Toward Real-Time Control of Gene Expression

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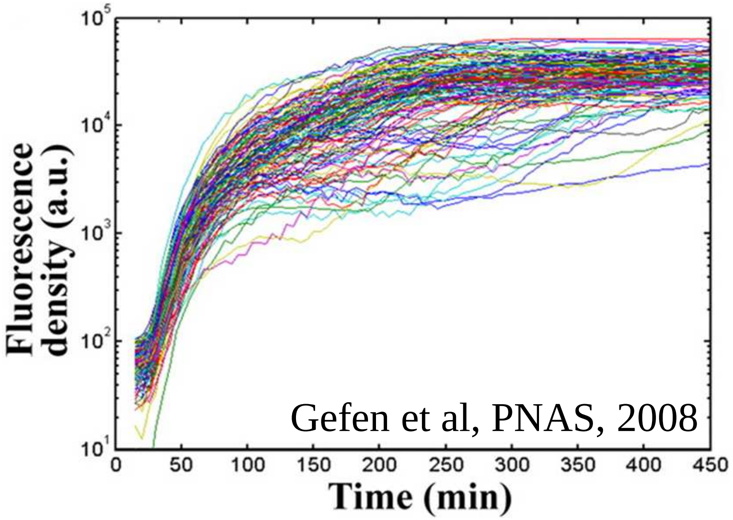
Motivation

- Need for controlling gene expression
  - biotech and synthetic biology applications: process optimization
  - systems biology studies: challenge system dynamics by perturbations (understanding/identification)
- Existing tools for controlling protein levels
  - genetic knock-outs, knock-ins
  - various forms of RNA interferences, riboregulators, riboswitches
  - **inducible promoters** (pLac, pTet, pMet,…)
    - amenable to dynamical control
    - broad dynamical range
    - but cell response is highly heterogeneous

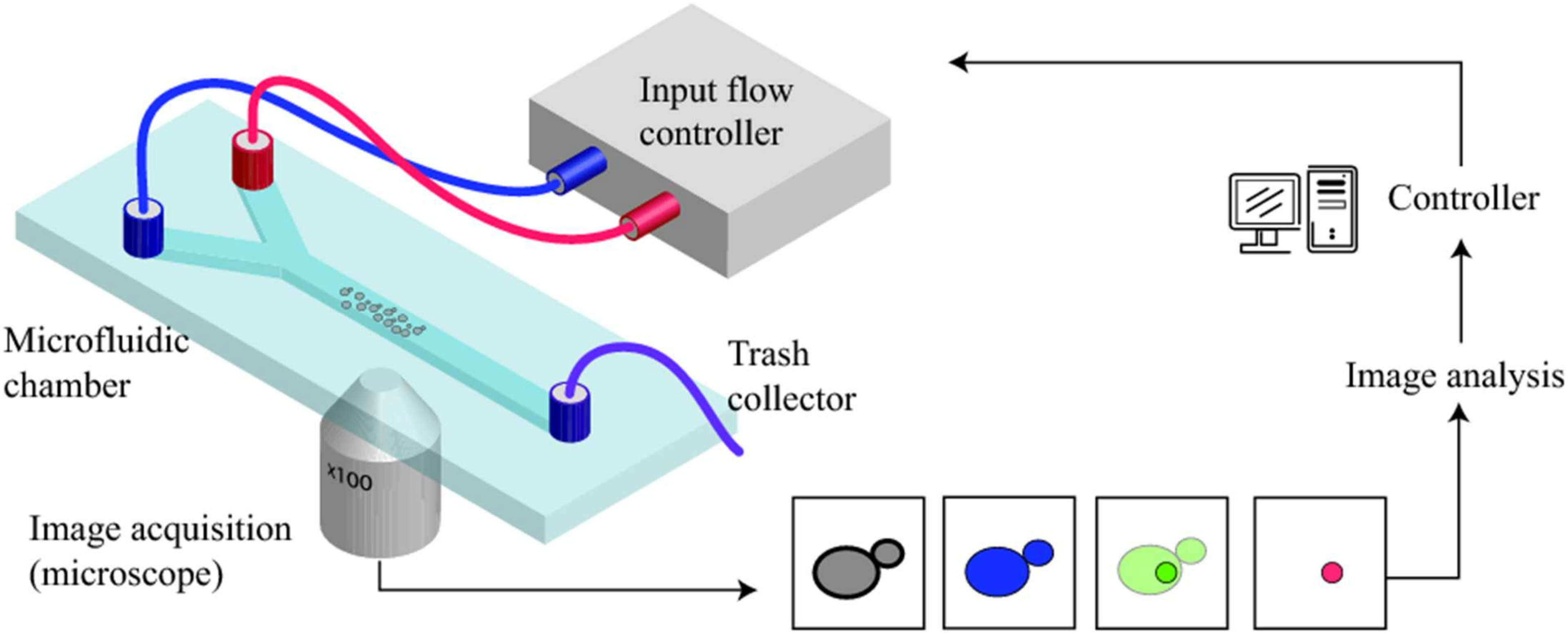


- **Need for experimental tools for tight control of gene expression**

Outline

- Control platform and controlled system
- *In vivo* control of a signal transduction pathway
- *In silico* control of gene expression

