

# MCT and Biochemical Control Theory

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# MCT and biochemical control theory

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- 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

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## ➤ 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

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- Laplace transform can be used to obtain the corresponding frequency **transfer function** as a function of frequency  $\omega$  :

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

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

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

# Frequency response

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- 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

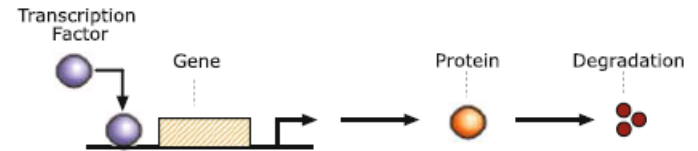
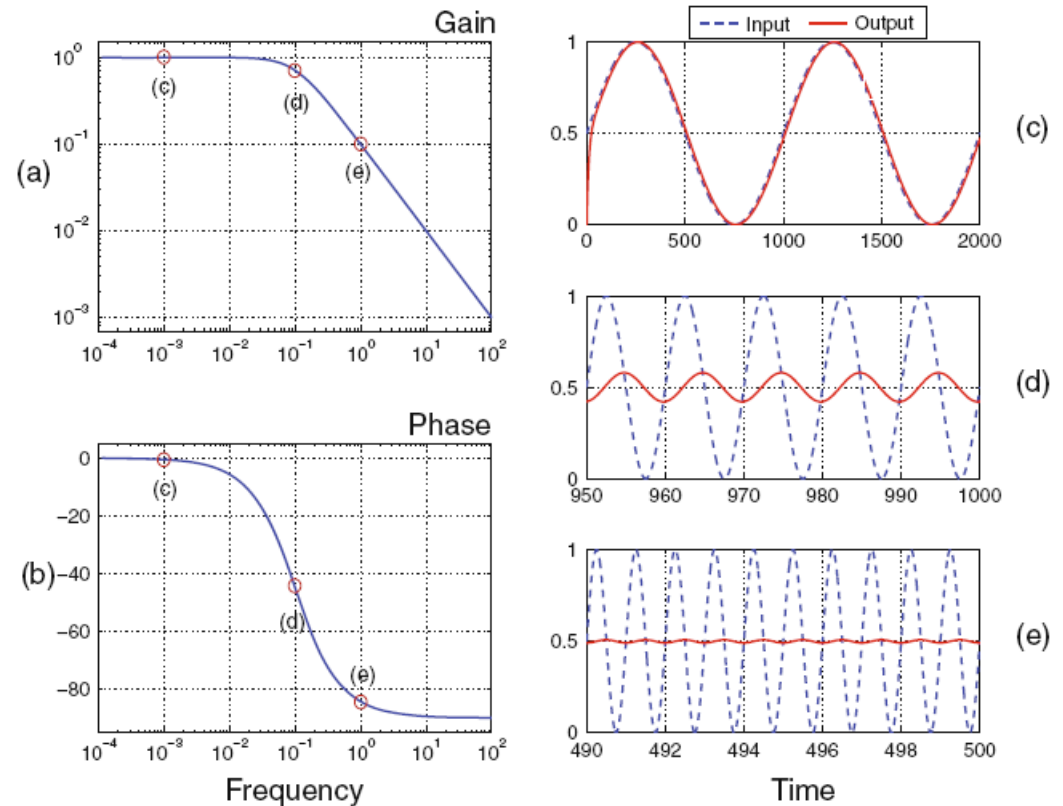
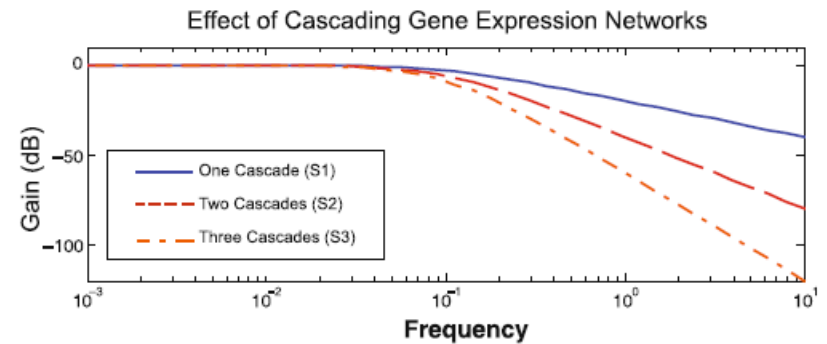
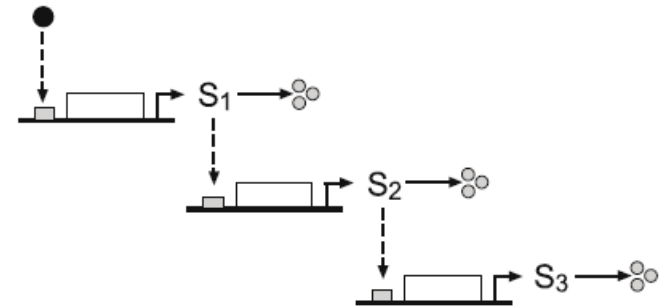


Fig. 13.9. Simple genetic circuit that can act as a low-pass filter.



