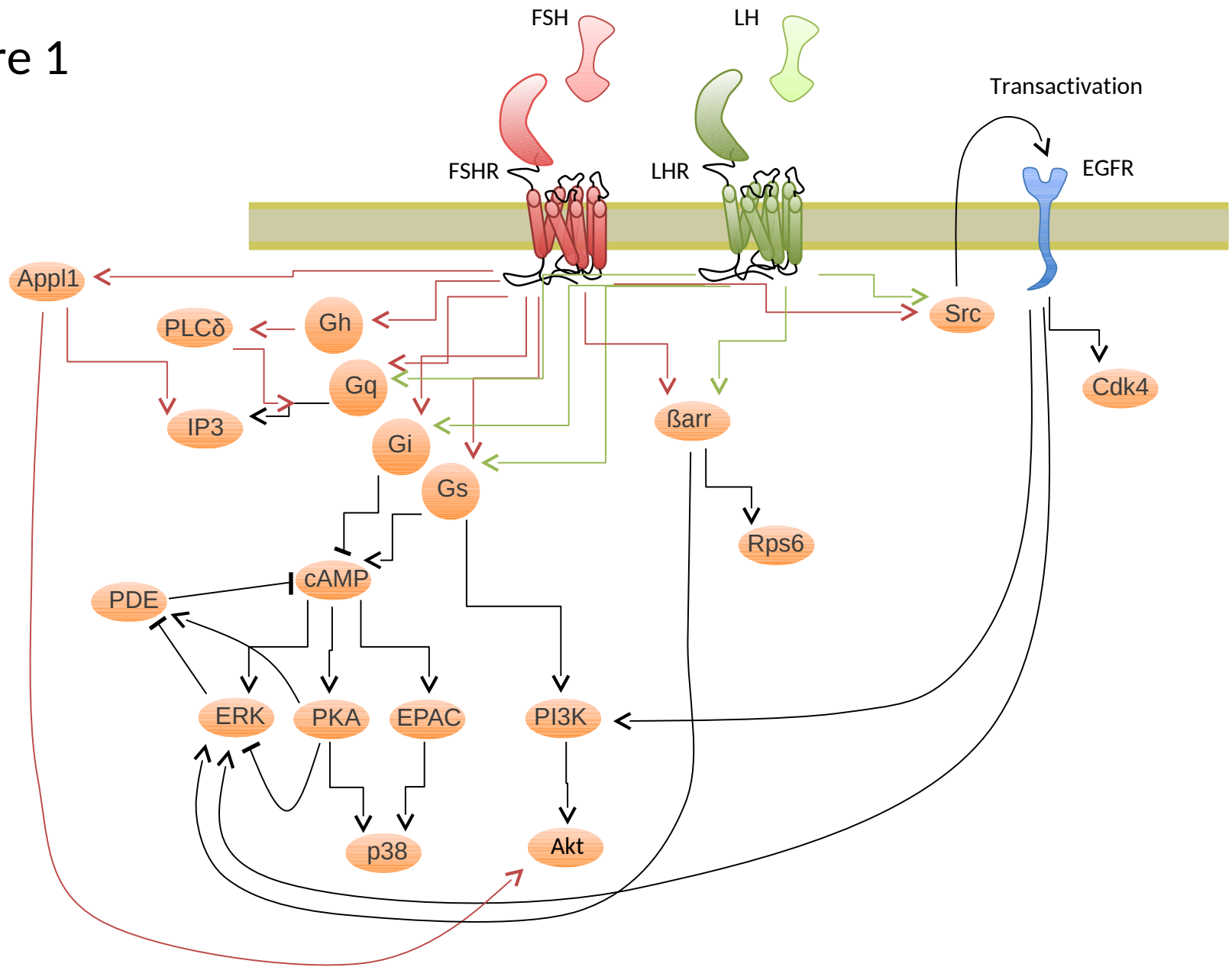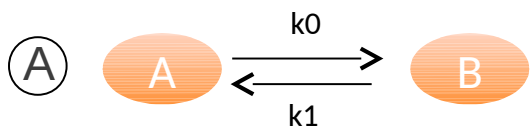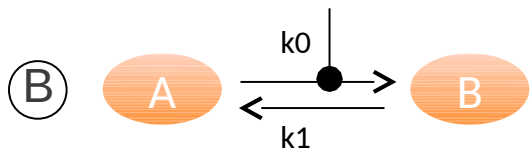Figure 1

