Supplementary Information: A comprehensive model of the photo-transduction cascade in mouse rod cells

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Supplementary Tables

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Table S1 Reactions and kinetics of the phototransduction model

Reaction Equation	Reaction kinetics	Comments
$R \xrightarrow{stimulus} R_0$	$v_f = \text{stimulus} \frac{R}{R_{tot}}$	Photoactivation of unphosphorylated R
$R \cdot G_t \xrightarrow{stimulus} R_0 \cdot G_t$	$v_f = \text{stimulus} \frac{R \cdot G_t}{R_{tot}}$	Photoactivation of pre-coupled $R \cdot G_t$
$R_n + RK \underset{kRK2}{\overset{kRK1_n}{\rightleftharpoons}} R_n \cdot RK_{pre} \mid_{n=0,1,\ldots,6}$	$v_f = kRK1_n \times R_n \times RK$ $v_r = kRK2 \times R_n \times RK_{pre}$	Binding of R_n and RK. The association rate constant is assumed to decrease exponentially with increasing phosphorylations: $kRK1_n = kRK1_0 \, e^{-\omega n}$
$R_n \cdot RK_{pre} \xrightarrow{kRK3_{ATP}} R_{n+1} \cdot RK_{post} \mid_{n=0,1,\ldots,5}$	$v_f = kRK3_{ATP} \times R_n \cdot RK_{pre}$	Phosphorylation of R_n to give R_{n+1}
$R_n \cdot RK_{post} \xrightarrow{kRK4} R_n + RK \mid_{n=1,2,\ldots,6}$	$v_f = kRK4 \times R_n \cdot RK_{post}$	Dissociation of the $R_n \cdot RK$ complex
$R_n + Arr \underset{kA2}{\overset{kA1_n}{\rightleftharpoons}} R_n \cdot Arr \mid_{n=1,2,\ldots,6}$	$v_f = kA1_n \times R_n \times Arr$ $v_r = kA2 \times R_n \cdot Arr$	Binding of R_n and Arr. The association rate constant increases linearly with the first four phosphorylations: $kA1_n = \begin{cases} kArr + (n-1)m_{Arr} & n \leq 4 \\ kArr + 3m_{Arr} & n > 4 \end{cases}$
$R_n \cdot Arr \xrightarrow{kA3} Ops + Arr \mid_{n=1,2,\ldots,6}$	$v_f = kA3 \times R_n \cdot Arr$	Arr-mediated inactivation of R_n. Ops indicates the ligand-free receptor
$Arr + Arr \underset{kA5}{\overset{kA4}{\rightleftharpoons}} Arr_{di}$	$v_f = kA4 \times Arr^2$ $v_r = kA5 \times Arr_{di}$	Arr homo-dimerization
$Arr_{di} + Arr_{di} \underset{kA5}{\overset{kA4}{\rightleftharpoons}} Arr_{tetra}$	$v_f = kA4 \times Arr_{di}^2$ $v_r = kA5 \times Arr_{tetra}$	Arr homo-tetramerization
$R_n \xrightarrow{ktherm} Ops \mid_{n=0,1,\ldots,6}$	$v_f = ktherm \times R_n$	Thermal decay of catalytic active form of R_n to give Ops
$Ops + G_t \underset{kG2}{\overset{kOps}{\rightleftharpoons}} Ops \cdot G_t$	$v_f = kOps \times Ops \times G_t$ $v_r = kG2 \times Ops.G_t$	Spontaneous Ops activity
$Ops \cdot G_t \underset{kG4_{GDP}}{\overset{kG3}{\rightleftharpoons}} Ops \cdot G$	$v_f = kG3 \times Ops \cdot G_t$ $v_r = kG4_{GDP} \times Ops \cdot G$	GDP dissociation from the $Ops \cdot G_t$ complex

