- Group 1: present Gardner paper
- Group 2: prediction of 3-step model for 3 data sets
- Group 3: come up with alternative ideas that fit (some of the) data

Cell

Depolymerizing Kinesins Kip3 and MCAK Shape Cellular Microtubule Architecture by Differential Control of Catastrophe

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DOI 10.1016/j.cell.2011.10.037

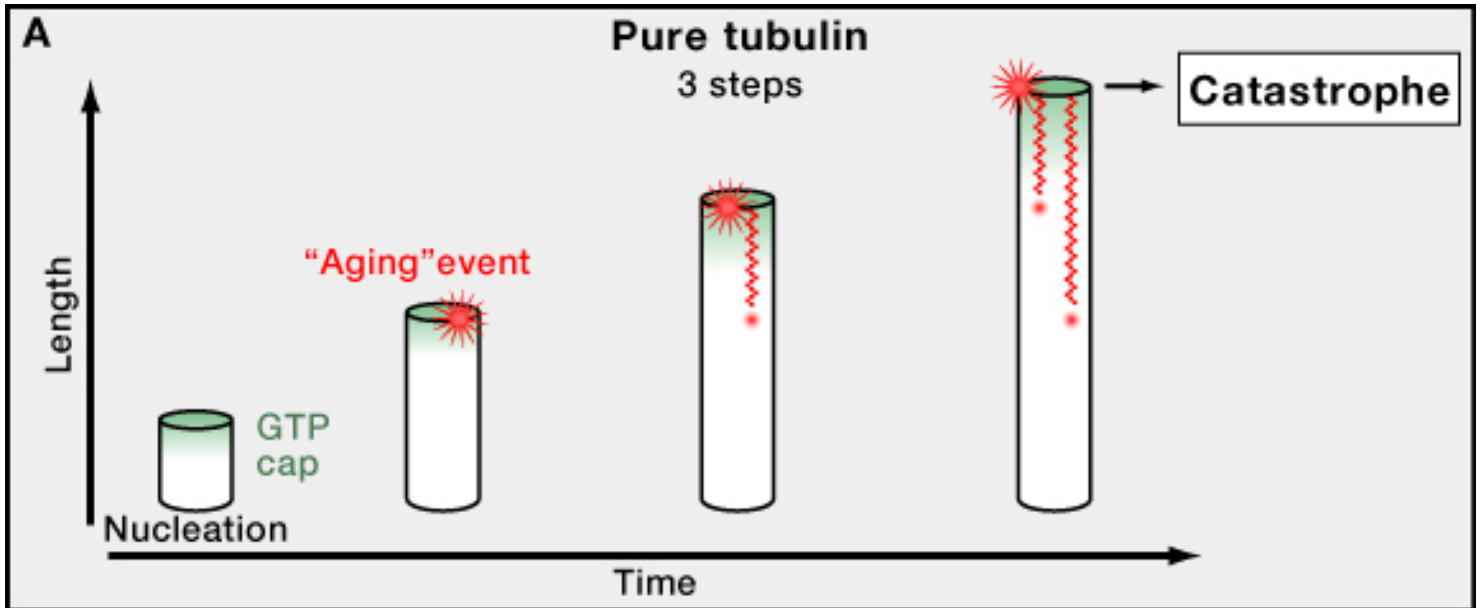
SUMMARY

Microtubules are dynamic filaments whose ends alternate between periods of slow growth and rapid shortening as they explore intracellular space and move organelles. A key question is how regulatory proteins modulate catastrophe, the conversion from growth to shortening. To study this process, we reconstituted microtubule dynamics in the absence and presence of the kinesin-8 Kip3 and the kinesin-13 MCAK. Surprisingly, we found that, even in the absence of the kinesins, the microtubule catastrophe frequency depends on the age of the microtubule, indicating that catastrophe is a multi-step process. Kip3 slowed microtubule growth in a length-dependent manner and increased the rate of aging. In contrast, MCAK eliminated the aging process. Thus, both kinesins are catastrophe factors; Kip3 mediates fine control of microtubule length by narrowing the distribution of maximum lengths prior to catastrophe, whereas MCAK promotes rapid restructuring of the microtubule cytoskeleton by making catastrophe a first-order random process.

lized at the microtubule-organizing center or at the centrosome and participates to a lesser extent in subunit exchange. The sudden random transition at the plus end between relatively slow growth and rapid shortening is termed catastrophe. Despite intense study for many years, the catastrophe mechanism and its regulation by so-called catastrophe factors are still poorly understood.

