Supplemental Materials

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# Formulations derivation for $\frac{ρ\_{uv}}{ρ\_{xy}}$

With the definitions shown in Table 1, the formulations describing the Pearson’s correlation coefficients at the single-cell ($ρ\_{xy}^{ }$) or the population level ($ρ\_{uv}$), as well as the correlation-within ($ρ\_{ixiy}$) were as follows:

|  |  |  |
| --- | --- | --- |
|  | $$ρ\_{xy}^{ }=\frac{cov\left(x,y\right)}{ σ\_{x}∙ σ\_{y}}$$ | (S1) |

|  |  |  |
| --- | --- | --- |
|  | $$ρ\_{uv}= \frac{cov\left(u,v\right)}{ σ\_{u}∙ σ\_{v}}$$ | (S2) |

|  |  |  |
| --- | --- | --- |
|  | $$ρ\_{ixiy}= \frac{cov\left(ix,iy\right)}{ σ\_{ix}∙ σ\_{iy}}$$ | (S3) |

By assuming that $i\_{x}$, $i\_{y}$, $u$ and $v$ were mutually independent, the correlation coefficient at single-cell level was yielded

|  |  |  |
| --- | --- | --- |
|  | $$ρ\_{xy}^{ }=\frac{cov\left(u,v\right)+cov(i\_{x},i\_{y})}{\sqrt[2]{(σ\_{u}^{2}+σ\_{ix}^{2})∙(σ\_{v}^{2}+σ\_{iy}^{2})}}$$ | (S4) |

Using Equations S2-S4 and assuming $ρ\_{xy}$might be close to but not zero, one could compare the correlations by calculating their ratio:

|  |  |  |
| --- | --- | --- |
|  | $$\frac{ρ\_{uv}}{ρ\_{xy}}=\frac{\frac{cov\left(u,v\right)}{ σ\_{u}∙ σ\_{v}}}{\frac{cov\left(u,v\right)+cov(i\_{x},i\_{y})}{\sqrt[2]{(σ\_{u}^{2}+σ\_{ix}^{2})∙(σ\_{v}^{2}+σ\_{iy}^{2})}}}=\frac{cov\left(u,v\right)}{cov\left(u,v\right)+cov(i\_{x},i\_{y})}∙\sqrt[2]{\frac{\left(σ\_{u}^{2}+σ\_{ix}^{2}\right)∙\left(σ\_{v}^{2}+σ\_{iy}^{2}\right)}{ σ\_{u}^{2}∙ σ\_{v}^{2}} }=\left(1-\frac{cov\left(i\_{x},i\_{y}\right)}{cov\left(u,v\right)+cov\left(i\_{x},i\_{y}\right)} \right)∙\sqrt[2]{\frac{\left(σ\_{u}^{2}+σ\_{ix}^{2}\right)∙\left(σ\_{v}^{2}+σ\_{iy}^{2}\right)}{ σ\_{u}^{2}∙ σ\_{v}^{2}}}=\sqrt[2]{\frac{\left(σ\_{u}^{2}+σ\_{ix}^{2}\right)∙\left(σ\_{v}^{2}+σ\_{iy}^{2}\right)}{ σ\_{u}^{2}∙ σ\_{v}^{2}}}-\frac{cov\left(i\_{x},i\_{y}\right)}{cov\left(u,v\right)+cov\left(i\_{x},i\_{y}\right)}∙\sqrt[2]{\frac{\left(σ\_{u}^{2}+σ\_{ix}^{2}\right)∙\left(σ\_{v}^{2}+σ\_{iy}^{2}\right)}{ σ\_{u}^{2}∙ σ\_{v}^{2}}}=\sqrt[2]{\left(1+\frac{σ\_{ix}^{2}}{σ\_{u}^{2}}\right)∙\left(1+\frac{σ\_{iy}^{2}}{σ\_{v}^{2}}\right)}-\frac{ρ\_{ixiy}∙σ\_{ix}∙ σ\_{iy}}{ρ\_{xy}^{ }∙\sqrt[2]{\left(σ\_{u}^{2}+σ\_{ix}^{2}\right)∙\left(σ\_{v}^{2}+σ\_{iy}^{2}\right)}}∙\sqrt[2]{\frac{\left(σ\_{u}^{2}+σ\_{ix}^{2}\right)∙\left(σ\_{v}^{2}+σ\_{iy}^{2}\right)}{ σ\_{u}^{2}∙ σ\_{v}^{2}}}=\sqrt[2]{\left(1+\frac{σ\_{ix}^{2}}{σ\_{u}^{2}}\right)∙\left(1+\frac{σ\_{iy}^{2}}{σ\_{v}^{2}}\right)}- \frac{σ\_{ix}}{σ\_{u}}∙\frac{σ\_{iy}}{σ\_{v}}∙\frac{ρ\_{ixiy}}{ρ\_{xy}}$$ | (S5) |