A

A $\xrightarrow[k1]{k0}$ B

C

Ordinary differential equation (ODE)

$$\frac{d[B]}{dt} = f([A], [B], k_0, k_1) \quad (1)$$

Mass action law:
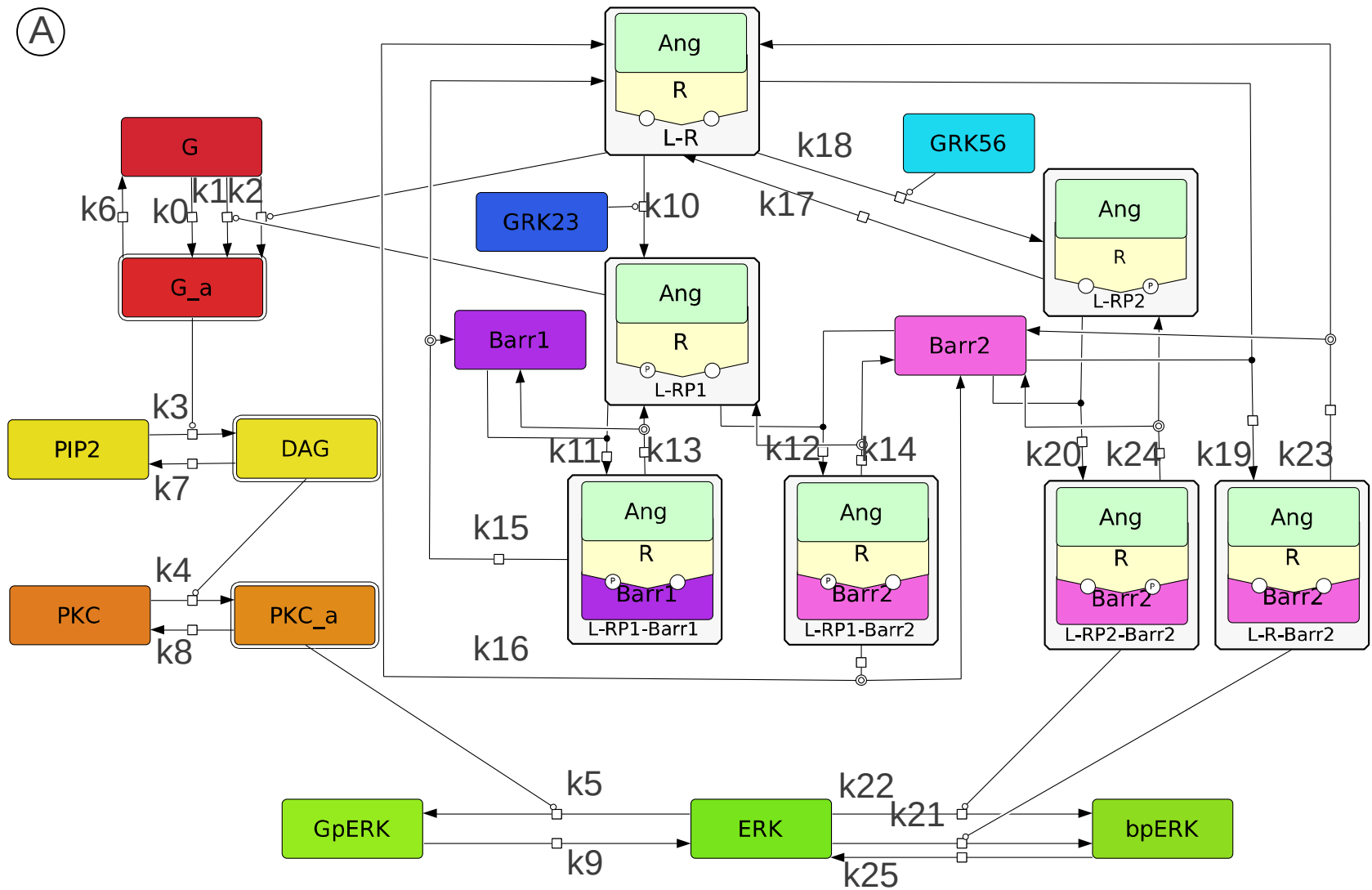
$$\frac{d[B]}{dt} = k_0[A] - k_1[B] \quad (2)$$

B

A $\xrightarrow[k1]{k0}$ B

Mass action law:

$$\frac{d[B]}{dt} = k_0.[A][C] - k_1[B] \quad (3)$$

C

A $\xrightarrow[k1]{k0}$ B

k2

k3

C $\rightarrow$ D $\rightarrow$ E

k4

F $\rightarrow$ G

D

[B]

$\delta 2^B$

$\delta 3^B$

$\delta 1^B$

$\delta 4^B$

$\delta 5^B$

Experimental points

Simulation

$\delta 0^B$

Time

error $= f(\delta 0^B, \delta 1^B, \delta 2^B, \delta 3^B, \delta 4^B, \delta 5^B)$

E

Initial parameter values (k0, ...,kn)

Simulation

Compute error

Change (k0,..., kn)

Error=0 ?

Done !

