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

$$\frac{d(\beta_{2act})}{dt} = kbas2\cdot\beta_2+\heartsuit_2\cdot(k_{iso2}+k_{ip2}+k_{ter})\cdot\heartsuit_2-k_{2a}\cdot\beta_{2act}\cdot(k_{GRK}\cdot\heartsuit_{act}+\heartsuit_{act}) \qquad \frac{d(G_{iact})}{dt} = k_{3c}\cdot\beta_{2p}\cdot\heartsuit_i - k_{3d}\cdot G_{iact}$$

$$\frac{d(G_s)}{dt} = k_{3b}\cdot G_{sact} - k_{3a}\cdot\heartsuit_s\cdot(\beta_{1act}+\beta_{2act}) \qquad \frac{d(\beta_{1act})}{dt} = k_{bas1}\cdot\beta_1+\heartsuit_1\cdot(k_{iso1}+k_{ip1})\cdot H_1-k1a\cdot\heartsuit_{1act}\cdot(k_{GRK}\cdot GRK_{act}+PKA_{act})$$

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

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

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

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

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

$$\frac{d(\heartsuit_{act})}{dt} = cAMP\cdot k_{6a}\cdot GRK - k_{6b}\cdot\heartsuit_{act} \qquad \frac{d(\beta_{2act})}{dt} = kbas2\cdot\beta_2+\heartsuit_2\cdot(k_{iso2}+k_{ip2}+k_{ter})\cdot\heartsuit_2-k_{2a}\cdot\beta_{2act}\cdot(k_{GRK}\cdot\heartsuit_{act}+\heartsuit_{act})$$

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

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

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

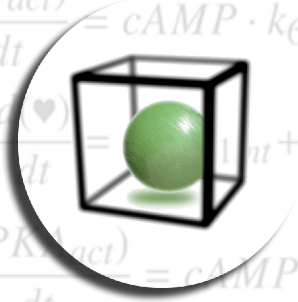
$$\frac{d(GRK)}{dt} = -\heartsuit\cdot k_{6a}\cdot GRK + k_{6b}\cdot GRK_{act} \qquad \frac{d(\beta_{1act})}{dt} = k_{bas1}\cdot\beta_1+\heartsuit_1\cdot(k_{iso1}+k_{ip1})\cdot H_1-k1a\cdot\heartsuit_{1act}\cdot(k_{GRK}\cdot GRK_{act}+PKA_{act})$$

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

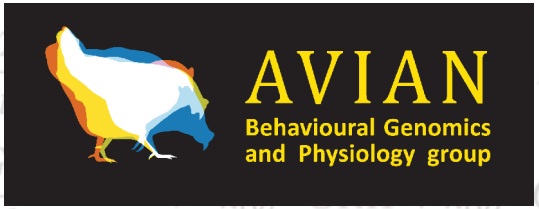
- Carl Sagan

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

Master Thesis by **Karin Lundengård**

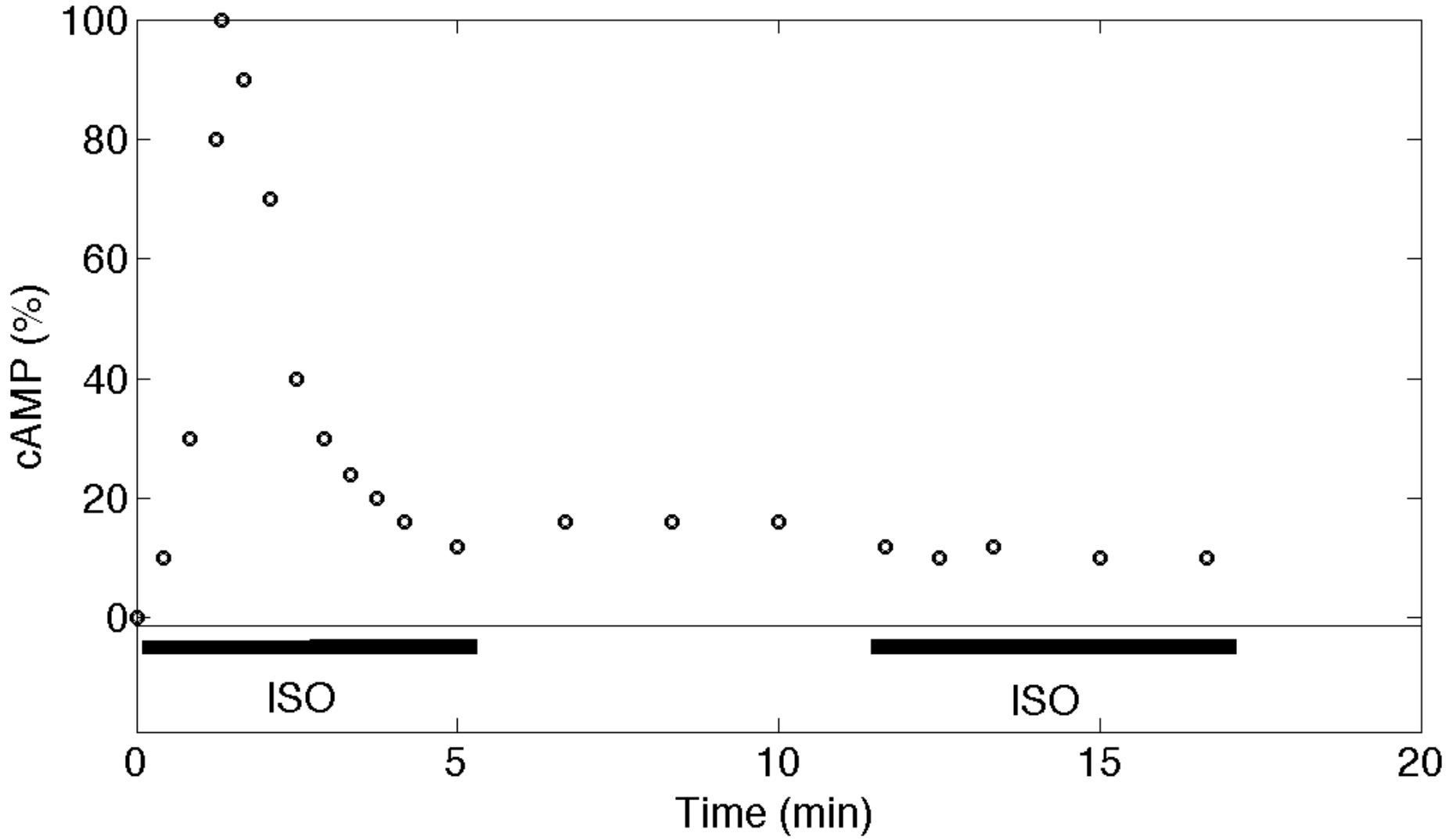


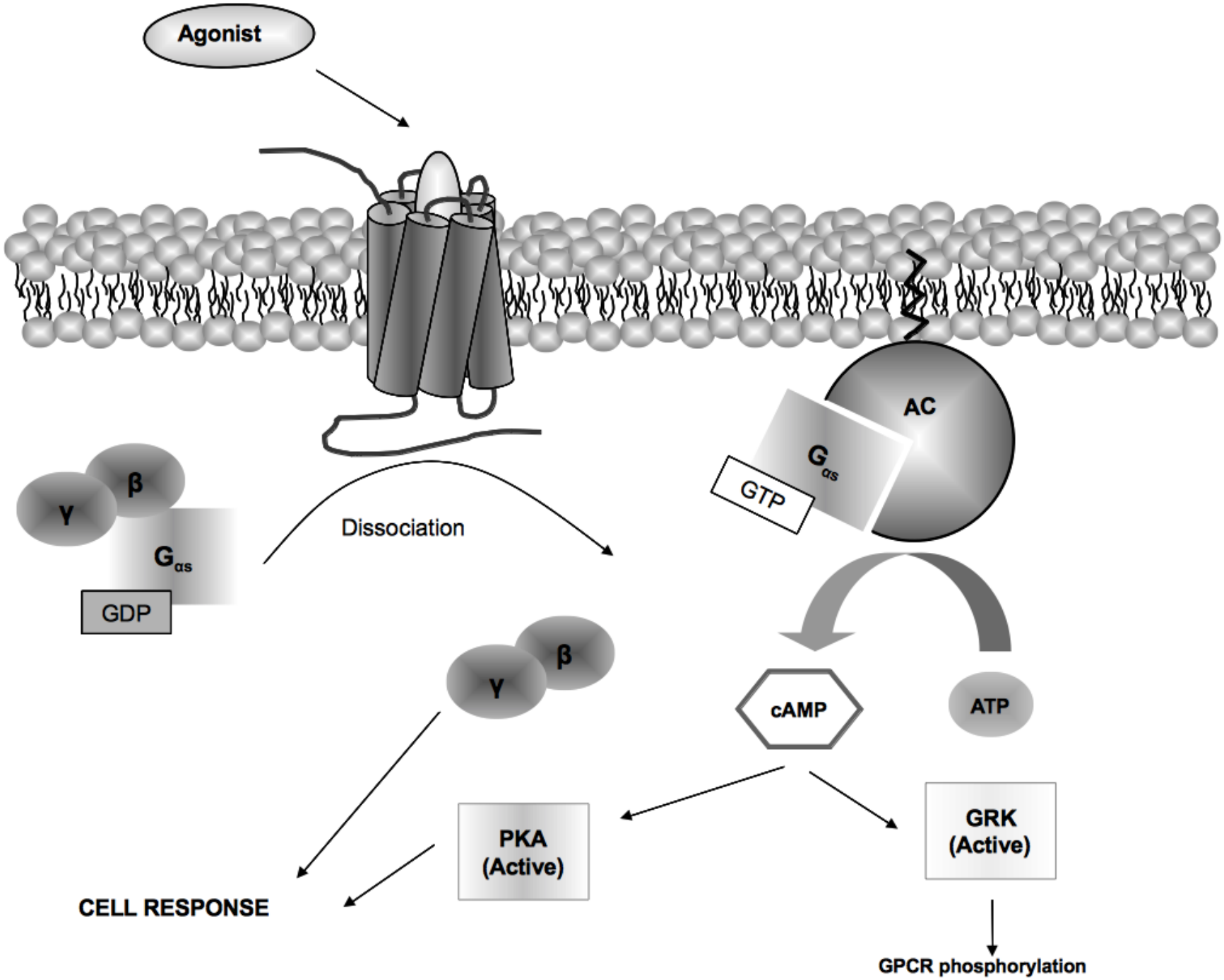
Supervisors: Jordi Altimiras,
Gunnar Cedersund and Elin Nyman

