Noise Can Induce Bimodality in Positive Transcriptional Feedback Loops Without Bistability

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Carles Boix

- Bistable response explained by deterministic models.
- Seek to determine the role of noise in bimodality in cell populations.
- *Can noise induce bimodality in positive feedback loops?*

A possible explanation for switch-like bistability:
Hill Equation for fraction of occupied binding sites Θ, ligand concentration $[L]$, and dissociation constant K_d:

$$\Theta = \frac{[L]^n}{K_d + [L]^n}$$

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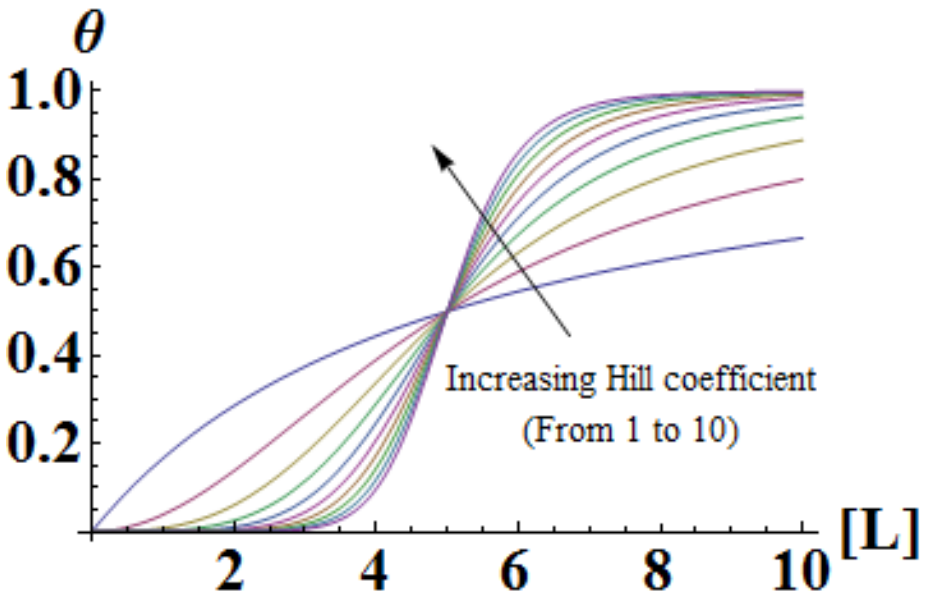
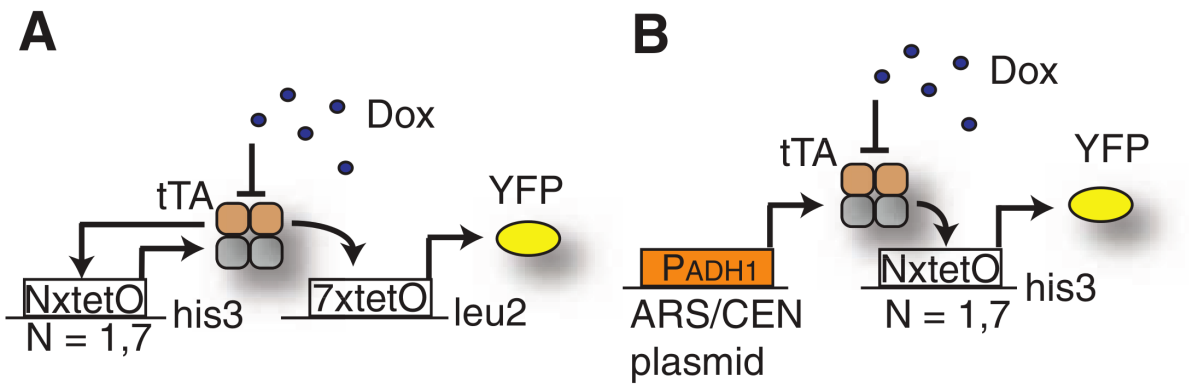
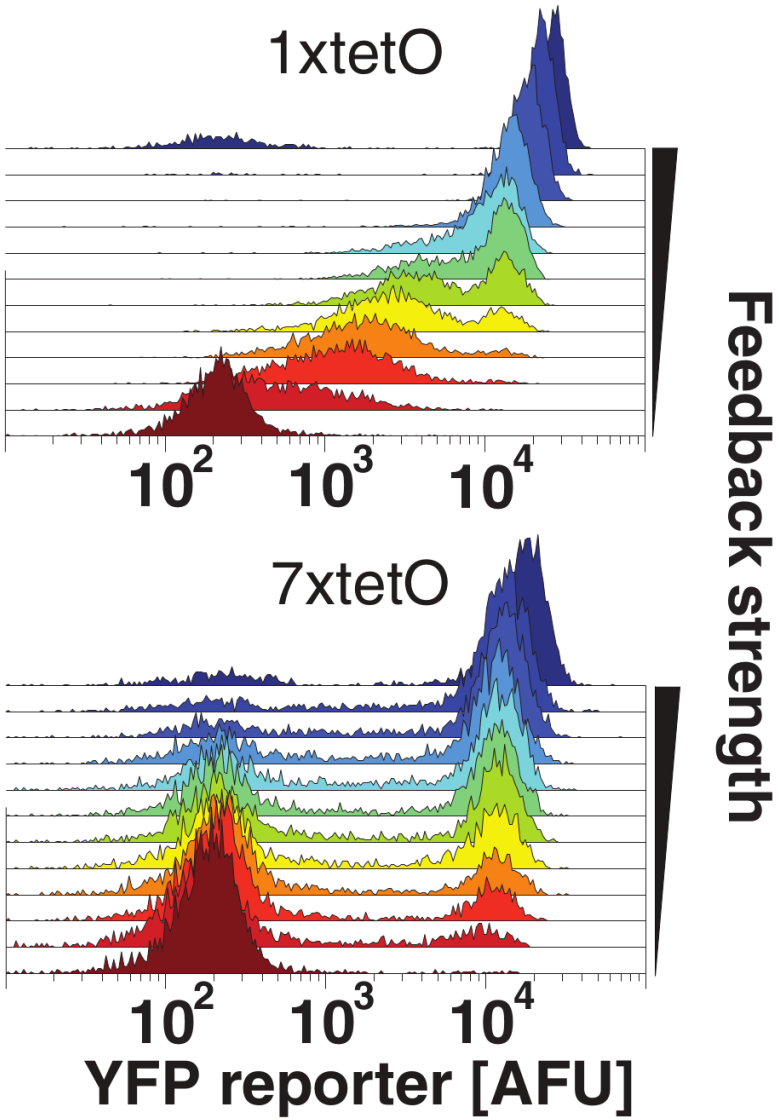
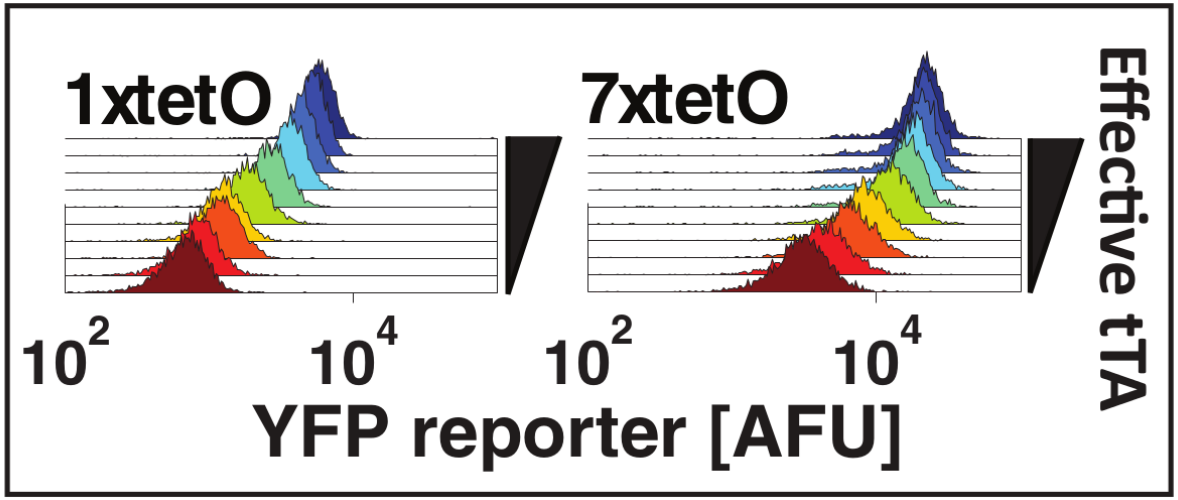
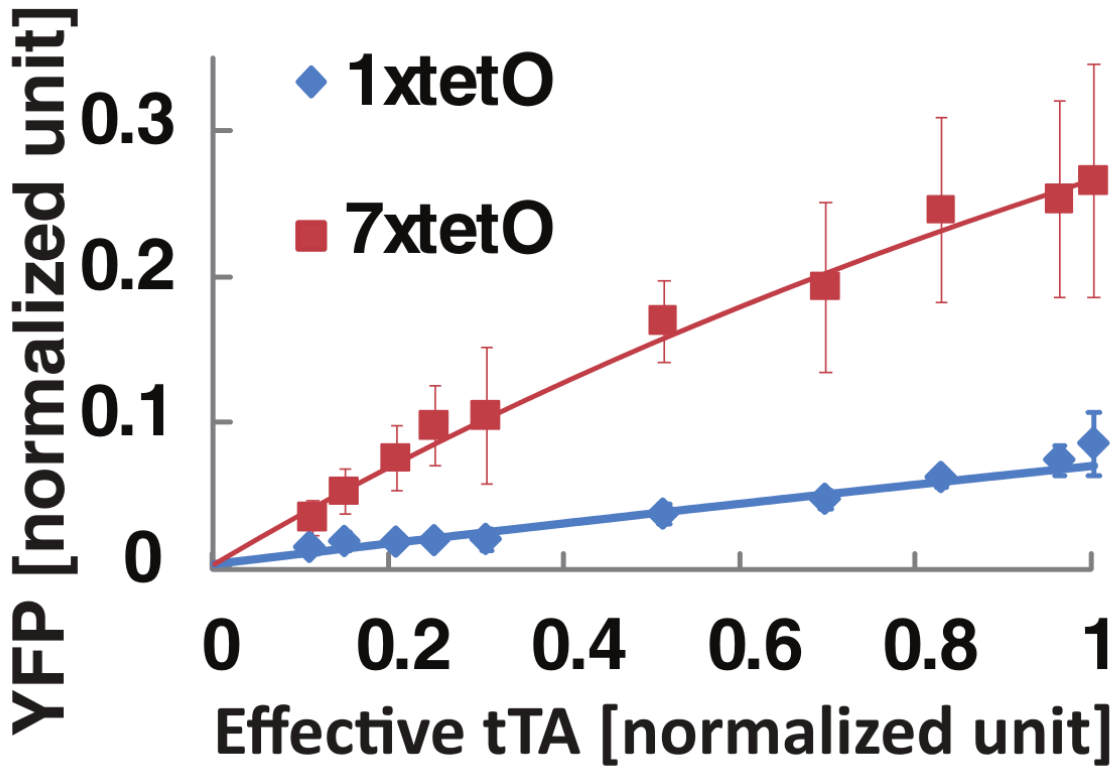




