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Directed elongation model for microtubule GTP hydrolysis

(treadmilling/tubulin/flux)

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ABSTRACT **We propose a role for GTP hydrolysis in microtubule assembly in which the GTPase reaction serves to stabilize tubulin subunits in the microtubule. The GTPase reaction in tubulin subunits containing GTP at microtubule ends is presumed to occur predominately in subunits at one of the interfaces between a cap of GTP-containing tubulin subunit and a core of GDP-containing tubulin subunit in the microtubule, resulting in elongation of the core. The proposed model interprets the effects of GDP on microtubule assembly, using a reaction scheme in which GDP-containing tubulin subunits are able to add to microtubule ends. The model can account for the GTP requirement for microtubule assembly, the GDP inhibition of the rate for microtubule elongation, and the fact that a metastable state exists after the enzymic conversion of GTP to GDP, with microtubules which are at steady state. To account for the fact that the microtubule assembly and disassembly rates are nonlinearly dependent upon the tubulin subunit concentration and for the effects of GDP-containing tubulin subunits on the kinetic properties of microtubules, our scheme includes nonproductive as well as productive binding of GTP- and GDP-containing tubulin subunits. We compare our model with an alternative scheme [Hill, T. L. & Carlier, M. F. (1983) *Proc. Natl. Acad. Sci. USA* 80, 7234–7238], which interprets the effects of GDP on microtubule assembly using a reaction scheme in which GDP is able to exchange with GTP in GTP-containing tubulin subunits in the microtubule and in which the principal GTPase occurs in GTP-containing tubulin subunits at the microtubule/solution interface.**

The observation that GTP hydrolysis does not occur concomitant with addition of GTP-containing tubulin subunits (TuT) to the microtubule (1) has raised a number of questions concerning the role of the hydrolysis reaction in microtubule assembly. The possibility that GTP plays no role in the assembly is ruled out because GDP-containing tubulin subunits (TuD) do not readily assemble into microtubules (2–5). In a recent analysis of this problem (6, 7), a mechanism was proposed in which: (*i*) TuT subunits are able to add to a microtubule without hydrolysis to form a cap of subunits containing GTP upon a much longer core of TuD subunit; (*ii*) the principal site for steady-state GTP hydrolysis is in subunits at the tip of the microtubule; (*iii*) terminal subunits in a microtubule are able to bind both GTP and GDP from solution; (*iv*) unhydrolyzed GTP in nonterminal tubulin subunits can readily exchange with GTP but not with GDP in solution; and (*v*) the presence of GDP in the terminal subunits precludes further subunit addition. This model can account for a number of interesting properties of microtubules, most notably, it allows the microtubule to exhibit different apparent equilibrium constants for TuT subunit addition at opposite ends of the microtubule. The dissimilar equilibrium constants will be manifested in subunit "treadmilling" at steady state (8).

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The Hill–Carlier mechanism (6) is based upon the observations (4, 5) that GDP acts competitively with GTP so as to decrease the rate constant for microtubule assembly (not simply by decreasing the TuT subunit concentration) and the rate for the steady-state GTPase reaction. Although it was pointed out (equation 8 in ref. 4) that these results could be interpreted as reflecting either an exchange of GDP into the microtubule's terminal subunits or a reaction of TuD at the microtubule ends, the Hill–Carlier mechanism considers the GDP exchange reaction only. We have studied (9) microtubules under conditions where the E-site nucleotide of tubulin subunits contains GDP, in the absence of excess GDP (or GTP) (9). Microtubules exist in a metastable state under these conditions (9–11), indicating that TuD subunits are able to readily react with microtubule ends. Since this means that the potential reaction, which was not used in the Hill–Carlier analysis, does in fact occur, we believe that it is appropriate to consider an alternate model based upon TuD-subunit addition rather than nucleotide exchange.

