In Silico Feedback for *In Vivo* Regulation of a Gene Expression Circuit.

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Feedback Control

- Regulation of Cell Behavior
- Feedback Control Important for Regulation
  - Processing measurements in real time
  - Determining inputs
- Robust regulation can be achieved!

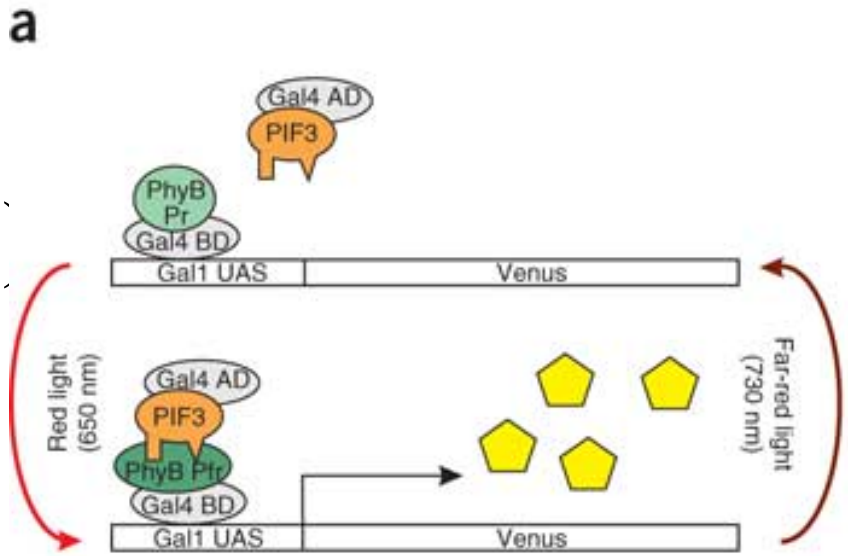
In Silico Feedback Control

- *In silico* – Performed on Computer or via Computer Simulation

- *In silico* feedback
  - Computer
  - Real time data
  - Inputs
  - Regulation

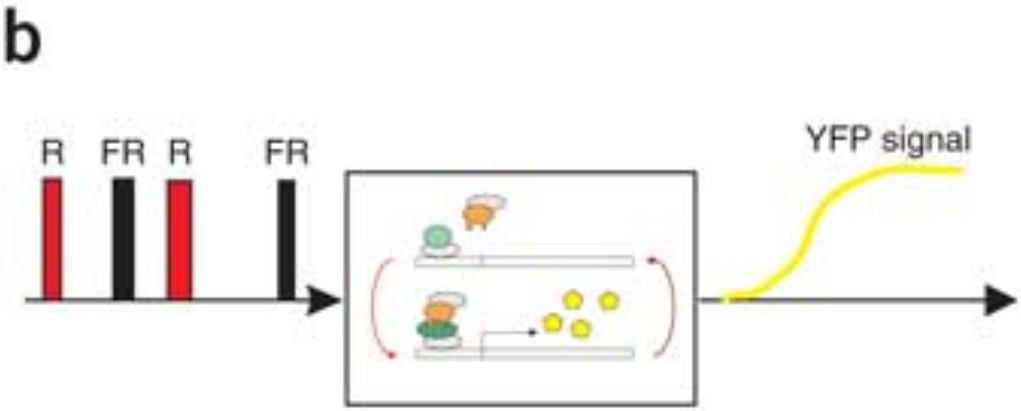
Implementation

- *S. cerevisiae*
- Light-switchable system (PhyB-PIF3)
- Transformed cells
  - Grown in Dark
  - PCB

