

Towards DNA-damage induced autophagy: A Boolean model of p53-induced cell fate mechanisms

Supplementary file S1

Shantanu Gupta^{1,+} | Daner A. Silveira^{1,+} and José C. M. Mombach^{1,*,+}

¹Departamento de Física, Universidade Federal de Santa Maria, Santa Maria, RS, 97105-900, Brazil

*Corresponding author (e-mail: jcmombach@ufsm.br)

⁺These authors contributed equally to this work

Code of the model in .ginml file format used for the GINsim 3.0.0b software.

```

1 <?xml version="1.0" encoding="UTF-8"?>
2 <!DOCTYPE gxl SYSTEM "http://ginsim.org/GINML_2.2.dtd">
3 <gxl xmlns:xlink="http://www.w3.org/1999/xlink">
4   <graph class="regulatory" id="p53-Tristable-Dynamics" nodeorder="Transfected_miRNA miR_16
      DDR_Activation AIM AMPK Mdn2 p53INP1 p53_A p53_K Wip1 Myc p21 CDK46_CycD CDK2_CycE
      Cdc25A BMI1 mTORC2 mTORC1 BCL2 Sirt1 PTEN RB AKT E2F1 PUMA BAX Caspase3 DRAM1 ULK1
      PROLIFERATION AUTOPHAGY APOPTOSIS SENESCENCE">
5     <nodestyle background="#ccffff" foreground="#000000" text="#000000" shape="ELLIPSE" width=
      "70" height="30" properties="intermediate:#ffff00 active:#ffc800"/>
6     <nodestyle name="Node style" background="#ffffff" foreground="#ffffff" shape="ELLIPSE"
      width="50" height="45"/>
7     <nodestyle name="Node style 2" background="#ffff00" foreground="#ffffff" shape="RECTANGLE"
      />
8     <nodestyle name="Node style 3" background="#cccccc" foreground="#000000" text="#000000"
      shape="RECTANGLE" width="100"/>
9     <nodestyle name="Node style 4" background="#ffffff" foreground="#ffffff" text="#000000"
      shape="RECTANGLE"/>
10    <nodestyle name="Node style 5" background="#ffffff" shape="RECTANGLE" width="160" height="
      35"/>
11    <nodestyle name="Node style 6"/>
12    <nodestyle name="Node style 7" background="#cccccc" width="90" height="40"/>
13    <nodestyle name="Node style 8" background="#ffffff" foreground="#ffffff" text="#000000"
      shape="RECTANGLE" width="95" height="30"/>
14    <nodestyle name="Node style 9" background="#ffffff" foreground="#ffffff" text="#000000"
      shape="RECTANGLE" width="45"/>
15    <nodestyle name="Node style 10" background="#ffffff" foreground="#ffffff" text="#000000"
      shape="RECTANGLE" width="40"/>
16    <nodestyle name="Node style 11"/>
17    <nodestyle name="Node style 12" background="#ff0000" foreground="#ffffff" text="#000000"
      shape="RECTANGLE" width="115"/>
18    <nodestyle name="Node style 13" background="#ffffff" foreground="#ffffff" text="#000000"
      shape="RECTANGLE" width="75"/>
19    <nodestyle name="Node style 14" background="#ffffff" foreground="#ffffff" text="#000000"
      shape="RECTANGLE" width="80"/>
20    <edgestyle color="#000000" pattern="SIMPLE" line_width="2" properties="positive:#000000
      negative:#000000 dual:#0000c8"/>
21    <edgestyle name="Edge style" line_width="1"/>
22    <edgestyle name="Edge style 2" pattern="DASH" line_width="3"/>
23    <edgestyle name="Edge style 3" line_width="4"/>
24    <edgestyle name="Edge style 4"/>
25    <edgestyle name="Edge style 5"/>
26    <node id="Transfected_miRNA" maxvalue="1" input="true">
27      <nodevisualsetting x="1299" y="303" style="Node style 12"/>
28    </node>
29    <node id="miR_16" maxvalue="1">
30      <value val="1">
31        <exp str="AIM & Transfected_miRNA"/>
32      </value>
33      <nodevisualsetting x="1174" y="302" style="Node style 2"/>
34    </node>
35    <node id="DDR_Activation" maxvalue="1">
36      <value val="1">
37        <exp str="Transfected_miRNA & !(Wip1 & BMI1 & Cdc25A)"/>
38      </value>
39      <nodevisualsetting x="268" y="21" style="Node style 5"/>
40    </node>
41    <node id="ATM" maxvalue="1">
42      <value val="1">

