

Listing 1: Source File for entire Ros/Wnt/beta-catenin model implemented in ML-Rules

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1  /*
2   * single-cell model (number of cells can be easily increased via parameter
3   *   nCells),
4   * no Wnt diffusion in space,
5   * no cell cycle dynamics included,
6   * compartment volumes are fixed,
7   */
8
9  /*
10  compartment volumes:
11
12 membrane: 0.137E-16 m3
13 cytoplasm: 8.73E-16 m3
14 nucleus: 3.55E-16 m3
15 */
16 // ++++++
17 // +++++ initial species counts +++++
18 // ++++++
19
20 // ** Membrane signalling **
21 nWnt: 0;
22 nLRP6: 4000;
23 nCK1y: 5000;
24 nP: 1;
25
26 // ** Ros-Dvl signalling **
27 nRos: 10000;
28 nDvl: 855;
29 nNrx: 18;
30 nDvlNrx: 36200;
31
32 // ** beta-catenin signalling **
33 nbetacyt: 12989;
34 nbetanuc: 5282;
35 nAxin: 252;
36 nAxinP: 219;
37
38 nCells: 1;
39 nLR: 5;
40
41 // ++++++
42 // +++++ reaction rate coefficients +++++
43 // ++++++
44
45 // ** Membrane Signalling **
46
47 // Wnt
48 kWdeg: 0.27;
49 kWsyn: 1.9;
50 kWdelay: 90;
51 kPsyn: 1;

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52 // LRP6
53 kLWntBind:      100;
54 kLWntUnbind:   0.1;
55 kLphos:          6.73E-1;
56 kLdephos:        4.7E-2;
57 kLA_diss:        3E-4;
58
59 kLd: 3.5E4;
60 kLad: 3.5E-4;
61
62 // Lipid Rafts
63 kRin:            1;
64 kRout:           1;
65
66 // ** Ros-Dvl Signalling **
67 kRosSyn:          0;
68 kRosDelay:        0;
69 kRosAct:          7.2E2;
70
71 // Nrx
72 kNrxRos:          5E2;
73 kNrxNo:           2E-2;
74
75 // Dvl
76 kDvlSponAgg:    5E-04;
77 kDvldisAgg:     0.5;
78
79 // Dvl-Nrx
80 kDvlNrxBind:    22.5;
81 kDvlNrxUnbind:  2.3E-2;
82 kDvlNrxRos:     3.2E2;
83
84 // ** beta-catenin signalling **
85
86 // Axin
87 kApA_act:         5;
88 kApA:             0.03;
89 kAAp:             0.03;
90 kAdeg:            4.48E-3;
91
92 kAsyn:            4E-4;
93
94 kDvlAxinBind:   0.075;
95 kDvlAxinUnbind: 6.8E-2;
96
97 //beta catenin
98 kbetasyn:        600;
99 kbetadeg_act:    2.1E-4;
100 kbetadeg:        1.13E-4;
101 kbetain:          0.0549;
102 kbetaout:        0.135;
103
104 // diffusion coefficient
105

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106 D:1;
107
108 // raft fluidity
109 rho:0.1;
110
111 //raft radius
112 radius: 4;
113
114 // threshold wnt production, corresponds to rounded values of those
115 // listed in Figure 3C of main manuscript, e.g. 10.35 -> 11.
116 // used only in validation experiments
117 // epsilonW: 11;
118
119 // ++++++ species definitions (number of attributes) +++++
120 // +++++ species definitions (number of attributes) +++++
121 // +++++ species definitions (number of attributes) +++++
122
123 // legend:
124 // [species name](number of attributes); // attr1 (variable - values -
125 // comment) | attr2 (variable - values - comment) ....
126
127 Cell(2); // cell cycle phase (phase - 'G1' - dummy for dynamic cell
128 // cycle states) | cytosolic compartment volume (vol - 1 - dummy for
129 // dynamic compartment volumes, e.g. growth processes)
130 Membrane(1); // area (A - 1000 - arbitrary unit, required for dynamic
131 // rate calculation wrt. raft-related processes)
132 Nuc(1); // volume (vol - 1 - dummy for dynamic compartment volumes, e.g.
133 // growth processes)
134 Wnt(0);
135 Bcat(0);
136 Axin(1); // phosphorylation state (x - 'u' & 'p' - phosphorylation state
137 // of Axin)
138 Lrp6(4); // diffusion rate (d - 1 & 0.1 - diffusion speed of LRP6,
139 // depending on localization) | raft affinity (ra - 0.15 - raft
140 // affinity of LRP6) | phosphorylation state (phos - 'uP' & 'P' -
141 // phosphorylation state of LRP6) | binding state (bind - 'uB' & 'B' -
142 // binding state of LRP6-Wnt complex)
143 Lrp6Dvl(4); // phosphorylation state (phos - 'uP' & 'P' -
144 // phosphorylation state of LRP6) | diffusion rate (d - 1 & 0.1 -
145 // diffusion speed of LRP6-Dvl comlex depending on localization) |
146 // raft affinity (ra - 0.15 - raft affinity of LRP6) | binding state
147 // (bind - 'uB' & 'B' - binding state of LRP6-Wnt complex)
148 Lrp6Axin(3); // phosphorylation state (phos - 'uP' & 'P' -
149 // phosphorylation state of axin) | diffusion rate (d - 1 & 0.1 -
150 // diffusion speed of LRP6-Axin comlex depending on localization) |
151 // raft affinity (ra - 0.15 - raft affinity of LRP6)
152 CK1y(2); // diffusion rate (d - 1 & 0.1 - diffusion speed of CK1y
153 // depending on localization) | raft affinity (ra - 1 - raft affinity
154 // of CK1y)
155
156 Dvl(1); // aggregation state (a - 'i' & 'a' - states whether Dvl is
157 // present in aggregated or 'single' form)