A closed loop control platform



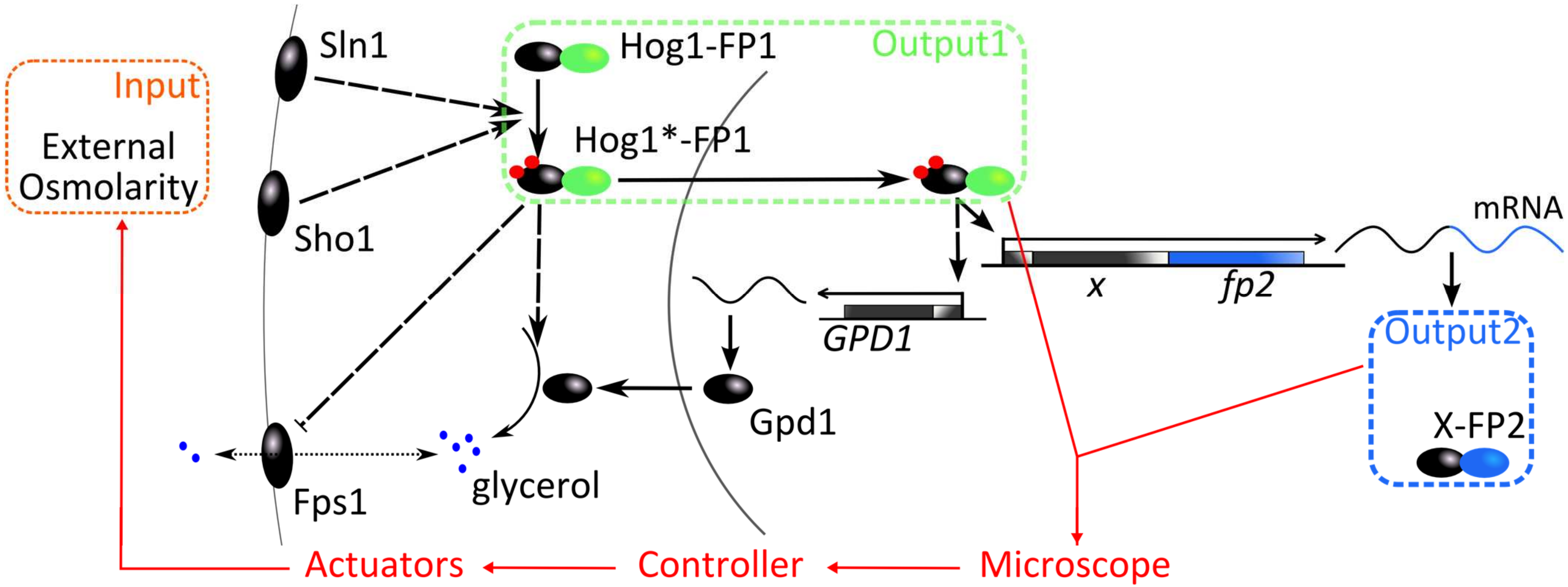
❖ Closed loop constraints

- real-time stimulation
- real-time observation & image analysis
- real-time control strategy computation