Figure 3

A

(diagram with species: G, G_a, PIP2, DAG, PKC, PKC_a, GpERK, ERK, bpERK, GRK23, GRK56, Barr1, Barr2, and receptor complexes L-R, L-RP1, L-RP2, L-RP1-Barr1, L-RP1-Barr2, L-RP2-Barr2, L-R-Barr2; rate constants k0–k25)

B
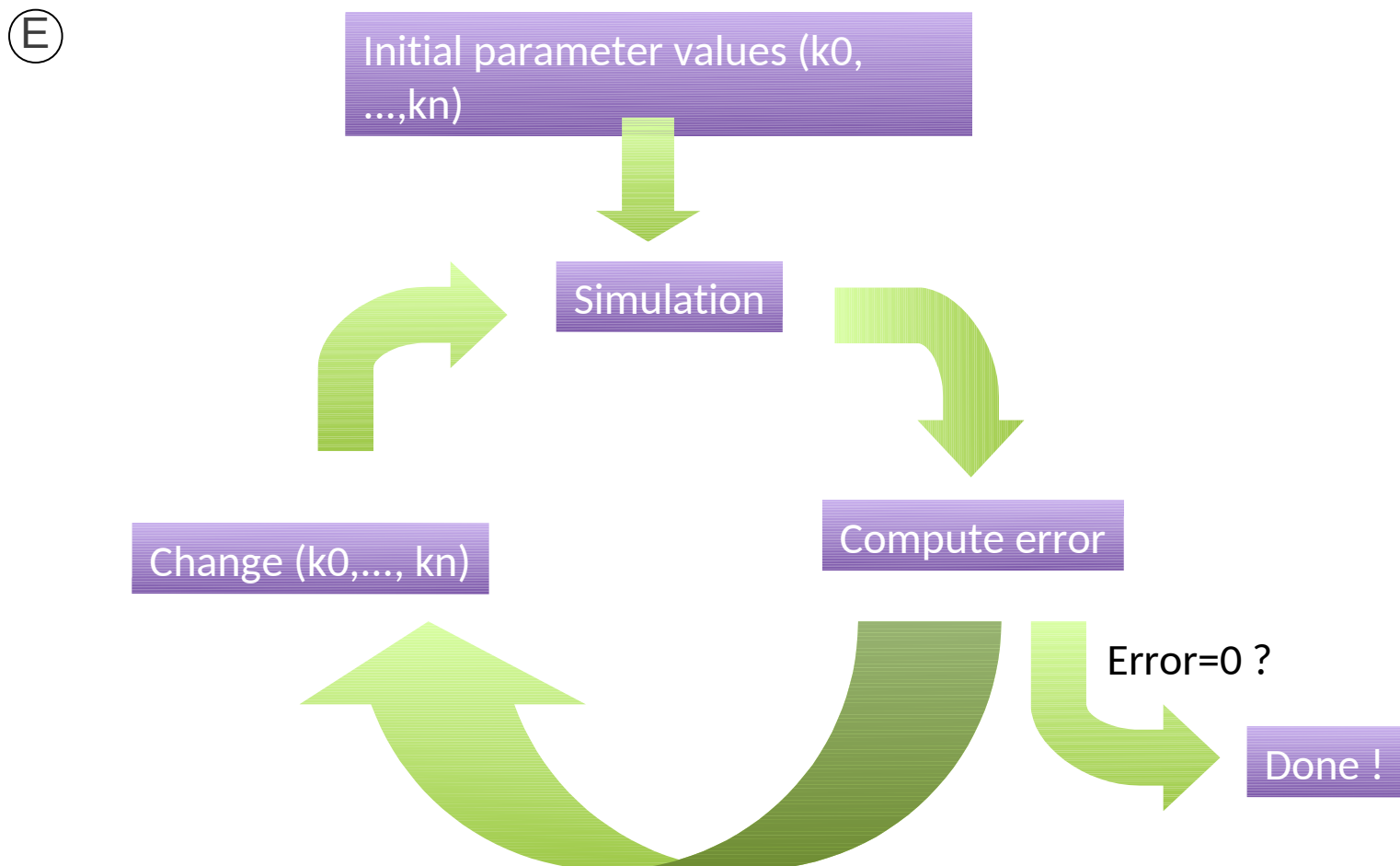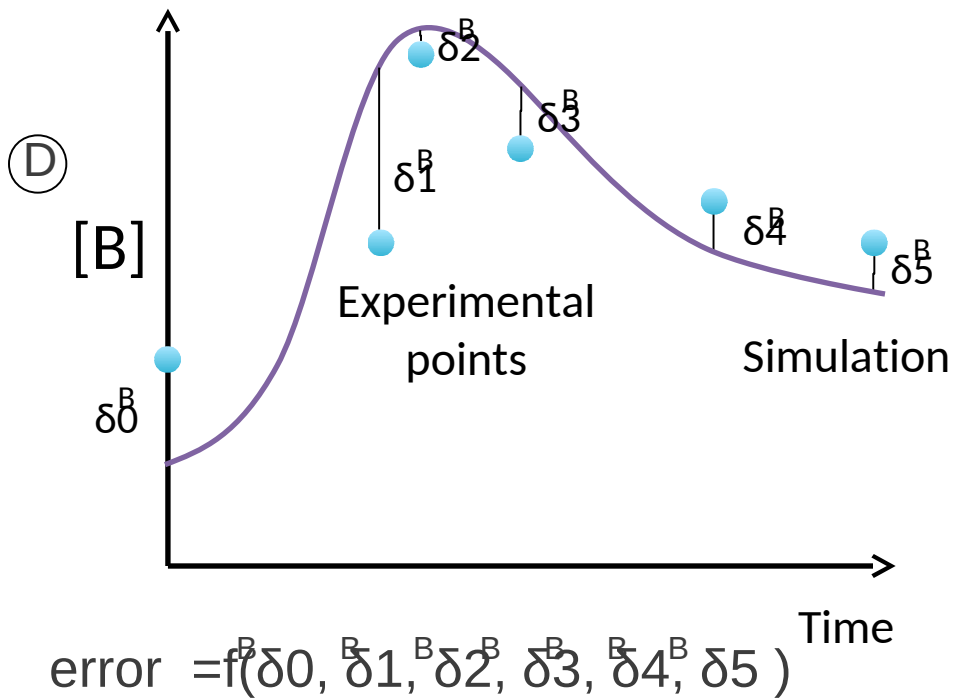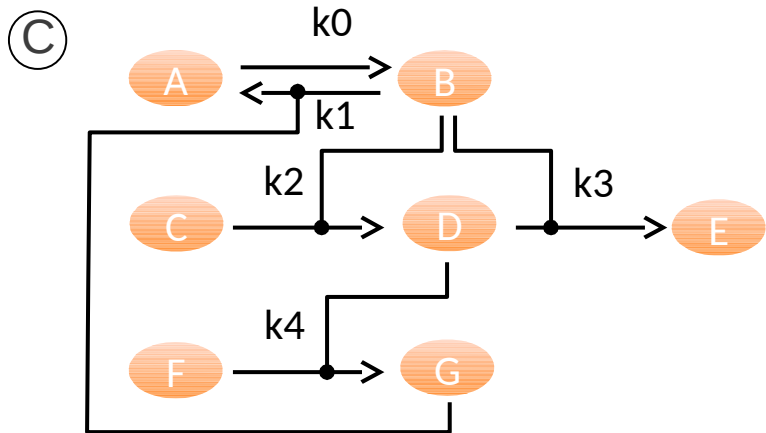
Model equations

