Bistability, trigger waves, and coupled oscillations in the embryonic cell cycle

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- Cdk1 has a bistable response to cyclin

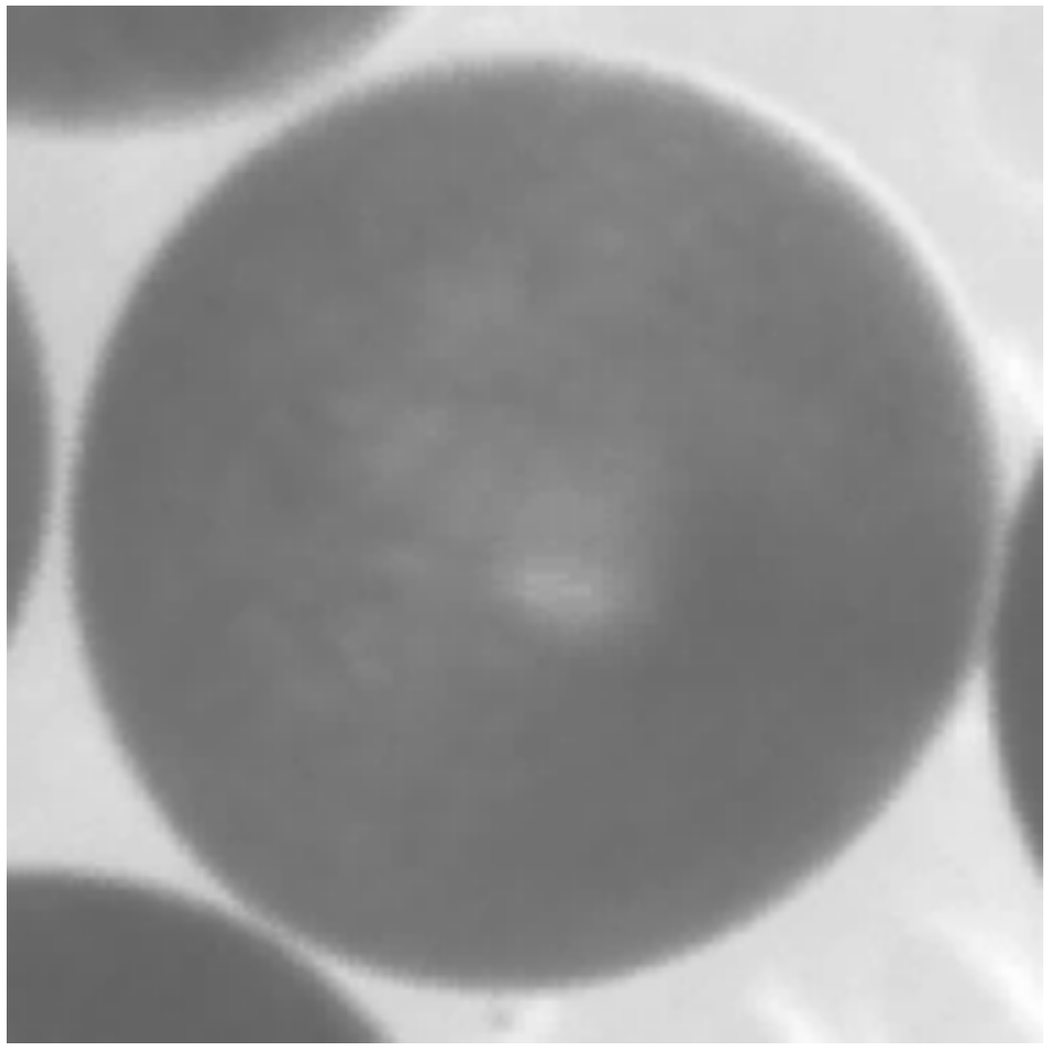
- This bistability gives rise to trigger waves, which help to spatially coordinate mitosis in the huge frog egg

