Model Equations

The model is written as a set of 21 ordinary differential equations. Model states are:

Per1 – Per1 mRNA,
Per2 – Per2 mRNA,
Cry1 – Cry1 mRNA,
Cry2 – Cry2 mRNA,
Rev-erbα – Rev-erbα mRNA,
Clk – Clk mRNA,
Bmal1 – Bmal1 mRNA,
Rorc – Rorc mRNA,
PER1 – PER1 protein,
PER2 – PER2 protein,
CRY1 – CRY1 protein,
CRY2 – CRY2 protein,
REV-ERBα – REV-ERBα protein,
CLK – CLK protein,
BMAL1 – BMAL1 protein,
RORc – RORc protein,
PER1/CRY1 – Heterodimer of PER1 and CRY1 proteins,
PER1/CRY2 – Heterodimer of PER1 and CRY2 proteins,
PER2/CRY1 – Heterodimer of PER2 and CRY1 proteins,
PER2/CRY2 – Heterodimer of PER2 and CRY2 proteins,
CLK/BMAL1 – Heterodimer of CLK and BMAL1 proteins.

All parameters are as specified in Supplementary Table I.

$$\frac{dPer1}{dt} = (\mathrm{v}_{0,Per1} + \mathrm{v}_{1,Per1} * \frac{\mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Per1}}}{\mathrm{KA}_{1,Per1}{}^{\mathrm{na}_{1,Per1}} + \mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Per1}}}) * \\ \frac{\mathrm{KI}_{1,Per1}{}^{\mathrm{ni}_{1,Per1}}}{\mathrm{KI}_{1,Per1}{}^{\mathrm{ni}_{1,Per1}} + \mathrm{PER1/CRY1}^{\mathrm{ni}_{1,Per1}}} * \frac{\mathrm{KI}_{2,Per1}{}^{\mathrm{ni}_{2,Per1}}}{\mathrm{KI}_{2,Per1}{}^{\mathrm{ni}_{2,Per1}} + \mathrm{PER1/CRY2}^{\mathrm{ni}_{2,Per1}}} * \\ \frac{\mathrm{KI}_{3,Per1}{}^{\mathrm{ni}_{3,Per1}}}{\mathrm{KI}_{3,Per1}{}^{\mathrm{ni}_{3,Per1}} + \mathrm{PER2/CRY1}^{\mathrm{ni}_{3,Per1}}} * \frac{\mathrm{KI}_{4,Per1}{}^{\mathrm{ni}_{4,Per1}}}{\mathrm{KI}_{4,Per1}{}^{\mathrm{ni}_{4,Per1}} + \mathrm{PER2/CRY2}^{\mathrm{ni}_{4,Per1}}} - \mathrm{k}_{m,Per1} * Per1 \tag{1}$$

$$\frac{dPer2}{dt}=(\mathrm{v}_{0,Per2}+\mathrm{v}_{1,Per2}*\frac{\mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Per2}}}{\mathrm{KA}_{1,Per2}{}^{\mathrm{na}_{1,Per2}}+\mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Per2}}})*$$
$$\frac{\mathrm{KI}_{1,Per2}{}^{\mathrm{ni}_{1,Per2}}}{\mathrm{KI}_{1,Per2}{}^{\mathrm{ni}_{1,Per2}}+\mathrm{PER1/CRY1}^{\mathrm{ni}_{1,Per2}}}*\frac{\mathrm{KI}_{2,Per2}{}^{\mathrm{ni}_{2,Per2}}}{\mathrm{KI}_{2,Per2}{}^{\mathrm{ni}_{2,Per2}}+\mathrm{PER1/CRY2}^{\mathrm{ni}_{2,Per2}}}* \tag{2}$$
$$\frac{\mathrm{KI}_{3,Per2}{}^{\mathrm{ni}_{3,Per2}}}{\mathrm{KI}_{3,Per2}{}^{\mathrm{ni}_{3,Per2}}+\mathrm{PER2/CRY1}^{\mathrm{ni}_{3,Per2}}}*\frac{\mathrm{KI}_{4,Per2}{}^{\mathrm{ni}_{4,Per2}}}{\mathrm{KI}_{4,Per2}{}^{\mathrm{ni}_{4,Per2}}+\mathrm{PER2/CRY2}^{\mathrm{ni}_{4,Per2}}}-\mathrm{k}_{\mathrm{m},Per2}*Per2$$