The controlled system

- Control of an hyperosmotic stress response gene in yeast

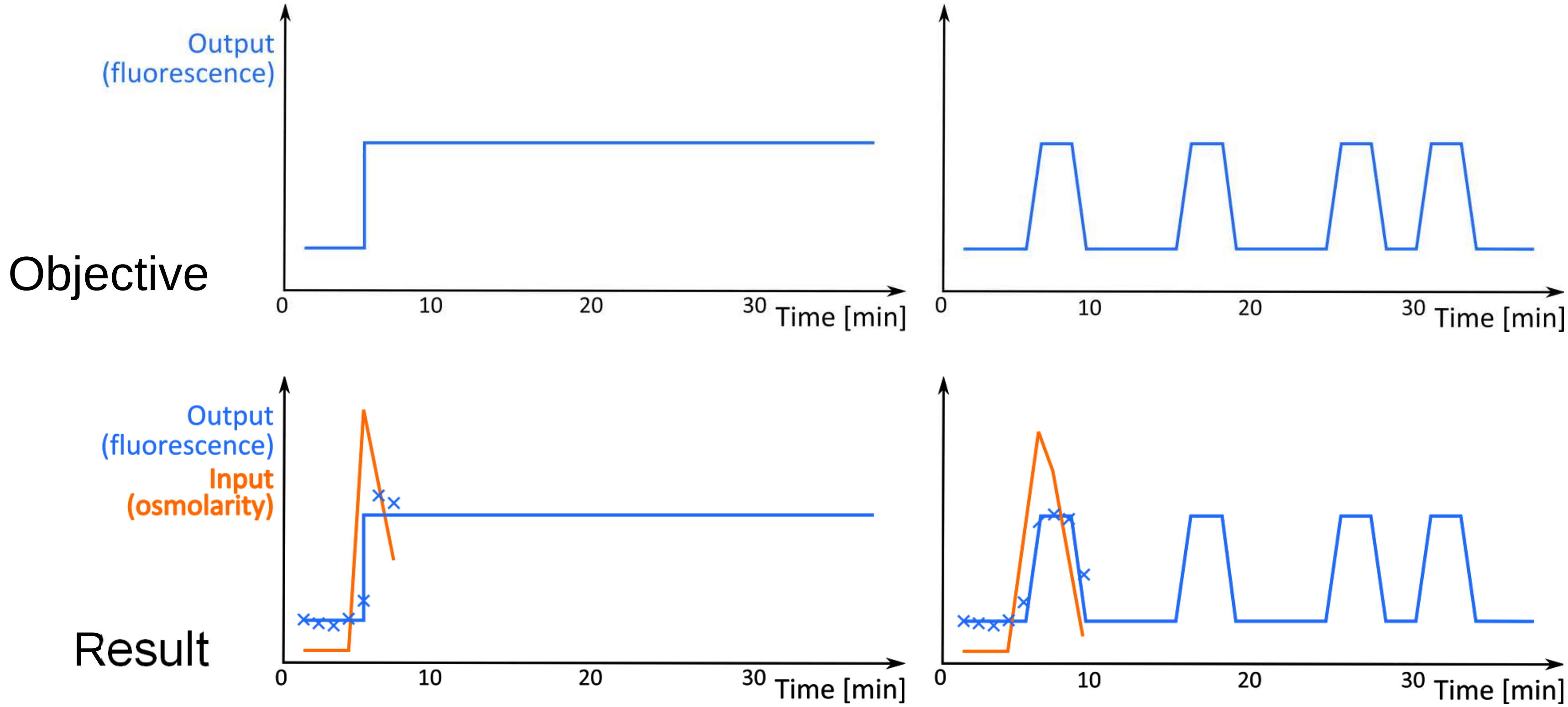
  HOG pathway well known, rapid actuation, quantifiable signal transduction, natural pathway



The control problem

❖ Control setup

- input: osmolarity
- output: (Hog1 nuclear enrichment and) protein concentration
- problem: find inputs to apply to achieve a desired behavior



