Oscillations in Biology

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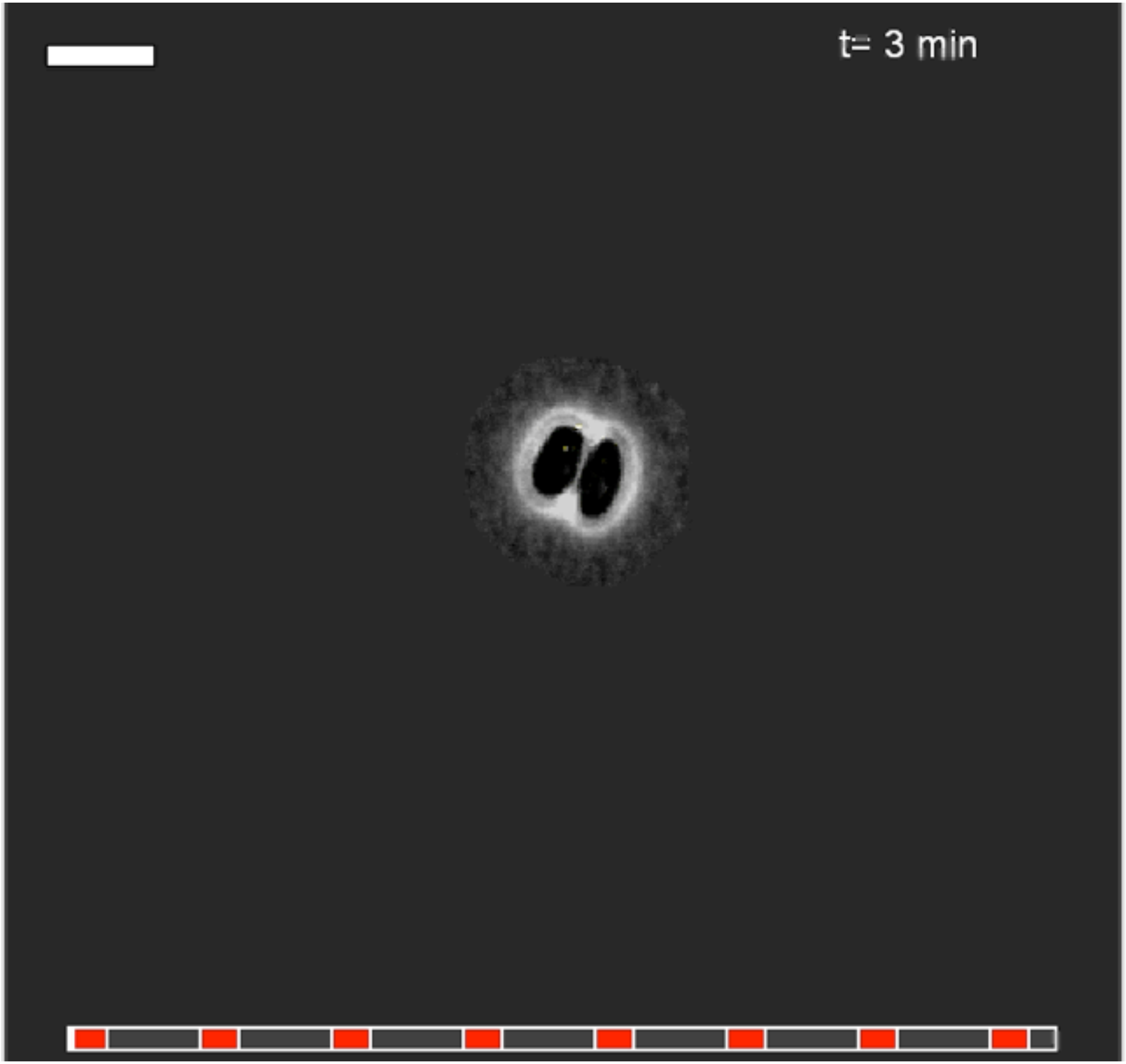
Oscillations

- Day/night: circadian rhythms, 24h period
- Summer/Winter: annual life cycles
- Fireflies (a few seconds)
- Cell cycle (20min to 2 days)

- Systems continue to oscillate even if cues are taken away
- harbor an intrinsic oscillator with approximately the same frequency as the external cues

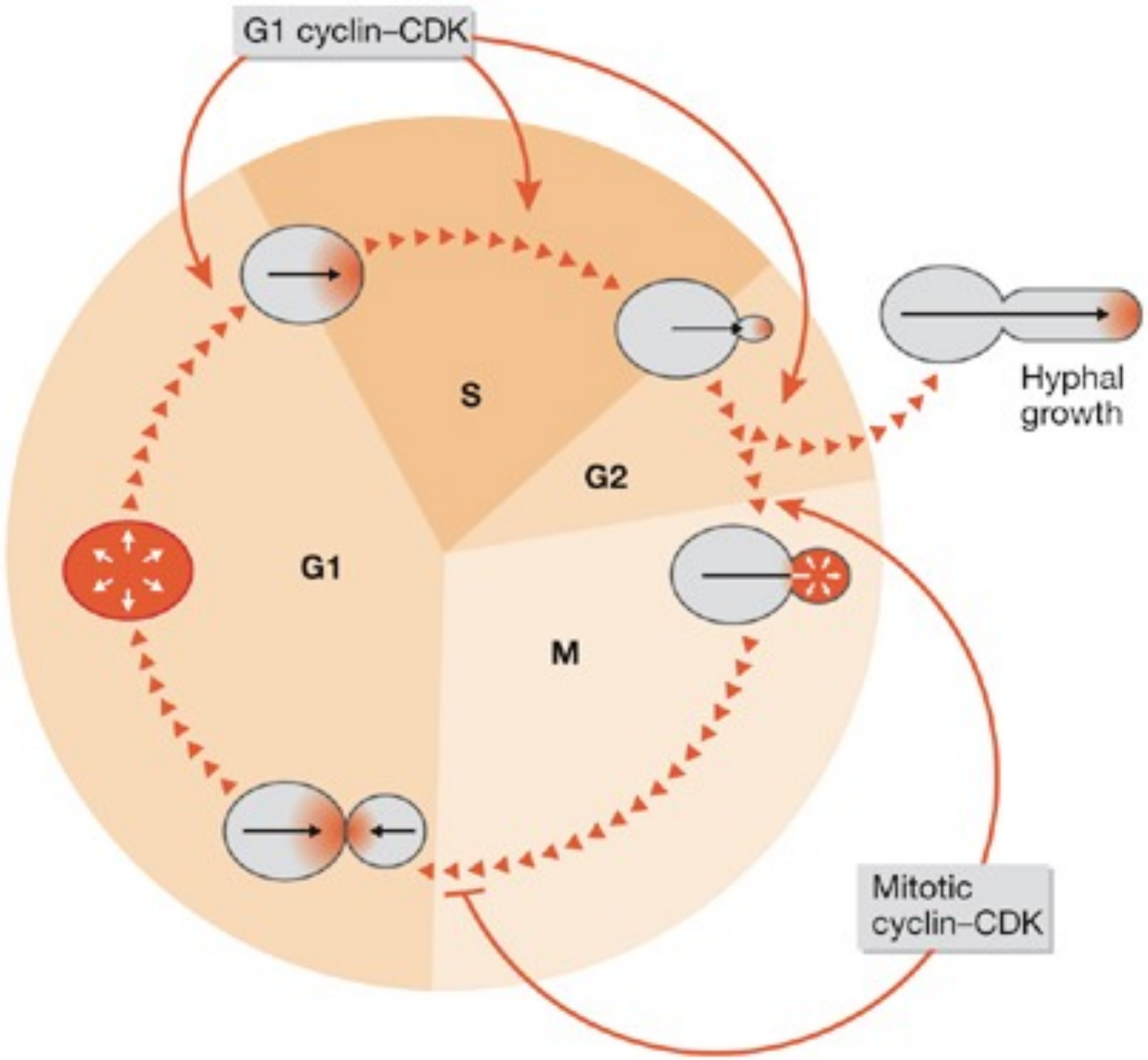
Further reading: Novak, Tyson, Nat. Rev. Mol. Cell Bio., 9, 2008

