

cascade - mapk

rule-based)

outline

- start with a basic motive of reversible covalent modification
- obtain a rule-based version of the Huang-Ferrell model of a protein activation cascade [2]
- and finally, rewire our cascade to illustrate how easy it is to do so

GK-loop

three types of agents:

- a kinase K ,
- a target T with 2 pho' sites x and y , and
- a phosphatase P

elementary triplet:

- K binds its target T at site x or y ,
- K may (but need not) phosphorylate the site to which it is bound,
- K dissociates from T

KPT - rules

$$\begin{aligned}K(a), \mathsf{T}(x) &\leftrightarrow K(a^1), \mathsf{T}(x^1) \\K(a^1), \mathsf{T}(x_u^1) &\rightarrow K(a^1), \mathsf{T}(x_p^1) \\K(a), \mathsf{T}(y) &\leftrightarrow K(a^1), \mathsf{T}(y^1) \\K(a^1), \mathsf{T}(y_u^1) &\rightarrow K(a^1), \mathsf{T}(y_p^1)\end{aligned}$$

$$\begin{aligned}P(a), \mathsf{T}(x) &\leftrightarrow P(a^1), \mathsf{T}(x^1) \\P(a^1), \mathsf{T}(x_p^1) &\rightarrow P(a^1), \mathsf{T}(x_u^1) \\P(a), \mathsf{T}(y) &\leftrightarrow P(a^1), \mathsf{T}(y^1) \\P(a^1), \mathsf{T}(y_p^1) &\rightarrow P(a^1), \mathsf{T}(y_u^1)\end{aligned}$$

typology of GK's

variations on multi-pho systems:

- processive vs. distributive
- smart = $\sim U$, $\sim P$ sensitive vs. dumb
- sequential vs. unordered
- exclusive vs. collective

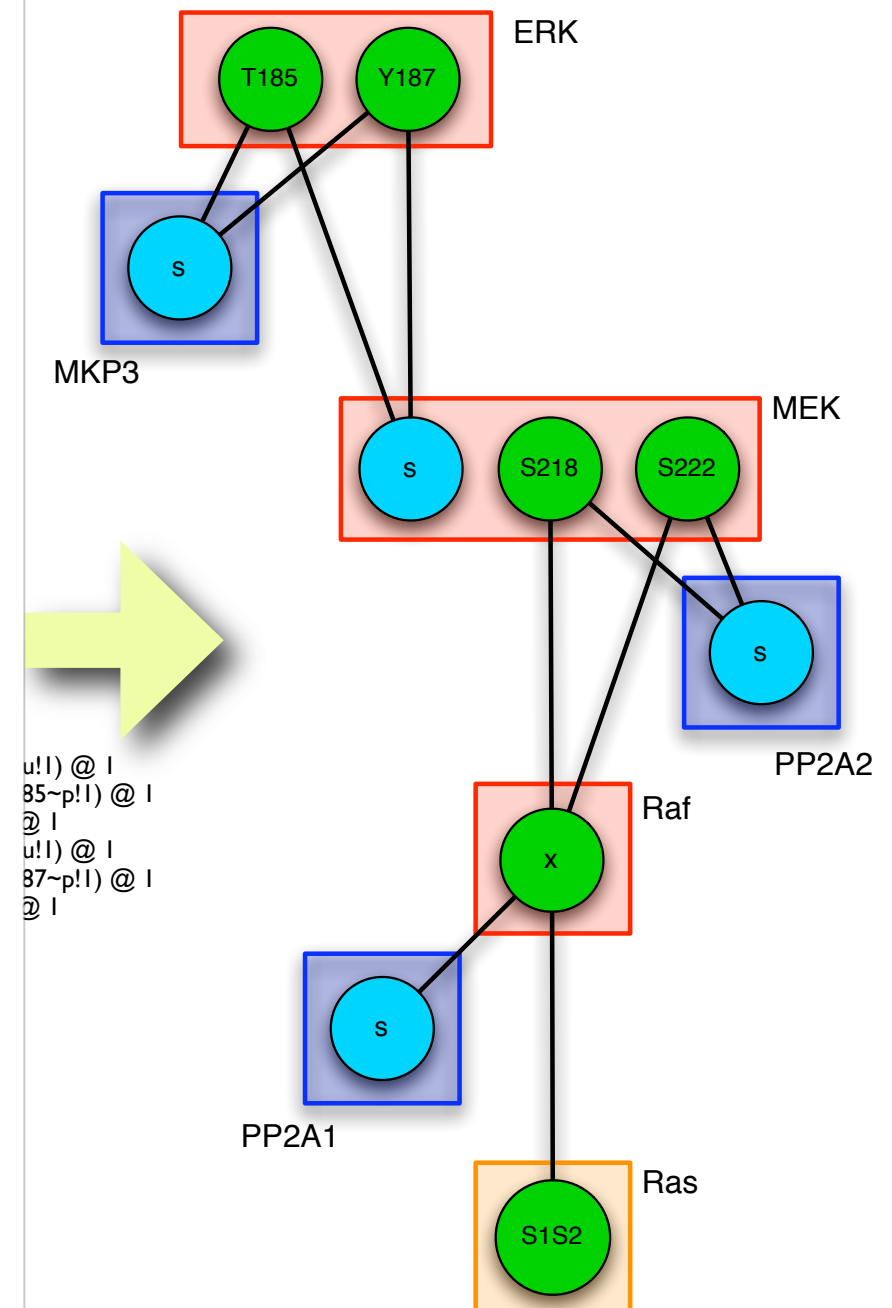
3 GKs in sequence

3 tiers:

- Ras \rightarrow Raf \leftarrow PP2A1
- Raf \rightarrow MEK \leftarrow PP2A2
- MEK \rightarrow ERK \leftarrow MKP3

$RAS(S1S2), RAF(x_u) \rightarrow RAS(S1S2^1), RAF(x_u^1)$
 $RAS(S1S2^1), RAF(x_u^1) \rightarrow RAS(S1S2^1), RAF(x_p^1)$
 $RAS(S1S2^1), RAF(x^1) \rightarrow RAS(S1S2), RAF(x)$

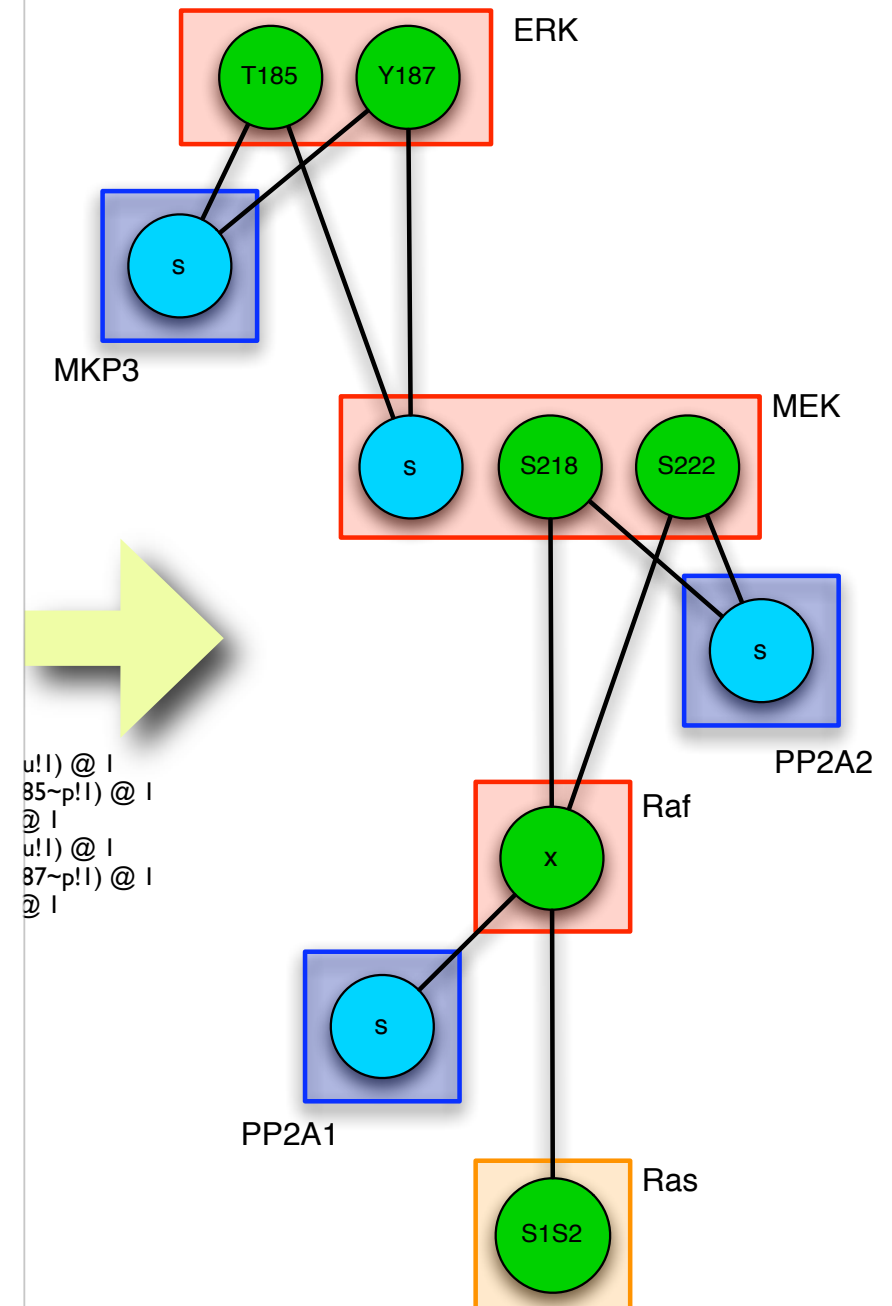
$PP2A1(s), RAF(x_p) \rightarrow PP2A1(s^1), RAF(x_p^1)$
 $PP2A1(s^1), RAF(x_p^1) \rightarrow PP2A1(s^1), RAF(x_u^1)$
 $PP2A1(s^1), RAF(x^1) \rightarrow PP2A1(s), RAF(x)$



