Dynamical decoration of stabilized-microtubules by tau-proteins: supplementary information

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S1. MICROTUBULE COVERAGE

Phase space: In general, analytical solutions of Eq.(2) in the main text providing expressions for ρ_p and ρ_h are not possible because of the non-linearities in the probabilities $\Phi_{\rm p}$ and $\Phi_{\rm h}$, However, some insights can already be gained by analyzing the phase space (ρ_p, ρ_h) without having solved Eq.(2), i.e., not explicitly determining ρ_p and ρ_h. The relation between ρ_p and ρ_h in the space is given by, equation

$$\frac{\rho_p}{\rho_h} = \kappa\, \frac{(1-\sigma_h\rho_h)^{\sigma_h}}{(1-\sigma_p\rho_p)^{\sigma_p}}\, [1-(1+\sigma_p)\rho_p-(1+\sigma_h)\rho_h]^{\sigma_p-\sigma_h} \quad , \quad \kappa = \frac{k_{\rm eq,p}}{k_{\rm eq,h}} \, . \tag{S1}$$

Now, solving Eq.(S1) allows us to portray ρ_h as a function of ρ_p within the triangular section of the phase space. In addition, combining the saturation line and Eq.(S1) allows determining $\rho_{p,s}$ and $\rho_{h,s}$. As analytical solutions of Eq.(S1) are only possible for $\sigma_i = 0, 1$, we consider the solution of Eq.(S1) for $\sigma_p = \sigma_h = 1$,

$$\rho_h(\rho_p,\kappa) = \frac{1}{2}\left[1-\sqrt{1-\frac{4\,\rho_p(1-\rho_p)}{\kappa}}\right] \quad \text{for} \quad \sigma_p=\sigma_h=1 \qquad \text{(see Fig. 4a)} \, . \tag{S2}$$

The position along the trajectory ρ_h *vs* ρ_p depend on the kinetic parameters: the tau:tubulin-dimer ratio, x, and the effective equilibrium constant, $k_{\rm eq} = k_{\rm eq,p} + k_{\rm eq,h}$. For example, in Fig. 4a, the points A and B on the trajectory $\rho_h(\rho_p, \kappa = 1) = \rho_p$ correspond to identical, $k_{\rm eq,p} = k_{\rm eq,h} = 1.5$ (i.e., $k_{\rm eq} = 3$) but to different ratios, $x = 0.15$ and $x = 10$, respectively. This indicates that for a given set of $(k_{\rm eq,p}, k_{\rm eq,h})$, the trajectory $\rho_h(\rho_p, \kappa)$ approaches the saturation line with increasing x. Using the saturation line [‡], $1 - 2\rho_{p,s} - 2\rho_{h,s} = 0$ (for $\sigma_p = \sigma_h = 1$), back into Eq.(S1) and solving for $\rho_{p,s}$ and $\rho_{h,s}$ leads to:

$$\rho_{p,s}(\kappa) = \frac{1-\sqrt{1-\kappa\,(1-\kappa)}}{2\,(1-\kappa)} \, , \quad \rho_{h,s}(\kappa) = \frac{\sqrt{1-\kappa\,(1-\kappa)}-\kappa}{2\,(1-\kappa)} \, . \tag{S3}$$

Note that the partial saturation densities $\rho_{p,s}$ and $\rho_{h,s}$ are functions of κ but the total density, $\rho_s = \rho_{p,s} + \rho_{h,s} = 1/2$, is not as it should be.

Diluted regime: The diluted regime, corresponding to a low MT coverage $\rho_p \ll 1$ and $\rho_h \ll 1$, is both especially relevant to the context of axons [39] and interesting as it allows deriving analytical solutions of Eq.(2). In this case, the insertion probabilities Φ's can be linearized to the leading order as,

$$\begin{cases} \Phi_{\rm p}(\rho_p,\rho_h) \approx 1-(1+2\sigma_p)\,\rho_p-(1+\sigma_h)\,(1+\sigma_p)\,\rho_h+O(\rho_p\rho_h) \, , \\ \\ \Phi_{\rm h}(\rho_p,\rho_h) \approx 1-(1+2\sigma_h)\,\rho_h-(1+\sigma_p)\,(1+\sigma_h)\,\rho_p+O(\rho_p\rho_h) \, . \end{cases} \tag{S4}$$