Budding yeast



Charvin et al, PNAS, 2009

Budding yeast cell cycle



- Microscopically very complicated
- roughly 15% of all genes are coupled to the cell cycle
- microscopic model: http://mpf.biol.vt.edu/research/budding_yeast_model/pp/index.php

Yoshida & Pellman EMBO reports (2008) **9**, 39 - 41

Microscopic model

Equations governing the inhibitors of Clb-dependent kinases:

$$\frac{d[\mathrm{Sic1}]}{dt} = (k'_{s,c1} + k''_{s,c1}\cdot[\mathrm{Swi5}]) + (V_{d,b2} + k_{di,b2})\cdot[\mathrm{C2}] + (V_{d,b5} + k_{di,b5})\cdot[\mathrm{C5}] + k_{pp,c1}\cdot[\mathrm{Cdc14}]\cdot[\mathrm{Sic1P}] - (k_{as,b2}\cdot[\mathrm{Clb2}] + k_{as,b5}\cdot[\mathrm{Clb5}] + V_{kp,c1})\cdot[\mathrm{Sic1}]$$

$$\frac{d[\mathrm{Sic1P}]}{dt} = V_{d,b2}\cdot[\mathrm{C2P}] + V_{d,b5}\cdot[\mathrm{C5P}] - k_{pp,c1}\cdot[\mathrm{Cdc14}]\cdot[\mathrm{Sic1P}] - k_{d3,c1}\cdot[\mathrm{Sic1P}] + V_{kp,c1}\cdot[\mathrm{Sic1}]$$

$$V_{kp,c1} = k_{d1,c1} + \frac{k_{d2,c1}\cdot(\varepsilon_{c1,n3}\cdot[\mathrm{Cln3}] + \varepsilon_{c1,k2}\cdot[\mathrm{Bck2}] + \varepsilon_{c1,n2}\cdot[\mathrm{Cln2}] + \varepsilon_{c1,b5}\cdot[\mathrm{Clb5}] + \varepsilon_{c1,b2}\cdot[\mathrm{Clb2}])}{J_{d2,c1} + [\mathrm{Sic1}]_T}$$

$$\frac{d[\mathrm{C2}]}{dt} = k_{as,b2}\cdot[\mathrm{Clb2}]\cdot[\mathrm{Sic1}] + k_{pp,c1}\cdot[\mathrm{Cdc14}]\cdot[\mathrm{C2P}] - (k_{di,b2} + V_{d,b2} + V_{kp,c1})\cdot[\mathrm{C2}]$$

$$\frac{d[\mathrm{C2P}]}{dt} = V_{kp,c1}\cdot[\mathrm{C2}] - (k_{pp,c1}\cdot[\mathrm{Cdc14}] + k_{d3,c1} + V_{d,b2})\cdot[\mathrm{C2P}]$$

$$\frac{d[\mathrm{C5}]}{dt} = k_{as,b5}\cdot[\mathrm{Clb5}]\cdot[\mathrm{Sic1}] + k_{pp,c1}\cdot[\mathrm{Cdc14}]\cdot[\mathrm{C5P}] - (k_{di,b5} + V_{d,b5} + V_{kp,c1})\cdot[\mathrm{C5}]$$

$$\frac{d[\mathrm{C5P}]}{dt} = V_{kp,c1}\cdot[\mathrm{C5}] - (k_{pp,c1}\cdot[\mathrm{Cdc14}] + k_{d3,c1} + V_{d,b5})\cdot[\mathrm{C5P}]$$

$$\frac{d[\mathrm{Cdc6}]}{dt} = (k'_{s,f6} + k''_{s,f6}\cdot[\mathrm{Swi5}]) + (V_{d,b2} + k_{di,f2})\cdot[\mathrm{F2}] + (V_{d,b5} + k_{di,f5})\cdot[\mathrm{F5}] + k_{pp,f6}\cdot[\mathrm{Cdc14}]\cdot[\mathrm{Cdc6P}] - (k_{as,f2}\cdot[\mathrm{Clb2}] + k_{as,f5}\cdot[\mathrm{Clb5}] + V_{kp,f6})\cdot[\mathrm{Cdc6}]$$

$$\frac{d[\mathrm{Cdc6P}]}{dt} = V_{kp,f6}\cdot[\mathrm{Cdc6}] - (k_{pp,f6}\cdot[\mathrm{Cdc14}] + k_{d3,f6})\cdot[\mathrm{Cdc6P}] + V_{d,b2}\cdot[\mathrm{F2P}] + V_{d,b5}\cdot[\mathrm{F5P}]$$

$$V_{kp,f6} = k_{d1,f6} + \frac{k_{d2,f6}\cdot(\varepsilon_{f6,n3}\cdot[\mathrm{Cln3}] + \varepsilon_{f6,k2}\cdot[\mathrm{Bck2}] + \varepsilon_{f6,n2}\cdot[\mathrm{Cln2}] + \varepsilon_{f6,b5}\cdot[\mathrm{Clb5}] + \varepsilon_{f6,b2}\cdot[\mathrm{Clb2}])}{J_{d2,f6} + [\mathrm{Cdc6}]_T}$$

$$\frac{d[\mathrm{F2}]}{dt} = k_{as,f2}\cdot[\mathrm{Clb2}]\cdot[\mathrm{Cdc6}] + k_{pp,f6}\cdot[\mathrm{Cdc14}]\cdot[\mathrm{F2P}] - (k_{di,f2} + V_{d,b2} + V_{kp,f6})\cdot[\mathrm{F2}]$$

$$\frac{d[\mathrm{F2P}]}{dt} = V_{kp,f6}\cdot[\mathrm{F2}] - (k_{pp,f6}\cdot[\mathrm{Cdc14}] + k_{d3,f6} + V_{d,b2})\cdot[\mathrm{F2P}]$$

