Motor driven microtubule shape fluctuations - force from within the lattice

Hervé Mohrbach\textsuperscript{1} and Igor M. Kulić\textsuperscript{2}

\textsuperscript{1}Laboratoire de Physique Moléculaire et des Collisions, Université Paul Verlaine - 57012 Metz, France
\textsuperscript{2}School of Engineering and Applied Sciences, Harvard University, Massachusetts 02138, USA

(Dated: February 1, 2008)

We develop a general theory of microtubule (MT) deformations by molecular motors generating internal force doublets within the MT lattice. We describe two basic internal excitations, the S and V shape, and compare them with experimental observations from literature. We explain the special role of tubulin vacancies and the dramatic deformation amplifying effect observed for katanin acting at positions of defects. Experimentally observed shapes are used to determine the ratio of MT shear and stretch moduli (≈ 6 × 10^{-5}) and to estimate the forces induced in the MT lattice by katanin (10's of pN). For many motors acting on a single MT we derive expressions for the end-to-end distance reduction and provide criteria for dominance of this new effect over thermal fluctuations. We conclude that molecular motors if acting cooperatively can ”animate” MTs from within the lattice and induce slack even without cross-bridging to other structures, a scenario very much reminiscent of the motor driven axoneme.

PACS numbers: 87.15.-v 87.16.Ka 87.16.Nn

Microtubules are the stiffest cytoskeletal component and constitute the main routes for motor mediated intracellular cargo transport in higher organisms \cite{1}. Understanding their physical properties is at the heart of many biological problems from cellular mechanics to information and material trafficking in the cell. Since the discovery of their high elastic anisotropy \cite{2} it became increasingly clear that MTs are mechanically more complex than other semiflexible biofilaments. The high anisotropy has been impressively confirmed by thermal fluctuation analysis of beads attached to MTs of different lengths \cite{3}. The emerging picture of the MT is that of an anisotropic fiber reinforced material \cite{2, 3} with the tubulin protofilaments (PF) acting as strong fibers weakly linked with easily shearable lateral bonds. Remarkably this type of design is also found in higher structures like axonemes (constituting the backbone of flagella and cilia) where relatively inextensible MTs are held together with highly stretchable nexin connections \cite{4}. This remarkable structural self-similarity of the two nested structures (MT and axoneme) indicates further analogies in the way they respond to external and internal forces. We explore here important consequences of MT geometry and elastic properties and show that motors acting on the MT surface can generate internal lattice strains sufficient to induce observable lateral and longitudinal deformations of the MT backbone.

In the following we describe a twist-free MT of length $L$ consisting of $N$ identical PFs with constant distance $a$ and a circular cross section, Fig 1. Each PF, parametrized by the MT backbone arc length $s$ has a position dependent displacement $u_k(s)$ from its equilibrium position, $k = 1, \ldots, N$. The backbone shape is described by a curvature vector $\vec{\kappa}(s) = \frac{d}{ds}\vec{\Gamma}(s)$ with $\vec{\Gamma}(s)$ the bundle centerline tangent. The elastic properties of the MT are characterized by a PF bending stiffness $B = \frac{1}{4\pi} a^4 Y$ and compressional modulus $K_c = \frac{E}{2a^2 Y}$ with $Y \approx 0.1 - 1.5 GPa$ \cite{2, 3} being the PF Young’s modulus. Additionally there are shear elastic forces restoring the longitudinal displacement between the PFs governed by a very soft elastic shear modulus $K_s \approx 10^{-3} - 1 MPa$ \cite{2, 3}. The elastic energy is given by

$$E_{MT} = \frac{1}{2} \sum_{k=1}^{N} \int_{-L/2}^{L/2} \left( B\kappa^2 + K_c u_k^2 + K_s \Delta_k^2 \right) ds \quad (1)$$

with the first term being the bending energy, the second the PF compression and the third describing the relative shear energy between the neighboring PFs. The shear displacement $\Delta_k$ is related to the difference of PF displacements $u_k - u_{k-1}$ and a curve induced additional displacement via

$$\Delta_k(s) = u_k(s) - u_{k-1}(s) + \int_{-L/2}^{s} \vec{\kappa}(s') \cdot \Delta\vec{r}_k ds' \quad (2)$$