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139 Nrx(1); // oxidation state ( - 'n0' & '0' - oxidation state based on ROS
    interaction)
140 DvlNrx(0);
141 DvlAxin(1); // phosphorylation state (phos - 'uP' & 'P' -
    phosphorylation state of axin)
142 Ros(1); // activation state ( - 'i' & 'a' - auxhiliary structure to
    control the release of ros)
143 P(0);
144 LR(2); // radius (radius - 4 - arbitrary unit, required for dynamic
    rate calculation) | fluidity (rho - 0.1 - raft fluidity determines
    the slow-down of raft-associated receptors)
145
146
147 // ++++++
148 // +++++ initial solution +++++
149 // ++++++
150 // ++++++
151
152 >>INIT[
153     (nWnt) Wnt +
154     (nP) P +
155     nCells Cell('G1', 1)[
156         (1) Membrane(1000)[
157             nLR LR(radius, rho) +
158             nLRP6 Lrp6(1, 'm', 0.15, 'uP', 'uB') +
159             nCK1y CK1y(1, 'm', 1)
160             ] +
161             (nDvl) Dvl('i') +
162             (nNrx) Nrx('n0') +
163             (nDvlNrx) DvlNrx +
164             (nRos) Ros('i') +
165             (nbetacyt) Bcat +
166             nAxin Axin('u') +
167             nAxinP Axin('p') +
168             Nuc(1)[(nbetanuc) Bcat]
169             ]
170     ];
171
172 // ++++++
173 // +++++ reaction rules ++++++
174 // ++++++
175
176 // ***** Lipid Raft Dynamics *****
177
178 // (R1) Lrp6 diffusion into lipid rafts
179 // note the change of diffusion rate of LRP6 due to raft entry
180 Membrane(A) [LR(radius, p)[s?]:l + Lrp6(d, ra, phos, bind):r + s_m?] ->
    Membrane(A) [LR(radius, p)[Lrp6(d*p, ra, phos, bind) + s?] + s_m?] @
    ra*kRin*(4*3.14*d*radius*#l)*(#r/(v-(3.14*radius*radius)));
181
182
183 // (R2) Lrp6 diffusion out of lipid rafts
184 // note the change of diffusion rate LRP6 due to raft exit
185 Membrane(A) [LR(radius, p)[Lrp6(d, ra, phos, bind):r + s?]:l + s_m?] ->
    Membrane(A) [LR(radius, p)[s?] + Lrp6(d/p, ra, phos, bind) + s_m?] @

