Real-time Control of Gene Expression

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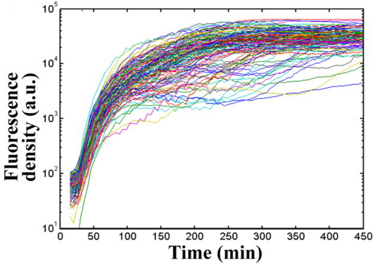
Identification and Control of Biological Interaction Networks Workshop

Motivation

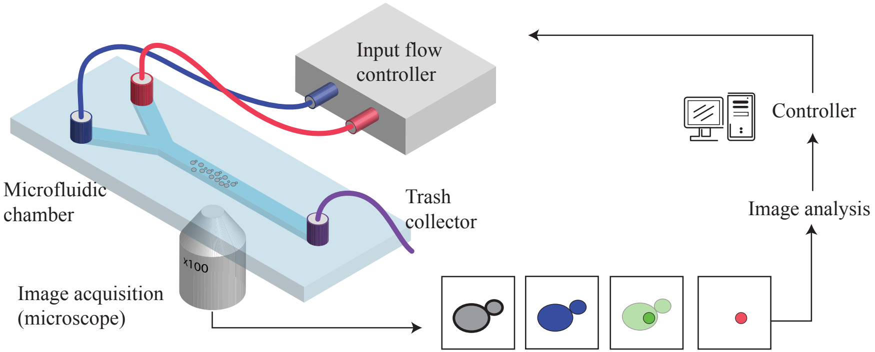
- Understanding **dynamics** of cellular processes
  - Monitor the time-response to perturbations
- No experimental methods for applying tightly controlled intracellular time-varying perturbations
  - Time varying perturbations more informative than static ones



Gefen *et al.* PNAS 2008

- **Goal: Experimental platform for the tight control of gene expression at the single cell level**

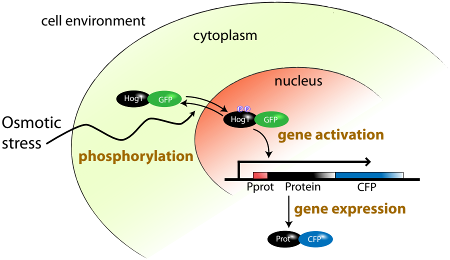
A closed loop control platform



- Main features:
  1. real-time observation
  2. real-time change of cellular stimulus
  3. real-time control

The control problem

- **Input:**
  - osmolarity
- **Output:**
  - fluorescent measurements of gene expression
- **Problem:**
  - what inputs to apply to achieve a desired behaviour?



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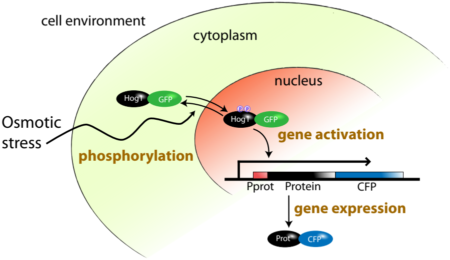

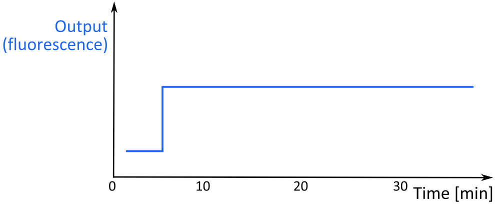

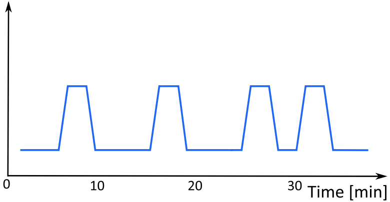

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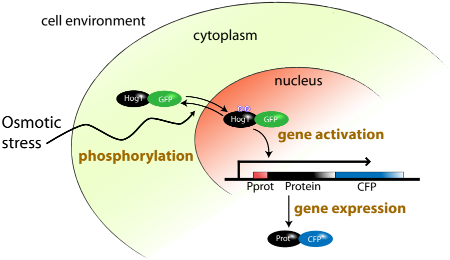