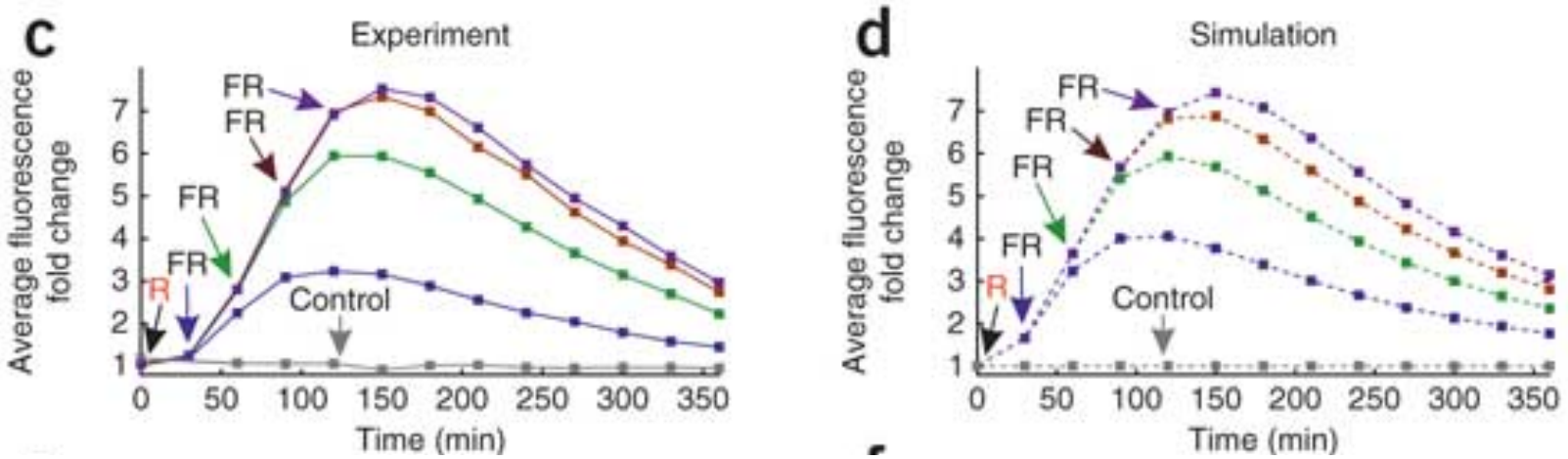


Exposure to Light

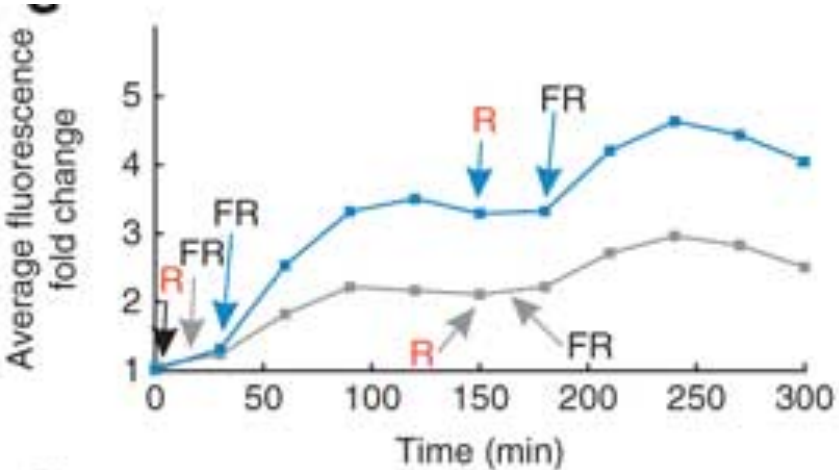
- Red (650 nm) and Far Red (730 nm) Pulses
- Input – Light Pulses
- YFP expression
- Output - YFP