Reaction Equation	Reaction kinetics	Comments
$\text{Ops} \cdot \text{G} \xrightarrow{kG5_{GTP}} \text{Ops} \cdot \text{G}_{\text{GTP}}$	$v_f = kG5_{GTP} \times Ops.G$	GTP binding to the $\text{Ops} \cdot \text{G}_t$ complex
$\text{Ops} \cdot \text{G}_{\text{GTP}} \xrightarrow{kG6} \text{Ops} + \text{G}_{\text{GTP}}$	$v_f = kG6 \times Ops \cdot G_{GTP}$	Dissociation of the $\text{Ops} \cdot \text{G}_{\text{GTP}}$ complex
$\text{Ops} \xrightarrow{kR_{recyc}} \text{R}$	$v_f = kR_{recyc} \times Ops$	Chromophore regeneration by 11-cis retinal binding to Ops
$\text{R} + \text{G}_t \underset{kG_{pre2}}{\overset{kG_{pre1}}{\rightleftharpoons}} \text{R} \cdot \text{G}_t$	$v_f = kG_{pre1} \times G_t \times R$ $v_r = kG_{pre2} \times R \cdot G_t$	Pre-coupling of inactive R to G_t, where $kG_{pre1} = 1.6\,kG1_0$ and $kG_{pre2} = 315\,kG2$
$\text{R}_n + \text{G}_t \underset{kG2}{\overset{kG1_n}{\rightleftharpoons}} \text{R}_n \cdot \text{G}_t \mid_{n=0,1,\dots,6}$	$v_f = kG1_n \times R \times G_t$ $v_r = kG2 \times R \cdot G_t$	Binding of R_n and G_t. The association rate constant is assumed to decrease exponentially with increasing phosphorylations: $kG1_n = kG1_0\,e^{-\omega_G n}$
$\text{R}_n \cdot \text{G}_t \underset{kG4_{GDP}}{\overset{kG3}{\rightleftharpoons}} \text{R}_n \cdot \text{G} \mid_{n=0,1,\dots,6}$	$v_f = kG3 \times R_n \cdot G_t$ $v_r = kG4_{GDP} \times R_n \cdot G$	GDP dissociation from the $\text{R}_n \cdot \text{G}_t$ complex
$\text{R}_n \cdot \text{G} \xrightarrow{kG5_{GTP}} \text{R}_n \cdot \text{G}_{\text{GTP}} \mid_{n=0,1,\dots,6}$	$v_f = kG5_{GTP} \times R_n \cdot G$	GTP binding to the $\text{R}_n \cdot \text{G}_t$ complex
$\text{R}_n \cdot \text{G}_{\text{GTP}} \xrightarrow{kG6} \text{R}_n + \text{G}_{\text{GTP}} \mid_{n=0,1,\dots,6}$	$v_f = kG6 \times R_n \cdot G_{GTP}$	Dissociation of the $\text{R}_n \cdot \text{G}_{\text{GTP}}$ complex
$\text{G}_{\text{GTP}} \xrightarrow{kG7} \text{G}_{\alpha\text{GTP}} + \text{G}_{\beta\gamma}$	$v_f = kG7 \times G_{GTP}$	Dissociation of trimeric G_t into α and $\beta\gamma$ subunits
$\text{PDE} + \text{G}_{\alpha\text{GTP}} \underset{kP1_{rev}}{\overset{kP1}{\rightleftharpoons}} \text{PDE} \cdot \text{G}_{\alpha\text{GTP}}$	$v_f = kP1 \times PDE \times G_{\alpha GTP}$ $v_r = kP1_{rev} \times PDE \cdot G_{\alpha GTP}$	Binding of $\text{G}_{\alpha\text{GTP}}$ to one PDE inactive subunit
$\text{PDE} \cdot \text{G}_{\alpha\text{GTP}} \xrightarrow{kP2} \text{PDE}^* \cdot \text{G}_{\alpha\text{GTP}}$	$v_f = kP2 \times PDE \cdot G_{\alpha GTP}$	Activation of the $\text{PDE} \cdot \text{G}_{\alpha\text{GTP}}$ complex
$\text{PDE}^* \cdot \text{G}_{\alpha\text{GTP}} + \text{G}_{\alpha\text{GTP}} \xrightarrow{kP3} \text{G}_{\alpha\text{GTP}} \cdot \text{PDE}^* \cdot \text{G}_{\alpha\text{GTP}}$	$v_f = kP3 \times PDE^* \cdot G_{\alpha GTP} \times G_{\alpha GTP}$	Binding of $\text{G}_{\alpha\text{GTP}}$ to singly active PDE
$\text{G}_{\alpha\text{GTP}} \cdot \text{PDE}^* \cdot \text{G}_{\alpha\text{GTP}} \xrightarrow{kP4} \text{G}_{\alpha\text{GTP}} \cdot {}^*\text{PDE}^* \cdot \text{G}_{\alpha\text{GTP}}$	$v_f = kP4 \times G_{\alpha GTP} \cdot PDE^* \cdot G_{\alpha GTP}$	Activation of the second $\text{G}_{\alpha\text{GTP}}$-bound PDE subunit
$\text{RGS} + \text{PDE}^* \cdot \text{G}_{\alpha\text{GTP}} \xrightarrow{kRGS1} \text{RGS} \cdot \text{PDE}^* \cdot \text{G}_{\alpha\text{GTP}}$	$v_f = kRGS1 \times RGS \times PDE^* \cdot G_{\alpha GTP}$	Binding of RGS9-1 complex to a singly-active PDE tetramer

