

$$\frac{d(\heartsuit_{2p})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p} \quad \frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act}) \quad \frac{d(G_{iact})}{dt} = k_{3c} \cdot \beta_{2p} \cdot \heartsuit_i - k_{3d} \cdot G_{iact}$$

$$\frac{d(G_s)}{dt} = k_{3b} \cdot G_{sact} - k_{3a} \cdot \heartsuit_s \cdot (\beta_{1act} + \beta_{2act}) \quad \frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit_{2p})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p} \quad \frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(AC_{act})}{dt} = k_{4a} \cdot \frac{G_{sact}}{(\heartsuit_{inh} + G_{iact})} \cdot AC - k_{4b} \cdot AC_{act} \quad \frac{d(G_i)}{dt} = k_{3d} \cdot \heartsuit_{iact} - k_{3c} \cdot \beta_{2p} \cdot G_i \quad \frac{d(\heartsuit_{2int})}{dt} = k_{2b} \cdot \beta_{2p} - k_{2d} \cdot \beta_{2int}$$

$$\frac{d(\beta_2)}{dt} = k_{2d} \cdot \heartsuit_{2int} + k_{2c} \cdot \beta_{2p} - k_{bas2} \cdot \beta_2 - \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot H_2 \quad \frac{d(\heartsuit_{act})}{dt} = cAMP \cdot k_{6a} \cdot GRK - k_{6b} \cdot \heartsuit_{act}$$

$$\frac{d(PKA)}{dt} = -\heartsuit \cdot k_{6c} \cdot PKA + k_{6d} \cdot \heartsuit_{act} \quad \frac{d(\heartsuit)}{dt} = k_{4b} \cdot AC_{act} - k_{4a} \cdot \frac{G_{sact}}{(k_{inh} + G_{iact})} \cdot \heartsuit \quad \frac{d(\heartsuit_{1int})}{dt} = k_{1b} \cdot \beta_{1p} - k_{1d} \cdot \beta_{1int}$$

$$\frac{d(\heartsuit_{1p})}{dt} = k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (k_{1b} + k_{1c}) \cdot \heartsuit_{1p} \quad \frac{d(\heartsuit_{sact})}{dt} = k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act}) - k_{3b} \cdot G_{sact}$$

$$\frac{d(\heartsuit_{act})}{dt} = cAMP \cdot k_{6a} \cdot GRK - k_{6b} \cdot \heartsuit_{act} \quad \frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit \quad \frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(PKA_{act})}{dt} = cAMP \cdot k_{6c} \cdot \heartsuit - k_{6d} \cdot PKA_{act} \quad \frac{d(\heartsuit_{1p})}{dt} = k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (k_{1b} + k_{1c}) \cdot \heartsuit_{1p}$$

$$\frac{d(\heartsuit_{2p})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p} \quad \frac{d(\heartsuit_{sact})}{dt} = k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act}) - k_{3b} \cdot G_{sact}$$

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \quad \frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

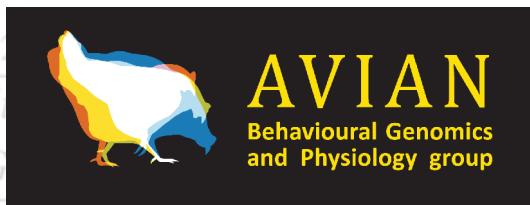
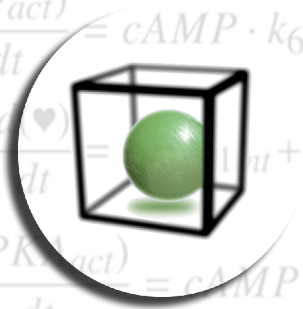
"The beauty of a living thing is not the atoms that go into it, but the way those atoms are put together."

- Carl Sagan

De- and Resensitisation of Cardiac β -Adrenergic Receptor Signaling: A Modelling Approach

Master Thesis by Karin Lundengård

Supervisors: Jordi Altimiras,
Gunnar Cedersund and Elin Nyman



Linköping University
INSTITUTE OF TECHNOLOGY

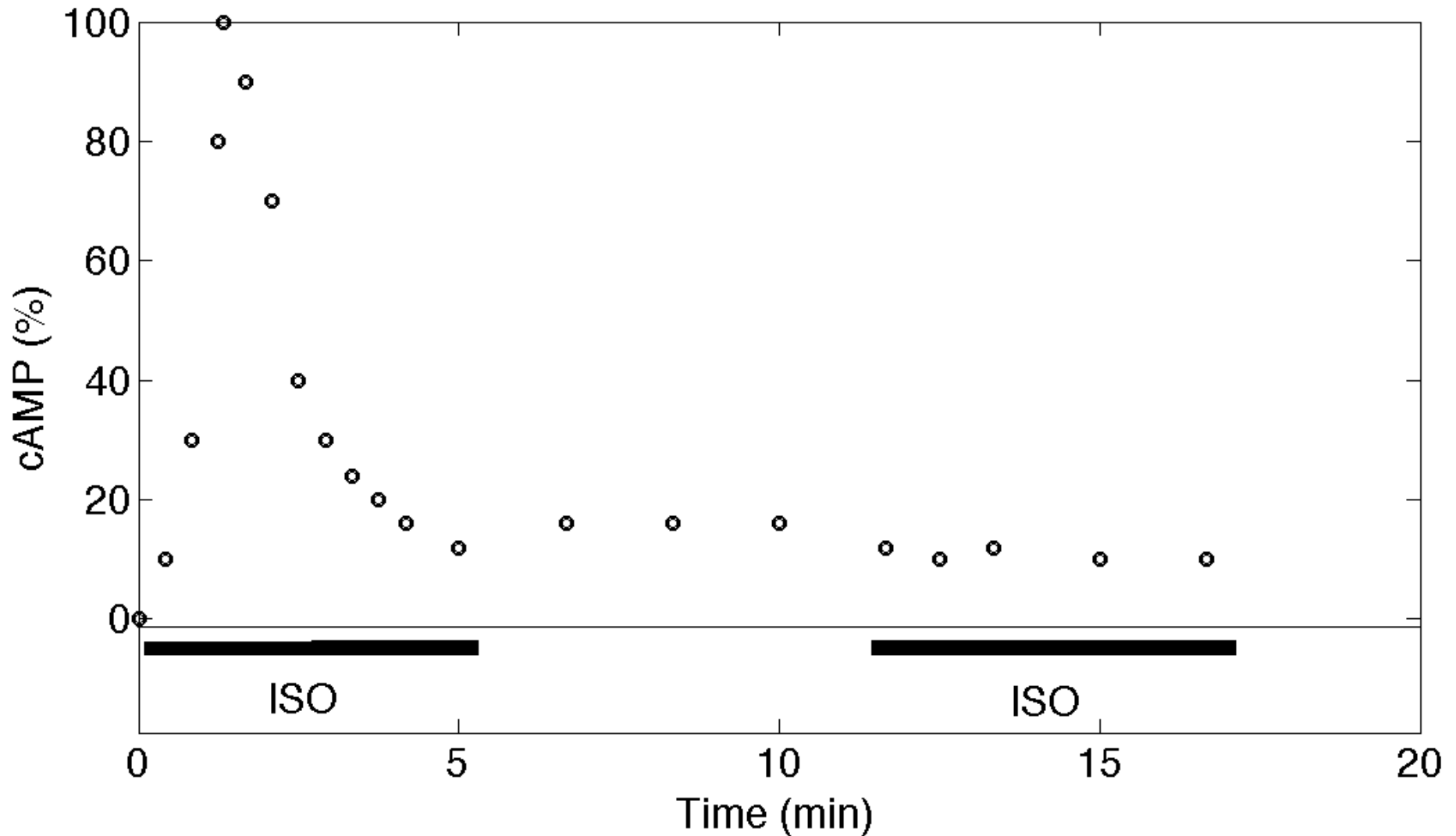
$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2}) \cdot \heartsuit_2 - k_{2d} \cdot \beta_{2act}$$

Desensitisation

$$\frac{d(G_{iact})}{dt} = k_{3c} \cdot \beta_{2p} \cdot \heartsuit_i - k_{3d} \cdot G_{iact}$$

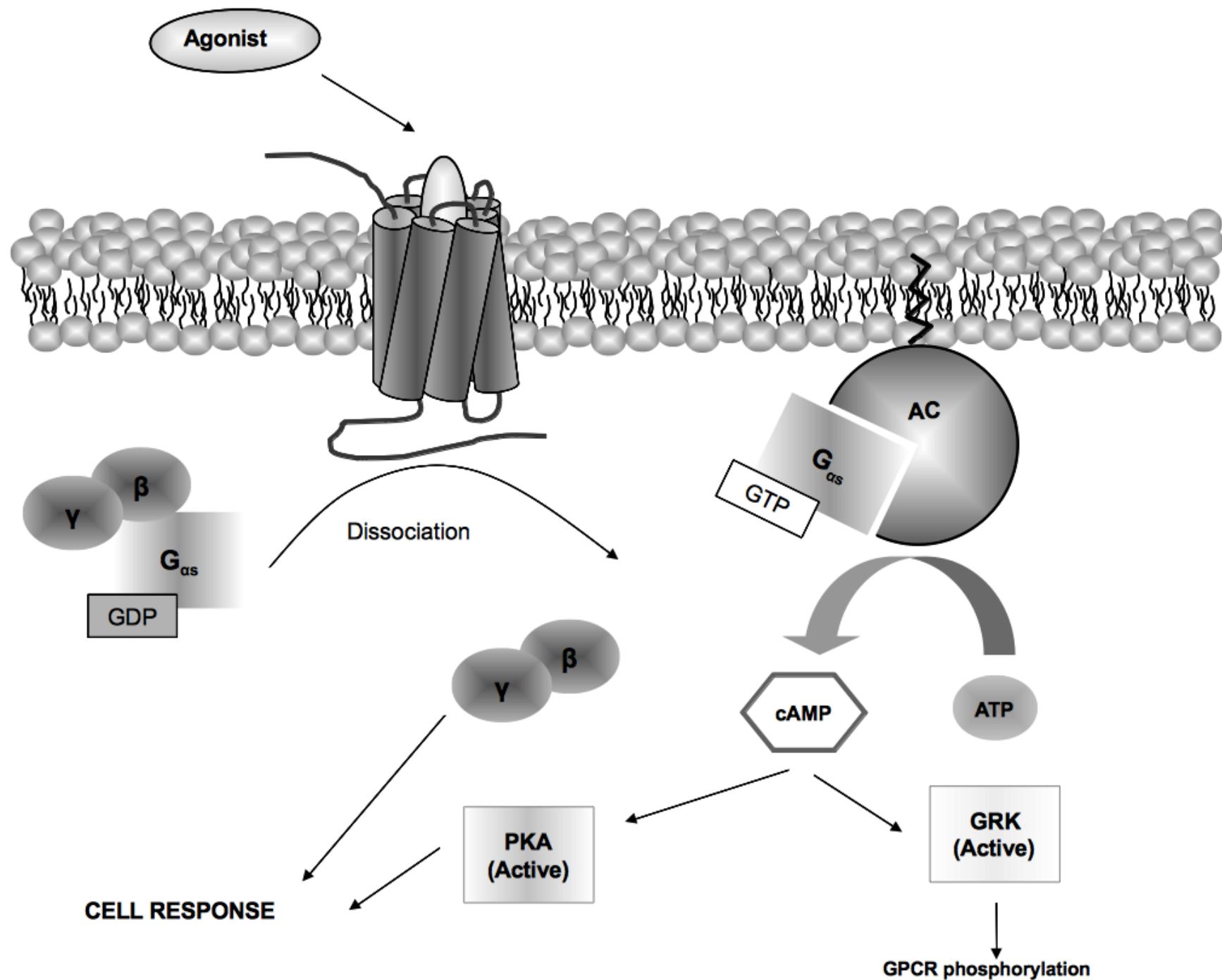


$$\frac{d(\heartsuit_1)}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \heartsuit_1$$

$$\frac{d(\heartsuit_2)}{dt} = k_{5a} \cdot \heartsuit_1 \cdot (\heartsuit_{1act} + \heartsuit_{2act}) - k_{5b} \cdot \heartsuit_{act}$$

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$



$\frac{d(\heartsuit)}{dt}$
 $\frac{d(\beta_2)}{dt}$
 $\frac{d(G)}{dt}$
 $\frac{d(A)}{dt}$
 $\frac{d(P)}{dt}$
 $\frac{d(\heartsuit)}{dt}$
 $\frac{d(F)}{dt}$
 $\frac{d(\heartsuit)}{dt}$
 $\frac{d(G)}{dt}$