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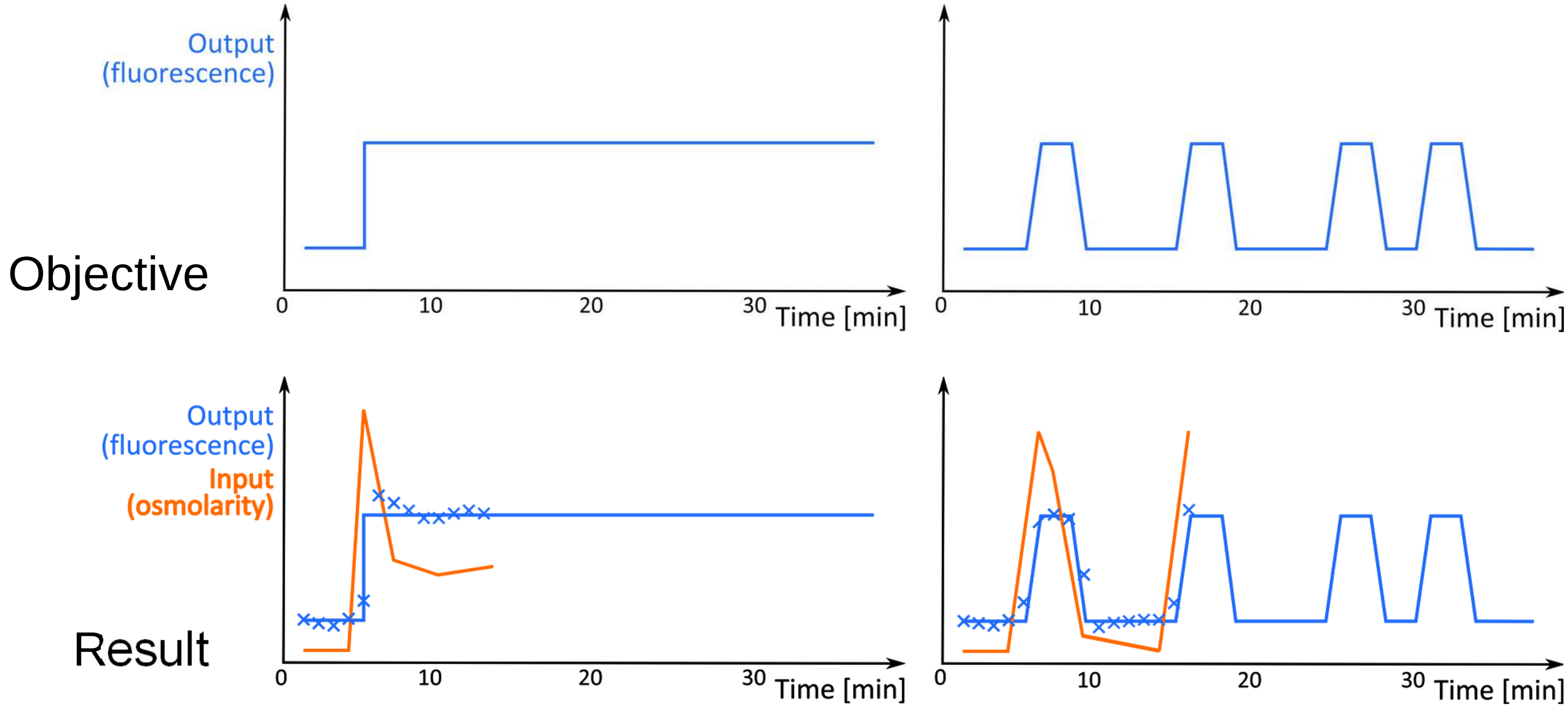

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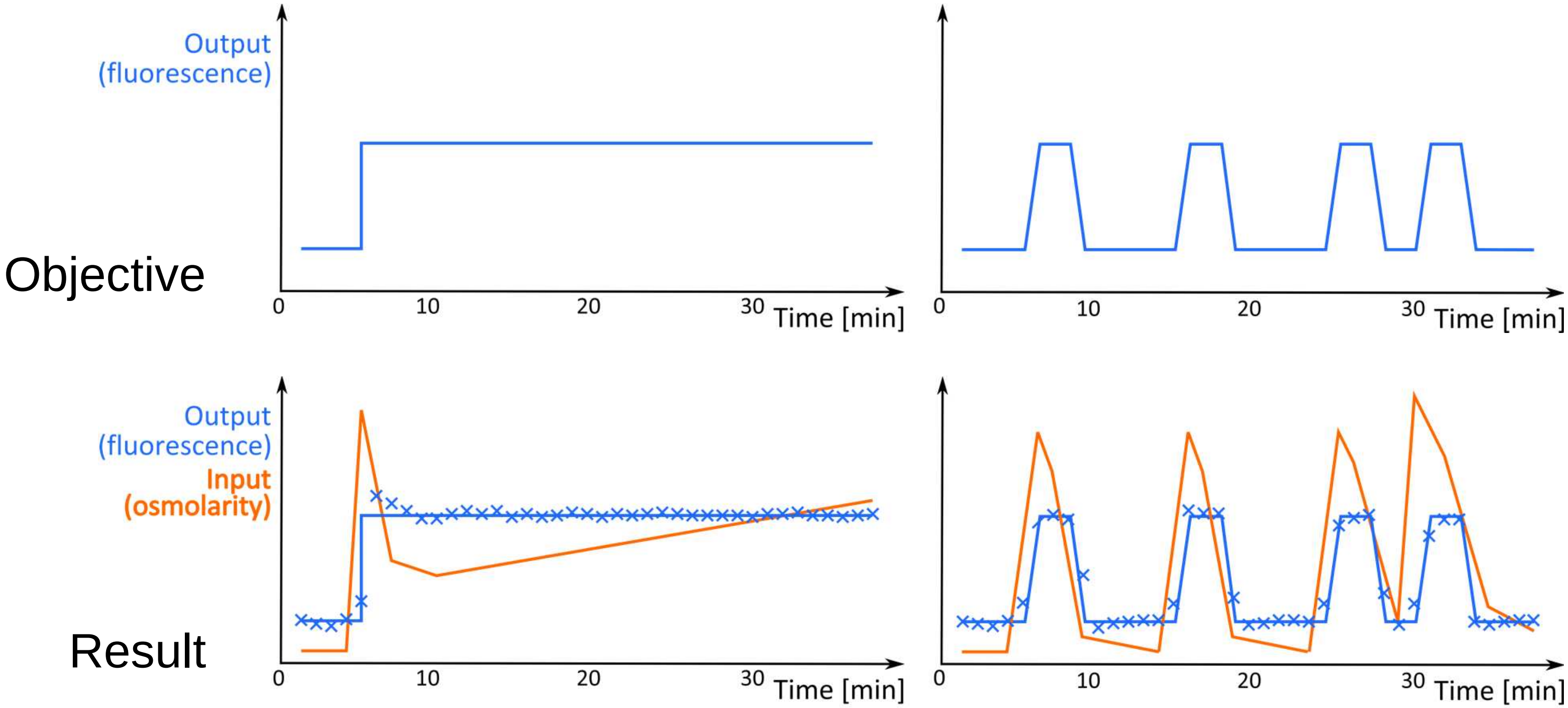