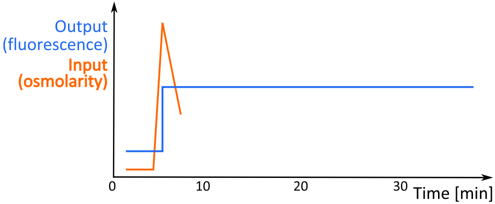

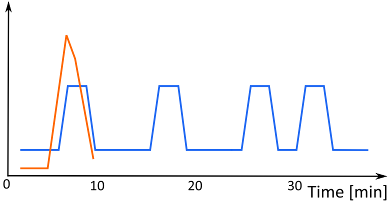

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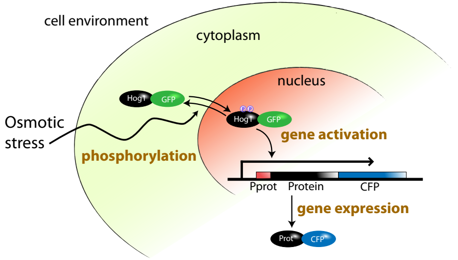

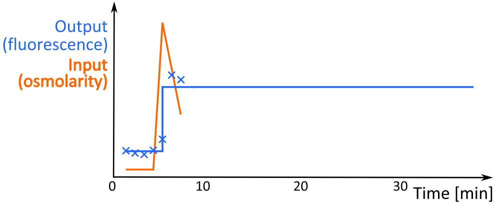

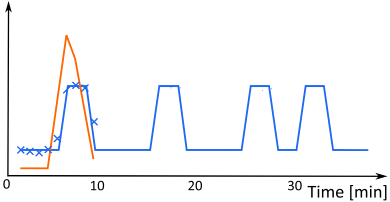

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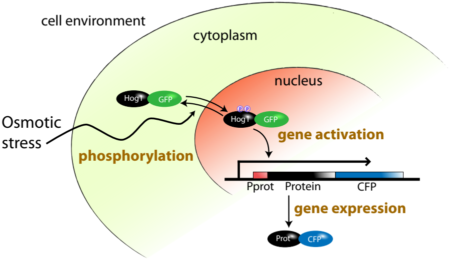

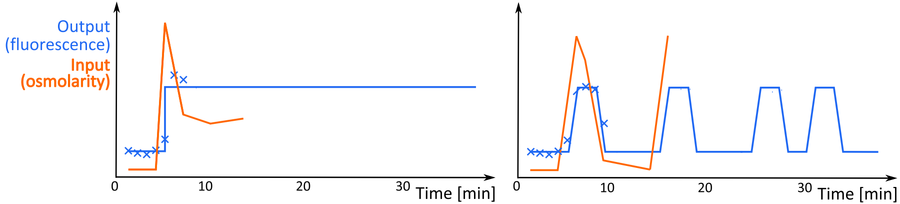

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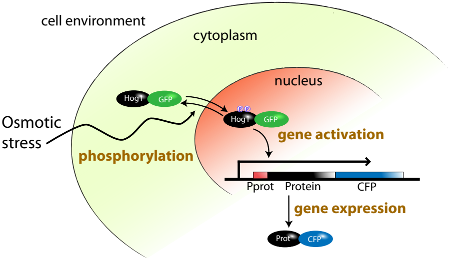

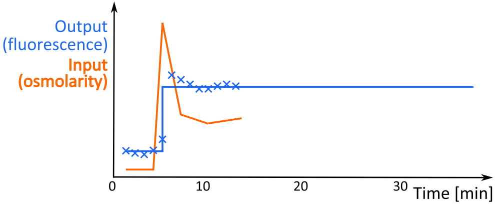

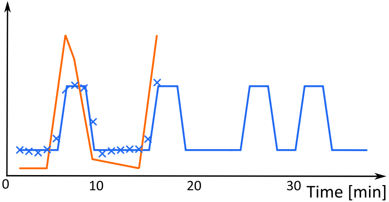

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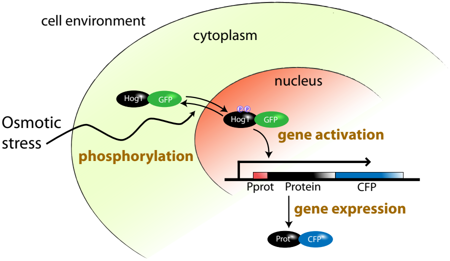