3 GKs - tier 2

$\text{RAF}(x_p), \text{MEK}(S222_u) \rightarrow \text{RAF}(x_p^1), \text{MEK}(S222_u^1)$
 $\text{RAF}(x_p^1), \text{MEK}(S222_u^1) \rightarrow \text{RAF}(x_p^1), \text{MEK}(S222_p^1)$
 $\text{RAF}(x_p^1), \text{MEK}(S222^1) \rightarrow \text{RAF}(x_p), \text{MEK}(S222)$
 $\text{RAF}(x_p), \text{MEK}(S218_u) \rightarrow \text{RAF}(x_p^1), \text{MEK}(S218_u^1)$
 $\text{RAF}(x_p^1), \text{MEK}(S218_u^1) \rightarrow \text{RAF}(x_p^1), \text{MEK}(S218_p^1)$
 $\text{RAF}(x_p^1), \text{MEK}(S218^1) \rightarrow \text{RAF}(x_p), \text{MEK}(S218)$

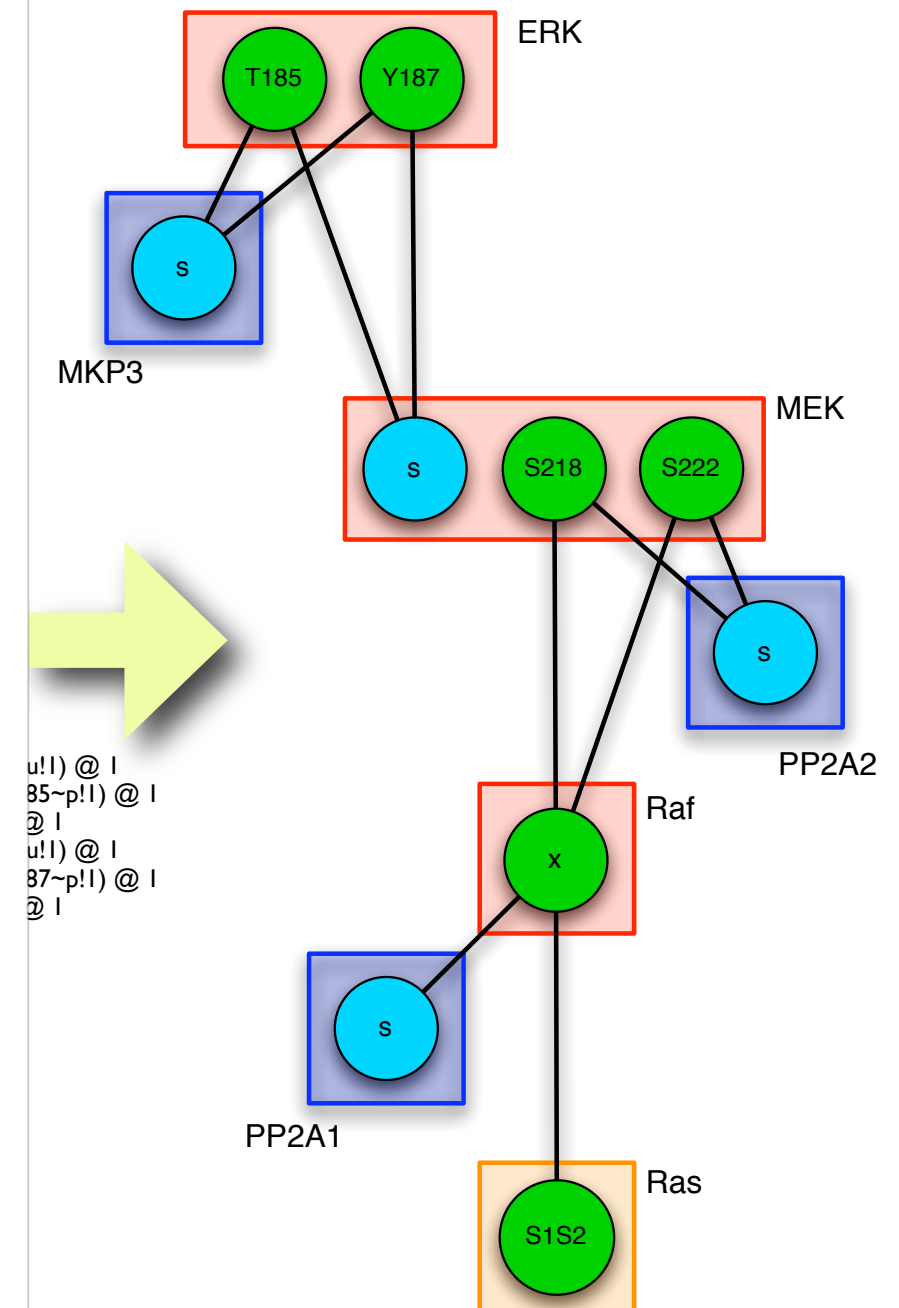
$\text{PP2A2}(s), \text{MEK}(S222_p) \rightarrow \text{PP2A2}(s^1), \text{MEK}(S222_p^1)$
 $\text{PP2A2}(s^1), \text{MEK}(S222_p^1) \rightarrow \text{PP2A2}(s^1), \text{MEK}(S222_u^1)$
 $\text{PP2A2}(s^1), \text{MEK}(S222^1) \rightarrow \text{PP2A2}(s), \text{MEK}(S222)$
 $\text{PP2A2}(s), \text{MEK}(S218_p) \rightarrow \text{PP2A2}(s^1), \text{MEK}(S218_p^1)$
 $\text{PP2A2}(s^1), \text{MEK}(S218_p^1) \rightarrow \text{PP2A2}(s^1), \text{MEK}(S218_u^1)$
 $\text{PP2A2}(s^1), \text{MEK}(S218^1) \rightarrow \text{PP2A2}(s), \text{MEK}(S218)$