Table S1 – *Continued from previous page*

Reaction Equation	Reaction kinetics	Comments
$RGS \cdot G_{\alpha GTP} \cdot {}^*PDE^* \cdot G_{\alpha GTP} \xrightarrow{kRGS2} PDE^* \cdot G_{\alpha GTP} + RGS + G_{\alpha GDP}$	$v_f = kRGS2 \times RGS \cdot G_{\alpha GTP} \cdot {}^* PDE^* \cdot G_{\alpha GTP}$	RGS9-1-mediated deactivation of one of two PDE active subunits
$RGS + PDE^* \cdot G_{\alpha GTP} \xrightarrow{kRGS1} RGS \cdot PDE^* \cdot G_{\alpha GTP}$	$v_f = kRGS1 \times RGS \times PDE^* \cdot G_{\alpha GTP}$	Binding of RGS9-1 complex to a singly active PDE
$RGS \cdot PDE^* \cdot G_{\alpha GTP} \xrightarrow{kRGS2} PDE + RGS + G_{\alpha GDP}$	$v_f = kRGS2 \times RGS \cdot PDE^* \cdot G_{\alpha GTP}$	RGS9-1-mediated deactivation of the singly active PDE
$PDE^* \cdot G_{\alpha GTP} \xrightarrow{kPDE_{shutoff}} PDE + G_{\alpha GDP}$	$v_f = kPDE_{shutoff} \times PDE^* \cdot G_{\alpha GTP}$	Inactivation of the $PDE^* \cdot G_{\alpha GTP}$ complex by $G_{\alpha GTP}$'s GTPase activity
$G_{\alpha GTP} \cdot {}^*PDE^* \cdot G_{\alpha GTP} \xrightarrow{kPDE_{shutoff}} PDE^* \cdot G_{\alpha GTP} + G_{\alpha GDP}$	$v_f = kPDE_{shutoff} \times G_{\alpha GTP} \cdot {}^* PDE^* \cdot G_{\alpha GTP}$	Inactivation of one of the two active PDE subunits by $G_{\alpha GTP}$'s GTPase activity
$G_{\alpha GTP} \xrightarrow{kG_{shutoff}} G_{\alpha GDP}$	$v_f = kG_{shutoff} \times G_{\alpha GTP}$	$G_{\alpha GTP}$ auto-catalytic GTPase activity
$G_{\alpha GDP} + G_{\beta\gamma} \xrightarrow{kG_{recyc}} G_t$	$v_f = kGrecyc \times G_{\alpha GDP} \times G_{\beta\gamma}$	Reconstitution of G_t heterotrimer from inactive subunits
$Rec_T + Ca^{2+}_{free} \underset{kRec2}{\overset{kRec1}{\rightleftharpoons}} Rec_R \cdot Ca^{2+}$	$v_f = kRec1 \times Rec_T \times Ca^{2+}_{free}$ $v_r = kRec2 \times Rec_R \cdot Ca^{2+}$	Ca^{2+}-induced Rec conformation change
$Rec_R \cdot Ca^{2+} + RK \underset{kRec4}{\overset{kRec3}{\rightleftharpoons}} Rec_R \cdot Ca^{2+} \cdot RK$	$v_f = kRec3 \times Rec_R \cdot Ca^{2+} \times RK$ $v_r = kRec4 \times Rec_R \cdot Ca^{2+} \cdot RK$	Binding of RK to Rec
$Ca^{2+}_{free} \underset{k2}{\overset{k1}{\rightleftharpoons}} Ca^{2+}_{buff}$	$v_f = k1 \times (eT - Ca^{2+}_{buff}) \times Ca^{2+}_{free}$ $v_r = k2 \times Ca^{2+}_{buff}$	Ca^{2+} association and dissociation from intracellular buffers with total concentration eT
$Ca^{2+}_{free} \xrightarrow{\gamma_{Ca}}$	$v_f = \gamma_{Ca} \times (Ca^{2+}_{free} - Ca^{2+}_0)$	Intracellular Ca^{2+}-efflux via the $Na^+/Ca^{2+} K^+$ exchanger
$\longrightarrow Ca^{2+}_{free}$	$v_f = \frac{10^6\ fCa \times J_{dark}}{(2+fCa) \times F \times V_{cyto}} \times \left(\frac{cGMP}{cGMP_{dark}}\right)^{n_{cg}}$	Extracellular Ca^{2+}-influx via the cGMP-gated cation channels
$\longrightarrow cGMP$	$v_f = \frac{\alpha_{max}}{1+\left(\frac{Ca^{2+}_{free}}{Kc_1}\right)^{m_1}} + \frac{\alpha_{max}}{1+\left(\frac{Ca^{2+}_{free}}{Kc_2}\right)^{m_2}}$	cGMP synthesis by guanylate cyclase