Experimental Observations to be Accounted for

A model for describing the non-steady-state and steady-state kinetic properties of microtubules must account for the following observations: (*i*) TuT subunits are apparently able to elongate a microtubule without GTP hydrolysis (1); (*ii*) TuD subunits do not readily elongate microtubules (2–5), although they are able to participate in a facile addition reaction to the microtubule ends (9–11); (*iii*) GTP hydrolysis in a subunit in the microtubule serves to generate a tighter binding tubulin species (12); (*iv*) at steady state there are TuD subunits at a fraction of microtubule ends at least—i.e., treadmilling is feasible (13–17); (*v*) the protein conformation is apparently different in nonpolymerized TuT and TuD subunits (18, 19); (*vi*) microtubules depolymerize faster below the critical concentration than is expected from determinations of the rate at tubulin concentrations that exceed the critical concentration (20, 21); and (*vii*) the microtubule assembly rate appears to reach a limiting value at high tubulin concentrations (22–24).

1. The Directed Elongation Model

Microtubule assembly/disassembly and the detailed scheme for individual reactions are outlined in Figs. 1 and 2. Our model (Fig. 2) is as follows. (*i*) Tubulin subunits in the microtubule containing either GTP or GDP are presumed to possess both front and rear interaction sites. The free subunits (designated I and II in Fig. 2) exist in two conformations, with I predominating for TuT and II predominating with TuD; however, TuD exists primarily in state I under reaction conditions where TuD is able to readily elongate microtubules [i.e., at high glycerol and magnesium concentrations (25)]. (*ii*) The microtubule consists of a TuD core, with TuT

Abbreviations: TuT, tubulin subunits containing GTP; TuD, tubulin subunits containing GDP.

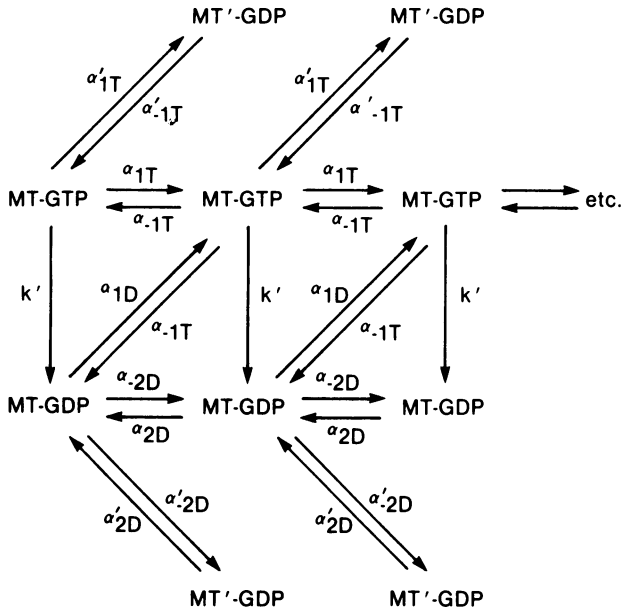

FIG. 1. Reaction scheme for microtubule (MT) assembly. The nomenclature in the text is based upon that of Hill and Carlier (6). To describe the steady-state net assembly (α) and disassembly (β) ends without distinction the letter i is used. The upper and lower lines describe nonproductive TuT and TuD subunit addition (primed rate constants), which is described in section 4 of the text. Hydrolysis at the interface between the TuT cap and TuD core is described by k'_α and k'_β at the α end and β end, respectively.

caps at each end (Fig. 2*A*). GTP hydrolysis results in a protein conformation change such that the subunit binds more tightly. (*iii*) Both TuD and TuT subunits are able to bind nonproductively (26) (III and IV in Fig. 2) so as to preclude further subunit addition. This situation might, for example, be generated by a pseudosymmetry between the α and β subunits such that a site that normally interacts with the β subunit reacts with the α subunit. The nonproductive binding of TuD subunits (III in Fig. 2) can account for the fact that when steady-state microtubules are exposed to an enzymic treatment that converts GTP to GDP, a metastable state is attained (9–11). This occurs even though under these conditions TuD subunits are not able to readily elongate microtubules (9). (*iv*) There is a unique site (VIII in Fig. 2) at one end where enhanced GTP hydrolysis may be expected—i.e., in the most strongly interacting TuT subunit at the TuT cap/TuD core interface (the analysis in sections 3 and 4 considers the possibility of a separate enhanced hydrolysis at sites VII and VIII).