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in vivo signal transduction control

- Control setup: input is osmolarity, output is Hog1 nuclear localization
- Use of a simple proportional-integral controller
  - input depends on current and recent past differences between desired and observed outputs: $u(t) = k_1\, e(t) + k_2 \int_{t-\delta}^{t} e(\tau) d\tau$
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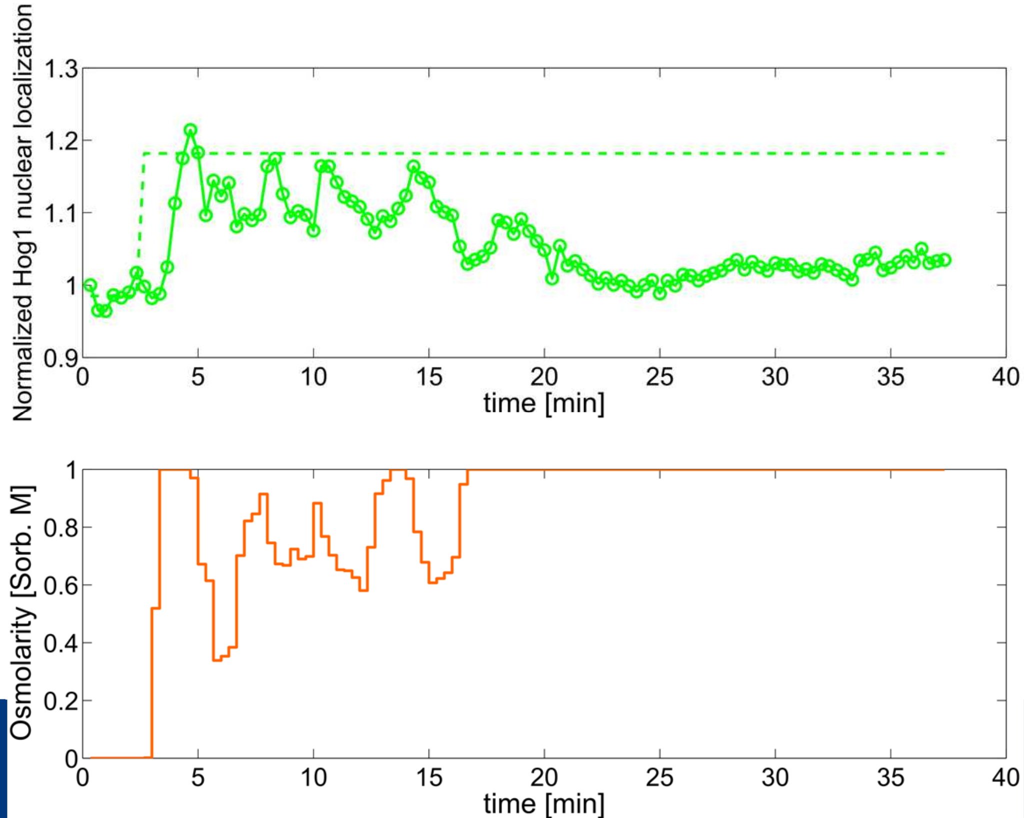
- Step control experiment
  - PI-controller is effective
  - Sustained activation not possible (cell shows perfect adaptation)