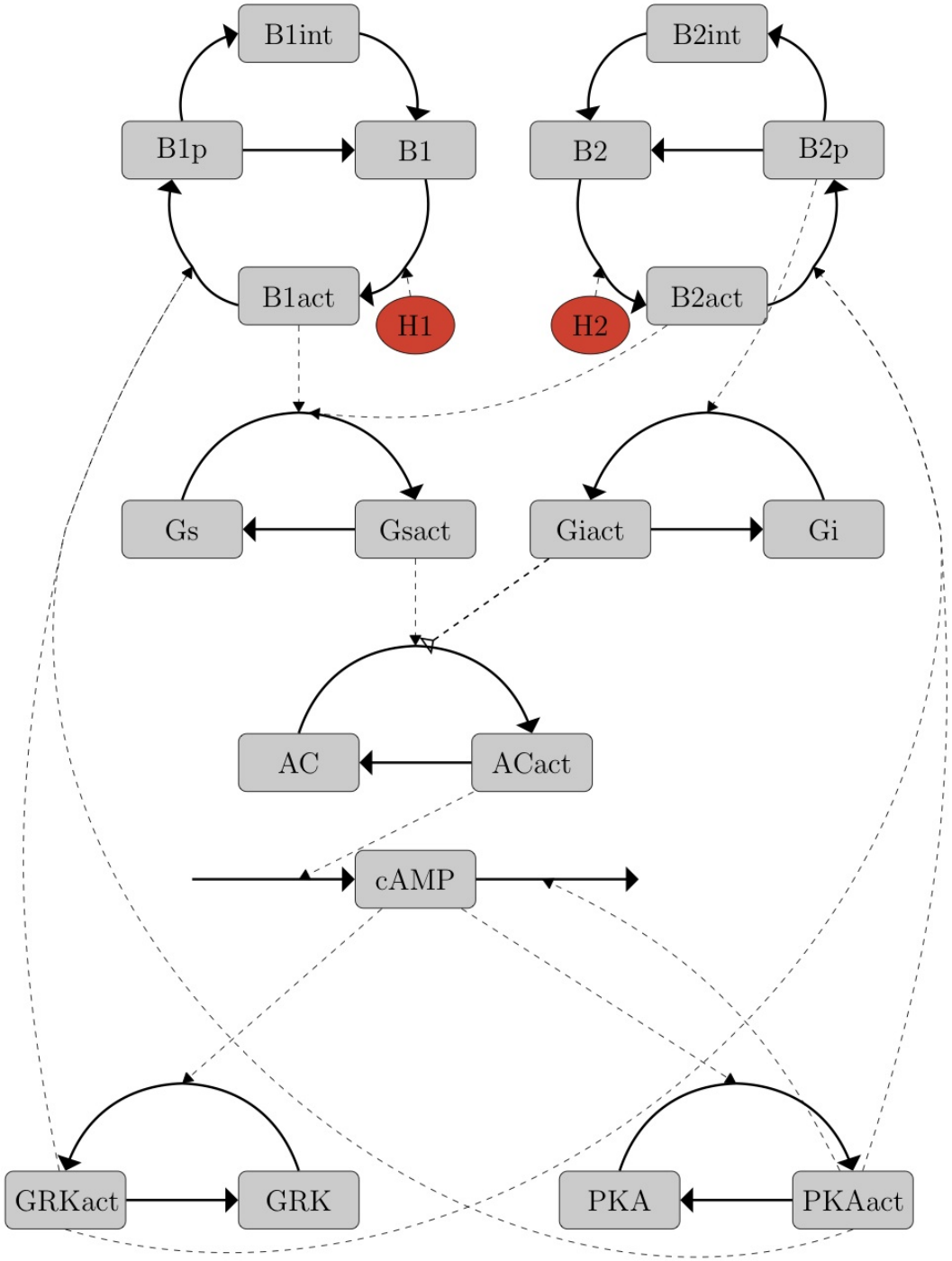


Linköping University
INSTITUTE OF TECHNOLOGY

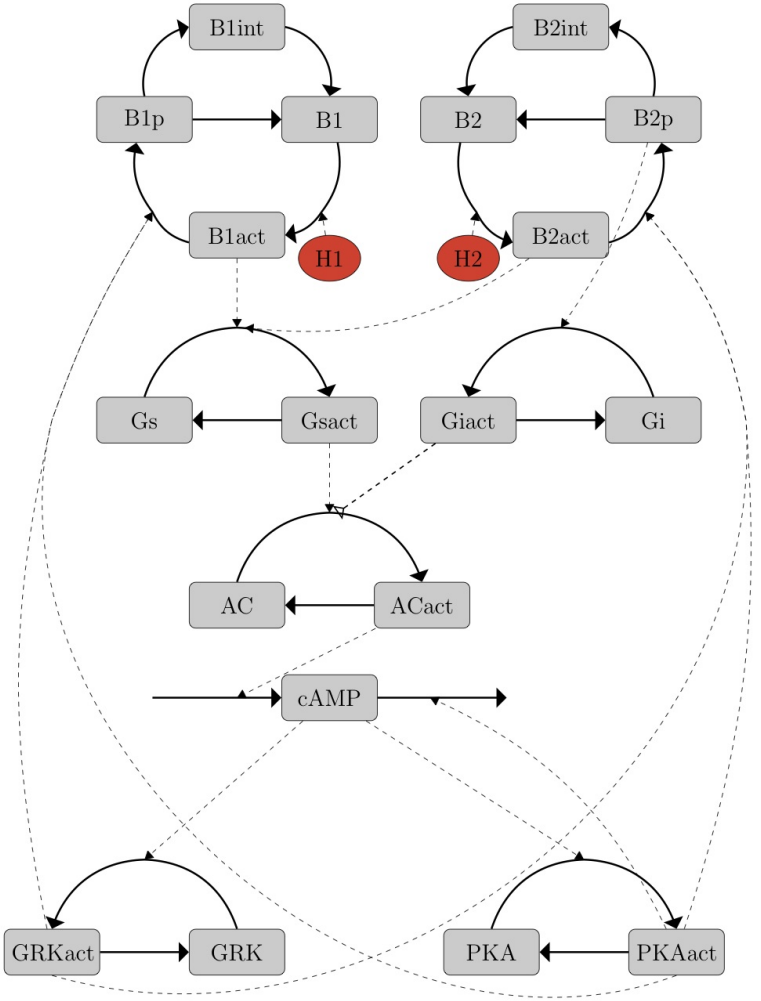
Desensitisation

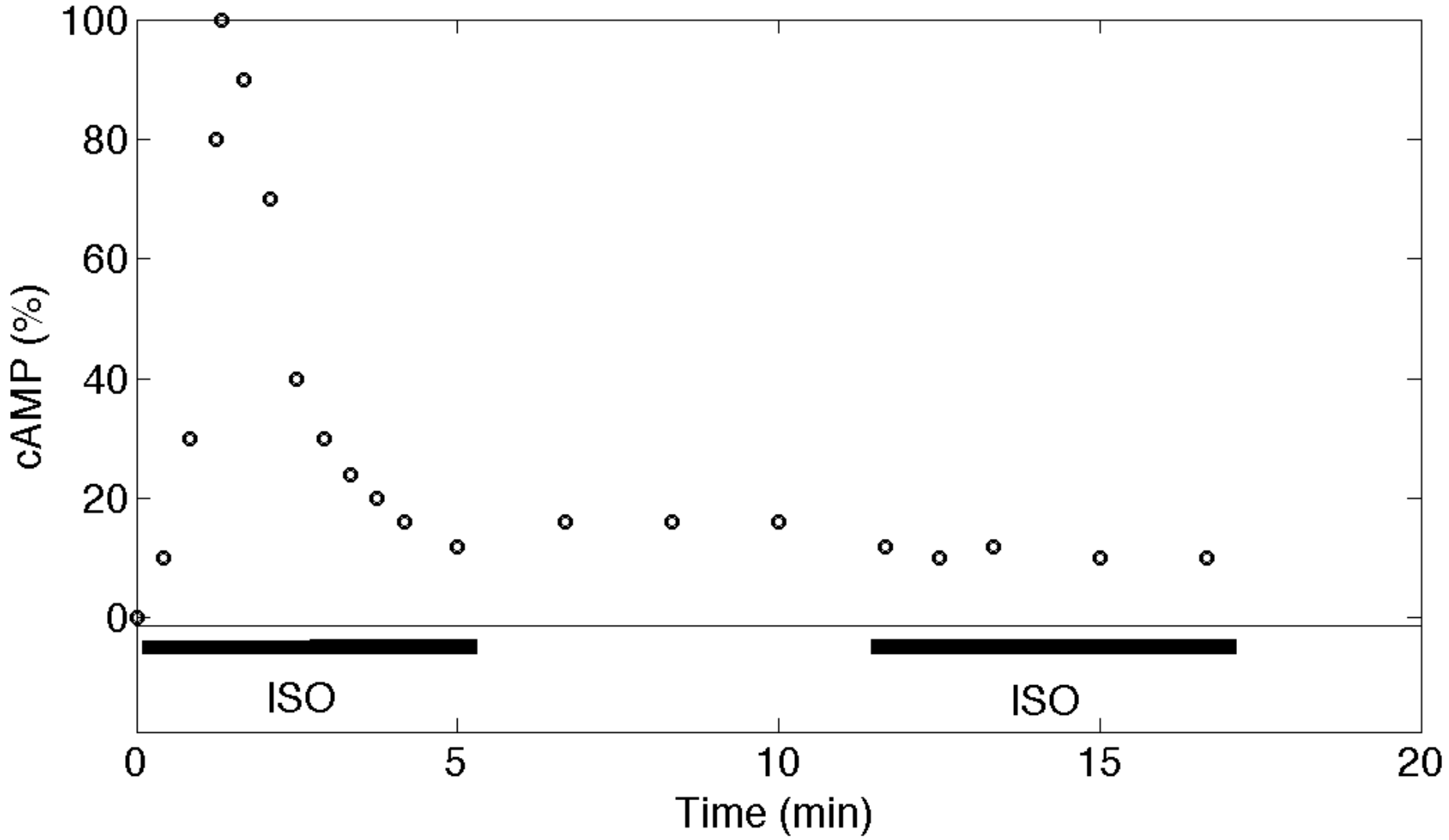


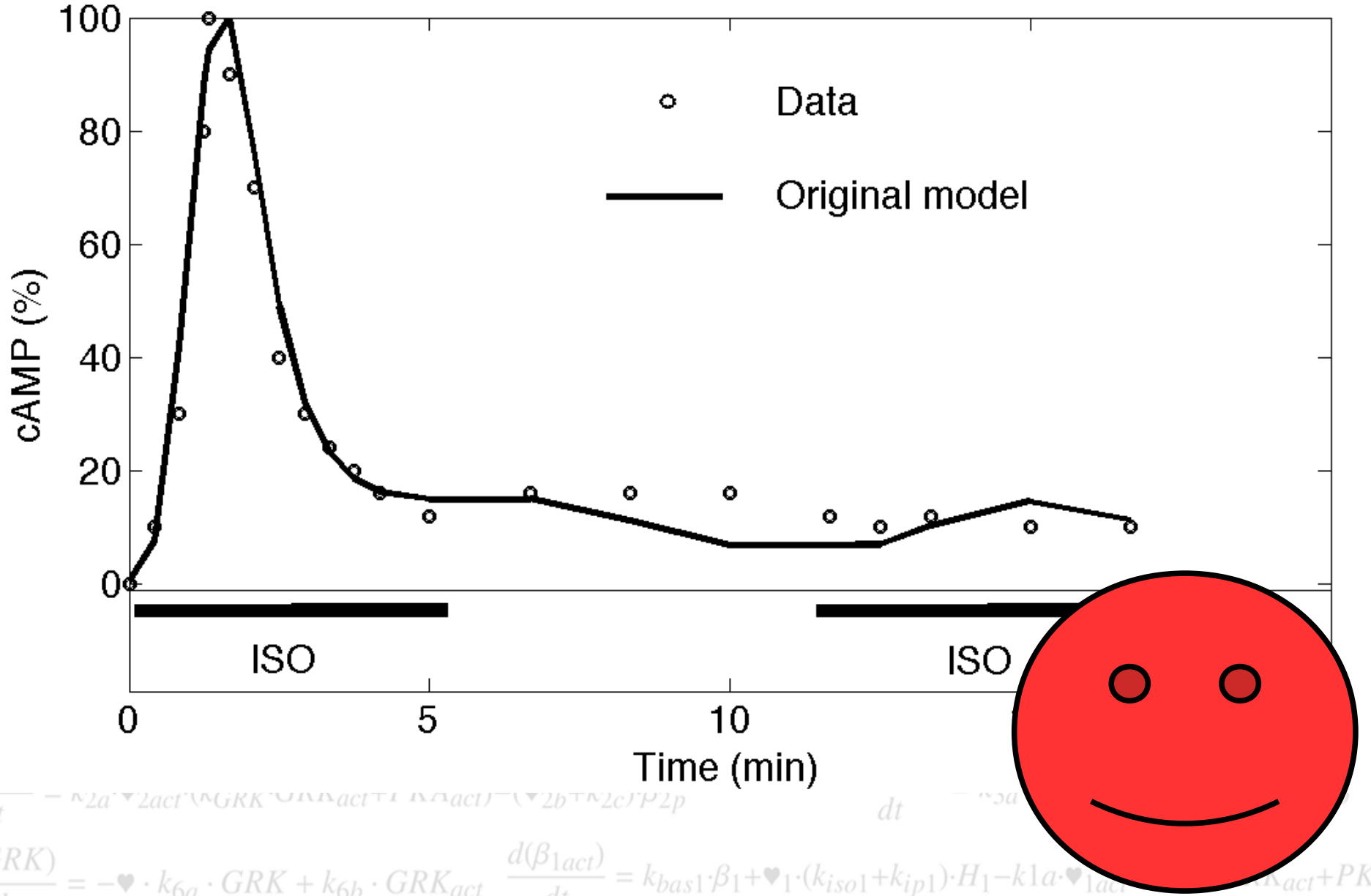

Agonist
β
γ
$G_{\alpha s}$
GDP
Dissociation
AC
$G_{\alpha s}$
GTP
cAMP
ATP
β
γ
PKA
(Active)
GRK
(Active)
CELL RESPONSE
GPCR phosphorylation

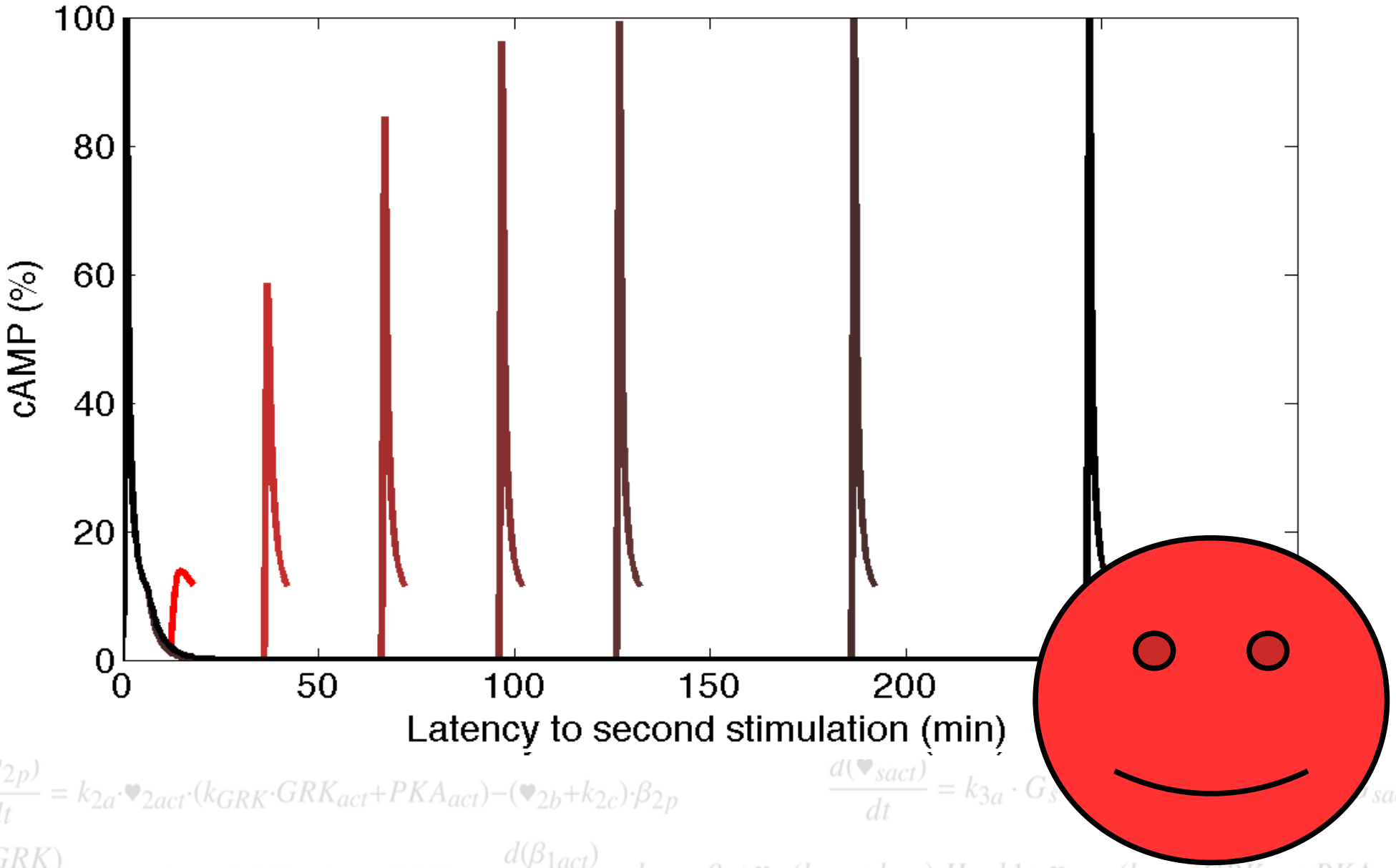

B1int
B2int
B1p
B1
B2
B2p
B1act
H1
H2
B2act
Gs
Gsact
Giact
Gi
AC
ACact
cAMP
GRKact
GRK
PKA
PKAact

```
d(B1)/dt = k1d*B1int + k1c*B1p - kbas1*B1 -
B1*(kiso+kip1)*H1
d(B1act)/dt = kbas1*B1 + B1*(kiso+kip1)*H1 -
k1a*B1act*(kGRK*GRKact+PKAact)
d(B1p)/dt = k1a*B1act*(kGRK*GRKact+PKAact) -
     (k1b+k1c)*B1p
d(B1int)/dt = k1b*B1p - k1d*B1int