Hydrolysis is a facilitated process, in which the TuD core serves to direct its own elongation. The alternate sites for the GTPase reaction are in the TuT subunits within the cap (sites VI and IX in Fig. 2) and in the terminal subunits at the TuT cap/solution interface (sites V or X in Fig. 2) (6, 7). It is not likely that the former reaction constitutes the principal steady-state GTPase reaction because, if it were, the GTP hydrolysis reaction would be expected to be much faster during pre-steady-state microtubule assembly than at steady state. This would be the case because, during the initial phase for microtubule assembly, almost the entire microtubule is composed of TuT subunits (1, 27), whereas at steady state the microtubule primarily contains TuD subunits. In contrast, the number concentration of interfaces involving the microtubule's TuT subunits does not significantly change during this period. Since the hydrolysis rate at steady state is about 67% (4) to >90% (unpublished data) of that during the initial phase of the pre-steady-state reaction (1), it can be concluded that the principal hydrolysis reaction at steady state occurs at an interface involving TuT subunits.

2. How GTP Hydrolysis at a Cap/Core Interface Can Make for a Positive Flux of Subunits

It may be difficult to picture how the asymmetry reflected by tubulin subunit treadmilling can be generated with microtubules that are apparently symmetrical in the sense that they have TuT caps at both ends. We next describe how the hydrolysis rates at the cap/core interfaces, through their influence on the proportion of ends that have an exposed TuD core, can generate an asymmetry in the microtubules and allow for treadmilling. A basic premise of our model is that GTP hydrolysis affects the stability of polymerized subunits. We will assume a "stable-core" model—that is, that the stability is increased through a decrease in off-rates:

$$i_{-1} > i_2. \qquad [1]$$

At steady state the ensemble of microtubule ends can be thought of as being composed of two subpopulations—i.e., ends with and without TuT caps. For simplification we ignore ends with nonproductively bound subunits (Fig. 1); this is considered in section 4. The fraction of the steady-state net assembly (α) and disassembly (β) end that is uncapped is defined as $(f_0)_i$, where $i = \alpha$ or β. As discussed in section 3,

$$(f_0)_i = 1 - \gamma_i, \qquad [2]$$

where we define γ_i by

$$\gamma_i = c\, i_1/(i_{-1} + k'_i), \qquad [3]$$

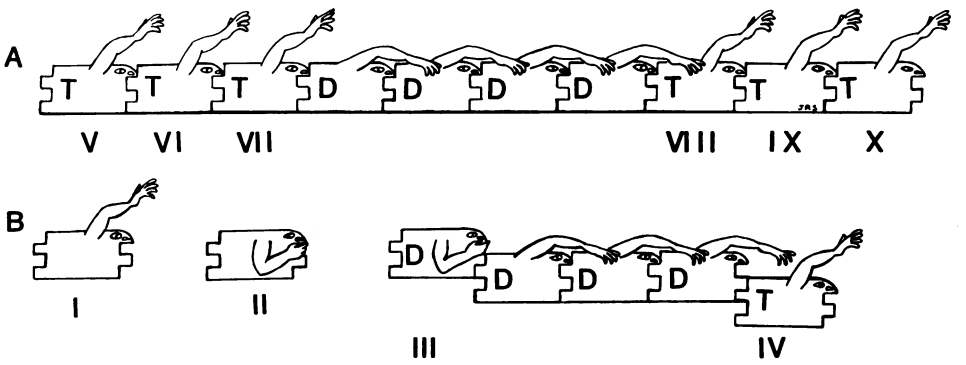

FIG. 2. Schematic model to account for the properties of microtubules. (*A*) Microtubule at steady state, with a TuT cap at each end. (*B*) Nonproductive TuD and TuT subunit addition at the two ends of a TuD core.

in which c is the steady-state tubulin dimer concentration.* A flux of subunits into steady-state microtubules obviously must pass through the TuD core, and although this core remains a constant total fraction of the microtubule mass, the core grows and dissolves by the reactions described by Eqs. 4 and 5.