3 GKs - tier 3

$MEK(s, S218_p, S222_p), ERK(T185_u) \rightarrow MEK(s^1, S218_p, S222_p), ERK(T185_u^1)$
 $MEK(s^1, S218_p, S222_p), ERK(T185_u^1) \rightarrow MEK(s^1, S218_p, S222_p), ERK(T185_p^1)$
 $MEK(s^1, S218_p, S222_p), ERK(T185^1) \rightarrow MEK(s, S218_p, S222_p), ERK(T185)$
 $MEK(s, S218_p, S222_p), ERK(Y187_u) \rightarrow MEK(s^1, S218_p, S222_p), ERK(Y187_u^1)$
 $MEK(s^1, S218_p, S222_p), ERK(Y187_u^1) \rightarrow MEK(s^1, S218_p, S222_p), ERK(Y187_p^1)$
 $MEK(s^1, S218_p, S222_p), ERK(Y187^1) \rightarrow MEK(s, S218_p, S222_p), ERK(Y187)$

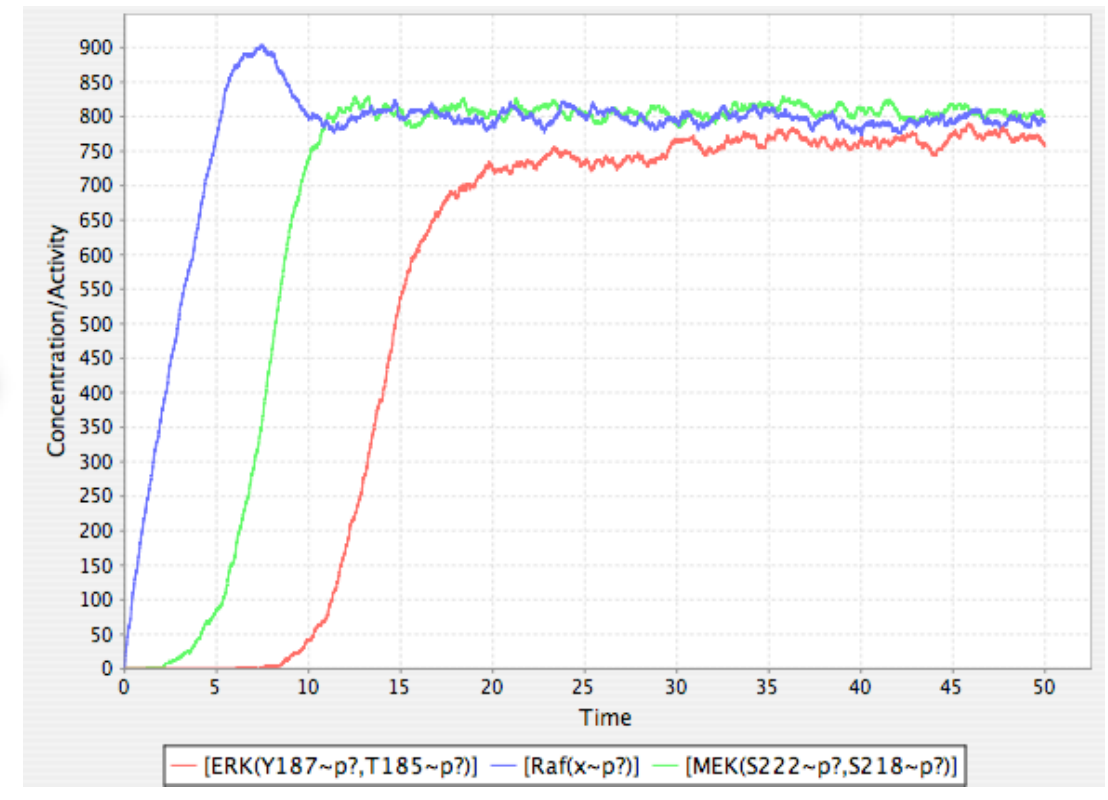
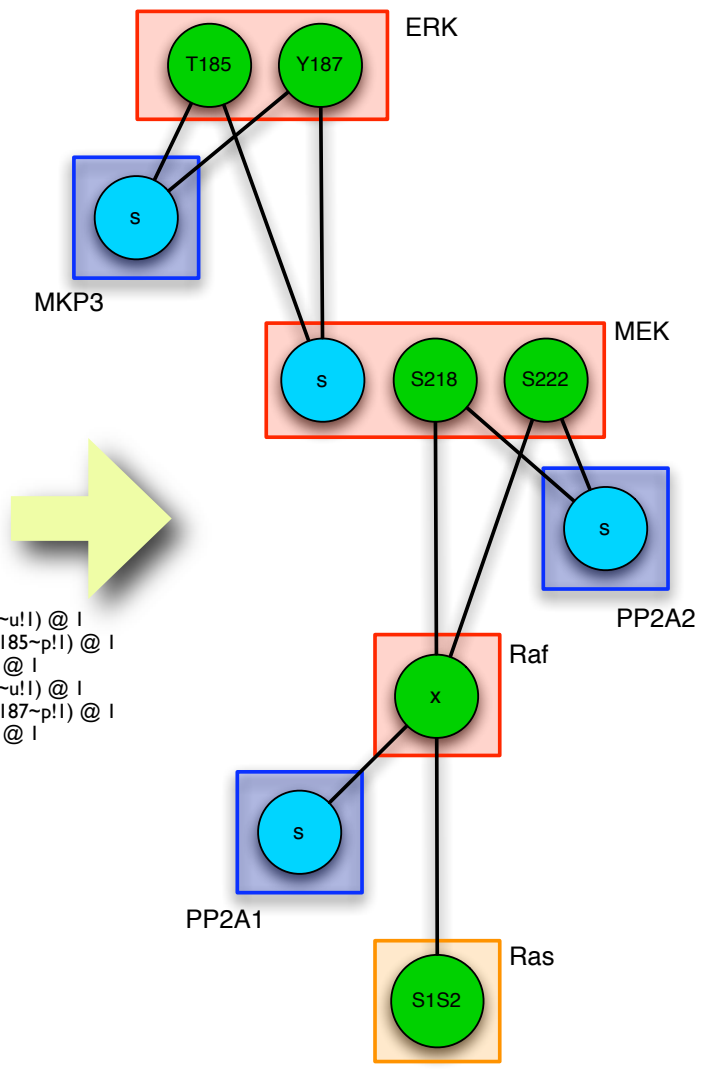
$MKP3(s), ERK(T185_p) \rightarrow MKP3(s^1), ERK(T185_p^1)$
 $MKP3(s^1), ERK(T185_p^1) \rightarrow MKP3(s^1), ERK(T185_u^1)$
 $MKP3(s^1), ERK(T185^1) \rightarrow MKP3(s), ERK(T185)$
 $MKP3(s), ERK(Y187_p) \rightarrow MKP3(s^1), ERK(Y187_p^1)$
 $MKP3(s^1), ERK(Y187_p^1) \rightarrow MKP3(s^1), ERK(Y187_u^1)$
 $MKP3(s^1), ERK(Y187^1) \rightarrow MKP3(s), ERK(Y187)$