Closed-loop and open-loop systems


1xtetO
7xtetO
Feedback strength
10^2
10^3
10^4
YFP reporter [AFU]


1xtetO
7xtetO
Effective tTA
10^2
10^4
10^2
10^4
YFP reporter [AFU]


YFP [normalized unit]
0.3
0.2
0.1
0
1xtetO
7xtetO
0
0.2
0.4
0.6
0.8
1
Effective tTA [normalized unit]

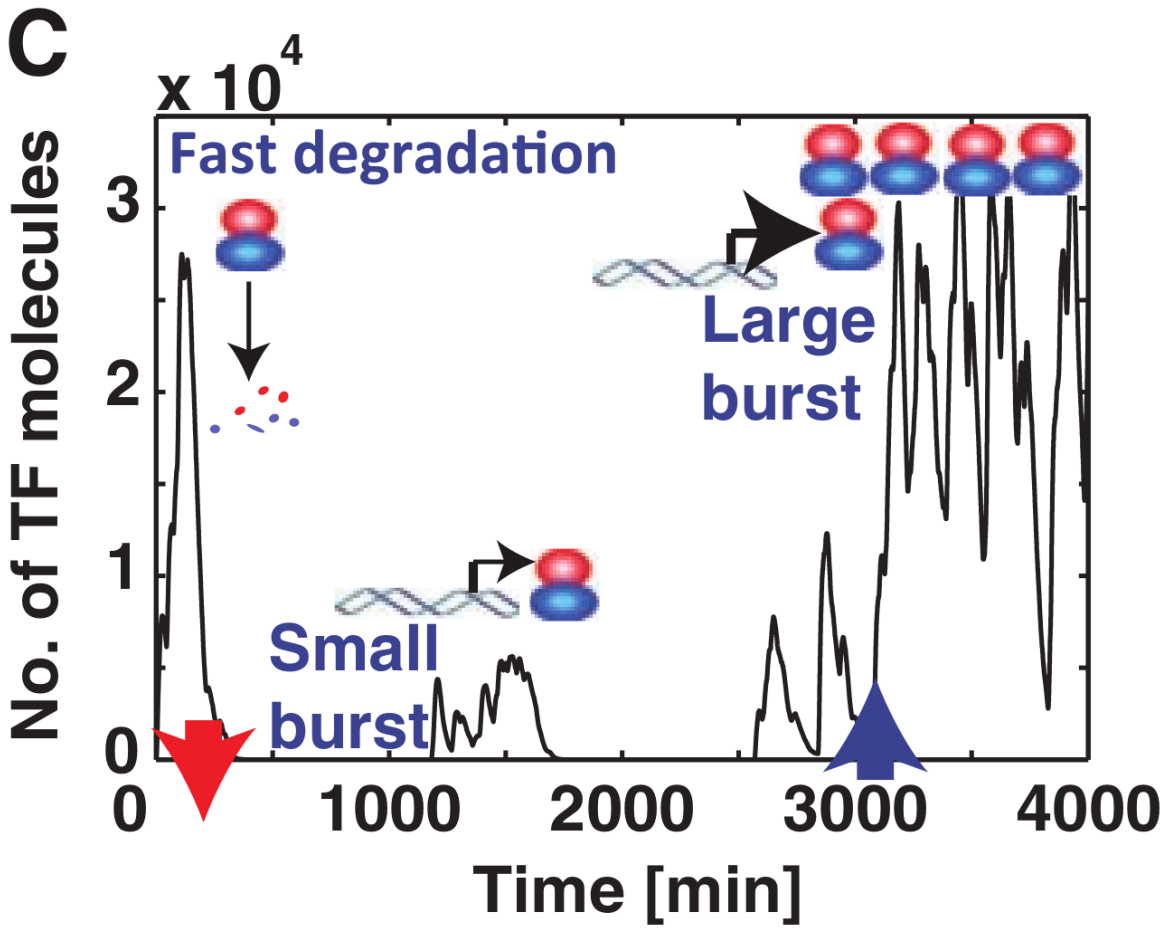
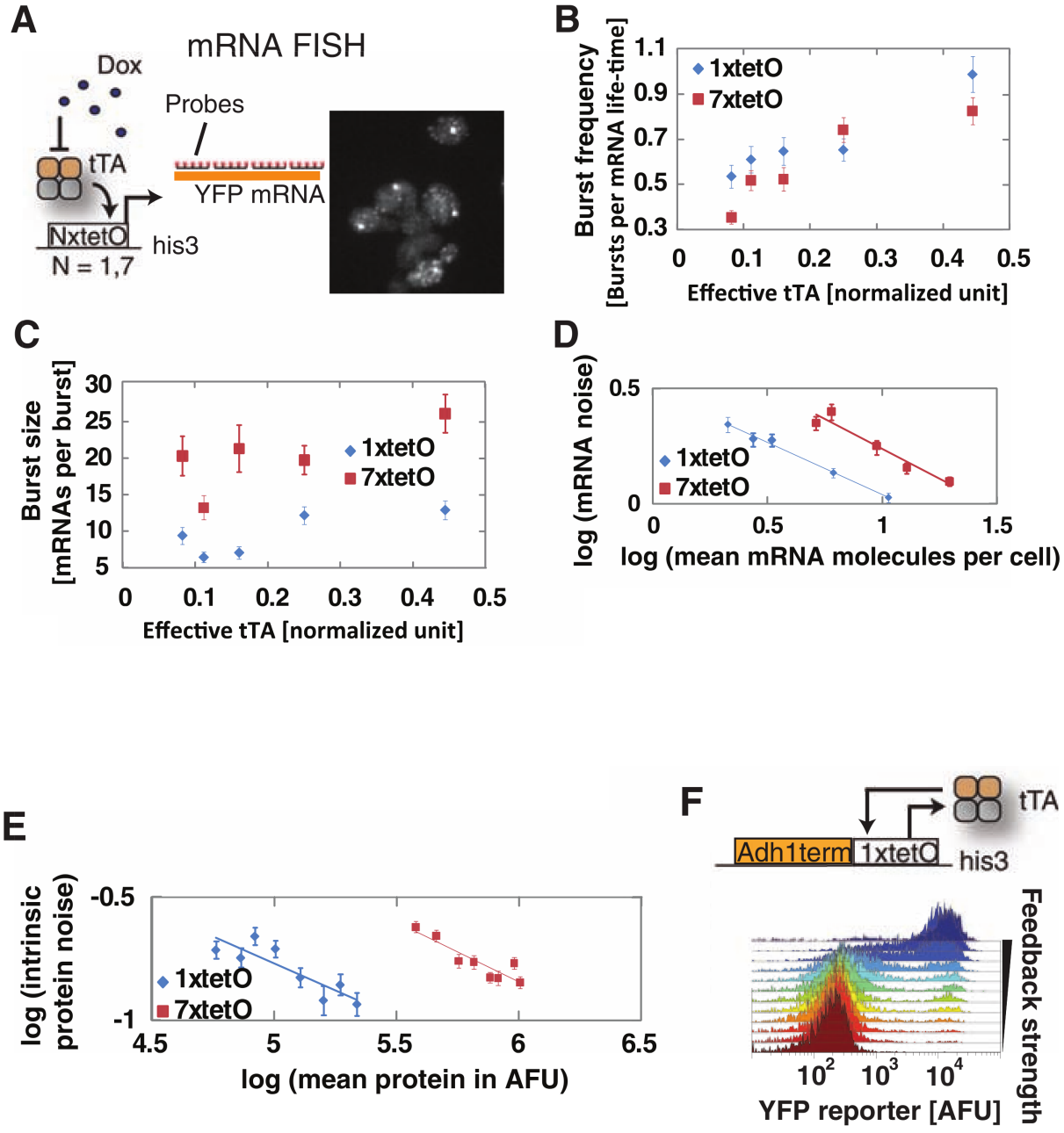