In addition, the trajectories ρ_h *vs* ρ_p, given in Eq.(S1) can also be linearized as, $\rho_h \simeq \rho_p/\kappa + O({\rho_p}^2)$. Now, using Eq.(S4) back into Eq.(2) and with linearized phase portraits leads to a system of equations that can be

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[‡] As the binding in mode "h" is not allowed at the MT seam, the saturation line becomes an approximation. Therefore, for $\sigma_h = 1$ and 13-protofilaments MT, the highest coverage in mode "h" is $\rho_h = 6/13 \approx 0.46$, instead of 1/2, corresponding to 6 Taus bound in mode "h" (i.e., 12 lattice binding sites are occupied) per MT helix. The correct saturation line is shown in Fig. 4a in dashed line and is given by: $\rho_{h,s}(\rho_{p,s}) = 6/13$ for $0 \le \rho_{p,s} < 1/26$, and, $\rho_{h,s}(\rho_{p,s}) = 1/2 - \rho_{p,s}$ for $1/26 \le \rho_{p,s} \le 1/2$. As it can be seen in Fig. 4a, the saturation line above is exact for $1/26 \le \rho_{p,s} \le 1/2$ but becomes an approximation for $\rho_{p,s} < 1/26$ yielding a maximum relative error of about 4%.

solved analytically to give,

$$\begin{cases} \rho_p = \dfrac{1}{2}\left\{ \dfrac{\kappa}{1+\kappa}\left(x+\dfrac{1}{\beta_p\, k_{\rm eq,p}}\right)+\dfrac{1}{\beta_p} - \sqrt{\left(\dfrac{\kappa}{1+\kappa}\left(x+\dfrac{1}{\beta_p\, k_{\rm eq,p}}\right)+\dfrac{1}{\beta_p}\right)^2 - \dfrac{4\,x\,\kappa}{\beta_p\,(1+\kappa)}} \right\}, \\ \rho_h = \dfrac{1}{2}\left\{ \dfrac{1}{1+\kappa}\left(x+\dfrac{1}{\beta_h\, k_{\rm eq,h}}\right)+\dfrac{1}{\beta_h} - \sqrt{\left(\dfrac{1}{1+\kappa}\left(x+\dfrac{1}{\beta_h\, k_{\rm eq,h}}\right)+\dfrac{1}{\beta_h}\right)^2 - \dfrac{4\,x}{\beta_h\,(1+\kappa)}} \right\}, \end{cases} \tag{S5}$$

where the coefficients β_p and β_h are given by

$$\beta_p = 1+2\sigma_p+\frac{1}{\kappa}\,(1+\sigma_p)\,(1+\sigma_h) \quad \text{and} \quad \beta_h = 1+2\sigma_h+\kappa\,(1+\sigma_p)\,(1+\sigma_h)\ . \tag{S6}$$

For low tau:tubulin-dimer ratio, $x \ll 1$, the coverages become linear functions of x as,

$$\begin{cases} \rho_p \approx x\left(\dfrac{k_{\rm eq,p}}{1+k_{\rm eq,p}+k_{\rm eq,h}}\right) \\ \rho_h \approx x\left(\dfrac{k_{\rm eq,h}}{1+k_{\rm eq,p}+k_{\rm eq,h}}\right) \end{cases} \quad \Rightarrow \quad \rho \equiv \rho_p+\rho_h \approx x\left(\frac{k_{\rm eff}}{1+k_{\rm eff}}\right)\ . \tag{S7}$$

Interestingly, in the limit $x \ll 1$, the coverage is independent of the binding reaction stoichiometries and, therefore, fitting the experimental data (as, for example, in cosedimentation assays) in this regime would allow determination of the effective equilibrium constant $k_{\rm eff} = k_{\rm eq,h} + k_{\rm eq,p}$. Out of the $x \ll 1$ regime, the ρ's given in Eq.(S5) are non-linear functions of x and depend on stoichiometries and dissociation constants.