$d(cAMP)$

t
 A_{act}
 int
 int
 act
 act
 \heartsuit
 act

$$\frac{d(G)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \quad \frac{d(cAMP)}{dt} = \kappa_{bas} [P_1 + \heartsuit] (\kappa_{iso} + \kappa_{ip}) [P_1] - \kappa_{1a} \heartsuit_{act} (\kappa_{GRK} \cdot G_{\alpha s} + \Gamma_{\Delta A_{act}})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p}$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot \beta_{2act}$$

$$\frac{d(G_s)}{dt} = k_{3b} \cdot G_{sact} - k_{3c} \cdot G_s$$

$$\frac{d(\heartsuit_{2p})}{dt} = k_{2a} \cdot \heartsuit_{2act}$$

$$\frac{d(AC_{act})}{dt} = k_{4a} \cdot \frac{G_{sact}}{(\heartsuit_{inh} + G_{sact})}$$

$$\frac{d(\beta_2)}{dt} = k_{2d} \cdot \heartsuit_{2int}$$

$$\frac{d(PKA)}{dt} = -\heartsuit \cdot k_{6c} \cdot PKA$$

$$\frac{d(\heartsuit_{1p})}{dt} = k_{1a} \cdot \heartsuit_{1c}$$

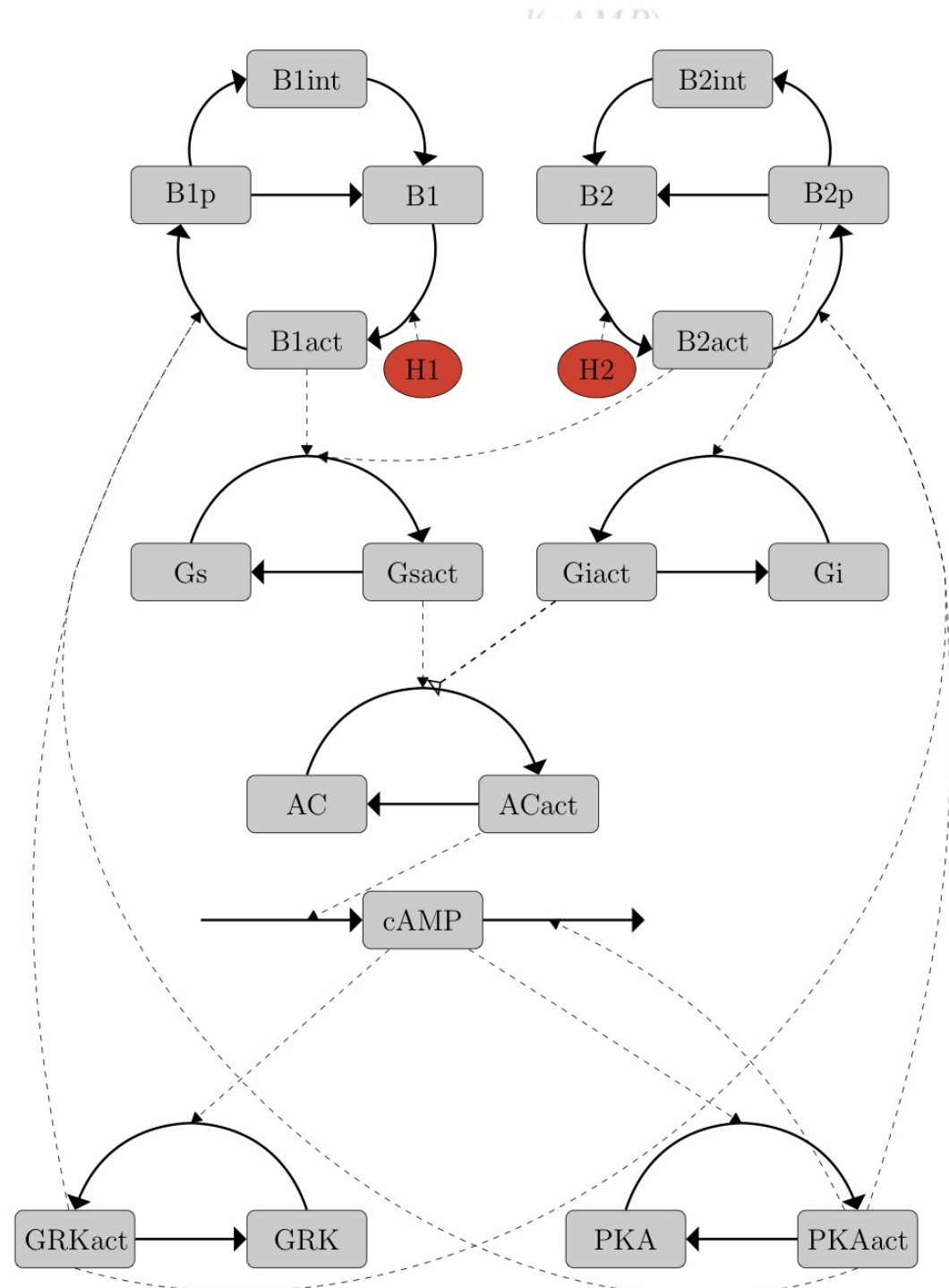
$$\frac{d(\heartsuit_{act})}{dt} = cAMP \cdot k_{6a} \cdot PKA_{act}$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p}$$

$$\frac{d(PKA_{act})}{dt} = cAMP \cdot k_{6a} \cdot PKA$$

$$\frac{d(\heartsuit_{2p})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act})$$

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK$$



$$- k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$3c \cdot \beta_{2p} \cdot \heartsuit_i - k_{3d} \cdot G_{iact}$$

$$1act \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$RK + k_{6b} \cdot GRK_{act}$$

$$\frac{d}{dt} = k_{2b} \cdot \beta_{2p} - k_{2d} \cdot \beta_{2int}$$

$$k_{6a} \cdot GRK - k_{6b} \cdot \heartsuit_{act}$$

$$\frac{nt}{dt} = k_{1b} \cdot \beta_{1p} - k_{1d} \cdot \beta_{1int}$$

$$1act + \heartsuit_{2act}) - k_{3b} \cdot G_{sact}$$

$$2a \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act})$$

$$\cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$) - (k_{1b} + k_{1c}) \cdot \heartsuit_{1p}$$

$$31act + \heartsuit_{2act}) - k_{3b} \cdot G_{sact}$$

$$1 \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} \dots \dots \dots$$

$$\frac{d(B1)}{dt} = k_{1d} \cdot B1_{int} + k_{1c} \cdot B1_p - k_{bas1} \cdot B1 - B1 \cdot (k_{iso} + k_{ip1}) \cdot H1$$

$$\frac{d(B1act)}{dt} = k_{bas1} \cdot B1 + B1 \cdot (k_{iso} + k_{ip1}) \cdot H1 - k_{1a} \cdot B1act \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(B1p)}{dt} = k_{1a} \cdot B1act \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (k_{1b} + k_{1c}) \cdot B1p$$

$$\frac{d(B1int)}{dt} = k_{1b} \cdot B1p - k_{1d} \cdot B1int$$

$$\frac{d(B2)}{dt} = k_{2d} \cdot B2_{int} + k_{2c} \cdot B2_p - k_{bas2} \cdot B2 - B2 \cdot (k_{iso} + k_{ip2} + k_{ter}) \cdot H2$$

$$\frac{d(B2act)}{dt} = k_{bas2} \cdot B2 + B2 \cdot (k_{iso} + k_{ip2} + k_{ter}) \cdot H2 - k_{2a} \cdot B2act \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(B2p)}{dt} = k_{2a} \cdot B2act \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (k_{2b} + k_{2c}) \cdot B2p$$

$$\frac{d(B2int)}{dt} = k_{2b} \cdot B2p - k_{2d} \cdot B2int$$

$$\frac{d(Gs)}{dt} = k_{3b} \cdot Gs_{act} - k_{3a} \cdot Gs \cdot (B1act + B2act)$$

$$\frac{d(Gsact)}{dt} = k_{3a} \cdot Gs \cdot (B1act + B2act) - k_{3b} \cdot Gsact$$

$$\frac{d(Gi)}{dt} = k_{3d} \cdot Gi_{act} - k_{3c} \cdot B2p \cdot Gi$$

$$\frac{d(Giact)}{dt} = k_{3c} \cdot B2p \cdot Gi - k_{3d} \cdot Giact$$

$$\frac{d(AC)}{dt} = k_{4b} \cdot AC_{act} - k_{4a} \cdot Gs_{act} / (k_{inh} + Giact) \cdot AC$$

$$\frac{d(ACact)}{dt} = k_{4a} \cdot Gs_{act} / (k_{inh} + Giact) \cdot AC - k_{4b} \cdot ACact$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + ACact \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot cAMP$$

$$\frac{d(GRK)}{dt} = -cAMP \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(GRKact)}{dt} = cAMP \cdot k_{6a} \cdot GRK - k_{6b} \cdot GRKact$$

$$\frac{d(PKA)}{dt} = -cAMP \cdot k_{6c} \cdot PKA + k_{6d} \cdot PKA_{act}$$

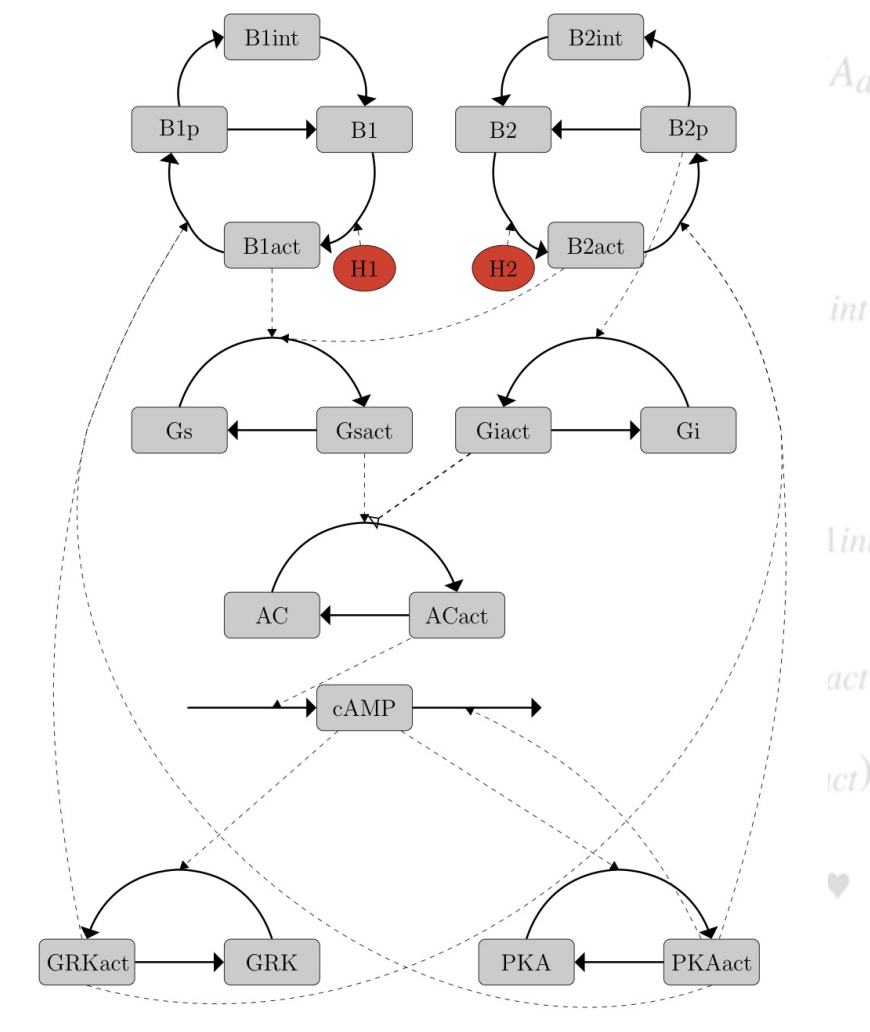
$$\frac{d(PKAact)}{dt} = cAMP \cdot k_{6c} \cdot PKA - k_{6d} \cdot PKAact$$

$$\frac{d(\heartsuit_{2p})}{dt} \dots \dots \dots$$

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(Giact)}{dt} = k_{3c} \cdot \beta_{2n} \cdot \heartsuit_i - k_{3d} \cdot Giact$$



$$\frac{d(Gs)}{dt} = k_{3a} \cdot Gs \cdot (\beta_{1act} + \heartsuit_{2act}) - k_{3b} \cdot Gs_{act}$$