d(B2)/dt = k2d*B2int + k2c*B2p - kbas2*B2 -
B2*(kiso+kip2+kter)*H2
d(B2act)/dt = kbas2*B2 + B2*(kiso+kip2+kter)*H2 -
k2a*B2act*(kGRK*GRKact+PKAact)
d(B2p)/dt = k2a*B2act*(kGRK*GRKact+PKAact) -
     (k2b+k2c)*B2p
d(B2int)/dt = k2b*B2p - k2d*B2int

d(Gs)/dt = k3b*Gsact - k3a*Gs*(B1act+B2act)
d(Gsact)/dt = k3a*Gs*(B1act+B2act) - k3b*Gsact

d(Gi)/dt = k3d*Giact - k3c*B2p*Gi
d(Giact)/dt = k3c*B2p*Gi - k3d*Giact

d(AC)/dt = k4b*ACact - k4a*Gsact/(kinh+Giact)*AC
d(ACact)/dt = k4a*Gsact/(kinh+Giact)*AC - k4b*ACact

d(cAMP)/dt = cAMP0 + ACact*k5 - kPKA*PKAact*cAMP

d(GRK)/dt = - cAMP*k6a*GRK + k6b*GRKact
d(GRKact)/dt = cAMP*k6a*GRK - k6b*GRKact

d(PKA)/dt = - cAMP*k6c*PKA + k6d*PKAact
d(PKAact)/dt = cAMP*k6c*PKA - k6d*PKAact
```

