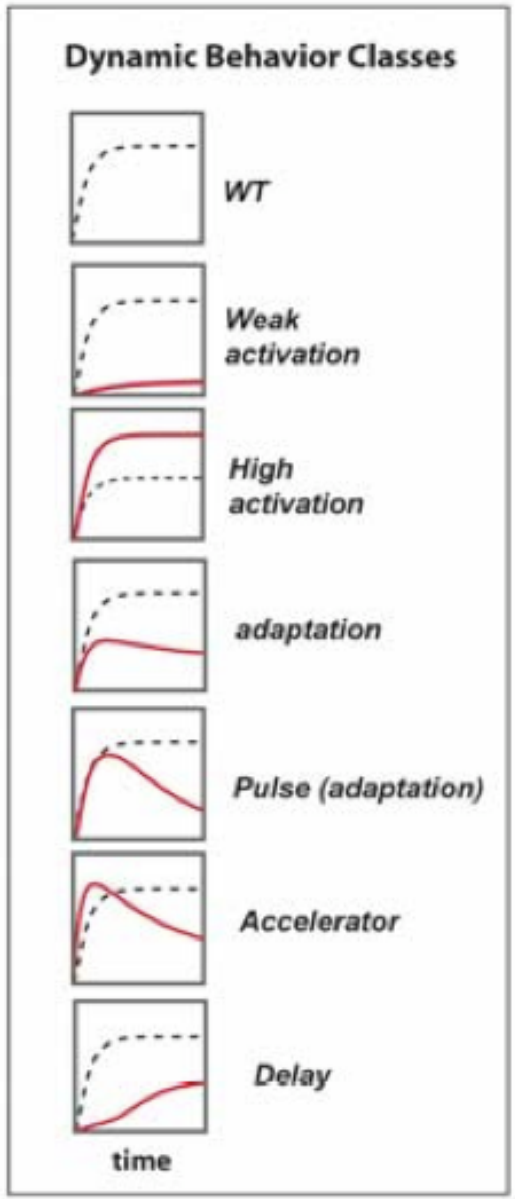
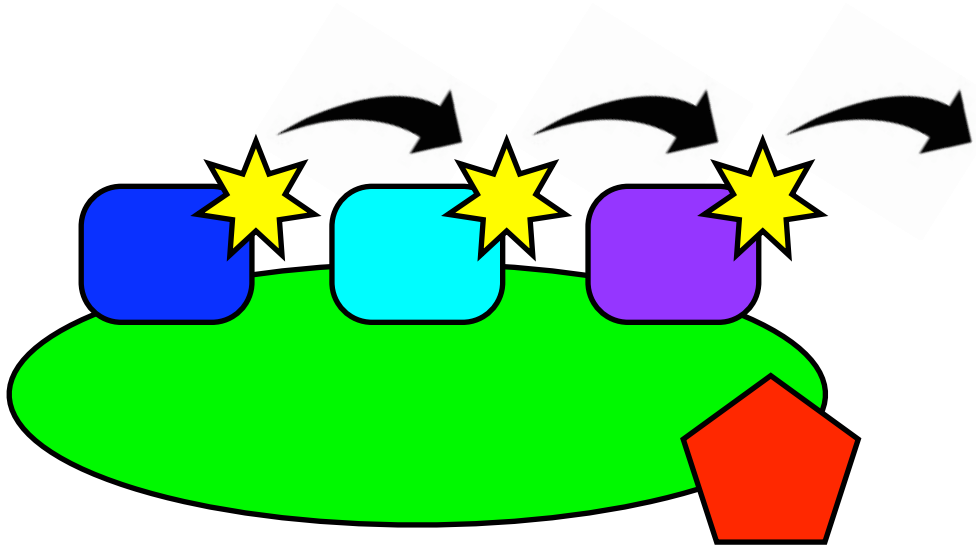


Using Engineered Scaffold Interactions to Reshape MAP Kinase Pathway Signaling Dynamics

