

$$\begin{aligned}
\frac{d(\text{CAMP}_2)}{dt} &= k_{2a} \cdot \text{CAMP}_{act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\text{CAMP}_2 + k_{2c}) \cdot \beta_{2p} & \frac{d(cAMP)}{dt} &= cAMP_0 + \text{CAMP}_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \text{CAMP}_{act} \\
\frac{d(\beta_{2act})}{dt} &= k_{bas2} \cdot \beta_2 + \text{CAMP}_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \text{CAMP}_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \text{CAMP}_{act} + \text{CAMP}_{act}) & \frac{d(G_iact)}{dt} &= k_{3c} \cdot \beta_{2p} \cdot \text{CAMP}_i - k_{3d} \cdot G_iact \\
\frac{d(G_s)}{dt} &= k_{3b} \cdot G_{sact} - k_{3a} \cdot \text{CAMP}_s \cdot (\beta_{1act} + \beta_{2act}) & \frac{d(\beta_{1act})}{dt} &= k_{bas1} \cdot \beta_1 + \text{CAMP}_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \text{CAMP}_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) \\
\frac{d(\text{CAMP}_2)}{dt} &= k_{2a} \cdot \text{CAMP}_{act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\text{CAMP}_2 + k_{2c}) \cdot \beta_{2p} & \frac{d(GRK)}{dt} &= -\text{CAMP} \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \\
\frac{d(AC_{act})}{dt} &= k_{4a} \cdot \frac{G_{sact}}{(\text{CAMP}_{inh} + G_iact)} \cdot AC - k_{4b} \cdot AC_{act} & \frac{d(G_i)}{dt} &= k_{3d} \cdot \text{CAMP}_{iact} - k_{3c} \cdot \beta_{2p} \cdot G_i & \frac{d(\text{CAMP}_{2int})}{dt} &= k_{2b} \cdot \beta_{2p} - k_{2d} \cdot \beta_{2int} \\
\frac{d(\beta_2)}{dt} &= k_{2d} \cdot \text{CAMP}_{2int} + k_{2c} \cdot \beta_{2p} - k_{bas2} \cdot \beta_2 - \text{CAMP}_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot H_2 & \frac{d(\text{CAMP}_{act})}{dt} &= cAMP \cdot k_{6a} \cdot GRK - k_{6b} \cdot \text{CAMP}_{act} \\
\frac{d(PKA)}{dt} &= -\text{CAMP} \cdot k_{6c} \cdot PKA + k_{6d} \cdot \text{CAMP}_{act} & \frac{d(\text{CAMP})}{dt} &= k_{4b} \cdot AC_{act} - k_{4a} \cdot \frac{G_{sact}}{(\text{CAMP}_{inh} + G_iact)} \cdot \text{CAMP} & \frac{d(\text{CAMP}_{1int})}{dt} &= k_{1b} \cdot \beta_{1p} - k_{1d} \cdot \beta_{1int} \\
\frac{d(\text{CAMP}_{1p})}{dt} &= k_{1a} \cdot \text{CAMP}_{act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (k_{1b} + k_{1c}) \cdot \text{CAMP}_{1p} & \frac{d(\text{CAMP}_{sact})}{dt} &= k_{3a} \cdot G_s \cdot (\beta_{1act} + \text{CAMP}_{2act}) - k_{3b} \cdot G_{sact} \\
\frac{d(\text{CAMP}_{act})}{dt} &= cAMP \cdot k_{6a} \cdot GRK - k_{6b} \cdot \text{CAMP}_{act} & \frac{d(\beta_{2act})}{dt} &= k_{bas2} \cdot \beta_2 + \text{CAMP}_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \text{CAMP}_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \text{CAMP}_{act} + \text{CAMP}_{act}) \\
\frac{d(\text{CAMP})}{dt} &= k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \text{CAMP}_1 \cdot (k_{iso1} + k_{ip1}) \cdot \text{CAMP}_1 & \frac{d(cAMP)}{dt} &= cAMP_0 + \text{CAMP}_{act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \text{CAMP}_{act} \\
\frac{d(PKA_{act})}{dt} &= cAMP \cdot k_{6c} \cdot \text{CAMP} - k_{6d} \cdot PKA_{act} & \frac{d(\text{CAMP}_{1p})}{dt} &= k_{1a} \cdot \text{CAMP}_{act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (k_{1b} + k_{1c}) \cdot \text{CAMP}_{1p} \\
\frac{d(\text{CAMP}_{2p})}{dt} &= k_{2a} \cdot \text{CAMP}_{act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\text{CAMP}_2 + k_{2c}) \cdot \beta_{2p} & \frac{d(\text{CAMP}_{sact})}{dt} &= k_{3a} \cdot G_s \cdot (\beta_{1act} + \text{CAMP}_{2act}) - k_{3b} \cdot G_{sact} \\
\frac{d(GRK)}{dt} &= -\text{CAMP} \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} & \frac{d(\beta_{1act})}{dt} &= k_{bas1} \cdot \beta_1 + \text{CAMP}_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \text{CAMP}_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})
\end{aligned}$$

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

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

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

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

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

- Carl Sagan

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

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

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

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

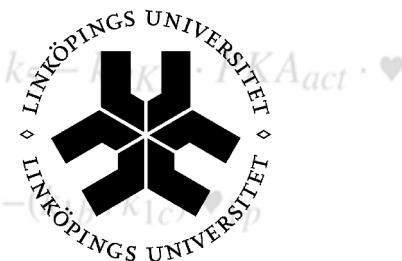
$$\frac{d(\text{act})}{dt} = k_{3a} \cdot G_s \cdot (\beta_{1act} + \beta_{2act}) - k_{3b} \cdot G_{sact}$$

# De- and Resensitisation

# of Cardiac $\beta$ -Adrenergic Receptor Signaling: A Modelling Approach

Master Thesis by Karin Lundengård

Supervisors: Jordi Altimiras,  
Gunnar Cedersund and Elin Nyman



**AVIAN**  
Behavioural Genomics  
and Physiology group

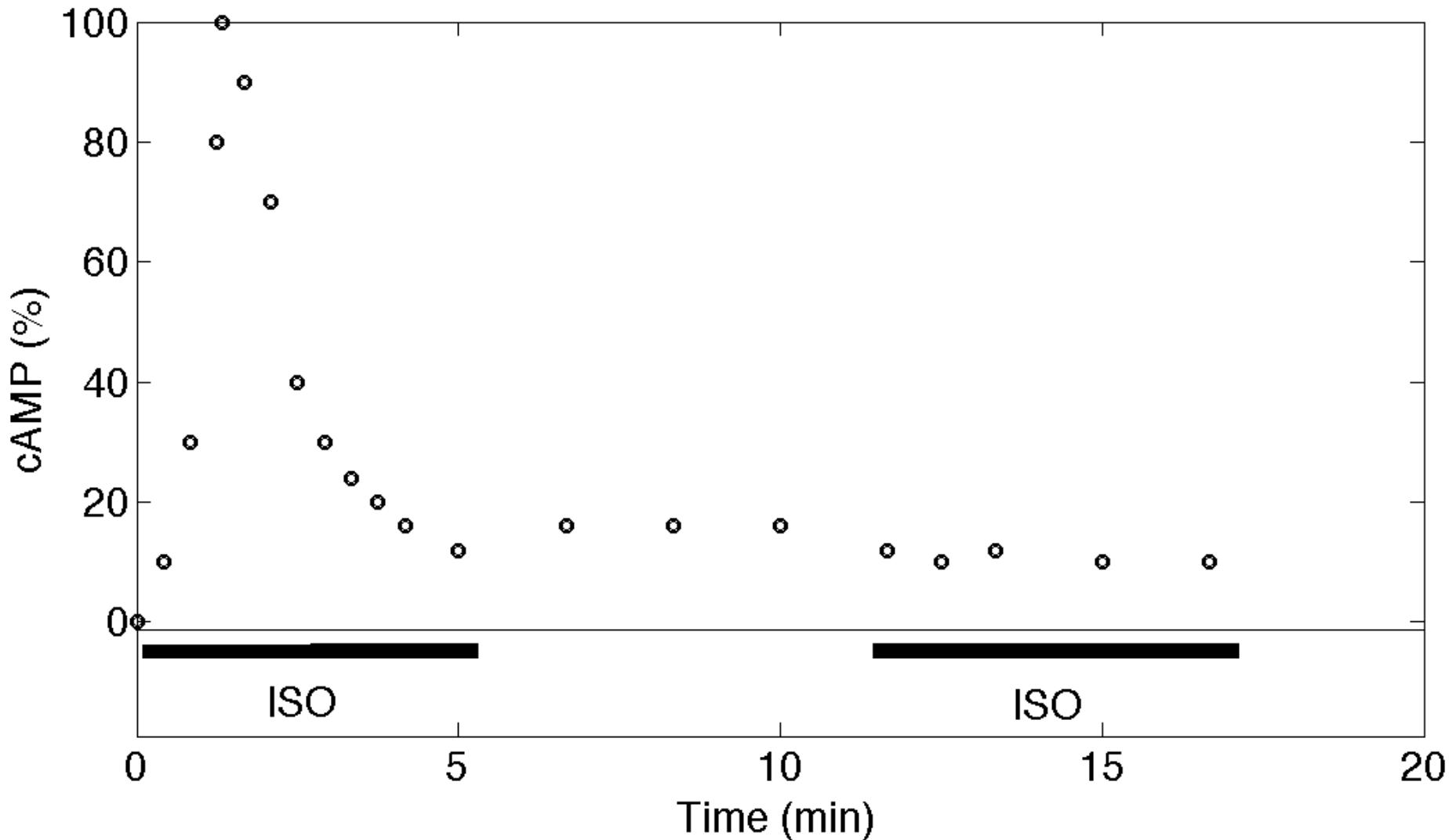
**Linköping University**  
**INSTITUTE OF TECHNOLOGY**

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

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

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{t_0}) \cdot \heartsuit_{act} / (k_{act} + \heartsuit_{act})$$

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

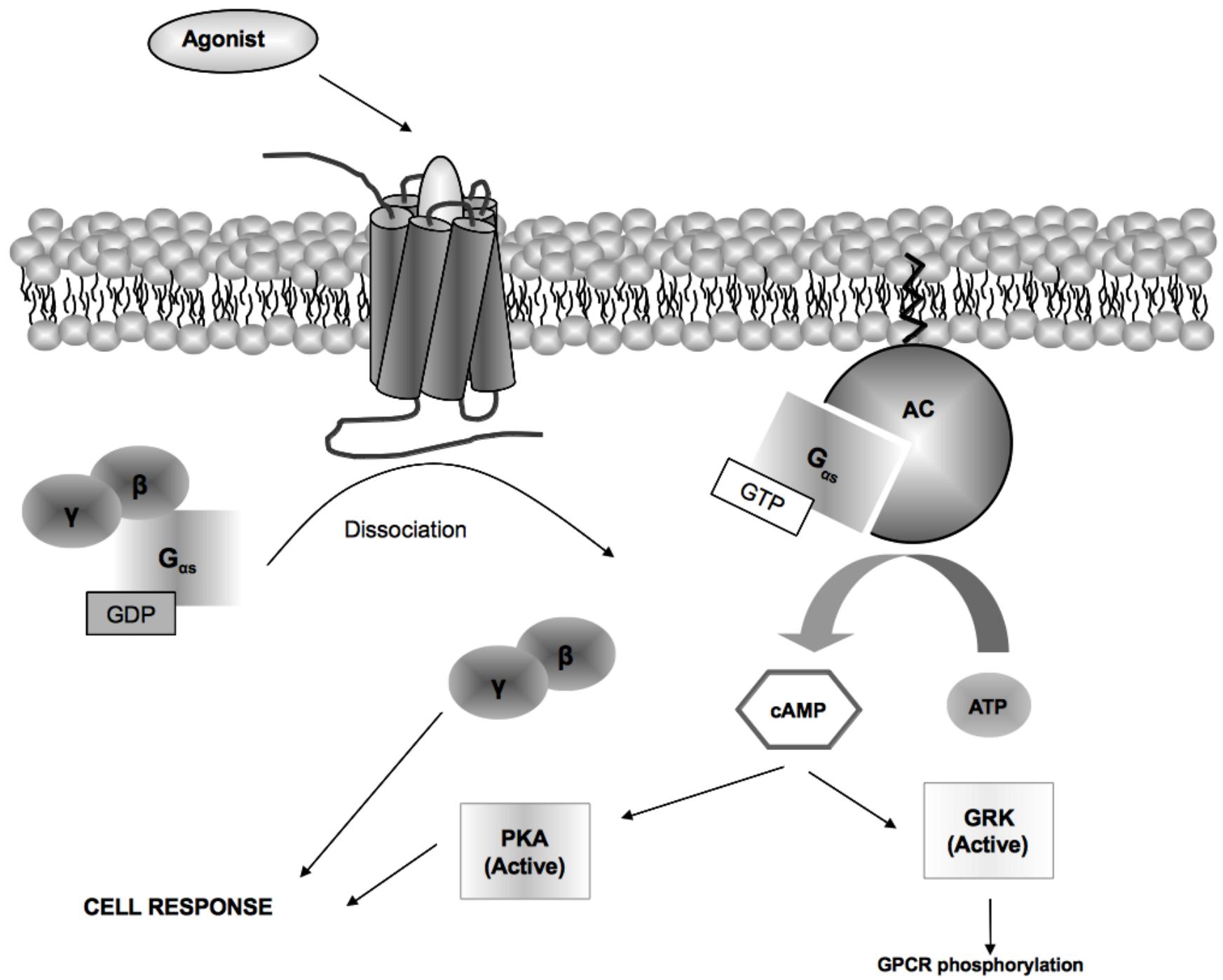


$$\frac{d}{dt} = \kappa_{2a} \cdot \nabla_{2act} \cdot (\kappa_{GRK} \cdot \nabla_{1act} + \kappa_{1act} \cdot \nabla_{2act}) - (\nabla_{2b} + \kappa_{2c}) \cdot P2p$$