S2. METHODS

To make the calculations tractable, the two-dimensional microtubule lattice shown in Fig. S1 is replaced by two coupled linear lattices: protofilament and helix. The underlying approximation is to consider each direction as an independent linear lattice. As illustrated in Fig. S1, for a protofilament "j" (helix "i") , Tau's bound in "p" ("h") mode cover $(1+\sigma_p)$ $[(1+\sigma_h)]$ consecutive sites while those bound in "h" ("p") mode cover 1 site. According to this, the directional coverages $\rho_{\parallel,p}$ and $\rho_{\parallel,h}$ can be expressed as a function of ρ_p and ρ_h as,

$$\begin{cases} \rho_{\parallel,p} = \rho_p \quad \text{and} \quad \rho_{\parallel,h} = (1+\sigma_h)\,\rho_h\ , \\ \rho_{\perp,h} = \rho_h \quad \text{and} \quad \rho_{\perp,p} = (1+\sigma_p)\,\rho_p\ . \end{cases} \tag{S8}$$

A. Distribution of gaps

The distribution of gaps $f_k(g)$ is defined as the probability of finding a gap of size g (i.e., g consecutive free lattice sites) along the direction k. According to the approximation shown in Fig. S1, two distributions of gaps have been considered: $f_\parallel(g)$ for the protofilament linear lattice and $f_\perp(g)$ for the helicoidal linear lattice shown in Fig. S1 in red and blue, respectively. McGhee and von Hippel [1] have shown that $f_k(g) \propto {u_k}^g$, where u_k is the conditional probability that a lattice site selected at random along the direction $k = \parallel, \perp$ is free and that its adjacent site (the immediate up and right site for $k = \parallel$ and $k = \perp$, respectively) is free as well. Using the normalization condition of the probability for $f_k(g)$, we find:

$$\sum_{g=0}^{g_{\rm m,k}} f_k(g) = 1 \quad \Rightarrow \quad f_k(g) = \left(\frac{1-u_k}{1-u_k^{\,g_{\rm m,k}+1}}\right){u_k}^g\ , \tag{S9}$$

where $g_{\rm m,k}$ is the maximum size of the physical gap between two bound Tau's along the direction k given by,

$$g_{\rm m,k} = [1-(1+\sigma_p)\,\rho_p-(1+\sigma_h)\,\rho_h] \times \begin{cases} h & \text{for} \quad k = \parallel\ , \\ p & \text{for} \quad k = \perp\ . \end{cases} \tag{S10}$$

Every microscopic configuration being equally likely, the conditional probability u_k can be obtained as the ratio between the number of free sites, $\#(\text{free sites})_k - 1$, and the total number of objects (free sites plus bound Tau's), $\#(\text{free sites})_k + \#(\text{tau})_k - 1$, forming the lattice along the direction k as,

$$u_k = \frac{\#(\text{free sites})_k - 1}{\#(\text{free sites})_k + \#(\text{tau})_k - 1}\ . \tag{S11}$$

The -1 term in Eq.(S11) accounts for that u_k is zero for a single site. Let ℓ_k (with $\ell_k = h$ and $\ell_k = p$ for $k =\|$ and $k =\perp$, respectively) be the total number of lattice sites along the k direction and, denote by $\rho_{\text{free,k}}$ and ρ_k the proportions of free lattice sites and bound Tau's, respectively, along the direction k, we have:

$$\rho_{\text{free,k}} = 1 - (1+\sigma_p)\,\rho_p - (1+\sigma_h)\,\rho_h\ , \tag{S12}$$

and

$$\rho_k = \begin{cases} \rho_{\|,p} + \rho_{\|,h} \ \equiv\ \rho_p + (1+\sigma_h)\,\rho_h & \text{for} \quad k =\|\ , \\ \\ \rho_{\perp,p} + \rho_{\perp,h} \ \equiv\ \rho_h + (1+\sigma_p)\,\rho_p & \text{for} \quad k =\perp\ . \end{cases} \tag{S13}$$