$$\frac{d[\mathrm{F5}]}{dt} = k_{as,f5}\cdot[\mathrm{Clb5}]\cdot[\mathrm{Cdc6}] + k_{pp,f6}\cdot[\mathrm{Cdc14}]\cdot[\mathrm{F5P}] - (k_{di,f5} + V_{d,b5} + V_{kp,f6})\cdot[\mathrm{F5}]$$

$$\frac{d[\mathrm{F5P}]}{dt} = V_{kp,f6}\cdot[\mathrm{F5}] - (k_{pp,f6}\cdot[\mathrm{Cdc14}] + k_{d3,f6} + V_{d,b5})\cdot[\mathrm{F5P}]$$

$$[\mathrm{Sic1}]_T = [\mathrm{Sic1}] + [\mathrm{Sic1P}] + [\mathrm{C2}] + [\mathrm{C5}] + [\mathrm{C2P}] + [\mathrm{C5P}]$$

$$[\mathrm{Cdc6}]_T = [\mathrm{Cdc6}] + [\mathrm{Cdc6P}] + [\mathrm{F2}] + [\mathrm{F5}] + [\mathrm{F2P}] + [\mathrm{F5P}]$$

$$[\mathrm{CKI}]_T = [\mathrm{Sic1}]_T + [\mathrm{Cdc6}]_T$$

Equations governing Clb degradation machinery:

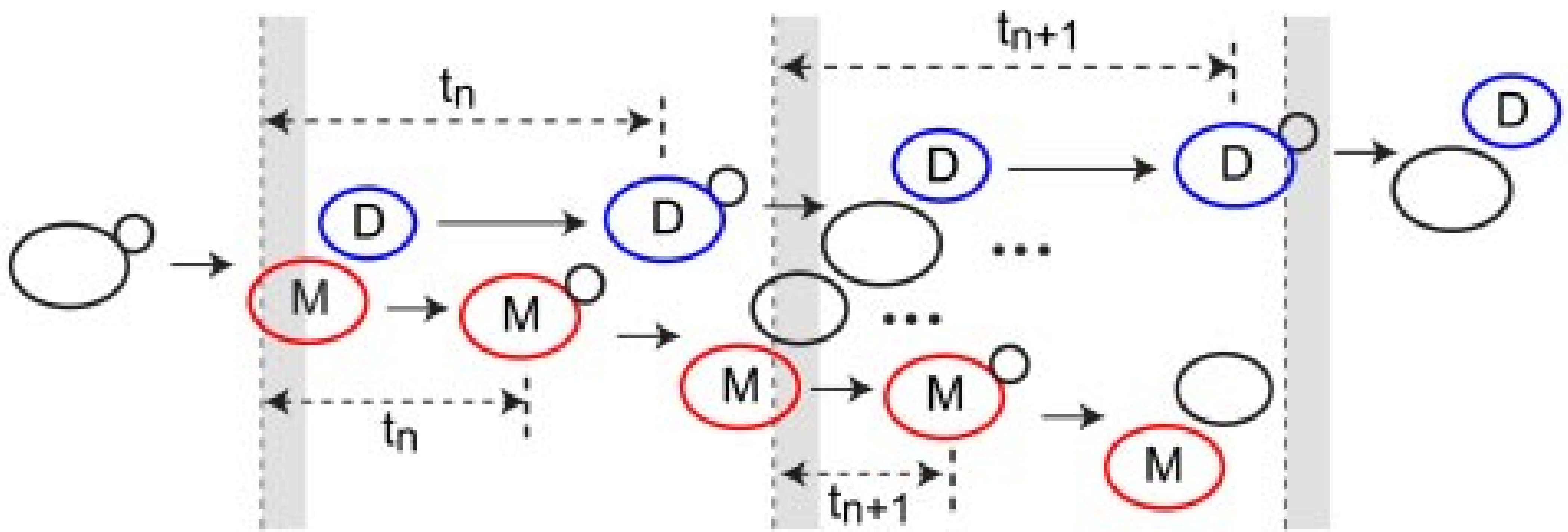
$$\frac{d[\mathrm{IEP}]}{dt} = \frac{k_{a,iep}\cdot[\mathrm{Clb2}]\cdot(1-[\mathrm{IEP}])}{J_{a,iep} + 1 - [\mathrm{IEP}]} - \frac{k_{i,iep}\cdot[\mathrm{IEP}]}{J_{i,iep} + [\mathrm{IEP}]}$$

HERE:

Generic features of oscillators

K Chen et al, 2004. http://mpf.biol.vt.edu/research/budding_yeast_model/pp/index.php