$$\frac{d}{dt} = \kappa_{5a} \cdot \nabla_{s} \cdot \nabla_{1act} + \nabla_{2act} - \kappa_{5b} \cdot \nabla_{sact}$$

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

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



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

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

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

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

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

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

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

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

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

$d(cAMP)$

$t$   
 $A_{act}$

$int$

$|int$

$act$

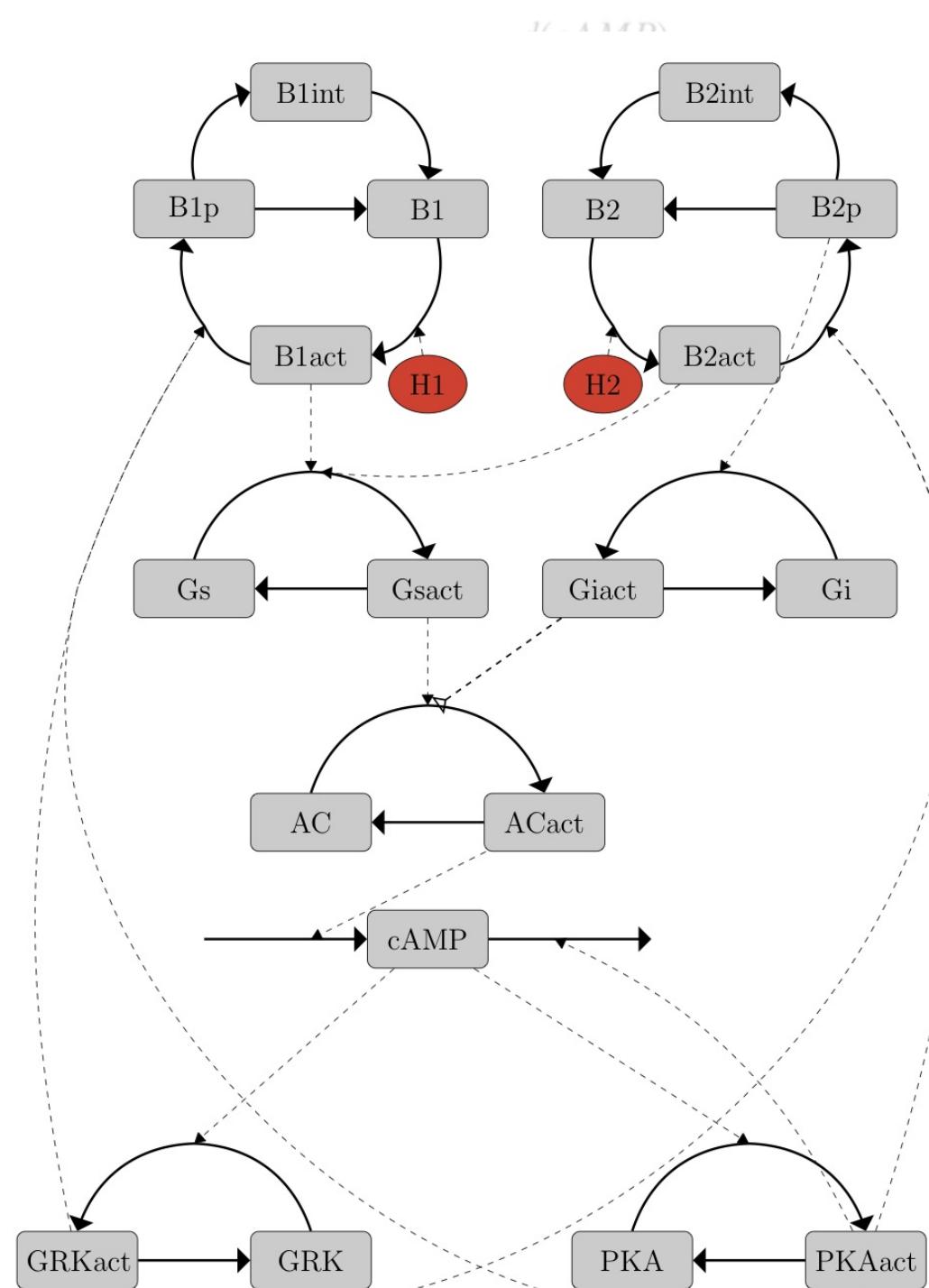
$ct$ )

$\heartsuit$

$act$

$$\frac{d(cAMP)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} - \frac{d(G)}{dt} = \kappa_{bas1} \cdot p_1 + \nabla_1 \cdot (\kappa_{isol} + \kappa_{ip1}) \cdot H_1 - \kappa_{1a} \cdot \nabla_1 \cdot act \cdot (\kappa_{GRK} \cdot GRK_{act} + \kappa_{KA} \cdot K_{Aact})$$

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



$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{is01} + k_{ip1}) \cdot \heartsuit$$

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

$$\begin{aligned} d(B1)/dt &= k_{1d} \cdot B1int + k_{1c} \cdot B1p - k_{bas1} \cdot B1 - \\ &\quad B1 \cdot (k_{iso} + k_{ip1}) \cdot H1 \\ d(G_s)/dt &: \\ d(B1act)/dt &= k_{bas1} \cdot B1 + B1 \cdot (k_{iso} + k_{ip1}) \cdot H1 - \\ &\quad k_{1a} \cdot B1act \cdot (k_{GRK} \cdot GRKact + PKAact) \\ d(B1p)/dt &= k_{1a} \cdot B1act \cdot (k_{GRK} \cdot GRKact + PKAact) - \\ &\quad (k_{1b} + k_{1c}) \cdot B1p \\ d(B1int)/dt &= k_{1b} \cdot B1p - k_{1d} \cdot B1int \end{aligned}$$

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

$$\begin{aligned} d(B2)/dt &= k_{2d} \cdot B2int + k_{2c} \cdot B2p - k_{bas2} \cdot B2 - \\ &\quad B2 \cdot (k_{iso} + k_{ip2} + k_{ter}) \cdot H2 \\ d(B2act)/dt &= k_{bas2} \cdot B2 + B2 \cdot (k_{iso} + k_{ip2} + k_{ter}) \cdot H2 - \\ &\quad k_{2a} \cdot B2act \cdot (k_{GRK} \cdot GRKact + PKAact) \\ d(B2p)/dt &= k_{2a} \cdot B2act \cdot (k_{GRK} \cdot GRKact + PKAact) - \\ &\quad (k_{2b} + k_{2c}) \cdot B2p \\ d(B2int)/dt &= k_{2b} \cdot B2p - k_{2d} \cdot B2int \end{aligned}$$

$$\begin{aligned} d(G_s)/dt &= k_{3b} \cdot Gsact - k_{3a} \cdot Gs \cdot (B1act + B2act) \\ d(Gsact)/dt &= k_{3a} \cdot Gs \cdot (B1act + B2act) - k_{3b} \cdot Gsact \end{aligned}$$

$$\begin{aligned} d(G_i)/dt &= k_{3d} \cdot Giact - k_{3c} \cdot B2p \cdot Gi \\ d(Giact)/dt &= k_{3c} \cdot B2p \cdot Gi - k_{3d} \cdot Giact \end{aligned}$$

$$\begin{aligned} d(AC)/dt &= k_{4b} \cdot ACact - k_{4a} \cdot Gsact / (kinh + Giact) \cdot AC \\ d(ACact)/dt &= k_{4a} \cdot Gsact / (kinh + Giact) \cdot AC - k_{4b} \cdot ACact \end{aligned}$$

$$d(cAMP)/dt = cAMP_0 + ACact \cdot k_5 - k_{PKA} \cdot PKAact \cdot cAMP$$

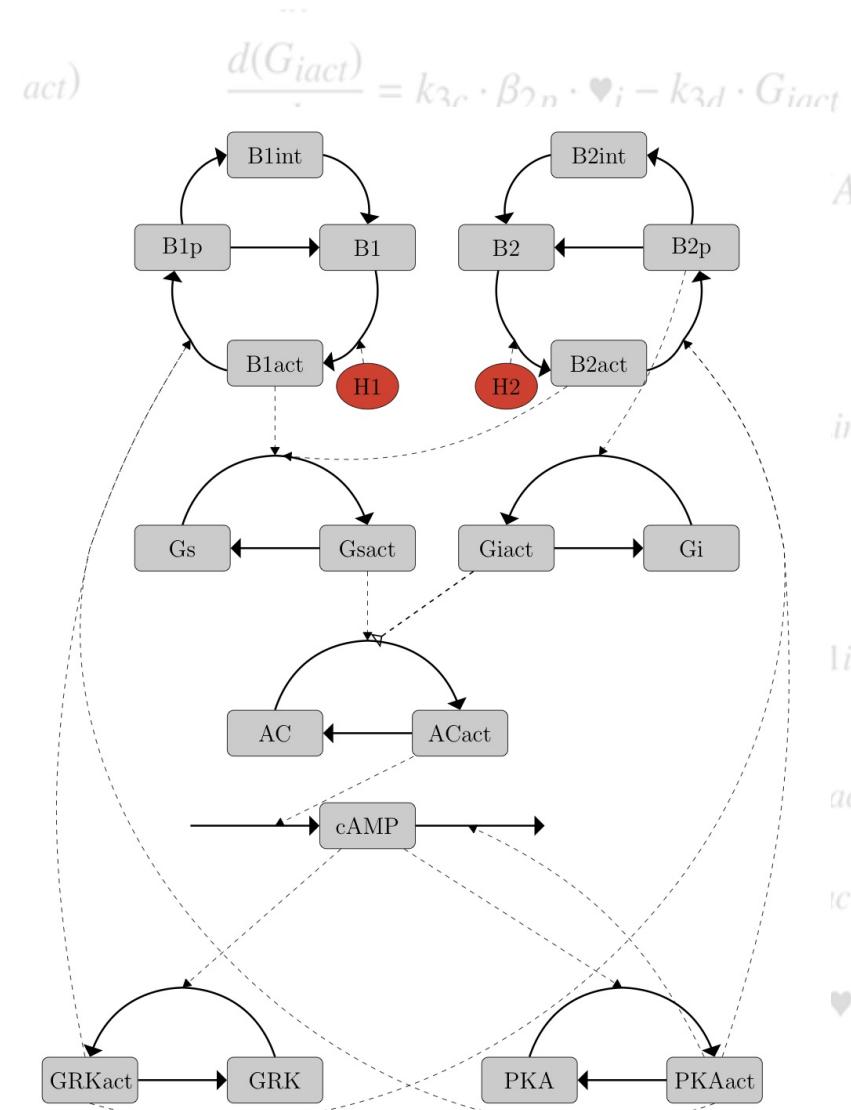
$$\begin{aligned} d(GRK)/dt &= -cAMP \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRKact \\ d(GRKact)/dt &= cAMP \cdot k_{6a} \cdot GRK - k_{6b} \cdot GRKact \end{aligned}$$

$$\begin{aligned} d(PKA)/dt &= -cAMP \cdot k_{6c} \cdot PKA + k_{6d} \cdot PKAact \\ d(PKAact)/dt &= cAMP \cdot k_{6c} \cdot PKA - k_{6d} \cdot PKAact \end{aligned}$$