Thus, Equation 1 in the main text was derived, which indicated the ratio of the aggregated correlation to the individual correlation.

# Demonstration of $ρ\_{uv}>ρ\_{xy}$ when the condition of $\frac{ρ\_{ixiy}}{ρ\_{xy}}\leq 1$ meets

Next, we would demonstrate that when the correlation within is weaker than individual correlation, or the signs of correlation within and individual correlation differ (one is positive and the other is negative), the correlation at bulk level is stronger than it at single cell level.

## When $0\leq \frac{ρ\_{ixiy}}{ρ\_{xy}}\leq 1$

Under the condition that

|  |  |  |
| --- | --- | --- |
|  | $$\left(\frac{ρ\_{ixiy}}{ρ\_{xy}}\right)\_{ }^{2}\leq 1$$ | (S6) |

Using Equations S1and S3, Equation S6 could be written as

|  |  |  |
| --- | --- | --- |
|  | $$\left(\frac{\frac{cov\left(ix,iy\right)}{ σ\_{ix}∙ σ\_{iy}}}{\frac{cov\left(x,y\right)}{ σ\_{x}∙ σ\_{y}}}\right)\_{ }^{2}\leq 1$$$$\left(\frac{cov\left(ix,iy\right)}{cov\left(x,y\right)}\right)\_{ }^{2}∙\frac{σ\_{x}^{2}∙σ\_{y}^{2}}{σ\_{ix}^{2}∙σ\_{ix}^{2}}\leq 1$$$$\left(\frac{cov\left(x-u,y-v\right)}{cov\left(x,y\right)}\right)\_{ }^{2}∙\frac{σ\_{x}^{2}∙σ\_{y}^{2}}{(σ\_{x}^{2}-σ\_{u}^{2})∙(σ\_{y}^{2}-σ\_{v}^{2})}\leq 1$$ | (S7) |

By taking the assumption that $x$ and $v$, $u$ and $y$ were independent and combining Equation S2, Equation S7 was derived as

|  |  |  |
| --- | --- | --- |
|  | $$\left(1-\frac{σ\_{u}^{ }∙σ\_{v}^{ }}{σ\_{x}^{ }∙σ\_{y}^{ }}∙\frac{ρ\_{uv}}{ρ\_{xy}}\right)\_{ }^{2}\leq \frac{(σ\_{x}^{2}-σ\_{u}^{2})∙(σ\_{y}^{2}-σ\_{v}^{2})}{σ\_{x}^{2}∙σ\_{y}^{2}}$$$$\frac{σ\_{u}^{2}∙σ\_{v}^{2 }}{σ\_{x}^{2}∙σ\_{y}^{2}}∙\left(\frac{ρ\_{uv}}{ρ\_{xy}}\right)\_{ }^{2}-2∙\frac{σ\_{u}^{ }∙σ\_{v}^{ }}{σ\_{x}^{ }∙σ\_{y}^{ }}∙\frac{ρ\_{uv}}{ρ\_{xy}}+\frac{σ\_{x}^{2}∙σ\_{v}^{2}+σ\_{u}^{2}∙σ\_{y}^{2}-σ\_{u}^{2}∙σ\_{v}^{2}}{σ\_{x}^{2}∙σ\_{y}^{2}}\leq 0$$ | (S8) |

Next, we would like to solve this quadratic inequality. We replaced $\frac{ρ\_{uv}}{ρ\_{xy}}$ in S8 by $x$ and get the function:

|  |  |  |
| --- | --- | --- |
|  | $$f\left(x\right)=\frac{σ\_{u}^{2}∙σ\_{v}^{2 }}{σ\_{x}^{2}∙σ\_{y}^{2}}∙x\_{ }^{2}-2∙\frac{σ\_{u}^{ }∙σ\_{v}^{ }}{σ\_{x}^{ }∙σ\_{y}^{ }}∙x+\frac{σ\_{x}^{2}∙σ\_{v}^{2}+σ\_{u}^{2}∙σ\_{y}^{2}-σ\_{u}^{2}∙σ\_{v}^{2}}{σ\_{x}^{2}∙σ\_{y}^{2}}$$ | (S9) |