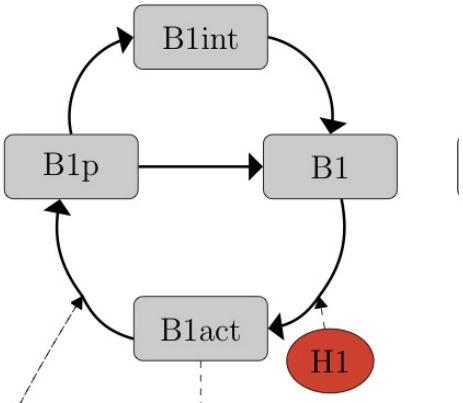


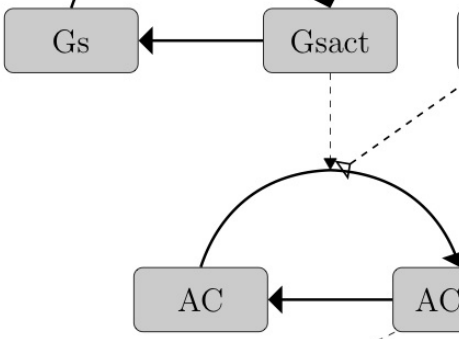

100
80
60
40
20
0
cAMP (%)
ISO
ISO
0
5
10
15
20
Time (min)


100
80
60
40
20
0
cAMP (%)
Data
Original model
ISO
ISO
0
5
10
Time (min)


100
80
60
40
20
0
cAMP (%)
0
50
100
150
200
Latency to second stimulation (min)

