_m*Kd2_m/gammad2_m ...
            + Dd1_m*W_m/gammad1_m + Dd1_m*Kd1_m/gammad1_m ) ;
    fd2_m = fn_m * Dd2_m ;
    fd1_m = fn_m * Dd1_m ;

    % Lysosomes
    L_l = 0.05+0.1*rand();                                         % lipid
fraction in mitochondria: unif [0.05, 0.15]
    W_l = 1-L_l ;                                                   % water
fraction in lysosomes
    Is_l = 0.3 ;                                                    % ion
strength in lysosomes (mol)
    Nd2_l = z2*E_l*F/(R*T) ;
```

```
    Nd1_l = z1*E_l*F/(R*T) ;
    gamman_l = 10^(0.3*Is_l) ;                                          %
activity coefficient of neutral molecules in lysosomes
    gammad1_l = 10^(-0.5*z1*z1*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of monovalent base in lysosomes
    gammad2_l = 10^(-0.5*z2*z2*(sqrt(Is_l)/(1+sqrt(Is_l))-0.3*Is_l));   %
activity coefficient of bivalent base in lysosomes
    Kn_l = L_l*1.22*10^(logPn) ;
    Kd1_l = L_l*1.22*10^(logPd1) ;
    Kd2_l = L_l*1.22*10^(logPd2) ;
    an_l = 1 / (1 + 10^(i1*(pKa1-pH_l)) + 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l))) ;
    ad2_l = an_l * 10^(i1*(pKa1-pH_l)+i2*(pKa2-pH_l)) ;
    ad1_l = an_l * 10^(i1*(pKa1-pH_l)) ;
    Dd2_l = ad2_l / an_l ;
    Dd1_l = ad1_l / an_l ;
    fn_l = 1 / (W_l/gamman_l + Kn_l/gamman_l + Dd2_l*W_l/gammad2_l +
Dd2_l*Kd2_l/gammad2_l ...
            + Dd1_l*W_l/gammad1_l + Dd1_l*Kd1_l/gammad1_l ) ;
    fd2_l = fn_l * Dd2_l ;
    fd1_l = fn_l * Dd1_l ;

    % AP Compartment (receiver compartment)
    fn_a = 1 / (1 + 10^(i1*(pKa1-pH_a)) + 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a))) ;
    fd2_a = fn_a * 10^(i1*(pKa1-pH_a)+i2*(pKa2-pH_a)) ;
    fd1_a = fn_a * 10^(i1*(pKa1-pH_a)) ;
    Nd2_a = z2*(-E_a)*F/(R*T) ;
    Nd1_a = z1*(-E_a)*F/(R*T) ;

    % Solve the differential equation system for each drug:
    % Given a system of linear ODE's expressed in matrix form:
    % Y' = AY+G with initial conditions Y(0) = RR,
        % Ccyto = Y(1)
        k11 = -(A_b/V_c)*Pn*fn_c-
(A_b/V_c)*Pd1*Nd1_b*fd1_c*exp(Nd1_b)/(exp(Nd1_b)-1)-
(A_b/V_c)*Pd2*Nd2_b*fd2_c*exp(Nd2_b)/(exp(Nd2_b)-1)...
            -(A_m/V_c)*Pn*fn_c-(A_m/V_c)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)-
(A_m/V_c)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1)...
            -(A_l/V_c)*Pn*fn_c-(A_l/V_c)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)-
(A_l/V_c)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1)...
            -(A_a/V_c)*Pn*fn_c-(A_a/V_c)*Pd1*Nd1_a*fd1_c/(exp(Nd1_a)-1)-
(A_a/V_c)*Pd2*Nd2_a*fd2_c/(exp(Nd2_a)-1) ;
        k12 =
(A_m/V_c)*Pn*fn_m+(A_m/V_c)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-
1)+(A_m/V_c)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1);
        k13 =
(A_l/V_c)*Pn*fn_l+(A_l/V_c)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-
1)+(A_l/V_c)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1);
        k14 =
(A_a/V_c)*Pn*fn_a+(A_a/V_c)*Pd1*Nd1_a*fd1_a*exp(Nd1_a)/(exp(Nd1_a)-
1)+(A_a/V_c)*Pd2*Nd2_a*fd2_a*exp(Nd2_a)/(exp(Nd2_a)-1);
        S1 = (A_b/V_c)*C_b*(Pn*fn_b+Pd1*Nd1_b*fd1_b/(exp(Nd1_b)-
1)+Pd2*Nd2_b*fd2_b/(exp(Nd2_b)-1)) ;

        % Cmito = Y(2)
        k21 = (A_m/V_m)*Pn*fn_c+(A_m/V_m)*Pd1*Nd1_m*fd1_c/(exp(Nd1_m)-1)...
            +(A_m/V_m)*Pd2*Nd2_m*fd2_c/(exp(Nd2_m)-1) ;
```

```
        k22 = -(A_m/V_m)*Pn*fn_m-
(A_m/V_m)*Pd1*Nd1_m*fd1_m*exp(Nd1_m)/(exp(Nd1_m)-1)...
            -(A_m/V_m)*Pd2*Nd2_m*fd2_m*exp(Nd2_m)/(exp(Nd2_m)-1) ;
        k23 = 0;
        k24 = 0 ;
        S2 = 0;