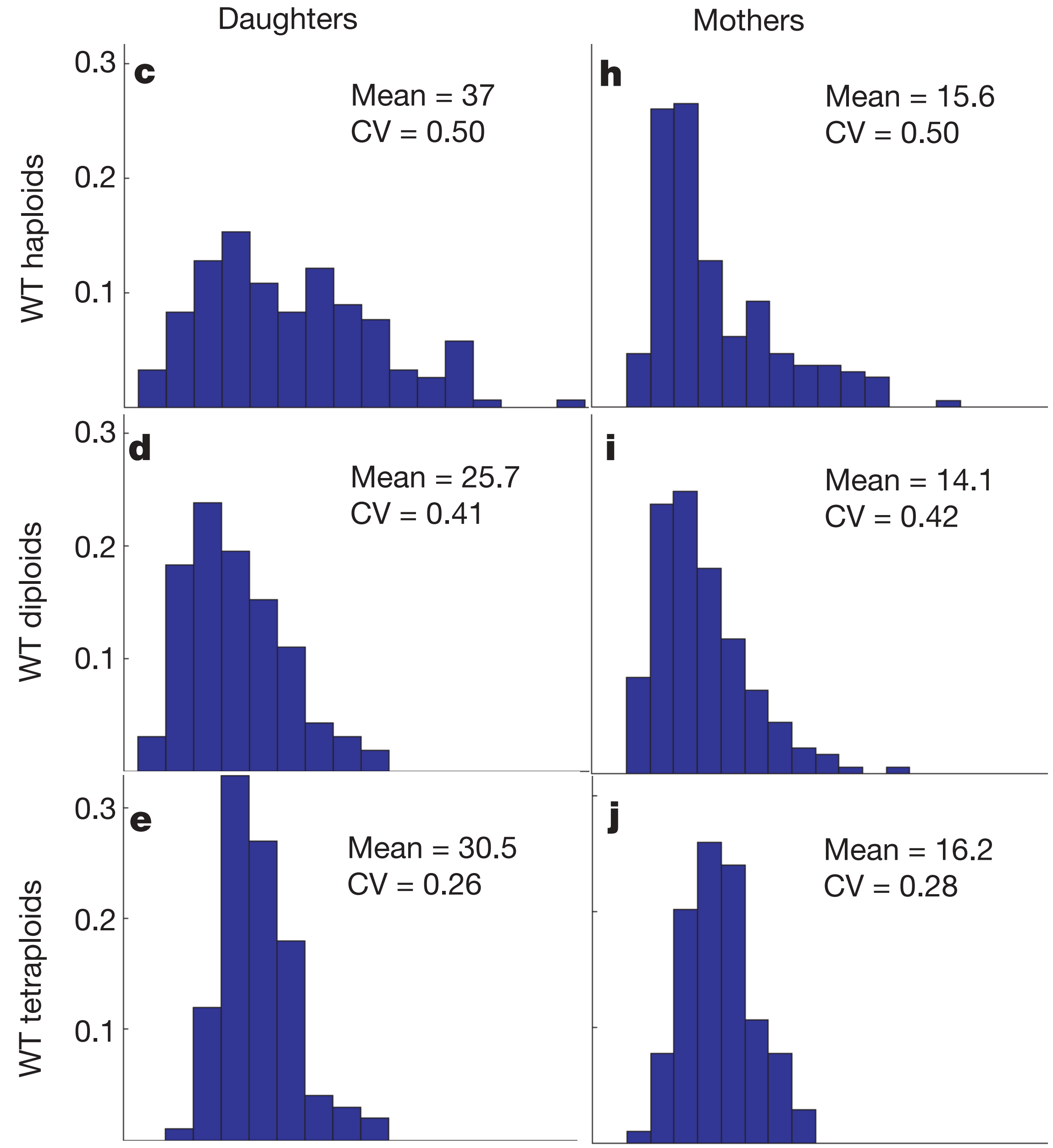
Examining the cell cycle

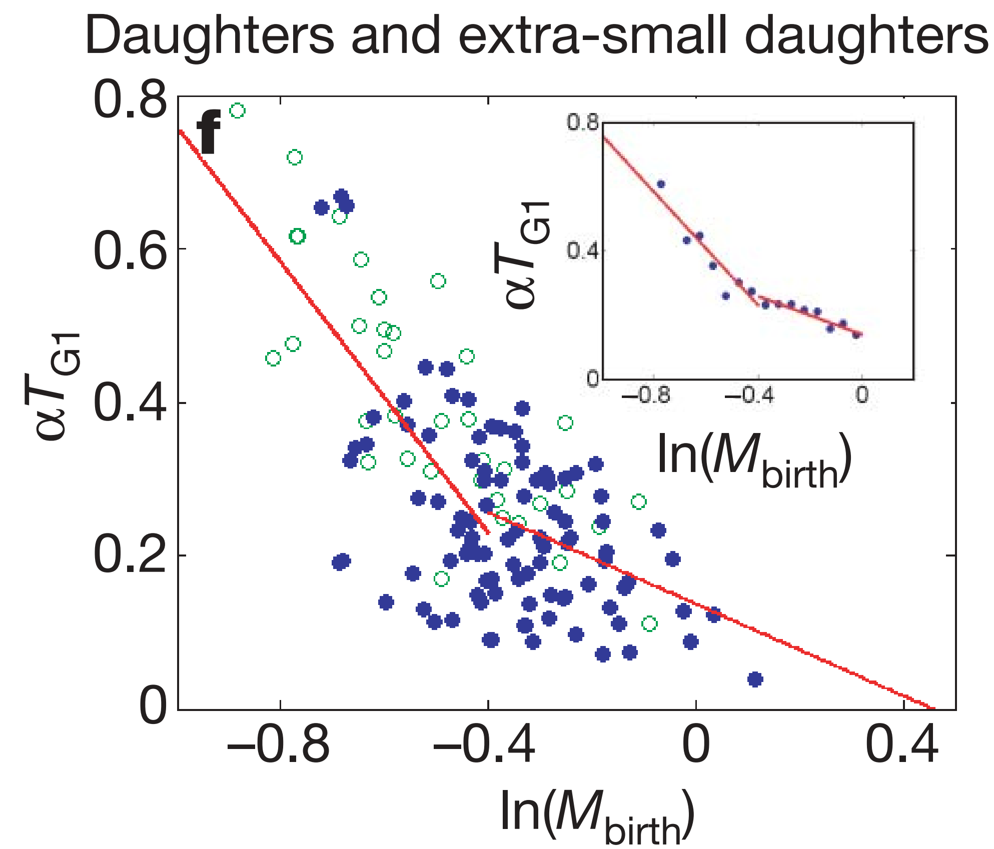


- Mothers and daughters have different sizes
- At budding, daughters are smaller than mothers
- Daughters take longer to bud than mothers
- Cells protein content grows exponentially

The number of molecules involved is small
$\longrightarrow$ noisy oscillations

Noise and size





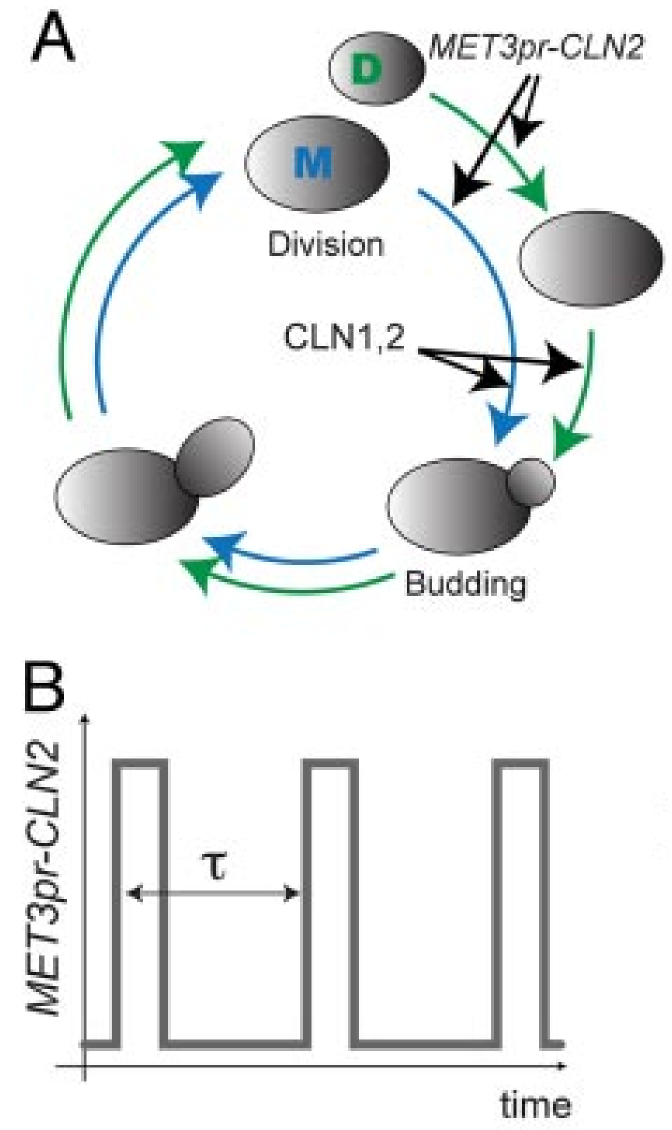
Small daughters need longer to grow to the right size before they can divide