# Example of low-pass filter

- Low-pass filter enhanced by cascade



# Example of frequency filtering

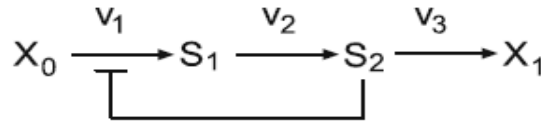


Fig. 13.8. Simple negative feedback loop.  $v_1$ ,  $v_2$ , and  $v_3$  are the reaction rates.  $S_2$  acts to inhibit its own production by inhibition of  $v_1$ .

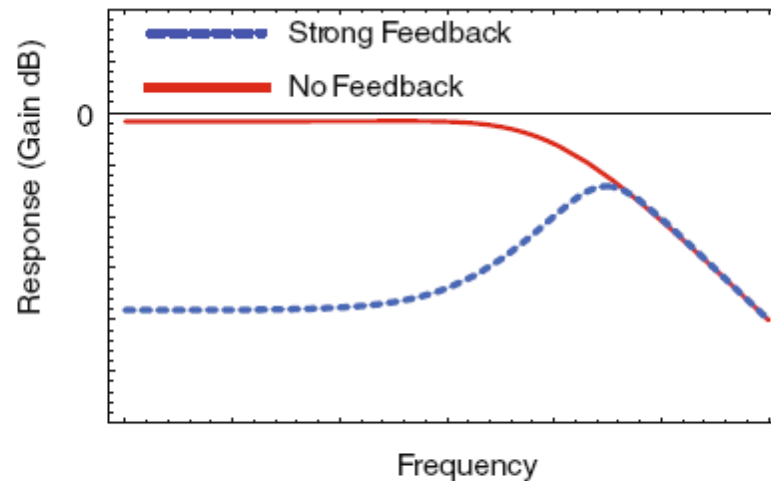


Fig. 13.12. Frequency response of end product  $S_2$  with respect to the input species  $X_0$  for a model of the kind shown in Fig. 13.8.

# Observing frequency response

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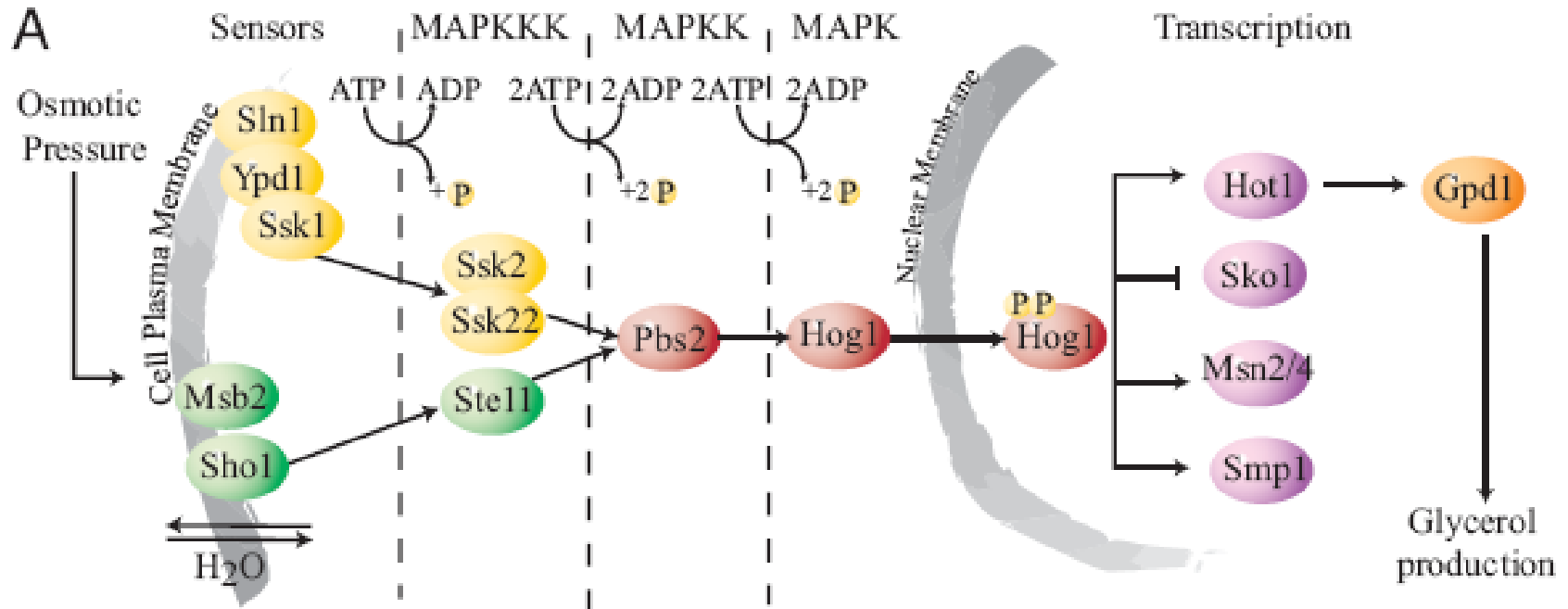
## Signal processing by the HOG MAP kinase pathway