simulation

```

Ras(S1S2~gtp),Raf(x~u) -> Ras(S1S2~gtp!),Raf(x~u!) @ 1
Ras(S1S2~gtp!),Raf(x~u!) -> Ras(S1S2~gtp!),Raf(x~p!) @ 1
Ras(S1S2~gtp!),Raf(x!) -> Ras(S1S2~gtp),Raf(x) @ 1
PP2A1(s),Raf(x~p) -> PP2A1(s!),Raf(x~p!) @ 1
PP2A1(s!),Raf(x~p!) -> PP2A1(s!),Raf(x~u!) @ 1
PP2A1(s!),Raf(x!) -> PP2A1(s),Raf(x) @ 1
Raf(x~p),MEK(S222~u) -> Raf(x~p!),MEK(S222~u!) @ 1
Raf(x~p!),MEK(S222~u!) -> Raf(x~p!),MEK(S222~p!) @ 1
Raf(x~p!),MEK(S222!) -> Raf(x~p),MEK(S222) @ 1
Raf(x~p),MEK(S218~u) -> Raf(x~p!),MEK(S218~u!) @ 1
Raf(x~p!),MEK(S218~u!) -> Raf(x~p!),MEK(S218~p!) @ 1
Raf(x~p!),MEK(S218!) -> Raf(x~p),MEK(S218) @ 1
PP2A2(s),MEK(S222~p) -> PP2A2(s!),MEK(S222~p!) @ 1
PP2A2(s!),MEK(S222~p!) -> PP2A2(s!),MEK(S222~u!) @ 1
PP2A2(s!),MEK(S222!) -> PP2A2(s),MEK(S222) @ 1
PP2A2(s),MEK(S218~p) -> PP2A2(s!),MEK(S218~p!) @ 1
PP2A2(s!),MEK(S218~p!) -> PP2A2(s!),MEK(S218~u!) @ 1
PP2A2(s!),MEK(S218!) -> PP2A2(s),MEK(S218) @ 1
MEK(s,S218~p,S222~p),ERK(T185~u) -> MEK(s!,S218~p,S222~p),ERK(T185~u!) @ 1
MEK(s!,S218~p,S222~p),ERK(T185~u!) -> MEK(s!,S218~p,S222~p),ERK(T185~p!) @ 1
MEK(s!,S218~p,S222~p),ERK(T185!) -> MEK(s,S218~p,S222~p),ERK(T185) @ 1
MEK(s,S218~p,S222~p),ERK(Y187~u) -> MEK(s!,S218~p,S222~p),ERK(Y187~u!) @ 1
MEK(s!,S218~p,S222~p),ERK(Y187~u!) -> MEK(s!,S218~p,S222~p),ERK(Y187~p!) @ 1
MEK(s!,S218~p,S222~p),ERK(Y187!) -> MEK(s,S218~p,S222~p),ERK(Y187) @ 1
MKP3(s),ERK(T185~p) -> MKP3(s!),ERK(T185~p!) @ 1
MKP3(s!),ERK(T185~p!) -> MKP3(s!),ERK(T185~u!) @ 1
MKP3(s!),ERK(T185!) -> MKP3(s),ERK(T185) @ 1
MKP3(s),ERK(Y187~p) -> MKP3(s!),ERK(Y187~p!) @ 1
MKP3(s!),ERK(Y187~p!) -> MKP3(s!),ERK(Y187~u!) @ 1
MKP3(s!),ERK(Y187!) -> MKP3(s),ERK(Y187) @ 1
    
```



