

Supplementary Information

Translational Modeling of Chloroquine and Hydroxychloroquine Dosimetry in Human Airways for Treating Viral Respiratory Infections

Aditya R. Kolli, Florian Calvinio-Martin, Julia Hoeng

PMI R&D, Philip Morris Products S.A., Quai Jeanrenaud 5, CH-2000 Neuchâtel, Switzerland

Corresponding author:

Aditya R. Kolli

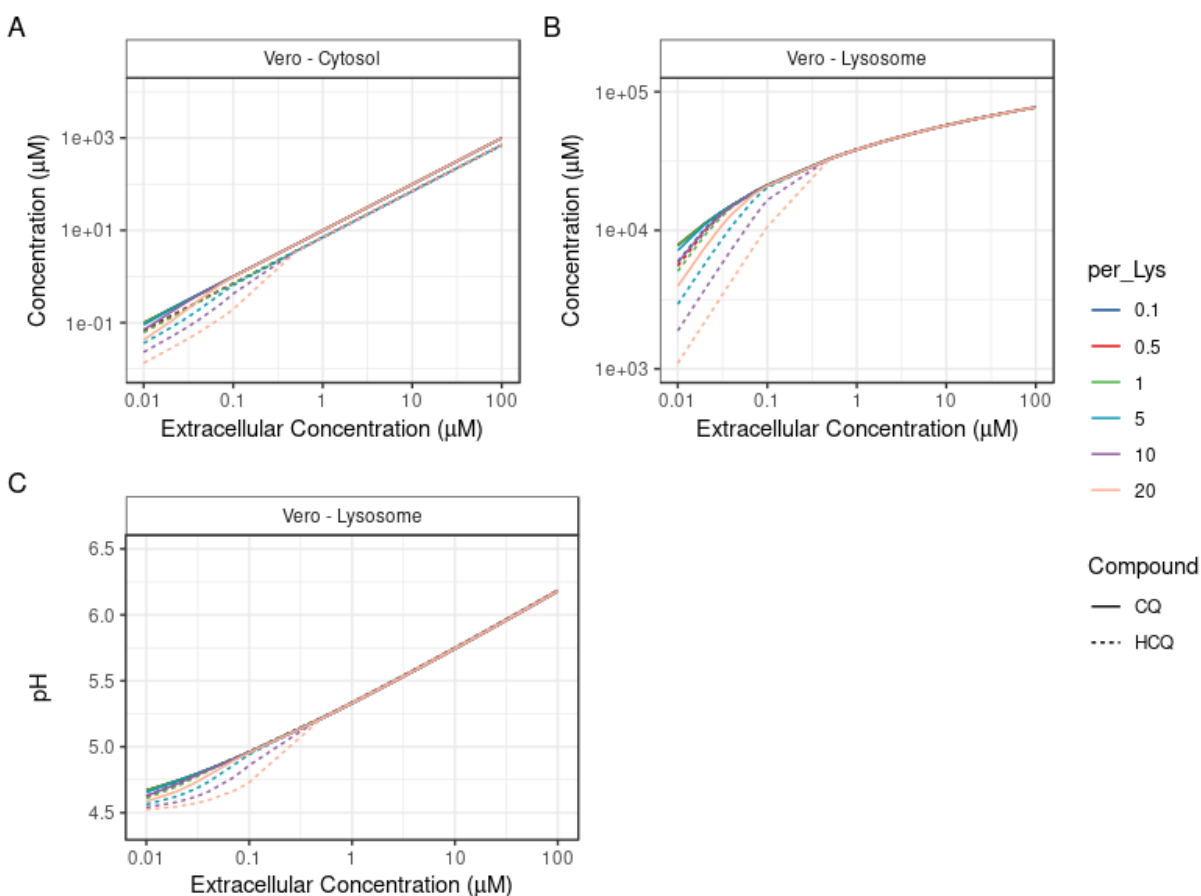
PMI R&D, Philip Morris Products S.A.