Pascal Hersen<sup>†‡</sup>, Megan N. McClean<sup>†§</sup>, L. Mahadevan<sup>§</sup>, and Sharad Ramanathan<sup>†¶||</sup>

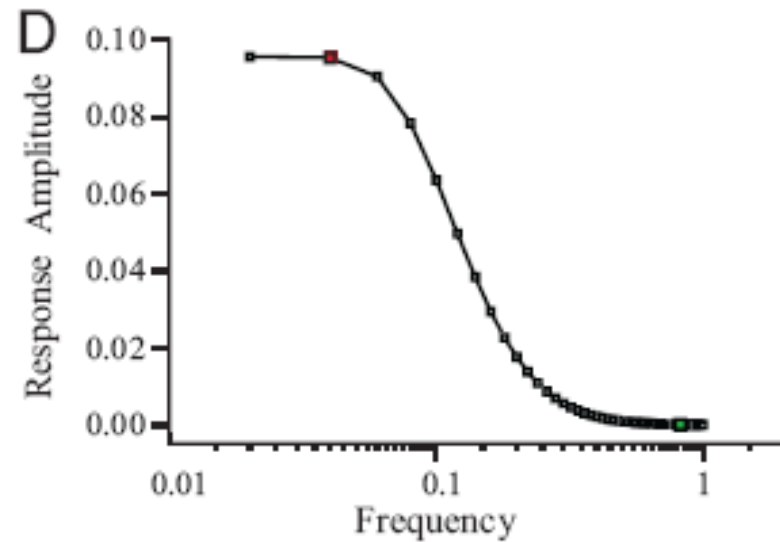
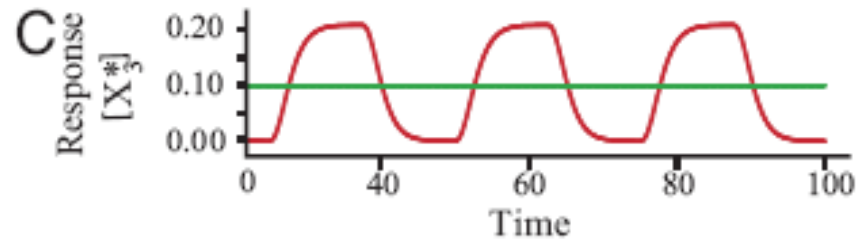
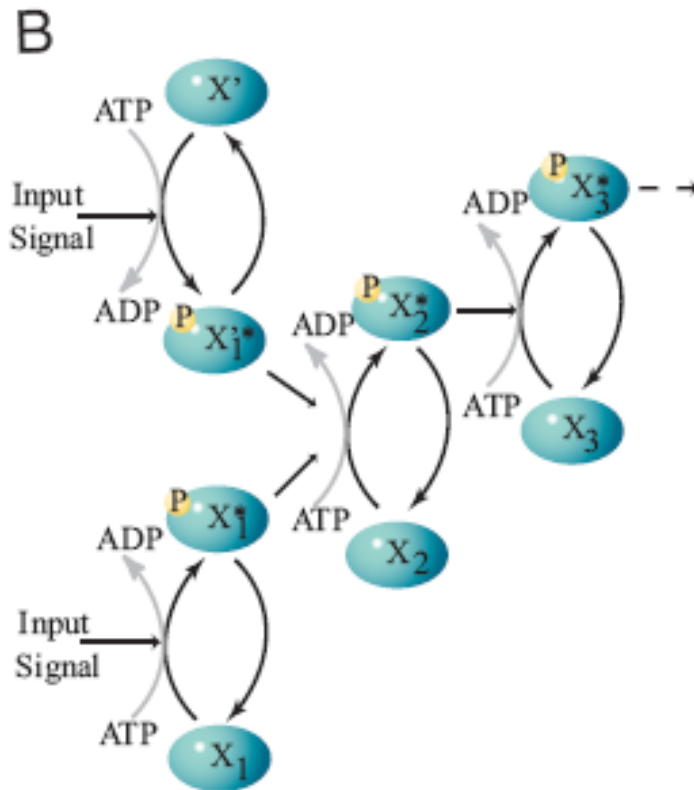
Hersen *et al.* (2008), *PNAS* 105:7165-7170