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

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{is01} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRKact + PKAact)$$

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



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

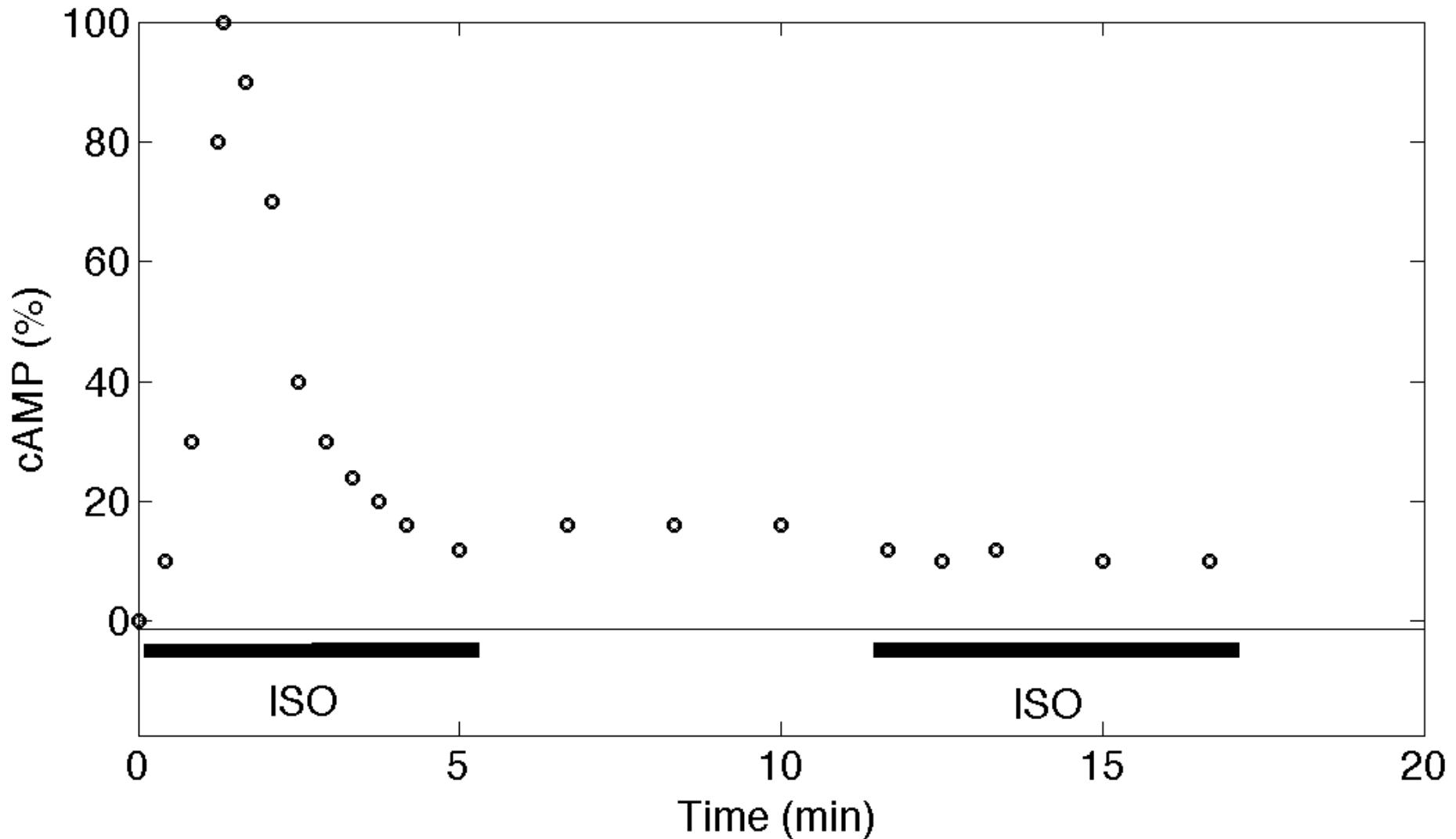
$$\frac{d(Giact)}{dt} = k_{3c} \cdot \beta_{2n} \cdot \heartsuit_i - k_{3d} \cdot Giact$$

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

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

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

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



$$\frac{d(\heartsuit_2)}{dt} = \kappa_{2a} \cdot \nabla_{2act} \cdot (\kappa_{GRK} \cdot \nabla_{1act} + \kappa_{2c} \cdot \nabla_{1act}) - (\nabla_{2b} + \kappa_{2c}) \cdot P2p$$

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

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

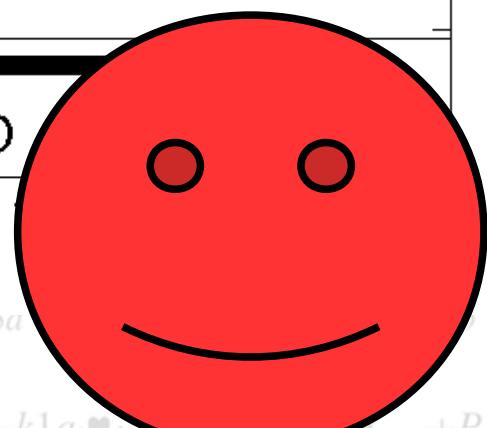
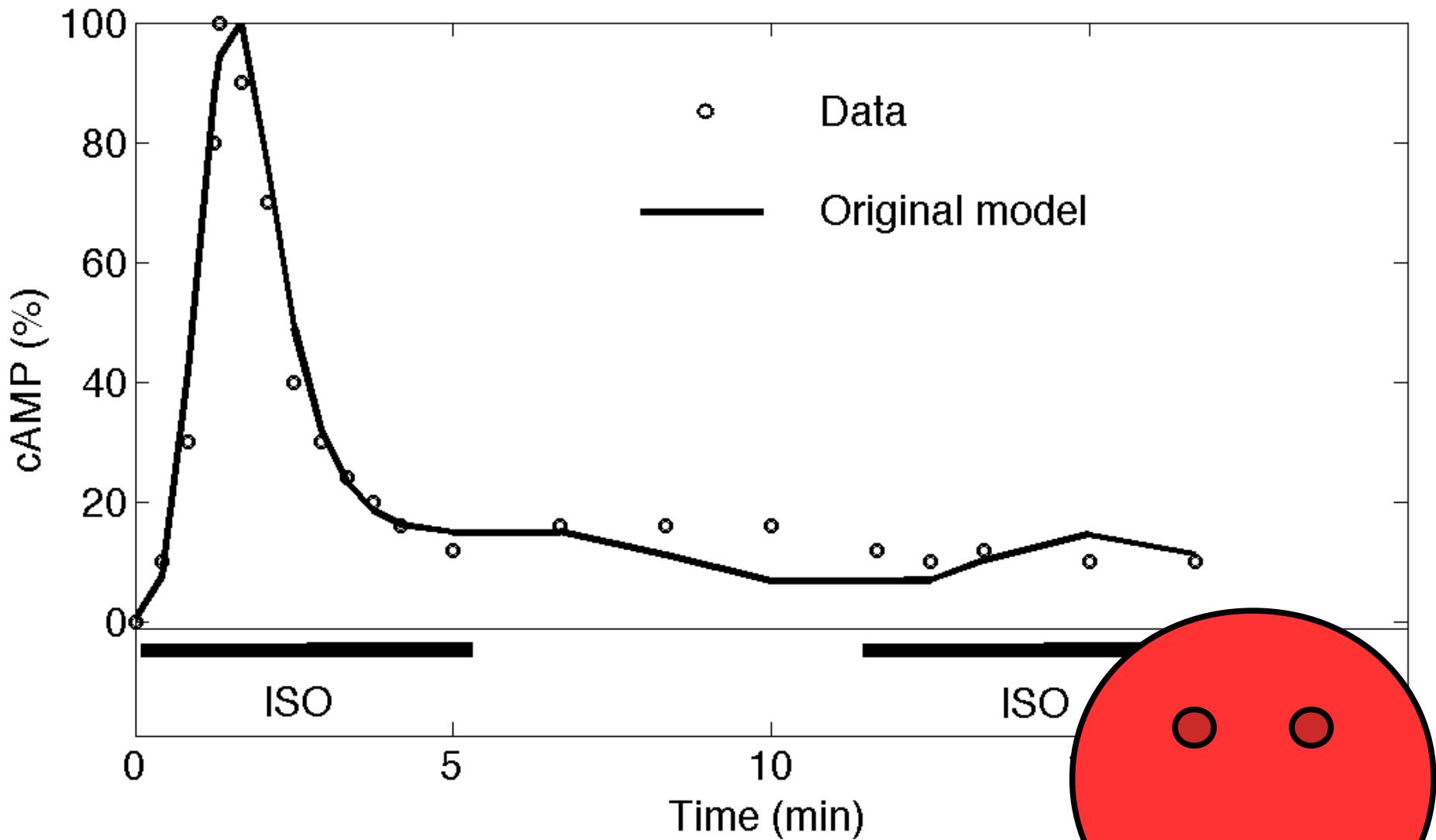
$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

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

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

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

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



$$\frac{d}{dt} (\text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---}) = (\text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---}) - (\text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---})$$

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

$$\frac{d}{dt} (\text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---}) = (\text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---}) - (\text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---} \cdot \text{---})$$

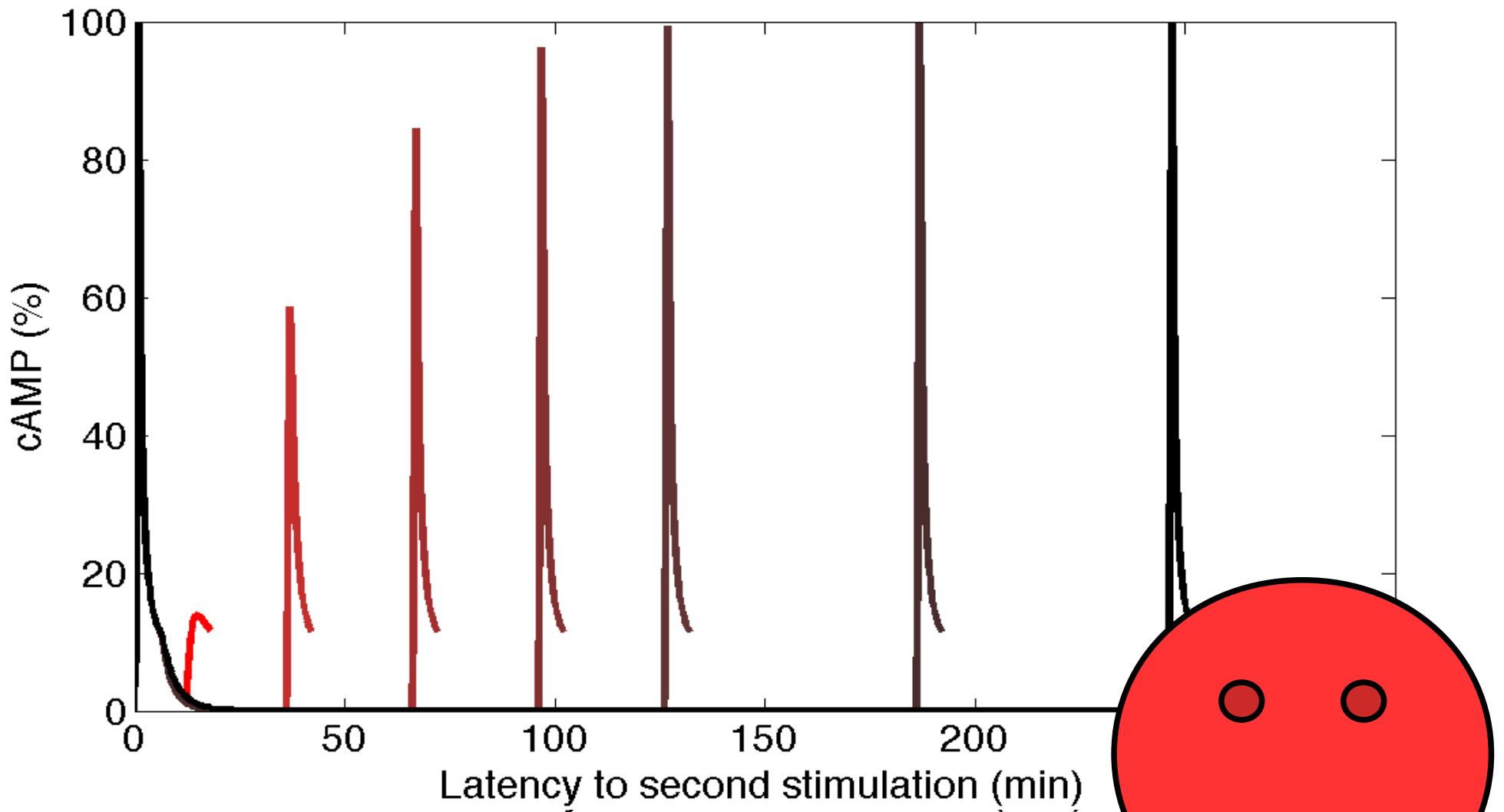
$$\frac{d(PKA_{act})}{dt} = k_{5a} \cdot cAMP_{act} + k_{5b} \cdot cAMP_{act} \cdot \heartsuit_{act} - k_{5c} \cdot PKA_{act} - k_{5d} \cdot PKA_{act} \cdot \heartsuit_{act}$$

$$\frac{d(\text{•})}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \text{•}_1 \cdot (k_{isol} + k_{ip1}) \cdot \text{•}$$