2-fold or 4-fold gene doses reduce stochasticity

Phase locking the cell cycle

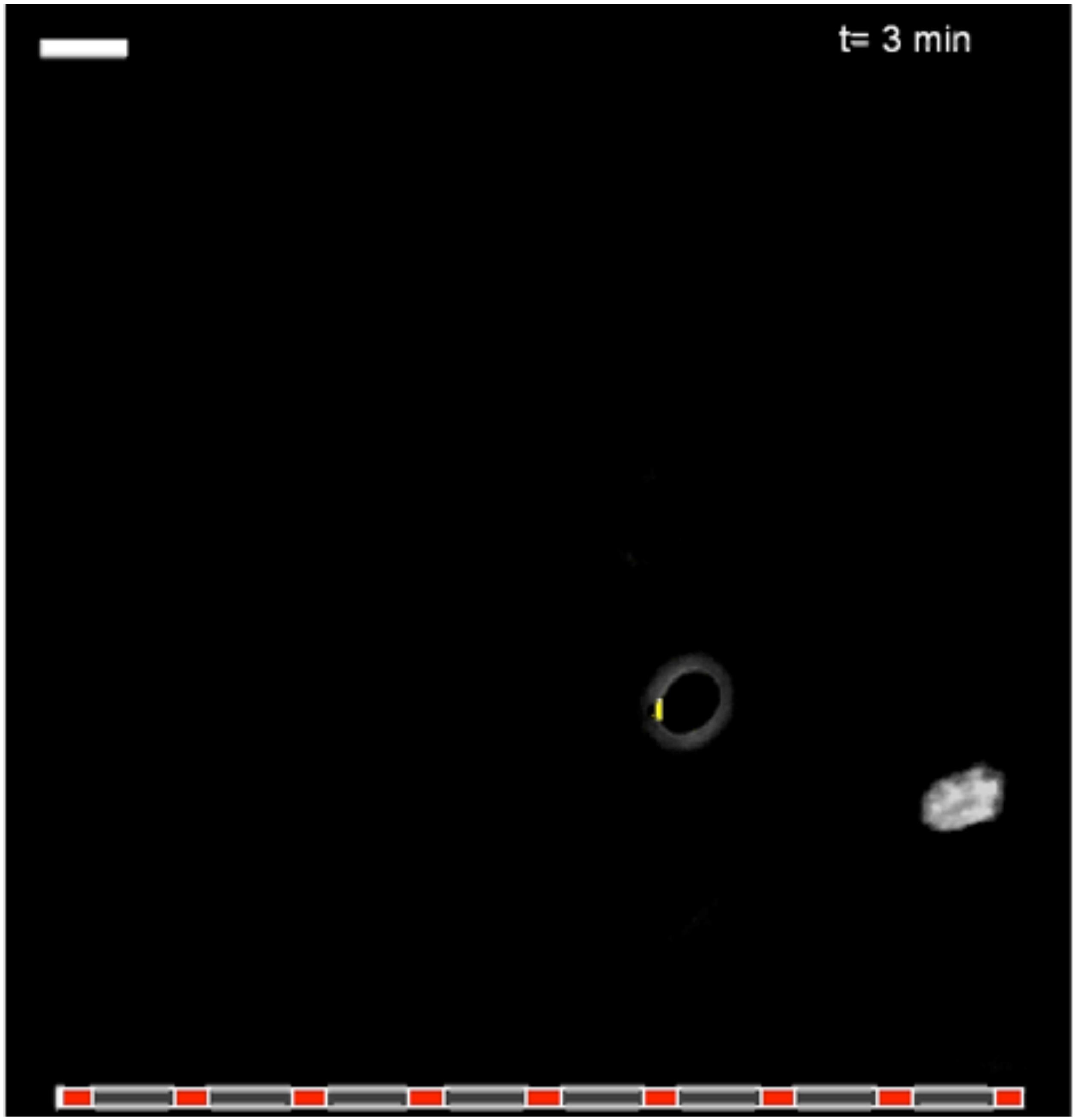
Cell cycle is heavily regulated, which many checkpoints that prevent progression (negative signals).

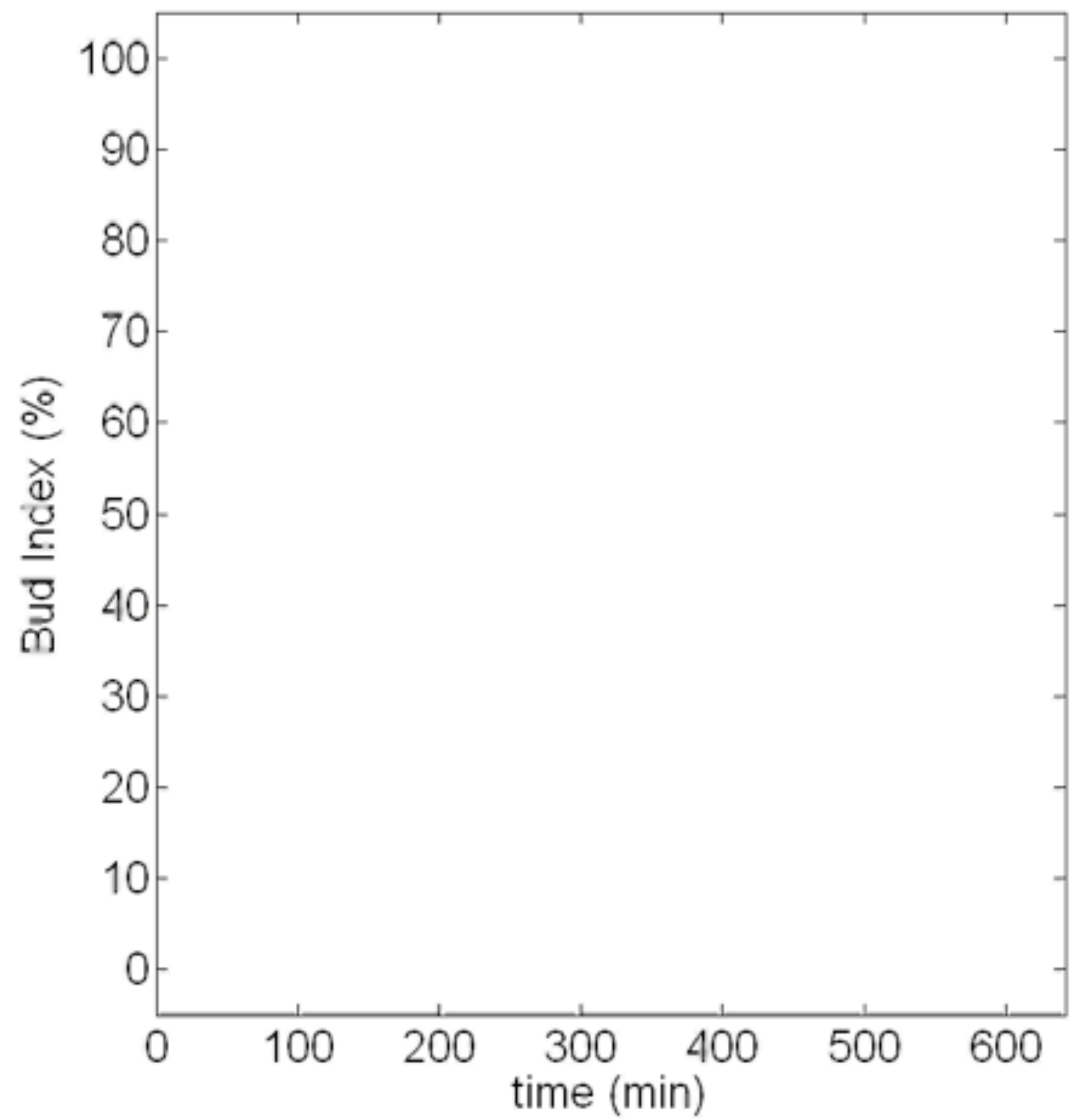
- unclear whether the period is plastic and can be driven by an external signal