$$\frac{dCry1}{dt}=(\mathrm{v}_{0,Cry1}+\mathrm{v}_{1,Cry1}*\frac{\mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Cry1}}}{\mathrm{KA}_{1,Cry1}{}^{\mathrm{na}_{1,Cry1}}+\mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Cry1}}}+$$
$$\mathrm{v}_{2,Cry1}*\frac{\mathrm{RORc}^{\mathrm{na}_{2,Cry1}}}{\mathrm{KA}_{2,Cry1}{}^{\mathrm{na}_{2,Cry1}}+\mathrm{RORc}^{\mathrm{na}_{2,Cry1}}})*\frac{\mathrm{KI}_{1,Cry1}{}^{\mathrm{ni}_{1,Cry1}}}{\mathrm{KI}_{1,Cry1}{}^{\mathrm{ni}_{1,Cry1}}+\mathrm{PER1/CRY1}^{\mathrm{ni}_{1,Cry1}}}*$$
$$\frac{\mathrm{KI}_{2,Cry1}{}^{\mathrm{ni}_{2,Cry1}}}{\mathrm{KI}_{2,Cry1}{}^{\mathrm{ni}_{2,Cry1}}+\mathrm{PER1/CRY2}^{\mathrm{ni}_{2,Cry1}}}*\frac{\mathrm{KI}_{3,Cry1}{}^{\mathrm{ni}_{3,Cry1}}}{\mathrm{KI}_{3,Cry1}{}^{\mathrm{ni}_{3,Cry1}}+\mathrm{PER2/CRY1}^{\mathrm{ni}_{3,Cry1}}}* \tag{3}$$
$$\frac{\mathrm{KI}_{4,Cry1}{}^{\mathrm{ni}_{4,Cry1}}}{\mathrm{KI}_{4,Cry1}{}^{\mathrm{ni}_{4,Cry1}}+\mathrm{PER2/CRY2}^{\mathrm{ni}_{4,Cry1}}}*\frac{\mathrm{KI}_{5,Cry1}{}^{\mathrm{ni}_{5,Cry1}}}{\mathrm{KI}_{5,\mathrm{Cry1}}{}^{\mathrm{ni}_{5,Cry1}}+\mathrm{REV-ERB}\alpha^{\mathrm{ni}_{5,Cry1}}}-\mathrm{k}_{\mathrm{m},Cry1}*Cry1$$

$$\frac{dCry2}{dt}=(\mathrm{v}_{0,Cry2}+\mathrm{v}_{1,Cry2}*\frac{\mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Cry2}}}{\mathrm{KA}_{1,Cry2}{}^{\mathrm{na}_{1,Cry2}}+\mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Cry2}}}+$$
$$\mathrm{v}_{2,Cry2}*\frac{\mathrm{RORc}^{\mathrm{na}_{2,Cry2}}}{\mathrm{KA}_{2,Cry2}{}^{\mathrm{na}_{2,Cry2}}+\mathrm{RORc}^{\mathrm{na}_{2,Cry2}}})*\frac{\mathrm{KI}_{1,Cry2}{}^{\mathrm{ni}_{1,Cry2}}}{\mathrm{KI}_{1,Cry2}{}^{\mathrm{ni}_{1,Cry2}}+\mathrm{PER1/CRY1}^{\mathrm{ni}_{1,Cry2}}}*$$
$$\frac{\mathrm{KI}_{2,Cry2}{}^{\mathrm{ni}_{2,Cry2}}}{\mathrm{KI}_{2,Cry2}{}^{\mathrm{ni}_{2,Cry2}}+\mathrm{PER1/CRY2}^{\mathrm{ni}_{2,Cry2}}}*\frac{\mathrm{KI}_{3,Cry2}{}^{\mathrm{ni}_{3,Cry2}}}{\mathrm{KI}_{3,Cry2}{}^{\mathrm{ni}_{3,Cry2}}+\mathrm{PER2/CRY1}^{\mathrm{ni}_{3,Cry2}}}* \tag{4}$$
$$\frac{\mathrm{KI}_{4,Cry2}{}^{\mathrm{ni}_{4,Cry2}}}{\mathrm{KI}_{4,Cry2}{}^{\mathrm{ni}_{4,Cry2}}+\mathrm{PER2/CRY2}^{\mathrm{ni}_{4,Cry2}}}*\frac{\mathrm{KI}_{5,Cry2}{}^{\mathrm{ni}_{5,Cry2}}}{\mathrm{KI}_{5,Cry2}{}^{\mathrm{ni}_{5,Cry2}}+\mathrm{REV-ERB}\alpha^{\mathrm{ni}_{5,Cry2}}}-\mathrm{k}_{\mathrm{m},Cry2}*Cry2$$