$$\frac{d}{dt}[G_a] = k_0.G + k_1.[LR] + k_2.[LRP1] - k_6.[G_a]$$

$$\frac{d}{dt}[DAG] = k_3.[PIP2] - k_7.[DAG]$$

$$\frac{d}{dt}[PKC_a] = k_4.[PKC] - k_8.[PKC_a]$$

$$\frac{d}{dt}[LRP1] = k_10.[GRK23][LR] - k_{11}.[LRP1][Barr1] + k_{13}.[LRP1Barr1]$$
$$- k_{12}.[LRP1][Barr2] + k_{14}.[LRP1Barr2]$$

$$\frac{d}{dt}[LRP1Barr1] = k_{11}.[LRP1][Barr1] - k_{13}.[LRP1Barr1] - k_{15}.[LRP1Barr1]$$

$$\frac{d}{dt}[LRP1Barr2] = k_{12}.[LRP1][Barr2] - k_{14}.[LRP1Barr2] - k_{16}.[LRP1Barr2]$$

$$\frac{d}{dt}[LRP2] = k_{18}.[LR].[GRK56] - k17.[LRP2] - k_{20}[LRP2][Barr2] + k_{24}.[LRP2Barr2]$$

$$\frac{d}{dt}[LRP2Barr2] = k_{20}[LRP2][Barr2] - k_{24}.[LRP2Barr2]$$

$$\frac{d}{dt}[LRBarr2] = k_{19}.[LR][Barr2] - k_{23}[LRBarr2]$$

$$\frac{d}{dt}[GpERK] = k_5.[ERK] - k_9.[GpERK]$$

$$\frac{d}{dt}[bpERK] = k_{21}.[LRBarr2] + k_{22}.[LRP2Barr2] - k_{25}.[ERK]$$

Conservation laws

$$k_{26} = [R_T] = [LR] + [LRP1] + [LRP1Barr1] + [LRP2] + [LRP2Barr2] + [LRBarr2]$$