It follows that, $\#(\text{free sites})_k = \ell_k \rho_{\text{free,k}}$ and $\#(\text{tau})_k = \ell_k \rho_k$, such that,

$$u_k = \frac{\ell_k \rho_{\text{free,k}} - 1}{\ell_k\,(\rho_{\text{free,k}} + \rho_k) - 1} = \begin{cases} \dfrac{1 - (1+\sigma_p)\,\rho_p - (1+\sigma_h)\,\rho_h - 1/h}{1 - \sigma_p \rho_p - 1/h} & \text{for} \quad k =\|\ , \\ \\ \dfrac{1 - (1+\sigma_p)\,\rho_p - (1+\sigma_h)\,\rho_h - 1/p}{1 - \sigma_h \rho_h - 1/p} & \text{for} \quad k =\perp\ . \end{cases} \tag{S14}$$

In the $h \gg 1$ and $p \gg 1$ limit, the distributions of gaps reads as:

$$f_k(g) \underset{\lim h,p\gg 1}{=} (1-u_k)\ {u_k}^g = \begin{cases} \dfrac{\rho_p + (1+\sigma_h)\,\rho_h}{1-\sigma_p\rho_p}\left[\dfrac{1-(1+\sigma_p)\,\rho_p - (1+\sigma_h)\,\rho_h}{1-\sigma_p\rho_p}\right]^g & \text{for} \quad k =\|\ , \\ \\ \dfrac{\rho_h + (1+\sigma_p)\,\rho_p}{1-\sigma_h\rho_h}\left[\dfrac{1-(1+\sigma_p)\,\rho_p - (1+\sigma_h)\,\rho_h}{1-\sigma_h\rho_h}\right]^g & \text{for} \quad k =\perp\ . \end{cases} \tag{S15}$$

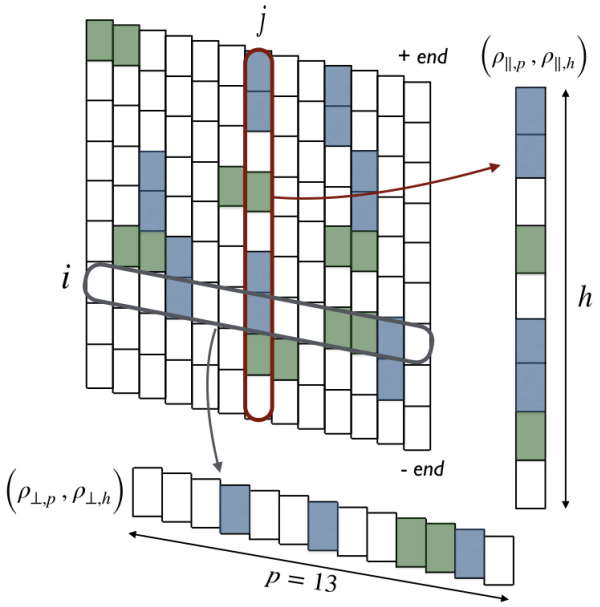

FIG. S1: Illustration of the approximation consisting of replacing the two-dimensional lattice by two linear-lattices: (i) a helix i consisting of $p = 13$ sites with particles bound in "h" mode covering $(1+\sigma_h)$ sites (in green) (coverage, $\rho_{\perp,h}$) and particles bound in "p" mode covering 1 site (in blue) (coverage $\rho_{\perp,p}$) and (ii) a protofilament j consisting of h sites with particles bound in "p" mode covering $(1+\sigma_p)$ sites (in blue) (coverage $\rho_{\|,p}$) and particles bound in "h" mode (in green) covering 1 site (coverage $\rho_{\|,h}$). Adapted from the manuscript of J.H.'s thesis [2].