$$(\text{Core-on})_i = k_i'\gamma_i \quad \text{and} \quad (\text{Core-off})_i = i_2(1 - \gamma_i) \quad [4]$$

$$(\text{Net flux})_i = J_i = k_i'\gamma_i - i_2(1 - \gamma_i) \quad [5]$$

At steady state, $J_\alpha + J_\beta = 0$. Considering this and Eqs. 3 and 5 yields a formula for the critical concentration:

$$c = (\alpha_2 + \beta_2)/(A_\alpha + A_\beta), \quad [6]$$

where we define $A_i = i_1[(i_2 + k_i')/(i_{-1} + k_i')]$ to simplify the expression. For the steady-state net assembly end (α end),

$$J_\alpha = cA_\alpha - \alpha_2. \quad [7]$$

Combining Eqs. 6 and 7 (to eliminate the dependence on c) yields

$$J_\alpha = \beta_2[A_\alpha/(A_\alpha + A_\beta)] - \alpha_2[A_\beta/(A_\alpha + A_\beta)]. \quad [8]$$

Algebraic manipulations of Eq. 8 using the following thermodynamic relationship (33)

$$\alpha_{-1}/\alpha_1 = \beta_{-1}/\beta_1 \quad [9]$$

show that J_α is positive at steady state (i.e., that there is a positive flux of subunits at the α end) if and only if

$$[(\alpha_{-1}/\alpha_2) - 1]\beta_{-1}\, k_\alpha' > [(\beta_{-1}/\beta_2) - 1]\alpha_{-1}\, k_\beta' + k_\alpha' k_\beta'[(\beta_{-1}/\beta_2) - (\alpha_{-1}/\alpha_2)]. \quad [10]$$

Since $\alpha_{-1} > \alpha_2$ (by Eq. 1), the term on the left is positive. One sufficient condition to have the inequality hold is to have k_β', the hydrolysis at the disassembly end, sufficiently slow. It is possible, however, for the inequality to hold when $k_\beta' > k_\alpha'$ (i.e., the fast hydrolysis end can also be the steady-state net disassembly end). For example, if $\alpha_{-1}/\alpha_2 = \beta_{-1}/\beta_2$ but $\alpha_{-1} < \beta_{-1}$ (i.e., the α end is less reactive), then the β end remains a net disassembly end, even with $k_\beta' > k_\alpha'$, as long as $k_\alpha' > (\alpha_{-1}/\beta_{-1})k_\beta'$. In summary, treadmilling can arise from circumstances such as the following ones. A high GTPase rate at one cap/core interface can impart TuD character to this end; since TuD subunits are relatively stable, a sufficiently high GTPase makes this end tend to grow. On the other hand, a low GTPase activity can impart TuT character by increasing the life expectancy of TuT subunits; since these tend to be lost rapidly, a sufficiently low GTPase will lead to disassembly.

3. Characteristics of the Cap and Core in Steady-State Microtubules

We here demonstrate that, under steady-state conditions, the only kinetically stable distribution for the length of TuT caps is a geometric one. [An argument similar to that of Oosawa (28) indicates that the short TuT caps on steady-state microtubules (1, 7, 27) will have reached this stable distribution in the time period usually allowed for attaining a steady state.] Based upon this fact we also show that the f_0 value (i.e., the fraction that is uncapped) is simply related to the mean length of the TuT caps [i.e., it is equal to 1/(1 + average TuT cap length)].

Under conditions where the distribution of cap lengths has reached equilibrium,

$$0 = \frac{d}{dt}\left[\sum_{m=n}^{\infty} f_m\right], \quad [11]$$

where f_n is the fraction of caps with length n and where $n \geqq 0$.

The right-hand term can be written in terms of the rate parameters; for $n \geqq 1$, we have Eq. 12:

$$\frac{d}{dt}\sum_{m=n}^{\infty} f_m = -(i_{-1} + k_i')f_n + ci_1 f_{n-1}. \quad [12]$$

Combining Eqs. 11 and 12, where $n \geqq 1$, yields (at each end)

$$f_n/f_{n-1} = \gamma \quad \text{and} \quad f_n = f_0\prod_{m=1}^{n}\left(\frac{f_m}{f_{m-1}}\right) = f_0\,\gamma^n, \quad [13]$$

where γ is defined in Eq. 3. Since

$$1 = \sum_{n=0}^{\infty} f_n = \sum_{n=0}^{\infty} f_0\,\gamma^n = f_0/(1 - \gamma), \quad [14]$$

we have $f_0 = 1 - \gamma$ (i.e., Eq. 2 holds). Thus, the most common single species is the microtubule end that is uncapped, and the distribution of TuT cap lengths at each end falls off in a geometric progression.