Reaction Equation	Reaction kinetics	Comments
cGMP $\longrightarrow$	$v_f = (\beta_{dark} + \beta_{sub} \times E) \times cGMP$	cGMP hydrolysis by PDE

Table S2 Signal amplification-related model parameter values and sources

Parameter	Description	Value	Source
ω_G	Exponential rate of decay of G_t affinity for R^* with increasing phosphorylations	0.6	ref. [1]
$kG1_0$	Binding rate of G_t to unphosphorylated R^*	$1 \times 10^{-3}\,\text{s}^{-1}$	manually tuned
$kG2$	Dissociation rate of the $R^* \cdot G_t$ complex	$2200\,\text{s}^{-1}$	manually tuned
$kG3$	Dissociation rate of GDP from the $R^* \cdot G_t$ complex	$8500\,\text{s}^{-1}$	manually tuned
$kG4_{GDP}$	Association rate of GDP to the $R^* \cdot G_t$ complex	$400\,\text{s}^{-1}$	manually tuned
$kG5_{GTP}$	Association rate of GTP to the $R^* \cdot G_t$ complex	$3500\,\text{s}^{-1}$	manually tuned
$kG6$	Dissociation rate of the $R^* \cdot G_{GTP}$ complex	$8500\,\text{s}^{-1}$	manually tuned
$kG7$	Dissociation rate of G_{GTP} into $G_{\beta\gamma}$ and $G_{\alpha GTP}$	$200\,\text{s}^{-1}$	ref. [2]
$kOps$	Association rate of Ops (ligand-free R) and G_t due to basal activity	$6.1172 \times 10^{-13}\,\text{s}^{-1}$	ref. [3]
$kP1$	Binding rate of PDE to $G_{\alpha GTP}$	$0.05497\,\text{s}^{-1}$	ref. [2]
$kP1_{rev}$	Dissociation rate of $PDE \cdot G_{\alpha GTP}$, without PDE activation	$0\,\text{s}^{-1}$	ref. [2]
$kP2$	Rate of activation of the first PDE_γ subunit of $PDE \cdot G_{\alpha GTP}$	$940.7\,\text{s}^{-1}$	ref. [2]
$kP3$	Binding rate of $G_{\alpha GTP}$ to an active $PDE \cdot G_{\alpha GTP}$ complex	$1.4983 \times 10^{-9}\,\text{s}^{-1}$	ref. [2]
$kP4$	Rate of activation of the second PDE_γ subunit of $G_{\alpha GTP} \cdot PDE \cdot G_{\alpha GTP}$	$21.088\,\text{s}^{-1}$	ref. [2]

Table S3 Signal recovery-related model parameter values and sources

Parameter	Description	Value	Source
$kRK1_0$	Binding rate of RK to unphosphorylated R^*	$0.1724\,\mathrm{s}^{-1}$	manually tuned
ω	Exponential rate of decay of RK affinity for R^* with increasing phosphorylations	2.5	manually tuned
$kRK2$	Dissociation rate of R^* from RK prior to phosphorylation	$250\,\mathrm{s}^{-1}$	ref.[2]
$kRK3_{ATP}$	Binding rate of ATP to $R^* \cdot RK$	$4000\,\mathrm{s}^{-1}$	estimated
$kRK4$	Dissociation rate of R^* from the $R^* \cdot RK$ complex following phosphorylation	$250\,\mathrm{s}^{-1}$	manually tuned
$kArr$	Binding rate of Arr to singly-phosphorylated R^*	$9.9147 \times 10^{-6}\,\mathrm{s}^{-1}$	manually tuned
$kA2$	Dissociation rate of R^* from the $Arr \cdot R^*$ complex prior to R^* inactivation	$0.026\,\mathrm{s}^{-1}$	manually tuned *c.f.* ref.[1]
m_{Arr}	Linear rate of increase of Arr affinity for R^* with increasing phosphorylations	9.5475×10^{-6}	manually tuned *c.f.* ref.[1]
$kA3$	Dissociation rate of R^* from the $Arr \cdot R^*$ complex following R^* inactivation	$1.1651\,\mathrm{s}^{-1}$	estimated
$kA4$	Binding rate of Arr to form homo-oligomers	$2.9965 \times 10^{-7}\,\mathrm{s}^{-1}$	estimated
$kA5$	Dissociation rate of Arr from homo-oligomers	$0.424\,\mathrm{s}^{-1}$	manually tuned *c.f.* ref.[4]
$kRrecyc$	Rate constant for R regeneration from Ops.	$0.0007\,\mathrm{s}^{-1}$	ref.[5]
k_{therm}	Thermal decay of R^*	$0.0238\,\mathrm{s}^{-1}$	ref.[6]
$kGrecyc$	Binding rate for $G_{\alpha GDP}$ to $G_{\beta\gamma}$	$2\,\mathrm{s}^{-1}$	ref.[7]
$kGshutoff$	Rate of $G_{\alpha GTP}$ auto-catalytic GTPase activity	$0.05\,\mathrm{s}^{-1}$	ref.[7]
$kPDEshutoff$	Rate of PDE-induced spontaneous $PDE \cdot G_{\alpha GTP}$ shutoff	$0.1\,\mathrm{s}^{-1}$	manually tuned
$kRGS1$	Binding rate of $RGS_9{-}1$ to $PDE \cdot G_{\alpha GTP}$ (one or both active subunits)	$4.8182 \times 10^{-5}\,\mathrm{s}^{-1}$	estimated
$kRGS2$	Rate of hydrolysis and dissociation of one PDE subunit from $G_{\alpha GTP}$	$98\,\mathrm{s}^{-1}$	ref.[8]