The quadratic inequation S8 indicates that Function S9 is negative, since Function S9 is negative between the two solutions of $f\left(x\right)=0$:

|  |  |  |
| --- | --- | --- |
|  | $$x=\frac{1}{σ\_{u}^{ }∙σ\_{v}^{ }}∙[σ\_{x}^{ }∙σ\_{y}^{ }\mp \sqrt[2]{σ\_{x}^{2}∙σ\_{y}^{2}+σ\_{u}^{2}∙σ\_{v}^{2 }-(σ\_{x}^{2}∙σ\_{v}^{2 }+σ\_{u}^{2}∙σ\_{y}^{2 })}$$ | (S10) |

Therefore, $x$ locates between these two solutions, i.e.

|  |  |  |
| --- | --- | --- |
|  | $$\frac{1}{σ\_{u}^{ }∙σ\_{v}^{ }}∙\left[σ\_{x}^{ }∙σ\_{y}^{ }-\sqrt[2]{σ\_{x}^{2}∙σ\_{y}^{2}+σ\_{u}^{2}∙σ\_{v}^{2 }-(σ\_{x}^{2}∙σ\_{v}^{2 }+σ\_{u}^{2}∙σ\_{y}^{2 })}\right]\leq x\leq \frac{1}{σ\_{u}^{ }∙σ\_{v}^{ }}∙\left[σ\_{x}^{ }∙σ\_{y}^{ }+\sqrt[2]{σ\_{x}^{2}∙σ\_{y}^{2}+σ\_{u}^{2}∙σ\_{v}^{2 }-(σ\_{x}^{2}∙σ\_{v}^{2 }+σ\_{u}^{2}∙σ\_{y}^{2 })}\right]$$ | (S11) |

As $σ\_{x}^{2}∙σ\_{v}^{2 }+σ\_{u}^{2}∙σ\_{y}^{2 }\geq 2∙σ\_{u}^{ }∙σ\_{v}^{ }∙σ\_{x}^{ }∙σ\_{y}^{ }$,

|  |  |  |
| --- | --- | --- |
|  | $$\frac{1}{σ\_{u}^{ }∙σ\_{v}^{ }}∙\left[σ\_{x}^{ }∙σ\_{y}^{ }-\sqrt[2]{σ\_{x}^{2}∙σ\_{y}^{2}+σ\_{u}^{2}∙σ\_{v}^{2 }-2∙σ\_{u}^{ }∙σ\_{v}^{ }∙σ\_{x}^{ }∙σ\_{y}^{ }}\right]\leq x\leq \frac{1}{σ\_{u}^{ }∙σ\_{v}^{ }}∙\left[σ\_{x}^{ }∙σ\_{y}^{ }+\sqrt[2]{σ\_{x}^{2}∙σ\_{y}^{2}+σ\_{u}^{2}∙σ\_{v}^{2 }-2∙σ\_{u}^{ }∙σ\_{v}^{ }∙σ\_{x}^{ }∙σ\_{y}^{ }}\right]$$$$\frac{1}{σ\_{u}^{ }∙σ\_{v}^{ }}∙\left[σ\_{x}^{ }∙σ\_{y}^{ }-\sqrt[2]{\left(σ\_{x}^{ }∙σ\_{y}^{ }–σ\_{u}^{ }∙σ\_{v}^{ }\right)\_{ }^{2}}\right]\leq x\leq \frac{1}{σ\_{u}^{ }∙σ\_{v}^{ }}∙\left[σ\_{x}^{ }∙σ\_{y}^{ }+\sqrt[2]{\left(σ\_{x}^{ }∙σ\_{y}^{ }–σ\_{u}^{ }∙σ\_{v}^{ }\right)\_{ }^{2}}\right]$$ | (S12) |

Since $σ\_{x}^{2}=σ\_{u}^{2}+σ\_{ix}^{2}$ and $σ\_{y}^{2}=σ\_{v}^{2}+σ\_{iy}^{2}$, we got

|  |  |  |
| --- | --- | --- |
|  | $$σ\_{x}^{ }\geq σ\_{u}^{ } and σ\_{y}^{ }\geq σ\_{v}^{ }$$ | (S13) |

