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% This script is to perform Monte Carlo simulations for 1CellPK
% This script includes the following situations (for figure 6):

% Case#19: AP->BL transport, pHa = 7.4, 0.4um-membrane, 4hrs, with lysosomal
swelling and lysosomal pH change, initial concentration = 50uM
% Case#20: AP->BL transport, pHa = 7.4, 3um-membrane, 4hrs, with lysosomal
swelling and lysosomal pH change, initial concentration = 50uM

% ====Case#19: AP->BL transport, pHa = 7.4, 0.4um-membrane, 4hrs, with lysosomal
swelling and lysosomal pH change, initial concentration = 50uM
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 = 0.05 ; % 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 = 0.0195; % calculated from regression line (figure 3c)

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

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    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)*(196.5+(906.3-196.5)*rand());    % lysosomal
volume: unif [196.5*10^(-18), 906.3*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 = 4.63+(6.37-4.63)*rand() ;    % pH in
lysosomes: unif [4.63, 6.37]
    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]

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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]

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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 ;

% Basolateral 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)) ;

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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 = 4*3600 ; % time in sec (4hrs)

[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,...

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        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_4hrs_swell.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 %12.4e %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') ;
title ('histogram of transport
rate', 'FontSize', 30, 'FontWeight', 'Bold', 'FontName', 'Times') ;

figure(4) ; clf ; hold on ;

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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', 'FontName', 'Times') ;
set(ax1, 'LineWidth', 2.0, 'FontSize', 30, 'FontWeight', 'Bold', 'FontName', 'Times') ;
title ('histogram of intracellular
mass', 'FontSize', 30, 'FontWeight', 'Bold', 'FontName', 'Times') ;

% ===Case#20: AP->BL transport, pHa = 7.4, 3um-membrane, 4hrs, with lysosomal
swelling and lysosomal pH change, initial concentration = 50uM
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 = 0.05 ; % 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 = 0.0107; % calculated from regression line (figure 3c)

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]

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    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)*(196.5+(906.3-196.5)*rand()); % lysosomal
volume: unif [196.5*10^(-18), 906.3*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 = 4.63+(6.37-4.63)*rand() ; % pH in
lysosomes: unif [4.63, 6.37]
    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) ;

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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 ;

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% Lysosomes
L_1 = 0.05+0.1*rand(); % lipid
fraction in mitochondria: unif [0.05, 0.15]
W_1 = 1-L_1 ; % water
fraction in lysosomes
Is_1 = 0.3 ; % ion
strength in lysosomes (mol)
Nd2_1 = z2*E_1*F/(R*T) ;
Nd1_1 = z1*E_1*F/(R*T) ;
gamman_1 = 10^(0.3*Is_1) ; %
activity coefficient of neutral molecules in lysosomes
gammad1_1 = 10^(-0.5*z1*z1*(sqrt(Is_1)/(1+sqrt(Is_1))-0.3*Is_1)); %
activity coefficient of monovalent base in lysosomes
gammad2_1 = 10^(-0.5*z2*z2*(sqrt(Is_1)/(1+sqrt(Is_1))-0.3*Is_1)); %
activity coefficient of bivalent base in lysosomes
Kn_1 = L_1*1.22*10^(logPn) ;
Kd1_1 = L_1*1.22*10^(logPd1) ;
Kd2_1 = L_1*1.22*10^(logPd2) ;
an_1 = 1 / (1 + 10^(i1*(pKa1-pH_1)) + 10^(i1*(pKa1-pH_1)+i2*(pKa2-pH_1))) ;
ad2_1 = an_1 * 10^(i1*(pKa1-pH_1)+i2*(pKa2-pH_1)) ;
ad1_1 = an_1 * 10^(i1*(pKa1-pH_1)) ;
Dd2_1 = ad2_1 / an_1 ;
Dd1_1 = ad1_1 / an_1 ;
fn_1 = 1 / (W_1/gamman_1 + Kn_1/gamman_1 + Dd2_1*W_1/gammad2_1 +
Dd2_1*Kd2_1/gammad2_1 ...
+ Dd1_1*W_1/gammad1_1 + Dd1_1*Kd1_1/gammad1_1 ) ;
fd2_1 = fn_1 * Dd2_1 ;
fd1_1 = fn_1 * Dd1_1 ;

% Basolateral 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)...

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+ (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 = 4*3600 ; % time in sec (4hrs)

[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_pH74_3um_4hrs.swell.dat','w');
fprintf(fid5,'%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 %12.4f %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
\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') ;

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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') ;
```