With $\Delta\vec{r}_k = \vec{r}_k - \vec{r}_{k-1}$ and $\vec{r}_k = R_{MT} \left( \cos \frac{2\pi k}{N}, \sin \frac{2\pi k}{N} \right)$ the vector pointing from the MT center to the k-th PF, cf. Fig 1. Equations (1,2) are 3-D analogues of the previously proposed stretchable railway-track \cite{4} or wormlike-bundle \cite{5} model for the case of a hollow circular bundle. While in general all the $N + 3$ fields, i.e. the 3 components of $\vec{\kappa}(s)$ and the PF displacements $\{u_k(s)\}_{k=1, \ldots, N}$ enter the eqs (1,2) in the limit of small MT deviations from a straight line the problem can be drastically simplified. We first expand the tangent $\vec{t} \approx (\theta_x, \theta_y, 1)$ and $\vec{\kappa} \approx \left( \theta_x', \theta_y', 0 \right)$ in terms of two angular projections $\theta_x$ and $\theta_y$ of $\vec{t}$ in $x$ and $y$ direction respectively. Exploiting the circular geometry of the PF arrangement and the Fourier representation $u_k(s) = \sum \hat{u}_q(s) e^{2\pi i q x} a$ over $k$ we quickly realize that only the longest wavelength mode $\hat{u}_1(s)$ couples to overall MT backbone shape given by the curvature $\vec{\kappa}$. This leads to total energy decoupling $E_{MT} = E_{\kappa,MT} + E_{MT} + E_{\kappa,MT}$ into a shape-independent
FIG. 1: (Color online) The basic geometry of motors inducing internal force doublets along the MT backbone: between two PFs (S-let) and along the same PF (V-let). The red and blue ovals represent two coupled motors or two motor subunits (legs) of the same motor. Tubulin lattice vacancies at the motor position strongly amplify the MT backbone deformation (V\textsuperscript{app} -let).

Elementary internal MT excitations. In the following we want to understand the properties of the two basic types of excitations from Fig 1 and focus on the S-type first. We assume a single motor (or a complex of two motors) at position \( s = s_0 \) bridging between two PF with index \( k_1 \) and \( k_2 \) and exerting opposing forces \( F \) and \(-F\) onto them respectively, Fig 1 a) (left) + b)

The total energy is \( E_{tot} = E_{MT} + E_{S-mot} \) with \( E_{MT} \) given by eqs (12) and the potential energy of the motor \( E_{S-mot} = -F \int_{-L/2}^{L/2} \delta (s-s_0) \Delta_k (s) ds \)

As we had for \( E_{MT} \) before \( E_{S-mot} \) also decouples into independent modes in the Fourier representation over \( k \) and \( E_{mot,S} = E_{S-mot}^0 + E_{S-mot}^\prime \) with \( E_{S-mot}^0 \) a curvature independent term and the two shape dependent contributions \( E_{S-mot}^\prime (xy) \) (in x and y direction) given by:

\[
E_i^{S-mot} = -F \int_{-L/2}^{L/2} \delta (s-s_0) \hat{\Delta}_i (s) ds \approx \begin{cases} 
\mu \cdot \hat{\Delta}_i (s) & \text{if } i = x, y \\
\mu \cdot \hat{\Delta}_i (s) N K_s & \text{if } i = \alpha \end{cases}
\]

With \( \hat{\Delta}_i (s) = a (\theta_i (s) - \theta_i (-L/2)) - U_i (s) \), \( a = |\Delta \hat{v}_i| \) the interprotofilament distance, \( i = x, y \) and \( \hat{U} (s) = (U_x, U_y) = (\alpha \hat{v}_x, \beta \hat{v}_y) \) with \( \chi = 1 - e^{-2\pi i/N} \) and renormalized constants \( \hat{B} = NB, \hat{K} = NK_c/\left(4 - 4 \cos (2\pi/N)\right) \) and \( \hat{K}_s = NK_s \). Visually the new variable \( \hat{U} (s) \) is a x-y vector at each MT crosscut and can be interpreted as the (vectorial) mean over relative PF displacements of neighboring PFs. With this enormous simplification at hand we can consider now basic motor induced MT excitations (Fig.1).

There are two elementary configurations in which motors can induce internal MT strains: 1) A motor (or a complex of several motors) acting between two (not necessarily neighboring) PFs and 2) A motor (or a complex of several motors) acting at two points within the same PF. For reasons that will soon become clear we call the excitation 1 S-type or simply an "S-let" and excitation 2 we call an V-type excitation or "V-let". Both excitations are "internal" in the sense that there is no net torque or force on the system motor+MT similarly to the case of a beating flagellum[3].

Elementary internal MT excitations. In the following we want to understand the properties of the two basic...
cates that many katanin motors might act cooperatively to generate the observed shape change in Fig 2b. Another interesting possibility is that katanin might be different from dynein/kinesin by generating only small contractile displacement “powerstrokes” ≲ 1nm with a more efficient chemical-mechanical ATP-energy conversion leading to larger contractile forces $F \gtrsim 15k_BT/nm = 60\ pN$.

