The physical basis of biological rhythms

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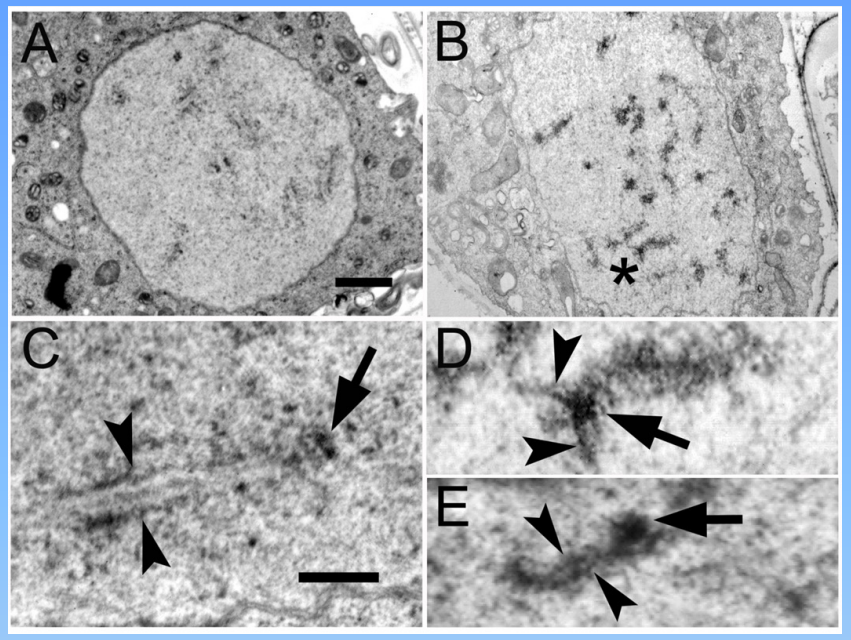
Main points of presentation

- Discrete spindle elongation in the anaphase of the cell cycle
- Slow diffusion of tubulins and rhythmic microtubule assembly
- Short reaction pauses, negative feedback, and long sustained long oscillations

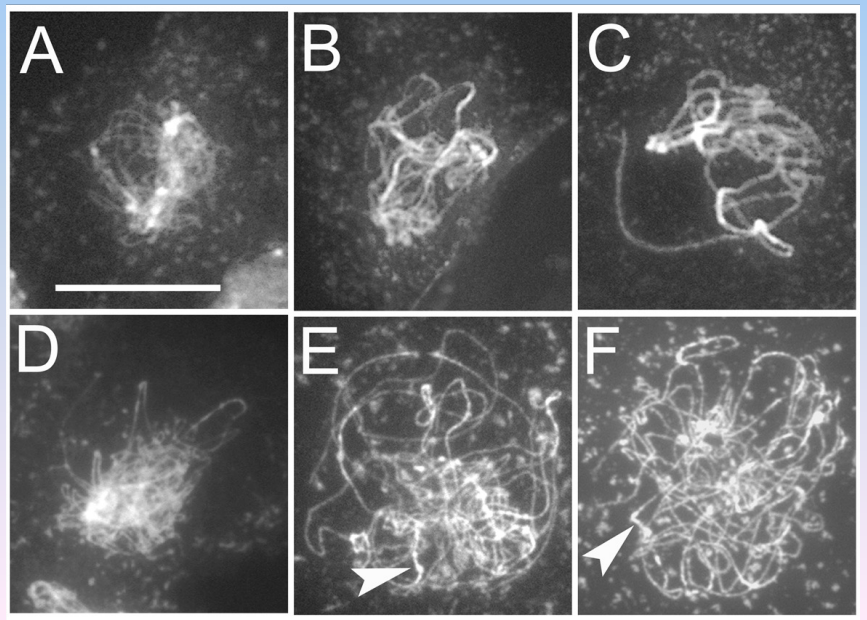
ask1-1 is asynaptic with many electron-dense foci