- In a multicellular frog embryo, the cell cycle oscillators are coupled

Cell cycles in *Xenopus laevis* embryos

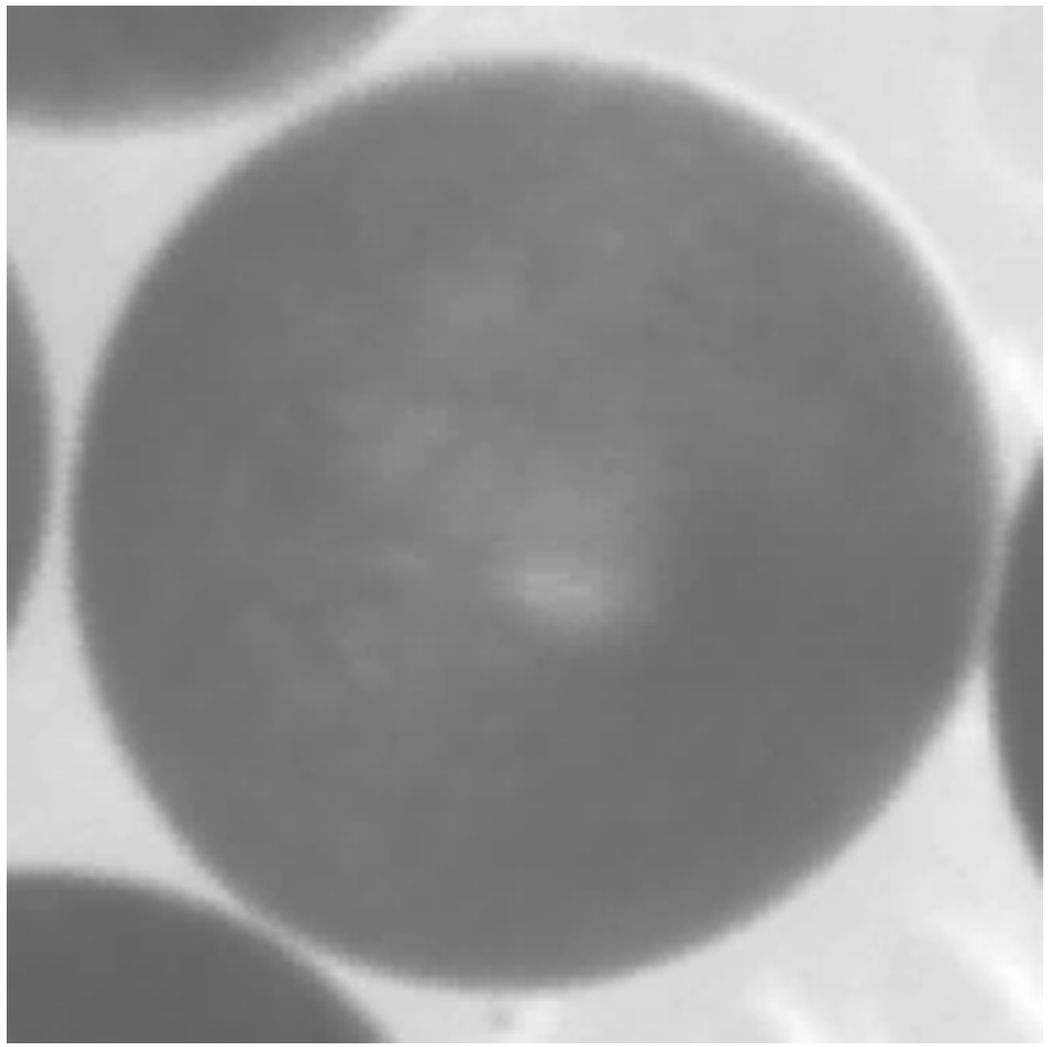
J Chang, unpublished

Cell cycles in *Xenopus laevis* embryos



J Chang, unpublished

Cell cycles in *Xenopus laevis* embryos



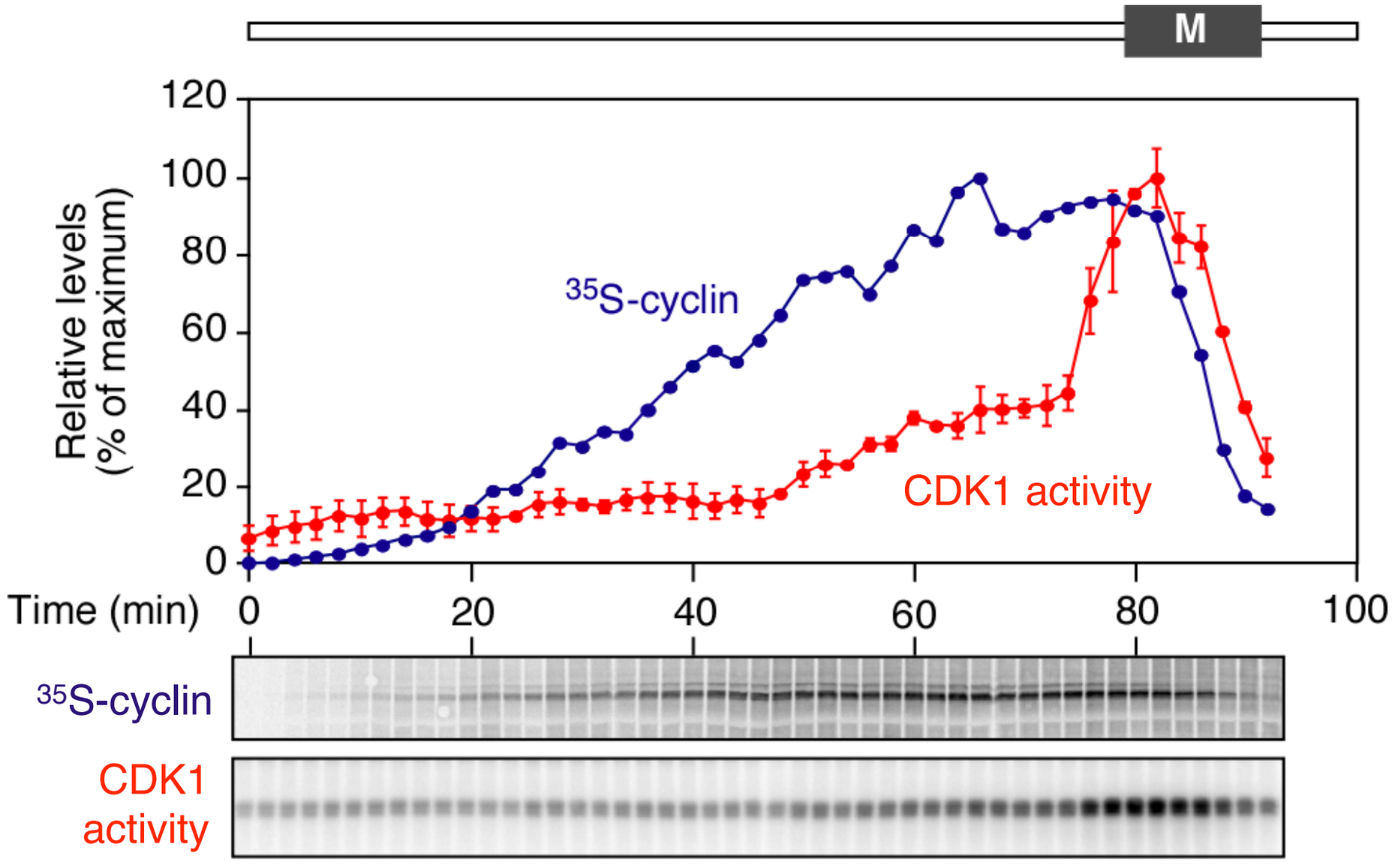
Autonomous, precise

How are these oscillations produced?

How is spatial coordination ensured?

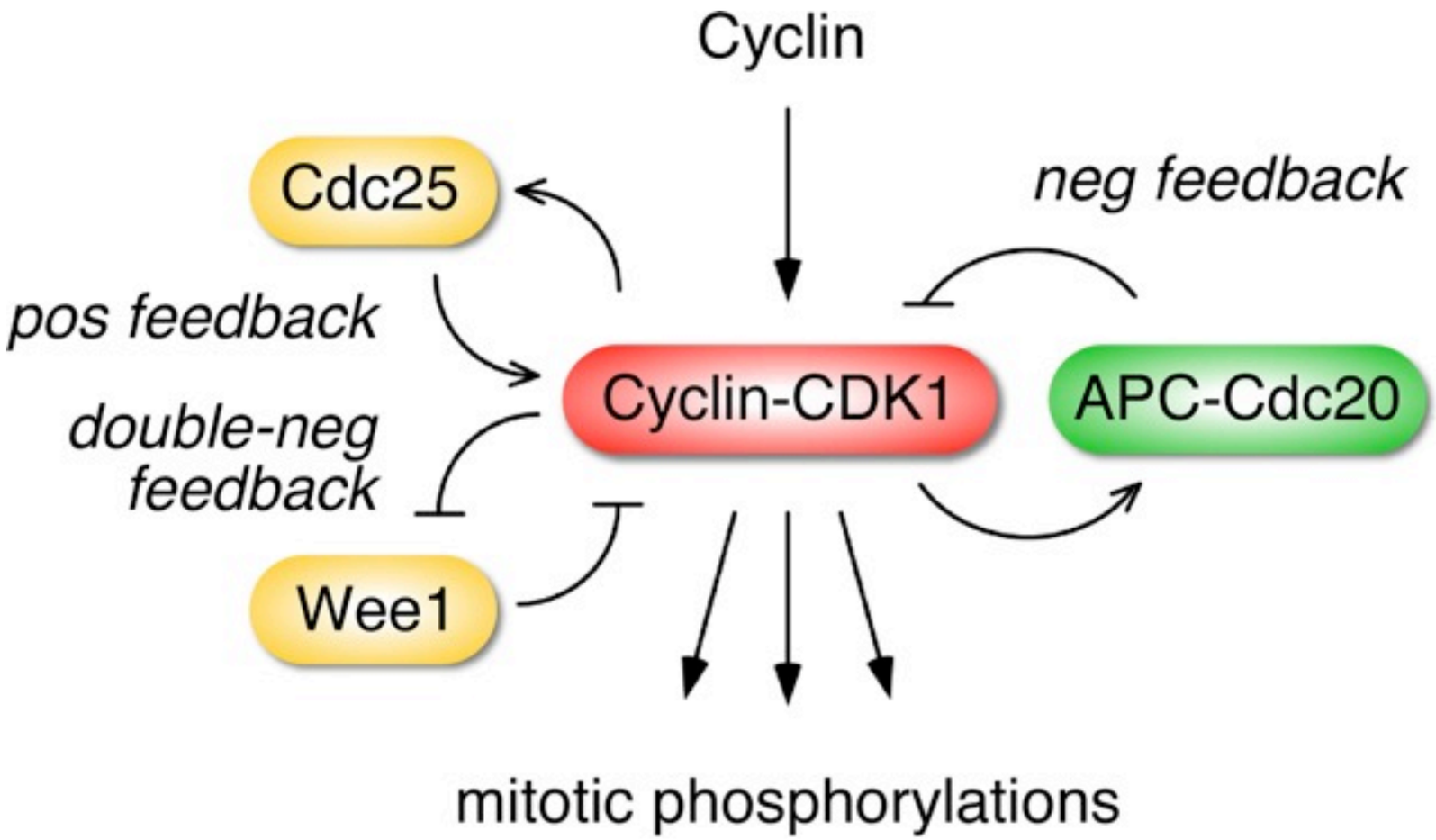
J Chang, unpublished

Periodic synthesis/degradation of cyclin drives the activation/inactivation of CDK1, which drives mitotic entry and exit