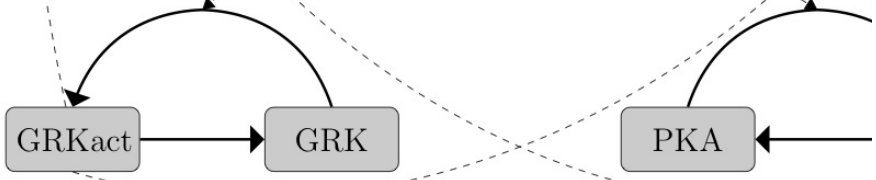

100
TON

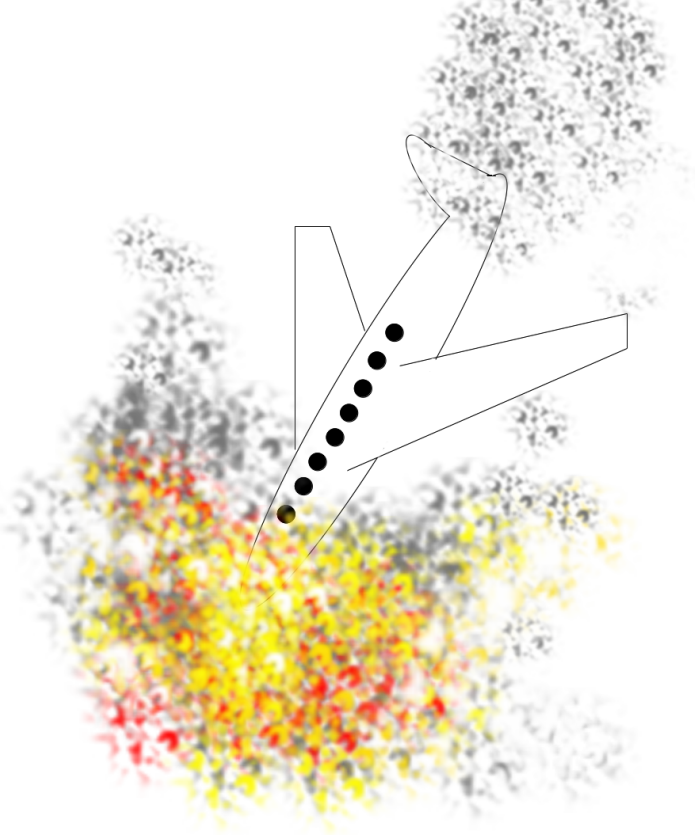

B1int
B1p
B1
B1act
H1

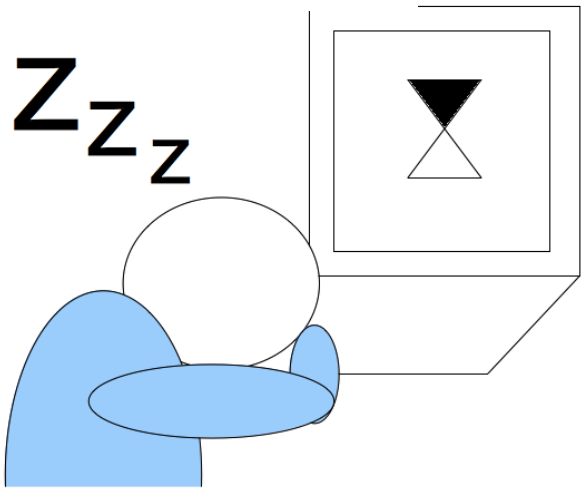

Gs
Gsact

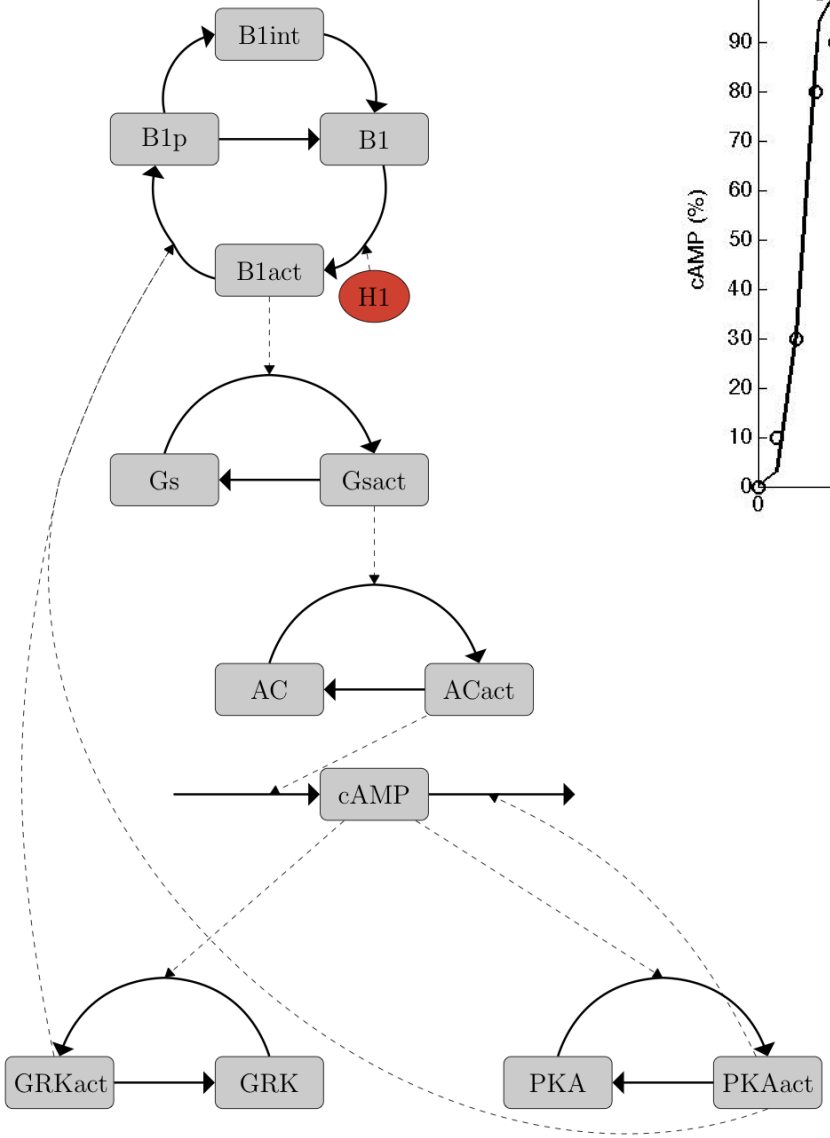
AC
AC

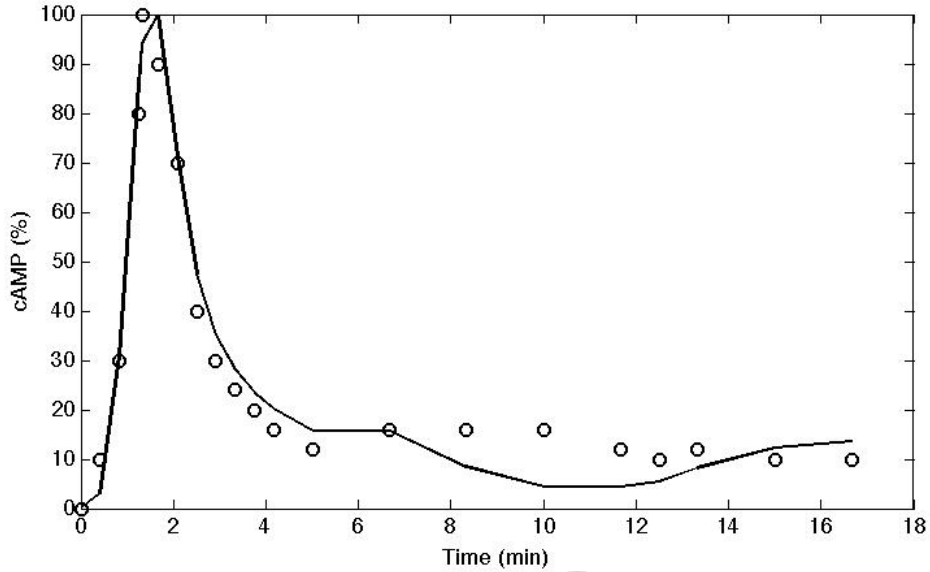

cAMP

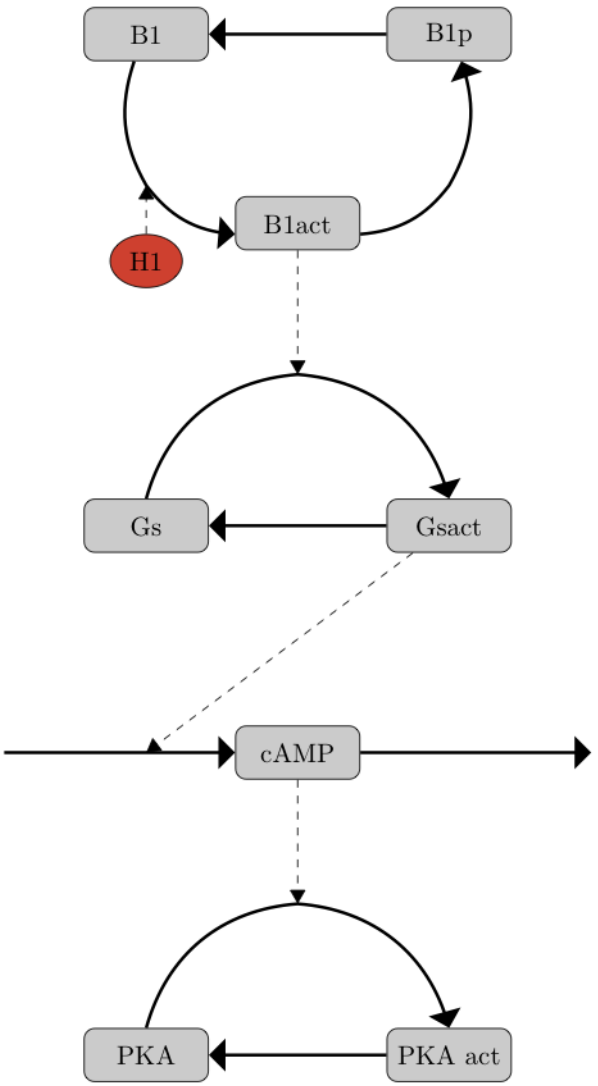

GRKact
GRK
PKA

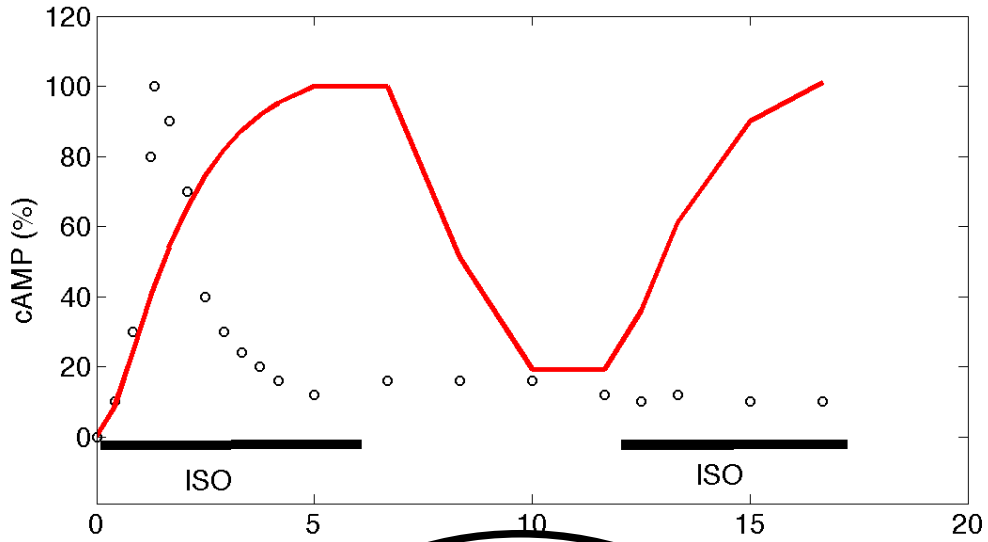


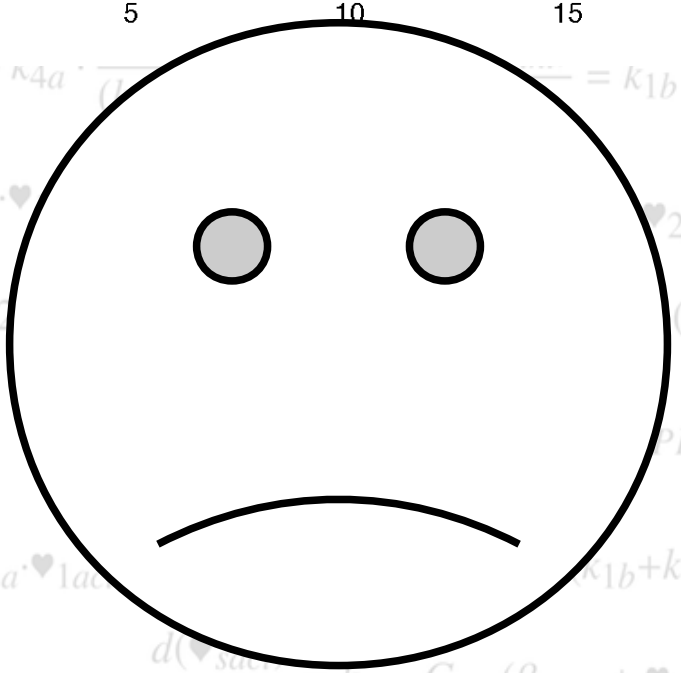

Z
Z
Z

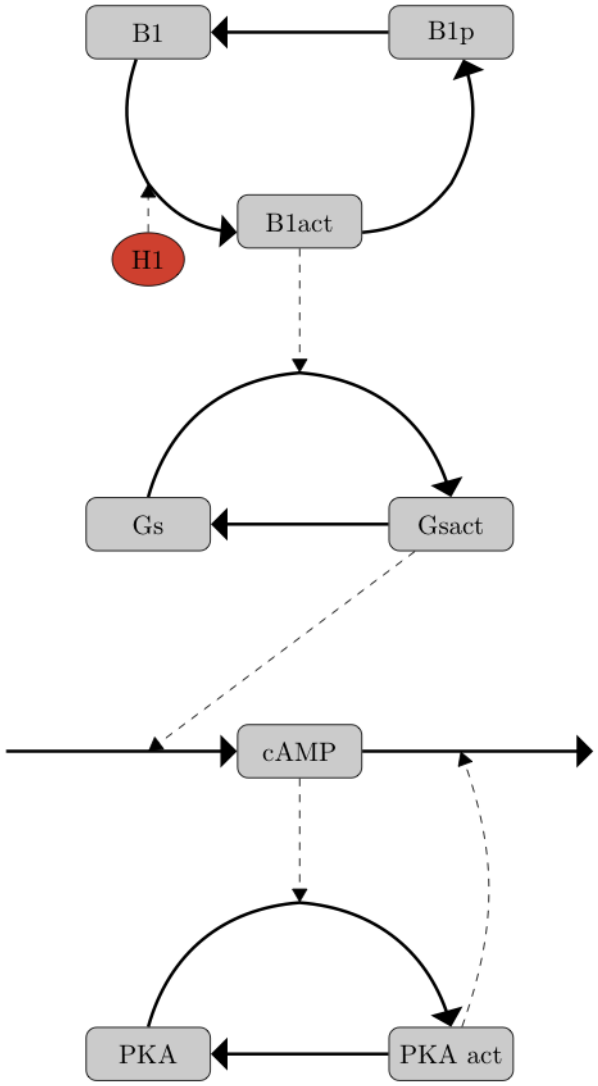

B1int
B1p
B1
B1act
H1
Gs
Gsact
AC
ACact
cAMP
GRKact
GRK
PKA