The inequation S12 could be simplified as

|  |  |  |
| --- | --- | --- |
|  | $$\frac{1}{σ\_{u}^{ }∙σ\_{v}^{ }}∙\left[σ\_{x}^{ }∙σ\_{y}^{ }–\left(σ\_{x}^{ }∙σ\_{y}^{ }–σ\_{u}^{ }∙σ\_{v}^{ }\right)\right]\leq x\leq \frac{1}{σ\_{u}^{ }∙σ\_{v}^{ }}∙\left[σ\_{x}^{ }∙σ\_{y}^{ }+\left(σ\_{x}^{ }∙σ\_{y}^{ }–σ\_{u}^{ }∙σ\_{v}^{ }\right)\right]$$$$1\leq x\leq 2∙\frac{σ\_{x}^{ }∙σ\_{y}^{ }}{σ\_{u}^{ }∙σ\_{v}^{ }}-1$$ | (S14) |

When we replace $x$ by $\frac{ρ\_{uv}}{ρ\_{xy}}$ back,

$$1\leq \frac{ρ\_{uv}}{ρ\_{xy}}\leq 2∙\frac{σ\_{x}^{ }∙σ\_{y}^{ }}{σ\_{u}^{ }∙σ\_{v}^{ }}-1$$

Up to now, we demonstrated that when the value of correlation-within is weaker than the individual correlation, the correlation at the bulk level is stronger than it at the single cell level.

## When $\frac{ρ\_{ixiy}}{ρ\_{xy}}<0$

|  |  |  |
| --- | --- | --- |
|  | $$\frac{ρ\_{uv}}{ρ\_{xy}}= \sqrt[2]{\left(1+\frac{σ\_{ix}^{2}}{σ\_{u}^{2}}\right)∙\left(1+\frac{σ\_{iy}^{2}}{σ\_{v}^{2}}\right)} – \frac{σ\_{ix}}{σ\_{u}}∙\frac{σ\_{iy}}{σ\_{v}}∙\frac{ρ\_{ixiy}}{ρ\_{xy}}=\left(1-\frac{ρ\_{ixiy}}{ρ\_{xy}}\right)∙\frac{σ\_{x}∙σ\_{y}-σ\_{ix}∙σ\_{iy}}{σ\_{v}∙σ\_{u}}\geq \frac{σ\_{x}∙σ\_{y}-σ\_{ix}∙σ\_{iy}}{σ\_{v}∙σ\_{u}}$$As | (S15) |
|  | $$(\frac{σ\_{x}∙σ\_{y}-σ\_{ix}∙σ\_{iy}}{σ\_{v}∙σ\_{u}})^{2}=\frac{σ\_{x}^{2}∙σ\_{y}^{2}+σ\_{iy}^{2}∙σ\_{iy}^{2}-2∙σ\_{x}∙σ\_{y}∙σ\_{ix}∙σ\_{iy}}{σ\_{u}^{2}∙σ\_{v}^{2}}=\frac{σ\_{x}^{2}∙σ\_{y}^{2}+σ\_{iy}^{2}∙σ\_{iy}^{2}-2∙σ\_{x}∙σ\_{y}∙σ\_{ix}∙σ\_{iy}}{σ\_{x}^{2}∙σ\_{y}^{2}+σ\_{iy}^{2}∙σ\_{iy}^{2}-(σ\_{x}^{2}∙σ\_{iy}^{2}+σ\_{y}^{2}∙σ\_{ix}^{2})}\geq 1$$ | (S16) |

As $σ\_{x}∙σ\_{y}\geq σ\_{ix}∙σ\_{iy}$,

|  |  |  |
| --- | --- | --- |
|  | $$\frac{σ\_{x}∙σ\_{y}-σ\_{ix}∙σ\_{iy}}{σ\_{v}∙σ\_{u}}\geq 1$$ | (S17) |

Thus,

|  |  |  |
| --- | --- | --- |
|  | $$\frac{ρ\_{uv}}{ρ\_{xy}}\geq \frac{σ\_{x}∙σ\_{y}-σ\_{ix}∙σ\_{iy}}{σ\_{v}∙σ\_{u}}\geq 1$$ | (S18) |

In summary, when the condition of $\frac{ρ\_{ixiy}}{ρ\_{xy}}\leq 1$ meets, the correlation at the bulk level is stronger than it at the single-cell level.