        % Clyso = Y(3)
        k31 = (A_l/V_l)*Pn*fn_c+(A_l/V_l)*Pd1*Nd1_l*fd1_c/(exp(Nd1_l)-1)...
            +(A_l/V_l)*Pd2*Nd2_l*fd2_c/(exp(Nd2_l)-1) ;
        k32 = 0;
        k33 = -(A_l/V_l)*Pn*fn_l-
(A_l/V_l)*Pd1*Nd1_l*fd1_l*exp(Nd1_l)/(exp(Nd1_l)-1)...
            -(A_l/V_l)*Pd2*Nd2_l*fd2_l*exp(Nd2_l)/(exp(Nd2_l)-1) ;
        k34 = 0 ;
        S3 = 0;


        % Cap = Y(4)
        k41 = (A_a/V_a)*Pn*fn_c+(A_a/V_a)*Pd1*Nd1_a*fd1_c/(exp(Nd1_a)-1)...
            +(A_a/V_a)*Pd2*Nd2_a*fd2_c/(exp(Nd2_a)-1) ;
        k42 = 0;
        k43 = 0;
        k44 = -(A_a/V_a)*Pn*fn_a-
(A_a/V_a)*Pd1*Nd1_a*fd1_a*exp(Nd1_a)/(exp(Nd1_a)-1)...
            -(A_a/V_a)*Pd2*Nd2_a*fd2_a*exp(Nd2_a)/(exp(Nd2_a)-1);
        S4 = 0;

        A = [k11, k12, k13, k14; k21, k22, k23, k24; k31, k32, k33, k34; k41,
k42, k43, k44];
        G = [S1, S2, S3, S4]';
        RR = [0,0,0,0]';
        t = 300;



        [V,E] = eig(A);
        E = diag(E);
        H = inv(V)*G;
        B = V \ RR;
        C = B + H./E;
        Z = -(H./E) + exp(t * E).*C ;
        Y = real(V * Z);
        Y = Y' ;


        Ppore = Y(4)*V_a /(t*A_aa*C_b)*10^(2)*10^6 ;                      %
Pcell, 10^(-6)cm/sec
        Peff = Y(4)*V_a*CellNo/(t*A_insert*C_b)*10^(2)*10^6;             %
Peff, 10^(-6)cm/sec, normalized by insert area, which is 1.12 cm^2
        Mass_cell = (Y(1)*V_c + Y(2)*V_m + Y(3)*V_l)*10^12 ;            %
cellular mass, pmol/cell
        dMdt = Y(4)*V_a/t*10^12;                                        %
transport rate: pmol/sec/cell
```

```
    Para(i,:) = [A_a*10^12,PoreNo_cell,
A_l*10^12,A_m*10^12,A_b*10^12,V_c*10^18,V_l*10^18,V_m*10^18,V_a*10^6,E_a*1000,E_
l*1000,E_m*1000,E_b*1000,...
                    pH_a,pH_c,pH_l,pH_m,pH_b,CellNo,PoreDens,
pKa1,pKa2,logPn,logPd1, logPd2];
    Results(i,:)=[Y(1),Y(2),Y(3),Ppore, Peff, dMdt, Mass_cell];

end

comb = [Results(:,1:7),Para];
fid5 = fopen('BtoA_pH74_3um_5min.dat','w');
fprintf(fid5,'%12.4e %12.4e %12.4e %12.4e %12.4e  %12.4e %12.4e %12.2e %12.0f %1
2.4e %12.4e %12.4e  %12.4e %12.4e %12.4e %12.4e %12.4f %12.4f %12.4f %12.4f %12.
2f %12.2f %12.2f %12.2f %12.2f %12.0f %12.0f %12.2f %12.2f %12.2f %12.2f %12.2f
\n', comb') ;
fclose(fid5);

figure(29) ; clf ; hold on ;
grid on;
hist (log10(comb(:,4)),1000);
line([log10(Ppore_exp), log10(Ppore_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{cell}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
xlim([0, 6]);
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of cell
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(30) ; clf ; hold on ;
grid on;
hist (log10(comb(:,5)),1000);
xlim([-3, 3]);
line([log10(Peff_exp), log10(Peff_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (P_{app}, 10^{-6}
cm/sec)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of apparent
permeability','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(31) ; clf ; hold on ;
grid on;
hist (log10(comb(:,6)),1000);
xlim([-8,-2]);
line([log10(dMdt_exp), log10(dMdt_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (dM/dt,
pmol/sec/cell)','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
```

```
title ('histogram of transport
rate','FontSize',30,'FontWeight','Bold','FontName','Times') ;

figure(32) ; clf ; hold on ;
grid on;
hist (log10(comb(:,7)),1000);
xlim([-5,-0]);
line([log10(IntraMass_exp),
log10(IntraMass_exp)],[0,50],'Color','r','LineWidth',3);
xlabel('log_{10} (intracellular mass, pmol/cell)
','FontSize',30,'FontWeight','Bold','FontName','Times');
ax1 = gca;
set(get(ax1,'Ylabel'),'String','Frequency','FontSize',30,'FontWeight','Bold','Fo
ntName','Times') ;
set(ax1,'LineWidth',2.0,'FontSize',30,'FontWeight','Bold','FontName','Times') ;
title ('histogram of intracellular
mass','FontSize',30,'FontWeight','Bold','FontName','Times') ;
```