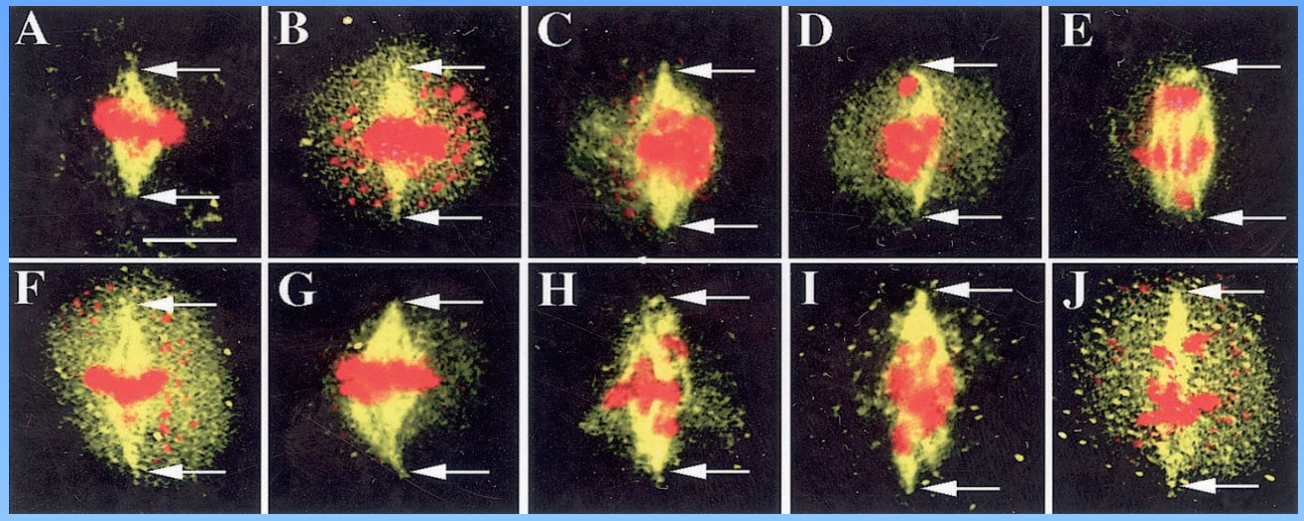
Chromosome spread

WT

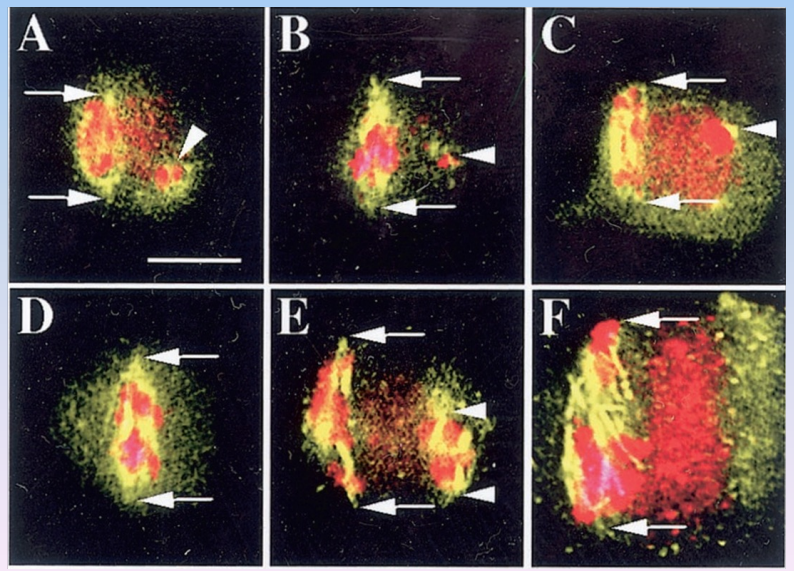
ask1-1



Spindle elongation in *ask1-1* male meiosis I



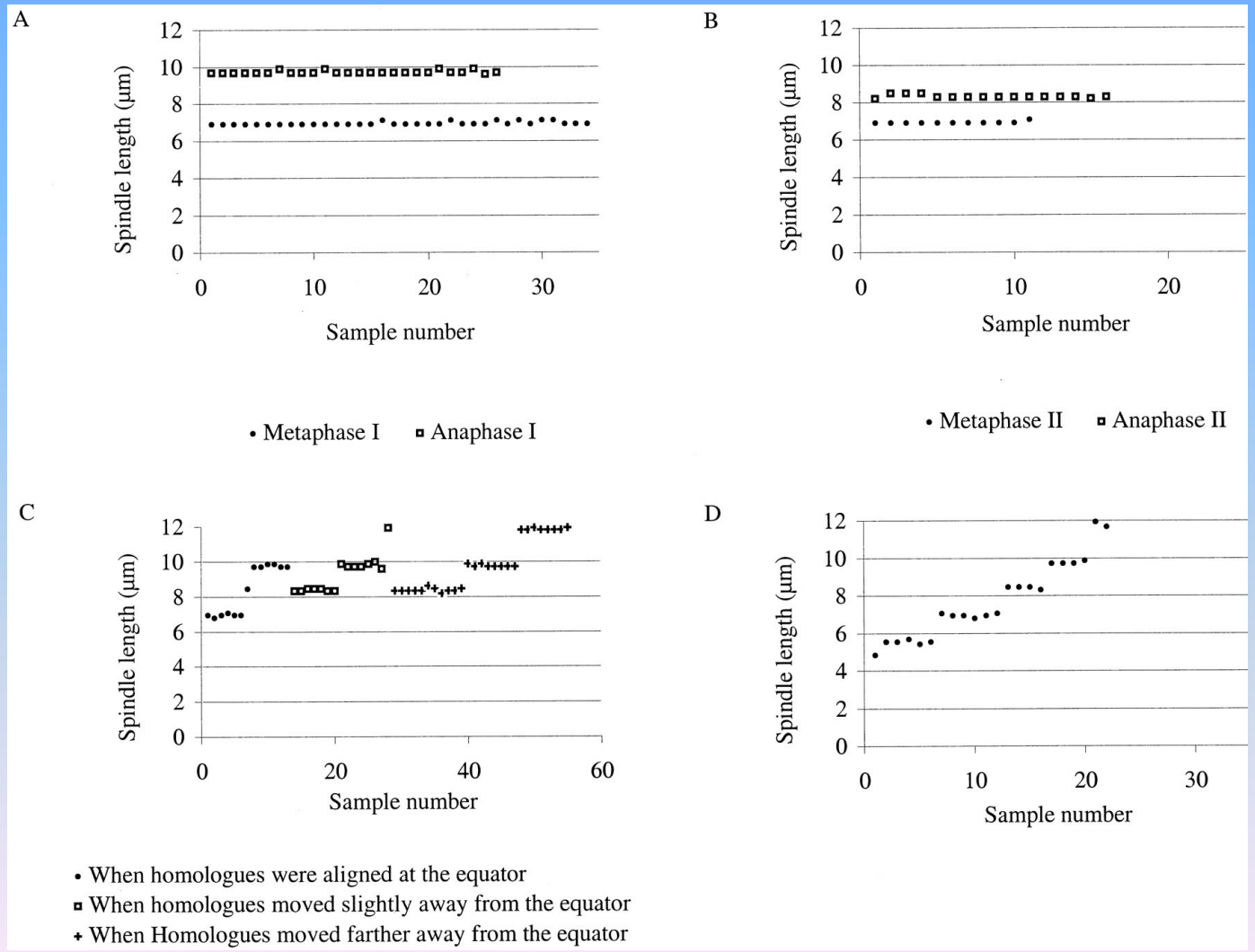
Spindle elongation in *ask1-1* male meiosis II



Distribution of WT and *ask1-1* spindle lengths in meiosis I and meiosis II

WT

ask1-1

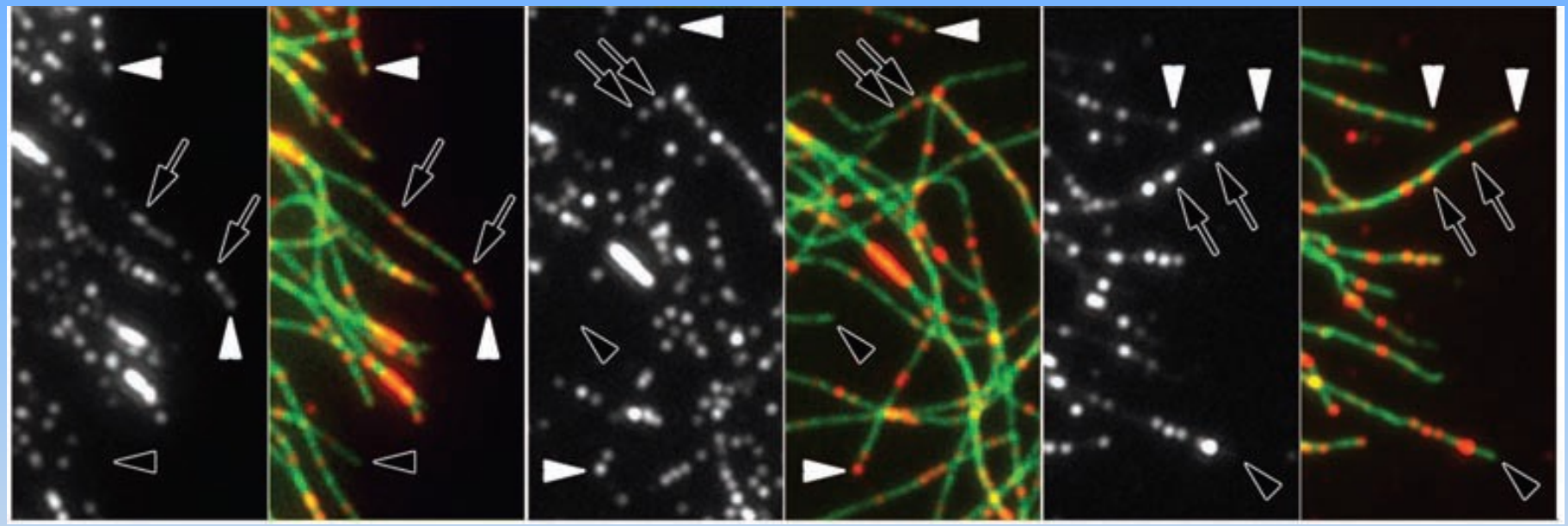


Spindle length differences in four other organisms

Organism	Length (μm)	Length Difference (μm)
S. cerevisiae (Winey et al., 1995)	L1 0.7 ± 0.1 (n = 4) L2 1.4 ± 0.1 (n = 6)	L2 - L1 = 0.7
F. capucina (Tippit et al., 1978)	L1 1.3 ± 0.1 (n = 2) L2 2.6 ± 0.1 (n = 25)	L2 - L1 = 1.3
Slime mold (Moens, 1976)	L1 2.1 ± 0.1 (n = 3) L2 4.9 ± 0.3 (n = 6)	L2 - L1 = 2.8
Rat kangaroo (PtK1 cells; Armstrong and Snyder, 1989)	L1 13.2 (n = 5) L2 17.4 (n = 5)	L2 - L1 = 4.2
Rat kangaroo (PtK1 cells; Snyder et al., 1986)	L1 12.2 (n = 6) L2 16.4 (n = 6)	L2 - L1 = 4.2