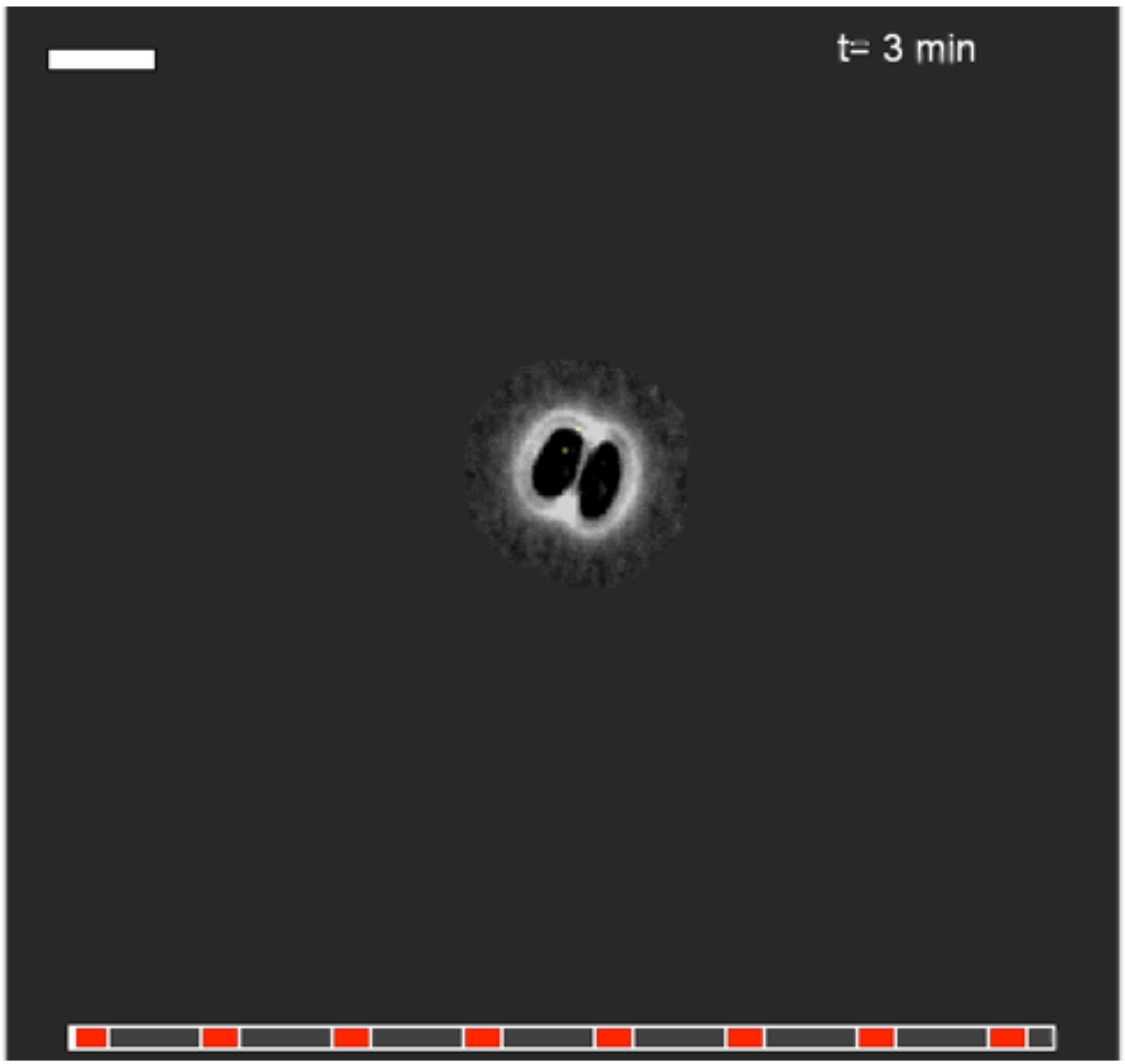
periodic expression of a cell cycle component