Quai Jeanrenaud 5, CH-2000 Neuchâtel, Switzerland

Tel: +41 (58) 242-2837

Email: AdityaReddy.Kolli@pmi.com

15 Supplemental Figures



16

17 Figure S1: Influence of different lysosomal volumes (based on cellular volume) on changes in the cytosolic and

18 lysosomal levels of CQ and HCQ at 48 h post-exposure to different extracellular concentrations of the drugs. The

19 initial lysosomal pH was 4.5. per_Lys, percent lysosomal volume.

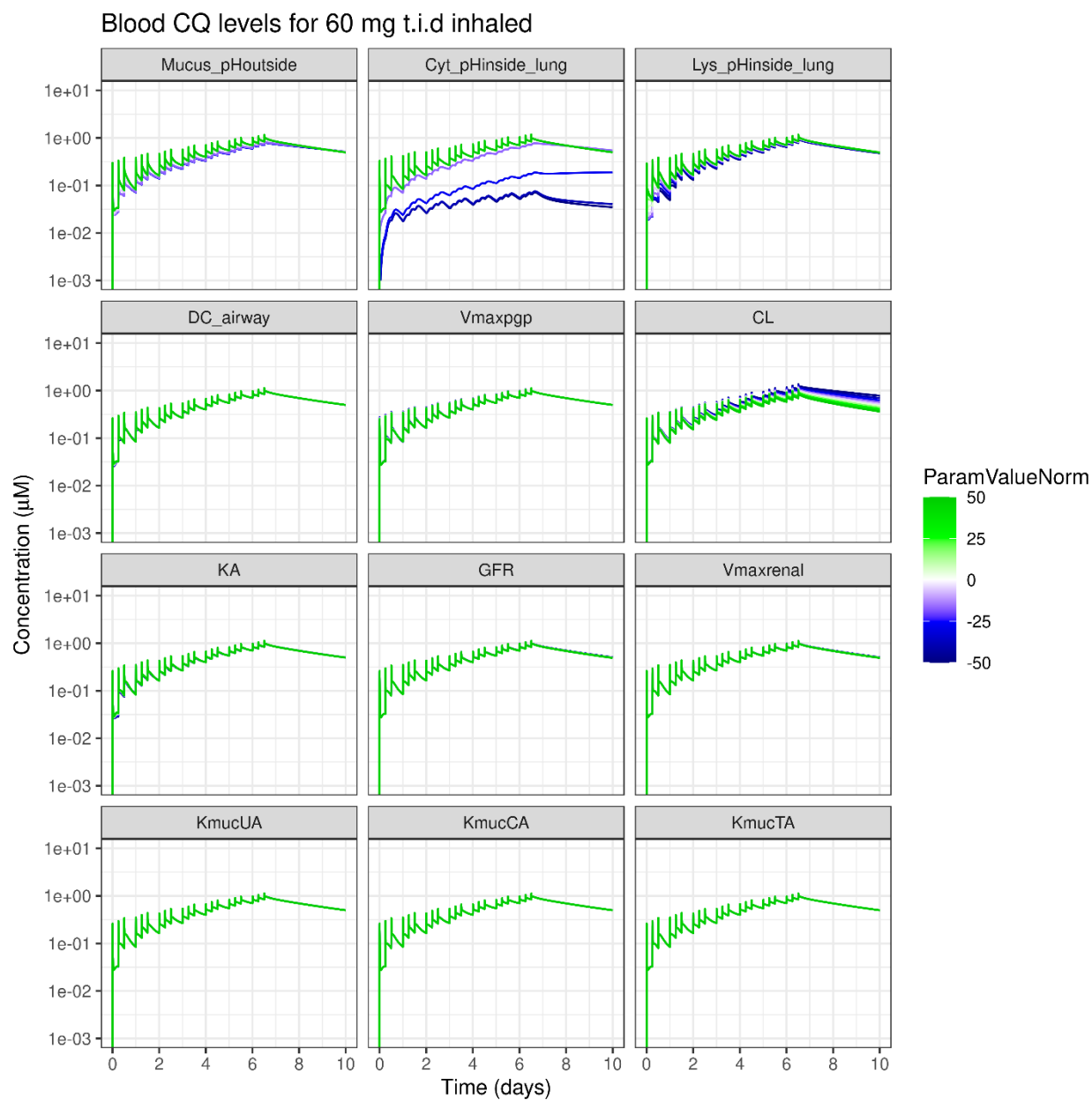


Figure S2: Influence of PBPK model parameters on systemic concentrations for 60 mg of inhaled CQ with a t.i.d dosing regimen. ParamValueNorm, is the percent change in PBPK model parameter from the nominal value.