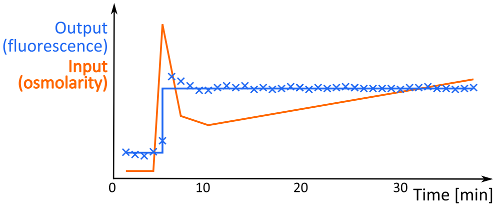

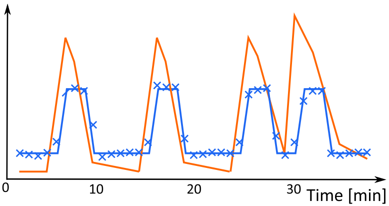

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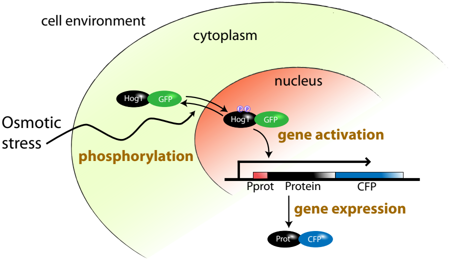

Outline

1. Experimental results on controling signal transduction
2. Computational results on controling gene expression

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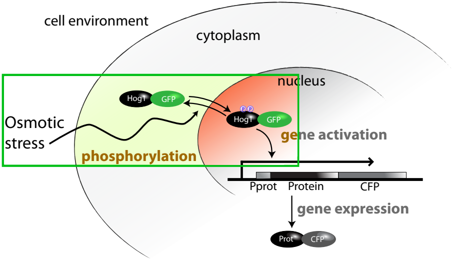


Outline

1. Experimental results on controling signal transduction

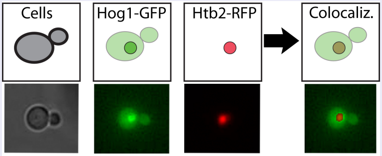
Methods

Which control algorithm?

- Proportional-integral-derivative (PID) controller
  - define error $e(t)$ as difference between desired and observed state
  - $u(t) = k_1 \cdot e(t) + k_2 \cdot \int_0^t e(\tau)d\tau + k_3 \cdot \frac{d}{dt} e(t)$
  - requires no structural knowledge about the controlled system
  - but requires tuning of parameters

How to quantify Hog1 nuclear localization?

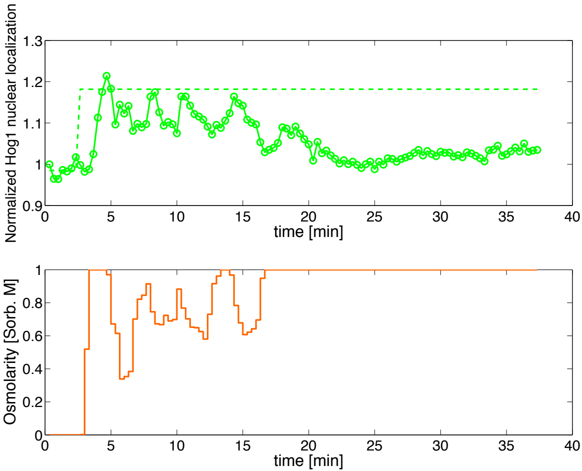
- Define colocalization with nuclear marker (Htb2)



Relative colocalization:

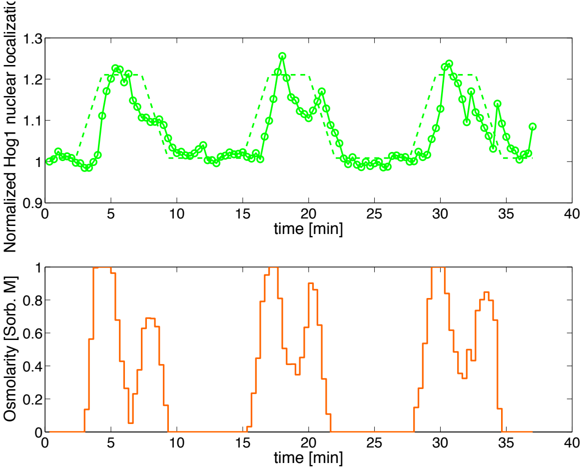
- $h(t) = \frac{<\text{Pixel intensity}>_{nuc}}{<\text{Pixel intensity}>_{cyt}}$