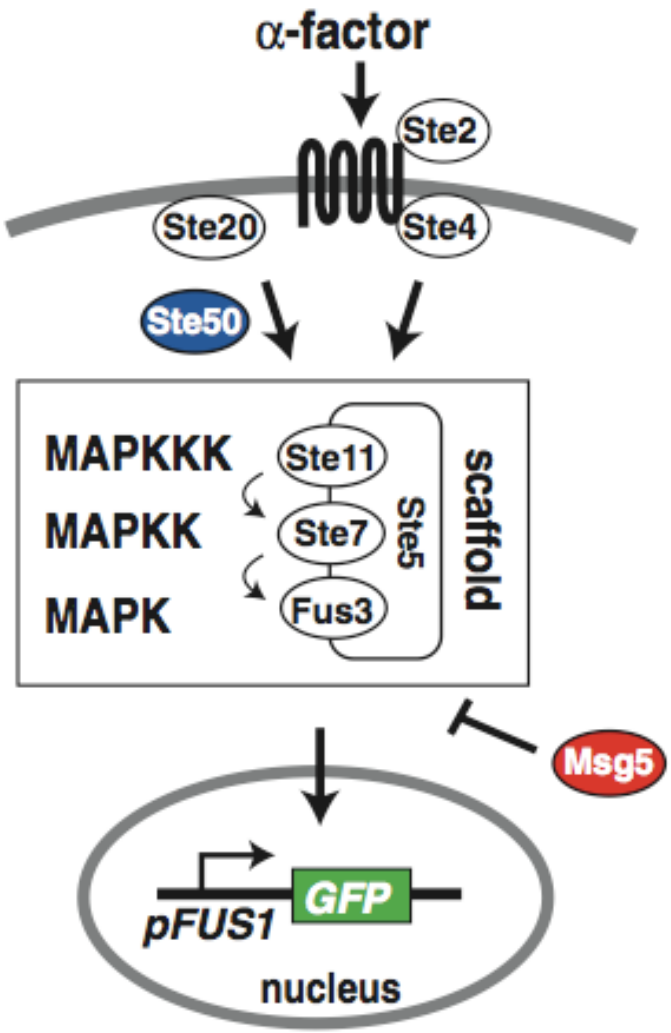
CJ Bashor, NC Helman, S Yan, WA Lim
Science, March 2008

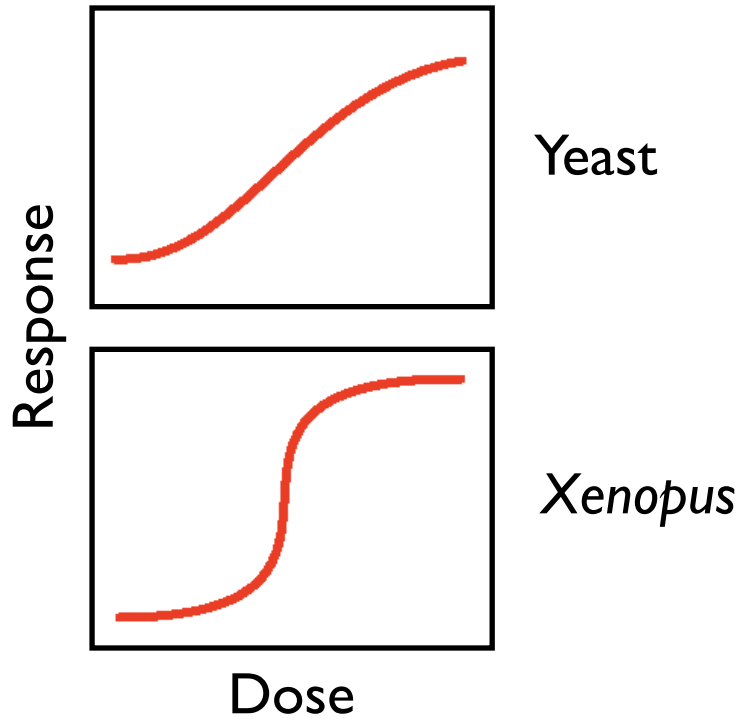
Kelly Drinkwater
20.385 Week 5
March 3, 2010