PKAact


cAMP (%)
Time (min)
0
10
20
30
40
50
60
70
80
90
100
0
2
4
6
8
10
12
14
16
18

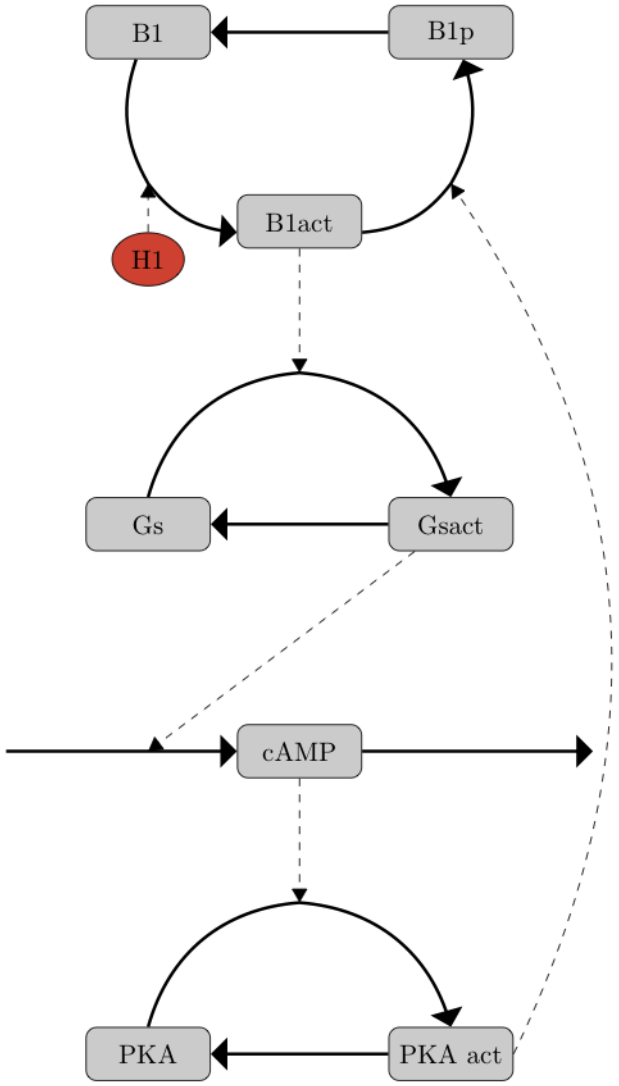

B1
B1p
B1act
H1
Gs
Gsact
cAMP
PKA
PKA act


cAMP (%)
120
100
80
60
40
20
0
ISO
ISO
0
5
10
15
20

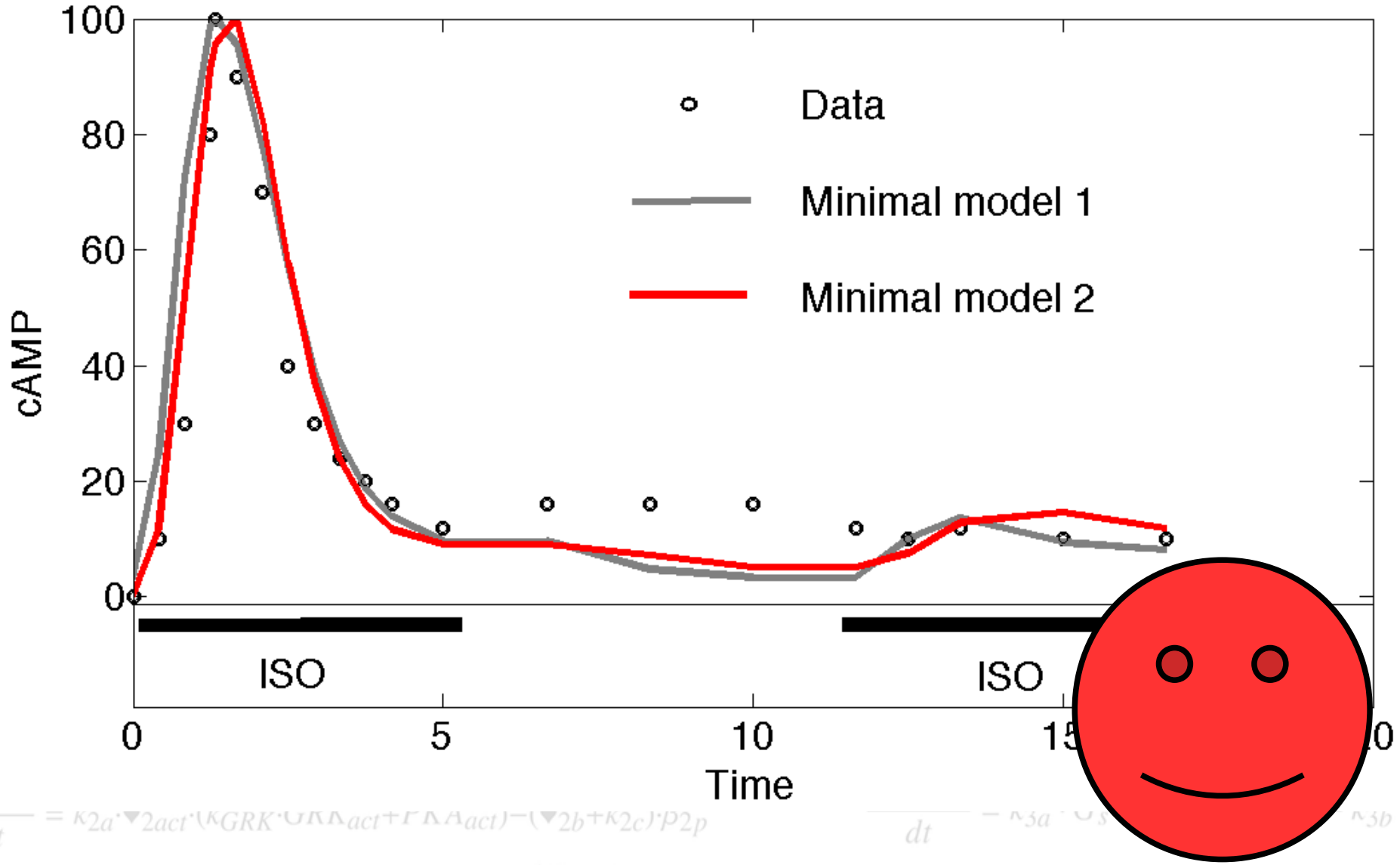


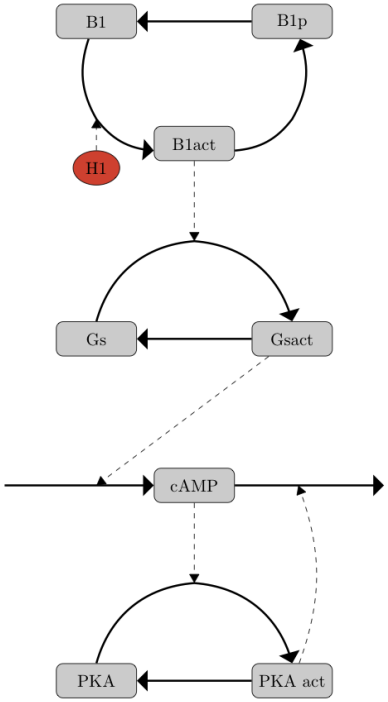

B1
B1p
B1act
H1
Gs
Gsact
cAMP
PKA
PKA act

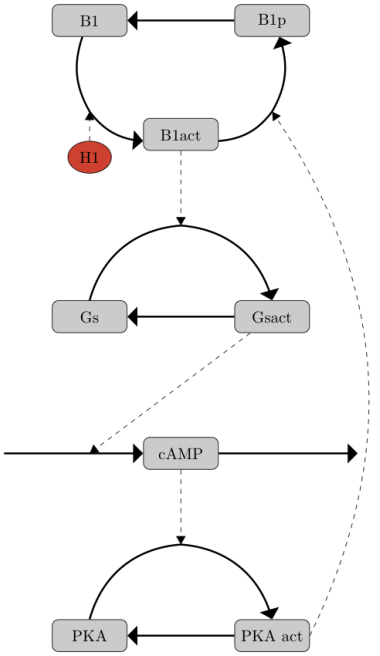
1

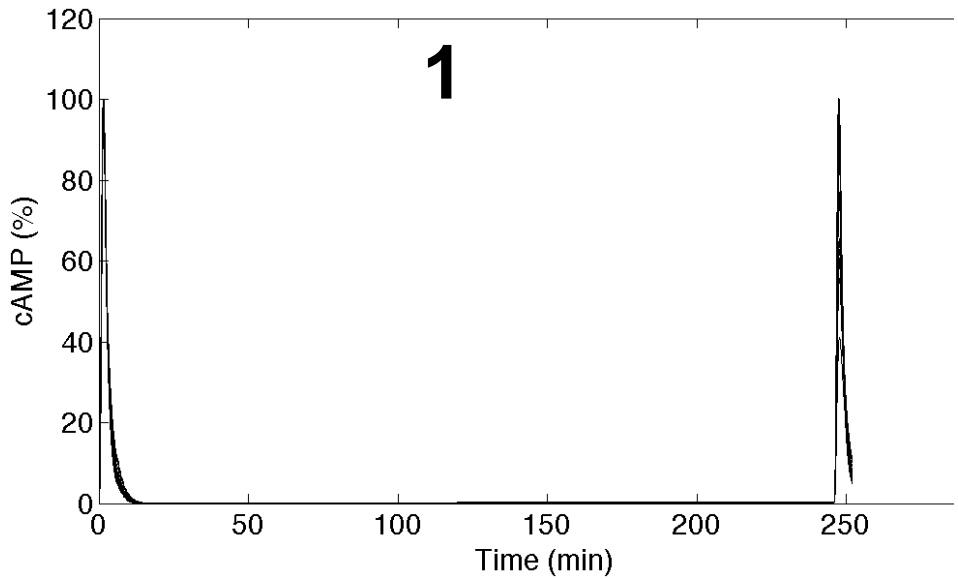

B1
B1p
B1act
H1
Gs
Gsact
cAMP
PKA
PKA act

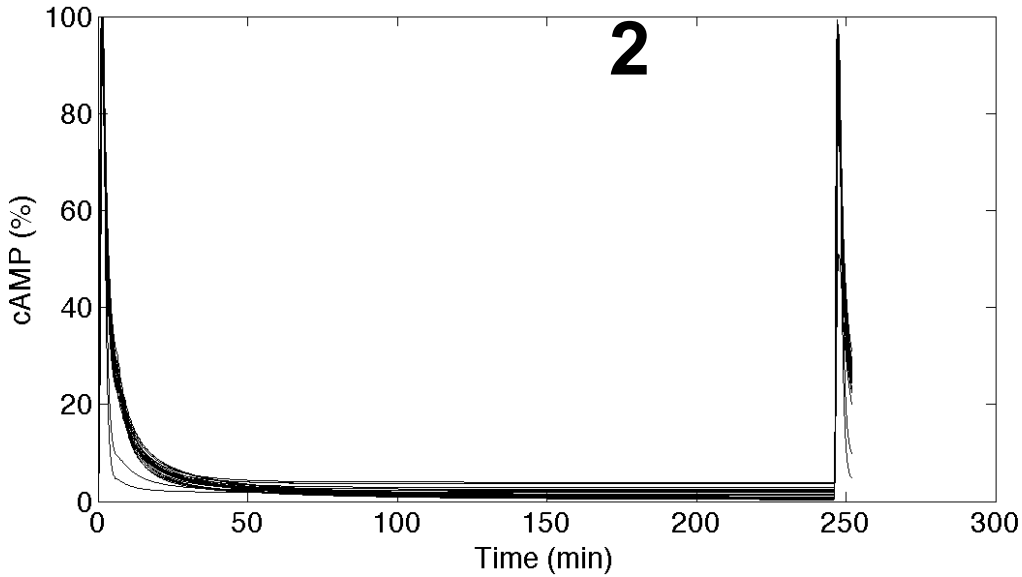