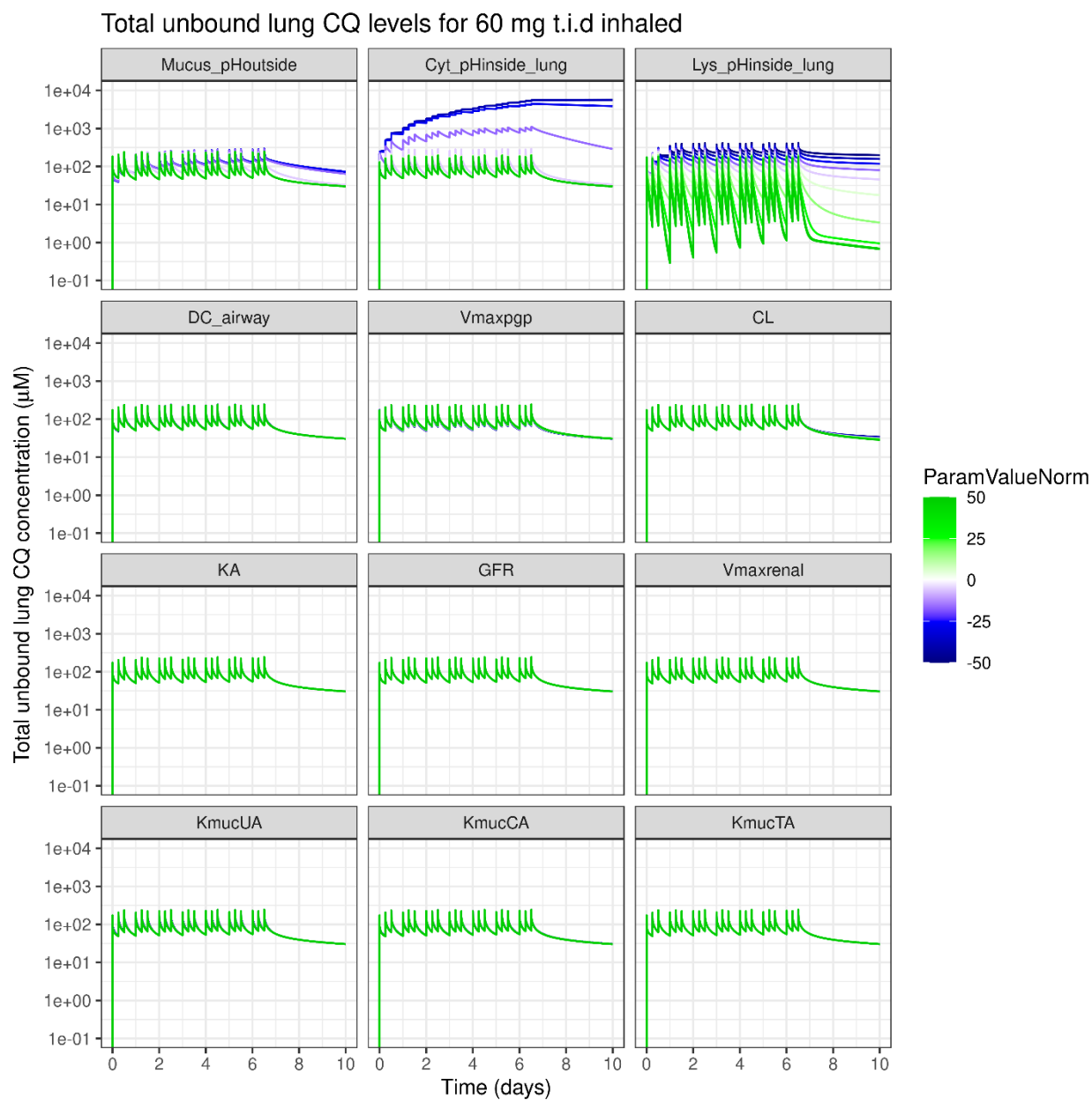


Figure S3: Influence of PBPK model parameters on total unbound lung concentrations for 60 mg of inhaled CQ with a t.i.d dosing regimen. ParamValueNorm, is the percent change in PBPK model parameter from the nominal value.