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186 kRout*(4*3.14*d*radius*#l)*(#r/(3.14*radius*radius));
187
188 // (R3) CK1y diffusion into lipid rafts
189 // note the change of diffusion rate CK1y due to raft entry
190 Membrane(A)[LR(radius, p)[s?]:l + CK1y(d, ra):r + s_m?] ->
191     Membrane(A)[LR(radius, p)[CK1y(d*p, ra) + s?] + s_m?] @
191     ra*kRin*(4*3.14*d*radius*#l)*(#r/(v-(3.14*radius*radius)));
192
193 // (R4) CK1y diffusion out of lipid rafts
194 // note the change of diffusion rate CK1y due to raft exit
195 LR(radius, p)[CK1y(d, ra):r + s?]:l -> LR(radius, p)[s?] + CK1y(d/p, ra)
195     @
196 kRout*(4*3.14*d*radius*#l)*(#r/(3.14*radius*radius));
197
198 // **** Membrane Signalling ****
199
200 // (R5) Pseudoparticle production
201 // Note, that it is (not yet) possible to specify delays explicitly.
202 // Therefore we have to find a workaround to schedule the production of
202 // Wnt after a certain amount of time
203 // This is done by counting a "pseudoparticle", of which exactly one
203 // particle is synthesised at every time step (see next rule)
204 Cell(phase,vol)[s?] -> P + Cell(phase,vol)[s?] @ kPsyn;
205
206 // (R6) Wnt production
207 P:p + Cell(phase,vol)[s?] -> Wnt + P + Cell(phase,vol)[s?] @ if
207     ((#p>kWdelay)) then kWsyn else 0;
208
209 // (R6a) Wnt production, restricted to certain threshold concentration -
209 // used for validation experiment
210 // P:p + Cell(phase,vol)[s?] + Wnt:w -> Wnt + P + Cell(phase,vol)[s?] @
210 // if ((#w<epsilon)) then kWsyn else 0;
211
212 // (R7) Wnt degradation
213 Wnt:w -> @ kWdeg*w;
214
215 // (R8) Binding of Wnt to Lrp6 (representing Fz,Lrp6 receptor complex)
216 Wnt:w + Cell(S, vol)[Membrane(A)[Lrp6(diff, ra, 'uP', 'uB')]:l + sm?] +
216     s?] -> Cell(S, vol)[Membrane(A)[Lrp6(diff, ra, 'uP', 'B') + sm?] +
216     s?]
216     @ kLWntBind*w*#l;
217
218 // (R9) Dissociation of Wnt from LRP6 (representing Fz, Lrp6 receptor
218 // complex)
219 Cell(S, vol)[Membrane(A)[Lrp6(diff, ra, 'uP', 'B')]:l + sm?] + s?] ->
219     Cell(S, vol)[Membrane(A)[Lrp6(diff, ra, 'uP', 'uB') + sm?] + s?] +
219     Wnt @ kLWntUnbind*#l;
220
221 // (R10) Phosphorylation of activated Lrp6 in LR
222 Membrane(vol)[LR(radius, p)[CK1y(diff_ck, ra_ck):ck + Lrp6(diff_l, ra_l,
222     'uP', 'B')]:l + s?] + s_m?]
223 -> Membrane(vol)[LR(radius, p)[Lrp6(diff_l, ra_l, 'P', 'B') +
223     CK1y(diff_ck, ra_ck) + s?] + s_m?]

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226 @ kLphos*#l*#ck / (3.14*radius*radius/vol) * p;
227
228 // (R11) Dephosphorylation of Lrp6
229 Lrp6(diff, ra, 'P', 'B'):l -> Lrp6(diff, ra, 'uP', 'B') @ kLdephos*#l;
230
231 // **** Beta-catenin signalling ****
232
233 // (R12) Basal AxinP dephosphorylation
234 Axin('p'):a -> Axin('u') @ kApA*#a;
235
236 // (R13) Axin phosphorylation
237 Axin('u'):a -> Axin('p') @ kAAp*#a;
238
239 // (R14) Axin degradation
240 Axin(phos):a -> @ kAdeg*#a;
241
242 // (R15) Activated beta-catenin degradation
243 Cell(phase,vol)[Axin('p'):a + Bcat:b + s?]:c ->
244     Cell(phase,vol)[Axin('p') + s?] @ #c*(kbetadeg_act*#a*#b));
245
246 // (R16) Beta-catenin synthesis
247 Cell(phase,vol)[s?]:c -> Cell(phase,vol)[Bcat + s?] @ #c*kbetasyn;
248
249 // (R17) Basal beta-catenin degradation
250 Bcat:b -> @ kbetadeg*#b;
251
252 // (R18) Beta-catenin shuttling into the nucleus
253 Bcat:b + Nuc(vol)[s?] -> Nuc(vol)[Bcat + s?] @ kbetain*#b;
254
255 // (R19) Beta-catenin shuttling out of the nucleus
256 Nuc(vol)[Bcat:b + s?] -> Bcat + Nuc(vol)[s?] @ kbetaout*#b;
257
258 // (R20) Axin synthesis
259 Nuc(vol)[Bcat:b + s?] -> Nuc(vol)[Bcat + s?] + Axin('u') @ kAsyn*#b;
260
261 // **** Axin LRP6 signalling ****
262
263 // (R21) Axin binding by LRP6 in membrane
264 Axin(phos):a + Membrane(vol)[Lrp6PP(diff, ra, 'P', 'B'):l + s?]
265     Membrane(vol)[Lrp6Axin(phos, diff, ra) + s?] @ ((kApA_act*#l*#a));
266
267 // (R22) Axin binding by LRP6 in lipid rafts
268 Axin(phos):a + Membrane(vol)[LR(radius_lr, p)[Lrp6PP(diff, ra,
269     'P', 'B'):l + s_lr?] + s?] ->
270 Membrane(vol)[LR(radius_lr, p)[Lrp6Axin(phos, diff, ra) + s_lr?] + s?]
271     @ ((kApA_act*#l*#a));
272
273 // (R23) Dissociation of receptor/Axin complex (signalosome) in membrane
274 Cell(phase, vol)[Membrane(vol_m)[Lrp6Axin(phos, diff, ra):la + s_m?]
275     + s?] ->
276 Cell(phase, vol)[Membrane(vol_m)[Lrp6(diff, ra, 'uP', 'uB') + s_m?]
277     + Axin(phos) + s?] @ (kLA_diss)*#la;
278
279 // (R24) Dissociation of receptor/Axin complex (signalosome) in LR