Scaffolds as regulation targets



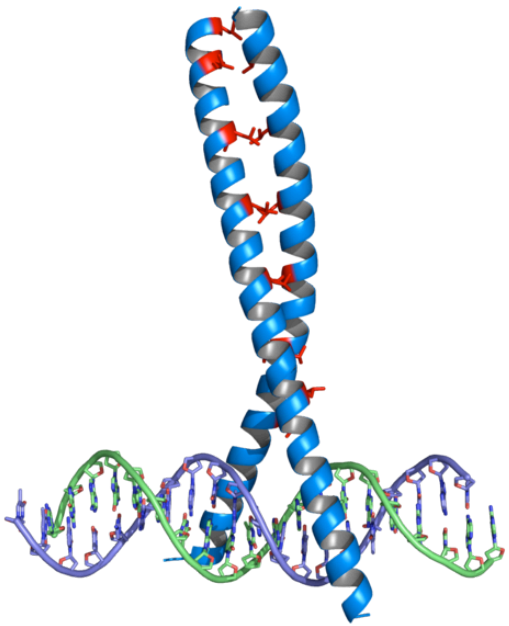
MAPK Pathway

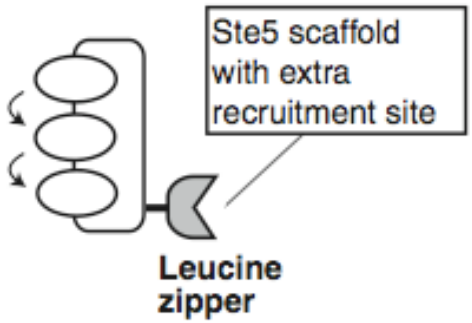


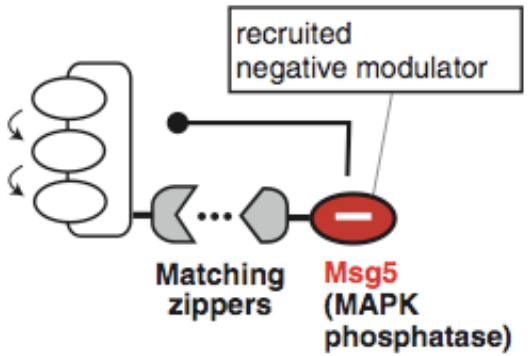


Core strategy: recruit regulators

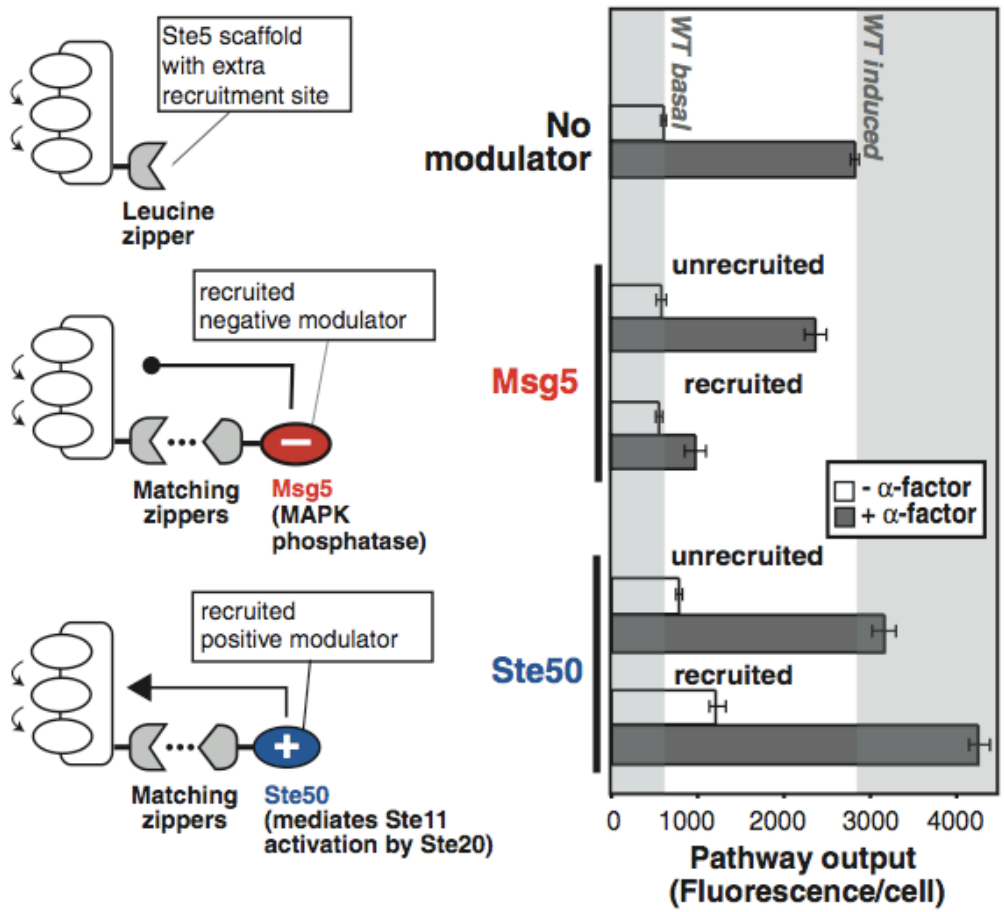
Leucine zipper (dimerization)