Catastrophe is thought to occur as a result of the loss of a stabilizing GTP-tubulin cap at the plus end of the microtubule. This GTP-cap model is supported by the following evidence: (1) microtubule growth involves addition of GTP-tubulin from solution, (2) there is a lag between subunit addition and GTP hydrolysis (Carlier et al., 1984; Nogales and Wang, 2006; Nogales et al., 1998), (3) tubulin subunits bound to the slowly hydrolyzable GTP analog GMPCPP dissociate slowly from the microtubule end (Hyman et al., 1992) and, when added to the ends of GDP-microtubules, prevent depolymerization (Mickey and Howard, 1995), (4) GDP-tubulin microtubules depolymerize rapidly following dilution of soluble tubulin or after microtubule severing (Walker et al., 1989, 1991), and (5) an antibody raised to GTPγS-tubulin, which also binds GMPCPP microtubules, preferentially labels the plus ends of microtubules (Dimitrov et al., 2008), similar to EB1 (Maurer et al., 2011; Zanic et al., 2009). However, the GTP cap has never been visualized on a dynamic, growing microtubule and thus remains hypothetical.

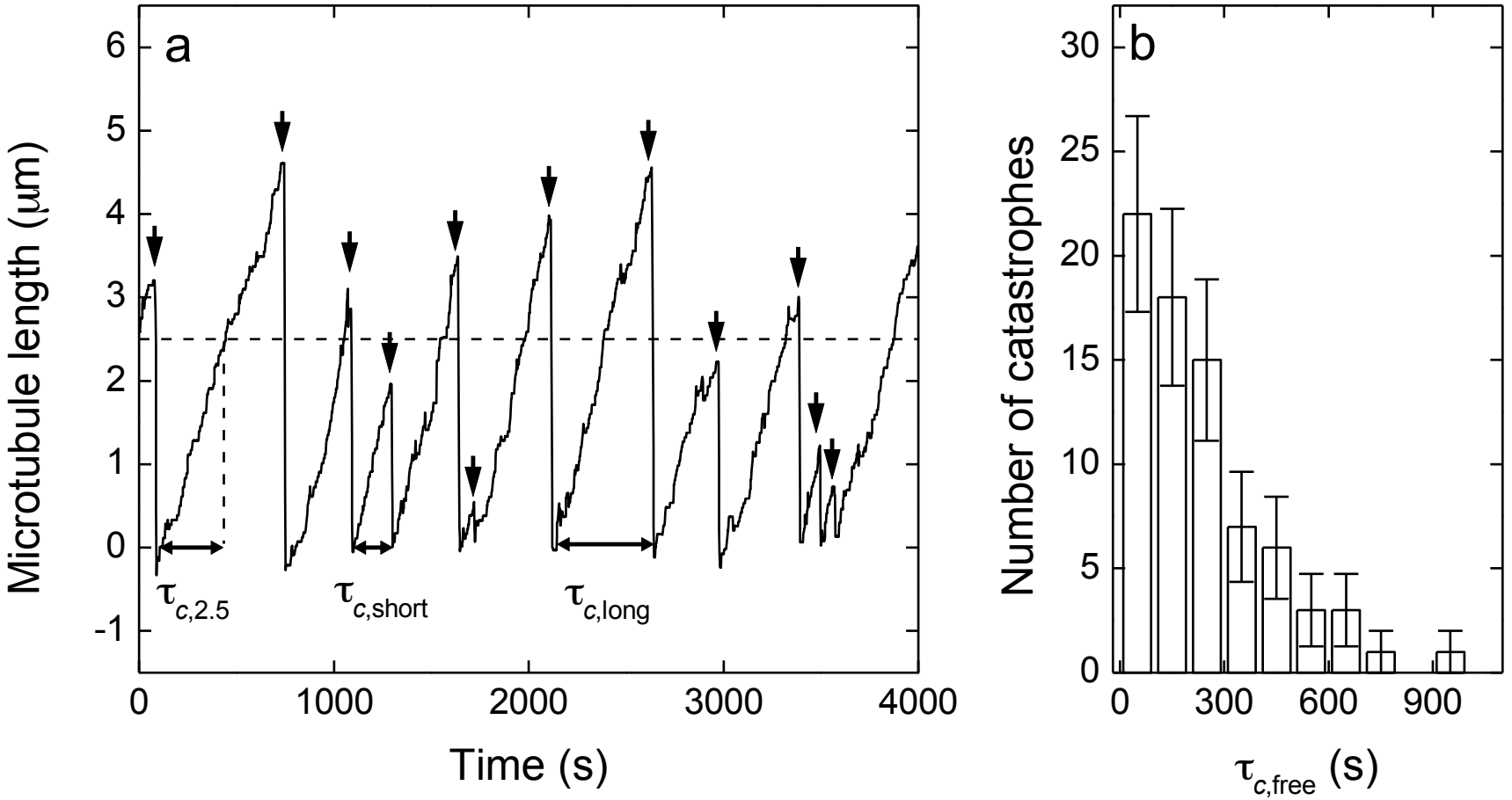
3-step process:

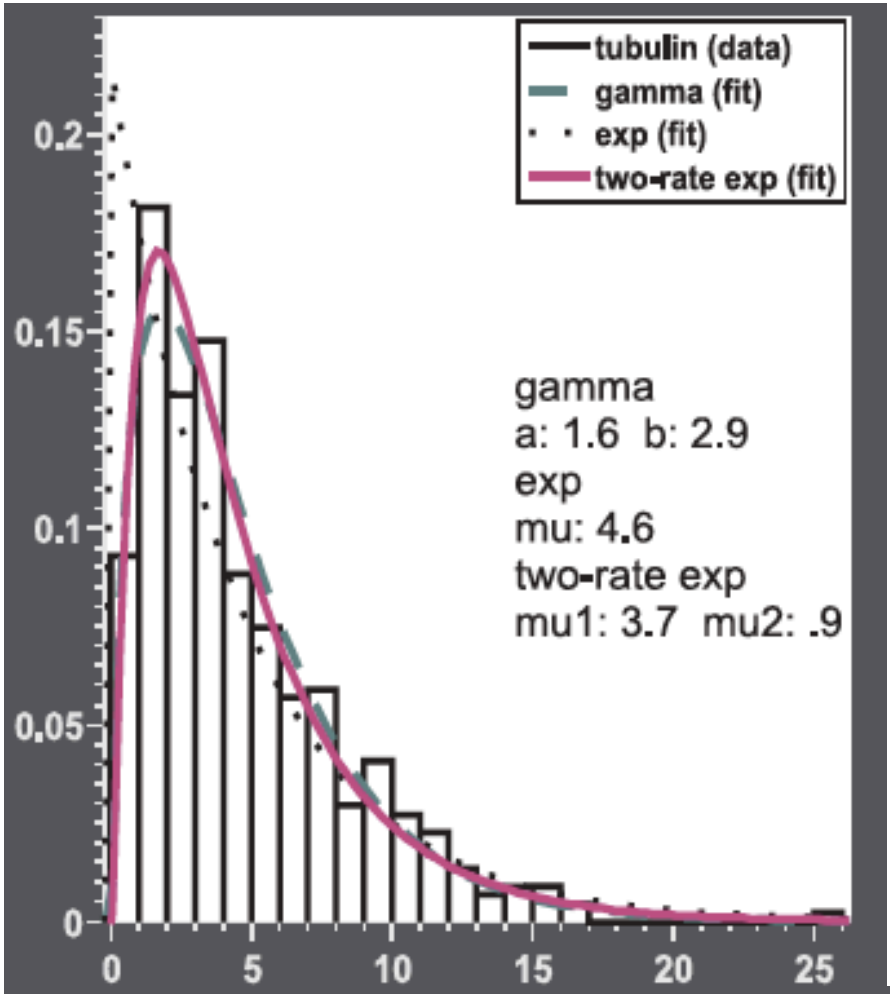


3 data sets:

- Distribution of catastrophe times for free MTs
- Average catastrophe rate as a function of growth velocity
- Distribution of catastrophe times for stalled MT

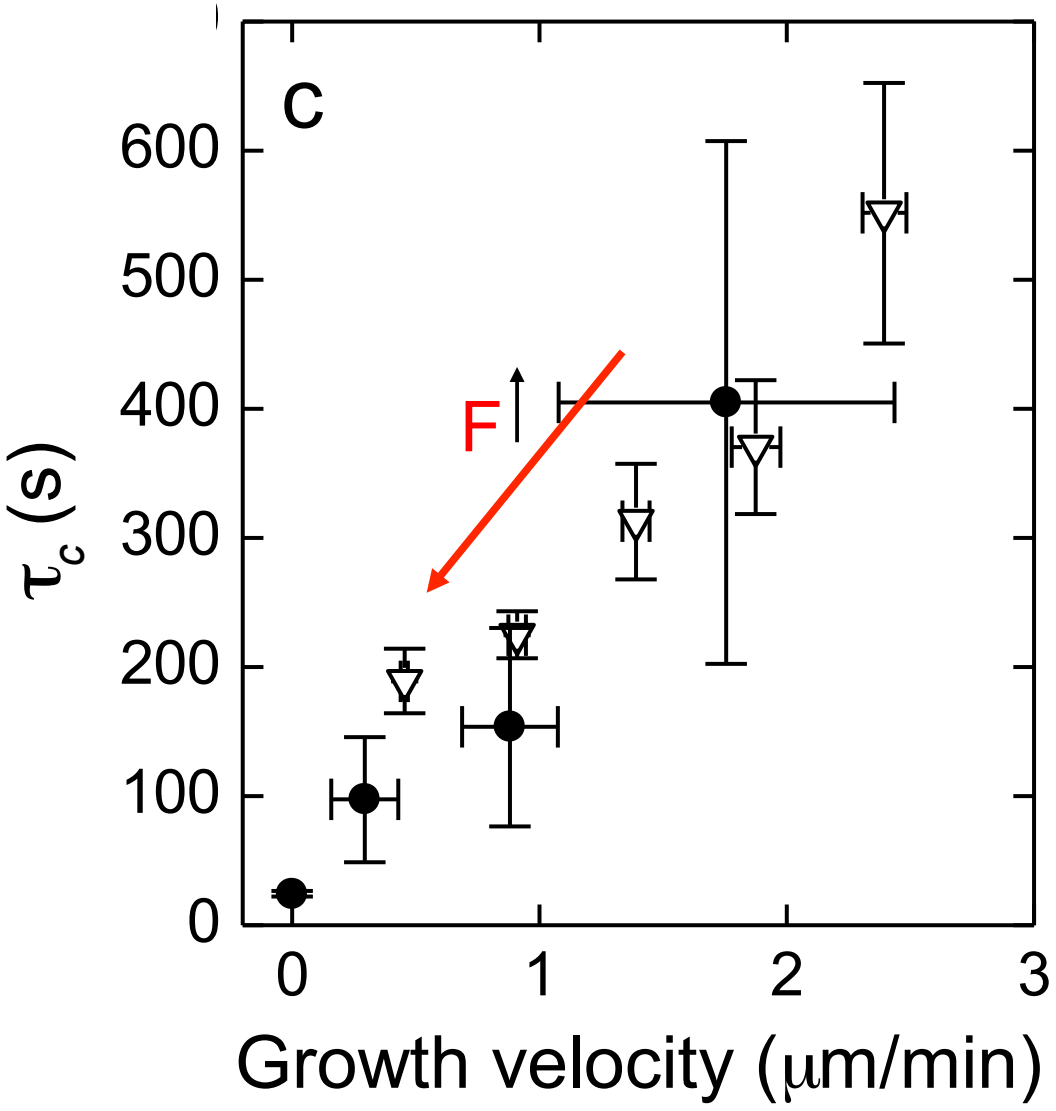
Catastrophe statistics for free microtubules





catastrophe time (min) of free MTs

Gamma: a=n (number of steps);
b=time scale (in min)
mu, mu1, mu2: times scales (in min)