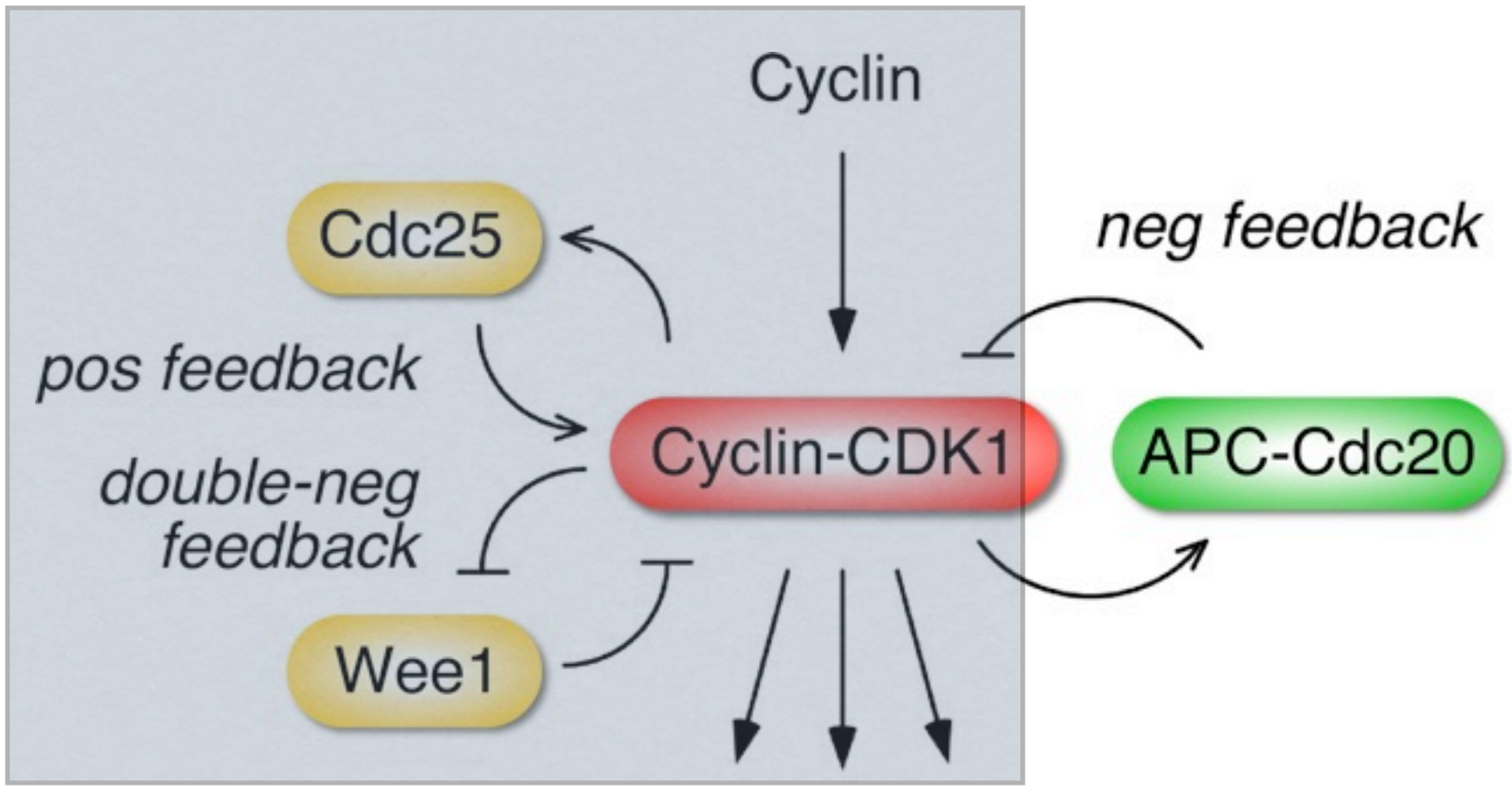


Pomerening JR et al. (2005) Cell 122 565-578.

The core oscillator circuit

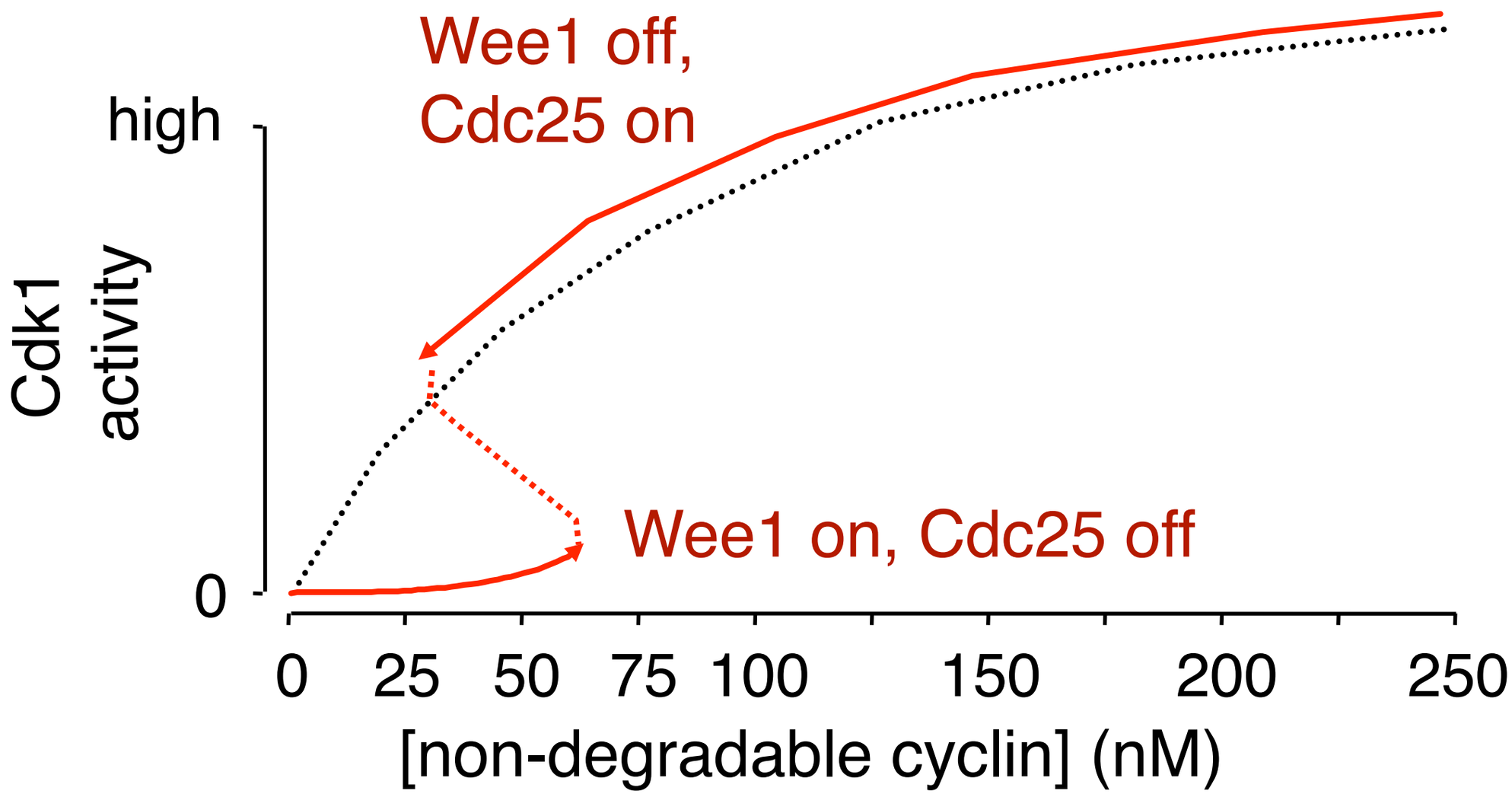


Function of the positive and double-negative feedback loops as a sub-module?