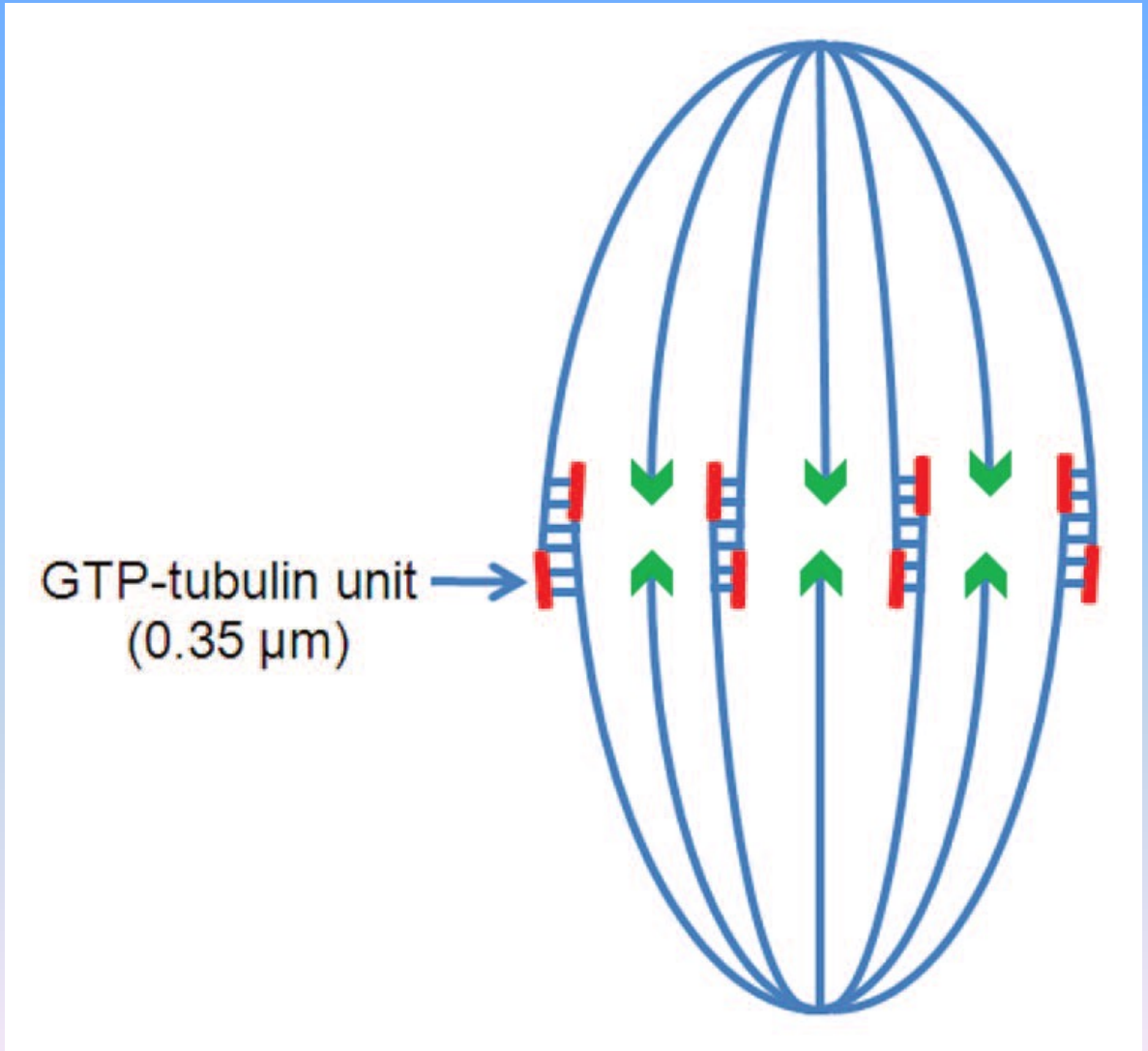
Spindles seem to elongate by multiples of 0.7 µm, but why?

Discrete lengths of GTP-tubulin segments on human microtubules



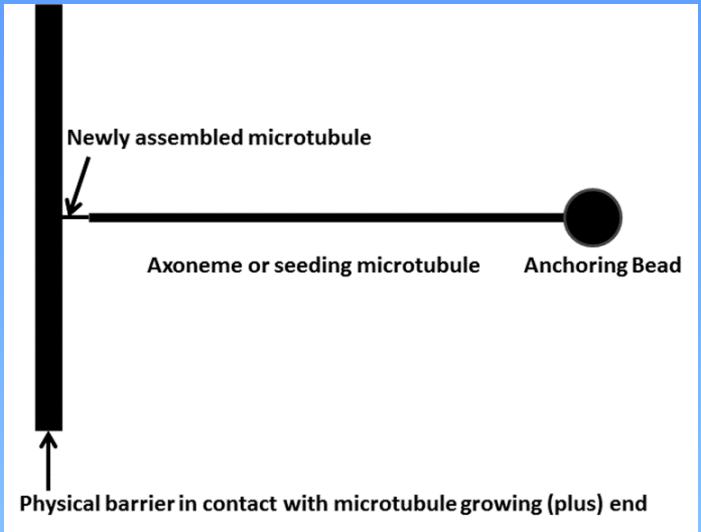
(Dimitrov et al., Science, 322: 1353-56, 2008)