B. Numerical solutions

Combining of Eqs.(2) and (3) in the main text of the manuscript leads to,

$$\begin{cases} \dfrac{\rho_p}{(x-\rho_p-\rho_h)} = k_{\mathrm{eq,p}} \left[\dfrac{\left[1-(1+\sigma_p)\rho_p-(1+\sigma_h)\rho_h\right]^{1+\sigma_p}}{(1-\sigma_p\,\rho_p)^{\sigma_p}} \right], \\ \dfrac{\rho_h}{(x-\rho_p-\rho_h)} = k_{\mathrm{eq,h}} \left[\dfrac{\left[1-(1+\sigma_h)\rho_h-(1+\sigma_p)\rho_p\right]^{1+\sigma_h}}{(1-\sigma_h\,\rho_h)^{\sigma_h}} \right]. \end{cases} \tag{S16}$$

For a given set of parameters σ_p, σ_h, $k_{\mathrm{eq,p}}$ and $k_{\mathrm{eq,h}}$, Eq.(S16) is solved for ρ_p and ρ_h using the function *fsolve* in MATLAB for several logarithmically spaced values of x. As shown in Fig. S2, each term in Eq.(S16) corresponds to surfaces in the space (ρ_p, ρ_h) and their intersections leads to an unique point solution of Eq.(S16).

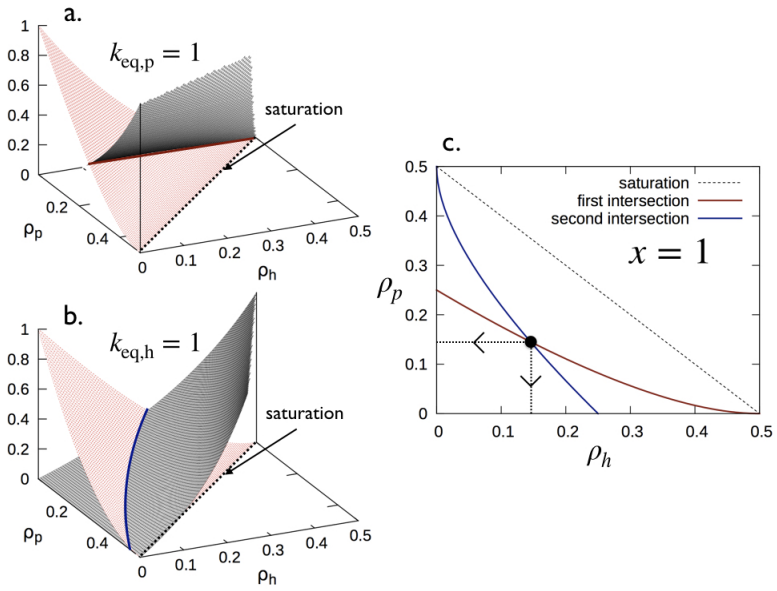

FIG. S2: Graphical representation of the resolution of Eq.(S16) for ρ_p and ρ_h for $\sigma_p = \sigma_h = 1$ with $x = 1$ and $k_{\mathrm{eq,p}} = k_{\mathrm{eq,h}} = 1$. (**a**,**b**) Surface plots corresponding to the first and second lines of Eq.(S16). Dashed lines represent the saturation line given by, $1-(1+\sigma_p)\rho_p-(1+\sigma_h)\rho_h = 0$. (**c**) Intersection between the two lines from Eq.(S16) in (**a**,**b**) leading to an unique point solution of Eq.(S16). Adapted from the manuscript of J.H.'s thesis [2].

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S3. BIBLIOGRAPHIC DATA BASE

A. Interaction tau-microtubule

The list of 54 papers below related to the interaction tau-microtubule have been obtained with PubMed and Google Scholar by using the following list of keywords: (i) *Tau microtubule binding site*, (ii) *Tau microtubule interaction*, (iii) *Tau microtubule topology*, (iv) *Tau microtubule binding modes*, (v) *Tau microtubule binding parameters*, (vi) *Tau microtubule binding stoichiometry*, (vii) *Tau microtubule binding dissociation constant*, (viii) *Tau microtubule assembly domain*, (ix) *Tau microtubule decoration*, (x) *Tau binding domain*, (xi) *Tau*

microtubule functions and (xii) *Tau tubulin complex*.

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B. Structure of the microtubule lattice

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