# Model construction

We developed two toy models to represent two typical biological regulatory systems respectively: Model1 described a multi-step signaling cascade (Figure 2A) and Model2 characterized a multi-regulator controlled gene expression (Figure 2B). The ODEs and the respective parameters were list as follows.

## Model1

### Mathematical equations of Model1

|  |  |  |
| --- | --- | --- |
|  | $$\frac{dX1}{dt}= -a\_{1}^{ }∙\frac{X1}{k\_{m1}^{ }+X1}∙\frac{K\_{ }^{n}}{K\_{ }^{n}+Y\_{ }^{\*n}}+a\_{2}^{ }∙\frac{X1\_{ }^{\*}}{k\_{m2}^{ }+X1\_{ }^{\*}}$$ | (S13) |
|  | $$\frac{dX1\_{ }^{\*}}{dt}= a\_{1}^{ }∙\frac{X1}{k\_{m1}^{ }+X1}∙\frac{K\_{ }^{n}}{K\_{ }^{n}+Y\_{ }^{\*n}}-a\_{2}^{ }∙\frac{X1\_{ }^{\*}}{k\_{m2}^{ }+X1\_{ }^{\*}}$$ | (S14) |
|  | $$\frac{dX2\_{ }^{ }}{dt}= -k\_{3}^{ }∙\frac{X1\_{ }^{\*}∙X2}{k\_{m3}^{ }+X2}+a\_{4}^{ }∙\frac{X2\_{ }^{\*}}{k\_{m4}^{ }+X2\_{ }^{\*}}$$ | (S15) |
|  | $$\frac{dX2\_{ }^{\* }}{dt}= k\_{3}^{ }∙\frac{X1\_{ }^{\*}∙X2}{k\_{m3}^{ }+X2}-a\_{4}^{ }∙\frac{X2\_{ }^{\*}}{k\_{m4}^{ }+X2\_{ }^{\*}}$$ | (S16) |
|  | $$\frac{dX3\_{ }^{ }}{dt}= -k\_{5}^{ }∙\frac{X2\_{ }^{\*}∙X3}{k\_{m5}^{ }+X3}+a\_{6}^{ }∙\frac{X3\_{ }^{\*}}{k\_{m6}^{ }+X3\_{ }^{\*}}$$ | (S17) |
|  | $$\frac{dX3\_{ }^{\* }}{dt}= k\_{5}^{ }∙\frac{X2\_{ }^{\*}∙X3}{k\_{m5}^{ }+X3}-a\_{6}^{ }∙\frac{X3\_{ }^{\*}}{k\_{m6}^{ }+X3\_{ }^{\*}}$$ | (S18) |
|  | $$\frac{dY\_{ }^{ }}{dt}= -k\_{7}^{ }∙\frac{X3\_{ }^{\*}∙Y}{k\_{m7}^{ }+Y}+a\_{8}^{ }∙\frac{Y\_{ }^{\*}}{k\_{m8}^{ }+Y\_{ }^{\*}}$$ | (S19) |
|  | $$\frac{dY\_{ }^{\*}}{dt}= k\_{7}^{ }∙\frac{X3\_{ }^{\*}∙Y}{k\_{m7}^{ }+Y}-a\_{8}^{ }∙\frac{Y\_{ }^{\*}}{k\_{m8}^{ }+Y\_{ }^{\*}}$$ | (S20) |

### Parameter values of Model1

**Table S1. Parameters for Model1**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Value | Parameter | Value |
| $$a\_{1}^{ }$$ | 2.5 | $$k\_{m1}^{ }$$ | 10 |
| $$a\_{2}^{ }$$ | 0.25 | $$k\_{m2}^{ }$$ | 8 |
| $$a\_{4}^{ }$$ | 0.5 | $$k\_{m3}^{ }$$ | 15 |
| $$a\_{6}^{ }$$ | 0.75 | $$k\_{m4}^{ }$$ | 15 |
| $$a\_{8}^{ }$$ | 0.75 | $$k\_{m5}^{ }$$ | 15 |
| $$k\_{3}^{ }$$ | 0.5 | $$k\_{m6}^{ }$$ | 15 |
| $$k\_{5}^{ }$$ | 0.5 | $$k\_{m7}^{ }$$ | 15 |
| $$k\_{7}^{ }$$ | 5 | $$k\_{m8}^{ }$$ | 15 |
| $$K\_{ }^{ }$$ | 9 | $$n\_{ }^{ }$$ | 1 |