$$\frac{dRev-erb\alpha}{dt}=\mathrm{v}_{1,Rev-erb\alpha}*\frac{\mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Rev-erb\alpha}}}{\mathrm{KA}_{1,Rev-erb\alpha}{}^{\mathrm{na}_{1,Rev-erb\alpha}}+\mathrm{CLK/BMAL1}^{\mathrm{na}_{1,Rev-erb\alpha}}}*$$
$$\frac{\mathrm{KI}_{1,Rev-erb\alpha}{}^{\mathrm{ni}_{1,Rev-erb\alpha}}}{\mathrm{KI}_{1,Rev-erb\alpha}{}^{\mathrm{ni}_{1,Rev-erb\alpha}}+\mathrm{PER1/CRY1}^{\mathrm{ni}_{1,Rev-erb\alpha}}}*\frac{\mathrm{KI}_{2,Rev-erb\alpha}{}^{\mathrm{ni}_{2,Rev-erb\alpha}}}{\mathrm{KI}_{2,Rev-erb\alpha}{}^{\mathrm{ni}_{2,Rev-erb\alpha}}+\mathrm{PER1/CRY2}^{\mathrm{ni}_{2,Rev-erb\alpha}}}* \tag{5}$$
$$\frac{\mathrm{KI}_{3,Rev-erb\alpha}{}^{\mathrm{ni}_{3,Rev-erb\alpha}}}{\mathrm{KI}_{3,Rev-erb\alpha}{}^{\mathrm{ni}_{3,Rev-erb\alpha}}+\mathrm{PER2/CRY1}^{\mathrm{ni}_{3,Rev-erb\alpha}}}*\frac{\mathrm{KI}_{4,Rev-erb\alpha}{}^{\mathrm{ni}_{4,Rev-erb\alpha}}}{\mathrm{KI}_{4,Rev-erb\alpha}{}^{\mathrm{ni}_{4,Rev-erb\alpha}}+\mathrm{PER2/CRY2}^{\mathrm{ni}_{4,Rev-erb\alpha}}}-$$
$$\mathrm{k}_{\mathrm{m},Rev-erb\alpha}*Rev-erb\alpha$$

$$\frac{dClk}{dt} = (v_{0,Clk} + v_{1,Clk} * \frac{RORc^{na_{1,Clk}}}{KA_{1,Clk}{}^{na_{1,Clk}} + RORc^{na_{1,Clk}}}) * \frac{KI_{1,Clk}{}^{ni_{1,Clk}}}{KI_{1,Clk}{}^{ni_{1,Clk}} + REV\text{-}ERB\alpha^{ni_{1,Clk}}} - k_{m,Clk} * Clk \qquad (6)$$

$$\frac{dBmal1}{dt} = (v_{0,Bmal1} + v_{1,Bmal1} * \frac{RORc^{na_{1,Bmal1}}}{KA_{1,Bmal1}{}^{na_{1,Bmal1}} + RORc^{na_{1,Bmal1}}}) * \frac{KI_{1,Bmal1}{}^{ni_{1,Bmal1}}}{KI_{1,Bmal1}{}^{ni_{1,Bmal1}} + REV\text{-}ERB\alpha^{ni_{1,Bmal1}}} - k_{m,Bmal1} * Bmal1 \qquad (7)$$