```

```

43     <exp str="DDR_Activation & !Wip1"/>
44 </value>
45 <nodevisualsetting x="176" y="74" style="Node style 4"/>
46 </node>
47 <node id="AMPK" maxvalue="1">
48   <value val="1">
49     <exp str="(ATM | DDR_Activation) & !ULK1"/>
50   </value>
51   <nodevisualsetting x="295" y="131" style="Node style 4"/>
52 </node>
53 <node id="Mdm2" maxvalue="1">
54   <value val="1">
55     <exp str="(!Wip1 | p53_A) & !ATM & AKT"/>
56   </value>
57   <nodevisualsetting x="175" y="232" style="Node style 4"/>
58 </node>
59 <node id="p53INP1" maxvalue="1">
60   <value val="1">
61     <exp str="p53_K | p53_A"/>
62   </value>
63   <nodevisualsetting x="446" y="189" style="Node style 4"/>
64 </node>
65 <node id="p53_A" maxvalue="1">
66   <value val="1">
67     <exp str="!Sirt1 & !p53_K & (ATM | !p53INP1 | (AMPK & !(Wip1 & Mdm2)))"
68       "/>
69   </value>
70   <nodevisualsetting x="298" y="187" style="Node style 4"/>
71 </node>
72 <node id="p53_K" maxvalue="1">
73   <value val="1">
74     <exp str="!p53_A & (!Sirt1 | !Wip1) & ATM & !Mdm2"/>
75   </value>
76   <nodevisualsetting x="296" y="308" style="Node style 4"/>
77 </node>
78 <node id="Wip1" maxvalue="1">
79   <value val="1">
80     <exp str="p53_A & !miR_16"/>
81   </value>
82   <nodevisualsetting x="819" y="373" style="Node style"/>
83 </node>
84 <node id="Myc" maxvalue="1">
85   <value val="1">
86     <exp str="(E2F1 | AMPK) & !RB & !p21"/>
87   </value>
88   <nodevisualsetting x="542" y="291" style="Node style 4"/>
89 </node>
90 <node id="p21" maxvalue="1">
91   <value val="1">
92     <exp str="p53_A | (!Myc & !Caspase3 & !BMI1 & !AKT)"/>
93   </value>
94   <nodevisualsetting x="706" y="107" style="Node style 4"/>
95 </node>
96 <node id="CDK46_CycD" maxvalue="1">
97   <value val="1">
98     <exp str="Cdc25A & !miR_16 & !p21"/>
99   </value>
100   <nodevisualsetting x="970" y="59" style="Node style 14"/>
101 </node>
102 <node id="CDK2_CycE" maxvalue="1">
103   <value val="1">
    <exp str="Cdc25A & E2F1 & !miR_16 & !p21"/>