Experimental results: Sustained high activation



- PI-control works in principle
- Sustained high activation not possible due to cell adaptation

Experimental results: Repeated trapezoidal motifs



- Frequency encoding seems to work better than amplitude encoding (cells have time to relax)
- Still room for improvement (e.g. time-lag, reproducibility)

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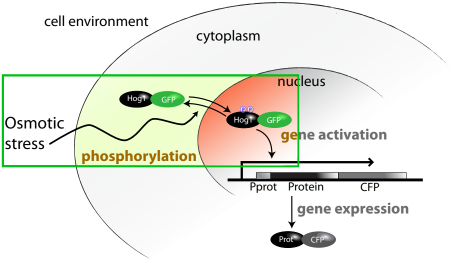

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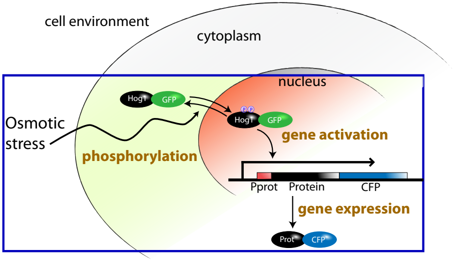

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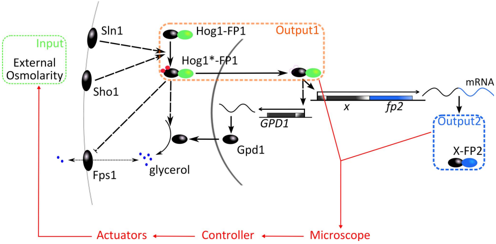
2. Computational results on controling gene expression

A model based control approach

- Mathematical model (similar to Mettetal *et al.*, 2008 and Muzzey *et al.*, 2009)



- if $osm_e \geq osm_i$: (hyperosm. env.)

$$\dot{osm_i} = \kappa_o hog - \gamma_o osm_i$$
$$\dot{hog} = \kappa_g (osm_e - osm_i) - \gamma_g hog$$
$$\dot{rna} = \kappa_m hog - \gamma_m rna$$
$$\dot{p} = \kappa_p rna - \gamma_p p$$

- if $osm_e < osm_i$: (hypoosm. env.)

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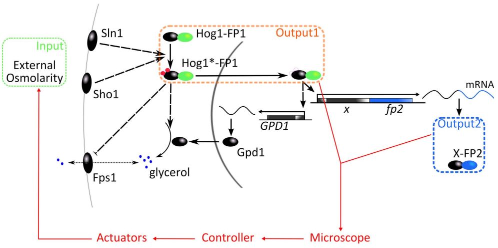

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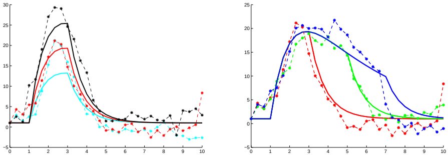
- Parameters fitting
  - signal transduction parameters fitted w.r.t our experimental data



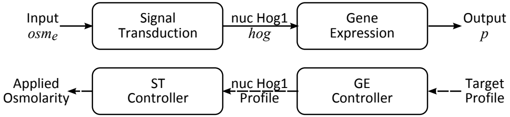
transduction response to osmotic shock of various durations or amplitude

  - gene expression parameters set to arbitrary but realistic values

Control strategy

- Taking advantage of system structure: backstepping

cascaded,
fast/slow system



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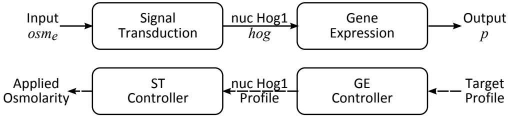
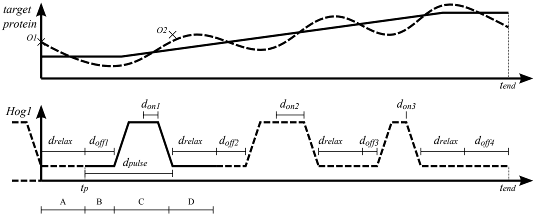
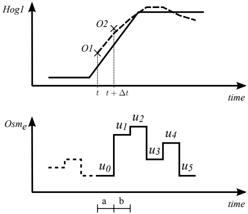