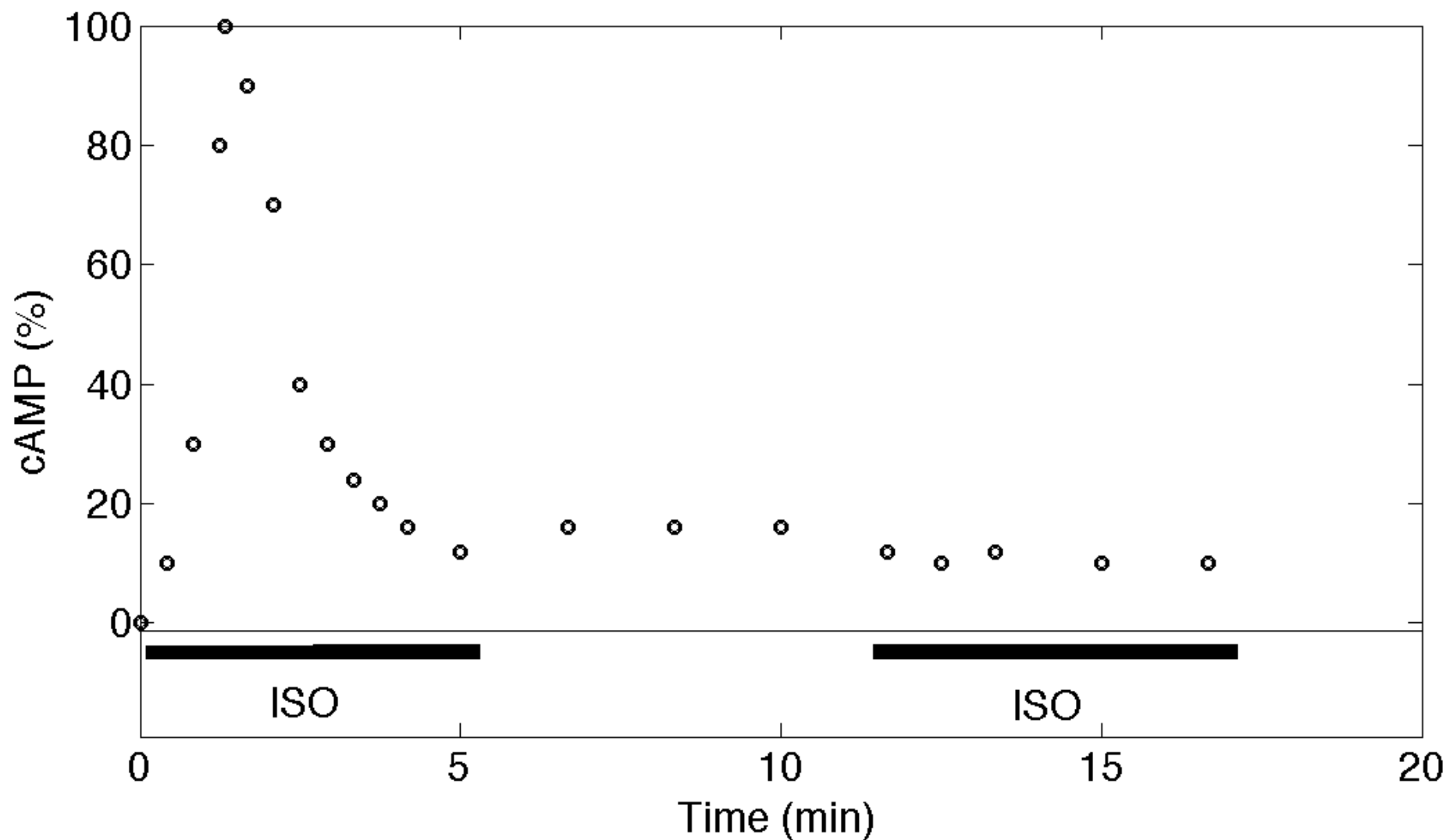
$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \quad \frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act})$$

$$\frac{d(G_{iact})}{dt} = k_{3c} \cdot \beta_{2p} \cdot \heartsuit_i - k_{3d} \cdot G_{iact}$$



$$\frac{d(\heartsuit_1)}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot P_{2p}$$

$$\frac{d(\heartsuit_2)}{dt} = k_{5a} \cdot \heartsuit_1 \cdot (\heartsuit_{1act} + \heartsuit_{2act}) - k_{5b} \cdot \heartsuit_{sact}$$

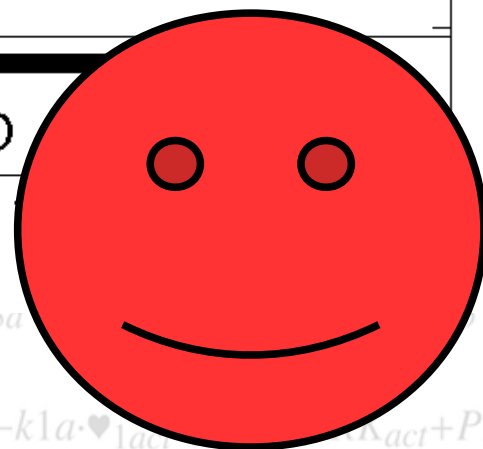
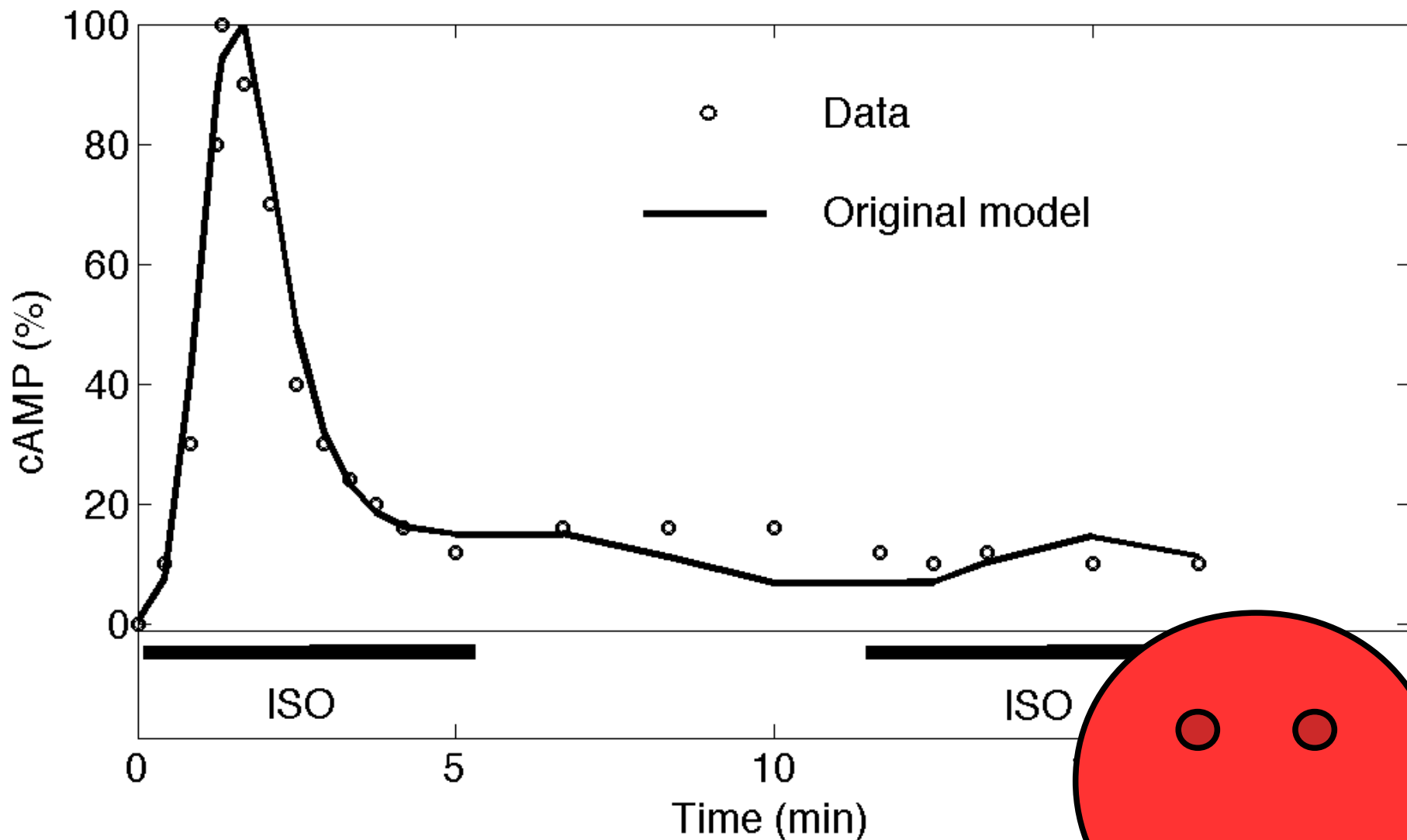
$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \quad \frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act})$$

$$\frac{d(G_{iact})}{dt} = k_{3c} \cdot \beta_{2p} \cdot \heartsuit_i - k_{3d} \cdot G_{iact}$$



$$\frac{d}{dt} = k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act}) - (k_{2b} + k_{2c}) \cdot \beta_{2p}$$

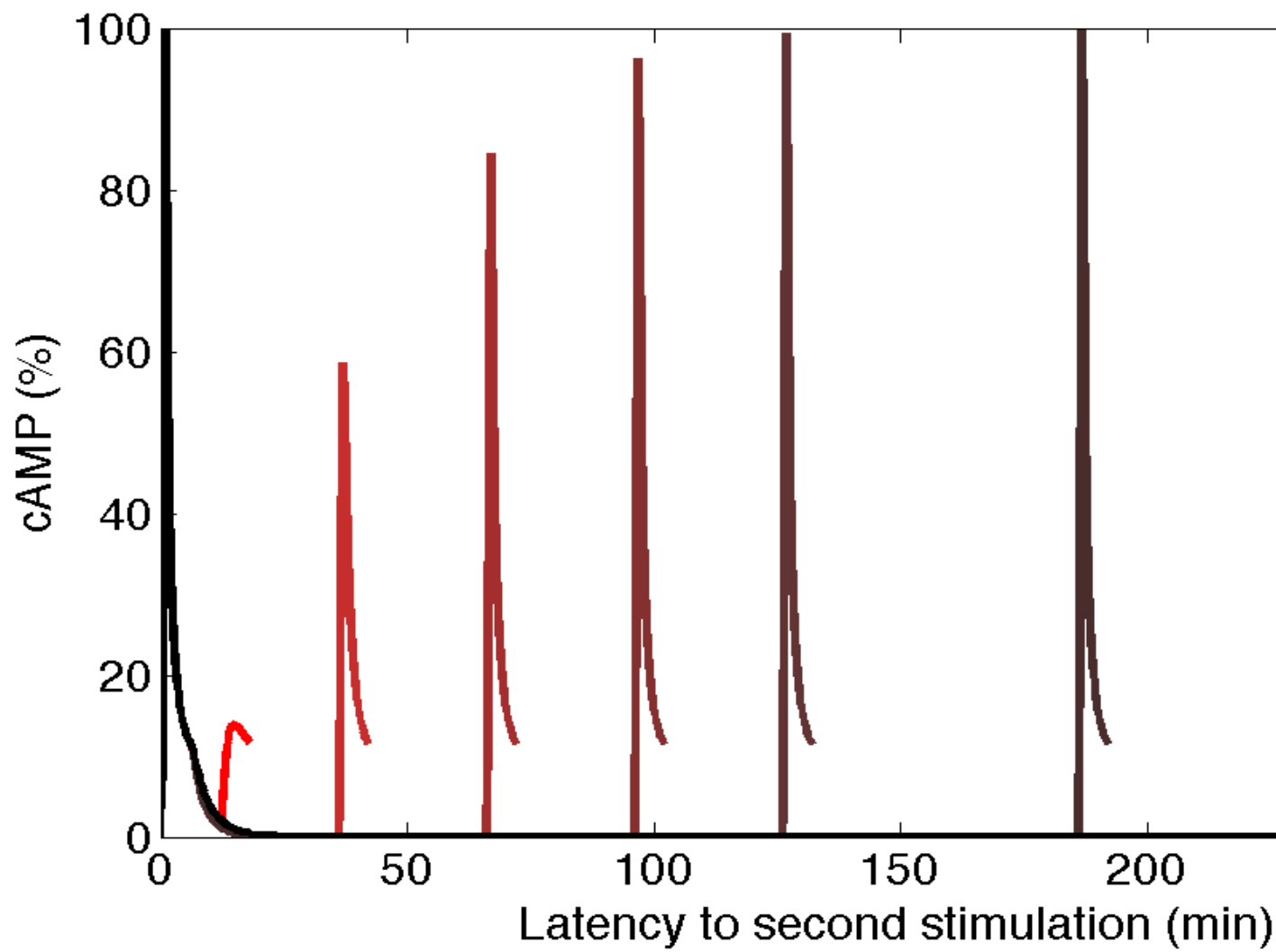
$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \quad \frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{act} \cdot PKA_{act} + PKA_{act}$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{\beta_2} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act})$$

$$\frac{d(G_{iact})}{dt} = k_{3a} \cdot G_3 - k_{3b} \cdot \beta_3 \cdot G_{iact} - k_{3c} \cdot G_{iact}$$



$$\frac{d(\heartsuit_{2p})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p}$$

$$\frac{d(\heartsuit_{sact})}{dt} = k_{3a} \cdot G_3 - k_{3b} \cdot \beta_3 \cdot \heartsuit_{sact} - k_{3c} \cdot \heartsuit_{sact}$$