```

```

104     </value>
105     <nodevisualsetting x="976" y="138" style="Node style 13"/>
106 </node>
107 <node id="Cdc25A" maxvalue="1">
108     <value val="1">
109         <exp str="!ATM & !miR_16"/>
110     </value>
111     <nodevisualsetting x="974" y="218" style="Node style 4"/>
112 </node>
113 <node id="BMI1" maxvalue="1">
114     <value val="1">
115         <exp str="!miR_16 & (E2F1 | Myc)"/>
116     </value>
117     <nodevisualsetting x="976" y="302" style="Node style 4"/>
118 </node>
119 <node id="mTORC2" maxvalue="1">
120     <value val="1">
121         <exp str="!miR_16 | AKT | !(DRAM1 | mTORC1 | Sirt1 | AMPK)"/>
122     </value>
123     <nodevisualsetting x="980" y="379" style="Node style 4"/>
124 </node>
125 <node id="mTORC1" maxvalue="1">
126     <value val="1">
127         <exp str="AKT & !((ULK1 & DRAM1 & miR_16) | AMPK)"/>
128     </value>
129     <nodevisualsetting x="835" y="581" style="Node style 4"/>
130 </node>
131 <node id="BCL2" maxvalue="1">
132     <value val="1">
133         <exp str="!miR_16 & !PUMA & !DRAM1"/>
134     </value>
135     <nodevisualsetting x="980" y="547" style="Node style 9"/>
136 </node>
137 <node id="Sirt1" maxvalue="1">
138     <value val="1">
139         <exp str="E2F1"/>
140     </value>
141     <nodevisualsetting x="535" y="162" style="Node style 10"/>
142 </node>
143 <node id="PTEN" maxvalue="1">
144     <value val="1">
145         <exp str="p53_K & !BMI1"/>
146     </value>
147     <nodevisualsetting x="660" y="378" style="Node style 4"/>
148 </node>
149 <node id="RB" maxvalue="1">
150     <value val="1">
151         <exp str="!CDK46_CycD & !CDK2_CycE"/>
152     </value>
153     <nodevisualsetting x="387" y="425" style="Node style 4"/>
154 </node>
155 <node id="AKT" maxvalue="1">
156     <value val="1">
157         <exp str="(!DDR_Activation & !PTEN) | mTORC2 | BMI1"/>
158     </value>
159     <nodevisualsetting x="674" y="451" style="Node style 4"/>
160 </node>
161 <node id="E2F1" maxvalue="1">
162     <value val="1">
163         <exp str="(!RB & ((Cdc25A & ATM) | !Sirt1)) | Myc"/>
164     </value>
165     <nodevisualsetting x="226" y="425" style="Node style 4"/>

```

```

166 </node>
167 <node id="PUMA" maxvalue="1">
168   <value val="1">
169     <exp str="p53_K" />
170   </value>
171   <nodevisualsetting x="538" y="378" style="Node style 4"/>
172 </node>
173 <node id="BAX" maxvalue="1">
174   <value val="1">
175     <exp str="!BCL2 & DRAM1 & !Wip1" />
176   </value>
177   <nodevisualsetting x="808" y="539" style="Node style 4"/>
178 </node>
179 <node id="Caspase3" maxvalue="1">
180   <value val="1">
181     <exp str="BAX | (!p21 & !BCL2)" />
182   </value>
183   <nodevisualsetting x="566" y="540" style="Node style 4"/>
184 </node>
185 <node id="DRAM1" maxvalue="1">
186   <value val="1">
187     <exp str="p53_K" />
188   </value>
189   <nodevisualsetting x="430" y="370" style="Node style 4"/>
190 </node>
191 <node id="ULK1" maxvalue="1">
192   <value val="1">
193     <exp str="(DRAM1 | AMPK) & !mTORC2 & !mTORC1" />
194   </value>
195   <nodevisualsetting x="565" y="587" style="Node style 8"/>
196 </node>
197 <node id="PROLIFERATION" maxvalue="1">
198   <value val="1">
199     <exp str="E2F1" />
200   </value>
201   <nodevisualsetting x="297" y="557" style="Node style 3"/>
202 </node>
203 <node id="AUTOPHAGY" maxvalue="1">
204   <value val="1">
205     <exp str="ULK1" />
206   </value>
207   <nodevisualsetting x="453" y="659" style="Node style 3"/>
208 </node>
209 <node id="APOPTOSIS" maxvalue="1">
210   <value val="1">
211     <exp str="(Caspase3 | DRAM1) & !ULK1" />
212   </value>
213   <nodevisualsetting x="924" y="658" style="Node style 3"/>
214 </node>
215 <node id="SENESCENCE" maxvalue="1">
216   <value val="1">
217     <exp str="p21 | p53_A" />
218   </value>
219   <nodevisualsetting x="698" y="659" style="Node style 3"/>
220 </node>
221 <edge id="p53_K:PUMA" from="p53_K" to="PUMA" minvalue="1" sign="positive">
222   <edgevisualsetting points="575,332" anchor="NE" style="" />
223 </edge>
224 <edge id="p53_K:p53_A" from="p53_K" to="p53_A" minvalue="1" sign="negative">
225   <edgevisualsetting anchor="NE" style="" />
226 </edge>
227 <edge id="p53_K:DRAM1" from="p53_K" to="DRAM1" minvalue="1" sign="positive">