mitotic phosphorylations

Bistability



The shape of the response can be determined in *Xenopus* egg extracts

Eggs

Packed

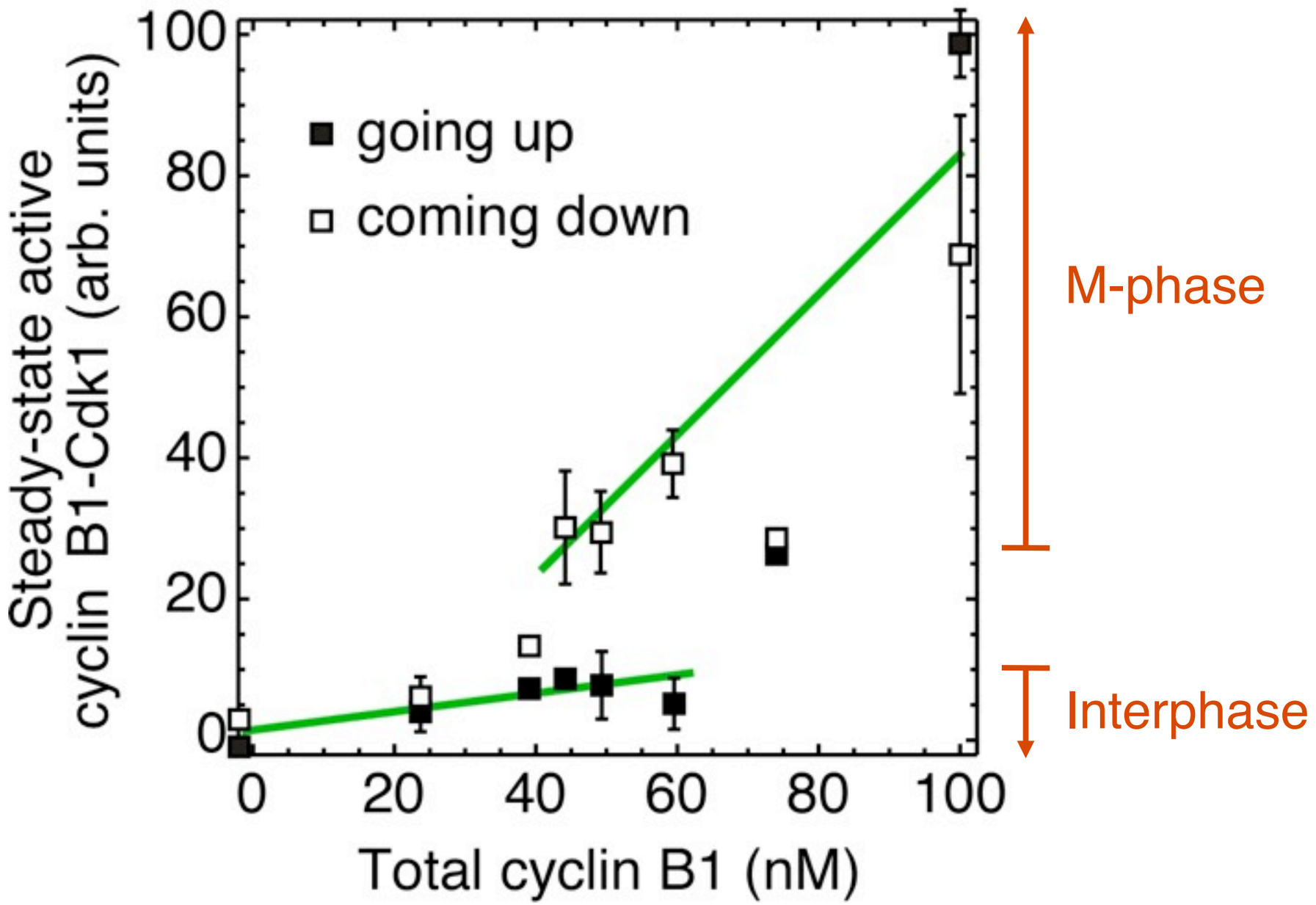
Spun a bit harder

Add some sperm chromatin as a ‘reporter’ of the extract’s cell cycle state…

Can make M-phase extracts, interphase extracts, cycling extracts

Murray AW, Kirschner MW (1989) *Nature* 339 275-280.

Hysteresis in the steady-state response



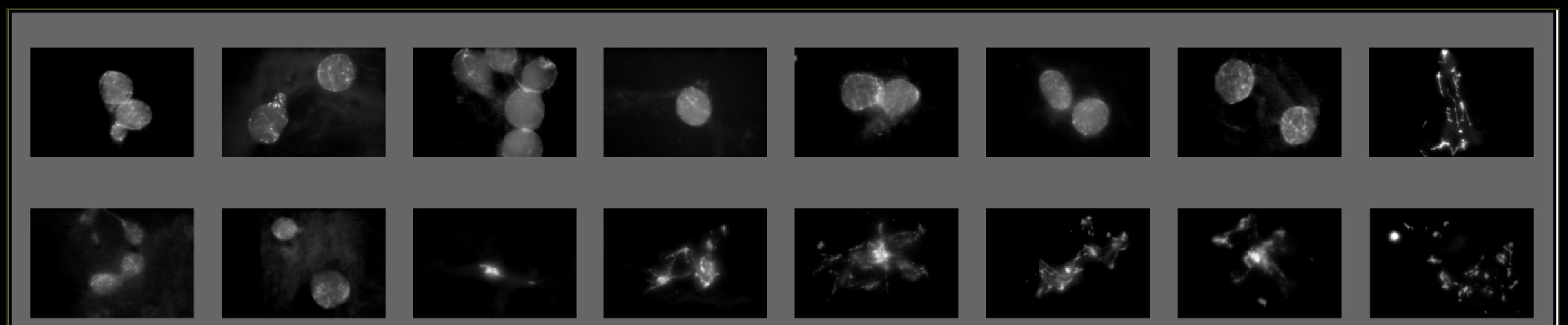
Sha W et al. (2003) *PNAS* **100**:975-980
Pomerening JR, Sontag ED, Ferrell JE Jr. (2003) *Nat Cell Biol* **5**:346-351