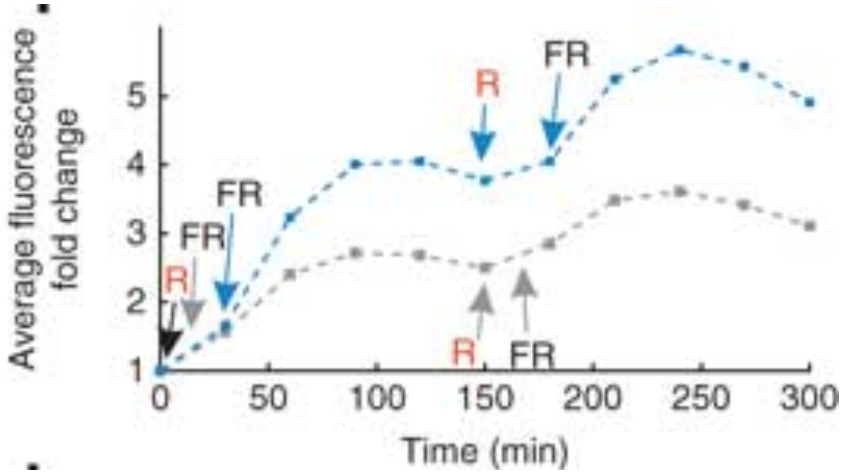


Results

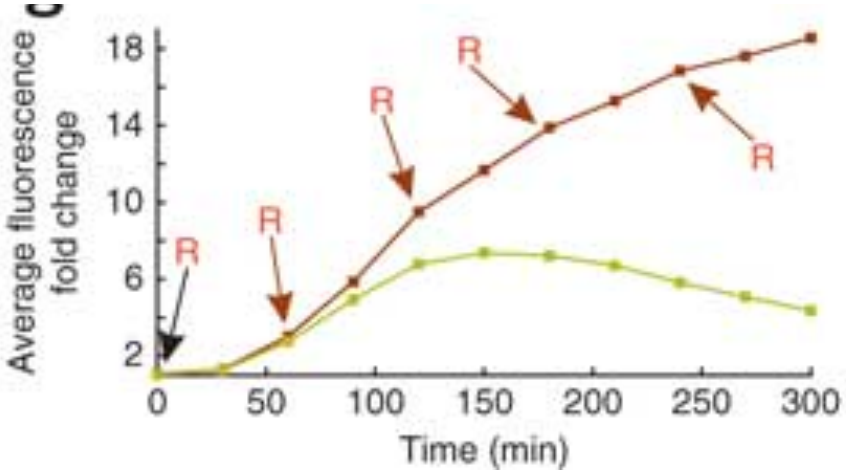

c
Experiment
Average fluorescence fold change
FR
FR
FR
FR
R
Control
1
2
3
4
5
6
7
0
50
100
150
200
250
300
350
Time (min)
d
Simulation
Average fluorescence fold change
FR
FR
FR
FR
R
Control
1
2
3
4
5
6
7
0
50
100
150
200
250
300
350
Time (min)

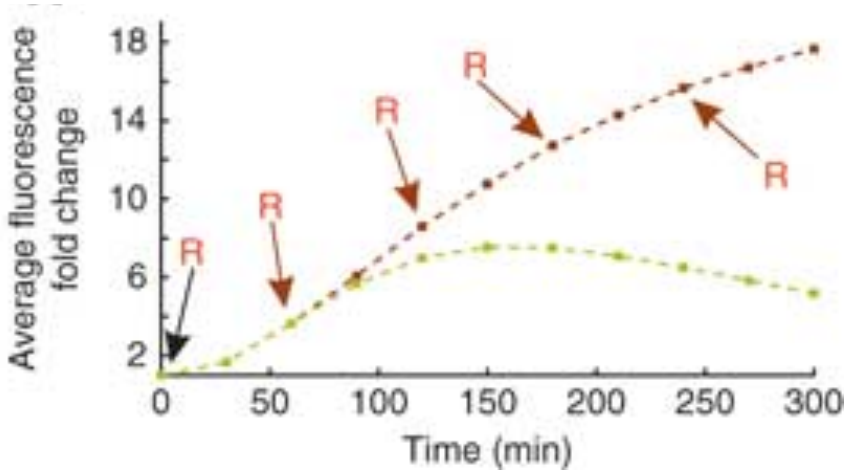
Results


Average fluorescence
fold change
1
2
3
4
5
0
50
100
150
200
250
300
Time (min)
R
FR
R
FR
R
FR


Average fluorescence
fold change
1
2
3
4
5
0
50
100
150
200
250
300
Time (min)
R
FR
FR
R
FR
R
FR