```

```

228     <edgevisualsetting points="466,338" anchor="NE" style=""/>
229 </edge>
230 <edge id="p53_K:PTEN" from="p53_K" to="PTEN" minvalue="1" sign="positive">
231     <edgevisualsetting points="685,324" anchor="NE" style=""/>
232 </edge>
233 <edge id="p53_K:p53INP1" from="p53_K" to="p53INP1" minvalue="1" sign="positive">
234     <edgevisualsetting points="480,319" anchor="NE" style=""/>
235 </edge>
236 <edge id="PTEN:AKT" from="PTEN" to="AKT" minvalue="1" sign="negative">
237     <edgevisualsetting points="701,421" anchor="NE" style=""/>
238 </edge>
239 <edge id="E2F1:Sirt1" from="E2F1" to="Sirt1" minvalue="1" sign="positive">
240     <edgevisualsetting points="146,426 147,161 251,161 251,111 400,111 401,100 555,100"
241         anchor="NE" style=""/>
242 </edge>
243 <edge id="E2F1:CDK2_CycE" from="E2F1" to="CDK2_CycE" minvalue="1" sign="positive">
244     <edgevisualsetting points="268,245 495,245 737,245 737,158" anchor="NE" style=""/>
245 </edge>
246 <edge id="E2F1:Myc" from="E2F1" to="Myc" minvalue="1" sign="positive">
247     <edgevisualsetting points="260,272 549,272" anchor="NE" style=""/>
248 </edge>
249 <edge id="E2F1:BMI1" from="E2F1" to="BMI1" minvalue="1" sign="positive">
250     <edgevisualsetting points="357,450 357,467 640,467 640,331" anchor="NE" style=""/>
251 </edge>
252 <edge id="E2F1:PROLIFERATION" from="E2F1" to="PROLIFERATION" minvalue="1" sign="positive">
253     <edgevisualsetting points="270,503 347,503" anchor="NE" style=""/>
254 </edge>
255 <edge id="PUMA:BCL2" from="PUMA" to="BCL2" minvalue="1" sign="negative">
256     <edgevisualsetting points="583,506 991,503" anchor="NE" style=""/>
257 </edge>
258 <edge id="p53INP1:p53_A" from="p53INP1" to="p53_A" minvalue="1" sign="negative">
259     <edgevisualsetting anchor="NE" style=""/>
260 </edge>
261 <edge id="Wip1:ATM" from="Wip1" to="ATM" minvalue="1" sign="negative">
262     <edgevisualsetting points="845,84" anchor="NE" style=""/>
263 </edge>
264 <edge id="Wip1:Mdm2" from="Wip1" to="Mdm2" minvalue="1" sign="negative">
265     <edgevisualsetting points="821,359 220,358" anchor="NE" style=""/>
266 </edge>
267 <edge id="Wip1:p53_K" from="Wip1" to="p53_K" minvalue="1" sign="negative">
268     <edgevisualsetting points="824,351 344,351" anchor="NE" style=""/>
269 </edge>
270 <edge id="Wip1:p53_A" from="Wip1" to="p53_A" minvalue="1" sign="negative">
271     <edgevisualsetting points="865,258 350,258" anchor="NE" style=""/>
272 </edge>
273 <edge id="Wip1:BAX" from="Wip1" to="BAX" minvalue="1" sign="negative">
274     <edgevisualsetting points="853,467" anchor="NE" style=""/>
275 </edge>
276 <edge id="Wip1:DDR_Activation" from="Wip1" to="DDR_Activation" minvalue="1" sign="negative"
277     ">
278     <edgevisualsetting points="829,26" anchor="NE" style=""/>
279 </edge>
280 <edge id="p21:CDK46_CycD" from="p21" to="CDK46_CycD" minvalue="1" sign="negative">
281     <edgevisualsetting points="738,65" anchor="NE" style=""/>
282 </edge>
283 <edge id="p21:CDK2_CycE" from="p21" to="CDK2_CycE" minvalue="1" sign="negative">
284     <edgevisualsetting points="986,115" anchor="NE" style=""/>
285 </edge>
286 <edge id="p21:Myc" from="p21" to="Myc" minvalue="1" sign="negative">
287     <edgevisualsetting points="435,132 435,299" anchor="NE" style=""/>
288 </edge>
289 <edge id="p21:Caspase3" from="p21" to="Caspase3" minvalue="1" sign="negative">