$$\frac{dRorc}{dt} = (v_{0,Rorc} + v_{1,Rorc} * \frac{CLK/BMAL1^{na_{1,Rorc}}}{KA_{1,Rorc}{}^{na_{1,Rorc}} + CLK/BMAL1^{na_{1,Rorc}}} + v_{2,Rorc} * \frac{RORc^{na_{2,Rorc}}}{KA_{2,Rorc}{}^{na_{2.Rorc}} + RORc^{na_{2,Rorc}}}) * \frac{KI_{1,Rorc}{}^{ni_{1,Rorc}}}{KI_{1,Rorc}{}^{ni_{1,Rorc}} + PER1/CRY1^{ni_{1,Rorc}}} * \frac{KI_{2,Rorc}{}^{ni_{2,Rorc}}}{KI_{2,Rorc}{}^{ni_{2,Rorc}} + PER1/CRY2^{ni_{2,Rorc}}} * \frac{KI_{3,Rorc}{}^{ni_{3,Rorc}}}{KI_{3,Rorc}{}^{ni_{3,Rorc}} + PER2/CRY1^{ni_{3,Rorc}}} * \frac{KI_{4,Rorc}{}^{ni_{4,Rorc}}}{KI_{4,Rorc}{}^{ni_{4,Rorc}} + PER2/CRY2^{ni_{4,Rorc}}} * \frac{KI_{5,Rorc}{}^{ni_{5,Rorc}}}{KI_{5,Rorc}{}^{ni_{5,Rorc}} + REV\text{-}ERB\alpha^{ni_{5,Rorc}}} - k_{m,Rorc} * Rorc \qquad (8)$$

$$\frac{dPER1}{dt} = t_{Per1} * Per1 - a_{PER1,CRY1} * PER1 * CRY1 - a_{PER1,CRY2} * PER1 * CRY2 + d_{PER1/CRY1} * PER1/CRY1 + d_{PER1/CRY2} * PER1/CRY2 - k_{p,PER1} * PER1 \qquad (9)$$

$$\frac{dPER2}{dt} = t_{Per2} * Per2 - a_{PER2,CRY1} * PER2 * CRY1 - a_{PER2,CRY2} * PER2 * CRY2 + d_{PER2/CRY1} * PER2/CRY1 + d_{PER2/CRY2} * PER2/CRY2 - k_{p,PER2} * PER2 \qquad (10)$$

$$\frac{dCRY1}{dt} = t_{Cry1} * Cry1 - a_{PER1,CRY1} * PER1 * CRY1 - a_{PER2,CRY1} * PER2 * CRY1 + d_{PER1/CRY1} * PER1/CRY1 + d_{PER2/CRY1} * PER2/CRY1 - k_{p,CRY1} * CRY1 \qquad (11)$$

$$\frac{dCRY2}{dt} = t_{Cry2} * Cry2 - a_{PER1,CRY2} * PER1 * CRY2 - a_{PER2,CRY2} * PER2 * CRY2 + d_{PER1/CRY2} * PER1/CRY2 + d_{PER2/CRY2} * PER2/CRY2 - k_{p,CRY2} * CRY2 \qquad (12)$$

$$\frac{dREV\text{-}ERB\alpha}{dt} = t_{Rev\text{-}erb\alpha} * Rev\text{-}erb\alpha - k_{p,REV\text{-}ERB\alpha} * REV\text{-}ERB\alpha \qquad (13)$$

$$\frac{d\mathrm{CLK}}{dt} = \mathrm{t}_{Clk} * Clk - \mathrm{a}_{\mathrm{CLK,BMAL1}} * \mathrm{CLK} * \mathrm{BMAL1} + \mathrm{d}_{\mathrm{CLK/BMAL1}} * \mathrm{CLK/BMAL1} - \mathrm{k}_{\mathrm{p,CLK}} * \mathrm{CLK} \tag{14}$$

$$\frac{d\mathrm{BMAL1}}{dt} = \mathrm{t}_{Bmal1} * Bmal1 - \mathrm{a}_{\mathrm{CLK,BMAL1}} * \mathrm{CLK} * \mathrm{BMAL1} + \mathrm{d}_{\mathrm{CLK/BMAL1}} * \mathrm{CLK/BMAL1} - \mathrm{k}_{\mathrm{p,BMAL1}} * \mathrm{BMAL1} \tag{15}$$

$$\frac{d\mathrm{RORc}}{dt} = \mathrm{t}_{Rorc} * Rorc - \mathrm{k}_{\mathrm{p,RORc}} * \mathrm{RORc} \tag{16}$$

$$\frac{d\mathrm{PER1/CRY1}}{dt} = \mathrm{a}_{\mathrm{PER1,CRY1}} * \mathrm{PER1} * \mathrm{CRY1} - \mathrm{d}_{\mathrm{PER1/CRY1}} * \mathrm{PER1/CRY1} \tag{17}$$