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

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \text{•}_2 \cdot (k_{iso2} + k_{in2} + k_{tor}) \cdot \text{•}_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \text{•}_{act} + \text{•}_{act})$$

$$\frac{d(G_{iact})}{dt} = L_s \cdot R_s \cdot \text{•}_s - L_s \cdot C_s$$



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

$$\frac{d(\text{•}_{sact})}{dt} = k_{3a} \cdot G_s \cdot \text{•}_{sact}$$

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

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \text{•}_1 \cdot (k_{isol} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \text{•}_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

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

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

$$d(G_e)$$

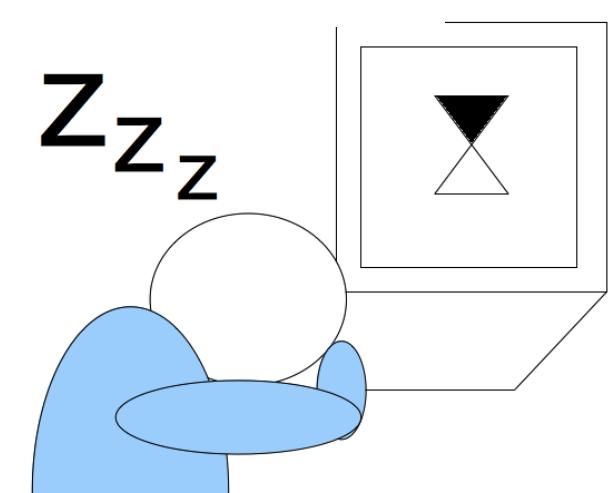
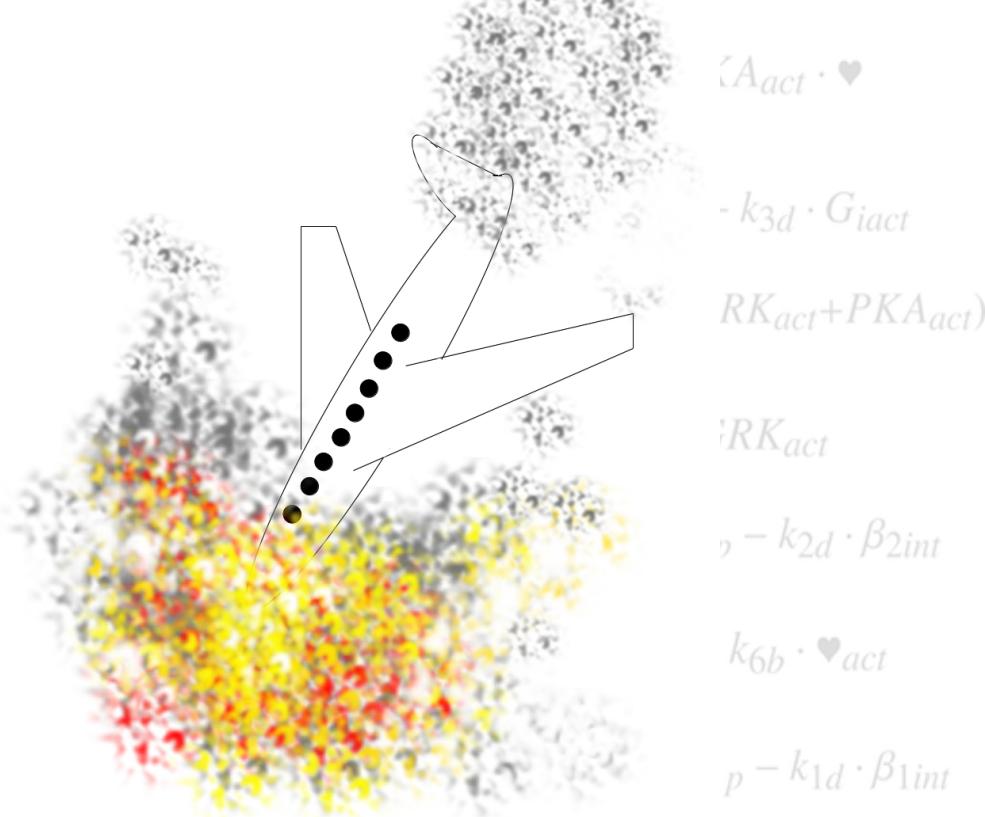
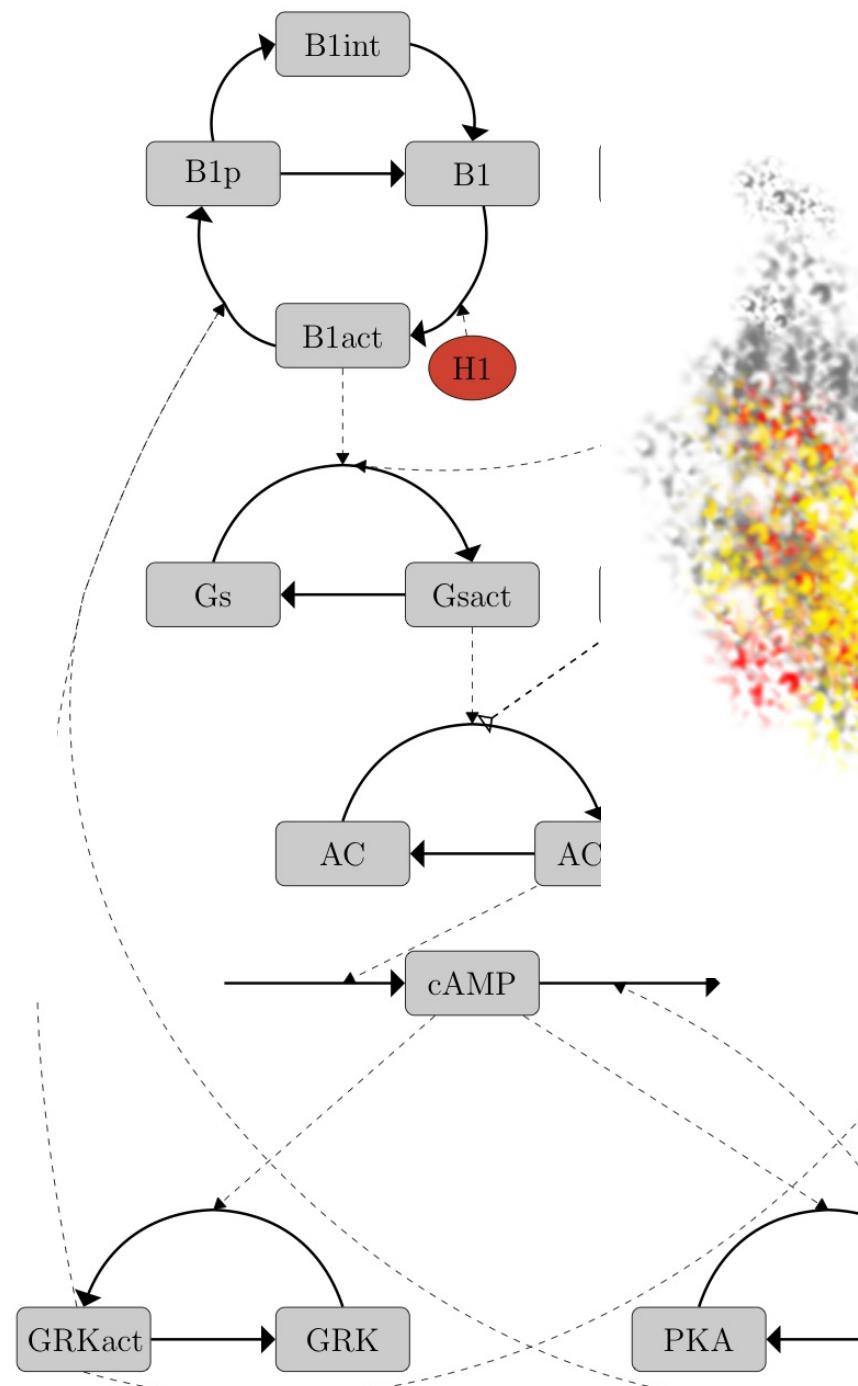