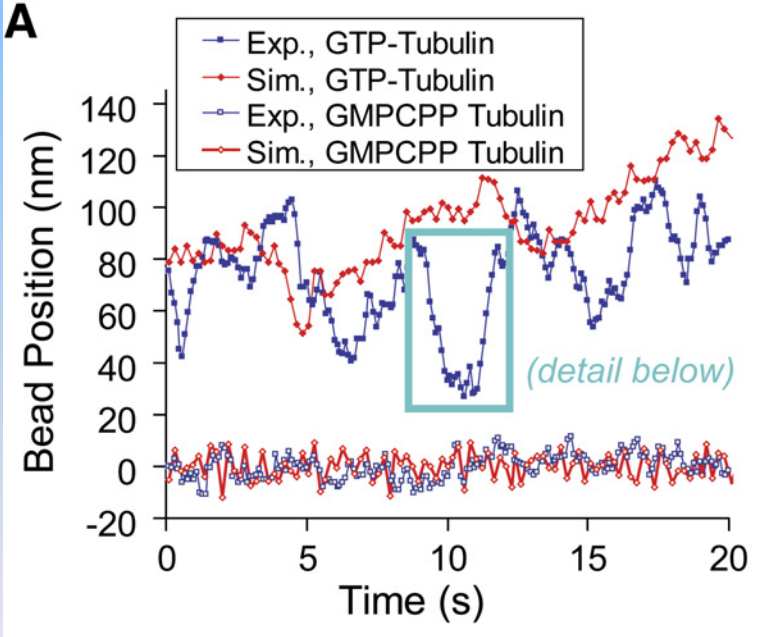
A model for discrete spindle elongation



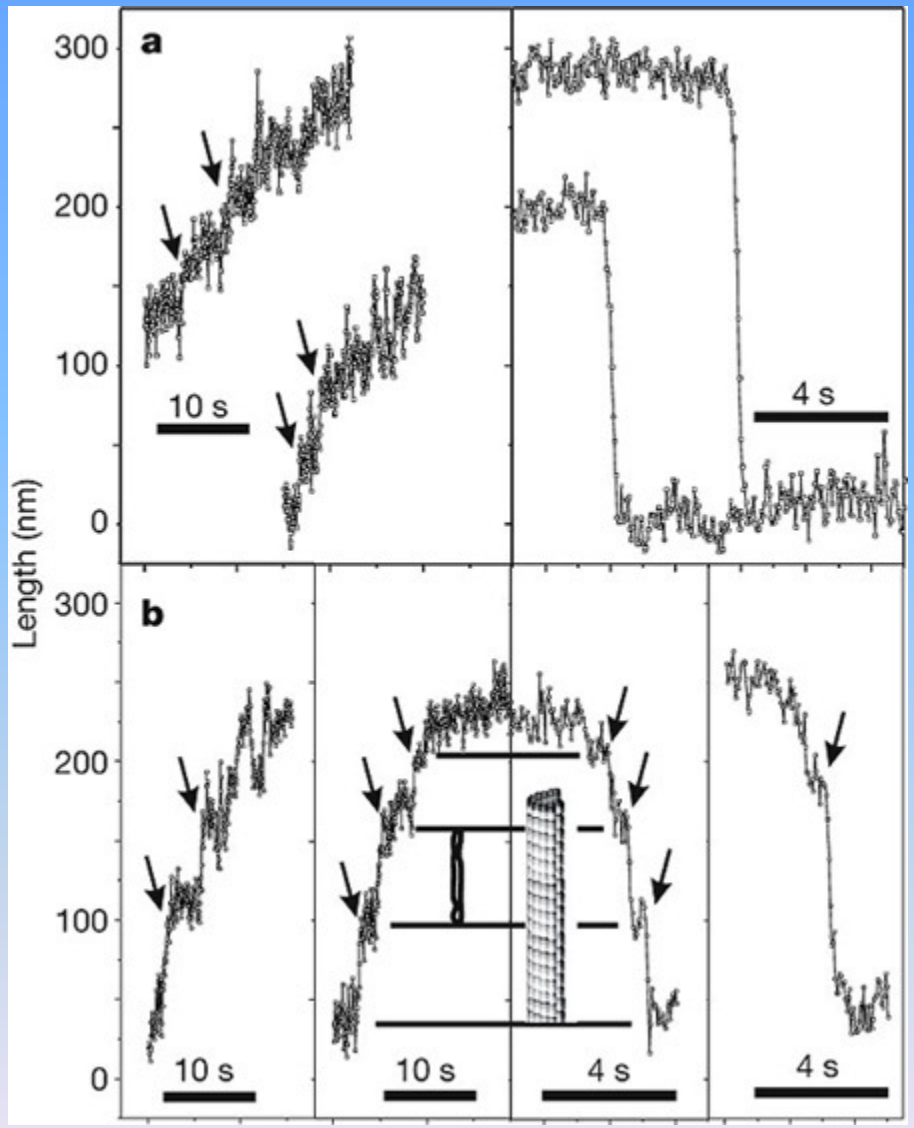
Kerssemakers et al., Assembly dynamics of microtubules at molecular resolution, *Nature*, 442: 709-712, 2006.

Schek et al., Microtubule assembly dynamics at the nanoscale, *Current Biology*, 17: 1445-1455, 2007.

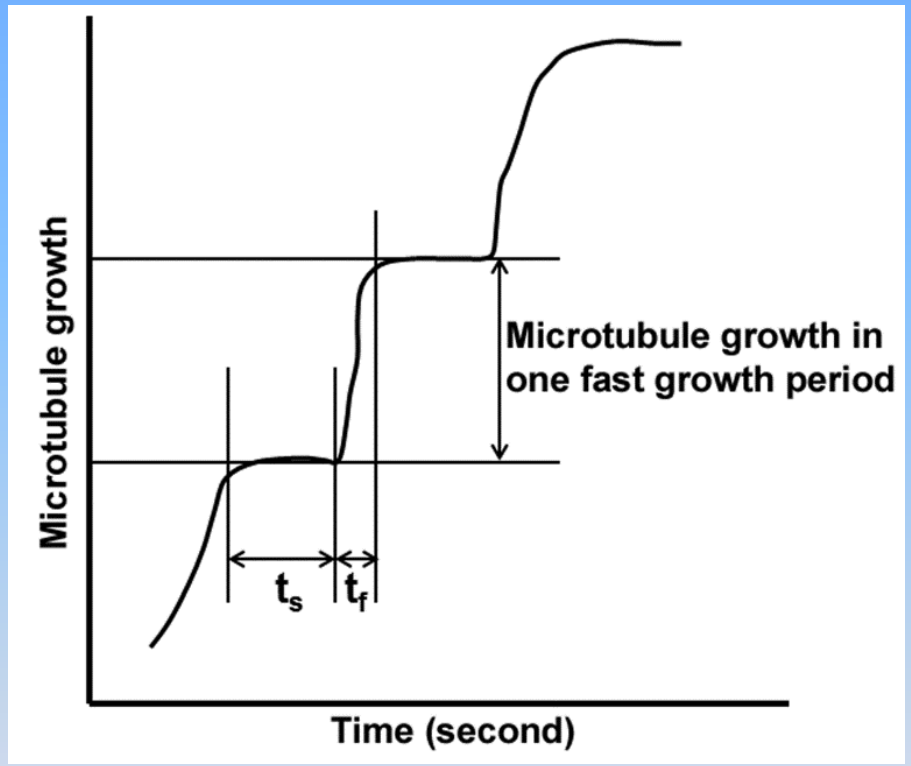




(Schek et al., *Current Biology*, 17: 1445-1455, 2007)



(Kerssemakers, et al., *Nature*, 442: 709-712, 2006)



$t_d = t_f + t_s$

$t_d \approx x^2/2D$

Average durations (in second) of t_f, t_s, and t_d in *in vitro* microtubule assembly

Mean t_f ± standard error	Mean t_s ± standard error	Mean t_d	Seed for microtubule assembly
0.55 ± 0.09 (n = 5)	3.85 ± 0.57 (n = 17)	4.4	Axoneme - XMAP215
0.63 ± 0.11 (n = 6)	2.33 ± 0.37 (n = 11)	2.96	Axoneme + XMAP215
0.44 ± 0.04 (n = 8)	0.54 ± 0.08 (n = 6)	0.98	Microtubule fragments

The flux of tubulin during the fast growth period can be expressed as the following according to Fick's First Law

$$J = -D(\partial C/\partial X) = -D[(C_0 - C_c)/L]$$

$$J_{-xmap215} = -D[(C_0 - C_{c\text{-}xmap215})/L_{-xmap215}] = [39/(6.022x10^{23})]/(at_{f\text{-}xamp215})$$

$$J_{+xmap215} = -D[(C_0 - C_{c+xmap215})/L_{+xmap215}] = [78/(6.022x10^{23})]/(at_{f+xamp215})$$

The calculated $t_{d+xmap215}/ t_{d\text{-}xmap215} = x_{+xmap215}^2/x_{-xmap215}^2 = 0.5$

For comparison, the experimental $t_{d+xmap215}/ t_{d\text{-}xmap215} = 2.96/4.4 = 0.67$

By the same principle

$J_{Schek} = -D_{Schek}(5 - 2)/L_{Schek} = [39/(6.022x10^{23})]/(at_{fSchek})$

It was then calculated that $D_{Schek} \approx 2.8D_{-xmap215}$

According to the descriptions of the two papers, it is clear that $D_{Schek} > D_{-xmap215}$

- The previous calculations support the idea that repetitions of a temporary disruption of the tubulin gradient followed by reestablishment of the gradient manifest into a rhythmic microtubule assembly behavior.