```

```

288     <edgevisualsetting points="615,138" anchor="NE" style="" />
289 </edge>
290 <edge id="p21:SENESCENCE" from="p21" to="SENESCENCE" minvalue="1" sign="positive">
291     <edgevisualsetting points="761,523" anchor="NE" style="" />
292 </edge>
293 <edge id="BCL2:BAX" from="BCL2" to="BAX" minvalue="1" sign="negative">
294     <edgevisualsetting points="914,559" anchor="NE" style="" />
295 </edge>
296 <edge id="BCL2:Caspase3" from="BCL2" to="Caspase3" minvalue="1" sign="negative">
297     <edgevisualsetting points="978,523 590,523" anchor="NE" style="" />
298 </edge>
299 <edge id="Mdm2:p53_A" from="Mdm2" to="p53_A" minvalue="1" sign="negative">
300     <edgevisualsetting points="234,202" anchor="NE" style="" />
301 </edge>
302 <edge id="Mdm2:p53_K" from="Mdm2" to="p53_K" minvalue="1" sign="negative">
303     <edgevisualsetting points="234,322" anchor="NE" style="" />
304 </edge>
305 <edge id="AMPK:Myc" from="AMPK" to="Myc" minvalue="1" sign="positive">
306     <edgevisualsetting points="392,159 391,288" anchor="NE" style="" />
307 </edge>
308 <edge id="AMPK:p53_A" from="AMPK" to="p53_A" minvalue="1" sign="positive">
309     <edgevisualsetting points="325,167" anchor="NE" style="" />
310 </edge>
311 <edge id="AMPK:mTORC1" from="AMPK" to="mTORC1" minvalue="1" sign="negative">
312     <edgevisualsetting points="699,146 699,301 797,300 798,584" anchor="NE" style="" />
313 </edge>
314 <edge id="AMPK:ULK1" from="AMPK" to="ULK1" minvalue="1" sign="positive">
315     <edgevisualsetting points="608,138 608,282 655,282" anchor="NE" style="" />
316 </edge>
317 <edge id="AMPK:mTORC2" from="AMPK" to="mTORC2" minvalue="1" sign="negative">
318     <edgevisualsetting points="365,92 662,92 938,92 938,385" anchor="NE" style="" />
319 </edge>
320 <edge id="BMI1:p21" from="BMI1" to="p21" minvalue="1" sign="negative">
321     <edgevisualsetting points="858,299 858,122" anchor="NE" style="" />
322 </edge>
323 <edge id="BMI1:AKT" from="BMI1" to="AKT" minvalue="1" sign="positive">
324     <edgevisualsetting points="993,343 912,343 912,448" anchor="NE" style="" />
325 </edge>
326 <edge id="BMI1:DDR_Activation" from="BMI1" to="DDR_Activation" minvalue="1" sign="negative
327     ">
328     <edgevisualsetting points="872,316 872,51" anchor="NE" style="" />
329 </edge>
330 <edge id="BMI1:PTEN" from="BMI1" to="PTEN" minvalue="1" sign="negative">
331     <edgevisualsetting points="706,324" anchor="NE" style="" />
332 </edge>
333 <edge id="BAX:Caspase3" from="BAX" to="Caspase3" minvalue="1" sign="positive">
334     <edgevisualsetting anchor="NE" style="" />
335 </edge>
336 <edge id="CDK2_CycE:RB" from="CDK2_CycE" to="RB" minvalue="1" sign="negative">
337     <edgevisualsetting points="900,163 898,426" anchor="NE" style="" />
338 </edge>
339 <edge id="ULK1:APOPTOSIS" from="ULK1" to="APOPTOSIS" minvalue="1" sign="negative">
340     <edgevisualsetting points="616,636 960,635" anchor="NE" style="" />
341 </edge>
342 <edge id="ULK1:AUTOPHAGY" from="ULK1" to="AUTOPHAGY" minvalue="1" sign="positive">
343     <edgevisualsetting points="519,614" anchor="NE" style="" />
344 </edge>
345 <edge id="ULK1:mTORC1" from="ULK1" to="mTORC1" minvalue="1" sign="negative">
346     <edgevisualsetting points="769,606" anchor="NE" style="" />
347 </edge>
348 <edge id="ULK1:AMPK" from="ULK1" to="AMPK" minvalue="1" sign="negative">
349     <edgevisualsetting points="429,586 429,512 120,512 120,147" anchor="NE" style="" />