- Model predictive control approaches



GE controller using pulse modulation



ST controller

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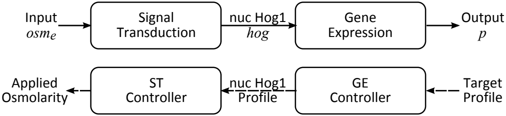

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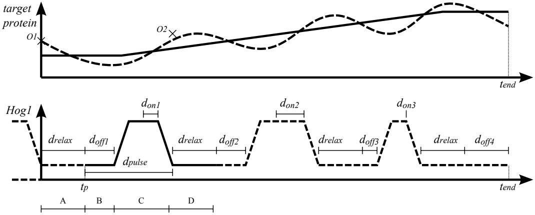

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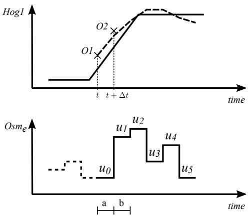
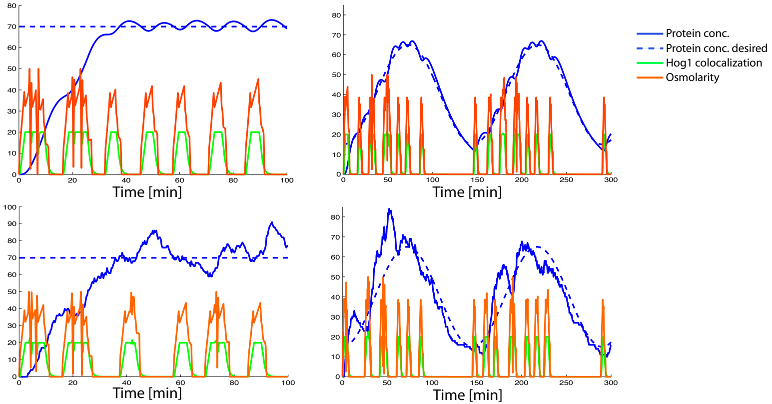


ST controller

- Optimization-based implementation in Matlab/CMAES

In silico evaluation of control strategy

- Testing various control objectives with deterministic or stochastic models (and ignoring observation and state estimation problems)



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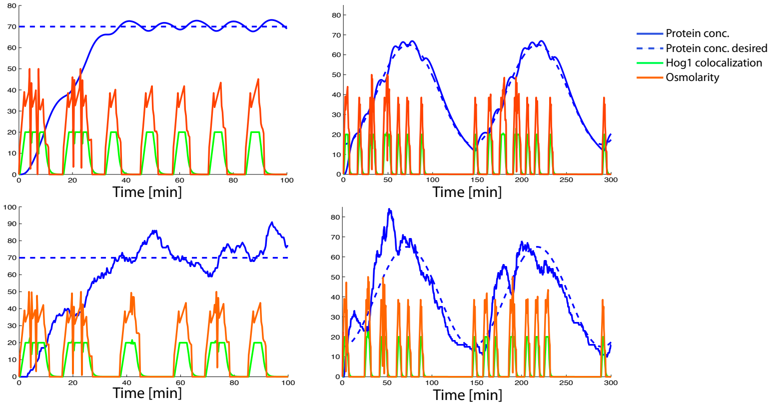

- Proposed control strategy is feasible wrt real-time requirement and fairly robust wrt large biological variability

Discussion

- Summary
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- From "I understand what I can build" to "I understand what I can control"

Thank you for your attention

- Uhlendorf, Bottani, Fages, Hersen, Batt (2011). Towards Real-time Control of Gene Expression: controlling the Hog Signalling Cascade. *PSB'11.*
- Uhlendorf, Hersen, Batt (2011). Towards Real-time Control of Gene Expression: *in silico* Analysis. *submitted.*

- Muzzey, Gómez-Uribe, Mettetal, van Oudenaarden (2009). A Systems-Level Analysis of Perfect Adaptation in Yeast Osmoregulation. *Cell.*
- Mettetal, Muzzey, Gomez-Uribe, van Oudenaarden (2008). The frequency dependence of osmo-adaptation in Saccharomyces cerevisiae. *Science*
- Geifen, Gabay, Mumcouglu, Engel, Balaban (2008). Single-cell protein induction dynamics reveals a period of vulnerability to antibiotics in persister bacteria. *PNAS*