Hysteresis in the "cell biology" of mitosis

going up

[Δ65 cyclin B1] (nM) →

25 40 45 50 55 60 100



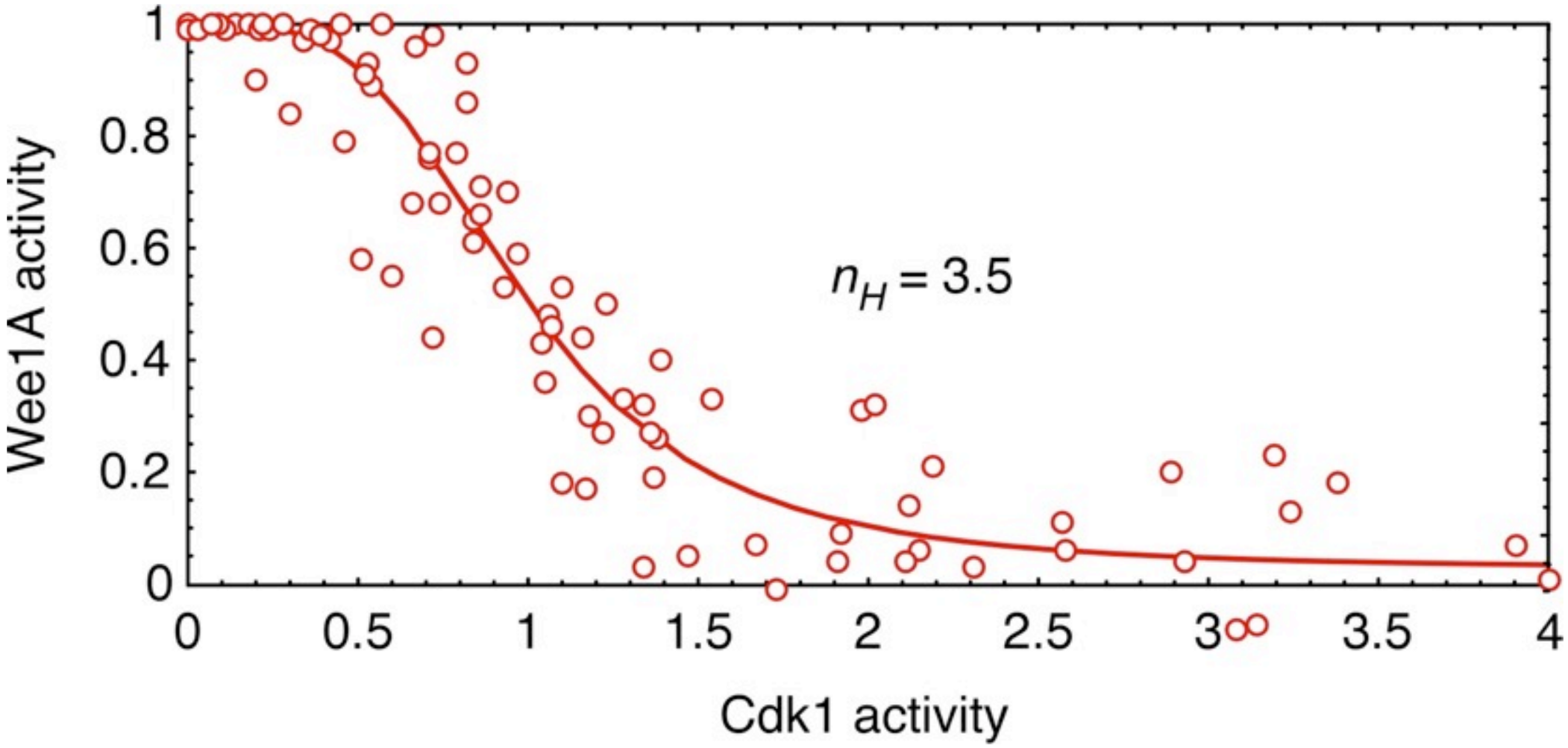
0 25 40 45 50 55 60 100

←

coming down

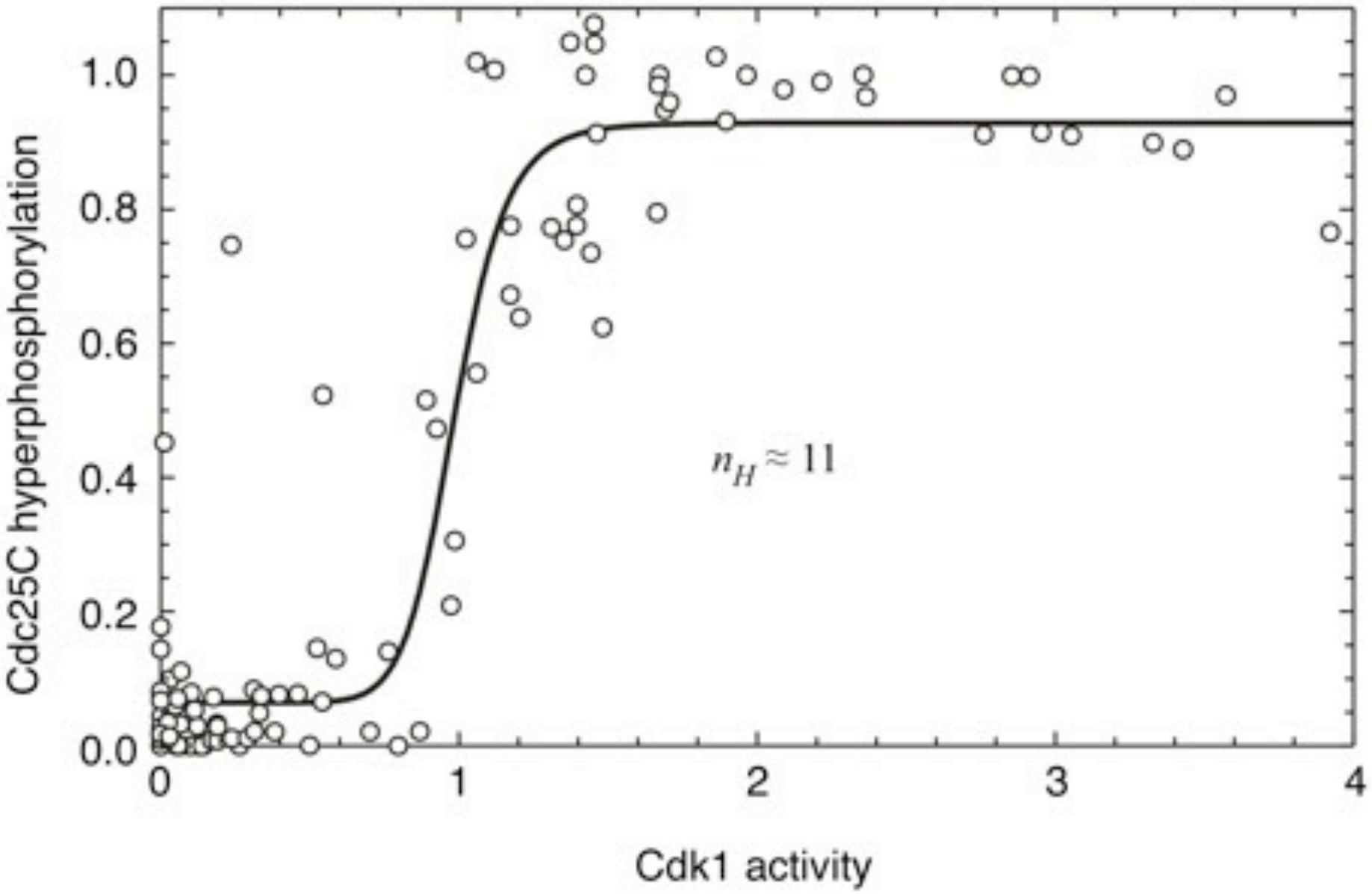
Pomerening JR, Sontag ED, Ferrell JE Jr. (2003) *Nat Cell Biol* **5**:346-351

This bistability is made possible by ultrasensitivity in the steady-state response of Wee1A to Cdk1... [mechanism?]



Kim SY, Ferrell JE Jr. (2007) *Cell* **128**:1133-1145.

and by ultrasensitivity in the steady-state response of Cdc25C to Cdk1... [mechanism?]