```

```

349 </edge>
350 <edge id="mTORC2:AKT" from="mTORC2" to="AKT" minvalue="1" sign="positive">
351   <edgevisualsetting points="883,394 883,455" anchor="NE" style=""/>
352 </edge>
353 <edge id="mTORC2:ULK1" from="mTORC2" to="ULK1" minvalue="1" sign="negative">
354   <edgevisualsetting points="990,428 949,428 949,511 532,511 533,594" anchor="NE" style=""/>
355 </edge>
356 <edge id="CDK46_CycD:RB" from="CDK46_CycD" to="RB" minvalue="1" sign="negative">
357   <edgevisualsetting points="880,71 877,435" anchor="NE" style=""/>
358 </edge>
359 <edge id="mTORC1:mTORC2" from="mTORC1" to="mTORC2" minvalue="1" sign="negative">
360   <edgevisualsetting points="878,626 1039,626" anchor="NE" style=""/>
361 </edge>
362 <edge id="mTORC1:ULK1" from="mTORC1" to="ULK1" minvalue="1" sign="negative">
363   <edgevisualsetting points="770,591" anchor="NE" style=""/>
364 </edge>
365 <edge id="AKT:Mdm2" from="AKT" to="Mdm2" minvalue="1" sign="positive">
366   <edgevisualsetting points="195,473" anchor="NE" style=""/>
367 </edge>
368 <edge id="AKT:mTORC2" from="AKT" to="mTORC2" minvalue="1" sign="positive">
369   <edgevisualsetting points="933,461 932,407" anchor="NE" style=""/>
370 </edge>
371 <edge id="AKT:p21" from="AKT" to="p21" minvalue="1" sign="negative">
372   <edgevisualsetting points="718,418 752,418" anchor="NE" style=""/>
373 </edge>
374 <edge id="AKT:mTORC1" from="AKT" to="mTORC1" minvalue="1" sign="positive">
375   <edgevisualsetting points="931,468 930,597" anchor="NE" style=""/>
376 </edge>
377 <edge id="DRAM1:ULK1" from="DRAM1" to="ULK1" minvalue="1" sign="positive">
378   <edgevisualsetting points="515,387 515,605" anchor="NE" style=""/>
379 </edge>
380 <edge id="DRAM1:BAX" from="DRAM1" to="BAX" minvalue="1" sign="positive">
381   <edgevisualsetting points="468,487 845,487" anchor="NE" style=""/>
382 </edge>
383 <edge id="DRAM1:BCL2" from="DRAM1" to="BCL2" minvalue="1" sign="negative">
384   <edgevisualsetting points="476,502 1001,499" anchor="NE" style=""/>
385 </edge>
386 <edge id="DRAM1:mTORC1" from="DRAM1" to="mTORC1" minvalue="1" sign="negative">
387   <edgevisualsetting points="497,490 497,630 855,630" anchor="NE" style=""/>
388 </edge>
389 <edge id="DRAM1:mTORC2" from="DRAM1" to="mTORC2" minvalue="1" sign="negative">
390   <edgevisualsetting points="505,393 505,442 1002,442" anchor="NE" style=""/>
391 </edge>
392 <edge id="DRAM1:APOPTOSIS" from="DRAM1" to="APOPTOSIS" minvalue="1" sign="positive">
393   <edgevisualsetting points="527,382 527,517 735,517 942,517" anchor="NE" style=""/>
394 </edge>
395 <edge id="miR_16:CDK46_CycD" from="miR_16" to="CDK46_CycD" minvalue="1" sign="negative">
396   <edgevisualsetting anchor="NE" style="Edge style 2"/>
397 </edge>
398 <edge id="miR_16:CDK2_CycE" from="miR_16" to="CDK2_CycE" minvalue="1" sign="negative">
399   <edgevisualsetting anchor="NE" style="Edge style 2"/>
400 </edge>
401 <edge id="miR_16:Cdc25A" from="miR_16" to="Cdc25A" minvalue="1" sign="negative">
402   <edgevisualsetting anchor="NE" style="Edge style 2"/>
403 </edge>
404 <edge id="miR_16:BMI1" from="miR_16" to="BMI1" minvalue="1" sign="negative">
405   <edgevisualsetting anchor="NE" style="Edge style 2"/>
406 </edge>
407 <edge id="miR_16:mTORC2" from="miR_16" to="mTORC2" minvalue="1" sign="negative">
408   <edgevisualsetting anchor="NE" style="Edge style 2"/>
409 </edge>