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \quad \frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_1$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2$$

$$d(G_c)$$

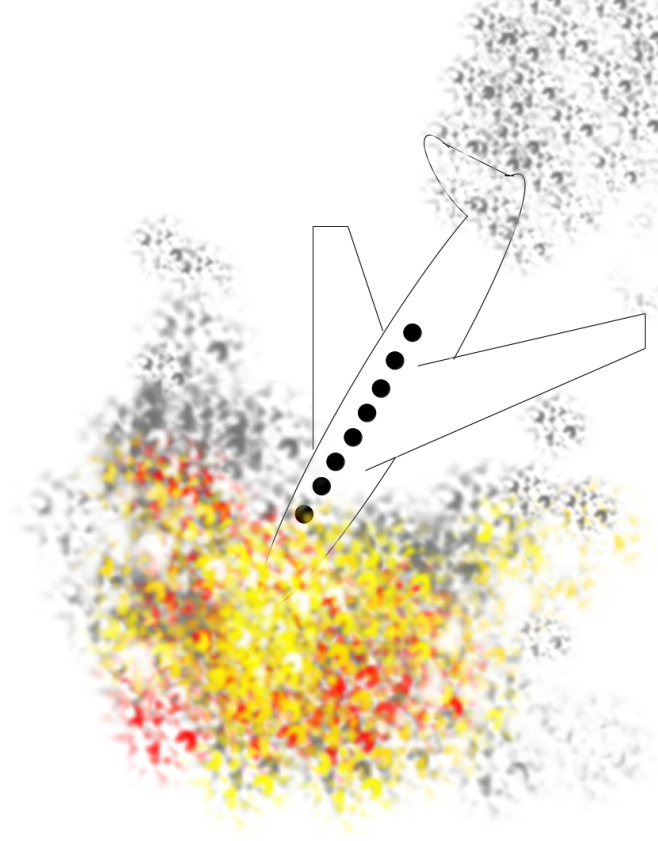
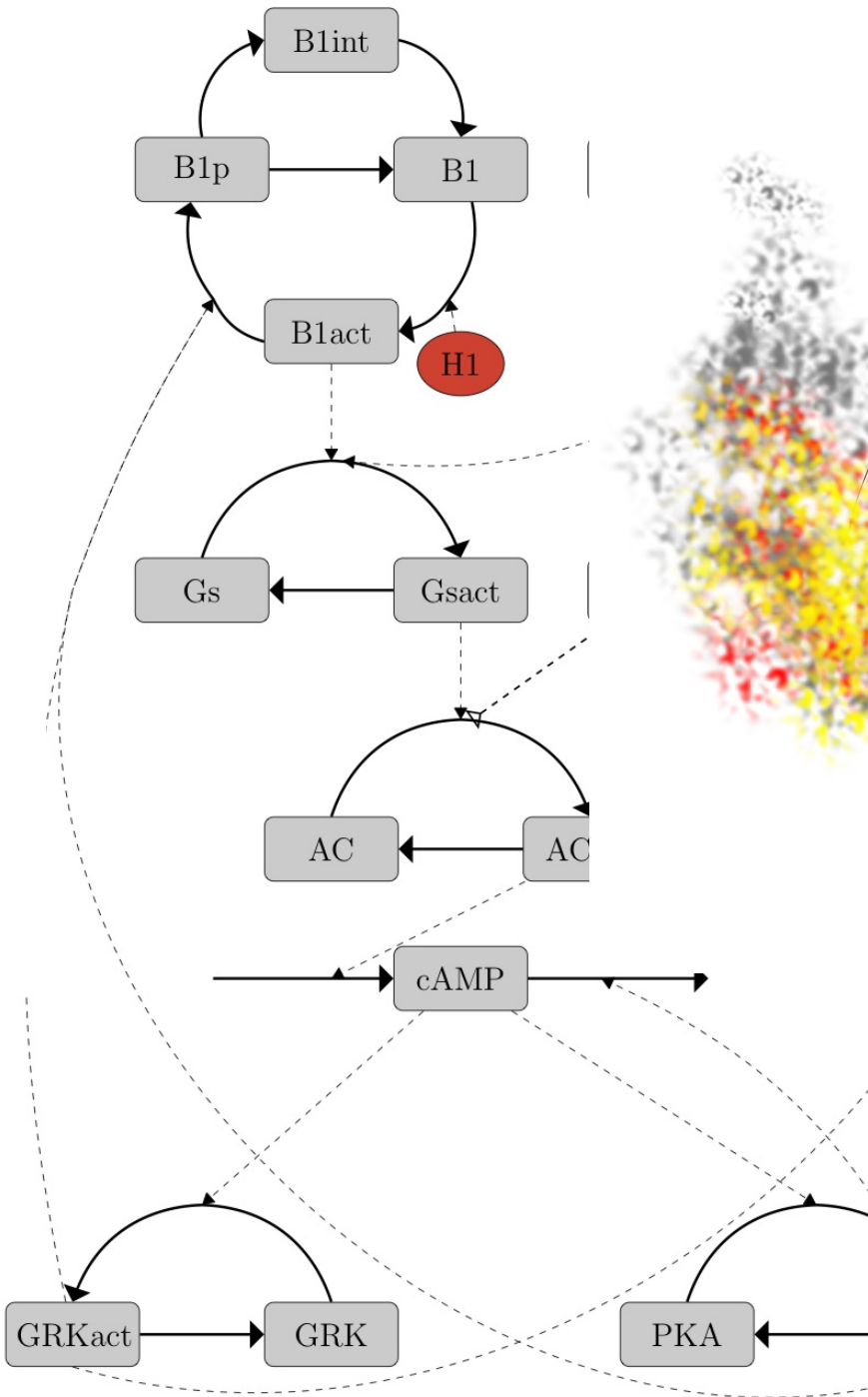


$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c}$$

$$\frac{d(PKA_{act})}{dt} = cAMP \cdot k$$

$$\frac{d(\heartsuit_{2p})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GR1})$$

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot G1$$



$$A_{act} \cdot \heartsuit$$

$$-k_{3d} \cdot G_{iact}$$

$$RK_{act} + PKA_{act}$$

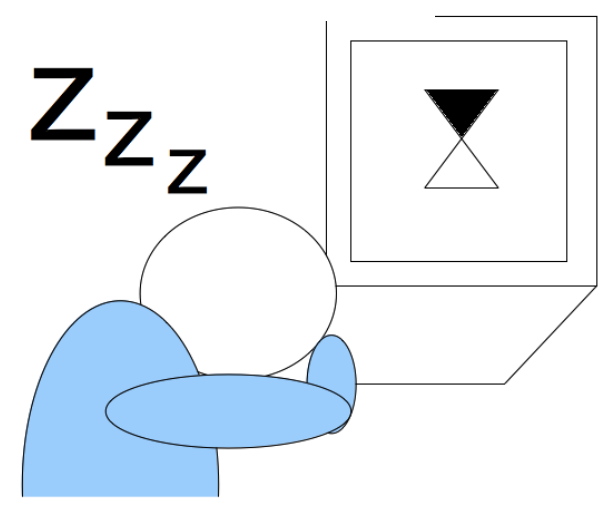
$$RK_{act}$$

$$-k_{2d} \cdot \beta_{2int}$$

$$k_{6b} \cdot \heartsuit_{act}$$

$$p - k_{1d} \cdot \beta_{1int}$$

$$-k_{3b} \cdot G_{sact}$$



$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt}$$

$$\frac{d(G_s)}{dt} =$$

$$\frac{d(AC_{act})}{dt}$$

$$\frac{d(PKA)}{dt}$$

$$\frac{d(\heartsuit_{act})}{dt}$$

$$\frac{d(\heartsuit)}{dt}$$

$$\frac{d(PKA)}{dt}$$

$$\frac{d(\heartsuit_{act})}{dt}$$

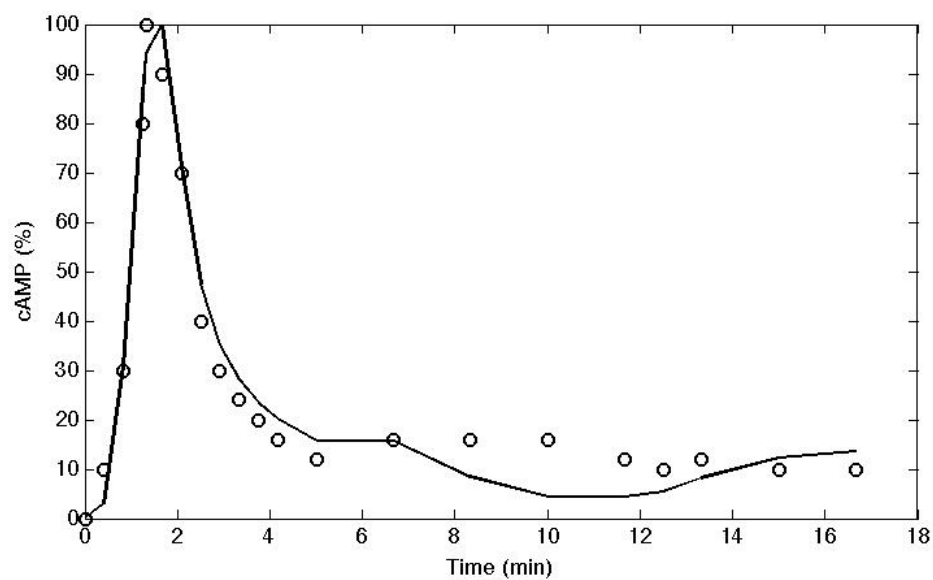
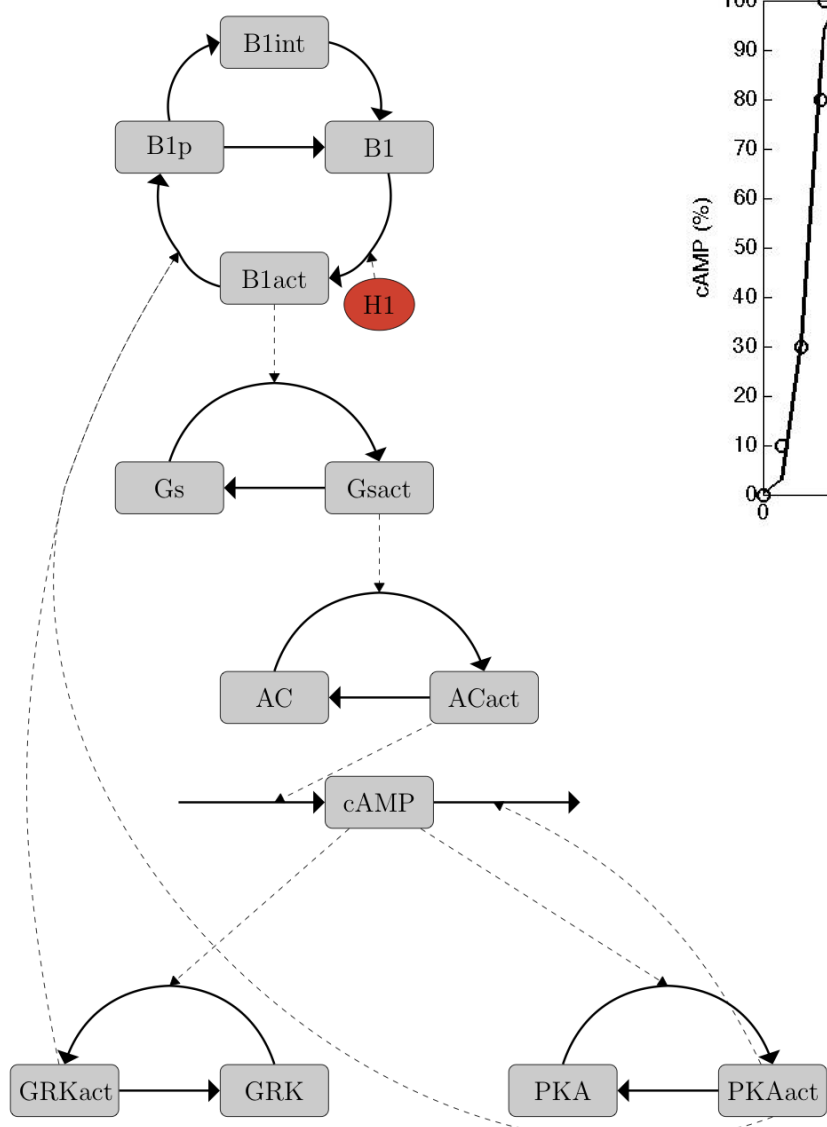
$$\frac{d(\heartsuit)}{dt}$$

$$\frac{d(PKA)}{dt}$$

$$\frac{d(\heartsuit_{2p})}{dt} :$$

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$



$\cdot G_{iact}$
 $ct + PKA_{act}$
 ict
 $2d \cdot \beta_{2int}$
 $\cdot \heartsuit_{act}$