Figure : Simulation of transcriptional noise


A
mRNA FISH
Dox
Probes
tTA
YFP mRNA
NxtetO
his3
N = 1,7
B
Burst frequency [Bursts per mRNA life-time]
1xtetO
7xtetO
Effective tTA [normalized unit]
C
Burst size [mRNAs per burst]
1xtetO
7xtetO
Effective tTA [normalized unit]
D
log (mRNA noise)
1xtetO
7xtetO
log (mean mRNA molecules per cell)
E
log (intrinsic protein noise)
1xtetO
7xtetO
log (mean protein in AFU)
F
tTA
Adh1term
1xtetO
his3
Feedback strength
YFP reporter [AFU]

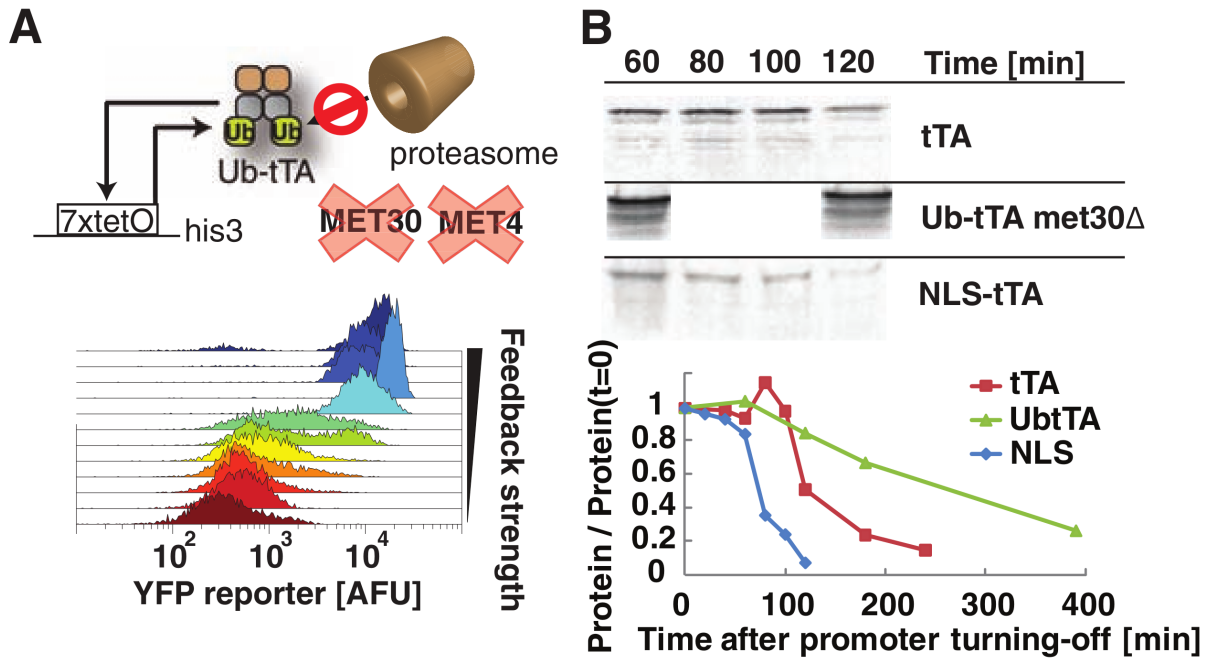