```



```

410 <edge id="miR_16:BCL2" from="miR_16" to="BCL2" minvalue="1" sign="negative">
411   <edgevisualsetting anchor="NE" style="Edge style 2"/>
412 </edge>
413 <edge id="miR_16:Wip1" from="miR_16" to="Wip1" minvalue="1" sign="negative">
414   <edgevisualsetting anchor="NE" style="Edge style 2"/>
415 </edge>
416 <edge id="miR_16:mTORC1" from="miR_16" to="mTORC1" minvalue="1" sign="negative">
417   <edgevisualsetting anchor="NE" style="Edge style 2"/>
418 </edge>
419 <edge id="ATM:AMPK" from="ATM" to="AMPK" minvalue="1" sign="positive">
420   <edgevisualsetting points="337,91" anchor="NE" style=""/>
421 </edge>
422 <edge id="ATM:E2F1" from="ATM" to="E2F1" minvalue="1" sign="positive">
423   <edgevisualsetting points="133,99 134,437" anchor="NE" style=""/>
424 </edge>
425 <edge id="ATM:Mdm2" from="ATM" to="Mdm2" minvalue="1" sign="negative">
426   <edgevisualsetting points="155,106 156,246" anchor="NE" style=""/>
427 </edge>
428 <edge id="ATM:Cdc25A" from="ATM" to="Cdc25A" minvalue="1" sign="negative">
429   <edgevisualsetting points="652,107 653,227" anchor="NE" style=""/>
430 </edge>
431 <edge id="ATM:p53_A" from="ATM" to="p53_A" minvalue="1" sign="positive">
432   <edgevisualsetting points="212,190" anchor="NE" style=""/>
433 </edge>
434 <edge id="ATM:p53_K" from="ATM" to="p53_K" minvalue="1" sign="positive">
435   <edgevisualsetting points="196,124 139,124 140,312" anchor="NE" style=""/>
436 </edge>
437 <edge id="ATM:miR_16" from="ATM" to="miR_16" minvalue="1" sign="positive">
438   <edgevisualsetting points="185,15 1218,16" anchor="NE" style=""/>
439 </edge>
440 <edge id="DDR_Activation:ATM" from="DDR_Activation" to="ATM" minvalue="1" sign="positive">
441   <edgevisualsetting points="210,40" anchor="NE" style=""/>
442 </edge>
443 <edge id="DDR_Activation:AKT" from="DDR_Activation" to="AKT" minvalue="1" sign="negative">
444   <edgevisualsetting points="112,31 113,479" anchor="NE" style=""/>
445 </edge>
446 <edge id="DDR_Activation:AMPK" from="DDR_Activation" to="AMPK" minvalue="1" sign="positive"
447   >
448   <edgevisualsetting points="352,97" anchor="NE" style=""/>
449 </edge>
450 <edge id="Caspase3:p21" from="Caspase3" to="p21" minvalue="1" sign="negative">
451   <edgevisualsetting points="629,125" anchor="NE" style=""/>
452 </edge>
453 <edge id="Caspase3:APOPTOSIS" from="Caspase3" to="APOPTOSIS" minvalue="1" sign="positive">
454   <edgevisualsetting points="703,573 771,573 771,640 996,640" anchor="NE" style=""/>
455 </edge>
456 <edge id="Sirt1:E2F1" from="Sirt1" to="E2F1" minvalue="1" sign="negative">
457   <edgevisualsetting points="404,178 404,395 276,395" anchor="NE" style=""/>
458 </edge>
459 <edge id="Sirt1:p53_A" from="Sirt1" to="p53_A" minvalue="1" sign="negative">
460   <edgevisualsetting points="345,170" anchor="NE" style=""/>
461 </edge>
462 <edge id="Sirt1:p53_K" from="Sirt1" to="p53_K" minvalue="1" sign="negative">
463   <edgevisualsetting points="415,186 414,312" anchor="NE" style=""/>
464 </edge>
465 <edge id="Sirt1:mTORC2" from="Sirt1" to="mTORC2" minvalue="1" sign="negative">
466   <edgevisualsetting points="721,178 721,252 904,251 903,356 998,355" anchor="NE" style=""/>
467 </edge>
468 <edge id="Transfected_miRNA:miR_16" from="Transfected_miRNA" to="miR_16" minvalue="1" sign="positive">
469   <edgevisualsetting points="1273,316" anchor="NE" style=""/>