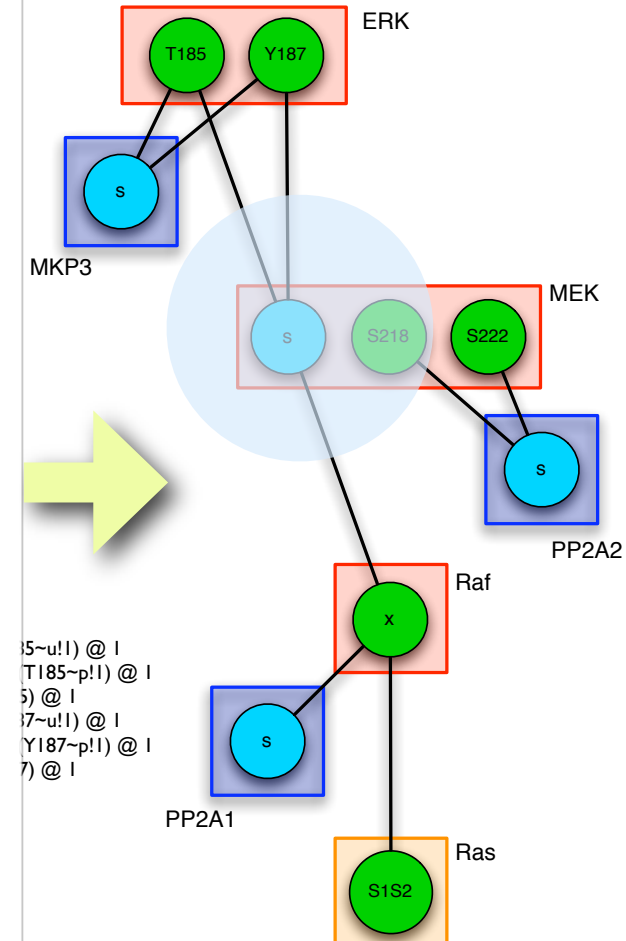
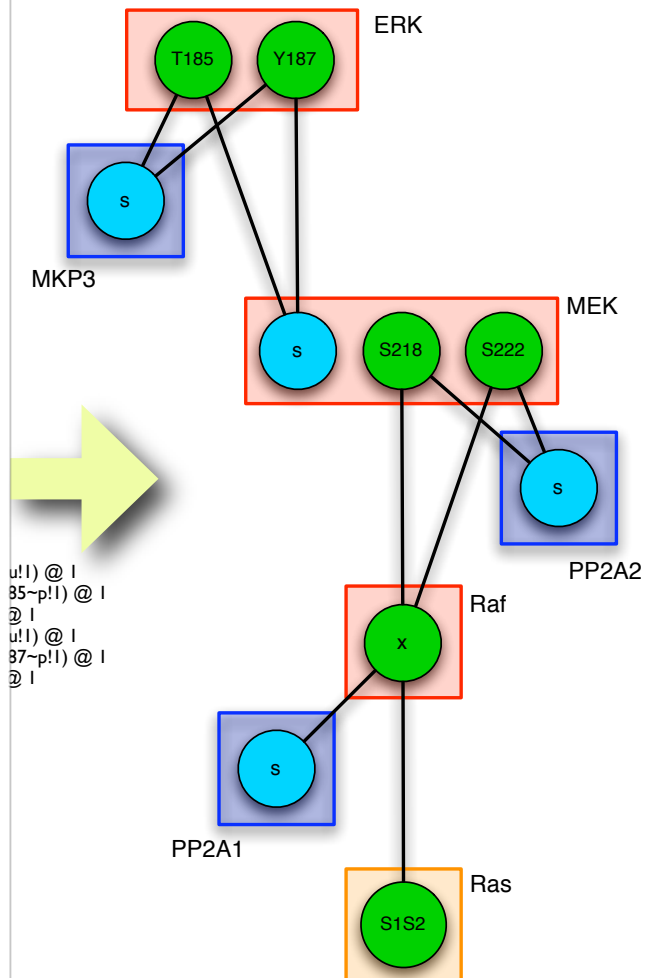
rewiring our GK*3