$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c}$$

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

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

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



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

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

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

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

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

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

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

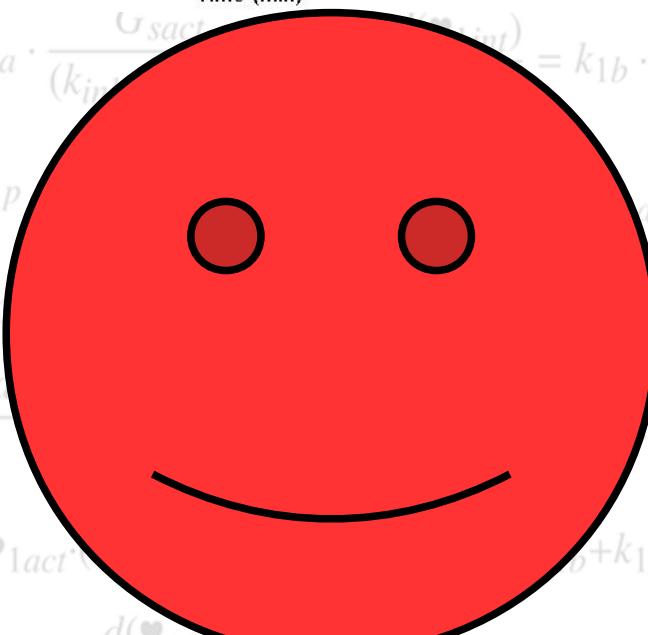
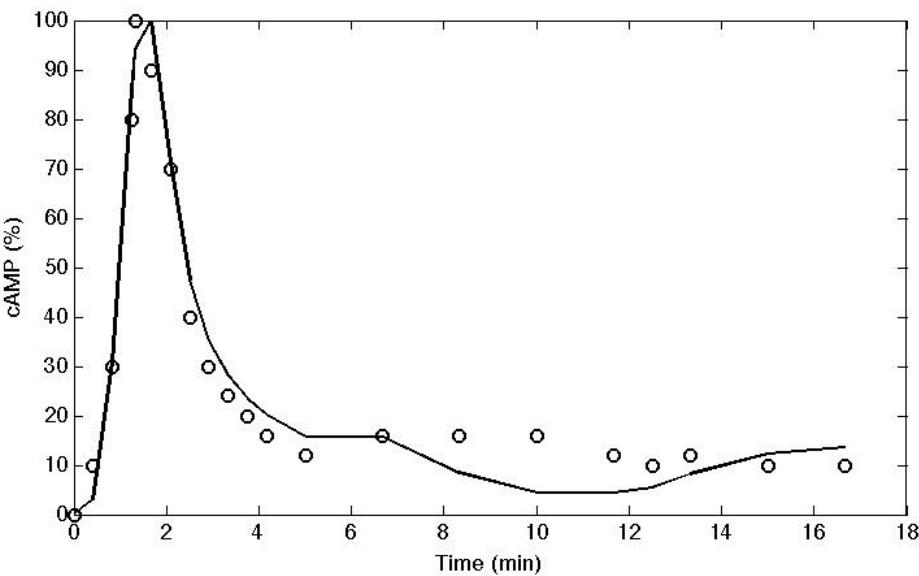
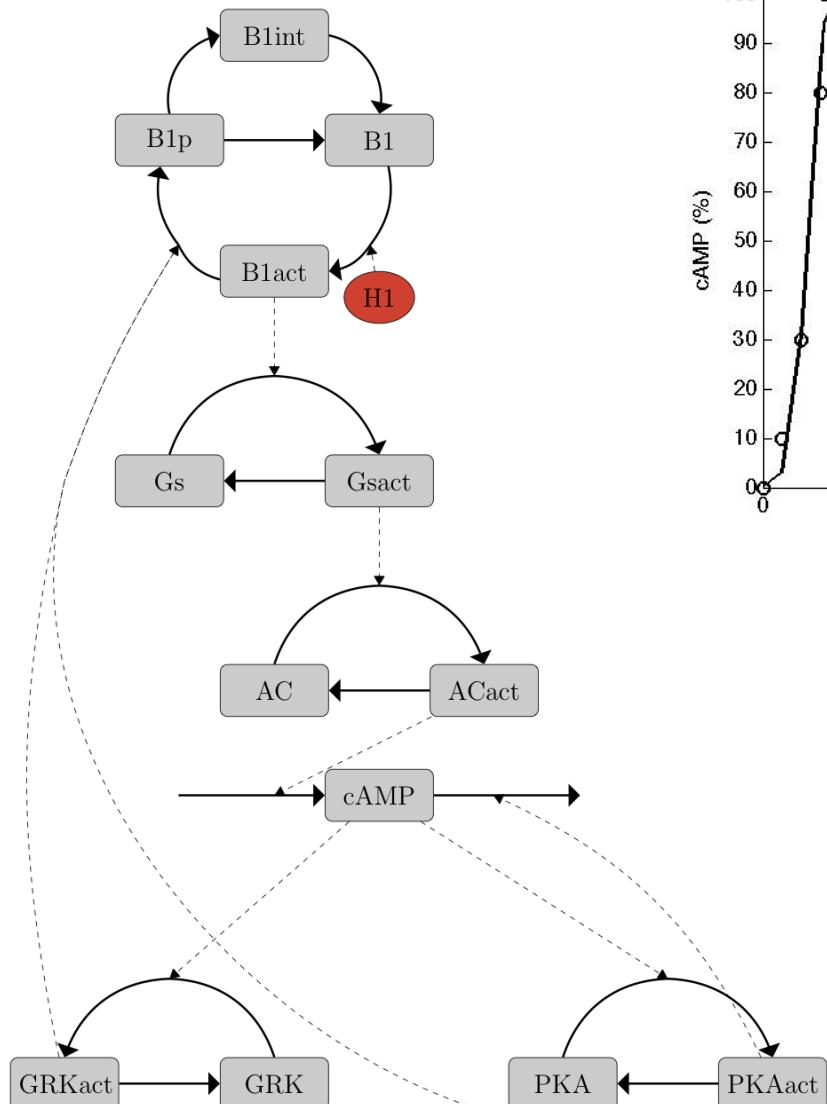
$$\frac{d(\heartsuit)}{dt}$$

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

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

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

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



$$\frac{d(\text{B1})}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \text{B1} \cdot (k_{isol} + k_{ip1}) \cdot \text{B1}$$

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \text{B2} \cdot (k_{1act} + k_{2act} + k_{iso}) \cdot \text{B2} - k_{2a} \cdot \text{B2}$$

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

$$\frac{d(Ac_{ac})}{dt} =$$

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

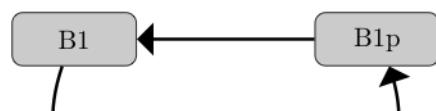
$$\frac{d(\text{B1act})}{dt} =$$

$$\frac{d(\text{B2act})}{dt} =$$

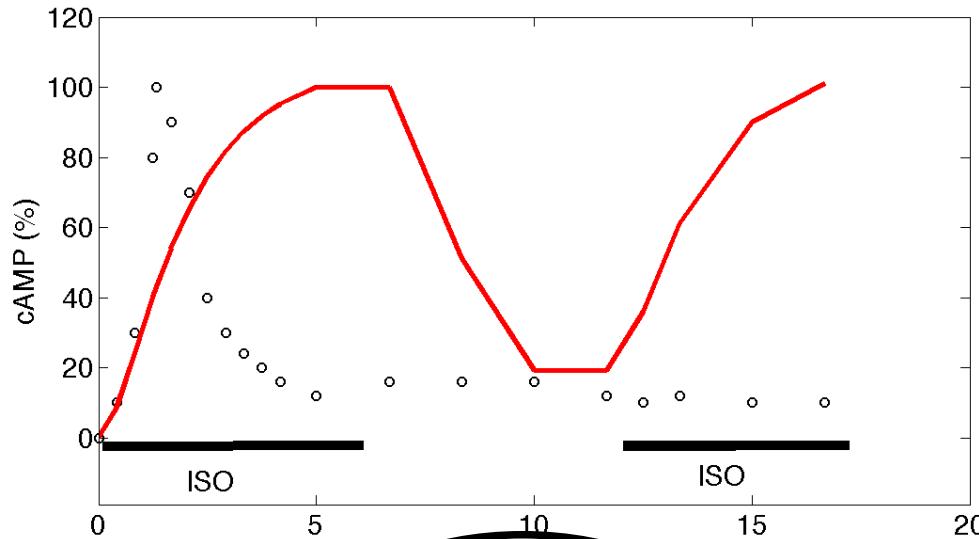
$$\frac{d(PKA_{act})}{dt} =$$

$$\frac{d(\text{B1p})}{dt} =$$

$$\frac{d(GRK)}{dt} = -\text{B1} \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$



$$\frac{d(cAMP)}{dt} = cAMP_0 + \text{B1act} \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \text{B1act}$$



$$\frac{d(\text{B1act})}{dt} = k_{bas1} \cdot \beta_1 + \text{B1} \cdot (k_{isol} + k_{ip1}) \cdot \text{B1} - (\text{B1act} - k_{1b} \cdot \text{B1p}) - (\text{B1act} - k_{1a} \cdot \text{B1act})$$

$$\frac{d(\text{B2act})}{dt} = k_{bas2} \cdot \beta_2 + \text{B2} \cdot (k_{1act} + k_{2act} + k_{iso}) \cdot \text{B2} - (\text{B2act} - k_{2b} \cdot \text{G}_{sact}) - (\text{B2act} - k_{2a} \cdot \text{B2})$$

$$\frac{d(G_sact)}{dt} = k_{3a} \cdot G_s \cdot (\text{B1act} + \text{B2act}) - k_{3b} \cdot \text{G}_{sact}$$

$$\frac{d(PKAact)}{dt} = k_{4a} \cdot \text{B1act} \cdot \text{B2act} \cdot (k_{GRK} \cdot \text{GRK}_{act} + \text{PKA}_{act}) - (\text{PKAact} - k_{4b} \cdot \text{PKA}) - (\text{PKAact} - k_{4c} \cdot \text{PKA}_{act})$$

$$\frac{d(B1p)}{dt} = k_{1a} \cdot \text{B1act} - (\text{B1p} - k_{1b} \cdot \text{B1p}) - (\text{B1p} - k_{1c} \cdot \text{B1act})$$

$$\frac{d(GRKn)}{dt} = -\text{B1} \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

$$\frac{d(PKA)}{dt} = k_{5a} \cdot \text{B1act} \cdot \text{B2act} \cdot (k_{GRK} \cdot \text{GRK}_{act} + \text{PKA}_{act}) - (\text{PKA} - k_{5b} \cdot \text{PKA}) - (\text{PKA} - k_{5c} \cdot \text{PKA}_{act})$$

$$\frac{d(H1)}{dt} = -\text{B1act} \cdot k_{6a} \cdot H1 + k_{6b} \cdot H1_{act}$$

$$\frac{d(\text{H}_1)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \text{H}_1 \cdot (k_{isol} + k_{ip1}) \cdot \text{H}_1$$

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

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

$$\frac{d(\text{H}_2p)}{dt} = k_{2p}$$

$$\frac{d(AC_{act})}{dt} = k_{2b} + k_{2c} \cdot \beta_2$$

$$\frac{d(\beta_i)}{dt} = k_{3d} \cdot G_i$$

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

$$\frac{d(\text{H}_1)}{dt} = k_{1b} + k_{1c} \cdot \text{H}_1$$

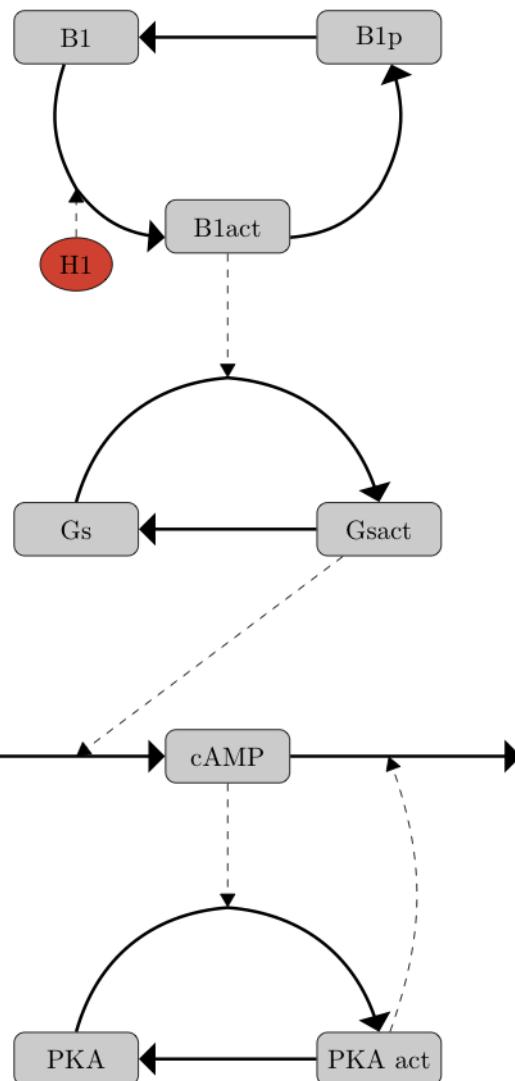
$$\frac{d(\text{H}_2act)}{dt} = k_{2act}$$

$$\frac{d(\text{H}_1)}{dt} = k_{1p} \cdot \text{H}_1$$

$$\frac{d(PKA_{act})}{dt} = k_{1a} \cdot \text{PKA}_{act}$$

$$\frac{d(\text{H}_2p)}{dt} = k_{2a} \cdot \text{H}_2act \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act}) - (\text{H}_2b + k_{2c}) \cdot \beta_{2p}$$

$$\frac{d(GRK)}{dt} = -\text{H}_1 \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$