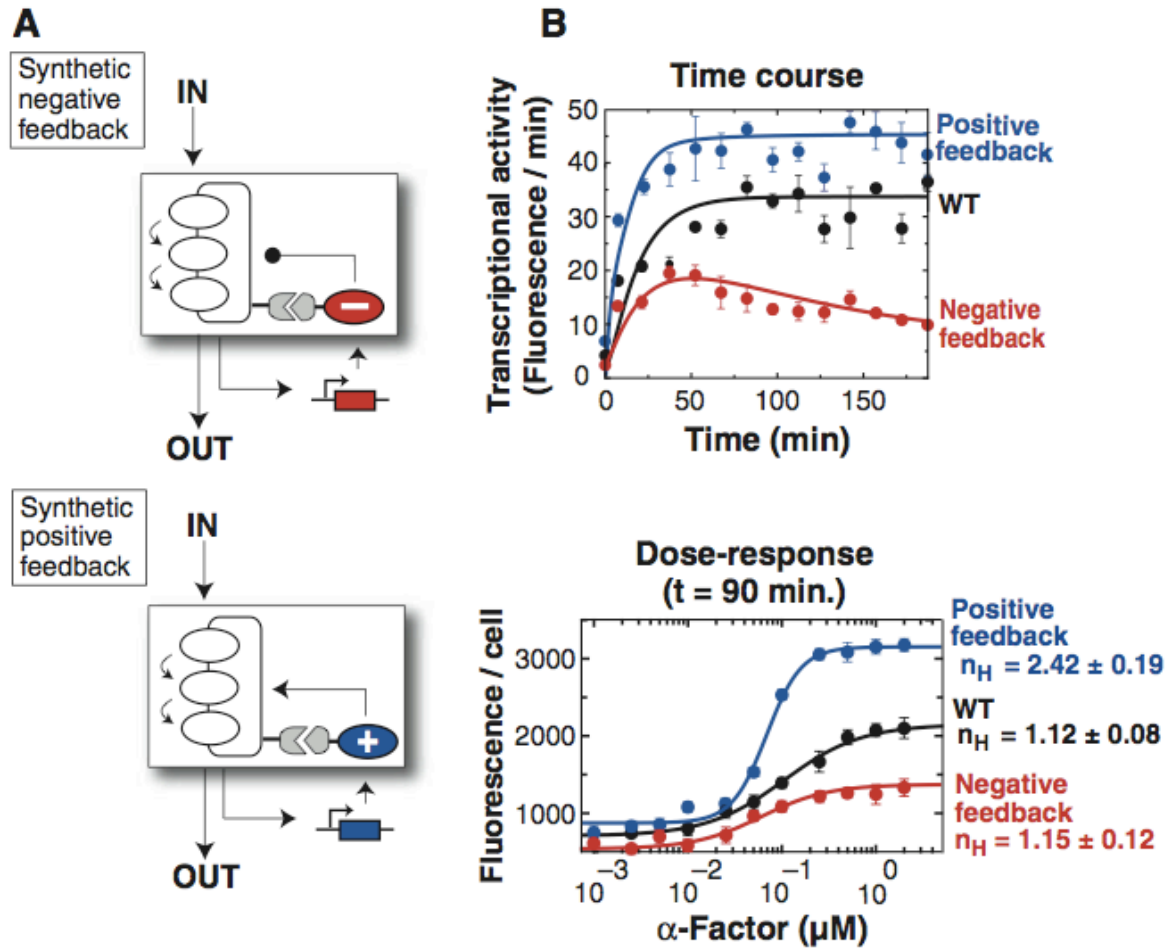




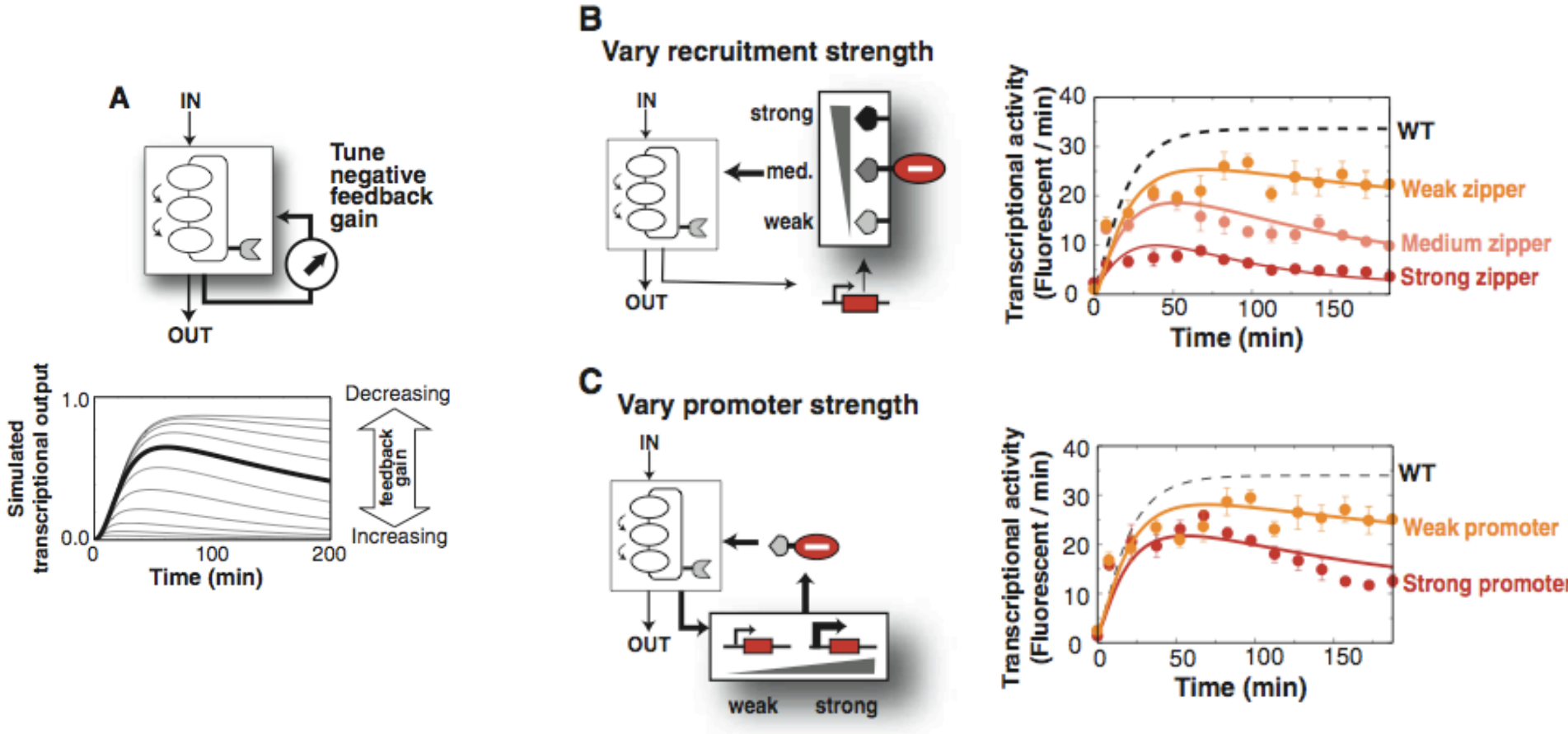
Recruited regulators work well



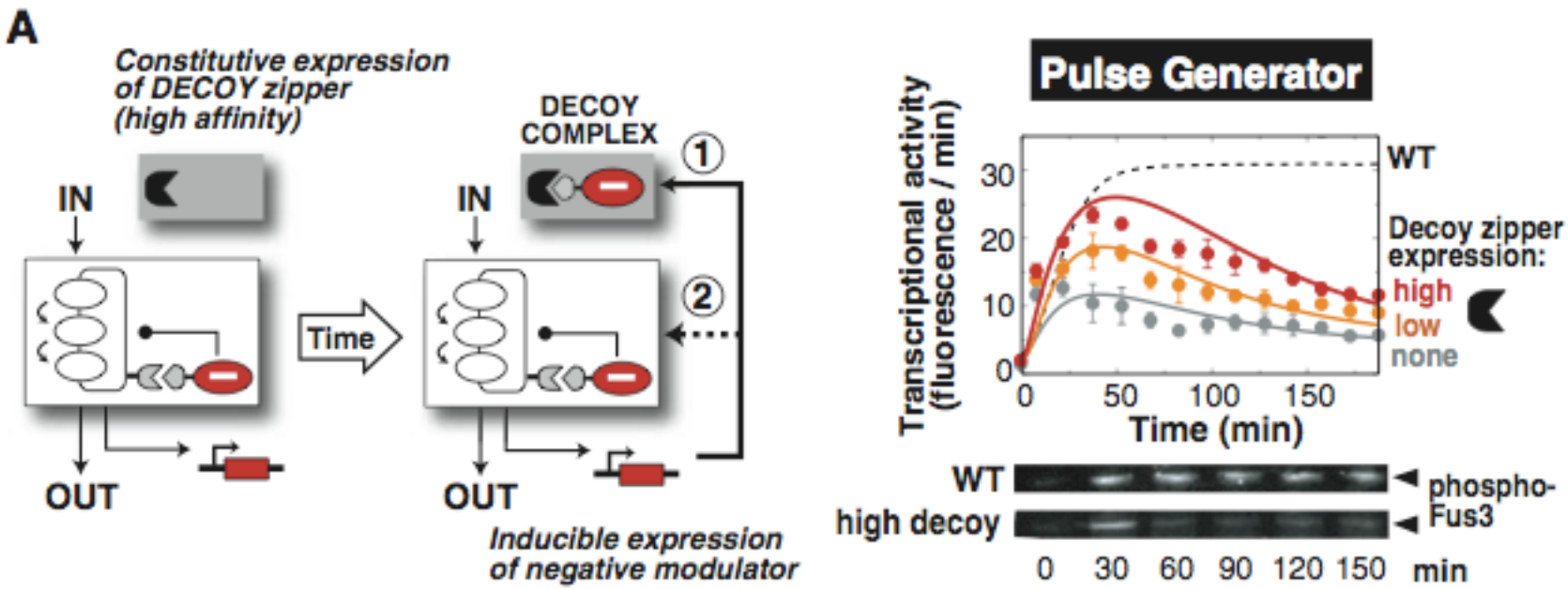
Simple feedback loops



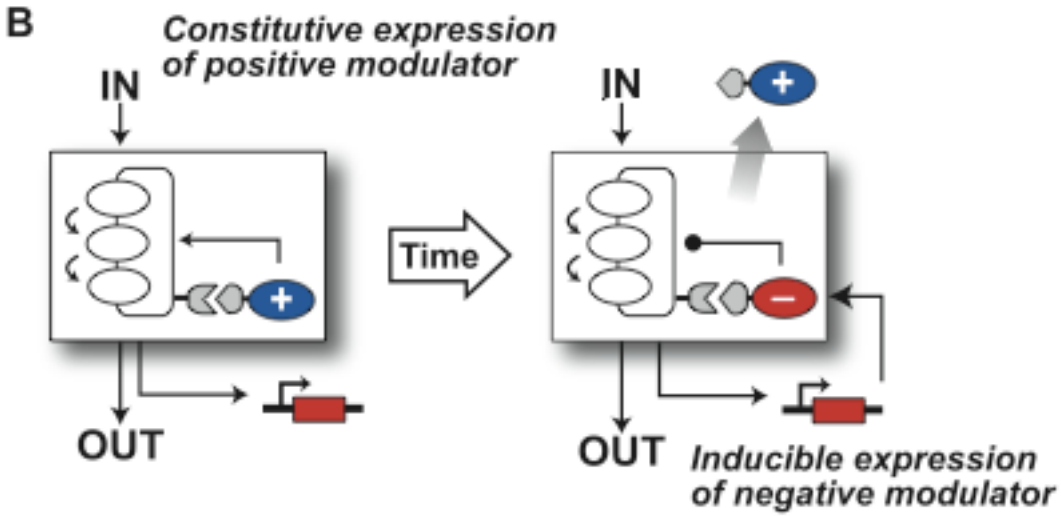
Adjusting gain of negative feedback