## Model2

### Mathematical equations of Model2

|  |  |  |
| --- | --- | --- |
|  | $$\frac{dX1}{dt}= -a\_{1}^{ }∙\frac{X1}{k\_{m1}^{ }+X1}∙\frac{K\_{ }^{n1}}{K\_{ }^{n1}+Y\_{ }^{\*n1}}+a\_{2}^{ }∙\frac{X1\_{ }^{\*}}{k\_{m2}^{ }+X1\_{ }^{\*}}$$ | (S21) |
|  | $$\frac{dX1\_{ }^{\*}}{dt}= a\_{1}^{ }∙\frac{X1}{k\_{m1}^{ }+X1}∙\frac{K\_{ }^{n1}}{K\_{ }^{n1}+Y\_{ }^{\*n1}}-a\_{2}^{ }∙\frac{X1\_{ }^{\*}}{k\_{m2}^{ }+X1\_{ }^{\*}}$$ | (S22) |
|  | $$\frac{dX2\_{ }^{ }}{dt}= -a\_{3}^{ }∙\frac{X2}{k\_{m3}^{ }+X2}∙\frac{K\_{ }^{n2}}{K\_{ }^{n2}+Y\_{ }^{\*n2}}+a\_{4}^{ }∙\frac{X2\_{ }^{\*}}{k\_{m4}^{ }+X2\_{ }^{\*}}$$ | (S23) |
|  | $$\frac{dX2\_{ }^{\* }}{dt}= a\_{3}^{ }∙\frac{X2}{k\_{m3}^{ }+X2}∙\frac{K\_{ }^{n2}}{K\_{ }^{n2}+Y\_{ }^{\*n2}}-a\_{4}^{ }∙\frac{X2\_{ }^{\*}}{k\_{m4}^{ }+X2\_{ }^{\*}}$$ | (S24) |
|  | $$\frac{dX3\_{ }^{ }}{dt}= -a\_{5}^{ }∙\frac{X3}{k\_{m5}^{ }+X3}∙\frac{K\_{ }^{n3}}{K\_{ }^{n3}+Y\_{ }^{\*n3}}+a\_{6}^{ }∙\frac{X3\_{ }^{\*}}{k\_{m6}^{ }+X3\_{ }^{\*}}$$ | (S25) |
|  | $$\frac{dX3\_{ }^{\* }}{dt}= a\_{5}^{ }∙\frac{X3}{k\_{m5}^{ }+X3}∙\frac{K\_{ }^{n3}}{K\_{ }^{n3}+Y\_{ }^{\*n3}}-a\_{6}^{ }∙\frac{X3\_{ }^{\*}}{k\_{m6}^{ }+X3\_{ }^{\*}}$$ | (S26) |
|  | $$\frac{dY\_{ }^{ }}{dt}= -(k\_{1}^{ }∙\frac{X1\_{ }^{\*}∙Y}{k\_{a1}^{ }+Y}+k\_{2}^{ }∙\frac{X2\_{ }^{\*}∙Y}{k\_{a2}^{ }+Y}+k\_{3}^{ }∙\frac{X2\_{ }^{\*}∙Y}{k\_{a2}^{ }+Y})+a\_{8}^{ }∙\frac{Y\_{ }^{\*}}{k\_{m8}^{ }+Y\_{ }^{\*}}$$ | (S27) |
|  | $$\frac{dY\_{ }^{\*}}{dt}= (k\_{1}^{ }∙\frac{X1\_{ }^{\*}∙Y}{k\_{a1}^{ }+Y}+k\_{2}^{ }∙\frac{X2\_{ }^{\*}∙Y}{k\_{a2}^{ }+Y}+k\_{3}^{ }∙\frac{X2\_{ }^{\*}∙Y}{k\_{a2}^{ }+Y})-a\_{8}^{ }∙\frac{Y\_{ }^{\*}}{k\_{m8}^{ }+Y\_{ }^{\*}}$$ | (S28) |