$$\frac{d\mathrm{PER2/CRY1}}{dt} = \mathrm{a}_{\mathrm{PER2,CRY1}} * \mathrm{PER2} * \mathrm{CRY1} - \mathrm{d}_{\mathrm{PER2/CRY1}} * \mathrm{PER2/CRY1} \tag{18}$$

$$\frac{d\mathrm{PER1/CRY2}}{dt} = \mathrm{a}_{\mathrm{PER1,CRY2}} * \mathrm{PER1} * \mathrm{CRY2} - \mathrm{d}_{\mathrm{PER1/CRY2}} * \mathrm{PER1/CRY2} \tag{19}$$

$$\frac{d\mathrm{PER2/CRY2}}{dt} = \mathrm{a}_{\mathrm{PER2,CRY2}} * \mathrm{PER2} * \mathrm{CRY2} - \mathrm{d}_{\mathrm{PER2/CRY2}} * \mathrm{PER2/CRY2} \tag{20}$$

$$\frac{d\mathrm{CLK/BMAL1}}{dt} = \mathrm{a}_{\mathrm{CLK,BMAL1}} * \mathrm{CLK} * \mathrm{BMAL1} - \mathrm{d}_{\mathrm{CLK/BMAL1}} * \mathrm{CLK/BMAL1} \tag{21}$$

Cost Function

The cost funtion for the iterative optimization is given as

$$f = \gamma_1 + \gamma_2 + \gamma_3 + \gamma_4 + \gamma_5 + \gamma_6 + \gamma_7 + \gamma_8 + \delta_1 + \delta_2 + \delta_3 + \delta_4 + \delta_5 + \delta_6 + \delta_7 + \varepsilon_1 + \varepsilon_2 + \varepsilon_3 + \varepsilon_4 + \varepsilon_5 + \varepsilon_6 + \varepsilon_7 + \varepsilon_8 + \varepsilon_9 + \varepsilon_{10} + \varepsilon_{11} + \varepsilon_{12} + \varepsilon_{13} + \varepsilon_{14} + \varepsilon_{15} + \varepsilon_{16} + \varepsilon_{17} + \varepsilon_{18} + \varepsilon_{19} + \varepsilon_{20} + \varepsilon_{21} + \varepsilon_{22} + \varepsilon_{23}.$$

γ_1 represents the cost associated with the phase difference between *Per1* mRNA and PER1 protein, minimized at 5/24 of a period.

γ_1 = 5 * abs(m_1/P-5/24), P = period of oscillation, m_1 = time at peak of PER1 protein minus time at peak of *Per1* mRNA.

γ_2 represents the cost associated with the phase difference between *Per2* mRNA and PER2 protein, minimized at 5/24 of a period.

γ_2 = 5 * abs(m_2/P-5/24), P = period of oscillation, m_2 = time at peak of PER2 protein minus time at peak of *Per2* mRNA.

γ_3 represents the cost associated with the phase difference between *Cry1* mRNA and CRY1 protein, minimized at 5/24 of a period.

γ_3 = 5 * abs(m_3/P-5/24), P = period of oscillation, m_3 = time at peak of CRY1 protein minus time at peak of *Cry1* mRNA.

γ_4 represents the cost associated with the phase difference between *Cry2* mRNA and CRY2 protein, minimized at 5/24 of a period.

γ_4 = 5 * abs(m_4/P-5/24), P = period of oscillation, m_4 = time at peak of CRY2 protein minus time at peak of *Cry2* mRNA.

γ_5 represents the cost associated with the phase difference between *Rev-erbα* mRNA and REV-ERBα protein, minimized at 1.5/24 of a period.

γ_5 = 5 * abs(m_5/P-1.5/24), P = period of oscillation, m_5 = time at peak of REV-ERBα protein minus time at peak of *Rev-erbα* mRNA.

γ_6 represents the cost associated with the phase difference between *Clk* mRNA and CLK protein, minimized at 5/24 of a period.

γ_6 = 5 * abs(m_6/P-5/24), P = period of oscillation, m_6 = time at peak of CLK protein minus time at peak of *Clk* mRNA.

γ_7 represents the cost associated with the phase difference between *Bmal1* mRNA and BMAL1 protein, minimized at 5/24 of a period.

γ_7 = 5 * abs(m_7/P-5/24), P = period of oscillation, m_7 = time at peak of BMAL1 protein minus time at peak of *Bmal1* mRNA.