Average catastrophe Time for:

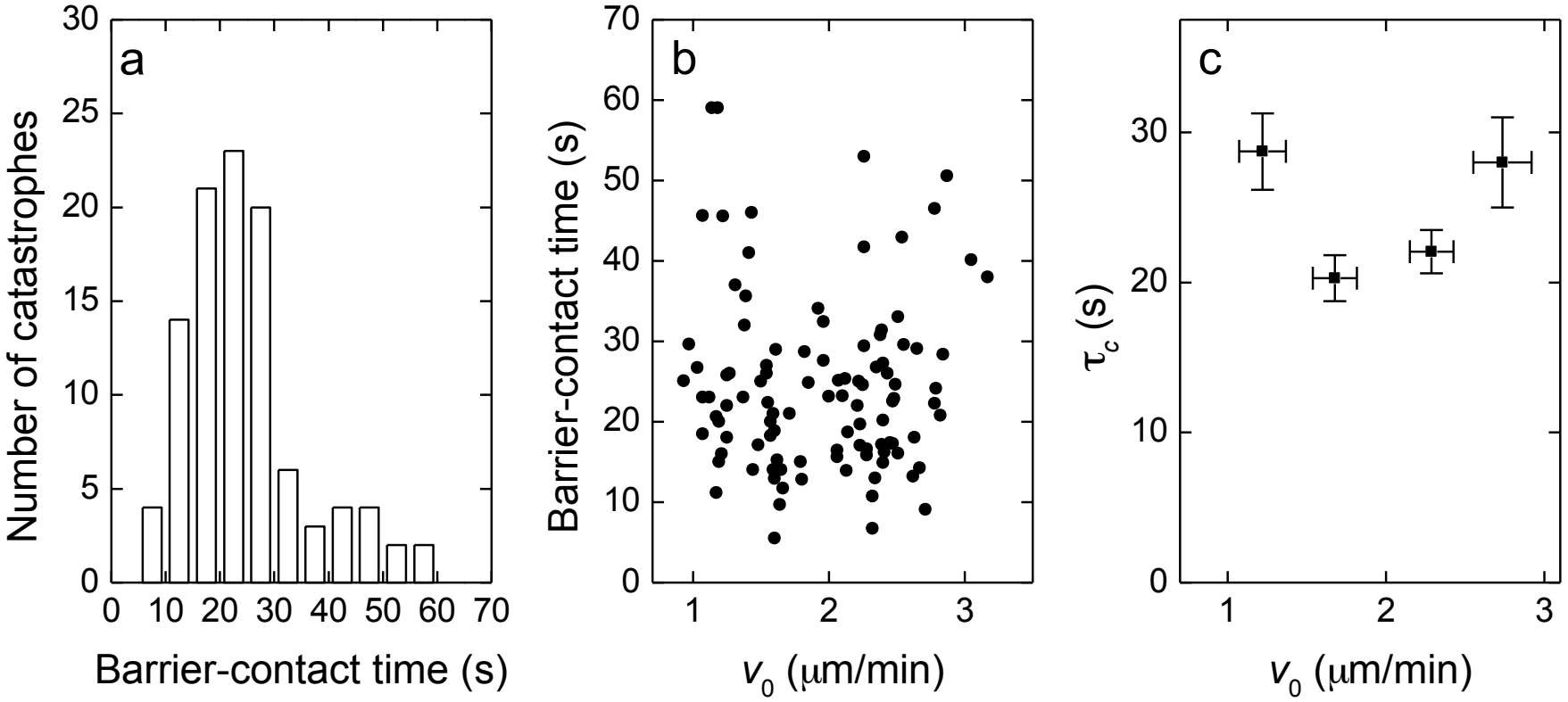
● MTs under load

▽ Free MTs

[Tub] down same effect as F up !

Janson, de Dood & Dogterom, JCB 2003

Catastrophe statistics for stalled microtubules



Peaked around 24 s, no [Tub] dependence