MCT and biochemical control theory

- Generalization of MCT to the response of biochemical systems to time-dependent parameter changes

  Sauro (2004) *in* Computational Systems Biology, *Methods in Molecular Biology* vol. 541, pp. 269-290, Humana Press

  Ingalls (2004) J*. Phys. Chem. B* 108:1143-1152

MCT and biochemical control theory

- System evolution

$$d\mathbf{x}^0/dt = \mathbf{N}^0 \cdot \mathbf{v}(\mathbf{x},\mathbf{p})$$

with Jacobian

$$\mathfrak{J} = \mathbf{N}^0 \cdot \partial\mathbf{v}/\partial\mathbf{x} \cdot \mathbf{L}$$

- Let us call $\mathbf{u}(t) = \mathbf{p}(t) - \mathbf{p}$ the input 'parameters' and linearize around steady-state $\mathbf{X}(\mathbf{p})$:

$$d\mathbf{x}^0/dt = \mathfrak{J} \cdot (\,\mathbf{x}^0(t) - \mathbf{X}^0\,) + \mathbf{N}^0 \cdot \partial\mathbf{v}/\partial\mathbf{p} \cdot \mathbf{u}(t)$$

Transfer function and control

- Laplace transform can be used to obtain the corresponding frequency transfer function as a function of frequency ω :

$$\mathbf{H}(\omega) = (2i\pi\omega\,\mathbf{I} - \mathfrak{I})^{-1} \cdot \mathbf{N}^0 \cdot \partial\mathbf{v}/\partial\mathbf{p}$$

- At zero frequency we recover the previous expression for concentration control :

$$\partial\mathbf{X}^0/\partial\mathbf{p} = -\,\mathfrak{I}^{-1} \cdot \mathbf{N}^0 \cdot \partial\mathbf{v}/\partial\mathbf{p}$$

Frequency response

- The modulus of $\mathbf{H}(\omega)$ expresses the amplitude of the response (the gain) to an oscillating perturbation around the steady-state
- The phase of $\mathbf{H}(\omega)$ corresponds to the phase of the response
- Biochemical systems frequently behave as low-pass filters