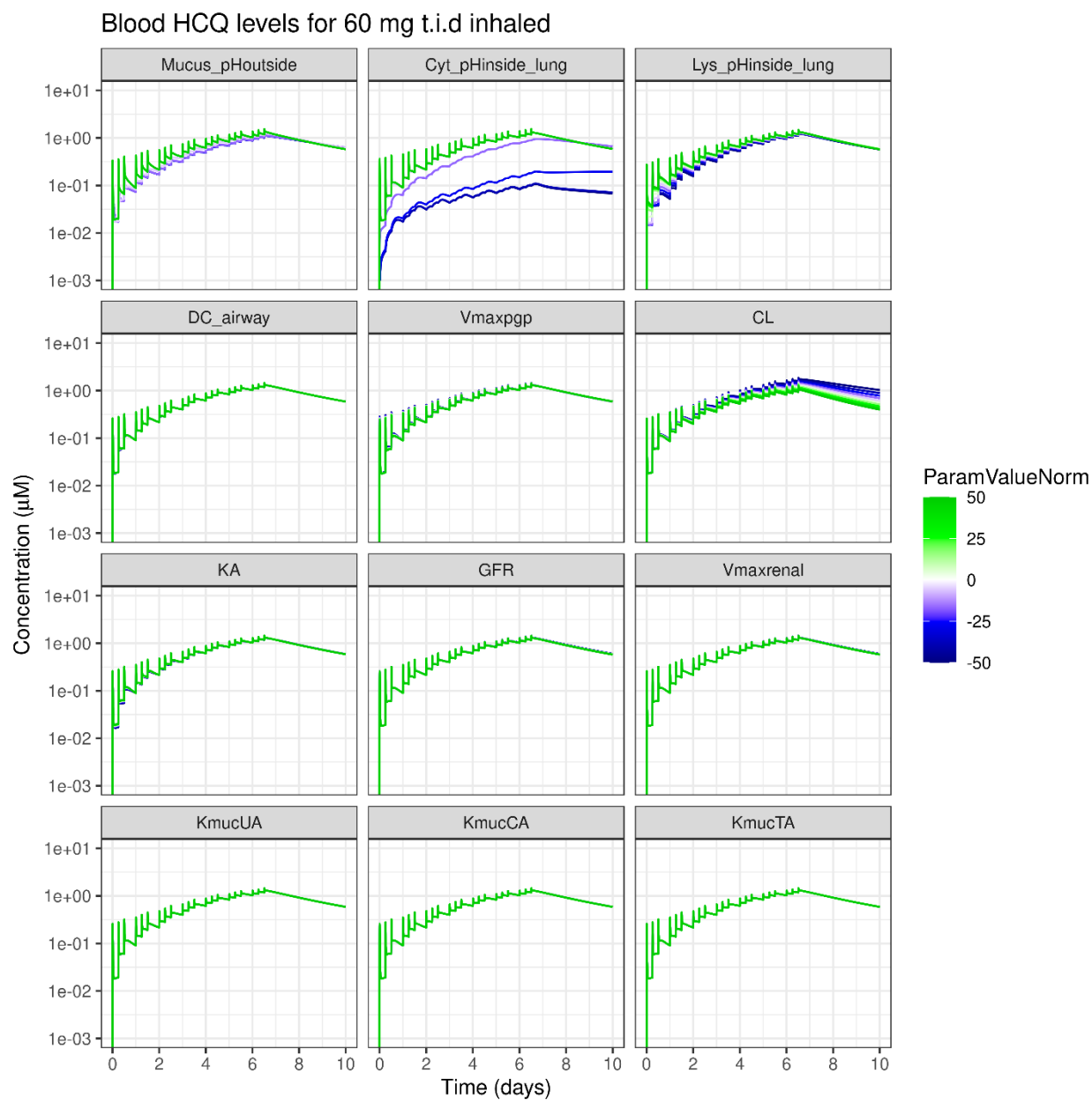


Figure S4: Influence of PBPK model parameters on systemic concentrations for 60 mg of inhaled HCQ with a t.i.d dosing regimen. ParamValueNorm, is the percent change in PBPK model parameter from the nominal value.