$$k_{27} = [G_T] = [G] + [G_a]$$

$$k_{28} = [DAG_T] = [DAG] + [PIP2]$$

$$k_{29} = [PKC_T] = [PKC] + [PKC_a]$$

$$k_{30} = [Barr1_T] = [Barr1] + [LRP1Barr1]$$

$$k_{31} = [Barr2_T] = [Barr2] + [LRP1Barr2] + [LRP2Barr2] + [LRBarr2]$$

$$k_{32} = [ERK_T] = [ERK] + [GpERK] + [bpERK]$$

Biological conditions

- Condition 1: control
- Condition 2: PKC inhibition, $k_{29} \longrightarrow k_{33}$
- Condition 3: siRNA Barr2, $k_{31} \longrightarrow k_{34}$
- Condition 4: siRNA GRK23, $k_{10} \longrightarrow k_{35}$
- Condition 5: siRNA GRK56, $k_{18} \longrightarrow k_{36}$

C

(graph: pERK (μmol/L) vs [Ang], with series CTL-exp, CTL-sim, siBarr1-exp, siBarr1-sim, siBarr2-exp, siBarr2-sim)
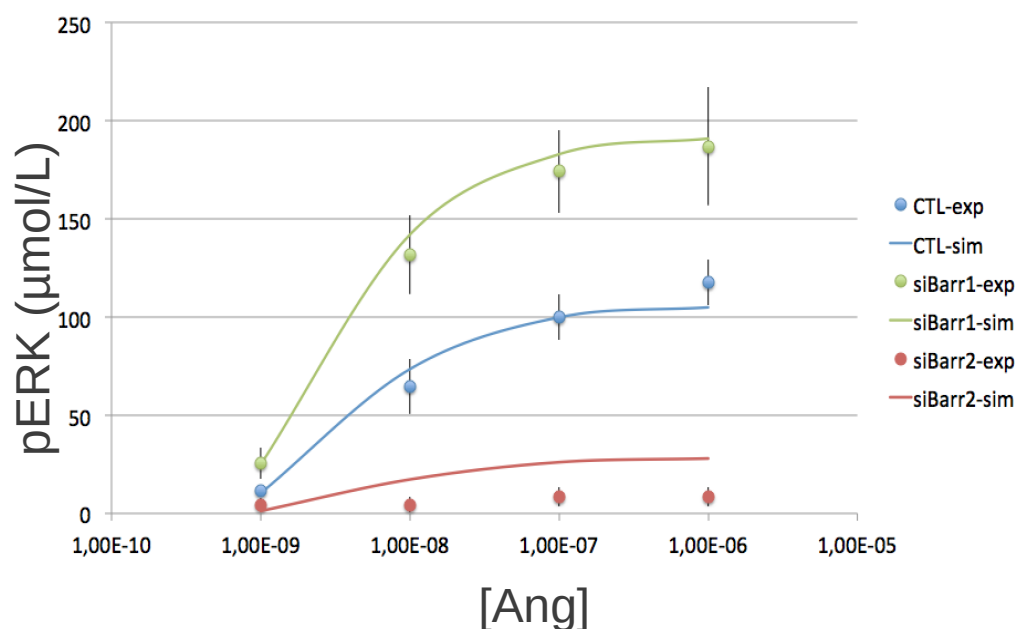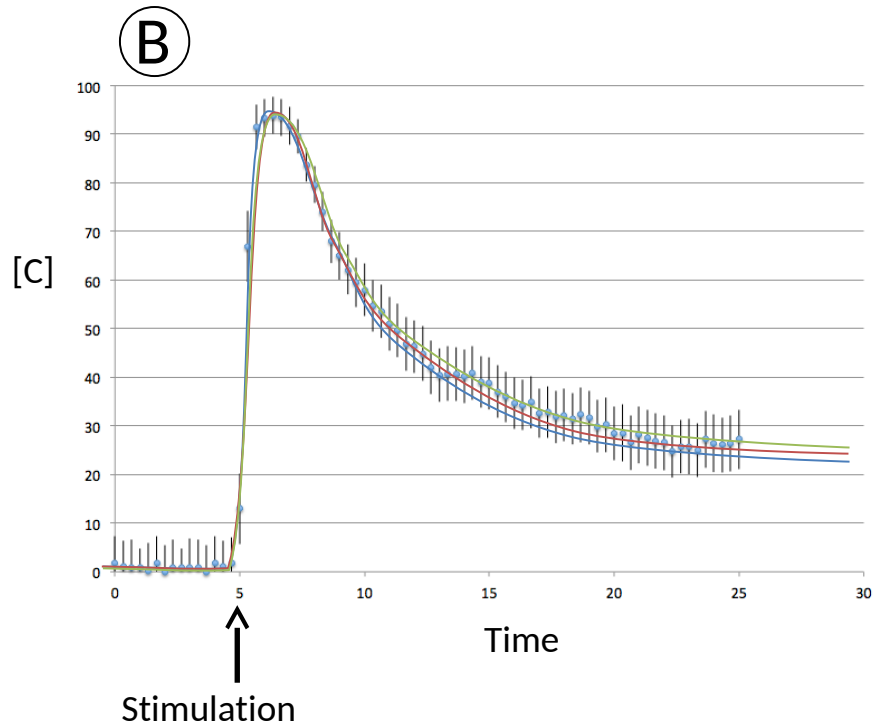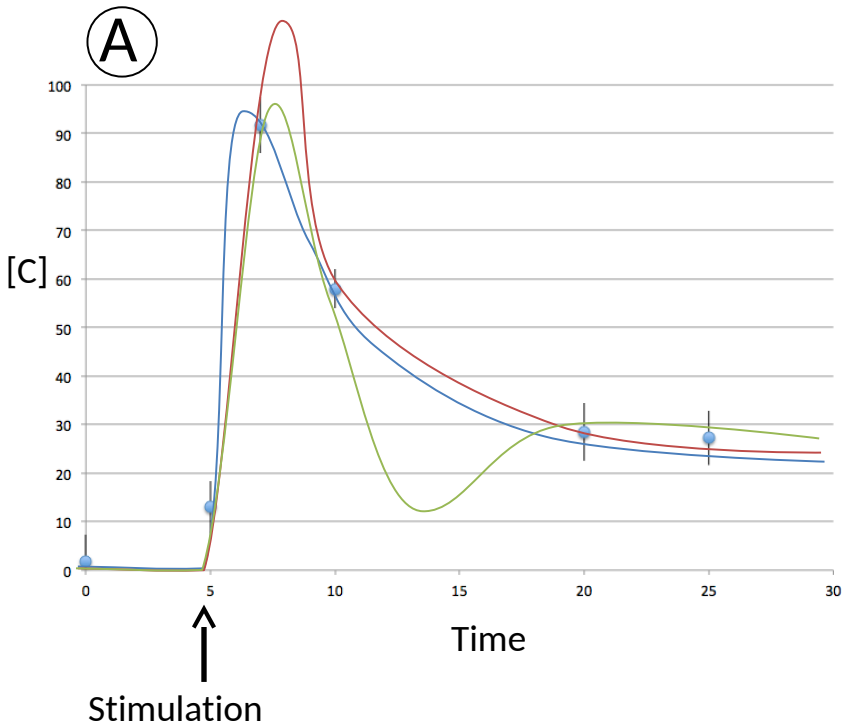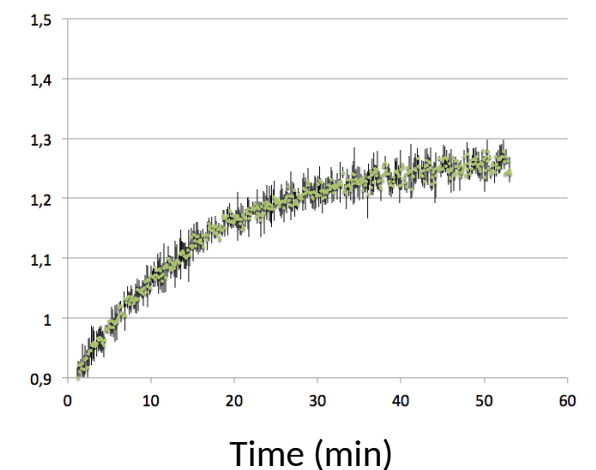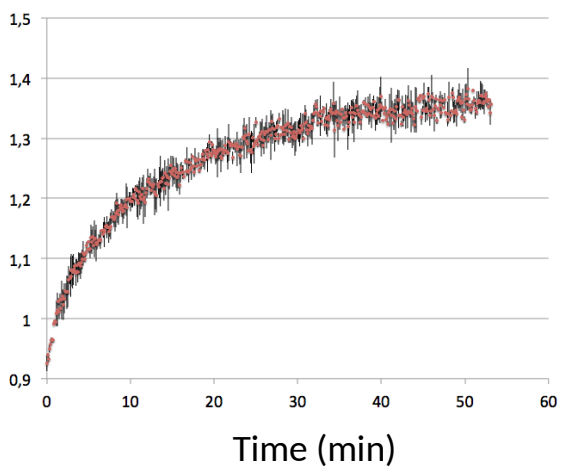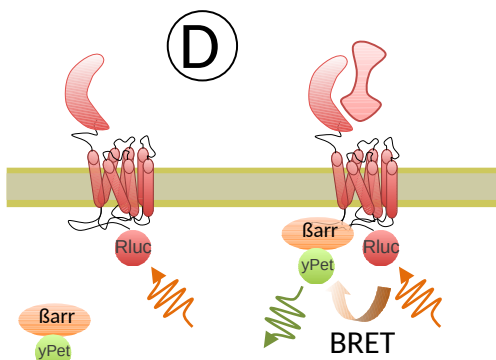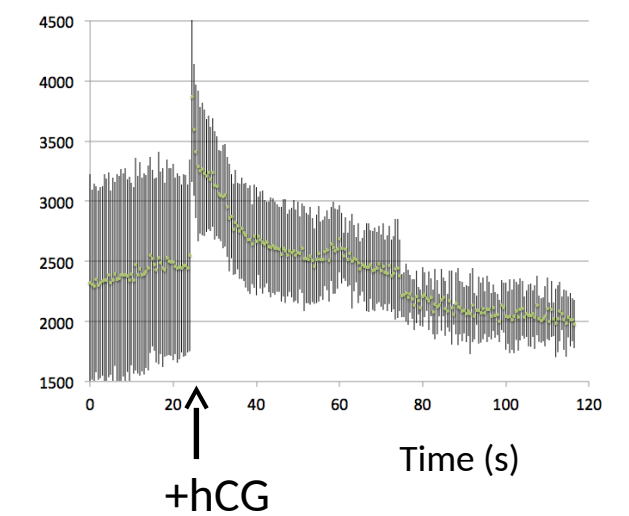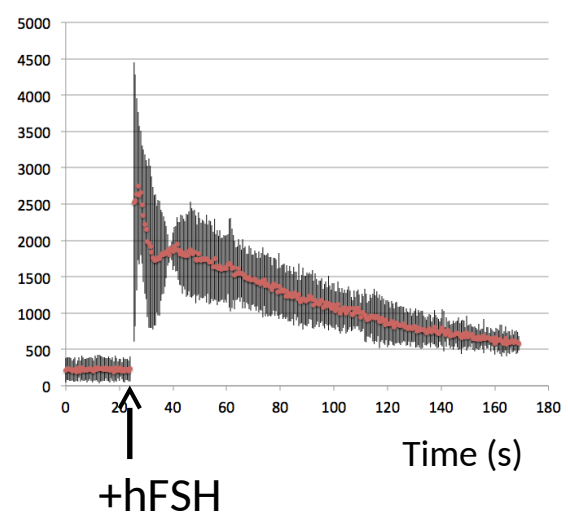