2

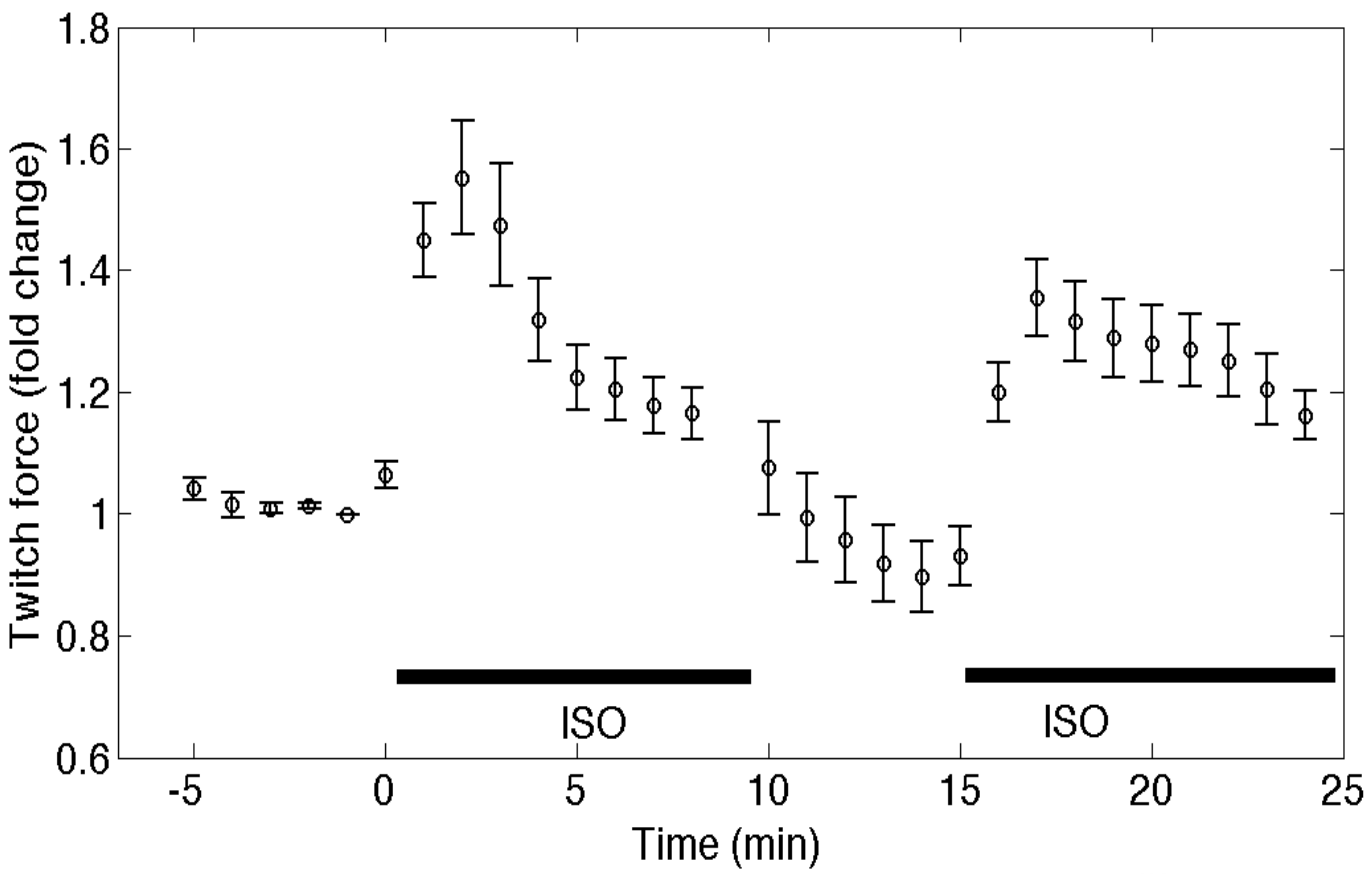

100
80
60
40
20
0
cAMP
Data
Minimal model 1
Minimal model 2
ISO
ISO
0
5
10
Time

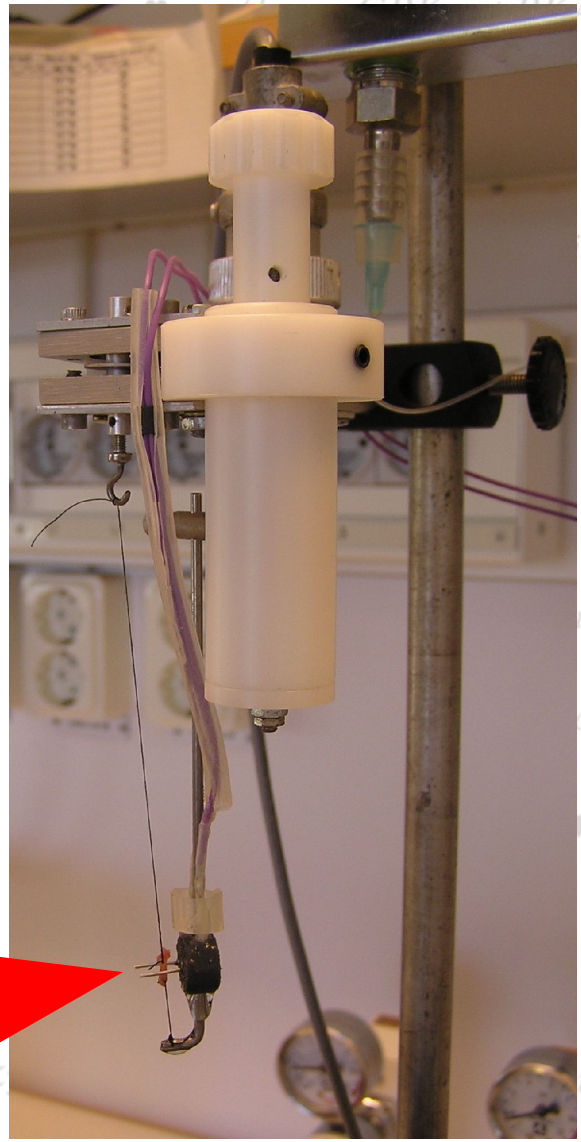

B1
B1p
B1act
H1
Gs
Gsact
cAMP
PKA
PKA act

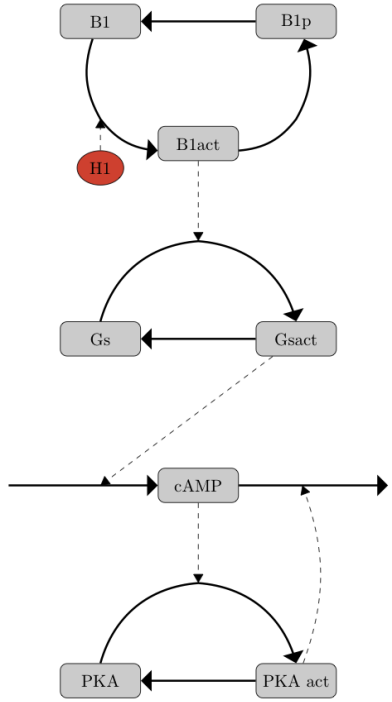

B1
B1p
B1act
H1
Gs
Gsact
cAMP
PKA
PKA act

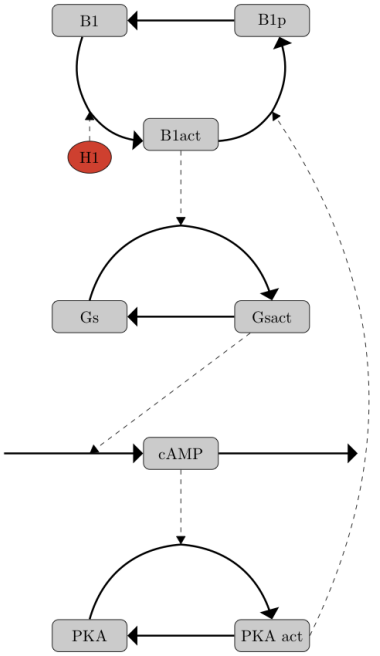

1
120
100
80
60
40
20
0
cAMP (%)
0
50
100
150
200
250
Time (min)

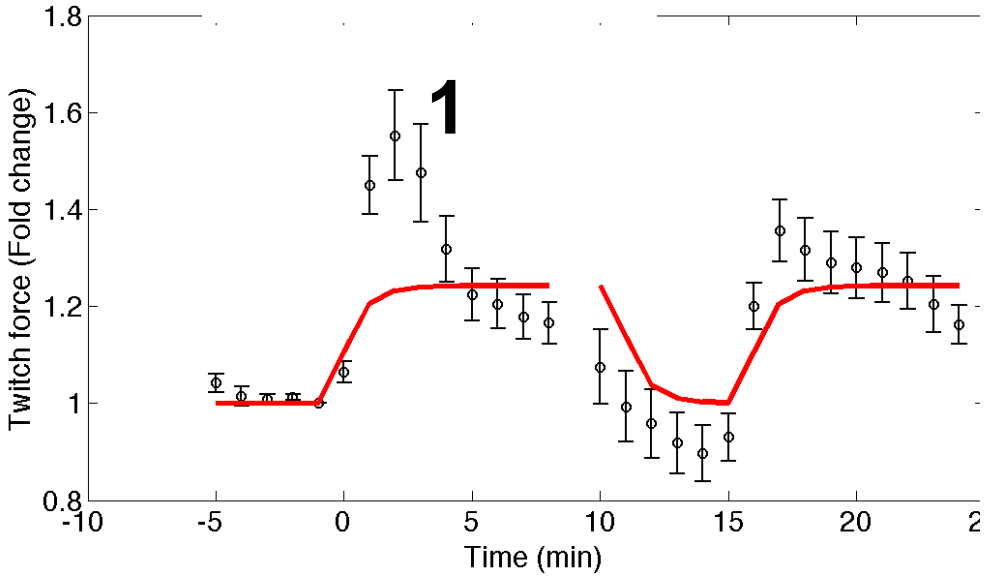

2
100
80
60
40
20
0
cAMP (%)
0
50
100
150
200
250
300
Time (min)