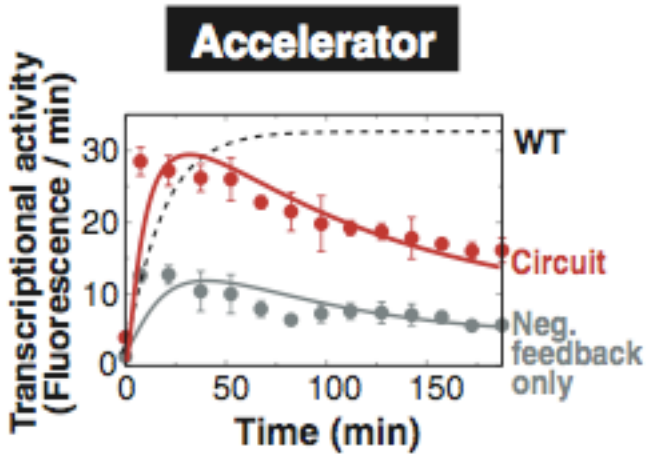


Pulse Generator

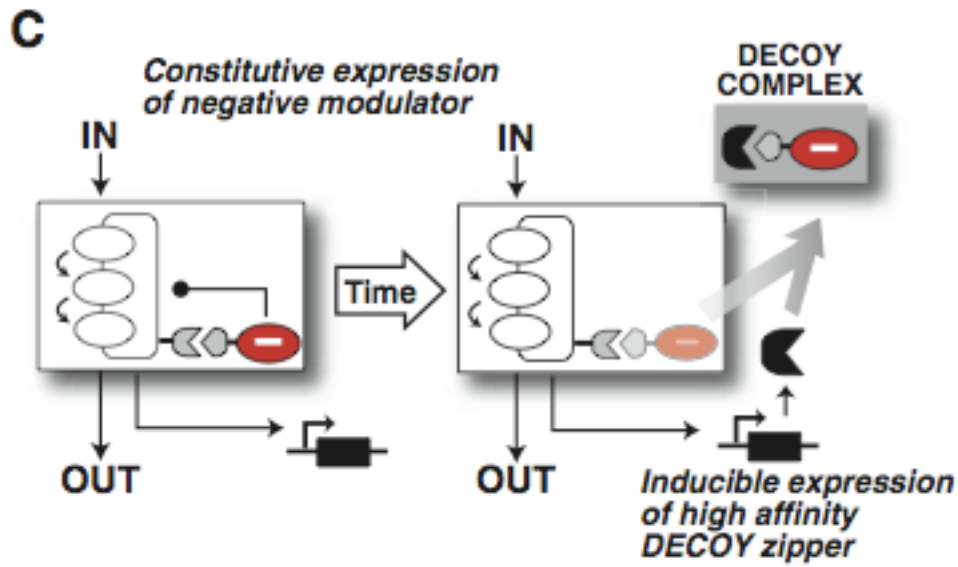


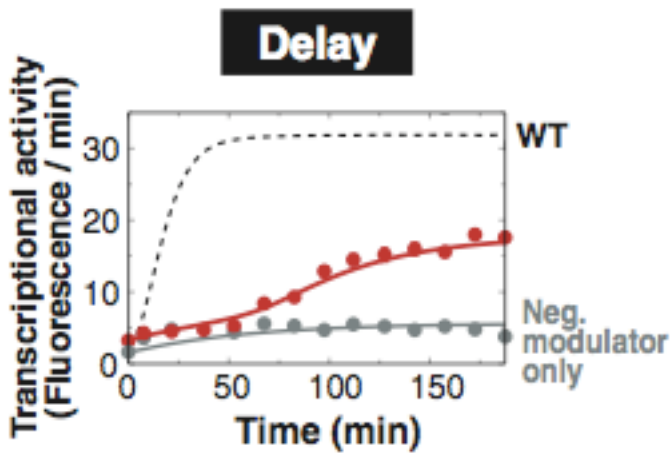
Accelerator



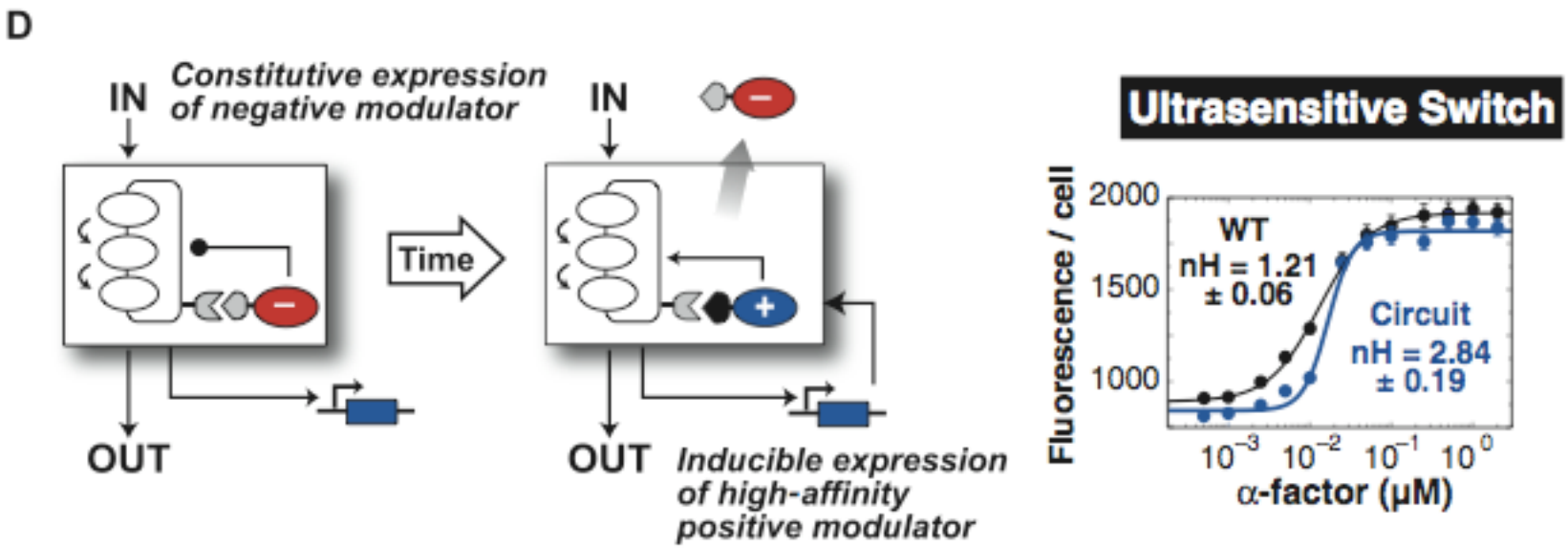


Delay

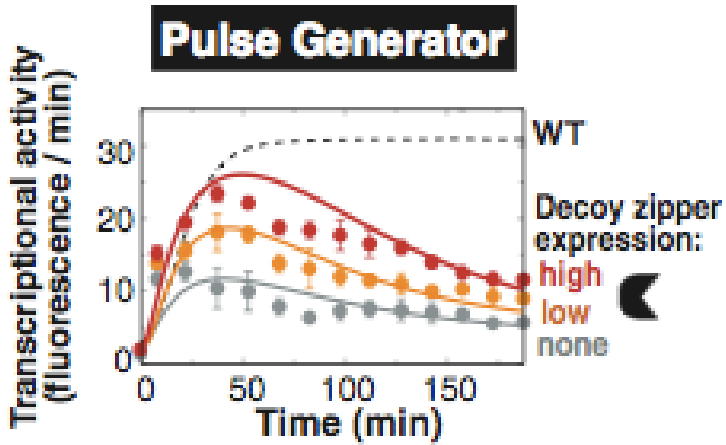

C
Constitutive expression