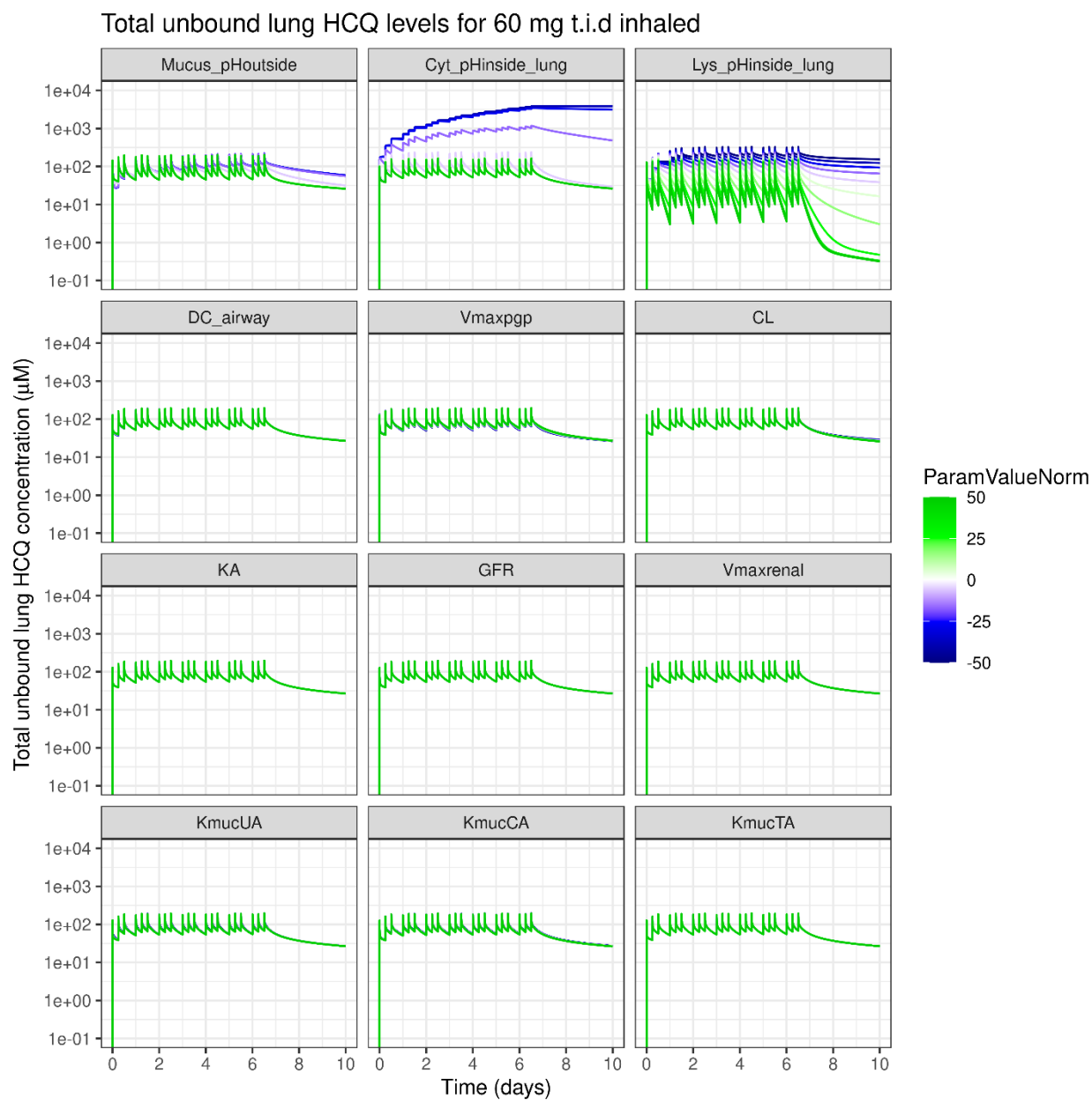


Figure S5: Influence of PBPK model parameters on total unbound lung concentrations for 60 mg of inhaled HCQ with a t.i.d dosing regimen. ParamValueNorm, is the percent change in PBPK model parameter from the nominal value.