- A hemisphere with a radius R of the length of the average diffusion distance during the time of t_f and the assembly site as the center is deemed a relevant space in which the disruption takes place.

Then, if the tubulin concentration within the hemisphere is reduced to the tubulin critical concentration, the number of consumed tubulin dimers, N, is

$$N = (2/3)\pi R^3[(C_{edge} - C_{center})/2](6.022x10^{23}) \approx (2/3)\pi R^3[(R/x)(C_0 - C_c)/2](6.022x10^{23}),$$

$$\text{or } N \approx 2.96(6.022x10^{23})t_f^{2}t_d^{-1/2}D^{3/2}(C_0 - C_c)$$

Calculated
(assuming D = 0.07 $\mu m^2/s$ in Kerssemakers et al.
and D = 0.07x2.8 $\mu m^2/s$ in Schek et al.)

$N_{-xmap215} \approx 40$

$N_{+xmap215} \approx 80$

$N_{Schek} \approx 91$

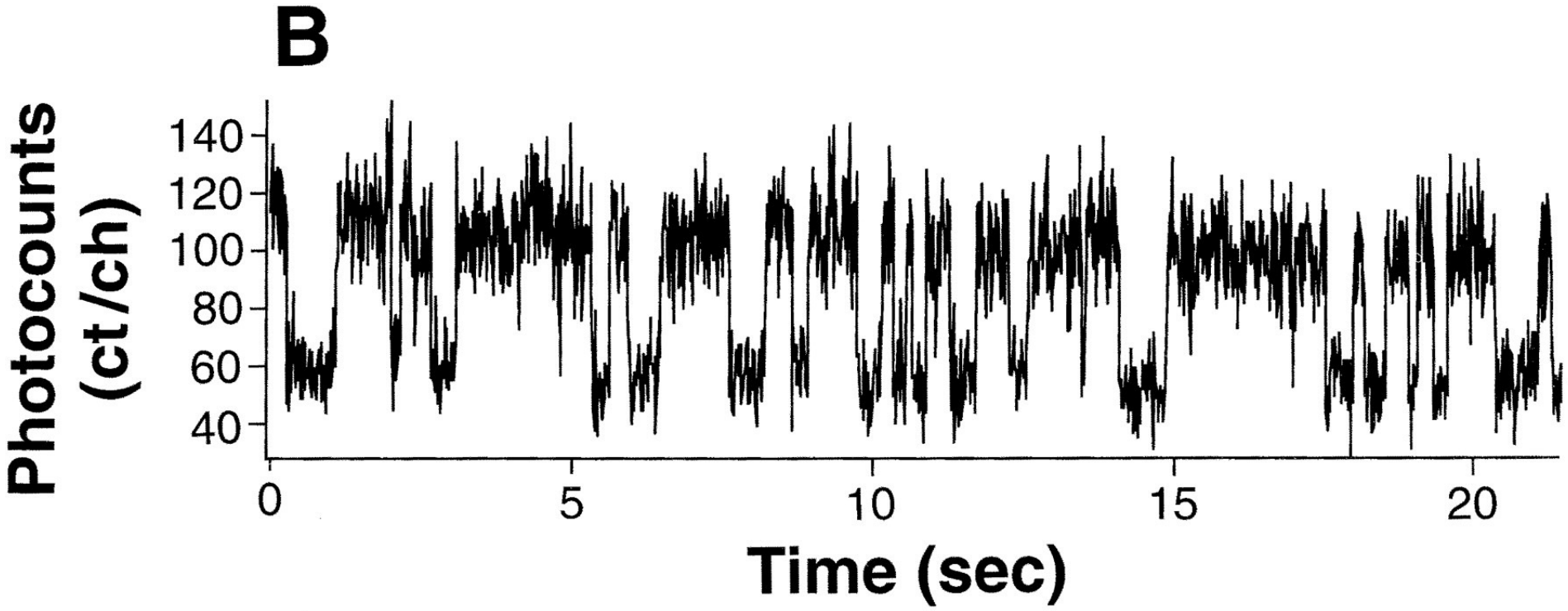
Experimental

$N_{-xmap215} \approx 39$

$N_{+xmap215} \approx 78$

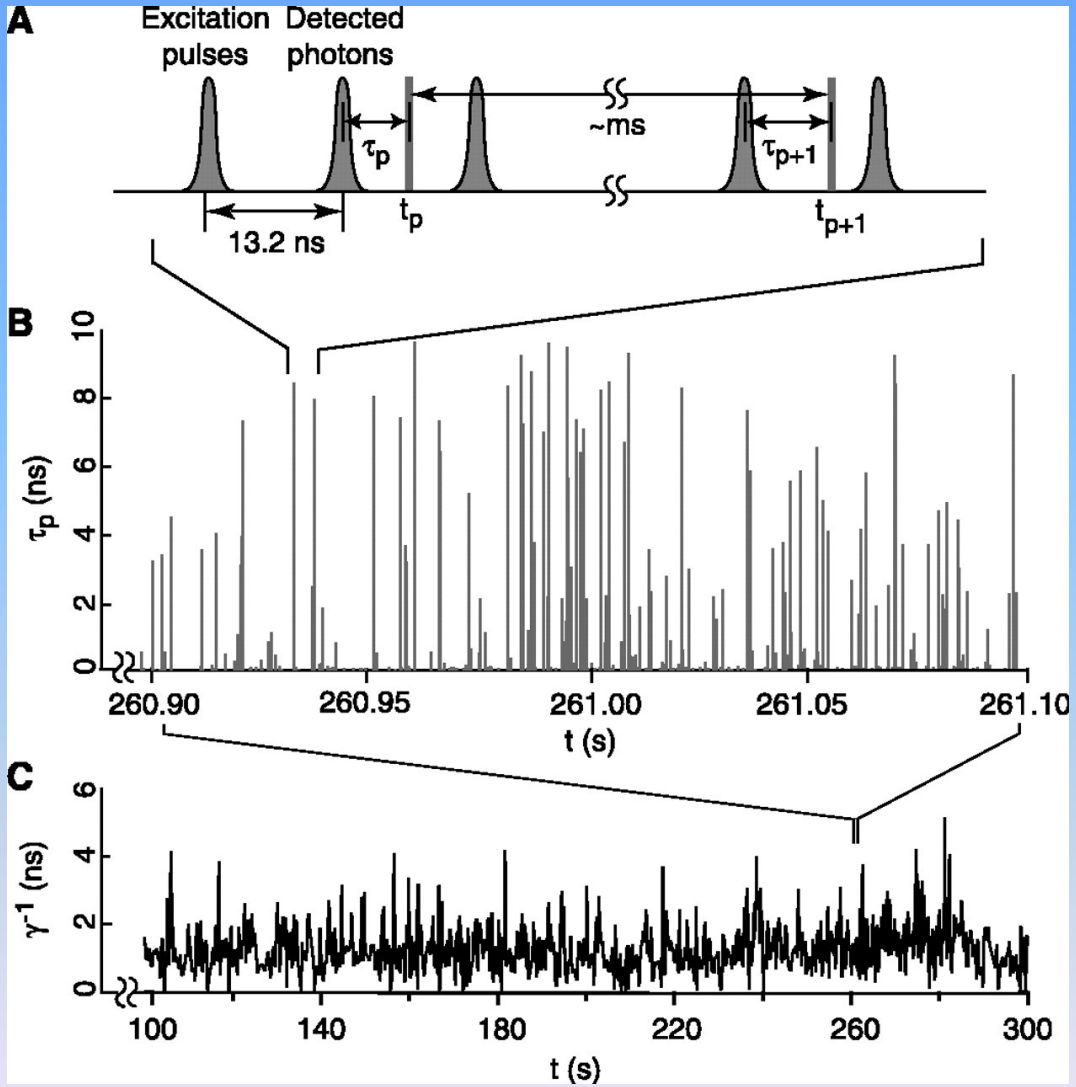
$N_{Schek} \approx 39$

Single-molecule enzymatic dynamics: cholesterol oxidase catalyzes cholesterol oxidation



Lu et al., *Science*, 1998, 282: 1877-1882

Protein conformational dynamics probed by single-molecule electron transfer



Yang et al., *Science* 302, 262–266

Conclusions

- A small diffusion coefficient of a reactant can lead to rhythmic behavior of the reaction in a heterogeneous reaction system.