Trunnell NB, Poon ACY, Ferrell JE Jr. (2011) *Mol Cell* **128**:1133-1145.

With these two ultrasensitive response functions, can we reconstruct the hysteretic response of Cdk1 to cyclin B1?

$$\frac{d}{dt}Cdk1_{act} = k_{act}Cdc25 * Cdk1_{inact} - k_{inact}Wee1 * Cdk1_{act}$$

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$$0 = \left(a_{Cdc25} + b_{Cdc25}\frac{Cdk1_{act}^{11}}{EC50_{Cdc25}^{11} + Cdk1_{act}^{11}}\right)Cdk1_{inact} - \left(a_{Wee1} + b_{Wee1}\frac{EC50_{Wee1}^{3.5}}{EC50_{Wee1}^{3.5} + Cdk1_{act}^{3.5}}\right)Cdk1_{act}$$

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$$0 = \left(a_{Cdc25} + b_{Cdc25}\frac{Cdk1_{act}^{11}}{EC50_{Cdc25}^{11} + Cdk1_{act}^{11}}\right)\left(Cyclin_{tot} - Cdk1_{act}\right) - \left(a_{Wee1} + b_{Wee1}\frac{EC50_{Wee1}^{3.5}}{EC50_{Wee1}^{3.5} + Cdk1_{act}^{3.5}}\right)Cdk1_{act}$$

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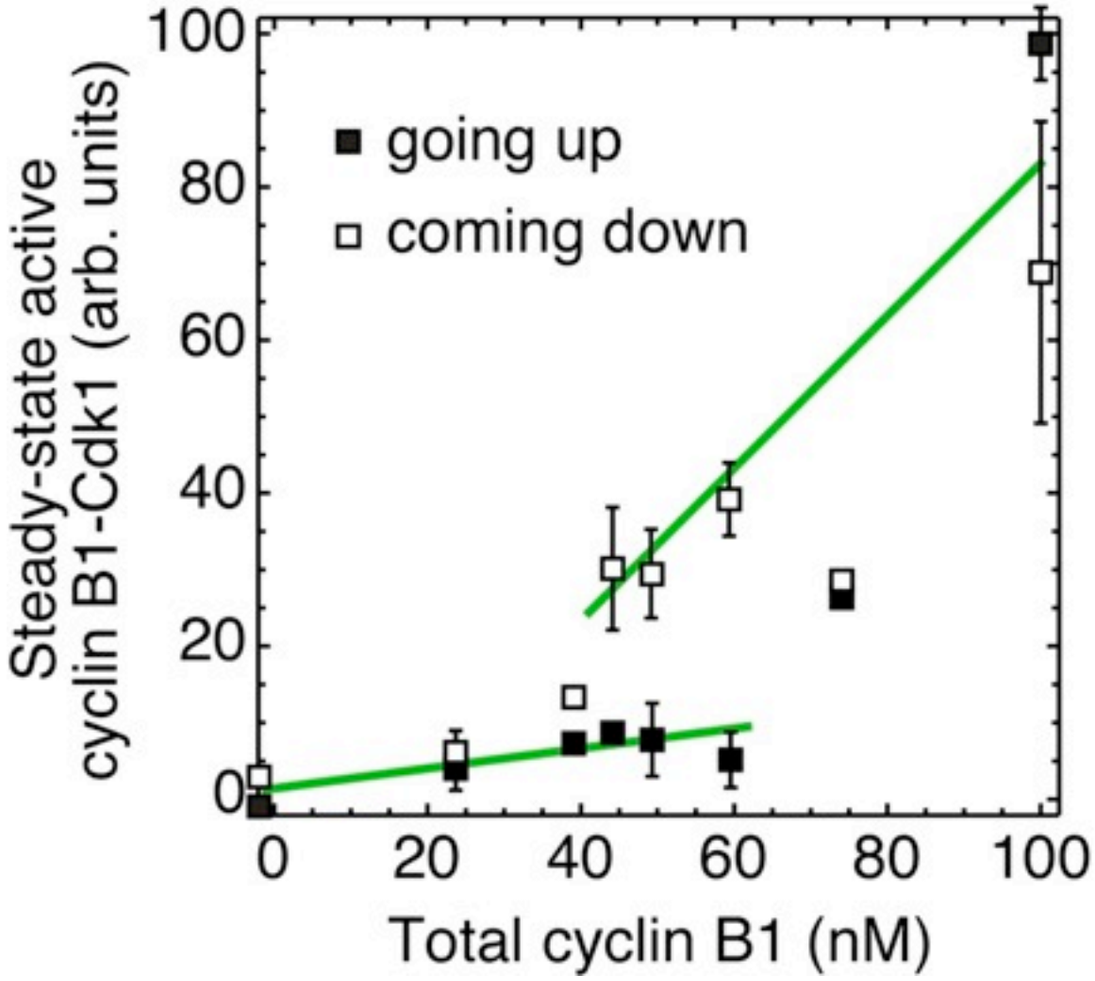
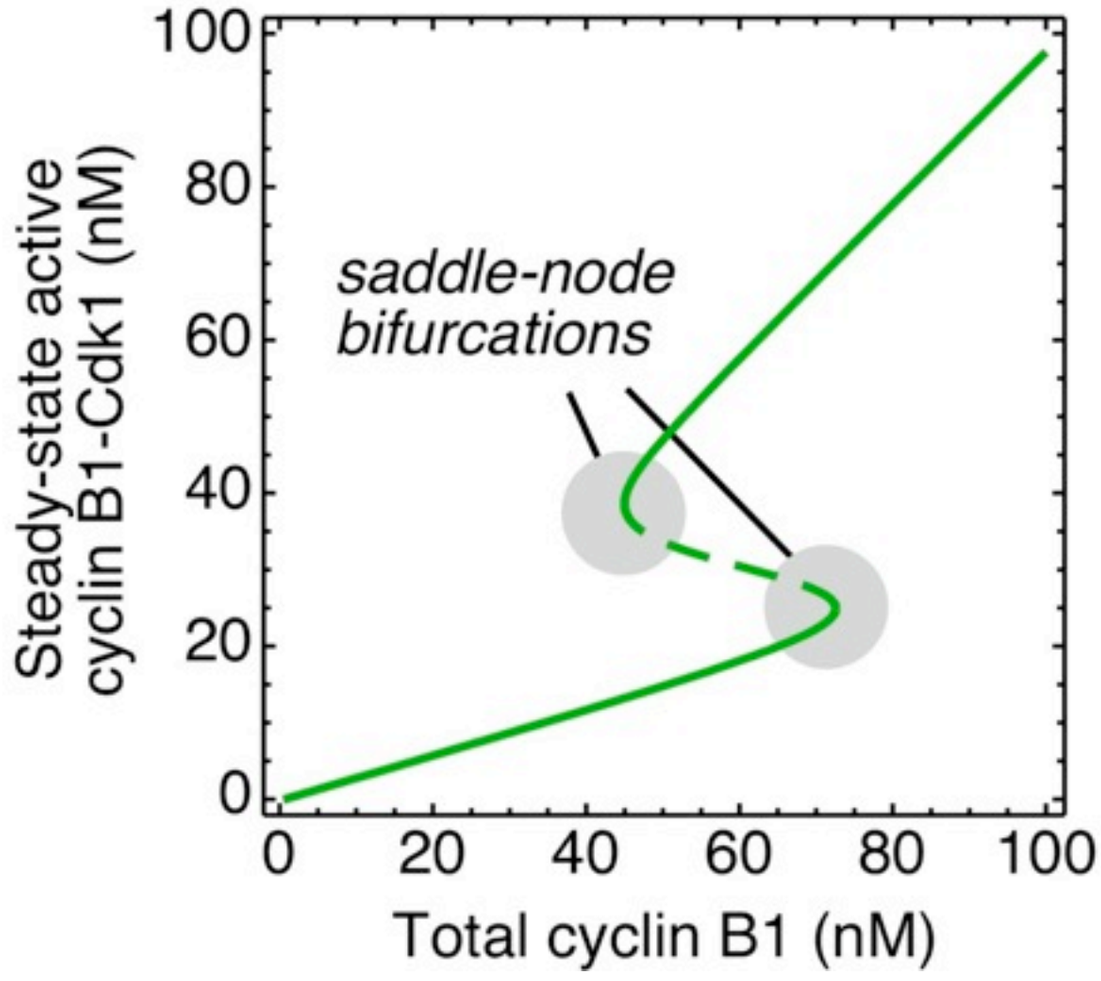
These two ultrasensitive response functions yield the hysteretic response of Cdk1 to cyclin B1





Trunnell NB, Poon ACY, Ferrell JE Jr. (2011) *Mol Cell* **128**:1133-1145.