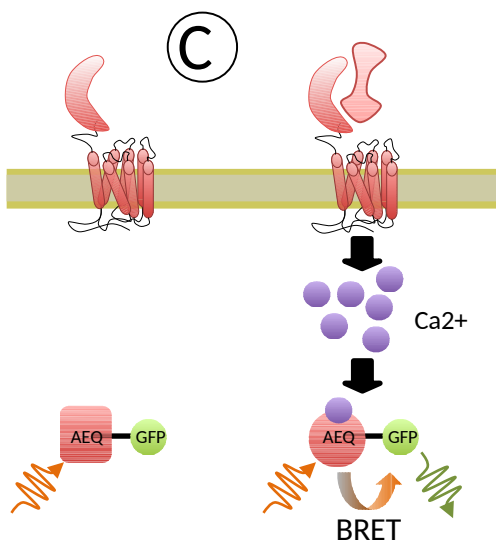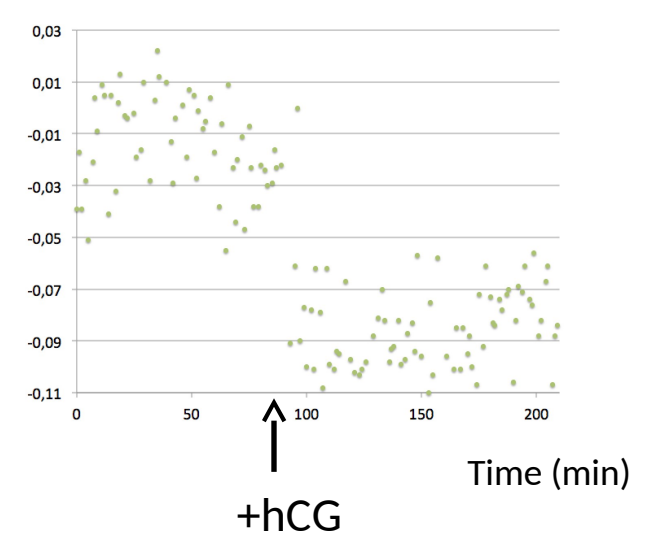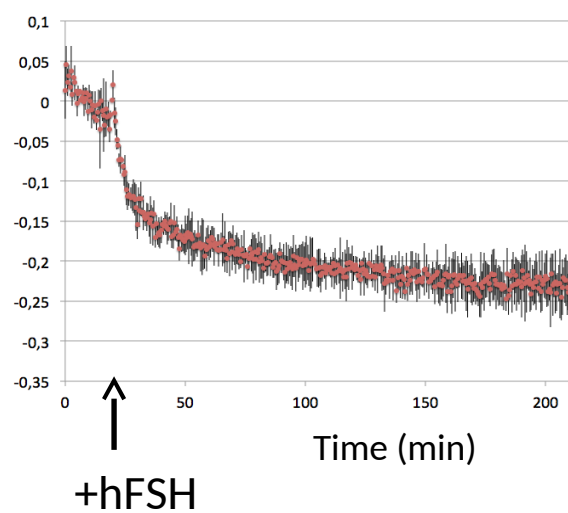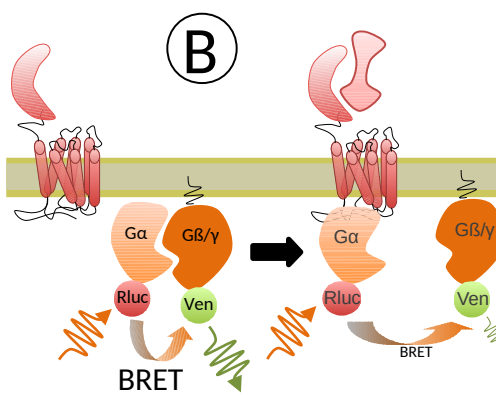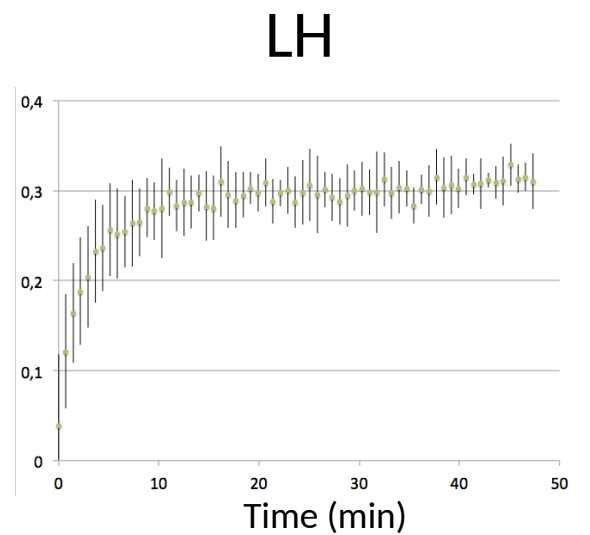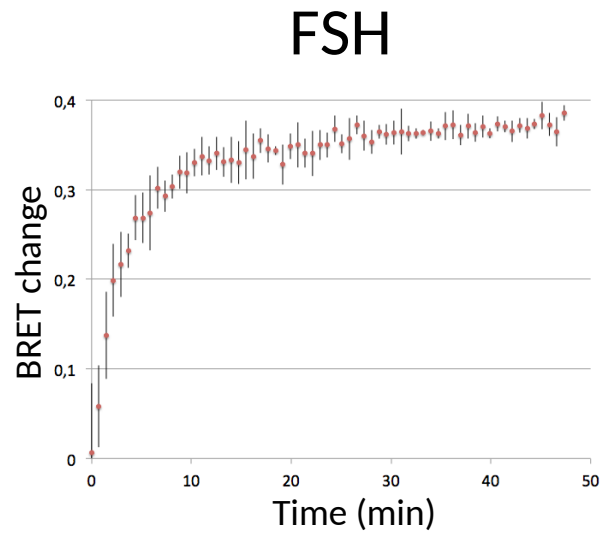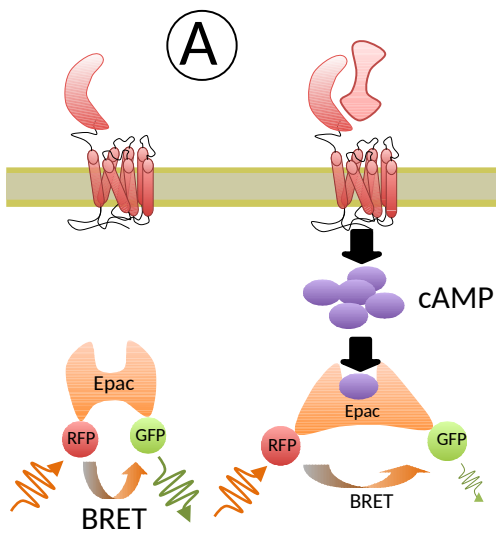
Figure 4

Figure 5

Figure 6

Figure 7

Figure 8