The fraction of the microtubule ends that are uncapped (f_0) depends on γ and, therefore, on the rates for addition and loss of TuT subunits and the GTP hydrolysis rate. These parameters determine the average length of the TuT cap (L_{avg}), which is defined by

$$L_{avg} = \sum_{n=0}^{\infty} nf_n. \quad [15]$$

L_{avg} can be calculated from f_0:

$$L_{avg} = \sum_{n=0}^{\infty} nf_n = \gamma f_0\left(\sum_{n=1}^{\infty} n\gamma^{n-1}\right), = \gamma f_0(1/1 - \gamma)^2. \quad [16]$$

Since $f_0 = 1 - \gamma$, we have

$$f_0 = 1/(1 + L_{avg}) \quad [17]$$

Eq. 17 helps to make clear how the rates for TuT subunit addition and GTP hydrolysis determine the characteristics of a microtubule's end. For example, consider the case where the first-order rate constant for the GTP hydrolysis at the cap/core interface (k_i') is equal to 5% of that for TuT dissociation from the microtubule end. Since $ci_1 \cong i_{-1}$ at steady state, the calculated value for f_0 is 0.05 (see Eqs. 2 and 3). Eq. 17 indicates that the average cap length is 20 subunits.

4. Concerning the Nonlinear Dependence of the Flux Rate on the Tubulin Concentration

The scheme described in Fig. 1 can account for the fact that microtubules depolymerize faster below the critical concentration than is expected from determinations of the rate at tubulin concentrations that exceed the critical concentration (20, 21). It is presumed that, concomitant with the assembly

*γ_α and γ_β are each <1 at steady state [for our assumptions $J_\beta < 0$ (treadmilling) and Eq. 1 imply that $c\beta_1$ = on-rate (β) < off-rate (β) $\leqq \beta_{-1}$; therefore, by Eq. 9 we have $1 > c\beta_1/\beta_{-1} = c\alpha_1/\alpha_{-1} \geqq ci_1/(i_{-1} + k_i') = \gamma_i$ for each i].

process (reactions α_{1T} and α_{-1T}), nonproductive ("wrong way") TuT subunit binding (26) occurs via the upward diagonal reactions to form an inactive MT' (see Fig. 1) species (see configuration IV in Fig. 2). When this reaction is taken into account, the assembly/disassembly is described by

$$d \text{ microtubule mass}/dt = (c_1\alpha_{1T} - \alpha_{-1T})/(1 + c_1\alpha'_{1T}/\alpha'_{-1T}), \quad [18]$$

where c_1 is the tubulin subunit concentration and the other constants are defined in Fig. 1. (Algebraically similar equations hold when the scheme is expanded to distinguish between ends and to allow exposed TuD subunits.) The curve calculated for the case where $\alpha_{1T} = \alpha'_{1T} = 10^8$ $M^{-1}\cdot sec^{-1}$, $\alpha_{-1T} = \alpha'_{-1T} = 10^2$ sec^{-1} (Fig. 3), shows that the rate for microtubule depolymerization is faster below the critical concentration than expected from determinations of the rate at tubulin concentrations that exceed the critical concentration. The leveling-out of the rate at high tubulin concentrations, which is predicted from Eq. **18**, has been observed (22–24).