**1**

$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \text{H}_1 \cdot (k_{isol} + k_{ip1}) - k_{1a} \cdot \text{H}_1 \cdot \text{H}_1 \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(cAMP)}{dt} = cAMP_0 + \text{H}_1 \cdot k_5 - k_{PKA} \cdot PKA_{act} \cdot \text{H}_1$$

$$\frac{d(\text{H}_1)}{dt} = k_{bas1} \cdot \beta_1$$

$$+ k_{2b} + k_{2c} \cdot \beta_2$$

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

$$+ k_{ip2} + k_{ter}$$

$$+ AC_{act} - k$$

$$(k_{1b} + k_{1c}) \cdot \text{H}_1$$

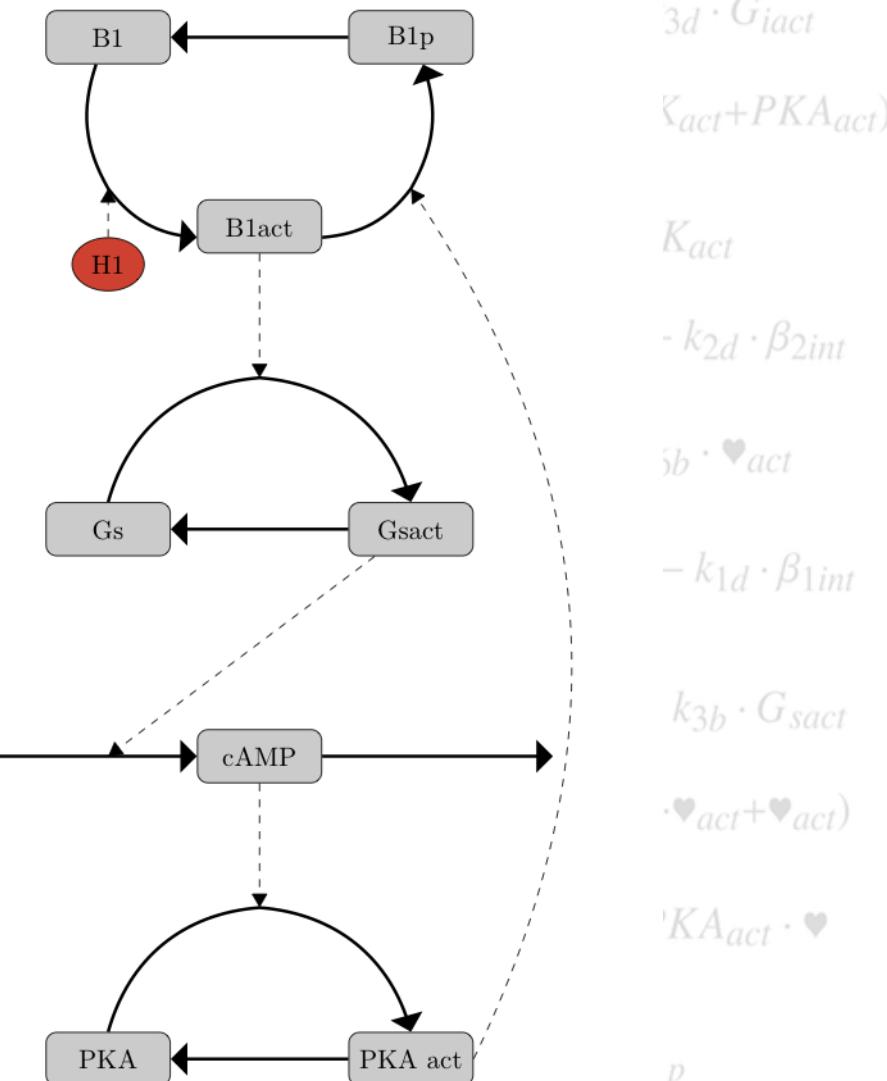
$$= k_{bas2} \cdot \text{H}_1$$

$$+ k_{ip1} \cdot \text{H}_1$$

$$\frac{d(\text{H}_2p)}{dt} = k_{1a} \cdot \text{H}_2p$$

$$\frac{d(\text{H}_1)}{dt} = k_{3a} \cdot G_s \cdot (\beta_{1act} + \text{H}_2act) - k_{3b} \cdot G_{sact}$$

$$\frac{d(PKA_{act})}{dt} = k_{1a} \cdot \text{H}_1 \cdot \text{H}_1 \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$



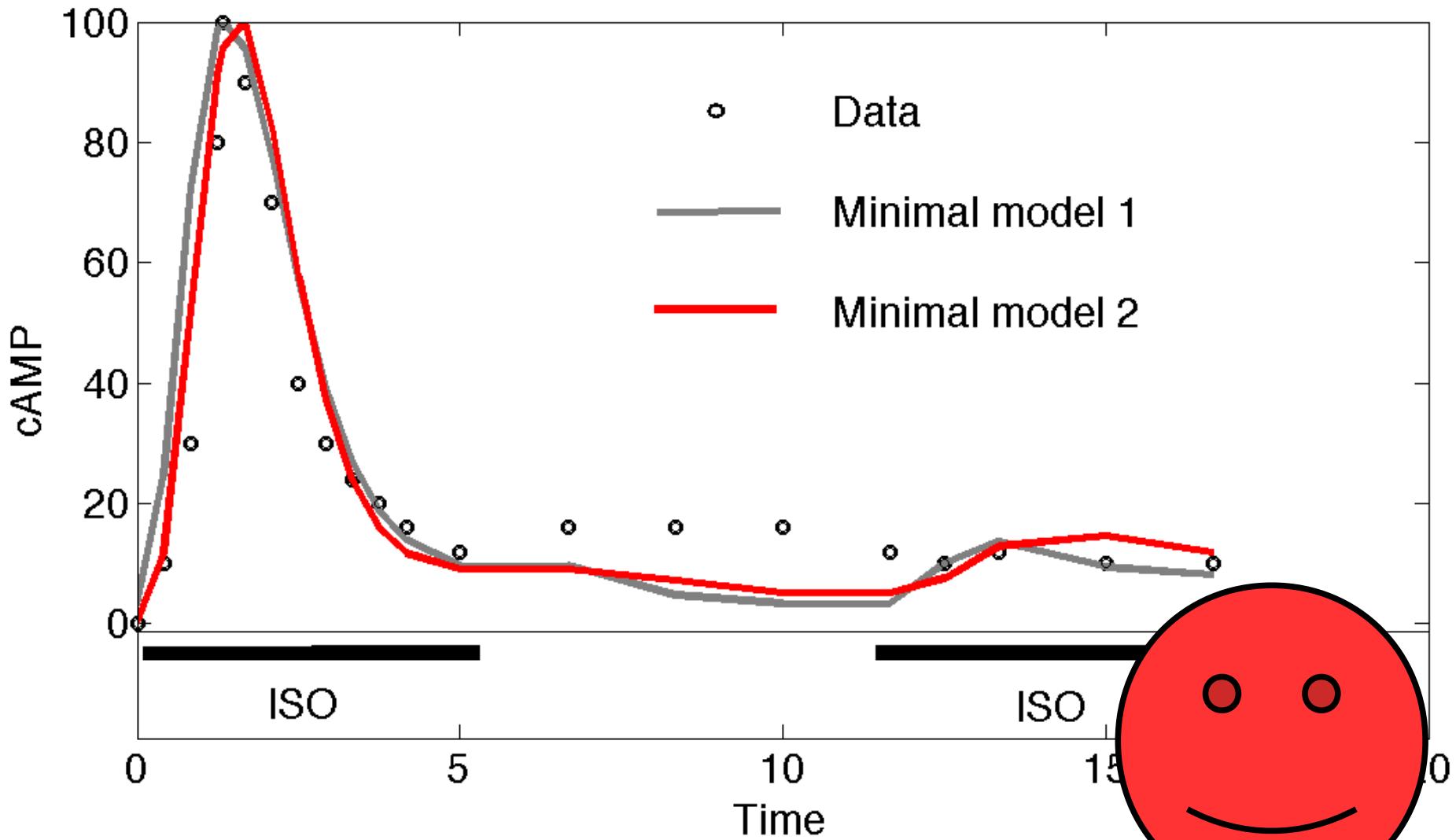
**2**

$$\frac{d(\text{•})}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \text{•}_1 \cdot (k_{iso1} + k_{ip1}) \cdot \text{•}$$

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

$$\frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \text{•}_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \text{•}_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \text{•}_{act} + \text{•}_{act})$$

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



$$\frac{d(\text{•}_2act)}{dt} = \kappa_{2a} \cdot \nabla_{2act} \cdot (\kappa_{GRK} \cdot \nabla_{GRKact} + \kappa_{2c} \cdot \nabla_{2act}) - (\nabla_{2b} + \kappa_{2c}) \cdot p_{2p}$$

$$\frac{d(\text{•}_5act)}{dt} = \kappa_{5a} \cdot \nabla_{5act} - \kappa_{5b} \cdot \nabla_{sact}$$

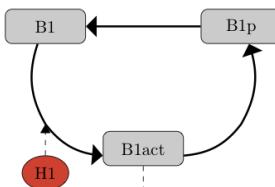
$$\frac{d(GRK)}{dt} = -\text{•} \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act} \quad \frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \text{•}_1 \cdot (k_{iso1} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \text{•}_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

$$\frac{d(\text{•}_1act)}{dt} = \kappa_{1a} \cdot \nabla_{1act} - \kappa_{1b} \cdot \nabla_{sact}$$

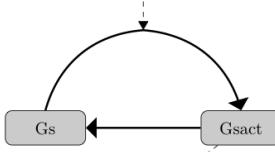
$$\frac{d(\heartsuit)}{dt} = k_{1d} \cdot \beta_{1int} + k_{1c} \cdot \beta_{1p} - k_{bas1} \cdot \beta_1 - \heartsuit_1 \cdot (k_{isol} + k_{ip1}) \cdot \heartsuit$$