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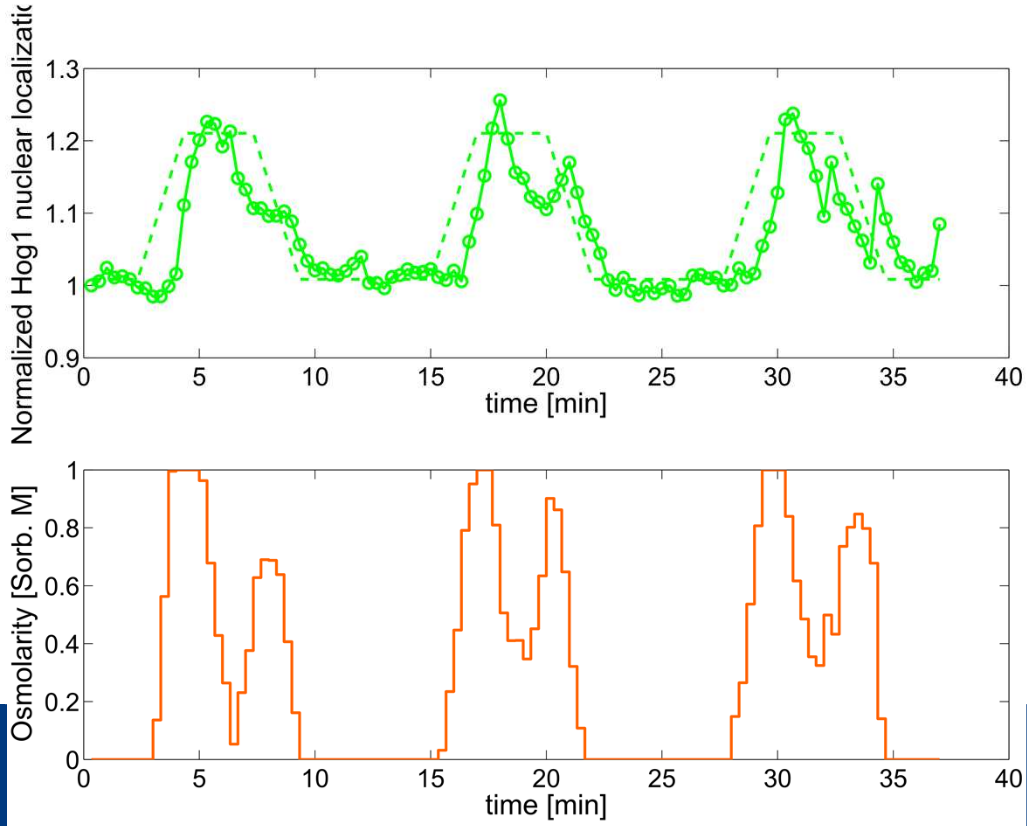
- Pulse control experiment
  - Repeated pulses are achievable: towards **pulse-modulated** gene expression control
  - Still room for improvement (time lag, reproducibility)



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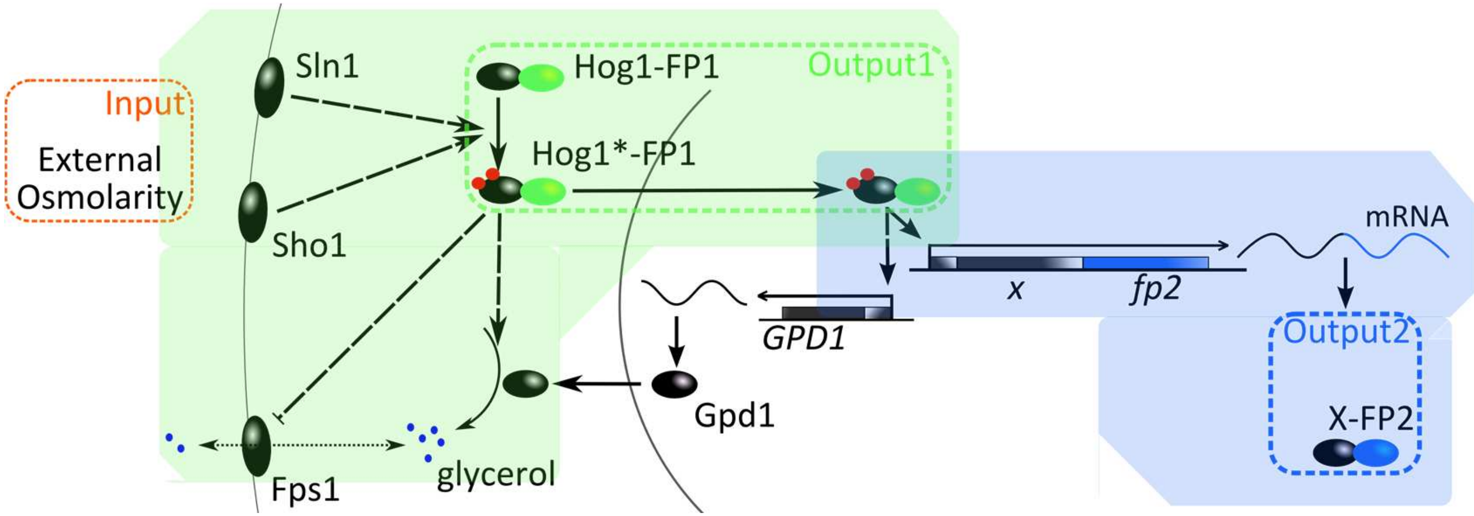
A model predictive control approach