The kinetic properties of TuD (2–5, 9–11) also can be accounted for within the same framework (Fig. 1). We assume that, as is the case for TuT, nonproductive binding of TuD subunits occurs (via the downward diagonal α_{-2D} path). The TuT and TuD reactions form MT'-GTP and MT'-GDP, respectively, in Fig. 1, both of which are unable to undergo further elongation reactions. The scheme shows that the microtubule can contain two different TuD species, MT-GDP formed by the hydrolysis (k') reaction and MT'-GDP, formed by the nonproductive binding process (α'_{-2D}). These are represented by the TuD core and configuration III, respectively, in Fig. 2. It should be noted that unlike the Hill–Carlier scheme (6), the MT-GDP species in Fig. 1 is able to be elongated readily by reaction of TuT (i.e., the mechanism does not require $\alpha_{1D} << \alpha_{1T}$). Also, it is possible for TuD to be an effective inhibitor for net microtubule assembly by TuT (4) at TuD concentrations that are below the critical concentration for this species (the critical concentration for TuD is immeasurably high; see refs. 4 and 5). This is true because TuD inhibition depends upon the $\alpha'_{-2D}/\alpha'_{2D}$ ratio and not the critical concentration (i.e., the α_{-2D}/α_{2D} ratio). Finally, under conditions where there is net microtubule assembly of TuD (3), this reaction is likely to proceed more slowly than the assembly of TuT, if we assume that nonproductive binding occurs more readily with TuD as compared with TuT.

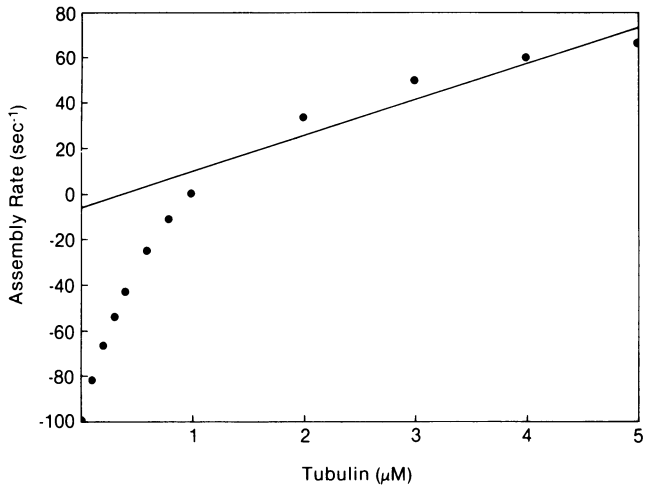

FIG. 3. Dependence of the rate for microtubule assembly/disassembly on the tubulin concentration, calculated for a scheme involving nonproductive binding. The solid line is a calculated least-squares fit of the results calculated for tubulin at 1–5 μM. Note that the extrapolate of this line yields a value for α_{-1T} that is only 6% of the actual value. The rate constant for TuT subunit addition, which would be obtained from the slope of the straight line, is only about 10% of the true value for α_{1T}. The shape of the curve shown here is in reasonable agreement with those in ref. 20, except for the discontinuity at the critical concentrations. The theoretical basis for the discontinuity has been eliminated (except where $\kappa = 0$) in a more recent formulation of the earlier model (29). The absence of a limiting rate at high tubulin concentrations (20) may result from experimental error or because the tubulin concentrations were not sufficiently high. Alternatively, it may have a more complex origin (e.g., if TuT nonproductive binding were more facile with a core than with a cap, the leveling out of the rate would be gradual).

The scheme outlined here suggests a continuum in the tendency for nonproductive as compared to productive binding of different tubulin subunits. Species such as colchicine-containing and podophyllotoxin-containing tubulin subunits bind almost exclusively in a nonproductive binding mode; this alternately can be described as a capping process (29–31). The tendency for nonproductive binding is presumed to decrease progressively with TuD and TuT—that is, GTP binding in tubulin subunits favors conformation I in Fig. 2 (which can bind nonproductively *and* productively), whereas form II in Fig. 2 (which only binds nonproductively) predominates with GDP. Thus, GTP would appear to play two roles in microtubule assembly: (*i*) tubulin subunit binding of GTP increases the assembly rate by increasing the tendency for productive subunit addition and (*ii*) GTP hydrolysis decreases the disassembly rate by stabilizing the subunit in the microtubule (see Eq. **1**).