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

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

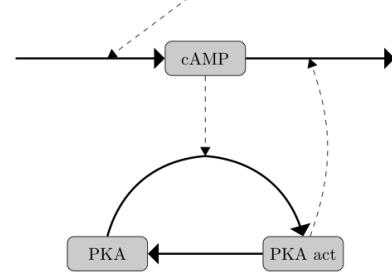


$$\frac{d(G_s)}{dt} = k_{3l}$$



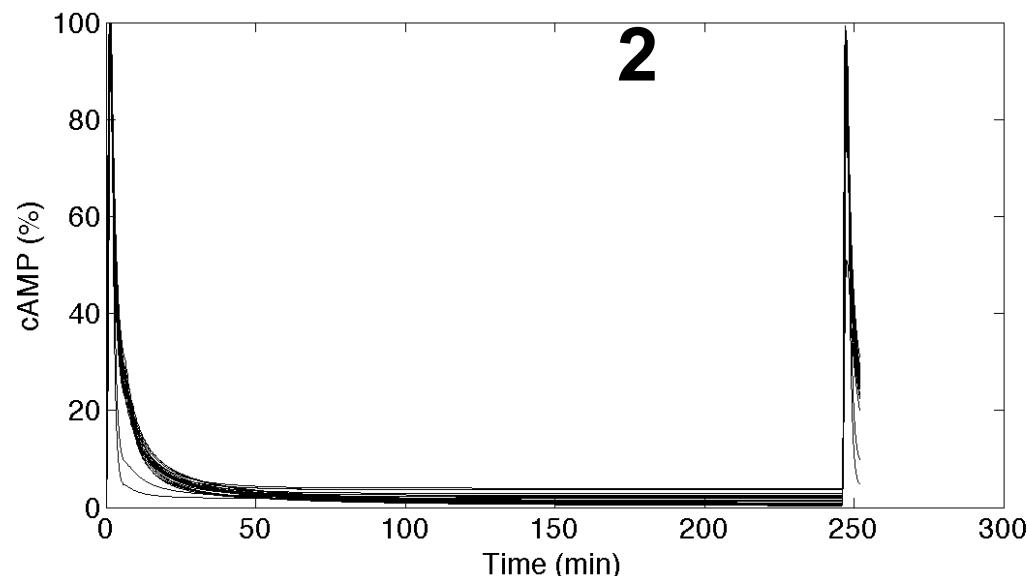
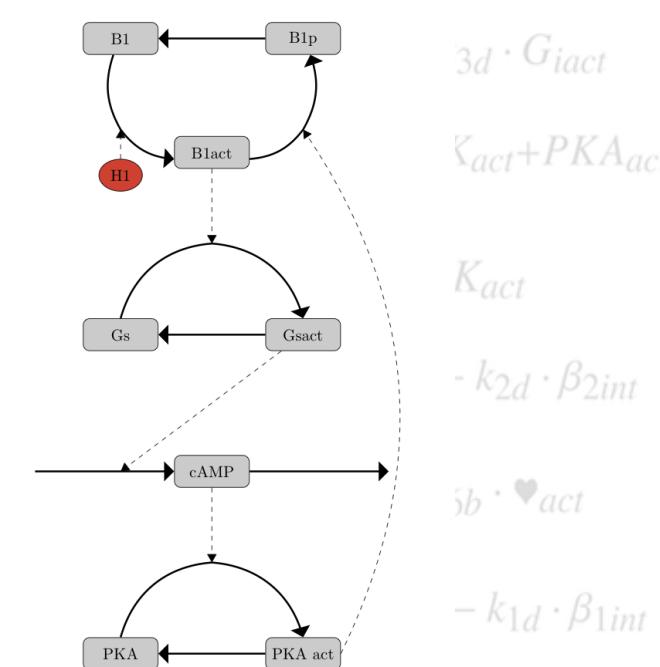
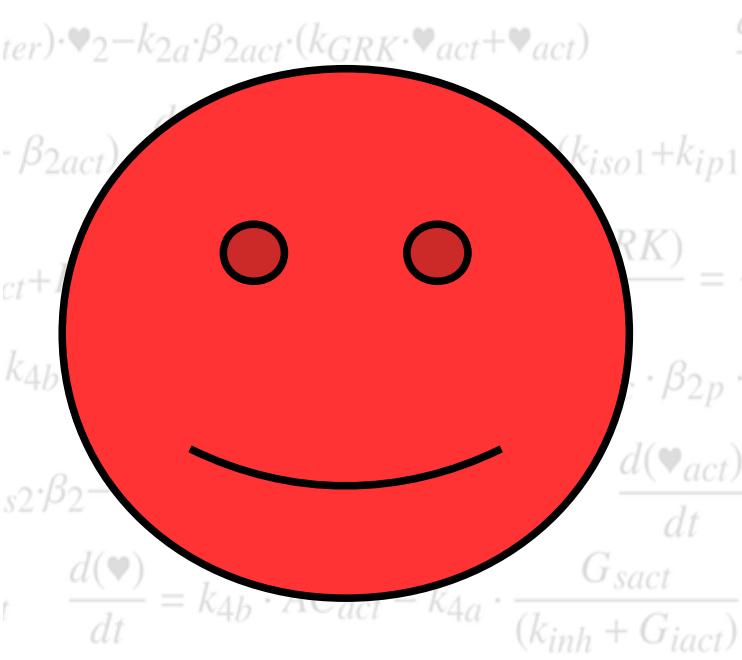
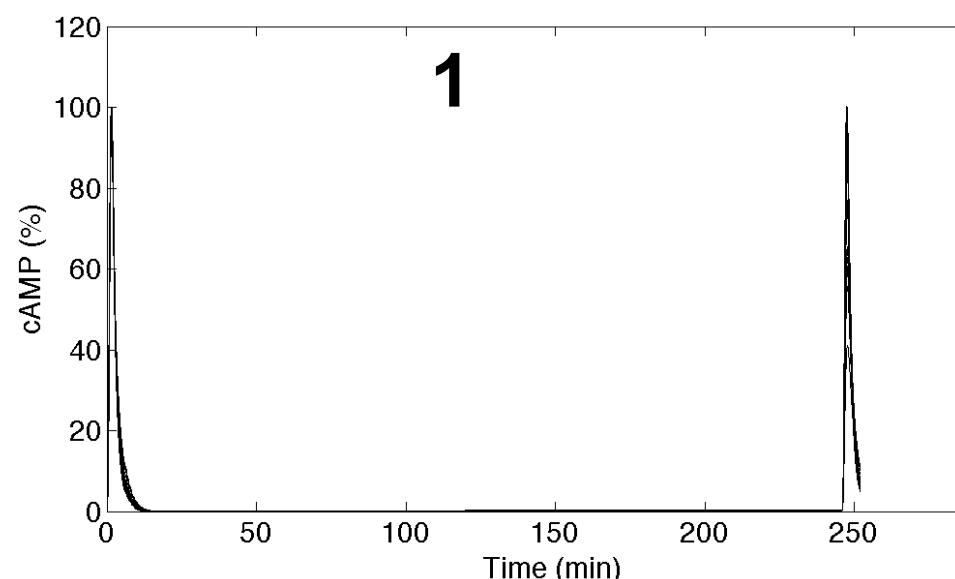
$$\frac{d(\heartsuit_{2p})}{dt} =$$

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



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

$$d(\heartsuit)$$



$$\frac{d(\heartsuit_2)}{dt} = -\heartsuit \cdot k_{6a} \cdot GRK + k_{6b} \cdot GRK_{act}$$

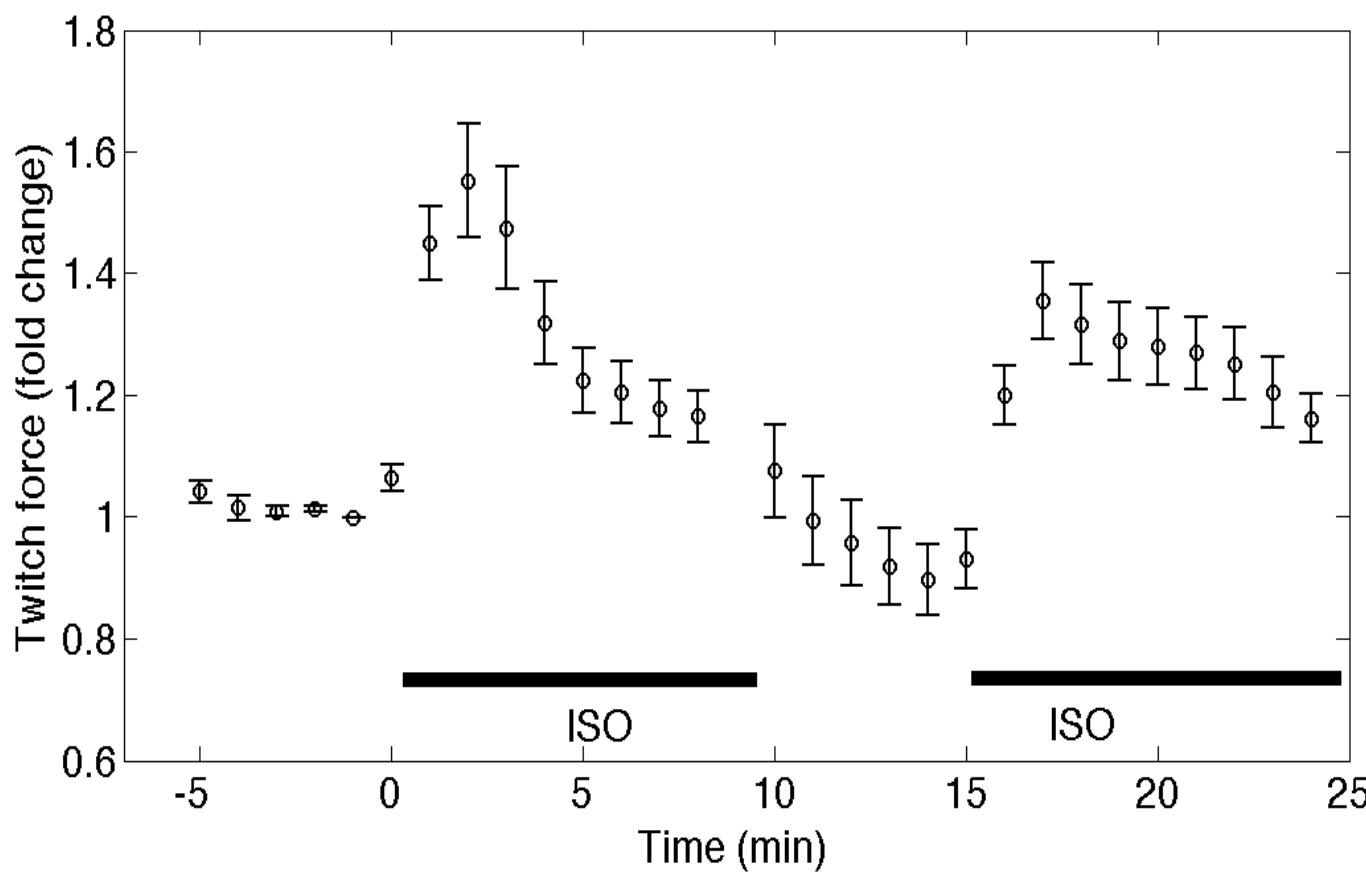
$$\frac{d(cAMP)}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{isol} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$

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

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

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

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



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

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

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

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

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

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

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

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

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

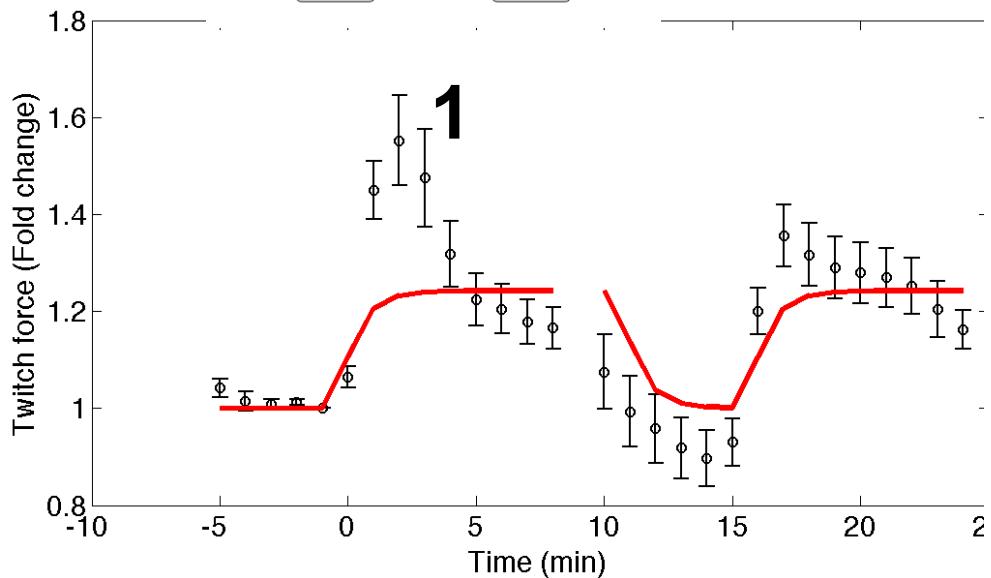
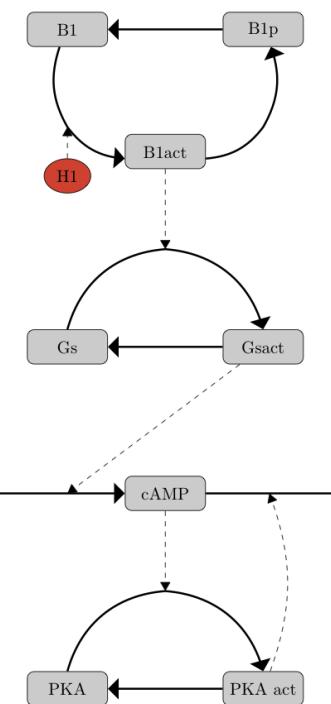
$$\frac{d(G_s)}{dt} = k_{3l}$$