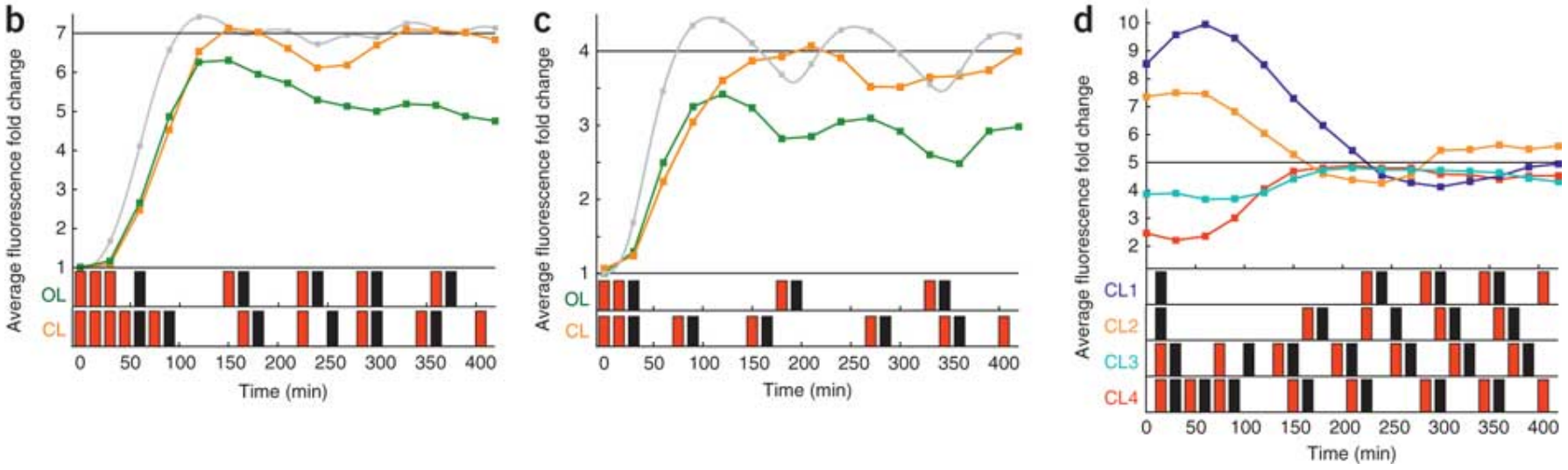
Results


Average fluorescence
fold change
18
14
10
6
2
0
50
100
150
200
250
300
Time (min)
R
R
R
R
R

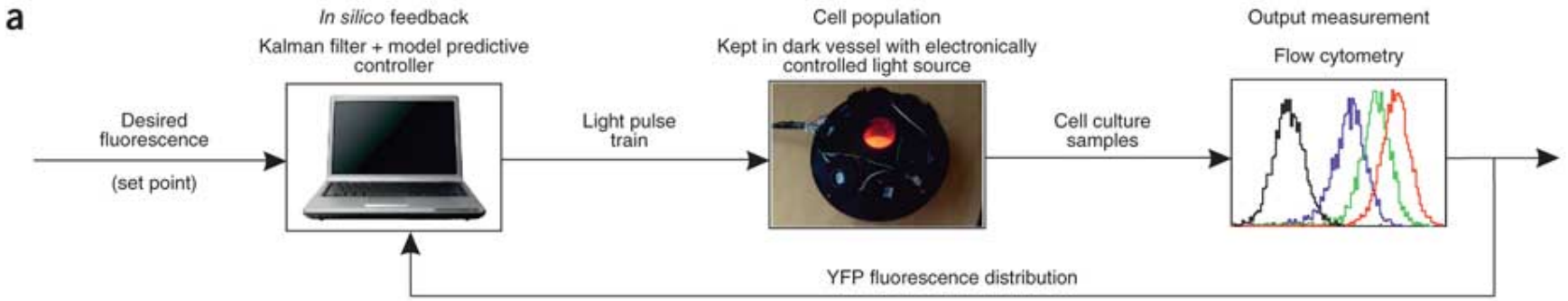

Average fluorescence
fold change
18
14
10
6
2
0
50
100
150
200
250
300
Time (min)
R
R
R
R
R

Using a Kalman Filter

- Real Time Regulation



Summary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In silico feedback
Kalman filter + model predictive controller
Cell population
Kept in dark vessel with electronically controlled light source
Output measurement
Flow cytometry
Desired fluorescence
(set point)
Light pulse train
Cell culture samples
YFP fluorescence distribution

Significance

- Enhancement of expression
- Electronic control over living cells
- Therapeutics
  - Regulation of expression
  - Regulation of toxic by-products

Questions?

Light Pulse Delivery System