- System decomposition and modeling



Signal transduction model (switched linear system)

Gene expression model (ODE or CTMC)

- if $osm_e \geq osm_i$: (hyperosmotic conditions)

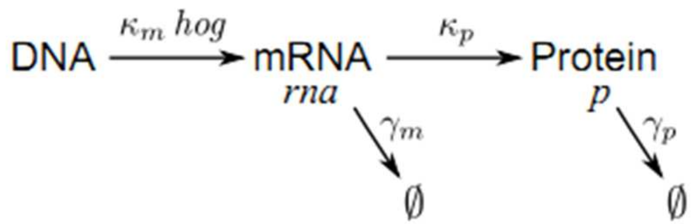
$$\dot{osm_i} = \kappa_o hog - \gamma_o osm_i \quad (1)$$

$$\dot{hog} = \kappa_g (osm_e - osm_i) - \gamma_g hog \quad (2)$$

- if $osm_e < osm_i$: (hypoosmotic conditions)

$$\dot{osm_i} = \kappa_o hog - (\gamma_o + \gamma_o') osm_i \quad (1')$$

$$\dot{hog} = -\gamma_g hog \quad (2')$$

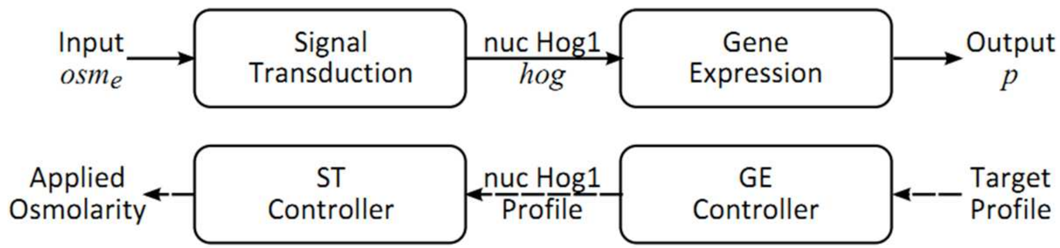


Parameters fitted to experimental data

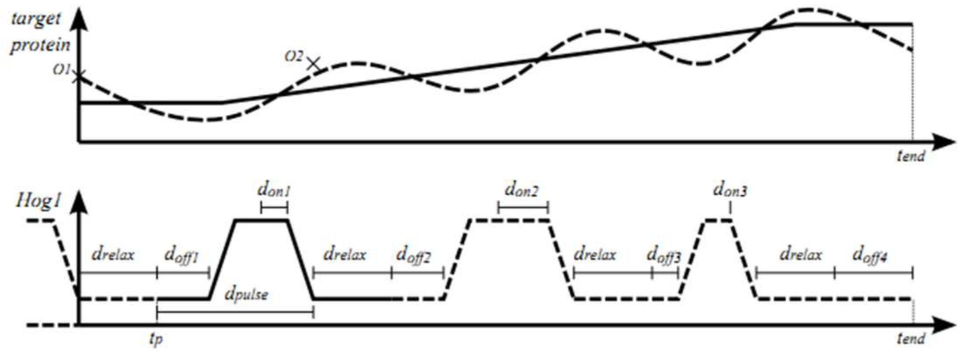
Parameters set to realistic values

A model predictive control approach

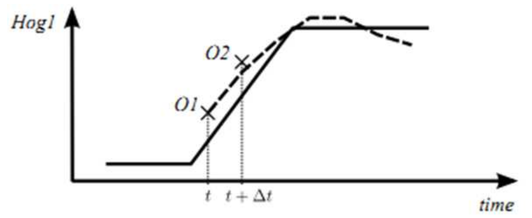
- Back-stepping control strategy



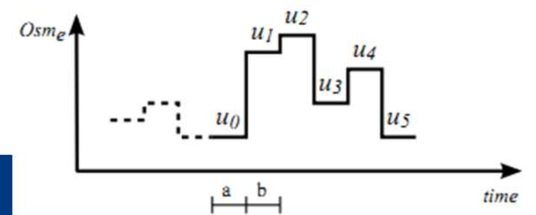
- Computing desired Hog1 profile (long-term prediction)