### Parameter values of Model2

**Table S2. Parameters for Model2**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Value | Parameter | Value |
| $$a\_{1}^{ }$$ | 2.5 | $$k\_{m1}^{ }$$ | 10 |
| $$a\_{2}^{ }$$ | 0.25 | $$k\_{m2}^{ }$$ | 8 |
| $$a\_{4}^{ }$$ | 0.5 | $$k\_{m3}^{ }$$ | 15 |
| $$a\_{6}^{ }$$ | 0.75 | $$k\_{m4}^{ }$$ | 15 |
| $$a\_{8}^{ }$$ | 0.75 | $$k\_{m5}^{ }$$ | 15 |
| $$k\_{3}^{ }$$ | 0.5 | $$k\_{m6}^{ }$$ | 15 |
| $$k\_{5}^{ }$$ | 0.5 | $$k\_{m7}^{ }$$ | 15 |
| $$k\_{7}^{ }$$ | 5 | $$k\_{m8}^{ }$$ | 15 |
| $$K\_{ }^{ }$$ | 9 | $$n\_{ }^{ }$$ | 1 |

## Model3

This model was previously published(1). We used the same notation as published: S = growth signals, M = Myc, E = E2F, CD = Cyclin D, CE = Cyclin E, R = unphosphorylated (active) Rb, RP = unphosphorylated (inactive) Rb, RE = Rb-E2F complex.

### Mathematical equations of Model3

|  |  |  |
| --- | --- | --- |
|  | $$\frac{d[M]}{dt}= k\_{M}^{ }∙\frac{\left[S\right]}{K\_{S}^{ }+\left[S\right]}-d\_{M}^{ }∙[M]$$ | (S29) |
|  | $$\frac{d\left[E\right]}{dt}= k\_{E}^{ }∙\frac{\left[M\right]}{k\_{M}^{ }+\left[M\right]}∙\frac{\left[E\right]}{K\_{E}^{ }+\left[E\right]}+k\_{b}^{ }∙\frac{\left[M\right]}{k\_{M}^{ }+\left[M\right]}+k\_{p1}^{ }∙\frac{\left[CD\right]∙\left[RE\right]}{K\_{CD}^{ }+\left[RE\right]}$$$$+k\_{p2}^{ }∙\frac{\left[CE\right]∙\left[RE\right]}{K\_{CE}^{ }+\left[RE\right]}-d\_{E}^{ }∙\left[E\right]-k\_{RE}^{ }∙\left[R\right]\left[E\right]$$ | (S30) |
|  | $$\frac{d\left[CD\right]}{dt}= k\_{CD}^{ }∙\frac{\left[M\right]}{K\_{M}^{ }+\left[M\right]}+k\_{CDS}^{ }∙\frac{\left[S\right]}{K\_{S}^{ }+\left[S\right]}-d\_{CD}^{ }∙\left[CD\right]$$ | (S31) |
|  | $$\frac{d\left[CE\right]}{dt}= k\_{CE}^{ }∙\frac{\left[E\right]}{K\_{E}^{ }+\left[E\right]}-d\_{CE}^{ }∙\left[CE\right]$$ | (S32) |
|  | $$\frac{d\left[R\right]}{dt}= k\_{R}^{ }+k\_{DP}^{ }∙\frac{\left[RP\right]}{K\_{RP}^{ }+\left[RP\right]}-k\_{RE}^{ }∙\left[R\right]\left[E\right]-k\_{p1}^{ }∙\frac{\left[CD\right]∙\left[R\right]}{K\_{CD}^{ }+\left[R\right]}-k\_{p2}^{ }∙\frac{\left[CE\right]∙\left[R\right]}{K\_{CE}^{ }+\left[R\right]}-d\_{R}^{ }∙\left[R\right]$$ | (S33) |
|  | $$\frac{d\left[RP\right]}{dt}= k\_{p1}^{ }∙\frac{\left[CD\right]∙\left[R\right]}{K\_{CD}^{ }+\left[R\right]}+k\_{p2}^{ }∙\frac{\left[CE\right]∙\left[R\right]}{K\_{CE}^{ }+\left[R\right]}+k\_{p1}^{ }∙\frac{\left[CD\right]∙\left[RE\right]}{K\_{CD}^{ }+\left[RE\right]}+k\_{p2}^{ }∙\frac{\left[CE\right]∙\left[RE\right]}{K\_{CE}^{ }+\left[RE\right]}$$$$-k\_{DP}^{ }∙\frac{\left[RP\right]}{K\_{RP}^{ }+\left[RP\right]}-d\_{R}^{ }∙\left[RP\right]$$ | (S34) |
|  | $$\frac{d\left[RE\right]}{dt}= k\_{RE}^{ }∙\left[R\right]\left[E\right]-k\_{p1}^{ }∙\frac{\left[CD\right]∙\left[RE\right]}{K\_{CD}^{ }+\left[RE\right]}-k\_{p2}^{ }∙\frac{\left[CE\right]∙\left[RE\right]}{K\_{CE}^{ }+\left[RE\right]}-d\_{RE}^{ }∙\left[RE\right]$$ | (S35) |