Example of low-pass filter

- Simple gene expression system

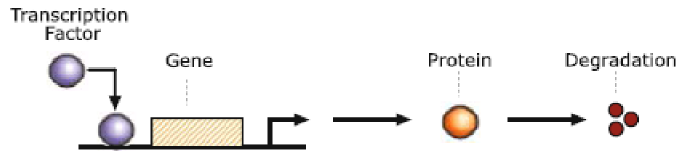
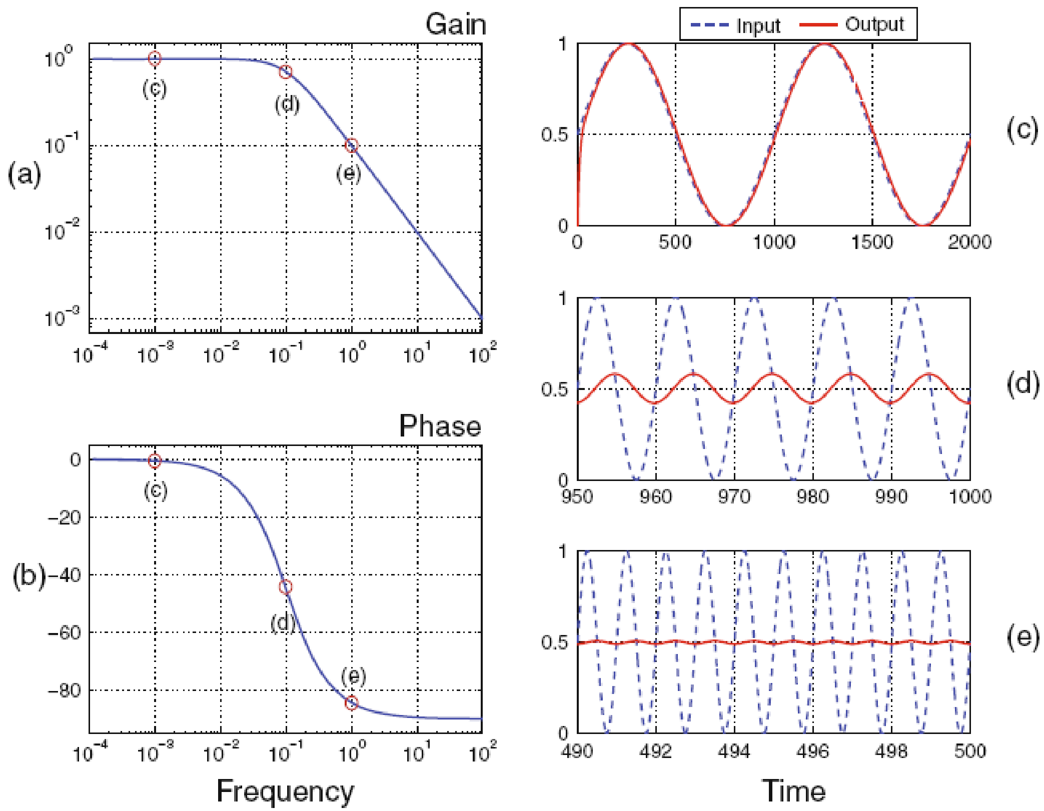
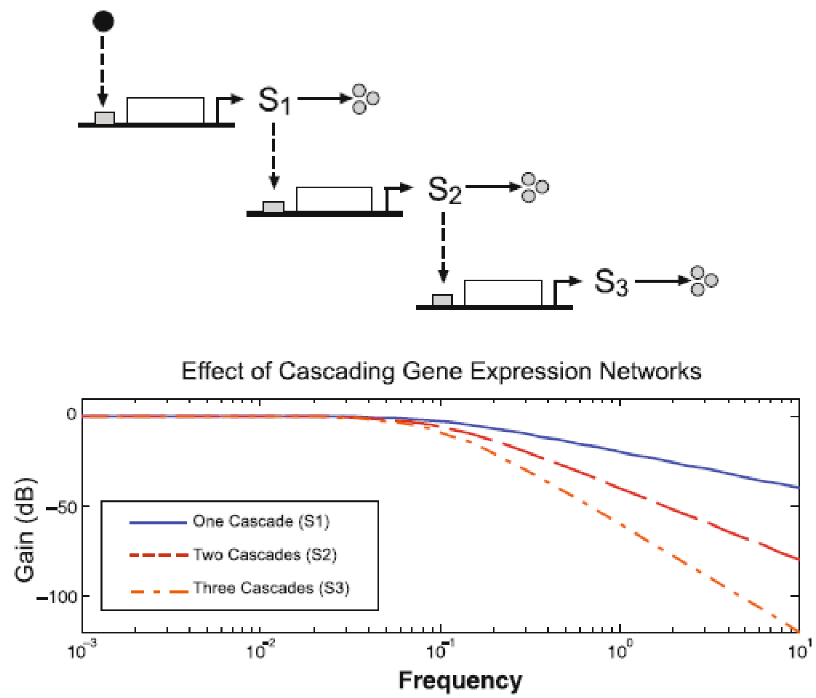


Fig. 13.9. Simple genetic circuit that can act as a low-pass filter.



Example of low-pass filter

- Low-pass filter enhanced by cascade



Example of frequency filtering

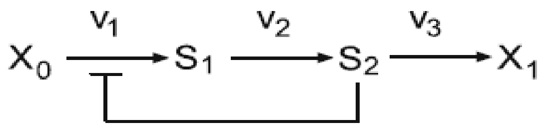


Fig. 13.8. Simple negative feedback loop. v_1, v_2, and v_3 are the reaction rates. S_2 acts to inhibit its own production by inhibition of v_1.