$-k_{4a} \cdot \frac{G_{sact}}{(k_{ij} + G_{sact})} = k_{1b} \cdot \beta_{1p} - k_{1d} \cdot \beta_{1int}$
 $\cdot \heartsuit_{1p}$
 $s_2 \cdot \beta_{1act}$
 $GRK \cdot \heartsuit_{act} + \heartsuit_{act}$
 $A \cdot PKA_{act} \cdot \heartsuit$
 $\cdot \heartsuit_{1act}$
 $\cdot \beta_{1c} \cdot \heartsuit_{1p}$

$$\frac{d(\heartsuit_{sact})}{dt} = k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act}) - k_{3b} \cdot G_{sact}$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{iso1} + k_{ip1}) \cdot \heartsuit_2 - k_{2a}$$

$$\frac{d(G_s)}{dt} = k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act}) - k_{3b} \cdot G_{sact}$$

$$\frac{d(PKA)}{dt} = k_{4b} \cdot PKA_{act} - k_{4a} \cdot PKA$$

$$\frac{d(\heartsuit_{act})}{dt} = k_{GRK} \cdot GRK_{act} + \heartsuit_{act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p}$$

$$\frac{d(\heartsuit_{1p})}{dt} = k_{1a} \cdot \heartsuit_{1act} \cdot (k_{1b} + k_{1c}) \cdot \heartsuit_{1p}$$

$$\frac{d(\heartsuit_{2act})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p}$$

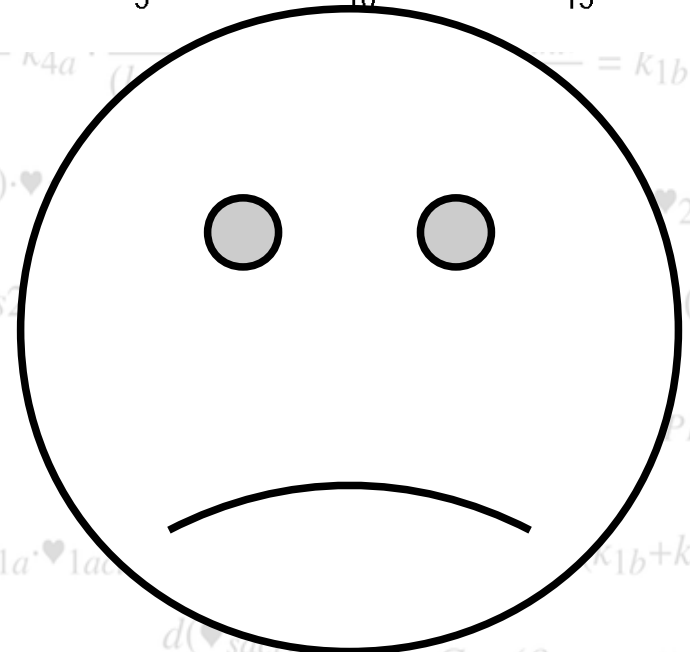
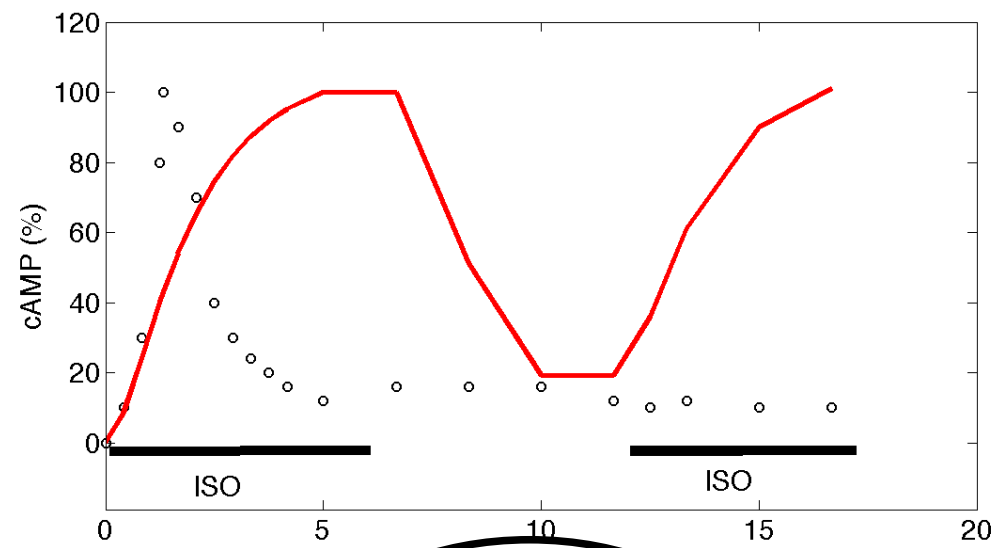
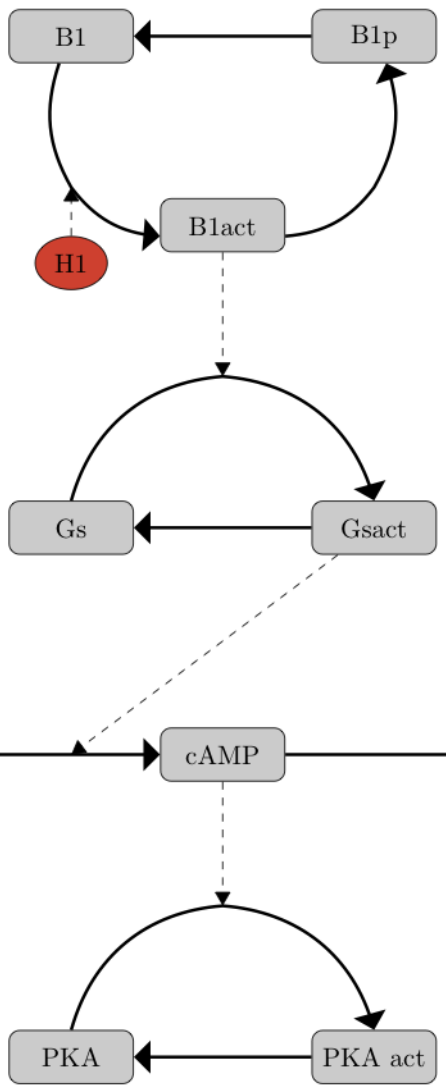
$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\beta_{1int})}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{iso1} + k_{ip1}) \cdot \heartsuit_2 - k_{2a}$$

$$\frac{d(\beta_{2p})}{dt} = k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p}$$



$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p}$$

$$\frac{d(G_s)}{dt} = k_{3l} \cdot G_i - k_{3d} \cdot G_s$$

$$\frac{d(\heartsuit_{2p})}{dt} = k_{2b} + k_{2c} \cdot \beta_{2p} - k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(AC_{act})}{dt} = k_{5b} \cdot \heartsuit_{act} - k_{5a} \cdot AC_{act} - k_{5c} \cdot AC_{act} \cdot \heartsuit$$

$$\frac{d(\beta_i)}{dt} = k_{1b} + k_{1c} \cdot \heartsuit - k_{1d} \cdot \beta_{1int} - k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_i$$

$$\frac{d(PKA)}{dt} = k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act}) - k_{3b} \cdot G_{sact}$$

$$\frac{d(\heartsuit)}{dt} = k_{1b} + k_{1c} \cdot \heartsuit - k_{1d} \cdot \beta_{1int} - k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_i$$

$$\frac{d(\heartsuit_{act})}{dt} = k_{5b} \cdot \heartsuit_{act} - k_{5a} \cdot AC_{act} - k_{5c} \cdot AC_{act} \cdot \heartsuit$$

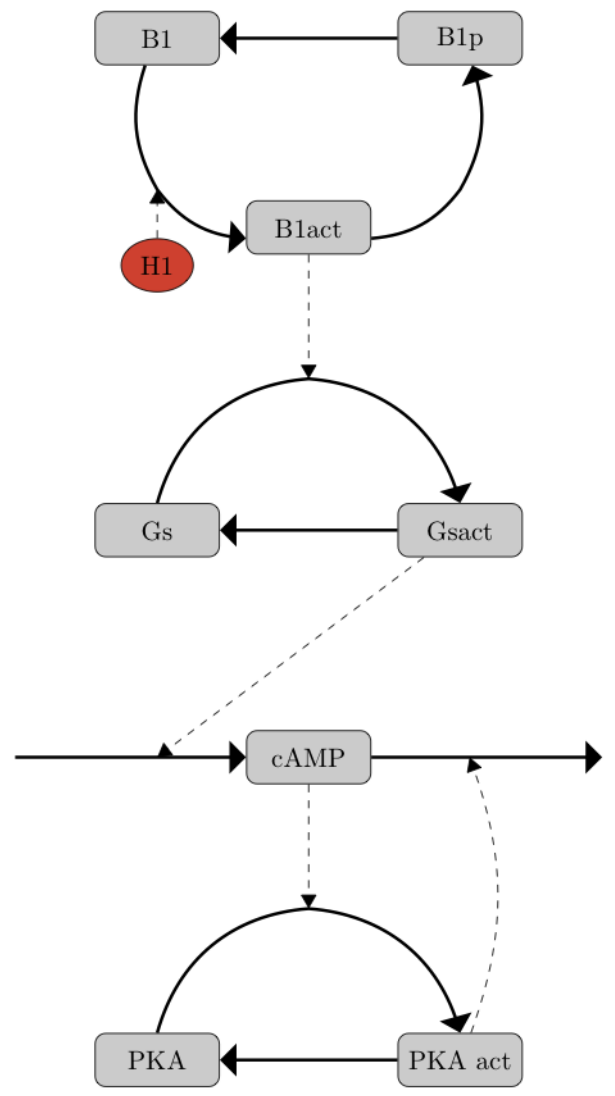
$$\frac{d(\heartsuit)}{dt} = k_{1b} + k_{1c} \cdot \heartsuit - k_{1d} \cdot \beta_{1int} - k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_i$$

$$\frac{d(PKA_{act})}{dt} = k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act}) - k_{3b} \cdot G_{sact}$$

$$\frac{d(\heartsuit_{2p})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p}$$

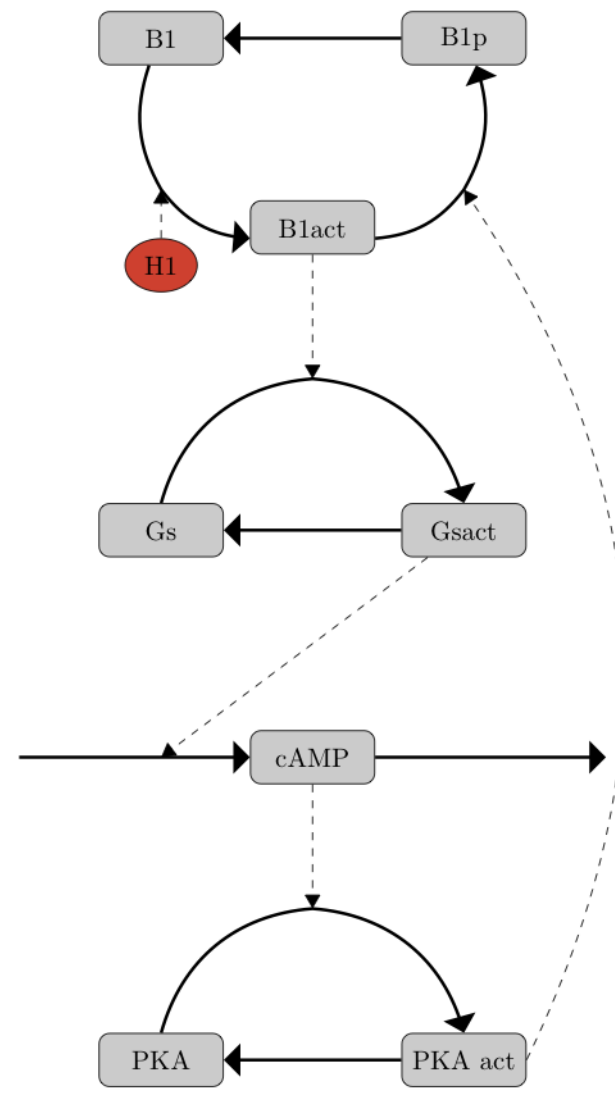
$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$



1

$k_{GRK} \cdot \heartsuit_{act}$
 $k_{bas1} \cdot \beta_1$
 $k_{2b} + k_{2c} \cdot \beta_{2p}$
 $k_{3d} \cdot G_s$
 $k_{2b} + k_{2c} \cdot \beta_{2p}$
 $k_{5b} \cdot \heartsuit_{act}$
 $k_{1b} + k_{1c} \cdot \heartsuit$
 $k_{5b} \cdot \heartsuit_{act}$
 $k_{1b} + k_{1c} \cdot \heartsuit$
 $k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act})$
 $k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$
 $k_{6a} \cdot GRK$
 $k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$