of negative modulator
IN
OUT
Time
IN
OUT
DECOY
COMPLEX
Inducible expression
of high affinity
DECOY zipper

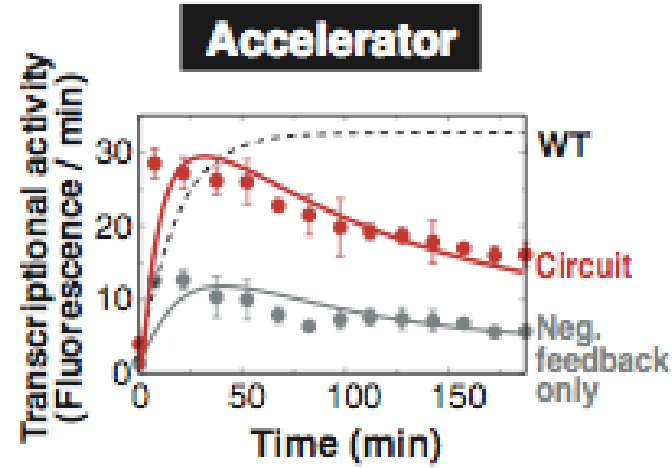

Delay
Transcriptional activity
(Fluorescence / min)
30
20
10
0
0
50
100
150
Time (min)
WT
Neg.
modulator
only

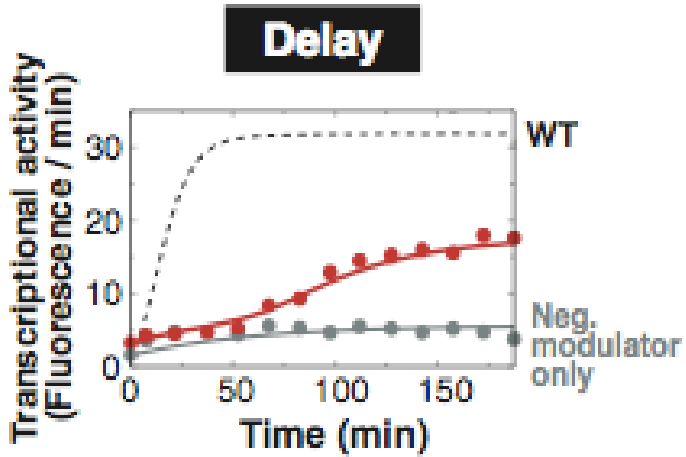