$$\text{RAF}(x_p), \text{MEK}(s) \rightarrow \text{RAF}(x_p^1), \text{MEK}(s^1)$$

$$\text{RAF}(x_p^1), \text{MEK}(s^1) \rightarrow \text{RAF}(x_p), \text{MEK}(s)$$

$$\text{RAF}(x_p^1), \text{MEK}(S222_u, s^1) \rightarrow \text{RAF}(x_p^1), \text{MEK}(S222_p, s^1)$$

$$\text{RAF}(x_p^1), \text{MEK}(S218_u, s^1) \rightarrow \text{RAF}(x_p^1), \text{MEK}(S218_p, s^1)$$



simulation - rewired

```

Ras(S1S2~gtp),Raf(x~u) -> Ras(S1S2~gtp!1),Raf(x~u!1) @ 1
Ras(S1S2~gtp!1),Raf(x~u!1) -> Ras(S1S2~gtp!1),Raf(x~p!1) @ 1
Raf_op' Ras(S1S2~gtp!1),Raf(x!1) -> Ras(S1S2~gtp),Raf(x) @ 1
PP2A1(s),Raf(x~p) -> PP2A1(s!1),Raf(x~p!1) @ 1
PP2A1(s!1),Raf(x~p!1) -> PP2A1(s!1),Raf(x~u!1) @ 1
PP2A1(s!1),Raf(x!1) -> PP2A1(s),Raf(x) @ 1
  
```

```

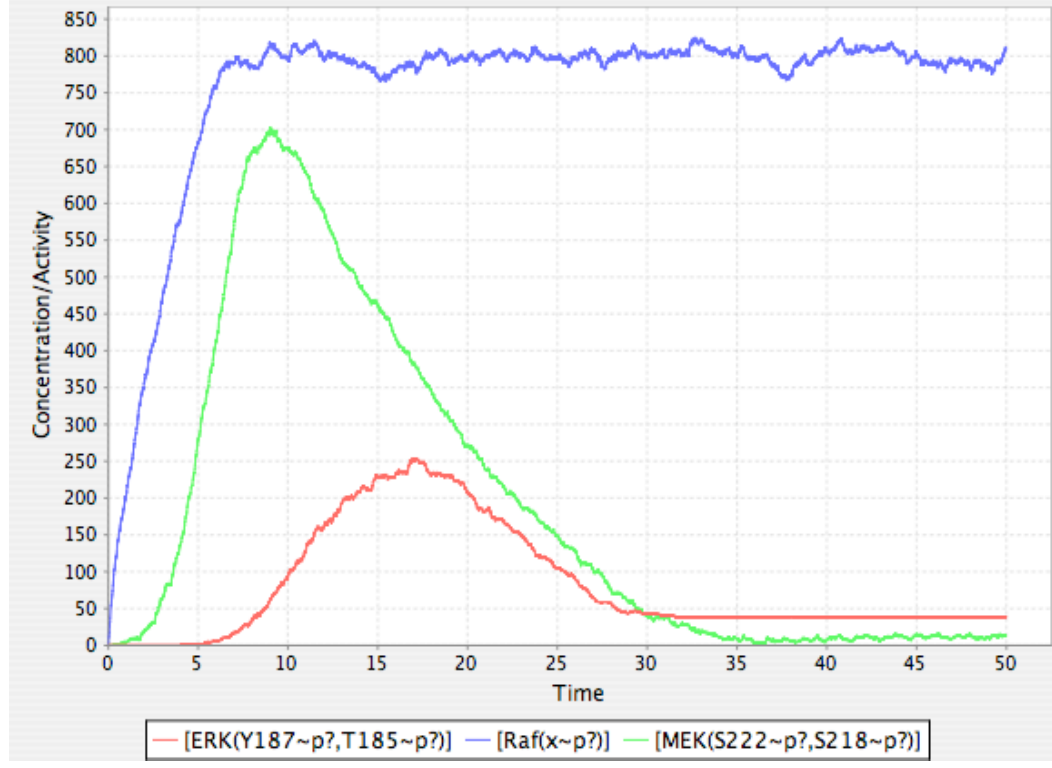
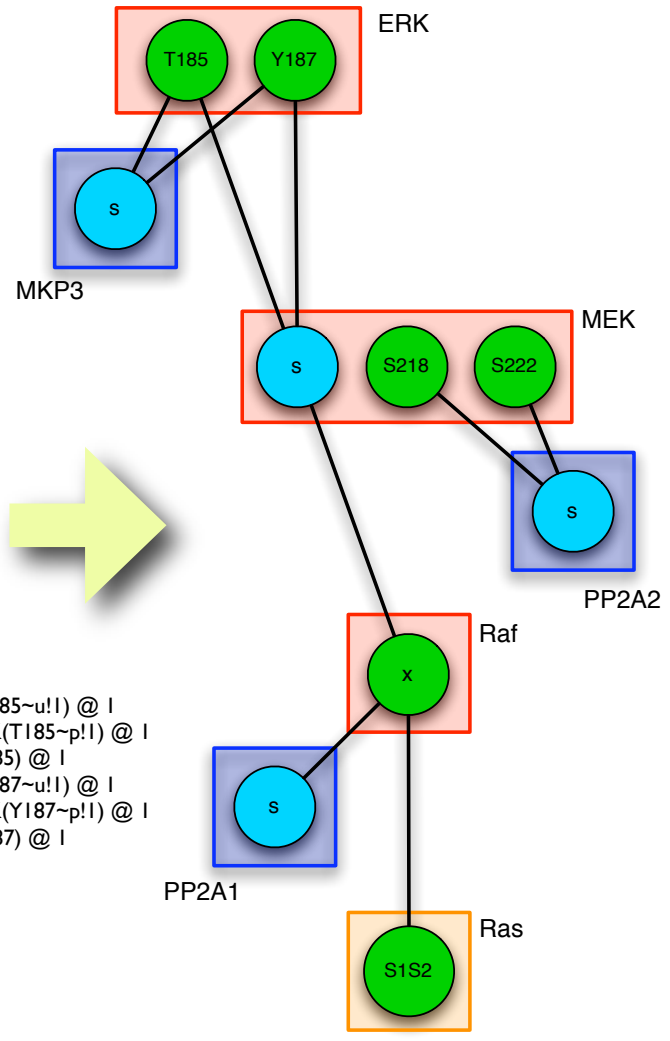
Raf(x~p),MEK(s) -> Raf(x~p!1),MEK(s!1) @ 1
Raf(x~p!1),MEK(s!1) -> Raf(x~p),MEK(s) @ 1
Raf(x~p!1),MEK(S222~u,s!1) -> Raf(x~p!1),MEK(S222~p,s!1) @ 1
Raf(x~p!1),MEK(S218~u,s!1) -> Raf(x~p!1),MEK(S218~p,s!1) @ 1
  