2

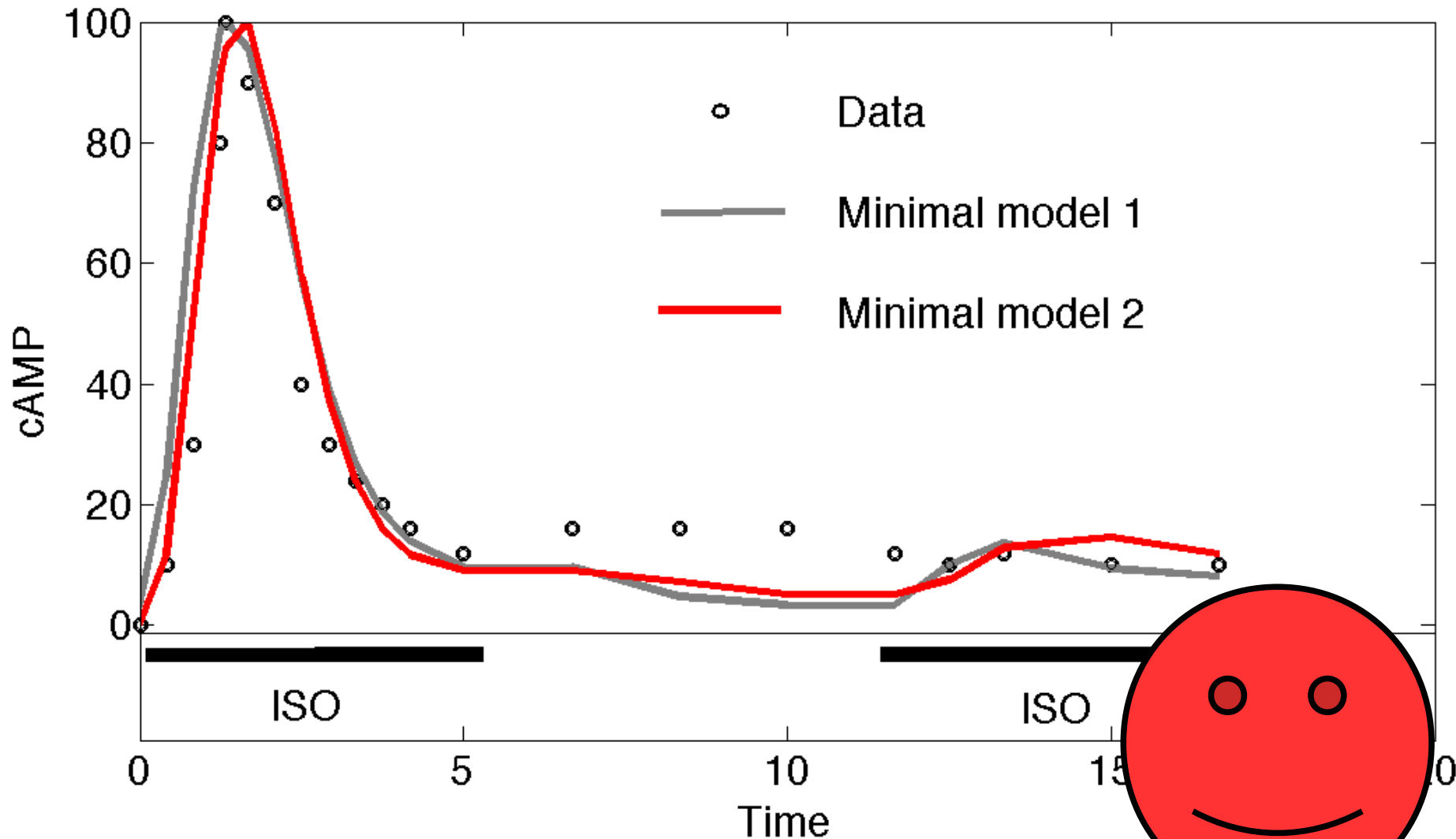
$k_{GRK} \cdot \heartsuit_{act}$
 $k_{bas1} \cdot \beta_1$
 $k_{2b} + k_{2c} \cdot \beta_{2p}$
 $k_{3d} \cdot G_s$
 $k_{2b} + k_{2c} \cdot \beta_{2p}$
 $k_{5b} \cdot \heartsuit_{act}$
 $k_{1b} + k_{1c} \cdot \heartsuit$
 $k_{5b} \cdot \heartsuit_{act}$
 $k_{1b} + k_{1c} \cdot \heartsuit$
 $k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act})$
 $k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$
 $k_{6a} \cdot GRK$
 $k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$
 $3d \cdot G_{iact}$
 $k_{act} + PKA_{act}$
 K_{act}
 $-k_{2d} \cdot \beta_{2int}$
 $k_{5b} \cdot \heartsuit_{act}$
 $-k_{1d} \cdot \beta_{1int}$
 $k_{3b} \cdot G_{sact}$
 $k_{5b} \cdot \heartsuit_{act}$
 $k_{5c} \cdot AC_{act} \cdot \heartsuit$
 $k_{PKA} \cdot PKA_{act} \cdot \heartsuit$
 p

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act})$$

$$\frac{d(G_{iact})}{dt} = k_{3c} \cdot \beta_{2p} \cdot \heartsuit_i - k_{3d} \cdot G_{iact}$$



$$\frac{d(\heartsuit_1)}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \heartsuit_{2p}$$

$$\frac{d(\heartsuit_2)}{dt} = k_{5a} \cdot \heartsuit_1 - k_{5b} \cdot \heartsuit_{act}$$

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \quad \frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = 1$$

$$\frac{d(G_s)}{dt} = k_{3l}$$

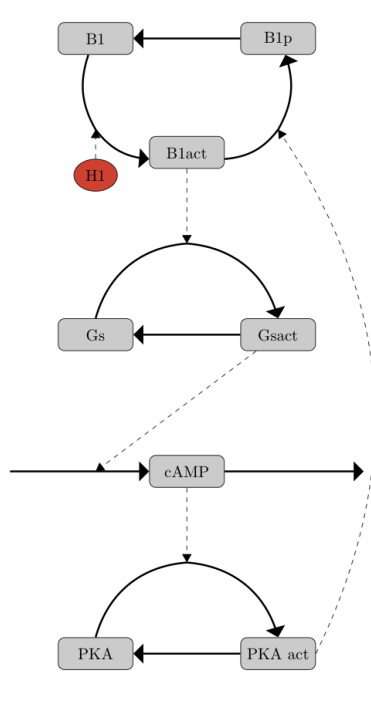
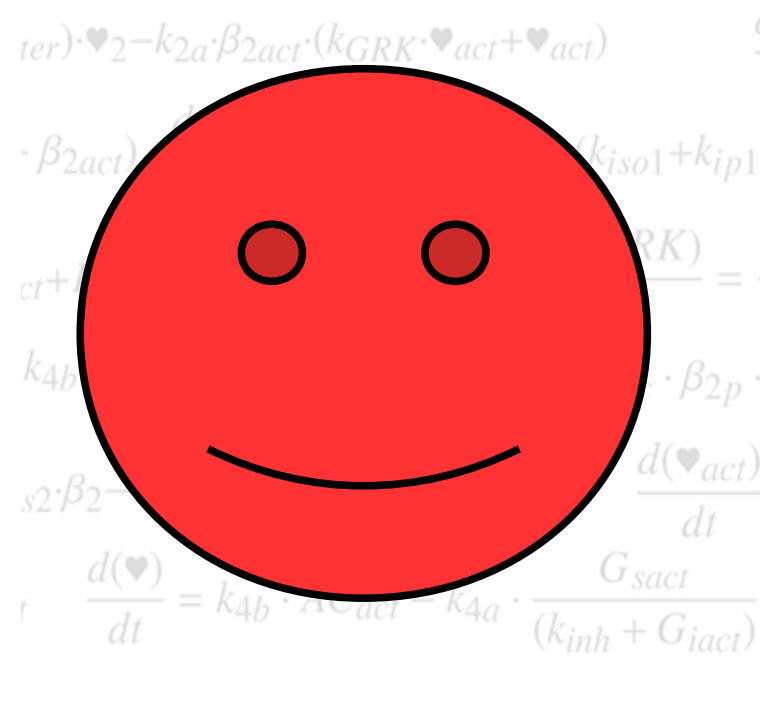
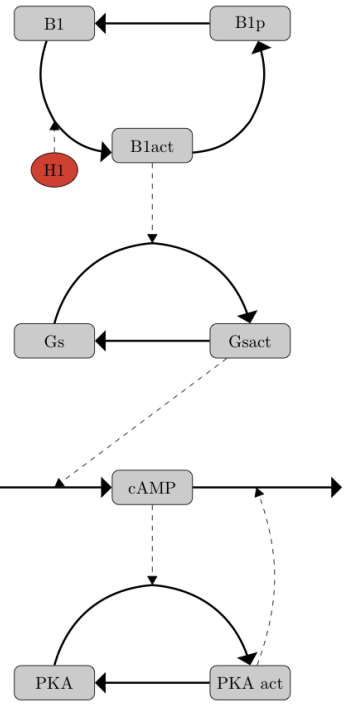
$$\frac{d(\heartsuit_{2p})}{dt} =$$

$$\frac{d(AC_{act})}{dt} =$$

$$\frac{d(\beta_{act})}{dt} =$$

$$\frac{d(PKA)}{dt} =$$

$$d(\heartsuit)$$



$$3d \cdot G_{iact}$$

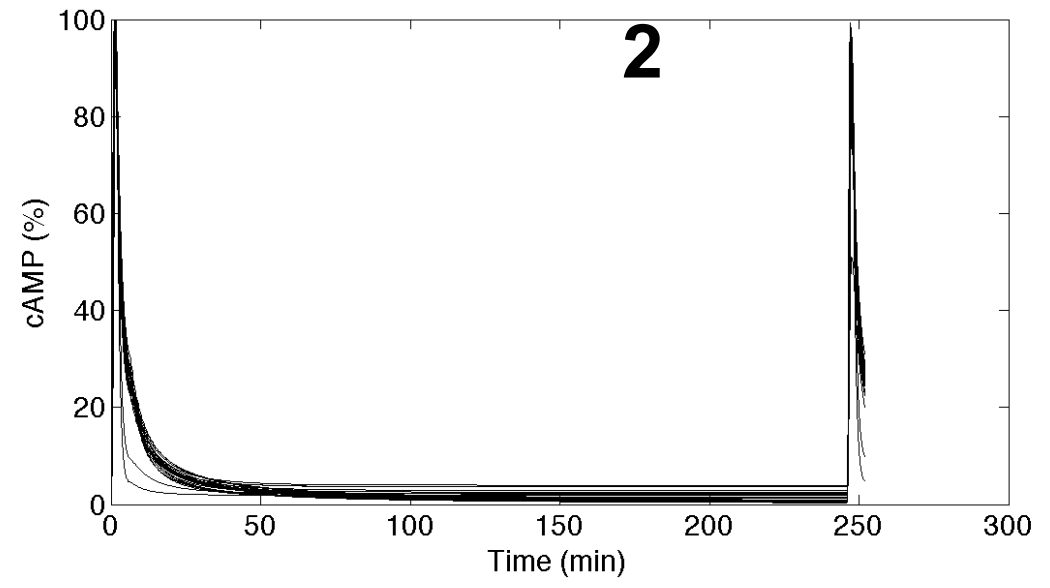
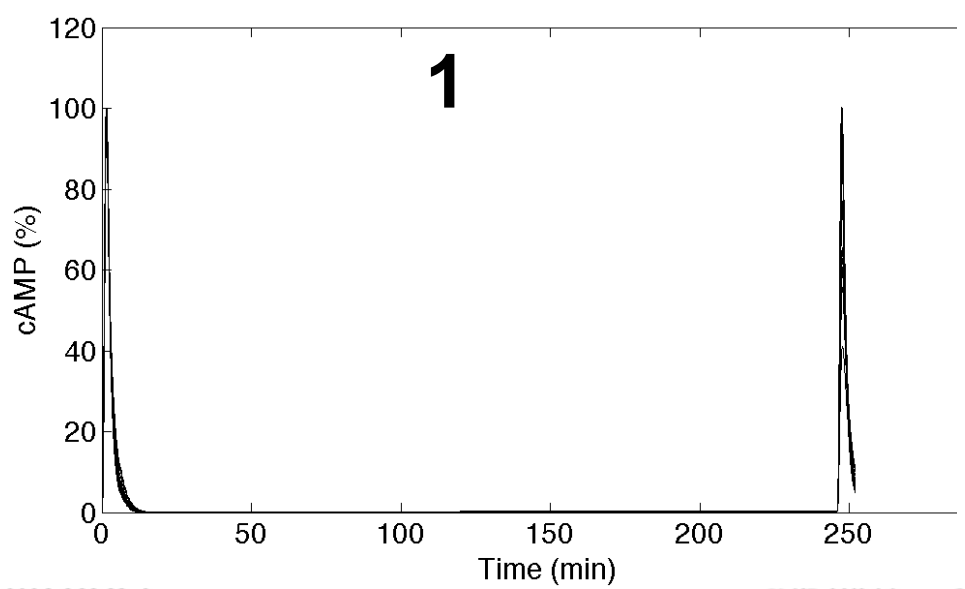
$$k_{act} + PKA_{act}$$