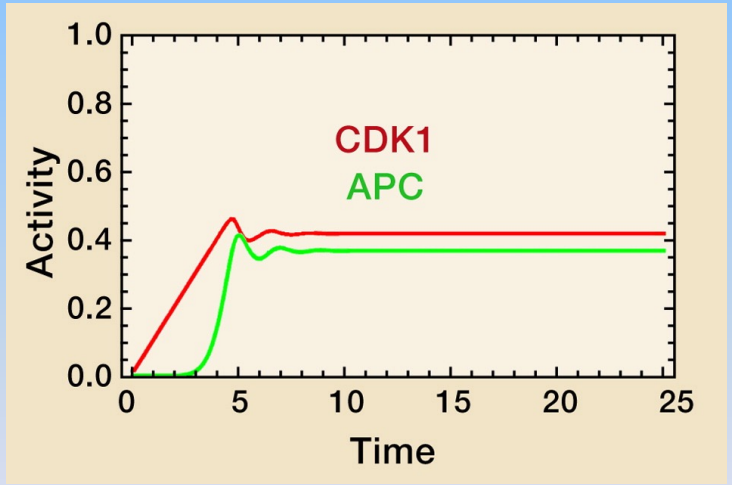
- This rhythmic behavior caused by slow diffusion of reactants is a common phenomenon in chemical reactions.

How discrete chemical reactions affect biological system behavior?

To answer the above question, we examined how periodic short pauses (several seconds) affect the behavior of a non-linear system with a negative feedback loop described by the following ordinary differential equations.

$$\frac{dx}{dt} = \alpha_1 - \beta_1 x \frac{y^{n_1}}{K_1^{n_1} + y^{n_1}}, \quad [1]$$

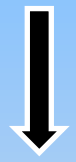
$$\frac{dy}{dt} = \alpha_2 (1 - y) \frac{x^{n_2}}{K_2^{n_2} + x^{n_2}} - \beta_2 y. \quad [2]$$



(Ferrell, J.E. Jr, Tsai, T.Y., Yang, Q. 2011. Modeling the cell cycle: why do certain circuits oscillate? *Cell* 144, 874-885)

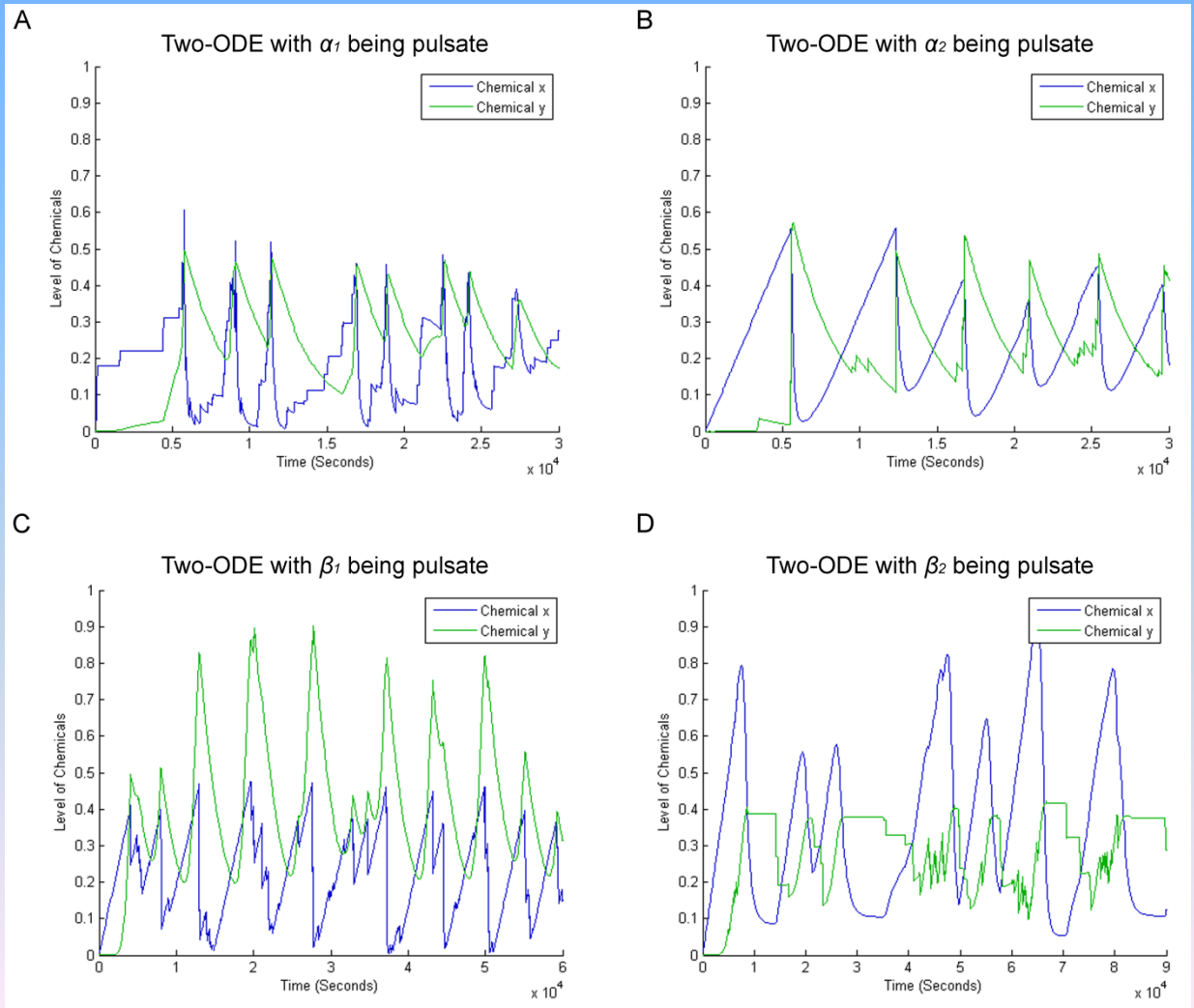
Equation for reactions with short pauses

$$\frac{dP}{dt} = \theta\left[\frac{t_f}{t_d} + \sum_{k=1}^{m-1} \frac{2m}{(\pi k)^2} \sin\frac{\pi k}{m} \sin\left(\frac{\pi k t_f}{t_d}\right) \cos\left(\frac{2\pi k}{t_d}\left(t - \frac{t_f}{2}\right)\right)\right]$$



$$P(t) = \begin{cases} \theta & \text{if} \quad t \bmod t_d > t_d - t_f \\ \frac{\theta}{2} & \text{if} \quad t \bmod t_d = 0 \quad \text{or} \quad t \bmod t_d = t_d - t_f \\ 0 & \text{otherwise} \end{cases}$$