```

```

# Raf(x~p),MEK(S222~u) -> Raf(x~p!1),MEK(S222~u!1) @ 1
# Raf(x~p!1),MEK(S222~u!1) -> Raf(x~p!1),MEK(S222~p!1) @ 1
# Raf(x~p!1),MEK(S222!1) -> Raf(x~p),MEK(S222) @ 1
# Raf(x~p),MEK(S218~u) -> Raf(x~p!1),MEK(S218~u!1) @ 1
# Raf(x~p!1),MEK(S218~u!1) -> Raf(x~p!1),MEK(S218~p!1) @ 1
# Raf(x~p!1),MEK(S218!1) -> Raf(x~p),MEK(S218) @ 1
  
```

```

PP2A2(s),MEK(S222~p) -> PP2A2(s!1),MEK(S222~p!1) @ 1
PP2A2(s!1),MEK(S222~p!1) -> PP2A2(s!1),MEK(S222~u!1) @ 1
PP2A2(s!1),MEK(S222!1) -> PP2A2(s),MEK(S222) @ 1
PP2A2(s),MEK(S218~p) -> PP2A2(s!1),MEK(S218~p!1) @ 1
PP2A2(s!1),MEK(S218~p!1) -> PP2A2(s!1),MEK(S218~u!1) @ 1
PP2A2(s!1),MEK(S218!1) -> PP2A2(s),MEK(S218) @ 1
MEK(s,S218~p,S222~p),ERK(T185~u) -> MEK(s!1,S218~p,S222~p),ERK(T185~u!1) @ 1
MEK(s!1,S218~p,S222~p),ERK(T185~u!1) -> MEK(s!1,S218~p,S222~p),ERK(T185~p!1) @ 1
MEK(s!1,S218~p,S222~p),ERK(T185!1) -> MEK(s,S218~p,S222~p),ERK(T185) @ 1
MEK(s,S218~p,S222~p),ERK(Y187~u) -> MEK(s!1,S218~p,S222~p),ERK(Y187~u!1) @ 1
MEK(s!1,S218~p,S222~p),ERK(Y187~u!1) -> MEK(s!1,S218~p,S222~p),ERK(Y187~p!1) @ 1
MEK(s!1,S218~p,S222~p),ERK(Y187!1) -> MEK(s,S218~p,S222~p),ERK(Y187) @ 1
MKP3(s),ERK(T185~p) -> MKP3(s!1),ERK(T185~p!1) @ 1
MKP3(s!1),ERK(T185~p!1) -> MKP3(s!1),ERK(T185~u!1) @ 1
MKP3(s!1),ERK(T185!1) -> MKP3(s),ERK(T185) @ 1
MKP3(s),ERK(Y187~p) -> MKP3(s!1),ERK(Y187~p!1) @ 1
MKP3(s!1),ERK(Y187~p!1) -> MKP3(s!1),ERK(Y187~u!1) @ 1
MKP3(s!1),ERK(Y187!1) -> MKP3(s),ERK(Y187) @ 1
  
```



the cascade no longer works - why?