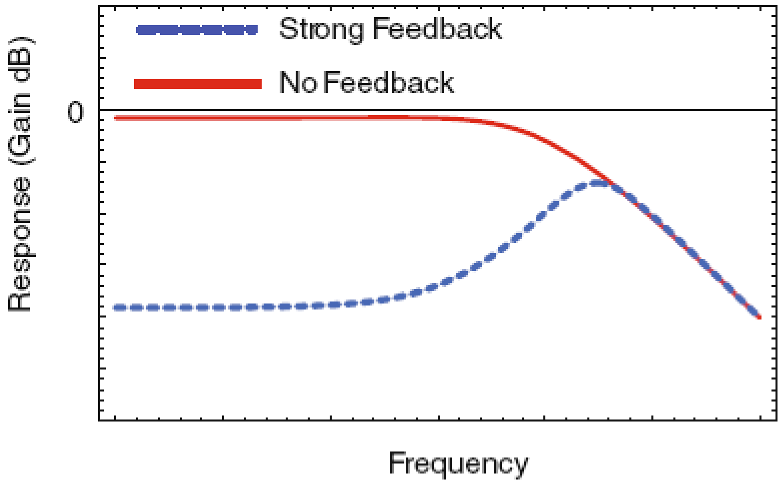


Fig. 13.12. Frequency response of end product S_2 with respect to the input species X_o for a model of the kind shown in **Fig. 13.8.**

Observing frequency response

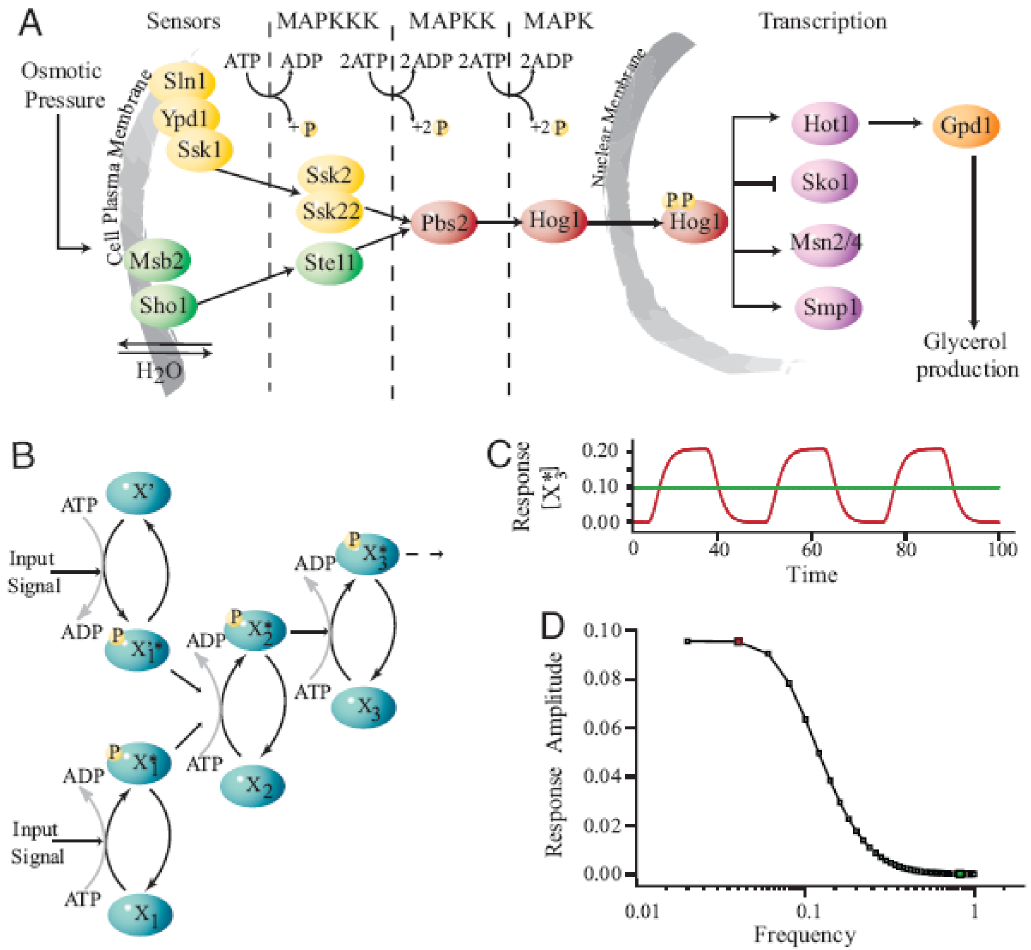
Signal processing by the HOG MAP kinase pathway