γ_8 represents the cost associated with the phase difference between *Rorc* mRNA and RORc protein, minimized at 1.5/24 of a period.

γ_8 = 5 * abs(m_8/P-1.5/24), P = period of oscillation, m_8 = time at peak of RORc protein minus time at peak of *Rorc* mRNA.

δ_1 represents the cost associated with the phase difference between *Rev-erbα* mRNA and *Per1* mRNA, minimized at 1/6 of a period.

δ_1 = 10 * abs(n_1/P-1/6), P = period of oscillation, n_1 = time at peak of *Per1* mRNA minus time at peak of *Rev-erbα* mRNA.

δ_2 represents the cost associated with the phase difference between *Rev-erbα* mRNA and *Per2* mRNA, minimized at 1/6 of a period.

δ_2 = 10 * abs(n_2/P-1/6), P = period of oscillation, n_2 = time at peak of *Per2* mRNA minus time at peak of *Rev-erbα* mRNA.

δ_3 represents the cost associated with the phase difference between *Rev-erbα* mRNA and *Cry1* mRNA, minimized at 1/3 of a period.

δ_3 = 10 * abs(n_3/P-1/3), P = period of oscillation, n_3 = time at peak of *Cry1* mRNA minus time at peak of *Rev-erbα* mRNA.

δ_4 represents the cost associated with the phase difference between *Rev-erbα* mRNA and *Cry2* mRNA, minimized at 1/3 of a period.

δ_4 = 10 * abs(n_4/P-1/3), P = period of oscillation, n_4 = time at peak of *Cry2* mRNA minus time at peak of *Rev-erbα* mRNA.

δ_5 represents the cost associated with the phase difference between *Rev-erbα* mRNA and *Rorc* mRNA, minimized at 1/3 of a period.

δ_5 = 10 * abs(n_5/P-1/3), P = period of oscillation, n_5 = time at peak of *Rorc* mRNA minus time at peak of *Rev-erbα* mRNA.

δ_6 represents the cost associated with the phase difference between *Rev-erbα* mRNA and *Clk* mRNA, minimized at 2/3 of a period.

δ_6 = 10 * abs(n_6/P-2/3), P = period of oscillation, n_6 = time at peak of *Clk* mRNA minus time at peak of *Rev-erbα* mRNA.

δ_7 represents the cost associated with the phase difference between *Rev-erbα* mRNA and *Bmal1* mRNA, minimized at 2/3 of a period.

δ_7 = 10 * abs(n_7/P-2/3), P = period of oscillation, n_7 = time at peak of *Bmal1* mRNA minus time at peak of *Rev-erbα* mRNA.

ε_1 represents the cost associated with the ratio between the minimum *Per1* mRNA level and the maximum *Per1* mRNA level, minimized at 0.2.

ε_1 = 0.5 * abs(min(*Per1* mRNA)/max(*Per1* mRNA)-0.2).

ε_2 represents the cost associated with the ratio between the minimum *Per2* mRNA level and the maximum *Per2* mRNA level, minimized at 0.2.

ε_2 = 0.5 * abs(min(*Per2* mRNA)/max(*Per2* mRNA)-0.2).

ε_3 represents the cost associated with the ratio between the minimum *Cry1* mRNA level and the maximum *Cry1* mRNA level, minimized at 0.5.

ε_3 = 0.5 * abs(min(*Cry1* mRNA)/max(*Cry1* mRNA)-0.5).

ε_4 represents the cost associated with the ratio between the minimum *Cry2* mRNA level and the maximum *Cry2* mRNA level, minimized at 0.5.

ε_4 = 0.5 * abs(min(*Cry2* mRNA)/max(*Cry2* mRNA)-0.5).

ε_5 represents the cost associated with the ratio between the minimum *Bmal1* mRNA level and the maximum *Bmal1* mRNA level, minimized at 0.1.

ε_5 = 0.5 * abs(min(*Bmal1* mRNA)/max(*Bmal1* mRNA)-0.1).

ε_6 represents the cost associated with the ratio between the minimum *Clk* mRNA level and the maximum *Clk* mRNA level, minimized at 0.5.

ε_6 = 0.5 * abs(min(*Clk* mRNA)/max(*Clk* mRNA)-0.5).

ε_7 represents the cost associated with the ratio between the minimum *Rev-erbα* mRNA level and the maximum *Rev-erbα* mRNA level, minimized at 0.2.