The system undergo sustained oscillations with periods in hours



$$\frac{dx[t]}{dt} = \alpha_1 - \beta_1 x[t] \frac{y[t-\tau_1]^{n_1}}{K_1^{n_1} + y[t-\tau_1]^{n_1}},$$

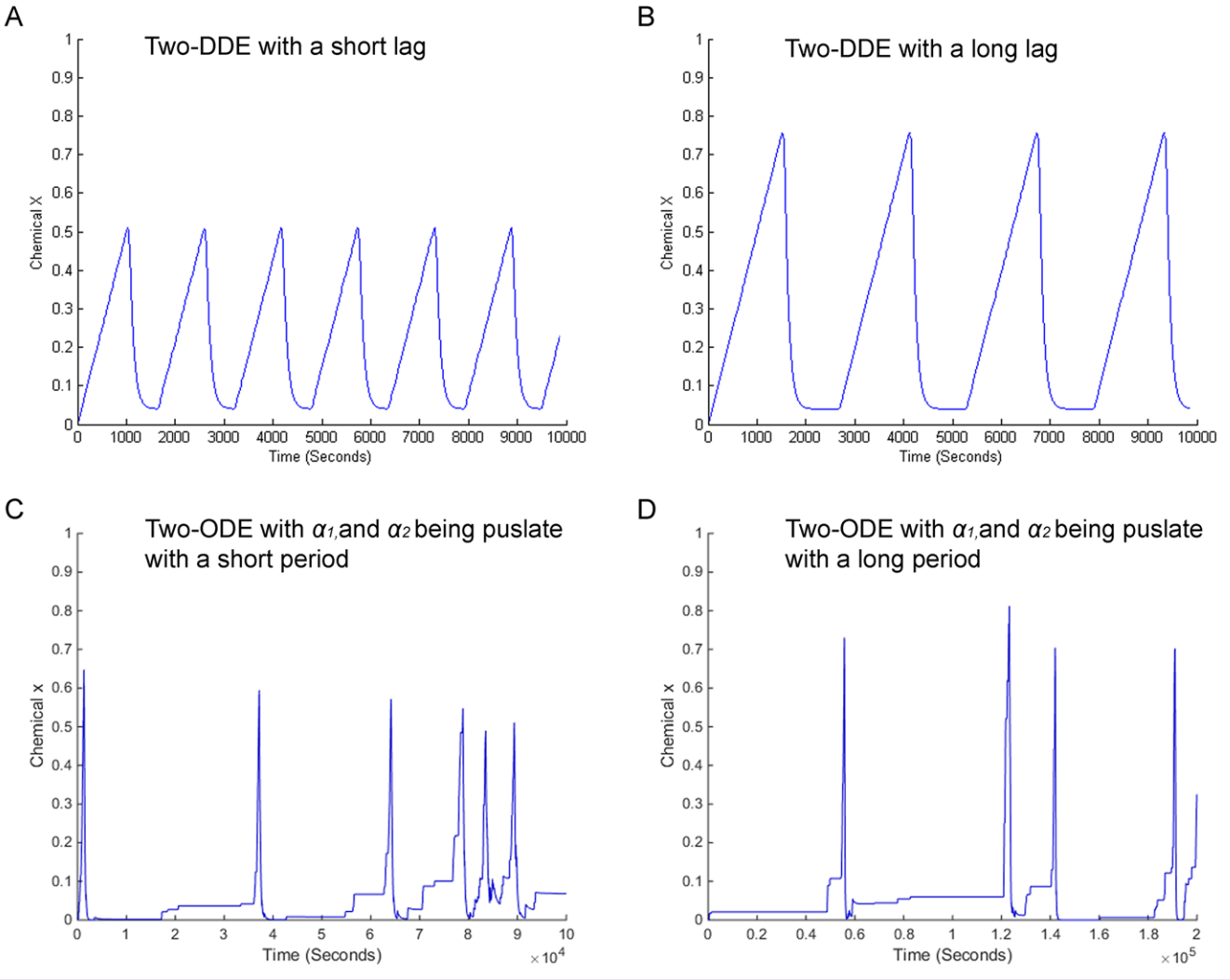
$$\frac{dy[t]}{dt} = \alpha_2 (1 - y[t]) \frac{x[t-\tau_2]^{n_2}}{K_2^{n_2} + x[t-\tau_2]^{n_2}} - \beta_2 y[t].$$

VS.

$$\frac{dx}{dt} = P_1(t) - \beta_1 x \frac{y^{n_1}}{K_1^{n_1} + y^{n_1}},$$

$$\frac{dy}{dt} = P_2(t)(1 - y) \frac{x^{n_2}}{K_2^{n_2} + x^{n_2}} - \beta_2 y.$$

Figure 5


A
Two-DDE with a short lag
Chemical X
Time (Seconds)
B
Two-DDE with a long lag
Chemical X
Time (Seconds)
C
Two-ODE with α1,and α2 being puslate with a short period
Chemical x
Time (Seconds)
×10^4
D
Two-ODE with α1,and α2 being puslate with a long period
Chemical x
Time (Seconds)
×10^5

$$\frac{dx}{dt} = \alpha_1 - \beta_1 x \frac{y^{n_1}}{K_1^{n_1} + y^{n_1}},$$

$$\frac{dy}{dt} = \alpha_2 (1 - y) \frac{z^{n_2}}{K_2^{n_2} + z^{n_2}} - \beta_2 y,$$

$$\frac{dz}{dt} = \alpha_3 (1 - z) \frac{x^{n_3}}{K_3^{n_3} + x^{n_3}} - \beta_3 z.$$

VS.

$$\frac{dx}{dt} = P_1(t) - \beta_1 x \frac{y^{n_1}}{K_1^{n_1} + y^{n_1}},$$

$$\frac{dz}{dt} = P_2(t)(1 - z) \frac{x^{n_2}}{K_2^{n_2} + x^{n_2}} - \beta_2 z,$$

$$\frac{dy}{dt} = P_3(t)(1 - y) \frac{z^{n_3}}{K_3^{n_3} + z^{n_3}} - \beta_3 y.$$

$$\frac{dx[t]}{dt} = \alpha_1 - \beta_1 x[t] \frac{y[t-\tau_1]^{n_1}}{K_1^{n_1} + y[t-\tau_1]^{n_1}},$$

$$\frac{dz[t]}{dt} = \alpha_2 (1 - z[t]) \frac{x[t-\tau_2]^{n_2}}{K_2^{n_2} + x[t-\tau_2]^{n_2}} - \beta_2 z[t],$$