Pascal Hersen[†‡], Megan N. McClean[†§], L. Mahadevan[§], and Sharad Ramanathan[†¶||]

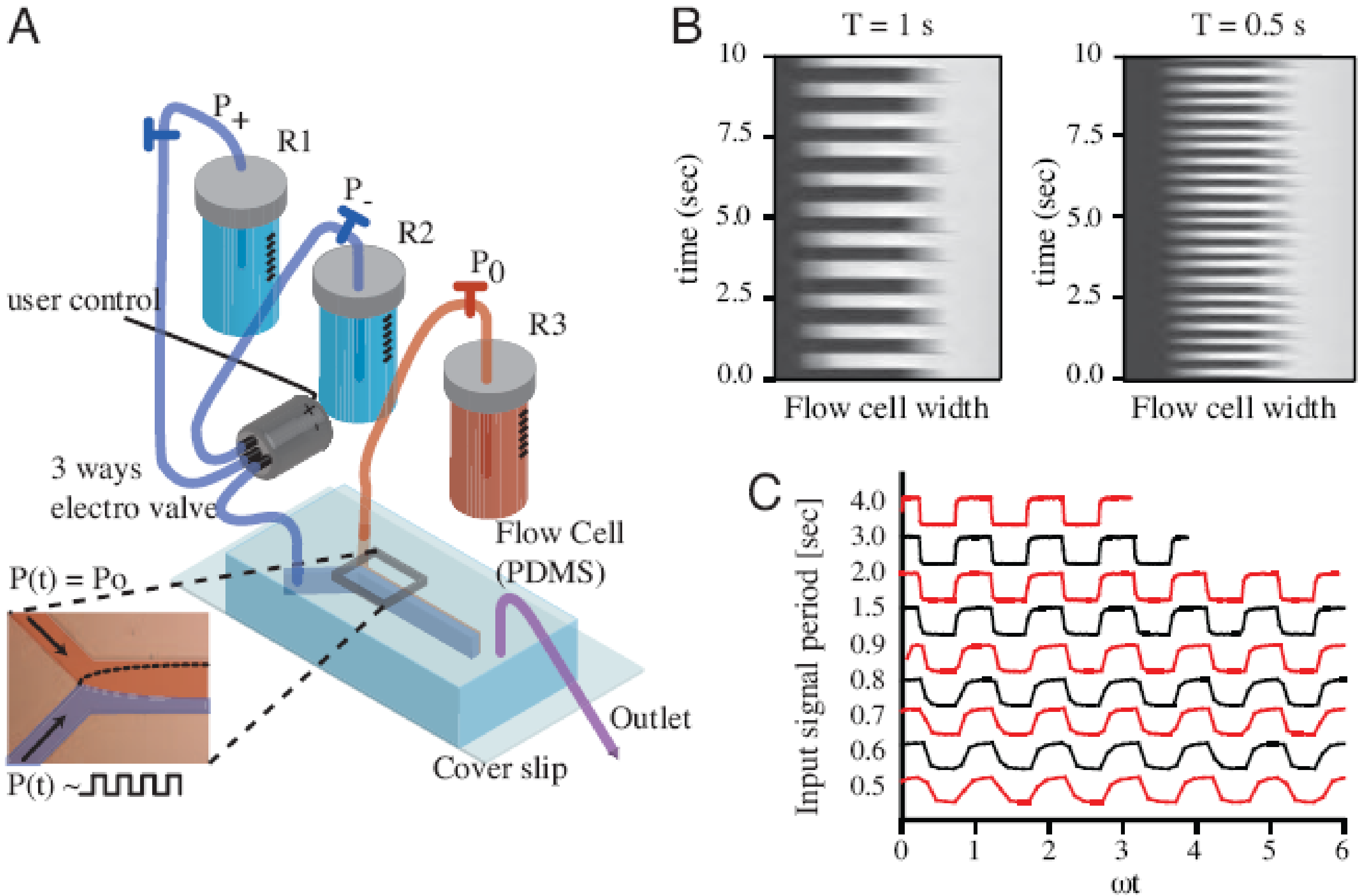
Hersen *et al.* (2008), *PNAS* 105:7165-7170