$$K_{act}$$

$$- k_{2d} \cdot \beta_{2int}$$

$$5b \cdot \heartsuit_{act}$$

$$- k_{1d} \cdot \beta_{1int}$$



$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

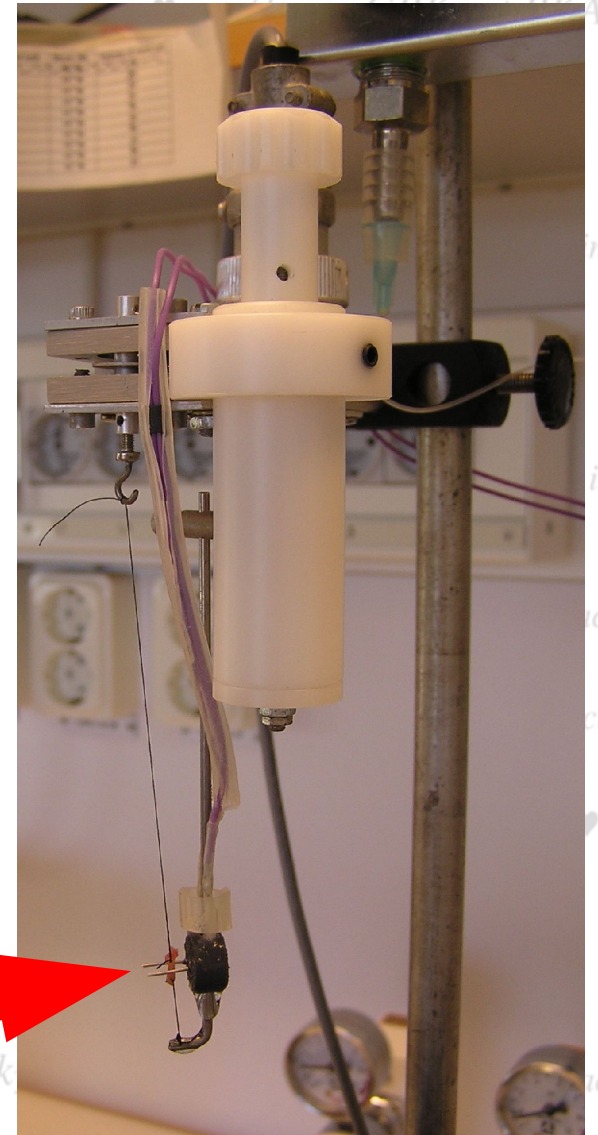
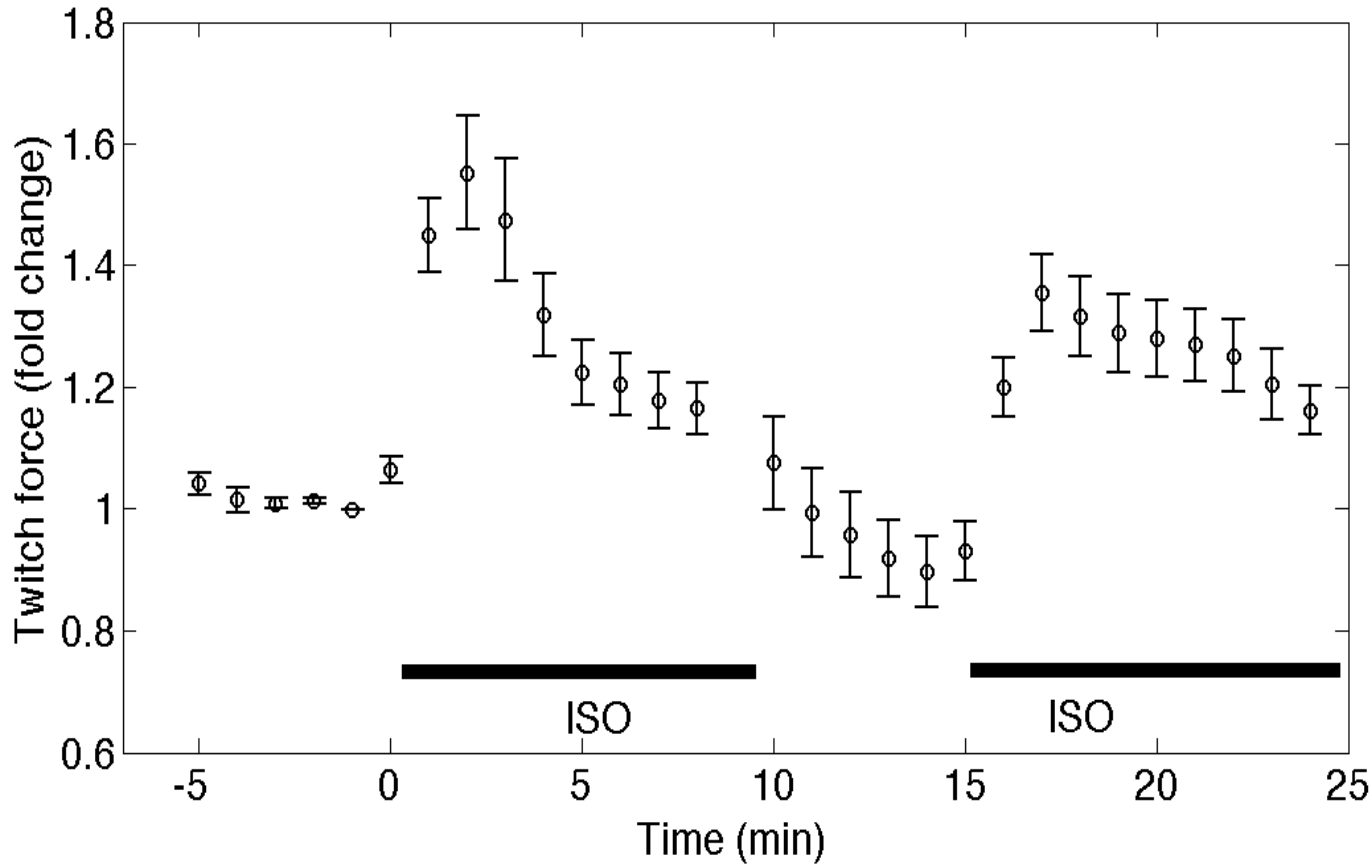
$$\frac{d(\heartsuit_{act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act})$$

$$\frac{d(G_{iact})}{dt} = k_{3c} \cdot \beta_{2p} \cdot \heartsuit_i - k_{3d} \cdot G_{iact}$$



$$\frac{d(PKA_{act})}{dt} = cAMP \cdot k_{6c} \cdot \heartsuit - k_{6d} \cdot PKA_{act}$$

$$\frac{d(\heartsuit_{1p})}{dt} = k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - k_{1b} \cdot \heartsuit_{1p} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit_{2p})}{dt} = k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p}$$

$$\frac{d(\heartsuit_{act})}{dt} = k_{3c} \cdot \beta_{2p} \cdot \heartsuit_i - k_{3d} \cdot \heartsuit_{act}$$

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - k_{1b} \cdot \beta_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt} = 1$$

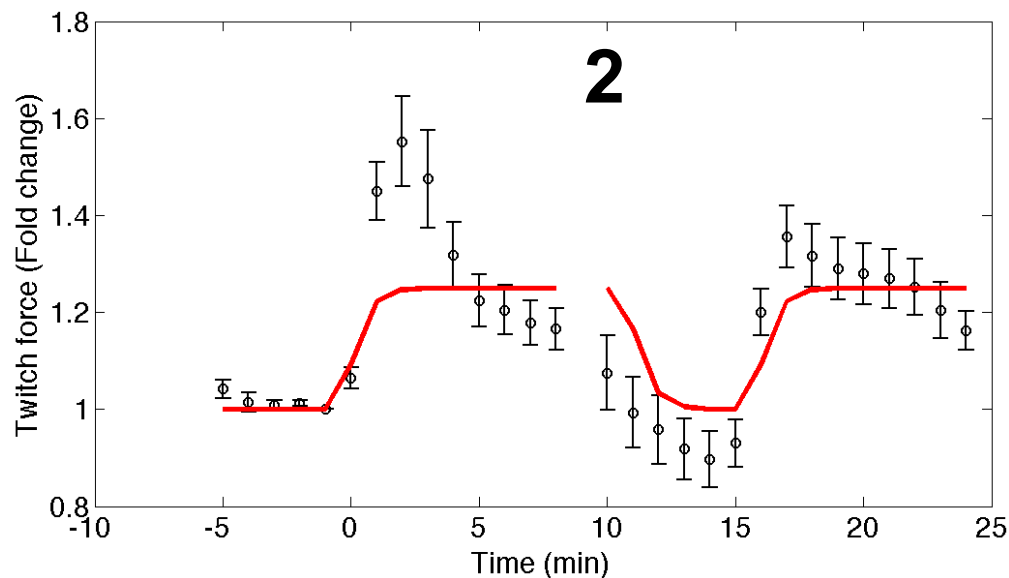
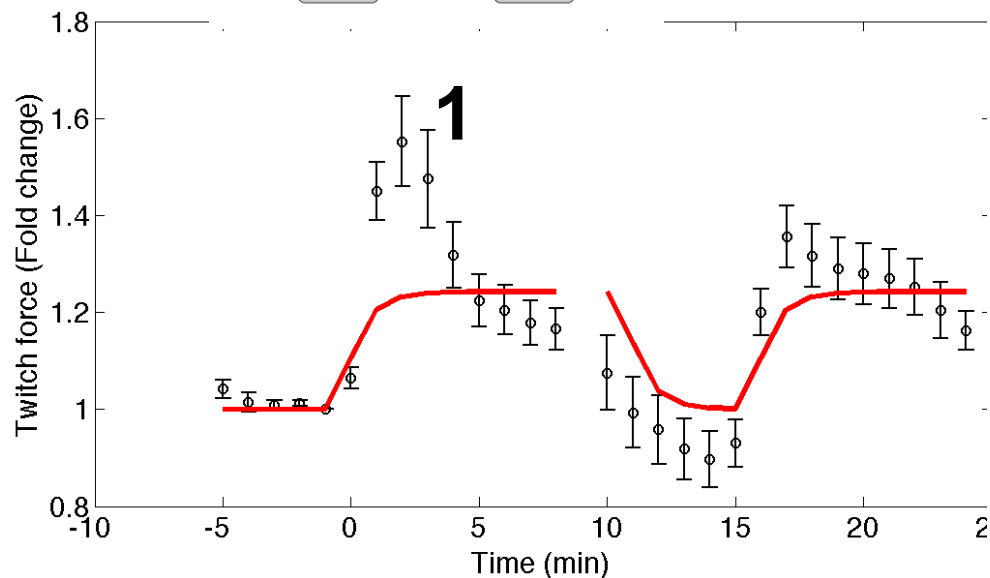
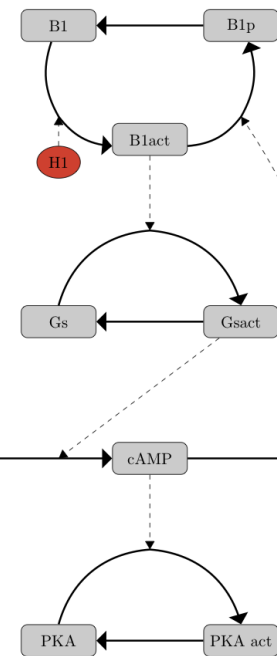
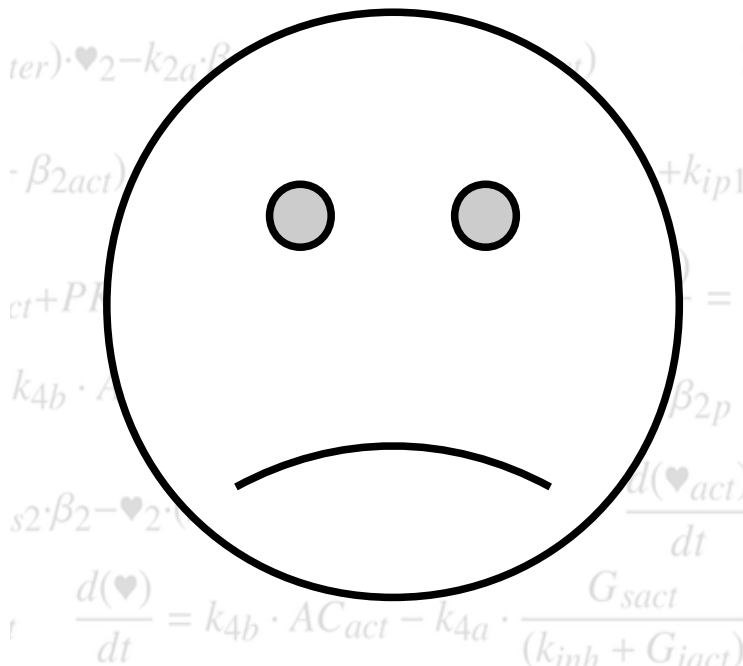
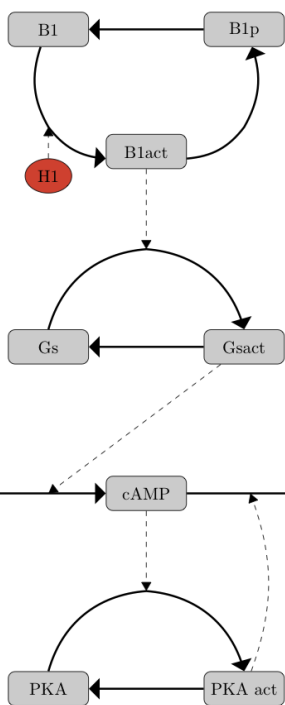
$$\frac{d(G_s)}{dt} = k_{3l}$$