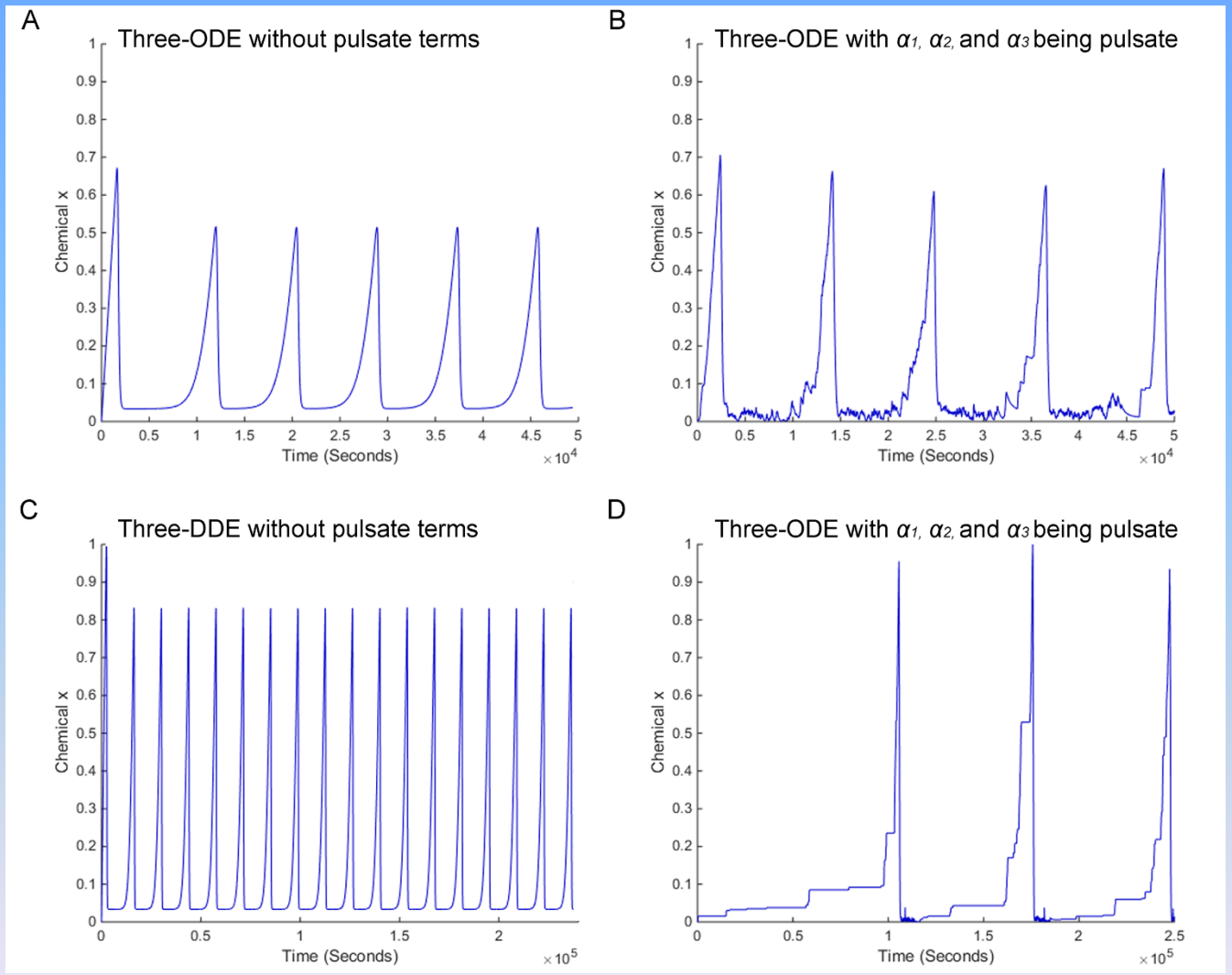
$$\frac{dy[t]}{dt} = \alpha_3 (1 - y[t]) \frac{z[t-\tau_3]^{n_3}}{K_3^{n_3} + z[t-\tau_3]^{n_3}} - \beta_3 y[t].$$

VS.

$$\frac{dx}{dt} = P_1(t) - \beta_1 x \frac{y^{n_1}}{K_1^{n_1} + y^{n_1}},$$

$$\frac{dz}{dt} = P_2(t)(1 - z) \frac{x^{n_2}}{K_2^{n_2} + x^{n_2}} - \beta_2 z,$$

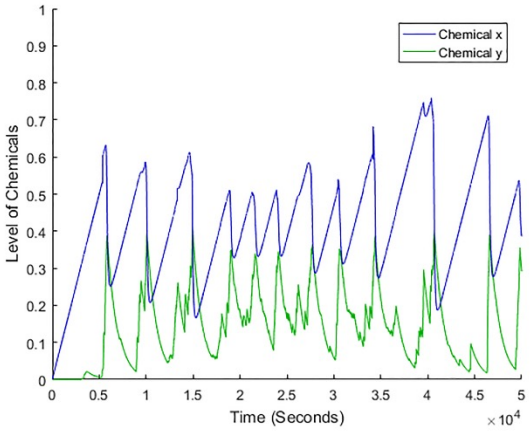
$$\frac{dy}{dt} = P_3(t)(1 - y) \frac{z^{n_3}}{K_3^{n_3} + z^{n_3}} - \beta_3 y.$$


A
Three-ODE without pulsate terms
Chemical x
Time (Seconds)
×10^4
B
Three-ODE with α1, α2, and α3 being pulsate
Chemical x
Time (Seconds)
×10^4
C
Three-DDE without pulsate terms
Chemical x
Time (Seconds)
×10^5
D
Three-ODE with α1, α2, and α3 being pulsate
Chemical x
Time (Seconds)
×10^5

10^{-4}

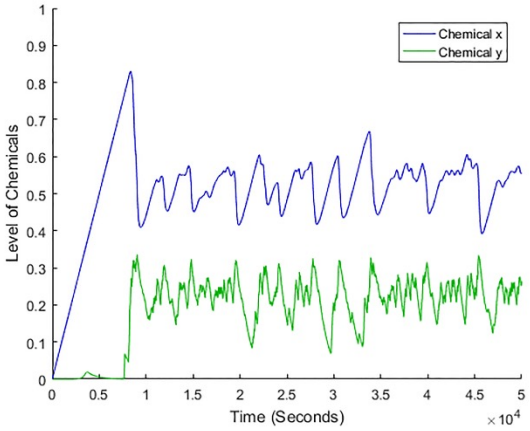
When chemical concentration values are expressed in ng/L (likely being reasonably large absolute numerical values in *in vivo* biochemical reactions), the relative numerical tolerance value can be reasonably set at or around 10^{-4} in simulation of biochemical reactions,

a



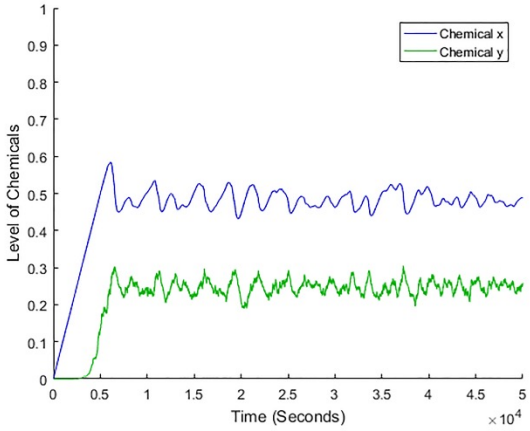
Relative numerical tolerance = 10^{-3}, and absolute numerical tolerance = 10^{-6}

b



Relative numerical tolerance = 10^{-5}, and absolute numerical tolerance = 10^{-8}.

c



Relative numerical tolerance = 10^{-10}, and absolute numerical tolerance = 10^{-12}.

Concluding remarks

- A biochemical system of a negative feedback loop with diffusion-based seconds-long periodic pauses exhibits sustained hours-long oscillations, which resembles actual oscillations such as ultradian rhythms in biological systems.

- Further expansion of the model may produce a unified model that can account for different types of oscillations with a range of periods.

- Rhythms in biochemical reactions are an inherent property of living systems, i.e., such rhythms cannot be abolished (although can be altered) as long as the organism or cell is living (a negative feedback loop is intact).

- Increasingly slow diffusion in the primordial soup might be a critical factor in the origin of life.

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