### Parameter values of Model3

**Table S3. Parameters for Model3**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Value | Parameter | Value |
| $$k\_{E}^{ }$$ | 0.4μM/hr  | $$d\_{CE}^{ }$$ | 1.5/hr |
| $$k\_{M}^{ }$$ | 1.0μM/hr | $$d\_{R}^{ }$$ | 0.06/hr |
| $$k\_{CD}^{ }$$ | 0.03μM/hr | $$d\_{RP}^{ }$$ | 0.06/hr |
| $$k\_{CDS}^{ }$$ | 0.45μM/hr | $$d\_{RE}^{ }$$ | 0.03/hr |
| $$k\_{R}^{ }$$ | 0.18μM/hr | $$k\_{P1}^{ }$$ | 18/hr |
| $$k\_{RE}^{ }$$ | 180μM/hr | $$k\_{P2}^{ }$$ | 18/hr |
| $$k\_{b}^{ }$$ | 0.003μM/hr | $$k\_{DP}^{ }$$ | 3.6μM/hr |
| $$K\_{S}^{ }$$ | 0.5μM | $$K\_{M}^{ }$$ | 0.15μM |
| $$k\_{CE}^{ }$$ | 0.35μM/hr | $$K\_{E}^{ }$$ | 0.15μM |
| $$d\_{M}^{ }$$ | 0.7/hr | $$K\_{CD}^{ }$$ | 0.92μM |
| $$d\_{E}^{ }\_{ }^{ }$$ | 0.25/hr | $$K\_{CE}^{ }$$ | 0.92μM |
| $$d\_{CD}^{ }$$ | 1.5/hr | $$K\_{RP}^{ }$$ | 0.01μM |

# Model simulation

### Model initial conditions for Model1 and Model2 in Figure2

10000 cells were simulated.

**Table S4. Initial conditions for Model1 and Model2**

|  |  |  |  |
| --- | --- | --- | --- |
| Species | Initial conditions | Species | Initial conditions |
| X1 | ～lognormal(-0.24, 0.198) | X1\* | 0 |
| X2 | ～lognormal(-0.53, 0.198) | X2\* | 0 |
| X3 | ～lognormal(-0.94, 0.198) | X3\* | 0 |
| Y | ～lognormal(-1.41, 0.198) | Y\* | 0 |

### Model initial conditions for Figure4

30000 cells were simulated.

**Table S5. Initial conditions for Model1 and Model2**

|  |  |  |  |
| --- | --- | --- | --- |
| Species | Initial conditions | Species | Initial conditions |
| X1 | ～lognormal(-0.24, 0.198) | X1\* | 0 |
| X2 | ～lognormal(-0.53, 0.198) | X2\* | 0 |
| X3 | ～lognormal(-0.94, 0.198) | X3\* | 0 |
| Y | ～lognormal(-1.41, 0.198) | Y\* | 0 |

### Initial conditions for Model3

10000 cells were simulated.

**Table S5. Initial conditions for Model3**

|  |  |  |  |
| --- | --- | --- | --- |
| Species | Initial conditions | Species | Initial conditions |
| S | ～lognormal(-3.39, 0.198) | CE | ～lognormal(-0.94, 0.198) |
| M | 0 | R | ～lognormal(-0.62, 0.198) |
| E | ～lognormal(-0.24, 0.198) | RP | 0 |
| CD | ～lognormal(-0.53, 0.198) | RE | 0 |

# Reference

1. Yao G, Lee TJ, Mori S, Nevins JR, & You L (2008) A bistable Rb-E2F switch underlies the restriction point. *Nat Cell Biol* 10(4):476-482.