33 **Model Code**

```

34  #=====
35                                     Model for Isolated Rat Hepatocytes
36  #=====
37
38  code <- '
39  $PROB
40  Author      : ARK
41  Affiliation  : PMI R&D
42  Date        : May 2020
43  Description  : Isolated Rat Hepatocyte Model
44
45  $SET
46  delta= 0, atol= 0, rtol=0, maxsteps=0,
47
48  $PARAM
49  MW = 0, logKow = 0,
50  pKa1 = 0, valency1 = 1, i1 = 1,
51  pKa2 = 0, valency2 = 2, i2 = 1,
52  Faraday = 0,
53  R = 0,
54  Temp = 0,
55  pn = 0,
56  pnz = 0,
57  Vol_Ext = 0,
58  Pkd_Volume = 0,
59  Lys_fraction = 0,
60  Cyt_Diameter = 0,
61  Cyt_pHinside = 0,
62  Cyt_pHoutside = 0,
63  Cyt_lipid= 0,
64  Cyt_water = 0,
65  Cyt_Ionstrength = 0,
66  Cyt_E = 0,
67  Lys_Diameter = 0,
68  Lys_pHinside = 0,
69  Lys_pHoutside = 0,
70  Lys_lipid = 0,
71  Lys_water=0,
72  Lys_Ionstrength = 0,
73  Lys_E = 0,
74  Buff_cap = 0;
75  gamman = 0;
76  gammad1 = 0;
77  gammad2 = 0;
78
79  $MAIN
80  double Vcytosol = (4/3) * 3.14 * pow(Cyt_Diameter/2, 3);
81  double Vlysosome = (4/3) * 3.14 * pow(Lys_Diameter/2, 3);