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274 Cell(phase, vol)[Membrane(vol_m)[LR(radius_lr, p)[Lrp6Axin(phos, diff,
275   ra):la + s_lr?] + s_m?] + s?] ->
276 Cell(phase, vol)[Membrane(vol_m)[LR(radius_lr, p)[Lrp6(diff, ra, 'uP',
277   'uB') + s_lr?] + s_m?] + Axin(phos) + s?] @ (kLA_diss)*#la;
278
279 // (R25) Binding of Dvl to LRP6/Wnt complex
280 Cell(S, vol)[Membrane(A)[LR(radius, p)[Lrp6(diff, r, ra, 'uP', 'B'):l +
281   sr?] + sm?] + Dvl(a):d + s?]
282 -> Cell(S, vol)[Membrane(A)[LR(radius, p)[Lrp6Dvl(diff, r, ra, 'uP',
283   'B') + sr?] + sm?] + s?] @ kLd*#l*#d;
284
285 // (R26) Unbinding of Dvl from LRP6/Wnt complex
286 Cell(S, vol)[Membrane(A)[LR(radius, p)[Lrp6Dvl(diff, r, ra, 'uP', 'B'):l +
287   sr?] + sm?] + s?] ->
288 Cell(S, vol)[Membrane(A)[LR(radius, p)[Lrp6(diff, r, ra, 'uP', 'B') +
289   sr?] + sm?] + Dvl('i') + s?] @ kLad*#l;
290
291 // **** Ros-Dvl Signalling ****
292
293 // (R27) Ros Synthesis
294 Cell(phase, vol)[s?] -> Cell(phase, vol)[Ros('a') + s?] @ kRosSyn;
295
296 // (R28) Ros activation after delay
297 Cell(phase, vol)[Ros('i'):r + s?] + P:p -> Cell(phase, vol)[Ros('a') +
298   s?] + P @ if ((#p>kRosDelay)) then kRosAct*#r else 0;
299
300 // (R29) Oxidation of Nrx by Ros
301 Cell(phase, vol)[Nrx('n0'):n + Ros('a'):r + s?] -> Cell(phase,
302   vol)[Nrx('0') + s?] @ kNrxRos*#n*#r;
303
304 // (R30) Reduction of Nrx
305 Nrx('0'):n -> Nrx('n0') @ kNrxNo*#n;
306
307 // (R31) Activation (by e.g. aggregation) of Dvl
308 Dvl('i'):d -> Dvl('a') @ kDvlSponAgg*#d;
309
310 // (R32) Dynamic deactivation (e.g. by disaggregation) of Dvl
311 Dvl('a'):d -> Dvl('i') @ kDvldisAgg*#d;
312
313 // (R33) Forced Disaggregation of Dvl by un-oxidized Nrx
314 Cell(phase, vol)[Dvl('a'):d + Nrx('n0'):n + s?] -> Cell(phase,
315   vol)[DvlNrx + s?] @ kDvlNrxBind*#d*#n ;
316
317 // (R34) Binding of Dvl by Nrx
318 Cell(phase, vol)[Dvl('i'):d + Nrx('n0'):n + s?] -> Cell(phase,
319   vol)[DvlNrx + s?] @ kDvlNrxBind*#d*#n;
320
321 // (R35) Basal unbinding of Dvl from Nrx
322 DvlNrx:dn -> Dvl('i') + Nrx('n0') @ kDvlNrxUnbind*#dn;
323
324 // (R36) Unbinding of Dvl from Nrx by Ros
325 Cell(phase, vol)[DvlNrx:dn + Ros('a'):r + s?] -> Cell(phase,
326   vol)[Dvl('i') + Nrx('0') + s?] @ kDvlNrxRos*#dn*#r;
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317 // **** Axin Dvl signalling ****
318
319 // (R37) Axin binding by activated Dvl
320 Cell(phase, vol)[Dvl('a'):d + Axin(phos):a + s?] -> Cell(phase,
321   vol)[DvlAxin(phos) + s?] @kDvlAxinBind*#d*#a;
322
323 // (R38) Axin Dvl unbinding
324 Cell(phase, vol)[DvlAxin(phos):da + s?] -> Cell(phase, vol)[Dvl('a') +
325   Axin(phos) + s?] @kDvlAxinUnbind*#da;

```