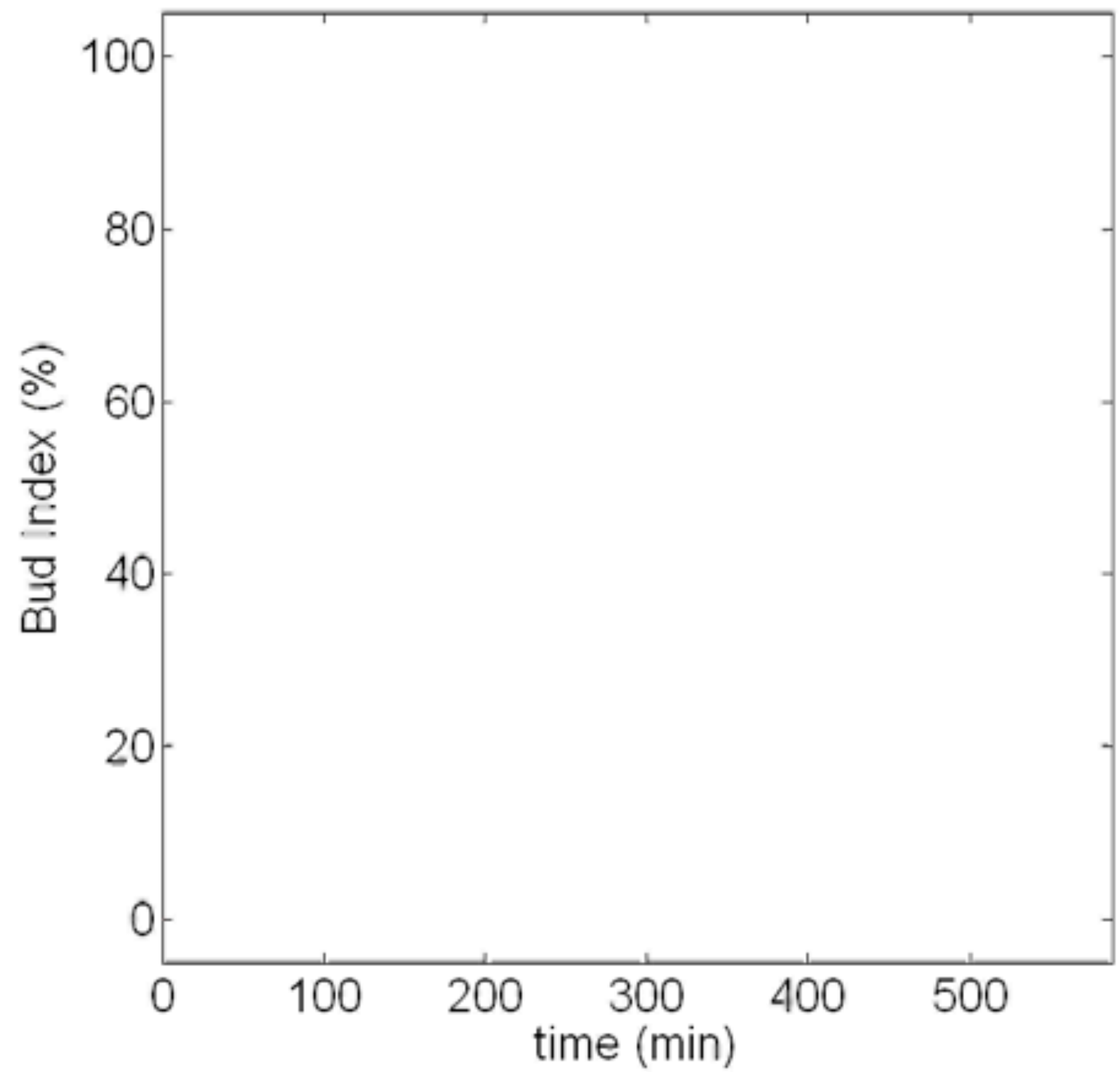
Stochastic effects desync cells



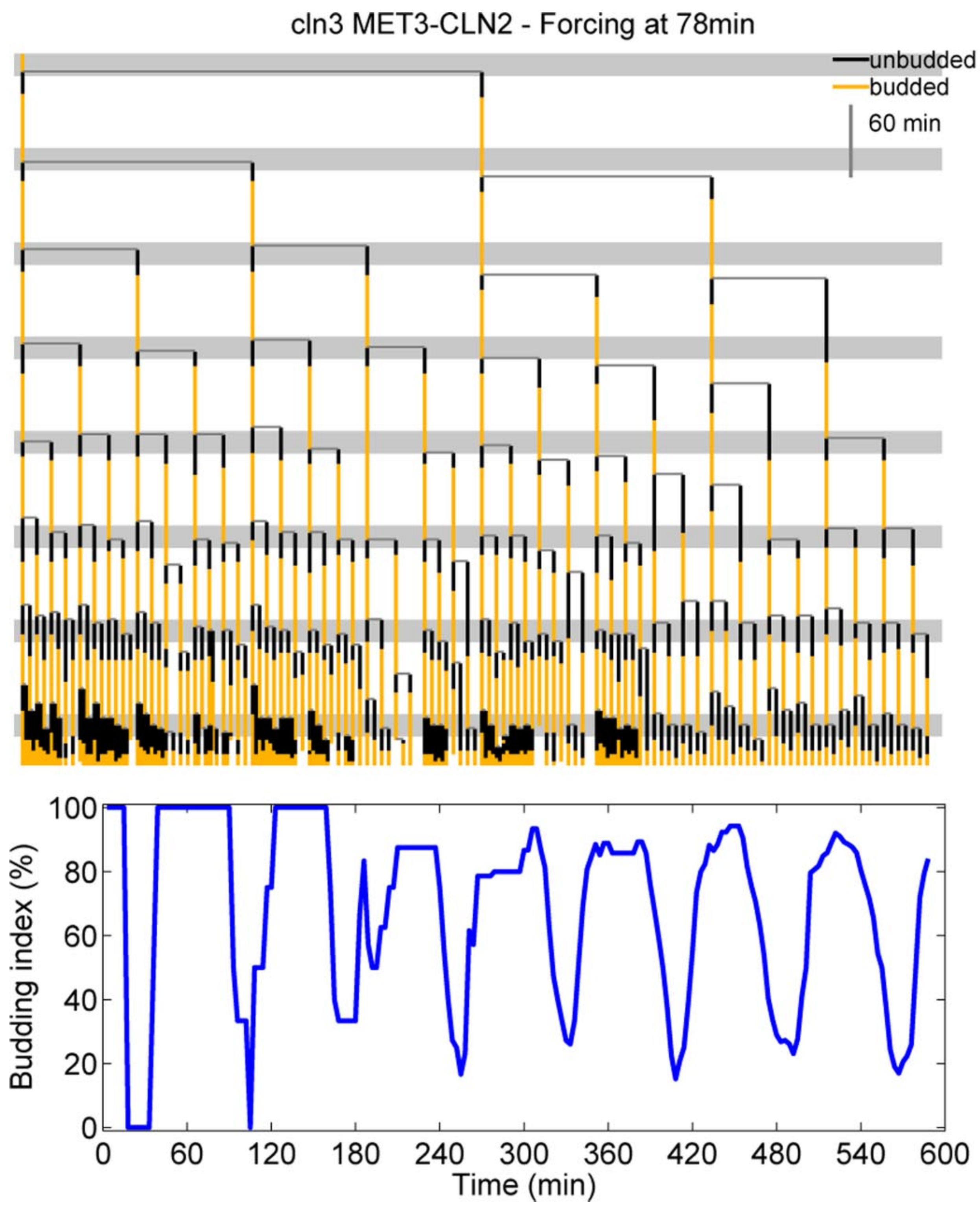


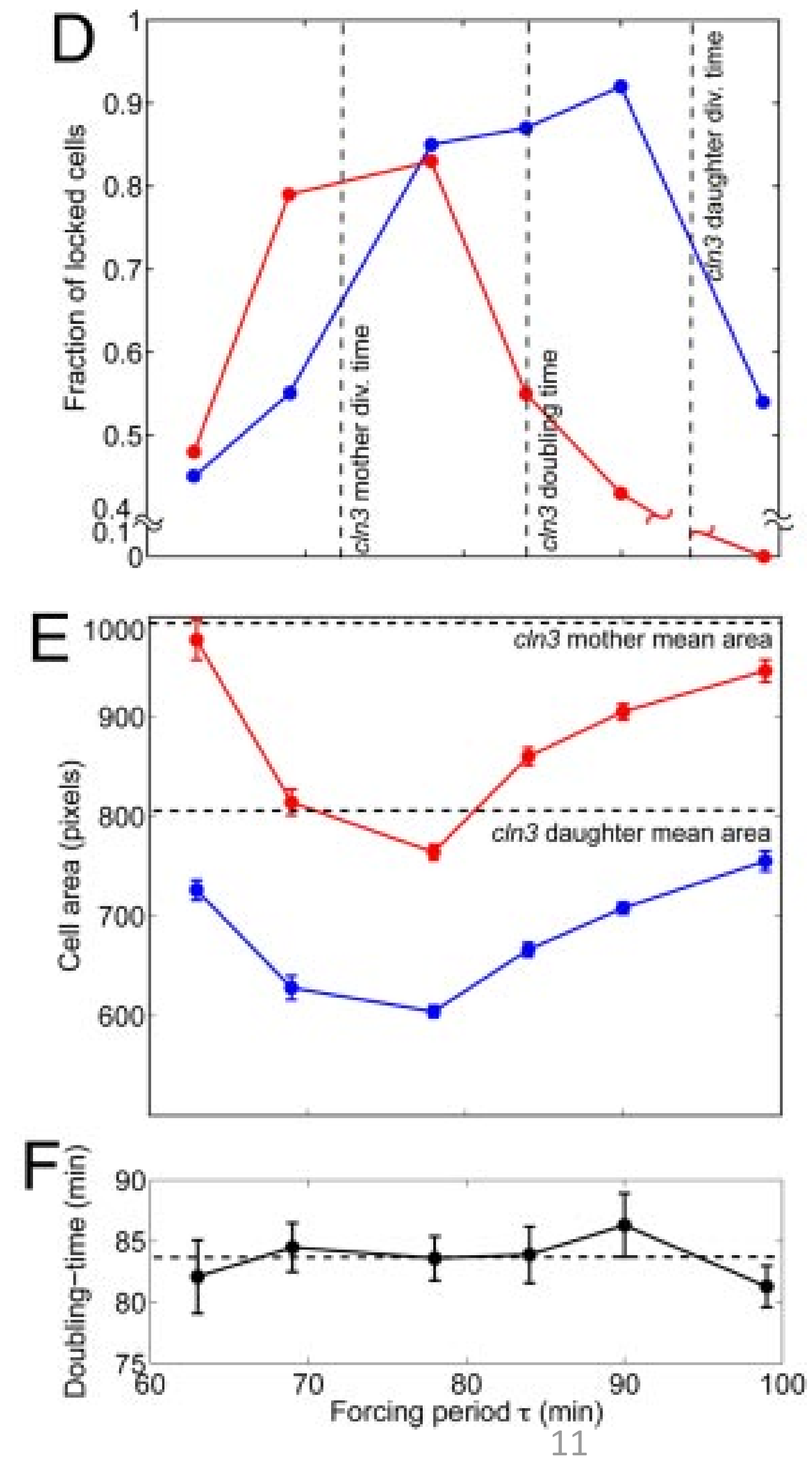