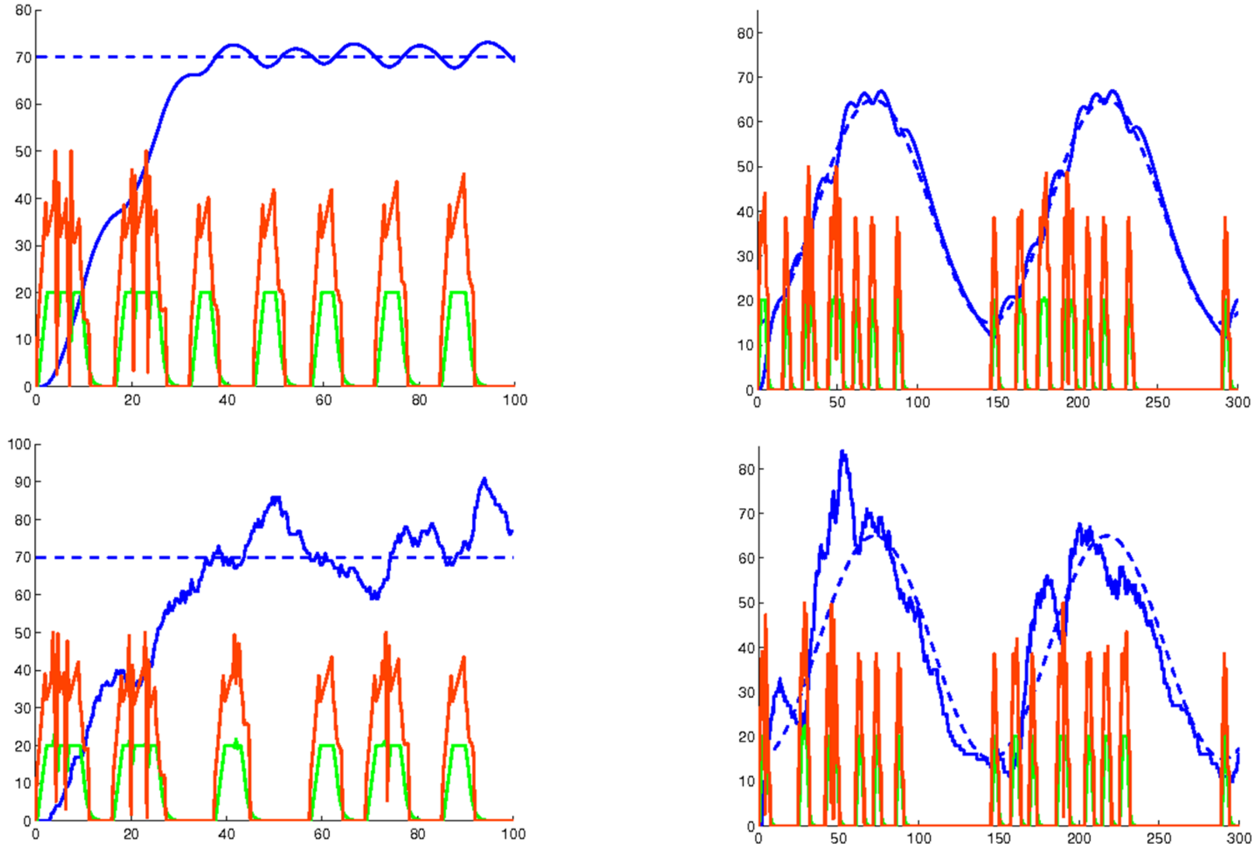
- Computing desired osmolarity profile (short term prediction)



- Parameter search problems solved by global optimization approach (CMA-ES)



Testing control approach on *in silico* data



❖ Pulse-modulated control strategy

- complies with real-time requirement and
- provides results of reasonable quality even in presence of realistic noise levels

Conclusions

- New problem: closed-loop *in vivo* control of a signal transduction pathway
- Experimental results suggest frequency-encoding strategy for gene expression control
- Proposed model predictive control strategy fits with real-time requirements
- Computational simulation suggests that proposed approach gives reasonably-robust results
- Future works involve
  - further model and controller developments, and intensive platform performance evaluation
  - transpose to other systems

Acknowledgments

Thank you for your attention

References

- J. Uhlendorf, S. Bottani, F. Fages, P. Hersen, G. Batt, Towards real-time control of gene expression: controlling the Hog signaling cascade, *PSB'11*
- J. Uhlendorf, P. Hersen, G. Batt, Towards real-time control of gene expression:in silico analysis, *IFAC'11*