```

```

82 double Vol_Cyt = (Pkd_Volume/100) * Vol_Ext;
83 double Vol_Lys = (Lys_fraction/100) * Vol_Cyt;
84 double SA_cell = Vol_Cyt/Vcytosol * 4*3.14*pow(Cyt_Diameter/2, 2);
85 double SA_lys = Vol_Lys/Vlysosome * 4*3.14*pow(Lys_Diameter/2, 2);
86 double Kow = pow(10, logKow);
87 double logKowdiss = logKow - (fabs(valency1)) *6.5;
88 double Kowdiss = pow(10, logKowdiss);
89 double logKowdiss2 = logKow - (fabs(valency2)) *6.5;
90 double Kowdiss2 = pow(10, logKowdiss2);
91 double Pn = pow(10, logKow - pn);
92 double Pd1 = pow(10, logKowdiss - pn);
93 double Pd2 = pow(10, logKowdiss2 - pn);
94 // Fractions Outside
95 double fnout = 1/(1+ pow(10, pKa1-Cyt_pHoutside) + pow(10, (pKa1-Cyt_pHoutside)+(pKa2-
96 Cyt_pHoutside)));
97 double fd1out = fnout * pow(10, (pKa1-Cyt_pHoutside)+(pKa2-Cyt_pHoutside));
98 double fd2out = fnout * pow(10, pKa1-Cyt_pHoutside);
99 double D1out = fd1out/fnout;
100 double D2out = fd2out/fnout;
101 //Fractions Cytosol
102 double Kncyt = 1.22 * Cyt_lipid * Kow;
103 double Kd1cyt = 1.22 * Cyt_lipid * Kowdiss;
104 double Kd2cyt = 1.22 * Cyt_lipid * Kowdiss2;
105 double ancyt = 1/(1+ pow(10, pKa1-Cyt_pHinside) + pow(10, (pKa1-Cyt_pHinside)+(pKa2-
106 Cyt_pHinside)));
107 double ad2cyt = ancyt * pow(10, (pKa1-Cyt_pHinside)+(pKa2-Cyt_pHinside));
108 double ad1cyt = ancyt * pow(10, pKa1-Cyt_pHinside);
109 double D1cyt = ad1cyt/ancyt;
110 double D2cyt = ad2cyt/ancyt;
111 double fncyt = 1/(Cyt_water/gamman + Kncyt/gamman + D2cyt*Cyt_water/gammad2 +
112 D2cyt*Kd2cyt/gammad2 + D1cyt*Cyt_water/gammad1 + D1cyt*Kd1cyt/gammad1);
113 double fd1cyt = fncyt * D1cyt;
114 double fd2cyt = fncyt * D2cyt;
115 double Nd1cyt = valency1*Cyt_E*Faraday/(R*Temp);
116 double Nd2cyt = valency2*Cyt_E*Faraday/(R*Temp);
117 double Joutcyt = fnout*Pn + fd2out*Pd2*Nd2cyt/(exp(Nd2cyt)-1) + fd1out*Pd1*Nd1cyt/(exp(Nd1cyt)-
118 1);
119 double Jcytout = fncyt*Pn + fd1cyt*Pd1*exp(Nd1cyt)*Nd1cyt/(exp(Nd1cyt)-1) +
120 fd2cyt*Pd2*exp(Nd2cyt)*Nd2cyt/(exp(Nd2cyt)-1);
121
122 //Fractions Lyosome
123 double Knlys = 1.22 * Lys_lipid * Kow;
124 double Kd1lys = 1.22 * Lys_lipid * Kowdiss;
125 double Kd2lys = 1.22 * Lys_lipid * Kowdiss2;
126 double anlys = 1/(1+ pow(10, pKa1-Lys_pH) + pow(10, (pKa1-Lys_pH)+(pKa2-Lys_pH)));
127 double ad2lys = anlys * pow(10, (pKa1-Lys_pH)+(pKa2-Lys_pH));
128 double ad1lys = anlys * pow(10, pKa1-Lys_pH);
129 double D1lys = ad1lys/anlys;
130 double D2lys = ad2lys/anlys;
131 double fnlys = 1/(Lys_water/gamman + Knlys/gamman + D2lys*Lys_water/gammad2 +
132 D2lys*Kd2lys/gammad2 + D1lys*Lys_water/gammad1 + D1lys*Kd1lys/gammad1);

```



```

133 double fd1lys = fnlys * D1lys;
134 double fd2lys = fnlys * D2lys;
135 double Nd1lys = valency1*Lys_E*Faraday/(R*Temp);
136 double Nd2lys = valency2*Lys_E*Faraday/(R*Temp);
137 double Jcytlys = fncyt*Pn + fd2cyt*Pd2*Nd2lys/(exp(Nd2lys)-1) + fd1cyt*Pd1*Nd1lys/(exp(Nd1lys)-1);
138 double Jlyscyt = fnlys*Pn + fd1lys*Pd1*exp(Nd1lys)*Nd1lys/(exp(Nd1lys)-1) +
139 fd2lys*Pd2*exp(Nd2lys)*Nd2lys/(exp(Nd2lys)-1);
140
141 $CMT
142 Out Cyto Lyso
143
144 $ODE
145 dxdt_Out = 1/Vol_Ext * (-SA_cell * (Joutcyt*Out - Jcytout*Cyto));
146 dxdt_Cyto = 1/(Vol_Cyt-Vol_Lys) * (SA_cell * (Joutcyt*Out - Jcytout*Cyto) - SA_lys * (Jcytlys*Cyto -
147 Jlyscyt*Lyso));
148 dxdt_Lyso = 1/Vol_Lys * (SA_lys * (Jcytlys*Cyto - Jlyscyt*Lyso));
149 double Lys_pH = Lys_pHinside + (Lyso/Buf_fcap);
150 '
151 #####
152                               # END #
153 #####
154
155 #####
156                               Model for cell lines – Vero cell
157 #####
158 code <- '
159 Author      : ARK
160 Affiliation  : PMI R&D
161 Date        : May 2020
162 Description  : Vero cell model
163
164 $SET
165 delta= 0, atol= 0, rtol=0, maxsteps=0,
166
167 $PARAM
168 MW = 0,
169 logKow= 0,
170 pKa1  = 0, valency1 = 1, i1 = 1,
171 pKa2  = 0, valency2 = 2, i2 = 1,
172 Faraday = 0,
173 R = 0,
174 Temp = 0,
175 Cyt_Diameter = 0,
176 Cyt_pHinside = 0,
177 Cyt_pHoutside = 0,
178 Cyt_lipid = 0,
179 Cyt_water = 0,
180 Cyt_Ionstrength = 0,
181 Cyt_E = 0,
182 Lys_Diameter = 0,
183 percLys_Volume = 0,