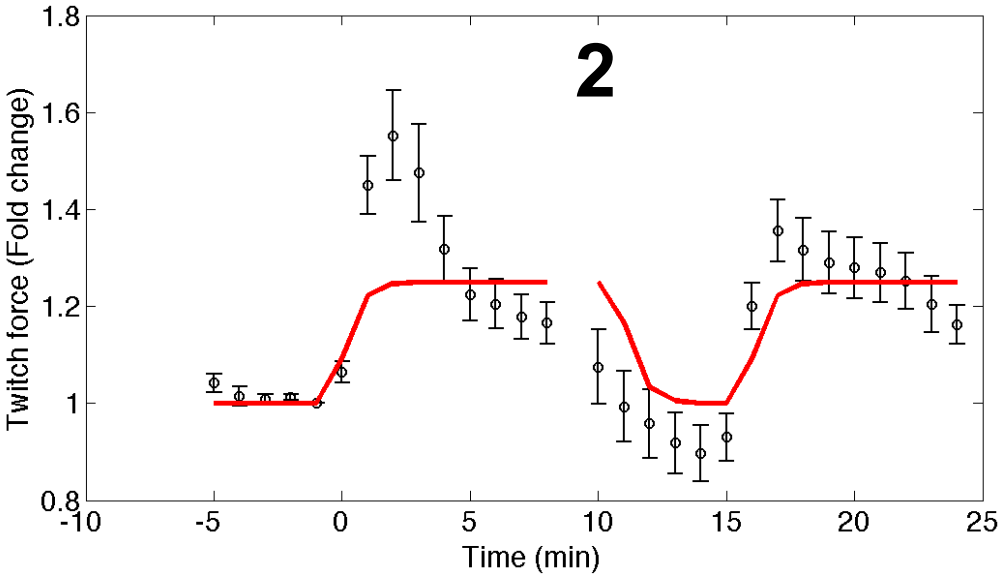

Twitch force (fold change)
1.8
1.6
1.4
1.2
1
0.8
0.6
-5
0
5
10
15
20
25
Time (min)
ISO
ISO

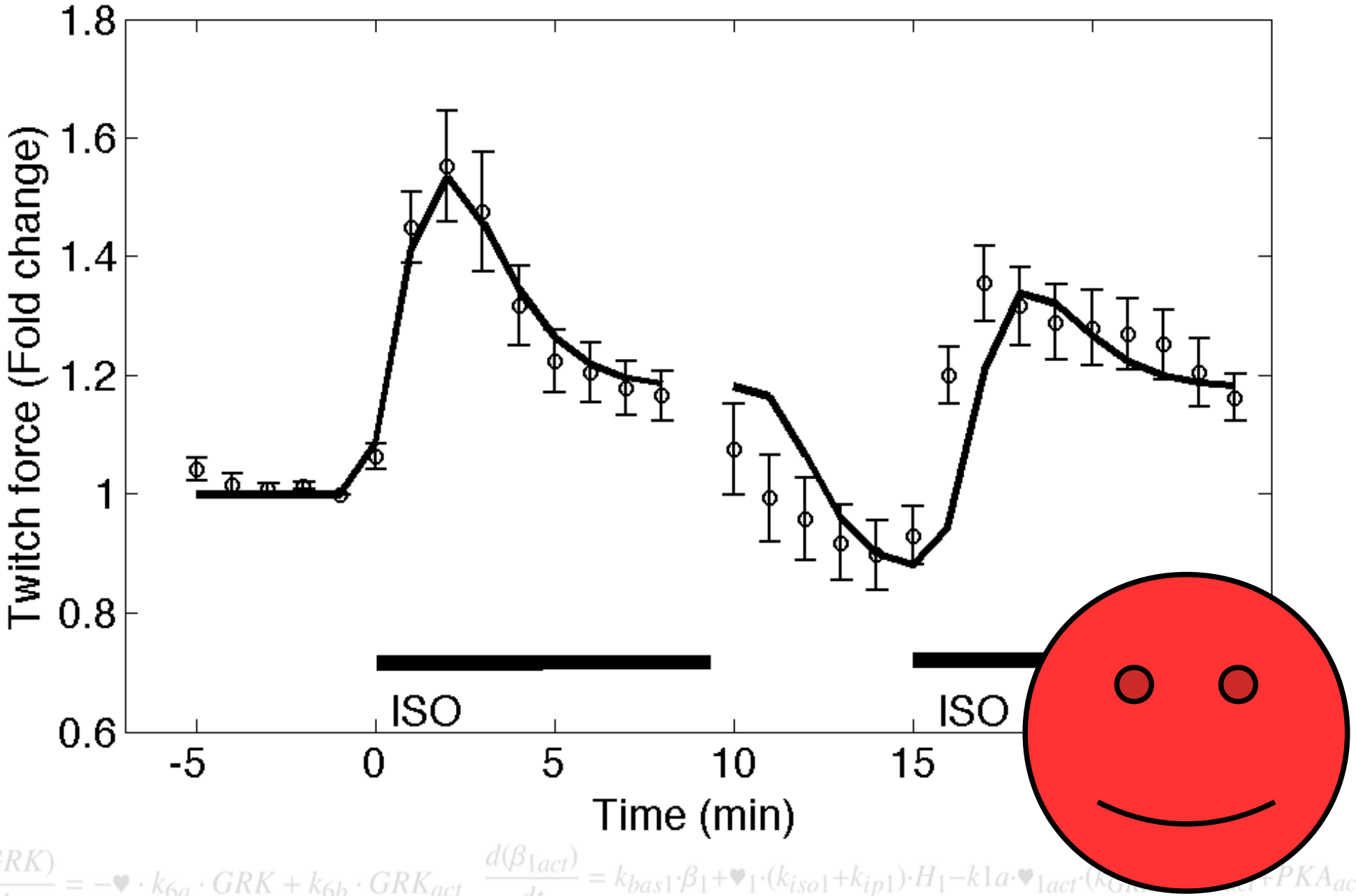


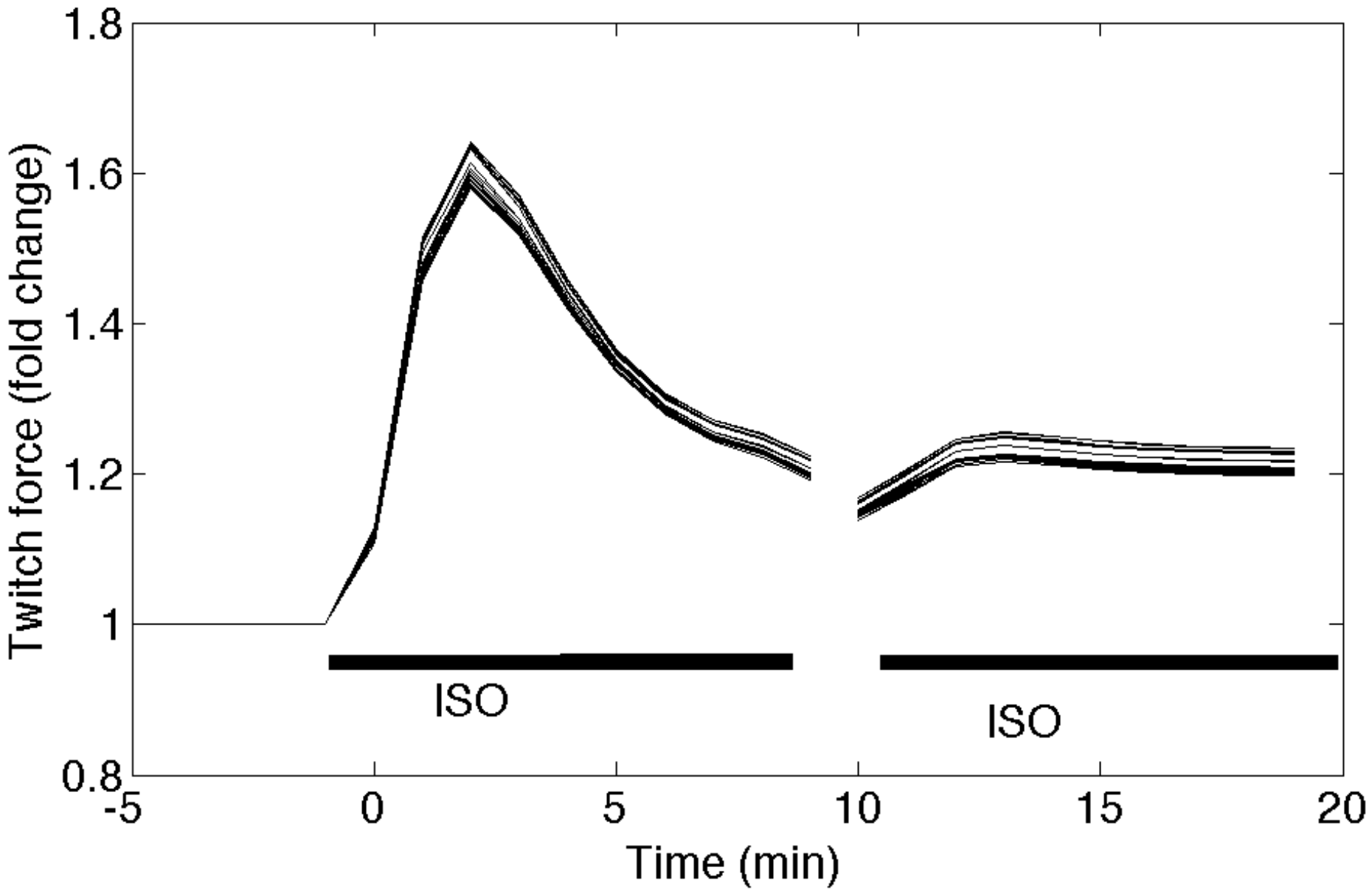

B1
B1p
B1act
H1
Gs
Gsact
cAMP
PKA
PKA act


B1
B1p
B1act
H1
Gs
Gsact
cAMP
PKA
PKA act


1
Twitch force (Fold change)
Time (min)
1.8
1.6
1.4
1.2
1
0.8
-10
-5
0
5
10
15
20


2
Twitch force (Fold change)
Time (min)
1.8
1.6
1.4
1.2
1
0.8
-10
-5
0
5
10
15
20
25


1.8
1.6
1.4
1.2
1
0.8
0.6
Twitch force (Fold change)
-5
0
5
10
15
Time (min)
ISO
ISO


1.8
1.6
1.4
1.2
1
0.8
Twitch force (fold change)
-5
0
5
10
15
20
Time (min)
ISO
ISO

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

Thank you!

Future prospects

- GRK
- Compartmentation
- Compare healthy adult hearts with fetal and failed hearts