ε_7 = 0.5 * abs(min(*Rev-erbα* mRNA)/max(*Rev-erbα* mRNA)-0.2).

ε_8 represents the cost associated with the ratio between the minimum PER1 protein level and the maximum PER1 protein level, minimized at 0.1.

ε_8 = 0.5 * abs(min(PER1 protein)/max(PER1 protein)-0.1).

ε_9 represents the cost associated with the ratio between the minimum PER2 protein level and the maximum PER2 protein level, minimized at 0.

ε_9 = 0.5 * abs(min(PER2 protein)/max(PER2 protein)).

ε_{10} represents the cost associated with the ratio between the minimum CRY1 protein level and the maximum CRY1 protein level, minimized at 0.3.

ε_{10} = 0.5 * abs(min(CRY1 protein)/max(CRY1 protein)-0.3).

ε_{11} represents the cost associated with the ratio between the minimum CRY2 protein level and the maximum CRY2 protein level, minimized at 0.5.

ε_{11} = 0.5 * abs(min(CRY2 protein)/max(CRY2 protein)-0.5).

ε_{12} represents the cost associated with the ratio between the minimum BMAL1 protein level and the maximum BMAL1 protein level, minimized at 0.3.

ε_{12} = 0.5 * abs(min(BMAL1 protein)/max(BMAL1 protein)-0.3).

ε_{13} represents the cost associated with the ratio between the minimum CLK protein level and the maximum CLK protein level, minimized at 0.3.

ε_{13} = 0.5 * abs(min(CLK protein)/max(CLK protein)-0.3).

ε_{14} represents the cost associated with the ratio between the maximum PER1 protein level and the maximum CRY1 protein level, minimized at 0.05.

ε_{14} = 0.5 * abs(max(PER1 protein)/max(CRY1 protein)-0.05).

ε_{15} represents the cost associated with the ratio between the minimum PER1 protein level and the maximum CRY1 protein level, minimized at 0.

ε_{15} = 0.5 * abs(min(PER1 protein)/max(CRY1 protein)).

ε_{16} represents the cost associated with the ratio between the maximum PER2 protein level and the maximum CRY1 protein level, minimized at 0.15.

ε_{16} = 0.5 * abs(max(PER2 protein)/max(CRY1 protein)-0.15).

ε_{17} represents the cost associated with the ratio between the minimum PER2 protein level and the maximum CRY1 protein level, minimized at 0.

ε_{17} = 0.5 * abs(min(PER2 protein)/max(CRY1 protein)).

ε_{18} represents the cost associated with the ratio between the maximum CRY2 protein level and the maximum CRY1 protein level, minimized at 0.6.

$$\varepsilon_{18} = 0.5 * \text{abs}(\max(\text{CRY2 protein})/\max(\text{CRY1 protein})-0.6).$$

ε_{19} represents the cost associated with the ratio between the minimum CRY2 protein level and the maximum CRY1 protein level, minimized at 0.3.

$$\varepsilon_{19} = 0.5 * \text{abs}(\min(\text{CRY2 protein})/\max(\text{CRY1 protein})-0.3).$$

ε_{20} represents the cost associated with the ratio between the maximum CLK protein level and the maximum CRY1 protein level, minimized at 0.75.

$$\varepsilon_{20} = 0.5 * \text{abs}(\max(\text{CLK protein})/\max(\text{CRY1 protein})-0.75).$$

ε_{21} represents the cost associated with the ratio between the minimum CLK protein level and the maximum CRY1 protein level, minimized at 0.3.

$$\varepsilon_{21} = 0.5 * \text{abs}(\min(\text{CLK protein})/\max(\text{CRY1 protein})-0.3).$$

ε_{22} represents the cost associated with the ratio between the maximum BMAL1 protein level and the maximum CRY1 protein level, minimized at 0.15.

$$\varepsilon_{22} = 0.5 * \text{abs}(\max(\text{BMAL1 protein})/\max(\text{CRY1 protein})-0.15).$$

ε_{23} represents the cost associated with the ratio between the minimum BMAL1 protein level and the maximum CRY1 protein level, minimized at 0.05.

$$\varepsilon_{23} = 0.5 * \text{abs}(\min(\text{BMAL1 protein})/\max(\text{CRY1 protein})-0.05).$$