Phase-locked yeast colony



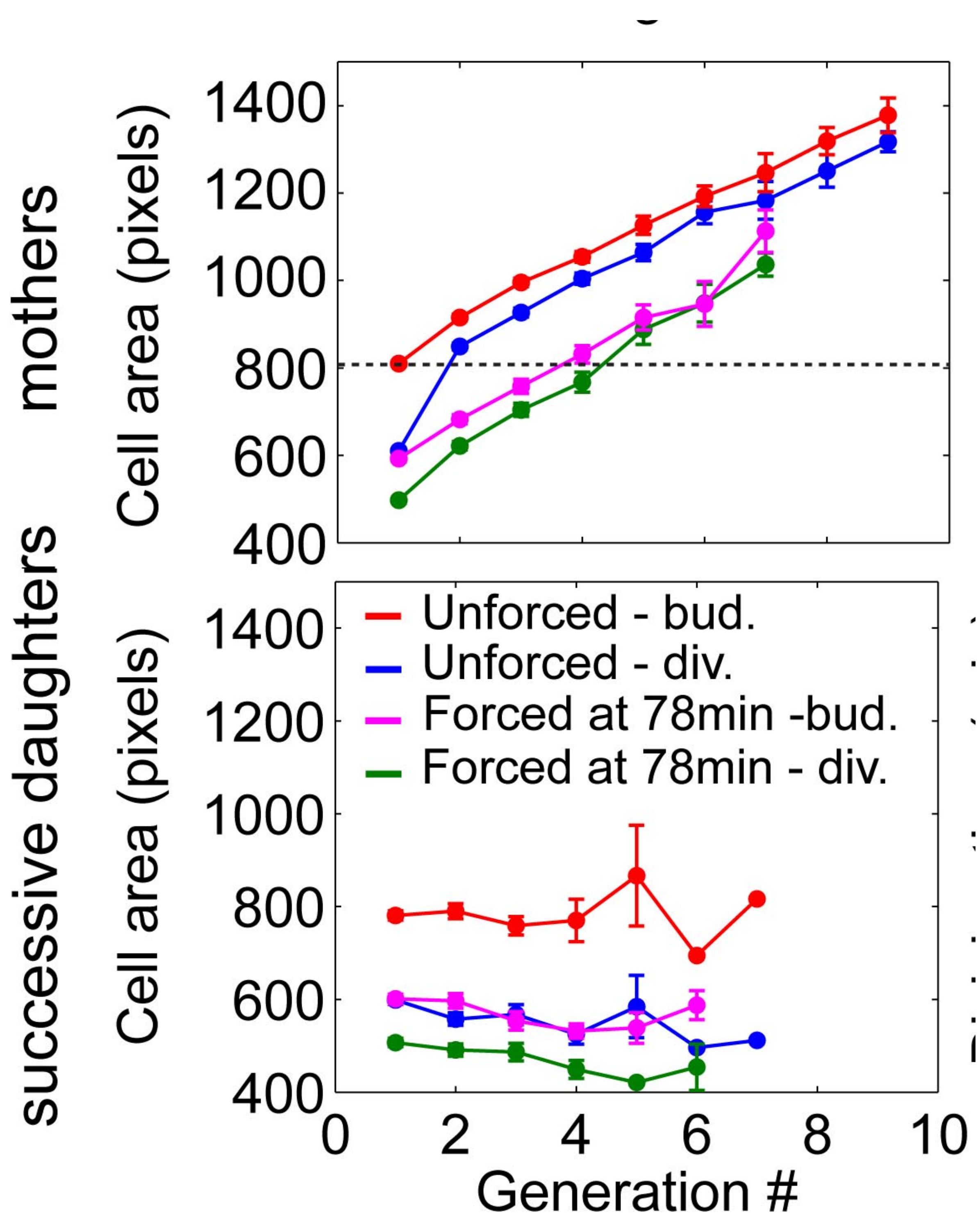


Phase-locking





Dynamics of cell volume over time



Mothers increase in size

Daughter size is constant