From bistability to oscillations

$$\frac{d}{dt}Cdk1_{act} = k_{act}Cdc25*\left(Cyclin_{tot} - Cdk1_{act}\right) - k_{inact}Wee1*Cdk1_{act} + k_{synth} - k_{dest}APC*Cdk1_{act}$$

$$\frac{d}{dt}Cyclin_{tot} = k_{synth} - k_{dest}APC*Cyclin_{tot}$$

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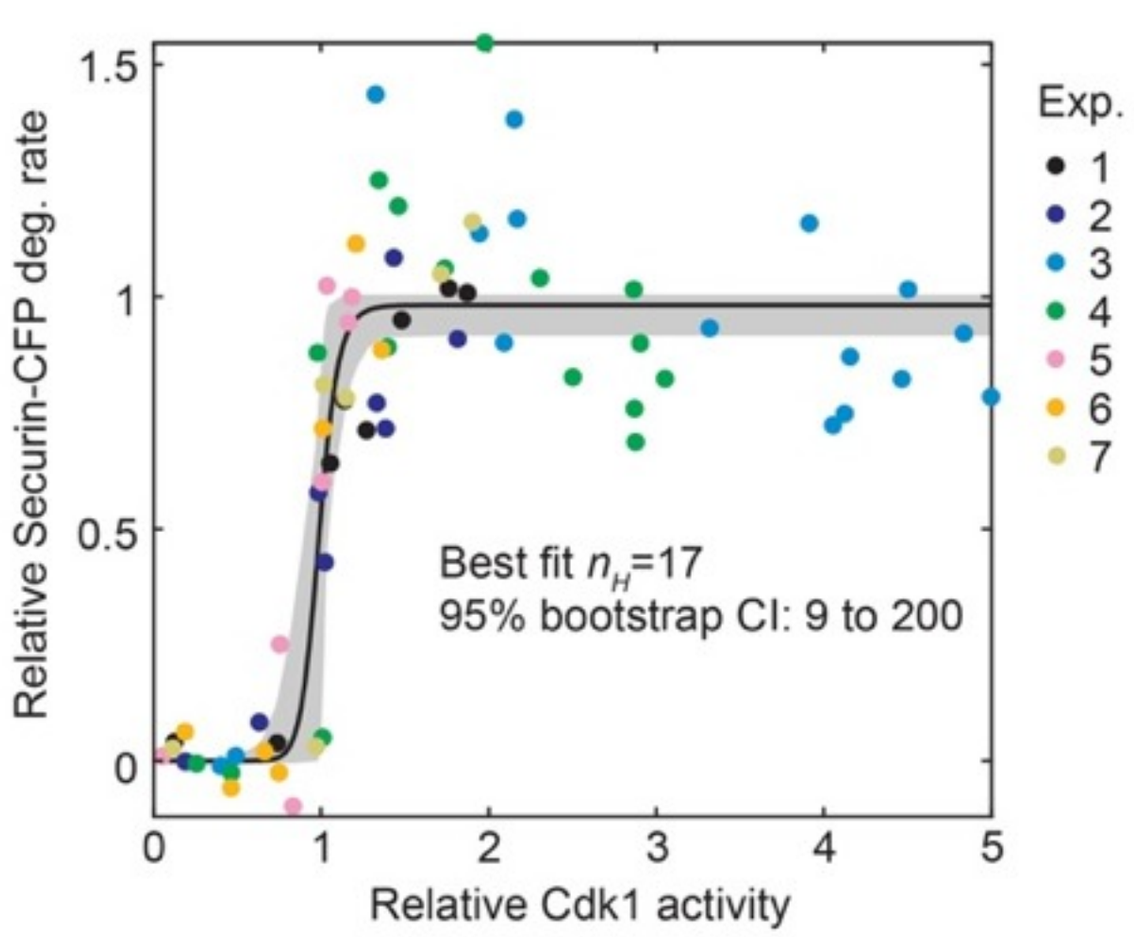

Yang Q, unpublished

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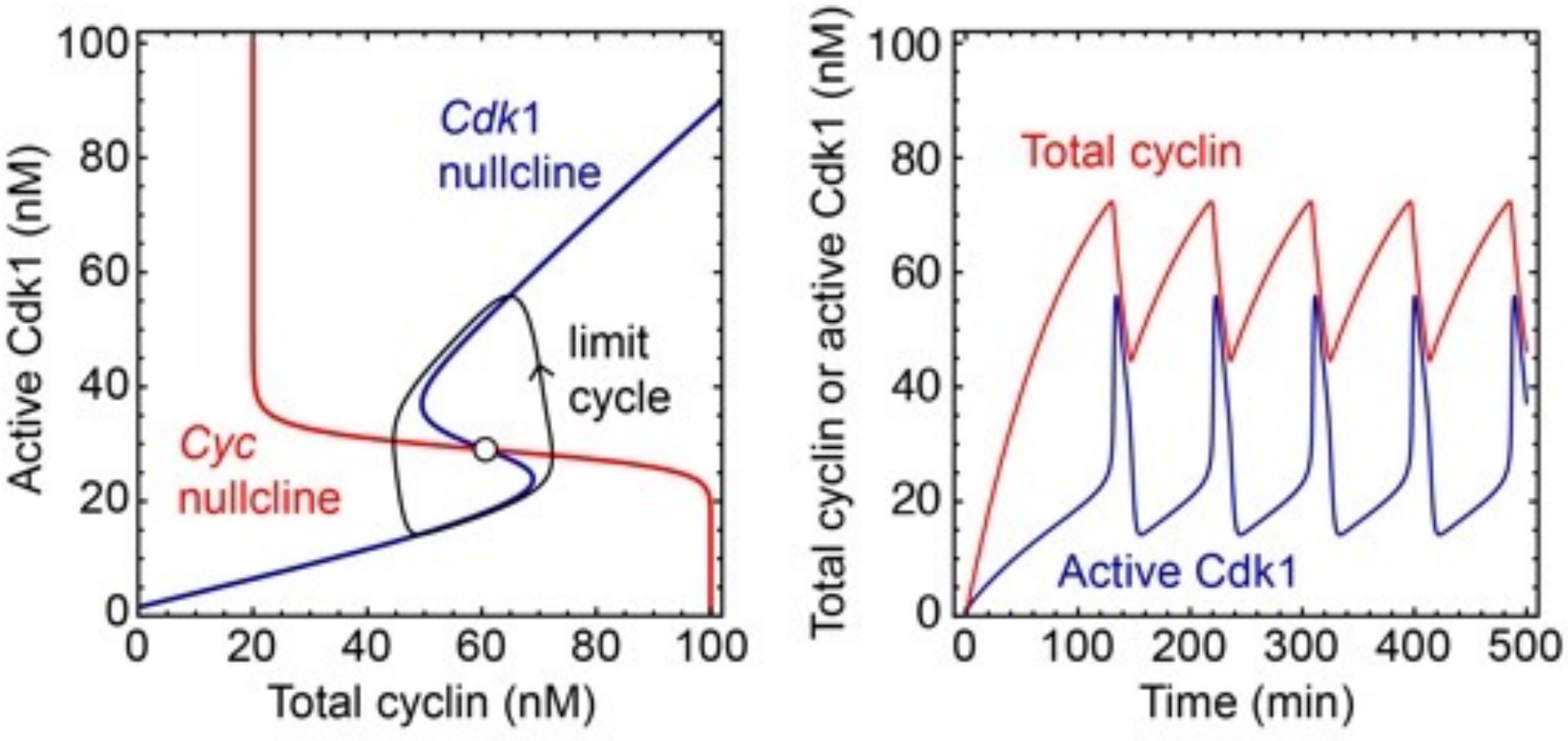