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

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

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

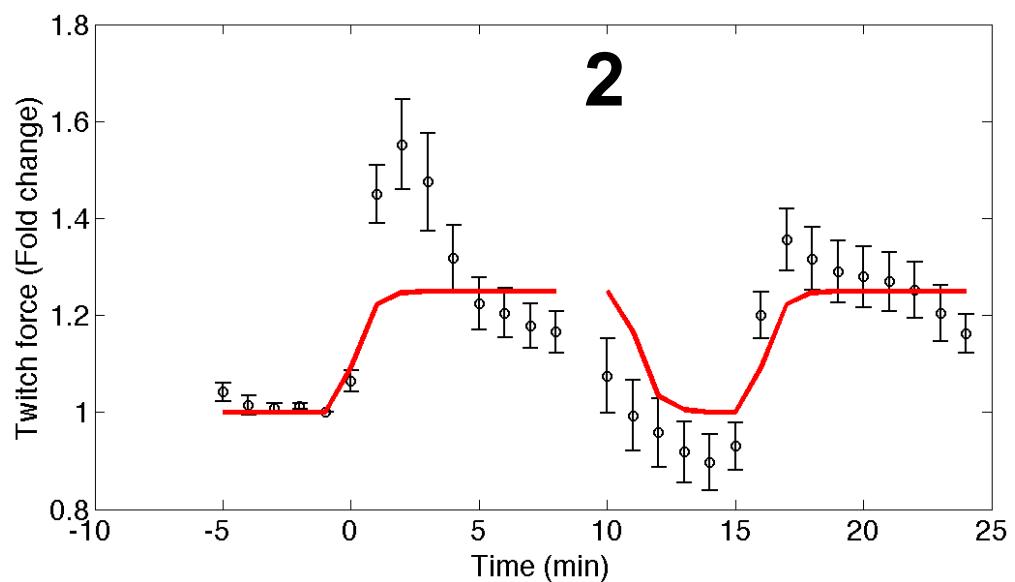
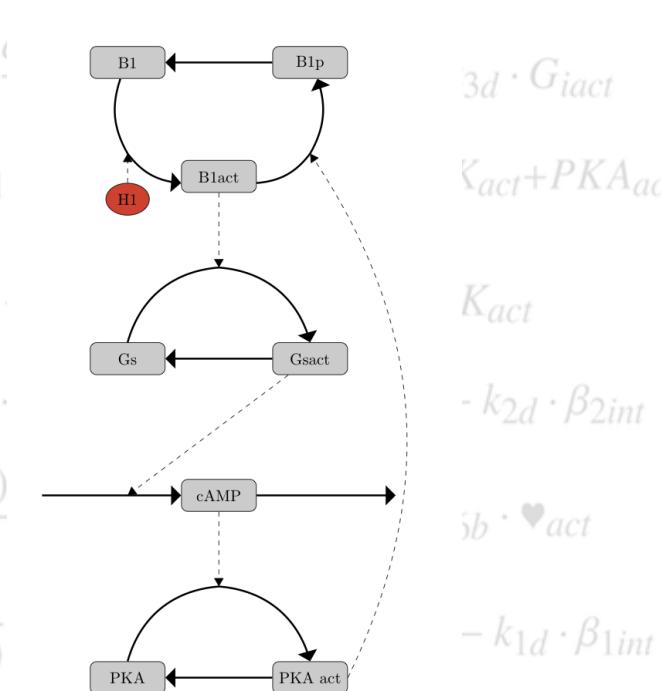
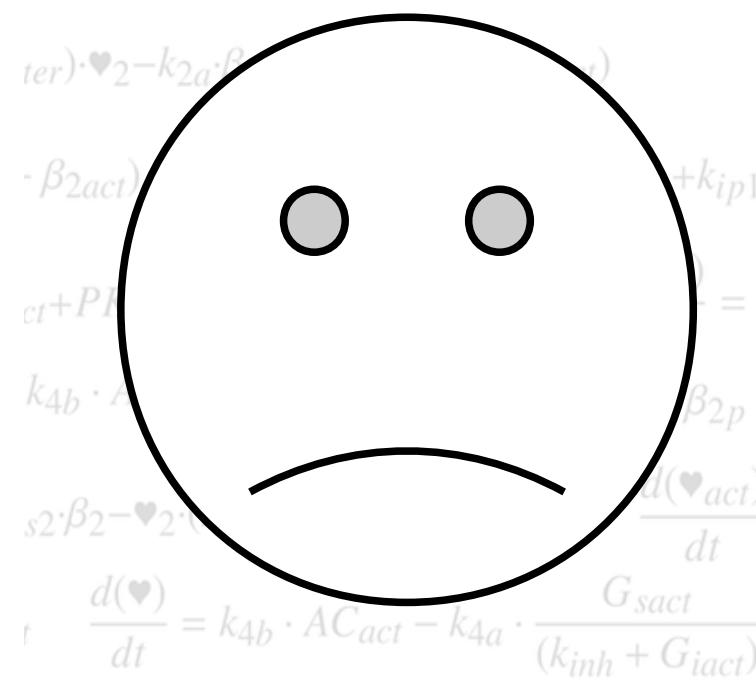
$$\frac{d(PKA)}{dt} =$$



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

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

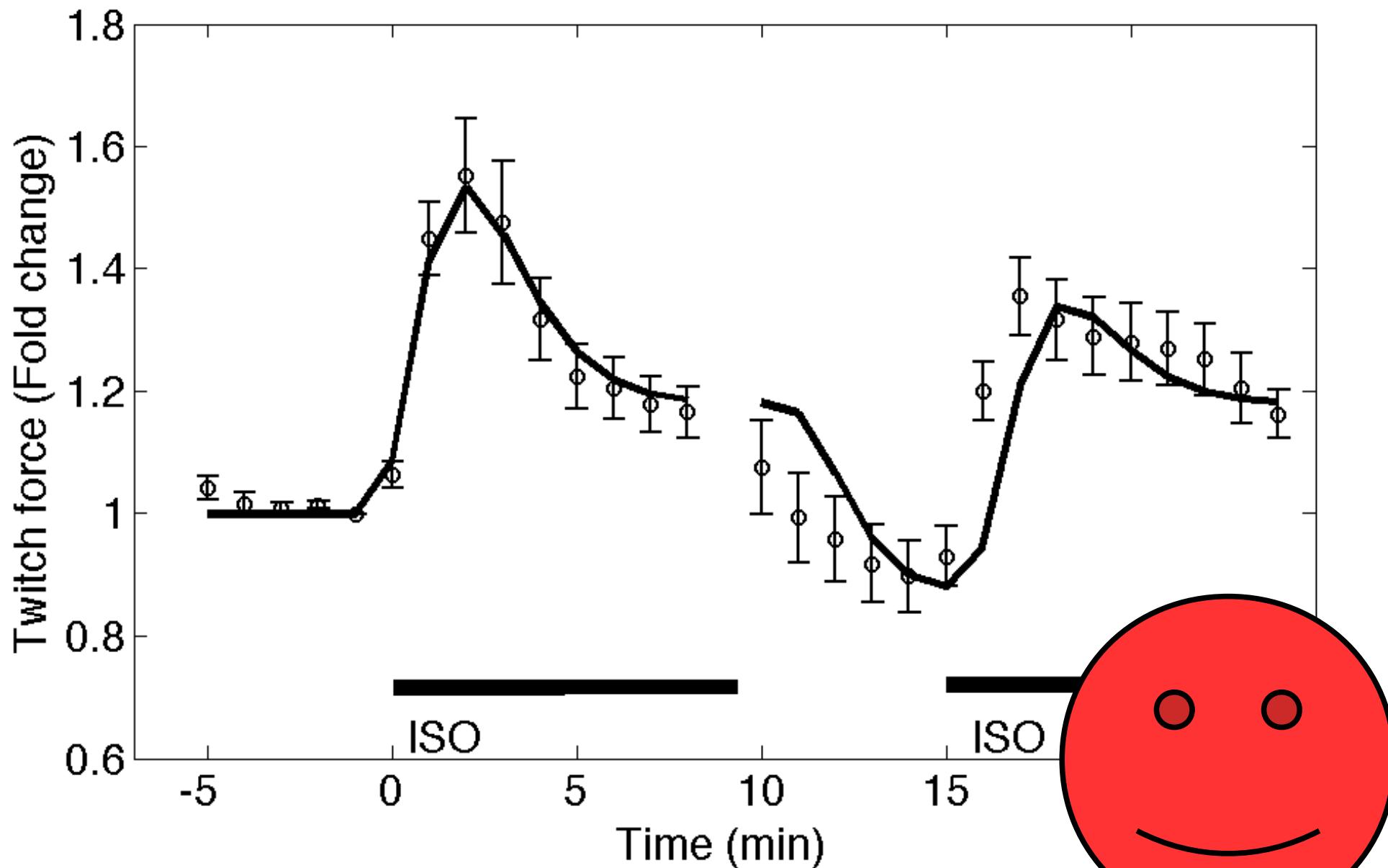
$$\frac{d(\beta_{1act})}{dt} = k_{bas1} \cdot \beta_1 + \heartsuit_1 \cdot (k_{isol} + k_{ip1}) \cdot H_1 - k_{1a} \cdot \heartsuit_{1act} \cdot (k_{GRK} \cdot GRK_{act} + PKA_{act})$$



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

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

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



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

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

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

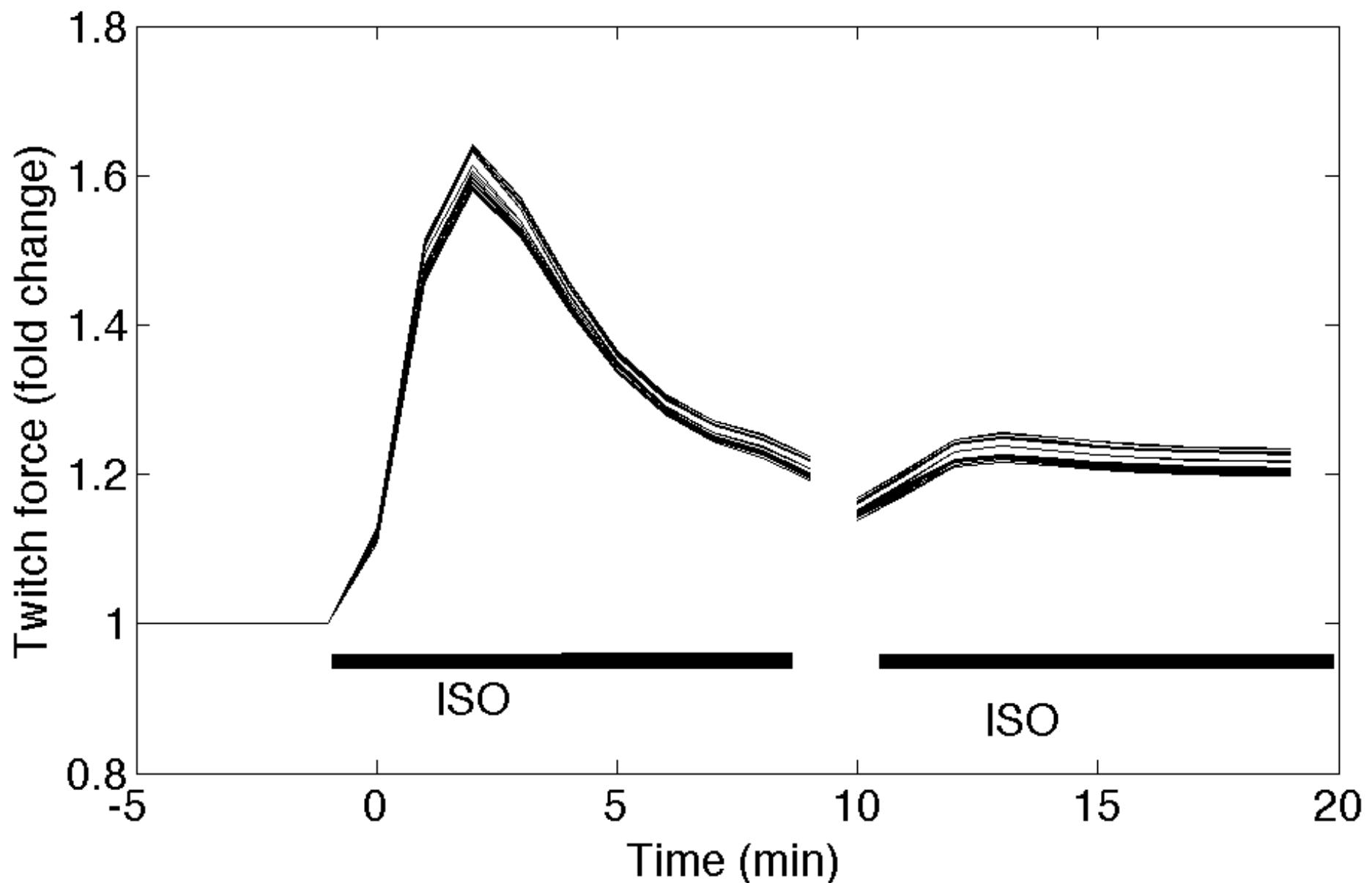
$\cdots$

$$A(t) = \sqrt{\dots}$$

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

$\cdots$

$$A(t) = \sqrt{\dots}$$



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

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

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

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

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

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

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

$$\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_{inh})}{dt} &= k_{4b} \cdot AC_{act} - k_{4a} \cdot \frac{G_{sact}}{(\heartsuit_{inh} + G_{iact})} \cdot \heartsuit_{inh} & \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!

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

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

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

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

- **GRK**

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

- **Compartmentation**

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

- **Compare healthy adult hearts with fetal and failed hearts**

$$\frac{d(\heartsuit_{act})}{dt} = cAMP \cdot k_{6a} \cdot GRK - k_{6b} \cdot \heartsuit_{act} \quad \frac{d(\beta_{2act})}{dt} = k_{bas2} \cdot \beta_2 + \heartsuit_2 \cdot (k_{iso2} + k_{ip2} + k_{ter}) \cdot \heartsuit_2 - k_{2a} \cdot \beta_{2act} \cdot (k_{GRK} \cdot \heartsuit_{act} + \heartsuit_{2act}) - k_{3b} \cdot G_{sact}$$

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

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

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