- Signal transduction cascade responding to osmotic pressure
- Time-dependent response observed in microfluidic device

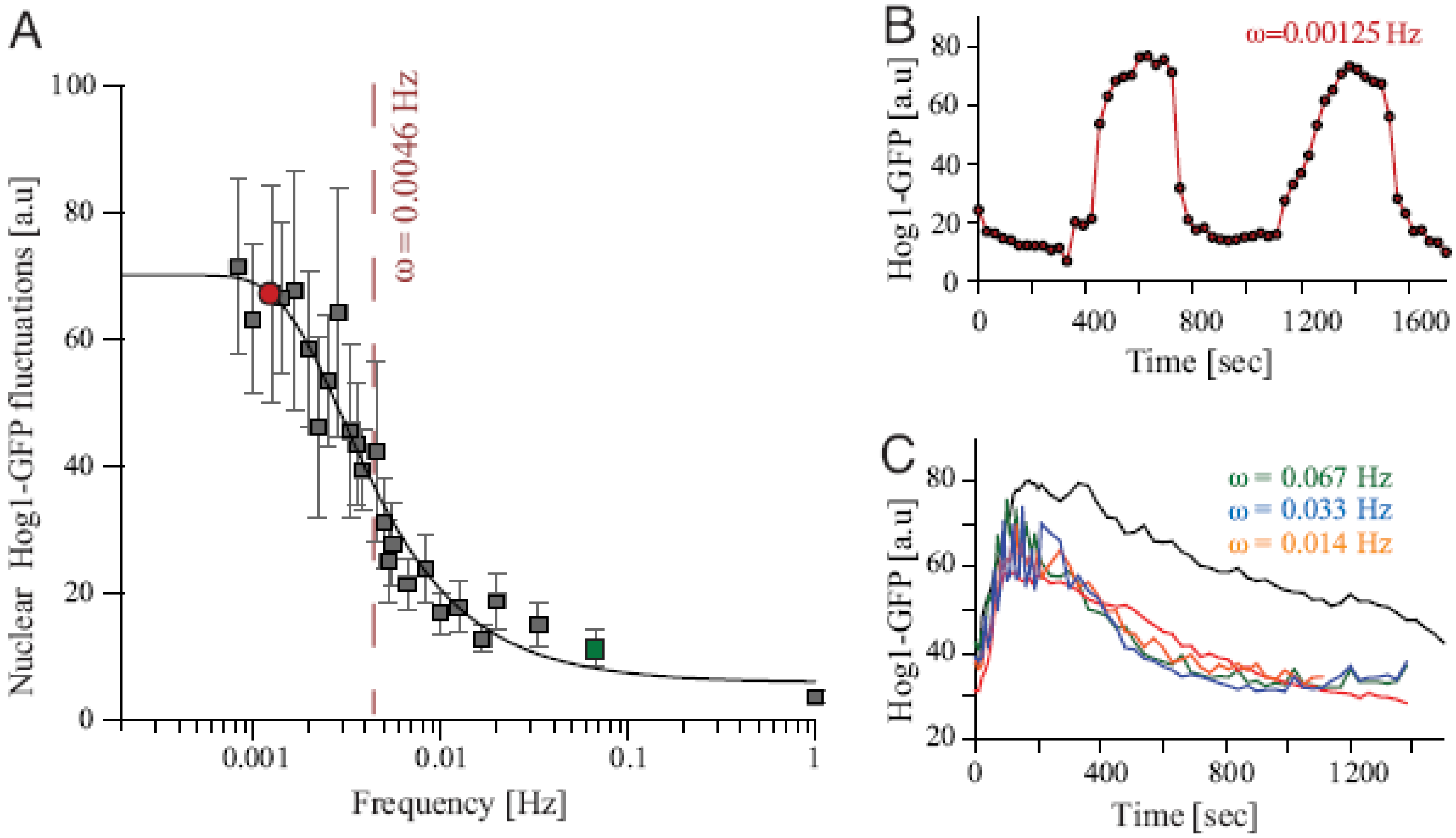