```

```

184  Lys_pHinside      = 0,
185  Lys_pHoutside     = 0,
186  Lys_lipid         = 0,
187  Lys_water         = 0,
188  Lys_Ionstrength   = 0,
189  Lys_E             = 0,
190  Buff_cap          = 0;
191  pn                = 0,
192  gamman            = 0;
193  gammad1           = 0;
194  gammad2           = 0;
195
196
197  $MAIN
198  double Cyt_area = 4 * 3.14 * pow(Cyt_Diameter/2, 2);
199  double Cyt_Volume = 4/3 * 3.14 * pow(Cyt_Diameter/2, 3);
200  double Lys_Volume1 = 4/3 * 3.14 * pow(Lys_Diameter/2, 3);
201  double Lys_Volume = Cyt_Volume * percLys_Volume/100;
202  double Lys_area = Lys_Volume* (4)*3.14 * pow(Lys_Diameter/2, 2) / Lys_Volume1;
203  double Kow = pow(10, logKow);
204  double logKowdiss = logKow - (fabs(valency1))*6.5;
205  double Kowdiss = pow(10, logKowdiss);
206  double logKowdiss2 = logKow - (fabs(valency2))*6.5;
207  double Kowdiss2 = pow(10, logKowdiss2);
208  double Pn = pow(10, logKow - pn);
209  double Pd1 = pow(10, logKowdiss - pn);
210  double Pd2 = pow(10, logKowdiss2 - pn);
211  double fnout = 1/(1+ pow(10, pKa1-Cyt_pHoutside) + pow(10, (pKa1-Cyt_pHoutside)+(pKa2-
212  Cyt_pHoutside))) ;
213  double fd1out = fnout * pow(10, (pKa1-Cyt_pHoutside)+(pKa2-Cyt_pHoutside));
214  double fd2out = fnout * pow(10, pKa1-Cyt_pHoutside);
215  double D1out = fd1out/fnout;
216  double D2out = fd2out/fnout;
217  double Kncyt = 1.22 * Cyt_lipid * Kow;
218  double Kd1cyt = 1.22 * Cyt_lipid * Kowdiss;
219  double Kd2cyt = 1.22 * Cyt_lipid * Kowdiss2;
220  double ancyt = 1/(1+ pow(10, pKa1-Cyt_pHinside) + pow(10, (pKa1-Cyt_pHinside)+(pKa2-
221  Cyt_pHinside)));
222  double ad2cyt = ancyt * pow(10, (pKa1-Cyt_pHinside)+(pKa2-Cyt_pHinside));
223  double ad1cyt = ancyt * pow(10, pKa1-Cyt_pHinside);
224  double D1cyt = ad1cyt/ancyt;
225  double D2cyt = ad2cyt/ancyt;
226  double fncyt = 1/(Cyt_water/gamman + Kncyt/gamman + D2cyt*Cyt_water/gammad2 +
227  D2cyt*Kd2cyt/gammad2 + D1cyt*Cyt_water/gammad1 + D1cyt*Kd1cyt/gammad1);
228  double fd1cyt = fncyt * D1cyt;
229  double fd2cyt = fncyt * D2cyt;
230  double Nd1cyt = valency1*Cyt_E*Faraday/(R*Temp);
231  double Nd2cyt = valency2*Cyt_E*Faraday/(R*Temp);
232  double Joutcyt = fnout*Pn + fd2out*Pd2*Nd2cyt/(exp(Nd2cyt)-1) + fd1out*Pd1*Nd1cyt/(exp(Nd1cyt)-
233  1);

```