Parameter	Description	Value	Source
*kRec*1	Rate of Ca^{2+}-triggered Rec conformational change (tense to relaxed)	$0.011\,\mu\text{M}^{-1}\,\text{s}^{-1}$	ref.[9]
*kRec*2	Rate of Rec conformational change (relaxed to tense)	$0.05\,\text{s}^{-1}$	ref.[9]
*kRec*3	Binding rate of Rec·Ca^{2+} to RK	$4.1081 \times 10^{-4}\,\text{s}^{-1}$	ref.[2]
*kRec*4	Dissociation rate of RK from Rec$-$Ca^{2+}	$0.610084\,\text{s}^{-1}$	ref.[2]

Table S4 Ca^{2+} and cGMP regulation-related model parameter values and sources

Parameter	Description	Value	Source
V_{cyto}	Outer segment cytoplasmic volume	0.039 16 pL	ref. [10]
Kc_1	EC_{50} for $GCAP_1$-mediated Ca^{2+} feedback on GC activity	171 nM	estimated
Kc_2	EC_{50} for $GCAP_2$-mediated Ca^{2+} feedback on GC activity	59 nM	ref. [11]
m_1	Hill coefficient for $GCAP_1$-mediated Ca^{2+} feedback on *GC* activity	3.0	estimated
m_2	Hill coefficient for $GCAP_2$-mediated Ca^{2+} feedback on GC activity	1.5	estimated
α_{max}	Maximal rate of cGMP synthesis	$60\,\mu M\,s^{-1}$	ref. [12]
β_{dark}	Dark rate of cGMP hydrolysis	$3.19\,s^{-1}$	steady-state analysis
β_{sub}	Rate constant for one catalytic PDE subunit	$2.1826 \times 10^{-3}\,s^{-1}$	calculated *c.f.* ref. [13] ($k_{cat} = 3500 s^{-1}$, $K_m = 17 \mu M$, $B_{cG} = 2$)
fCa	Fraction of the circulating current carried by Ca^{2+}	0.12	ref. [14]
J_{dark}	Dark circulating current	14.87 pA	manually tuned
$cGMP_{dark}$	Dark cGMP concentration	$6.5\,\mu M$	manually tuned
n_{cg}	Hill coefficient for opening cGMP-gated ion channels	3.8	manually tuned
γ_{Ca}	Rate of Ca^{2+} extrusion by $Na^+/Ca^{2+}\,K^+$ ion exchanger	$981.3558\,s^{-1}$	steady-state analysis
Ca^{2+}_{dark}	Dark Ca^{2+} concentration	$0.25\,\mu M$	ref. [15]
Ca^{2+}_0	Minimum intracellular Ca^{2+} concentration	$0.023\,\mu M$	ref. [15]
k_1	Binding rate of Ca^{2+} to cytoplasmic buffers	$9.37059\,\mu M^{-1}\,s^{-1}$	estimated
k_2	Dissociation rate of Ca^{2+} from cytoplasmic buffers	$46.412\,s^{-1}$	steady-state analysis
eT	Total Ca^{2+} buffer molecules concentration	$400\,\mu M$	ref. [2]

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