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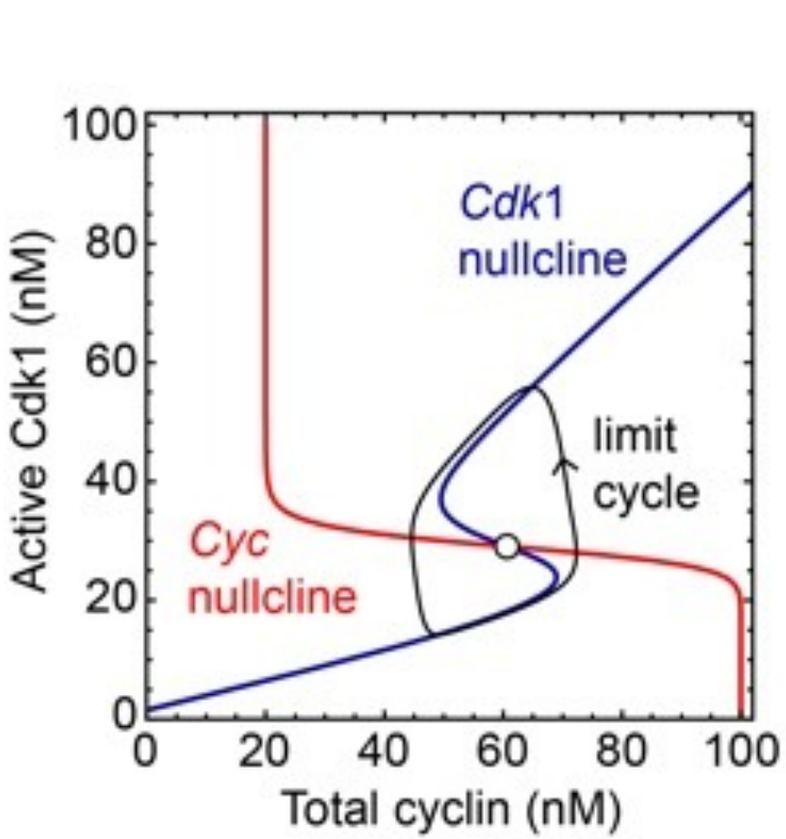

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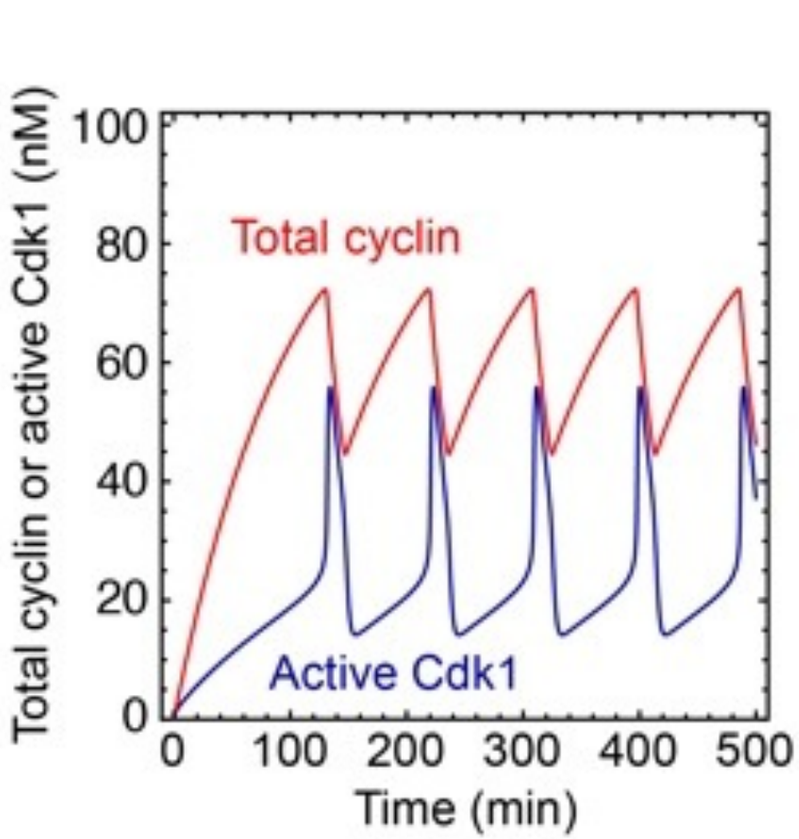

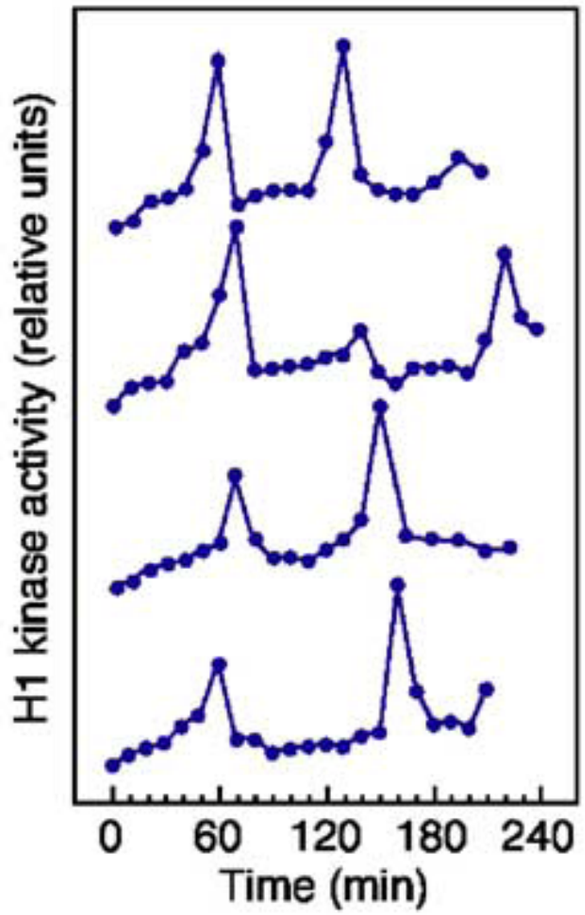

Pomerening & Ferrell Cell 2005

Summary of Part 1:

- Cdk1 activation is hysteretic, bistable
- The positive and double-negative feedback loops are built with highly ultrasensitive response functions
- The transition into mitosis occurs through the traversal of a saddle-node bifurcation
- Add cyclin synthesis and (ultrasensitive) destruction and you get a relaxation oscillator

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