$$\frac{d(\heartsuit_{2p})}{dt} =$$

$$\frac{d(AC_{act})}{dt} =$$

$$\frac{d(\beta_{act})}{dt} =$$

$$\frac{d(PKA)}{dt} =$$

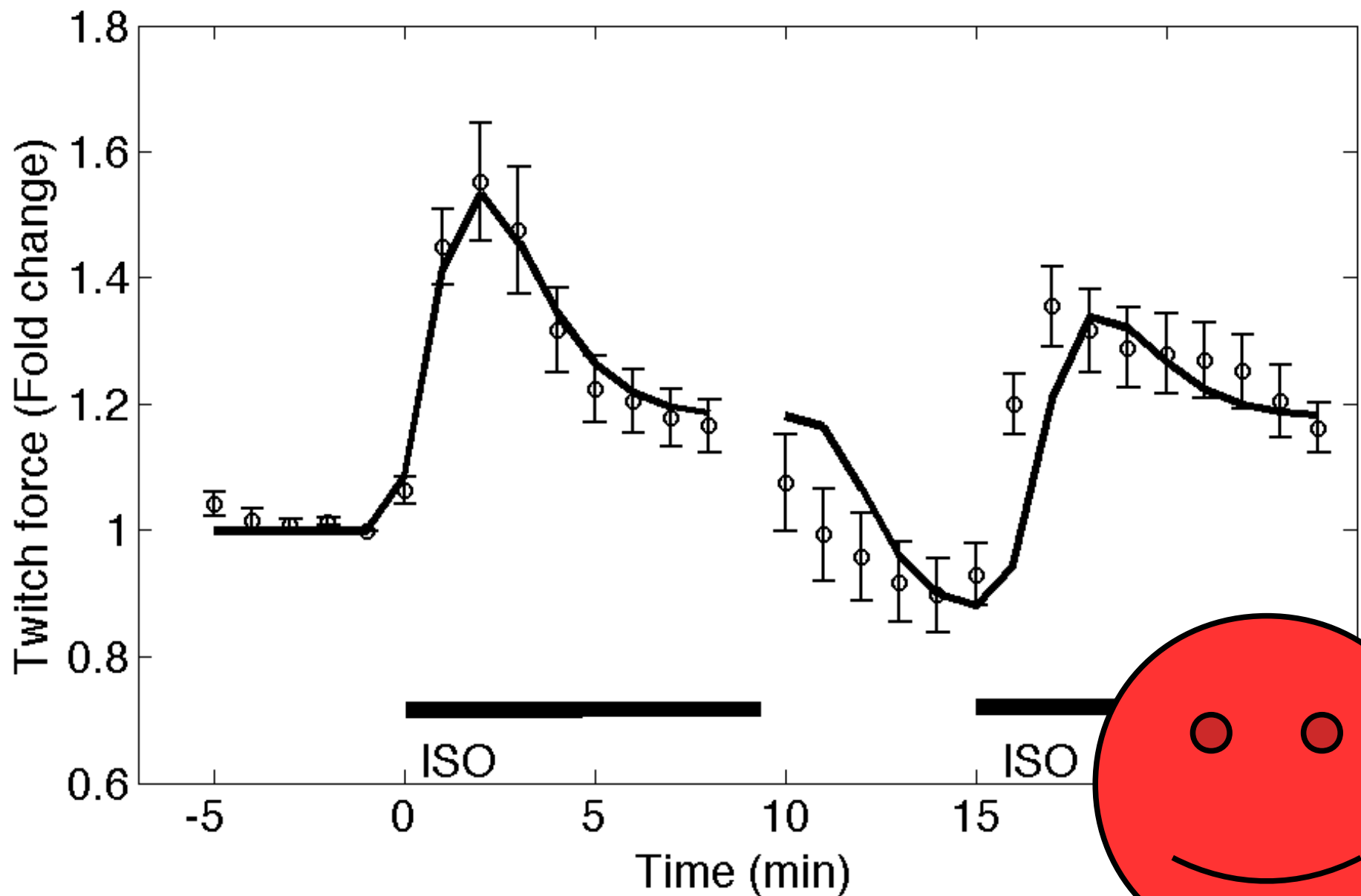


$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

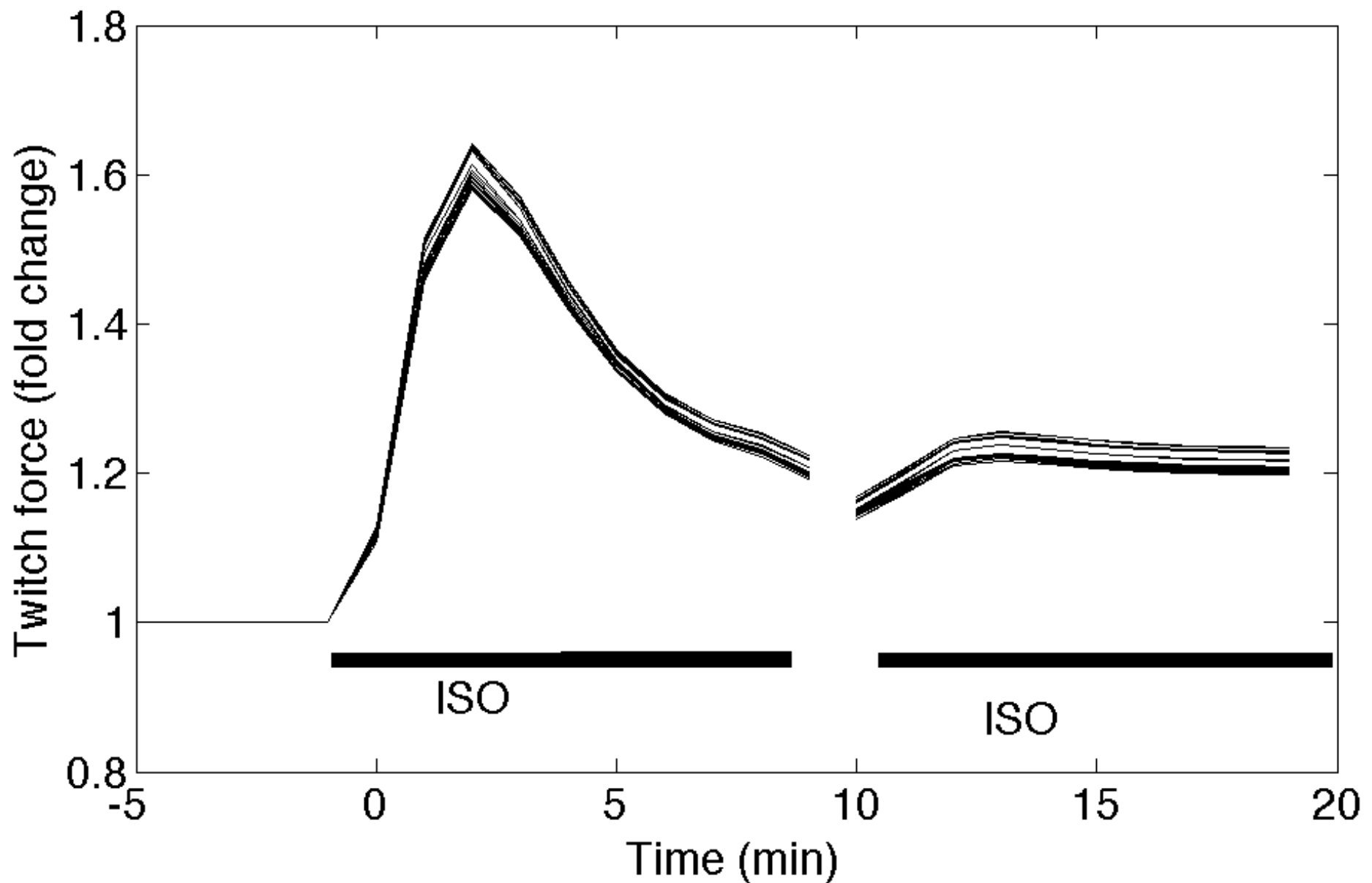


$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$



$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$







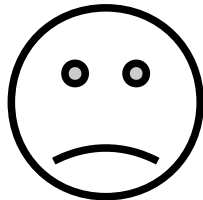

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit$$

$$\frac{d(\beta_{2act})}{dt}$$

$$\frac{d(G_{sact})}{dt}$$

| | Theoretical data | Return of signal | Experimental data | Predict resting time |
|--------------------|---|---|--|---|
| Original model |  |  |  |  |
| Minimal models |  |  |  | — |
| All smaller models |  | — | — | — |

$$\frac{d(GRK)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\begin{aligned}
 \frac{d(\heartsuit)}{dt} &= k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit & \frac{d(cAMP)}{dt} &= cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit \\
 \frac{d(\beta_{2act})}{dt} &= k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act}) & \frac{d(G_{iact})}{dt} &= k_{3c} \cdot \beta_{2p} \cdot \heartsuit_i - k_{3d} \cdot G_{iact} \\
 \frac{d(G_s)}{dt} &= k_{3b} \cdot G_{sact} - k_{3a} \cdot \heartsuit_s \cdot (\beta_{1act} + \beta_{2act}) & \frac{d(\beta_{1act})}{dt} &= k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) \\
 \frac{d(\heartsuit_{2p})}{dt} &= k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p} & \frac{d(GRK)}{dt} &= -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \\
 \frac{d(AC_{act})}{dt} &= k_{4a} \cdot \frac{G_{sact}}{(\heartsuit_{inh} + G_{iact})} \cdot AC - k_{4b} \cdot AC_{act} & \frac{d(G_i)}{dt} &= k_{3d} \cdot \heartsuit_{iact} - k_{3c} \cdot \beta_{2p} \cdot G_i & \frac{d(\heartsuit_{2int})}{dt} &= k_{2b} \cdot \beta_{2p} - k_{2d} \cdot \beta_{2int} \\
 \frac{d(\beta_2)}{dt} &= k_{2d} \cdot \heartsuit_{2int} - k_{2a} \cdot \beta_2 - \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot H_2 & \frac{d(\heartsuit_{act})}{dt} &= cAMP \cdot k_{6a} \cdot GRK - k_{6b} \cdot \heartsuit_{act} \\
 \frac{d(PKA)}{dt} &= -\heartsuit \cdot k_{6c} \cdot PKA + k_{6d} \cdot PKA_{act} & \frac{d(\heartsuit_{1int})}{dt} &= k_{1b} \cdot \beta_{1p} - k_{1d} \cdot \beta_{1int} \\
 \frac{d(\heartsuit_{1p})}{dt} &= k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (k_{1b} + k_{1c}) \cdot \heartsuit_{1p} & \frac{d(\heartsuit_{sact})}{dt} &= k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act}) - k_{3b} \cdot G_{sact} \\
 \frac{d(\heartsuit_{act})}{dt} &= cAMP \cdot k_{6a} \cdot GRK - k_{6b} \cdot \heartsuit_{act} & \frac{d(\beta_{2act})}{dt} &= k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{act}) \\
 \frac{d(\heartsuit)}{dt} &= k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit & \frac{d(cAMP)}{dt} &= cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit \\
 \frac{d(PKA_{act})}{dt} &= cAMP \cdot k_{6c} \cdot \heartsuit - k_{6d} \cdot PKA_{act} & \frac{d(\heartsuit_{1p})}{dt} &= k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (k_{1b} + k_{1c}) \cdot \heartsuit_{1p} \\
 \frac{d(\heartsuit_{2p})}{dt} &= k_{2a} \cdot \heartsuit_{2act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\heartsuit_{2b} + k_{2c}) \cdot \beta_{2p} & \frac{d(\heartsuit_{sact})}{dt} &= k_{3a} \cdot G_s \cdot (\beta_{1act} + \heartsuit_{2act}) - k_{3b} \cdot G_{sact} \\
 \frac{d(cAMP)}{dt} &= cAMP_0 + \heartsuit_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \heartsuit & \frac{d(\heartsuit)}{dt} &= k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot \heartsuit
 \end{aligned}$$

Thank you!

Future prospects

- GRK

- Compartmentmentation

- Compare healthy adult hearts with fetal and failed hearts