Switchlike

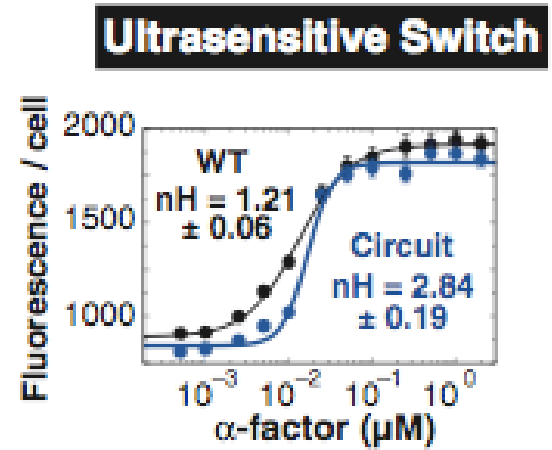

D
IN
Constitutive expression of negative modulator
Time
OUT
IN
OUT
Inducible expression of high-affinity positive modulator
Ultrasensitive Switch
Fluorescence / cell
2000
1500
1000
WT
nH = 1.21
± 0.06
Circuit
nH = 2.84
± 0.19
10^-3
10^-2
10^-1
10^0
α-factor (μM)

Comparing all four









Different behaviors -- *functionally* distinct?

Can you drive a complex downstream circuit? (Like what?)

Can you drive a cellular behavior such as invasion?

Why didn't they do so?