The HOG pathway



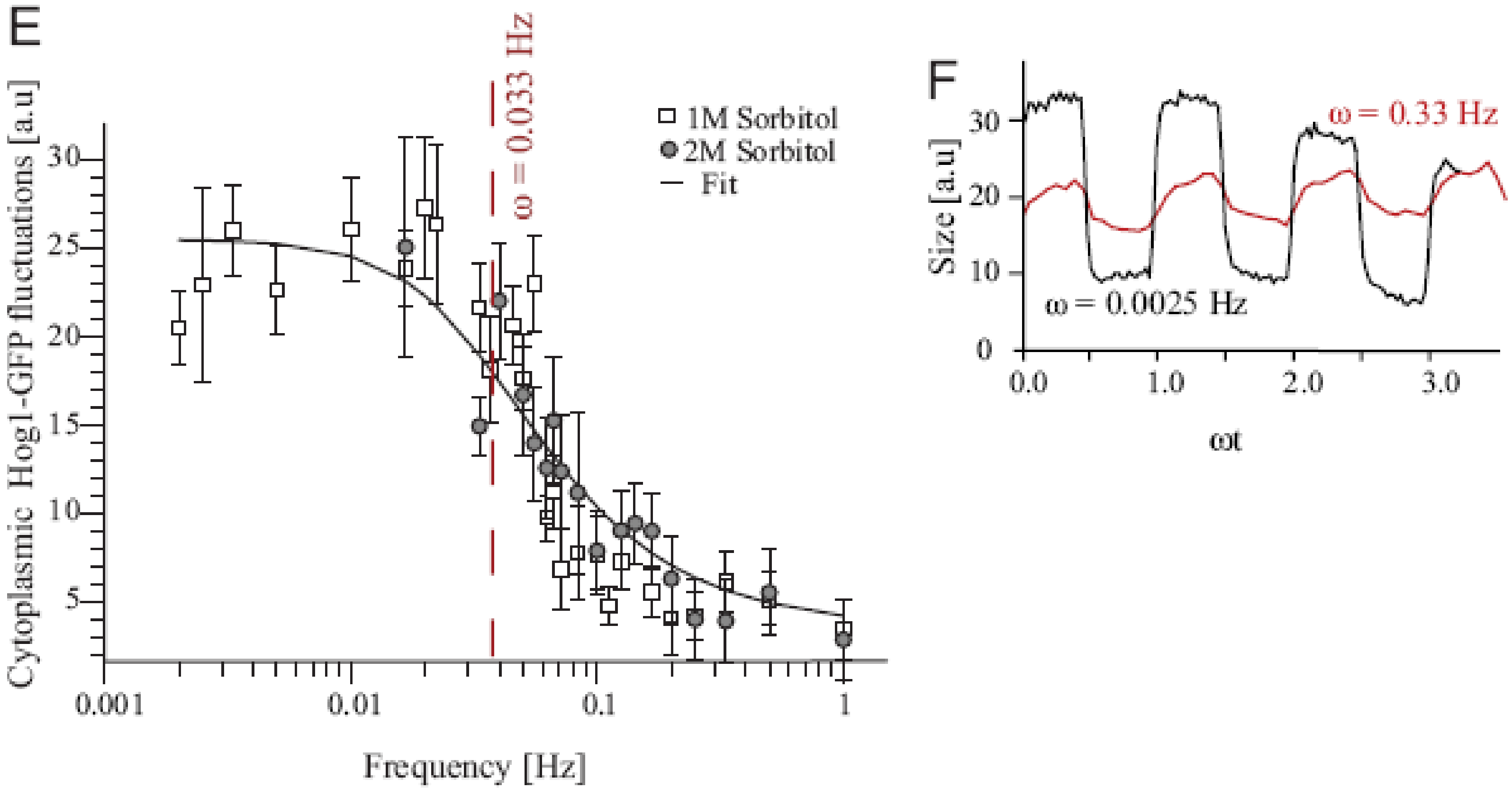
Experimental microfluidic setup



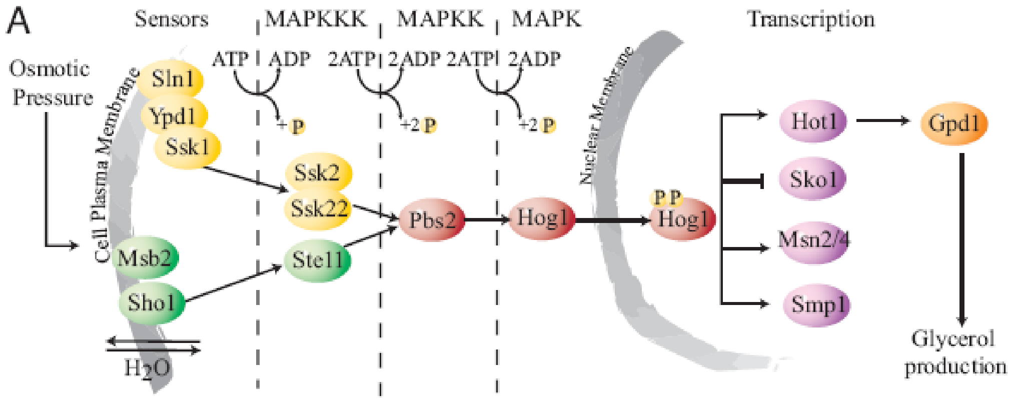
Nuclear HOG1 fluctuations