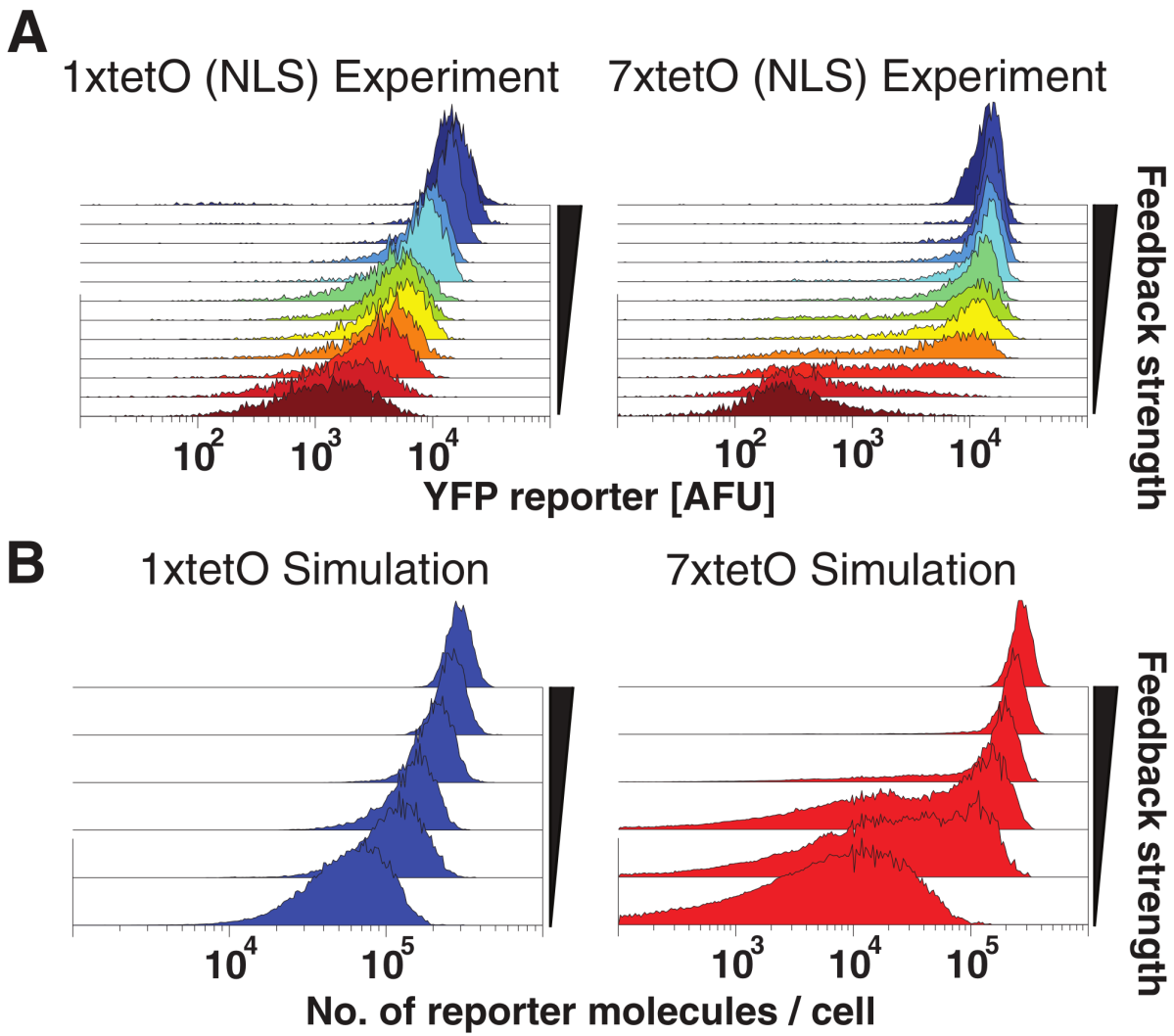


Figure : Test of model by stabilizing TF


A
1xtetO (NLS) Experiment
7xtetO (NLS) Experiment
Feedback strength
10^2 10^3 10^4
YFP reporter [AFU]
B
1xtetO Simulation
7xtetO Simulation
Feedback strength
10^4 10^5
10^3 10^4 10^5
No. of reporter molecules / cell

- Noise can induce bimodality.
- System relies on having large and infrequent bursts of transcription.
- The 7xtetO has high sensitivity high noise.
- Can achieve this by having a unstable TF. For example, $t_{1/2} =\sim 15$ minutes.