```

```

469 </edge>
470 <edge id="Transfected_miRNA:DDR_Activation" from="Transfected_miRNA" to="DDR_Activation"
      minvalue="1" sign="positive">
471   <edgevisualsetting points="1323,42" anchor="NE" style=""/>
472 </edge>
473 <edge id="p53_A:p21" from="p53_A" to="p21" minvalue="1" sign="positive">
474   <edgevisualsetting points="429,195 428,120" anchor="NE" style=""/>
475 </edge>
476 <edge id="p53_A:p53_K" from="p53_A" to="p53_K" minvalue="1" sign="negative">
477   <edgevisualsetting anchor="NE" style=""/>
478 </edge>
479 <edge id="p53_A:Wip1" from="p53_A" to="Wip1" minvalue="1" sign="positive">
480   <edgevisualsetting points="360,280 510,280 510,343 855,343" anchor="NE" style=""/>
481 </edge>
482 <edge id="p53_A:p53INP1" from="p53_A" to="p53INP1" minvalue="1" sign="positive">
483   <edgevisualsetting points="435,203" anchor="NE" style=""/>
484 </edge>
485 <edge id="p53_A:Mdm2" from="p53_A" to="Mdm2" minvalue="1" sign="positive">
486   <edgevisualsetting points="312,238" anchor="NE" style=""/>
487 </edge>
488 <edge id="p53_A:SENESCENCE" from="p53_A" to="SENESCENCE" minvalue="1" sign="positive">
489   <edgevisualsetting points="315,291 224,291 224,394 203,394 203,498 469,498 469,642
      515,642 734,642" anchor="NE" style=""/>
490 </edge>
491 <edge id="Cdc25A:CDK2_CycE" from="Cdc25A" to="CDK2_CycE" minvalue="1" sign="positive">
492   <edgevisualsetting points="1006,195" anchor="NE" style=""/>
493 </edge>
494 <edge id="Cdc25A:CDK46_CycD" from="Cdc25A" to="CDK46_CycD" minvalue="1" sign="positive">
495   <edgevisualsetting points="988,203 889,203 889,79" anchor="NE" style=""/>
496 </edge>
497 <edge id="Cdc25A:E2F1" from="Cdc25A" to="E2F1" minvalue="1" sign="positive">
498   <edgevisualsetting points="991,257 921,257 920,494 254,494" anchor="NE" style=""/>
499 </edge>
500 <edge id="Cdc25A:DDR_Activation" from="Cdc25A" to="DDR_Activation" minvalue="1" sign="
      negative">
501   <edgevisualsetting points="916,216 916,34" anchor="NE" style=""/>
502 </edge>
503 <edge id="RB:E2F1" from="RB" to="E2F1" minvalue="1" sign="negative">
504   <edgevisualsetting anchor="NE" style=""/>
505 </edge>
506 <edge id="RB:Myc" from="RB" to="Myc" minvalue="1" sign="negative">
507   <edgevisualsetting points="425,312" anchor="NE" style=""/>
508 </edge>
509 <edge id="Myc:E2F1" from="Myc" to="E2F1" minvalue="1" sign="positive">
510   <edgevisualsetting points="417,306 417,411 293,411" anchor="NE" style=""/>
511 </edge>
512 <edge id="Myc:p21" from="Myc" to="p21" minvalue="1" sign="negative">
513   <edgevisualsetting points="593,164 729,164" anchor="NE" style="Edge style 5"/>
514 </edge>
515 <edge id="Myc:BM1" from="Myc" to="BM1" minvalue="1" sign="positive">
516   <edgevisualsetting points="558,269 1013,269" anchor="NE" style=""/>
517 </edge>
518 </graph>
519 </gxl>

```