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

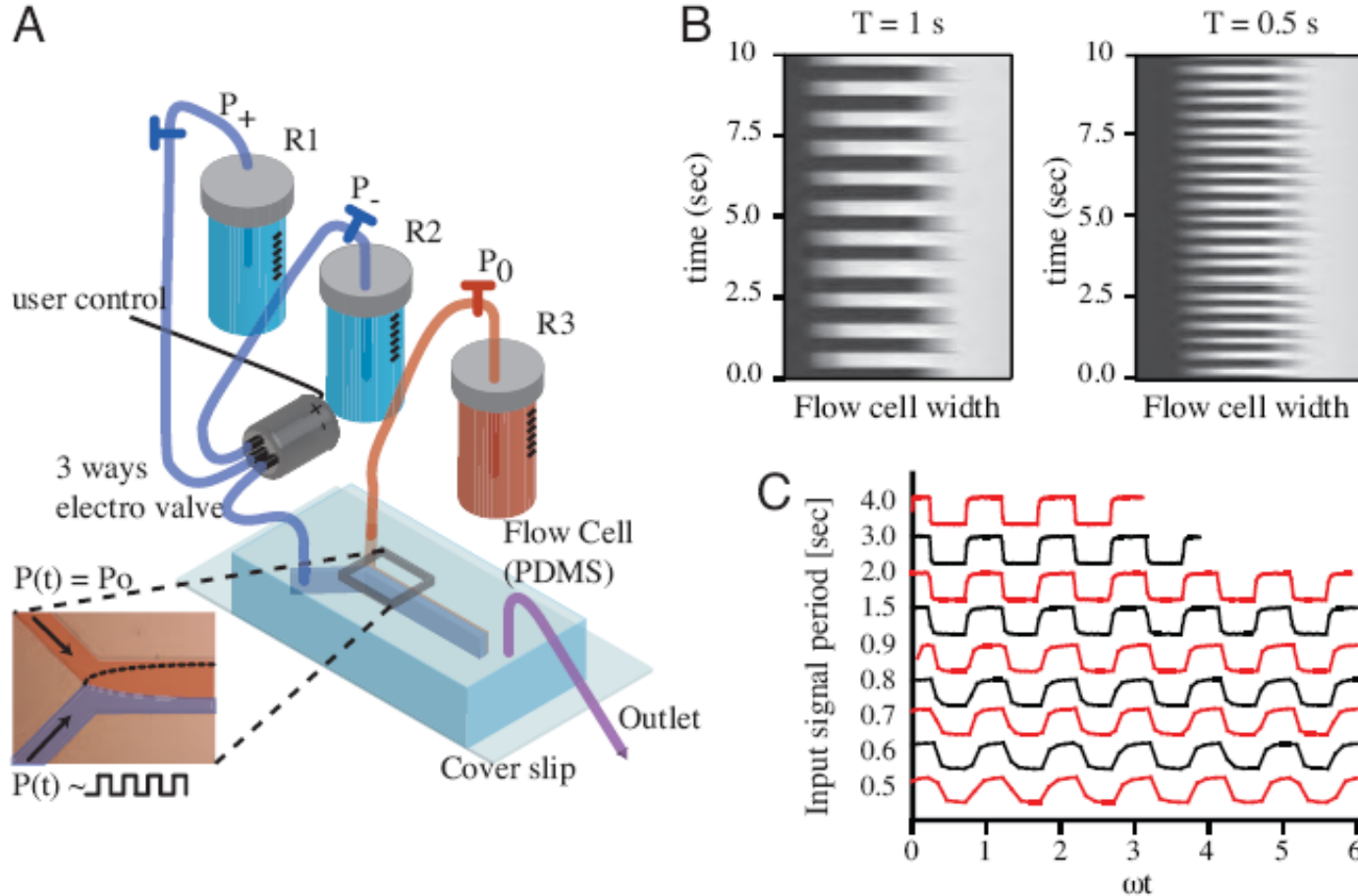
# The HOG pathway



# HOG pathway model



# Experimental microfluidic setup



# Nuclear HOG1 fluctuations