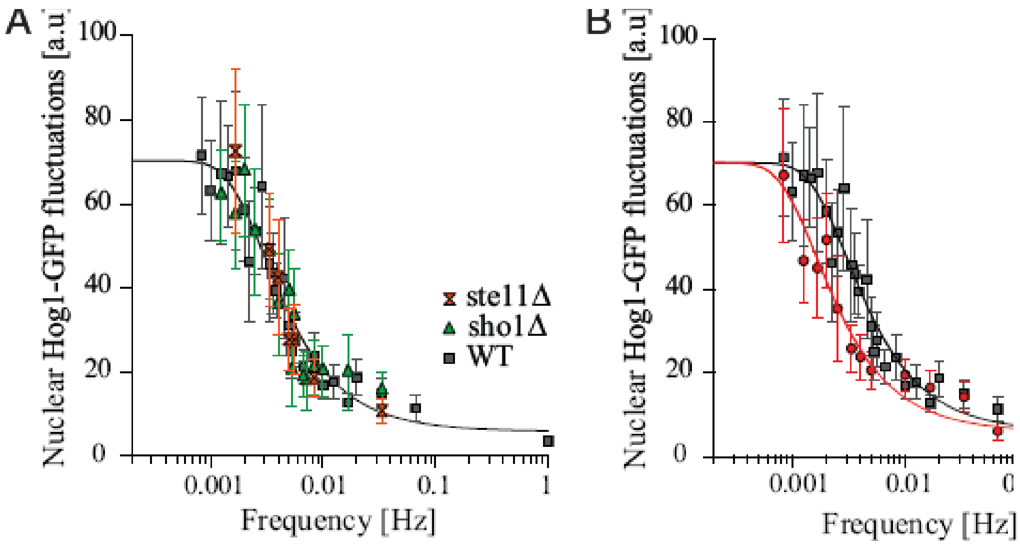


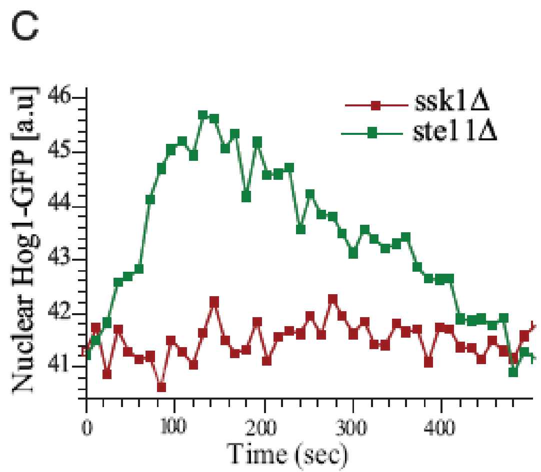
Cell size flucutations



Branch-specific bandwidths







at 0.2 Hz