5. Comparison with the Hill–Carlier Model

The differences between the model proposed here and that previously adduced (6, 7) are: (*i*) the location of the treadmilling-related GTPase reaction; (*ii*) the nature of the driving force for subunit treadmilling; (*iii*) no need for a nucleotide exchange reaction into the microtubule's terminal subunits; and (*iv*) prediction that the assembly rate reaches a limiting value at high tubulin concentrations (22, 23).

These differences are further expanded as follows. (*i*) In the model presented here, the principal steady-state GTPase reaction is at the interface of a TuT cap and the TuD core at one end of the microtubule. In the previously published model (6, 7), the principal steady-state GTPase reaction is in subunits at the microtubule/solution interface.† (*ii*) In the earlier model, treadmilling results because GTP hydrolysis generates an end that cannot accept additional subunits ($\alpha_{1D} \cong 0$ is assumed) until the resultant TuD subunit dissociates (in the case where the penultimate subunit is TuT) or the product GDP exchanges for a GTP molecule from solution; thus, the hydrolysis serves to modulate tubulin subunit "on-reactions." This last assumption (that $\alpha_{1D} \cong 0$) is puzzling in the light of the observation (25) that under these conditions TuT and TuD are equally reactive in elongating microtubules (i.e., $\alpha_{1T} = \alpha_{-2D}$). In our model treadmilling results primarily from a change in the strength of a tubulin subunit's interactions with adjacent subunits as a result of a protein conformation change that occurs after GTP hydrolysis; we present here the case where the interaction is strengthened. This interaction is expected to result in a decreased rate for TuD

†In the appendix to ref. 20, GTP hydrolysis at a cap/core interface is considered. For this to be the *principal* GTPase rather than "relatively small," as assumed in ref. 6, would require a new explanation for the observed GDP inhibition of the GTPase reaction (figure 2 in ref. 4), which was previously assumed to require nucleotide exchange at the principal GTPase site. This would not be expected if the principal GTPase is not at the terminal subunit, since interior GTP does not exchange with GDP (figure 4 in ref. 4).

subunit dissociation as compared with TuT subunit dissociation; thus, the GTPase reaction serves to modulate the subunit "off-reactions." It has been found that TuD dissociates more slowly than does TuT from a microtubule end (12). (*iii*) The scheme that we propose here does not require nucleotide exchange into microtubule-associated subunits, but rather assumes that an exposed TuD core can readily accept both TuT and TuD subunits; a TuD core can react with subunits in conformation I of Fig. 2 productively (conformations VII and VIII) and nonproductively (conformation IV), while subunits in conformation II can bind nonproductively (conformation III). [For simplicity of exposition we assumed in sections 3 and 4 (e.g., Eq. 2) that $i_{1T} = i_{1D}$.] Thus, TuD stabilization of exposed TuD core (9–11) is allowed.

In the previous mechanism (6), it is assumed that terminal TuD subunits are able to exchange bound GDP for unbound GTP; this will allow regrowth of the cap and protection of exposed TuD core from monotonic TuD subunit loss. It is required that this exchange reaction (κ'' in figure 6 of ref. 6) be rate-limiting in the GTPase cycle in terminal subunits because, if the exchange were to be rapid, then the hydrolysis reaction would not "poison" the assembly process, and the observed nonlinear dependence of the rate at tubulin concentrations that are below the critical concentration (20, 21) is not predicted (see figure 6 in ref. 6).

The Hill–Carlier model does not include difference *iv*, and it does not appear to account for the observed TuD stabilization of microtubules under conditions where TuD is not able to readily elongate microtubule ends (9–11) (see figure 11 in ref. 7); free TuD subunits cannot add to and stabilize an α end or exposed TuD core at either end). A recently revised model (32) suggests that GTP hydrolysis yields subunits that dissociate more rapidly. If this is correct (see, however, ref. 12), then our suggestions concerning the basis for treadmilling (*ii* above) do not hold. However, this does not influence our suggestions concerning the location of the GTPase reaction (*i*), the mechanism for GDP effects on microtubules (*iii*), or the proposal that nonproductive binding accounts for the limiting rate at high tubulin concentrations (*iv*) and for the observed kinetic behavior below the tubulin critical concentration.

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