The second fundamental internal MT excitation appears when a motor (or motor complex) acts along a single PF with index $k$ compressing or stretching it. The motor energy in this case can be written as $E_{V,mot} = F(u_k(s_0 + |\mu|/2) - u_k(s_0 - |\mu|/2)) \approx F|\mu|L_0^2 \delta (s - s_0) u'_k(s) ds$ where $|\mu|$ is the size of the motor step. Like in the previous case it is sufficient to keep the energy contribution of the mode $q = 1$ as the others decouple from each other and from the curvature term. Along very similar line of derivation as in the S-type excitation case we obtain a solution which is planar and contained in the plane spanned by the vector $\vec{n}_k$ and $\vec{l}$. The resulting tangent angles for an excitation in the middle of the MT $s_0 = 0$ are given by eq [3] with $\Theta_i = \Theta_i^{(V)}(s) = \frac{\Delta \vec{r}_k}{2L_0} (\vec{e}_i \cdot \Delta \vec{r}_k) \frac{2|\mu|}{L_0(1 + |\mu|)}B$ which is now $s$ dependent and changes sign at $s = 0$. Here $(\gamma_x,\gamma_y) = \sin(\pi/N) (1 - \cos(2\pi/N))^{-1}$ $(\sin(2\pi(k + 1/2)/N), -\cos(2\pi(k + 1/2)/N))$. The resulting shape, that we call a ”V-let”, is a smooth V-shaped planar kink in the MT backbone with continuous curvature which relaxes on the length-scale $\lambda$. While suf-
motion \( (\theta,q,\mu)_{T} = 2k_{B}TL^{-1}G(\rho)\delta_{q} \) with the propagator \( G(q) = \left( \hat{B}q^{2} + \frac{\sqrt{k_{B}a^{2}}}{q^{2}+k_{B}/K} \right)^{-1} \) and a motor contribution \( (\theta,q,\mu)_{S/VJ} = \Psi_{S/V}(p)\Psi_{S/V}(q)C_{S/V}(q,p) \).

For S- and V-let case we have respectively \( \Psi_{S}(p) = \frac{2F_{0}K_{s}^{2}p^{2}}{L(K_{s}^{2}+p^{2}+k_{t}^{2})}G(p) \) and \( \Psi_{V}(p) = \frac{2F_{0}K_{s}^{2}p^{2}}{L(K_{s}^{2}+p^{2}+k_{t}^{2})}G(p) \), with the motor position and orientation correlator \( C_{S/V}(q,p) = \left( \sum_{j,l}^{N} \mu_{S/V,j}\delta_{S/V,j}C_{\alpha}(\cos(q_{j}),\sin(p_{j})) \right) \) which naturally decomposes in a sum of a thermal fluctuation term and a motor term \( (\Delta z)^{2}/L = \left( (\Delta z)^{2}/T \right)^{2} + (\Delta z)^{2}/N \). In the relevant limiting case \( L/\lambda \gg 1 \) we obtain for the thermal part

\[
\frac{\langle \Delta z \rangle}{L} \approx \frac{L}{a^{2}G_{s}h_{p}^{2}} + \frac{1}{2} \sqrt{\frac{k_{B}T}{a^{2}K_{s}h_{p}^{2}}} \tag{5}
\]

with the large and small scale persistence lengths given by \( h_{p}^{2} = \left( \hat{B} + \alpha^{2}K_{s} \right) /k_{B}T \) and \( h_{0} = \left( \alpha / (1+\alpha) \right)^{-3} \hat{B} /k_{B}T \). Interestingly the term \( a^{2}K_{s} \) can be formally understood as an intrinsic self-tension straightening the MT at small scales. Similar formulas appear in different geometries for the railway-track \( \mathcal{B} \) and wormlike-bundle model \( \mathcal{B} \). The motor dependent length reduction for the S-, V- and \( V^{gap} \)-let excitations with line density \( \rho \) is given by:

\[
\frac{\langle \Delta z \rangle}{L} = \frac{c_{S}\rho F^{2}a^{2}}{a^{2}K_{s}^{2}L} \tag{6}
\]

\[
\frac{\langle \Delta z \rangle}{L} = \frac{c_{V}\rho F^{2}a^{2}L}{a^{2}K_{s}^{2}L} = \frac{c_{Vgap}\rho F^{2}a^{2}L}{a^{2}K_{s}^{2}L} \tag{7}
\]

with \( c_{S} = \alpha^{2}(1+\alpha)^{2}/16 \approx 6 \times 10^{-2}, c_{V} = 0.18\alpha^{2}(1+\alpha)^{-2} \approx 1.3 \times 10^{-4} \) and \( c_{Vgap} = 0.73\alpha^{2}(1+\alpha)^{-2} \approx 0.7 \). Remarkably the S- and V/\( V^{gap} \)-lets show different scaling. In particular \( \langle \Delta z \rangle_{V^{gap}} / \langle \Delta z \rangle_{S} \) grows with \( L \) (in analogy to the first term in the thermal contribution \( \mathcal{B} \)) while \( \langle \Delta z \rangle_{V} / \langle \Delta z \rangle_{S} \) stays length independent. The physical reason for this difference becomes obvious from Fig. 2, as the relative slack \( \langle \Delta z \rangle /L \) induced by a single S-let scales with \( \lambda /L \), while for an \( V/\langle V^{gap} \)-let it is essentially length independent. For longer Mts this effect leads to a strong dominance of \( V^{gap} \)-lets over S-lets \( \langle \Delta z \rangle_{V^{gap}} / \langle \Delta z \rangle_{S} \sim (L/\lambda) \gg 1 \). Although having the same \( L \) scaling the minute prefactor of defect free V-lets renders their contribution relatively insignificant \( \langle \Delta z \rangle_{V} / \langle \Delta z \rangle_{S} \approx a^{2}\lambda^{-1}L \approx 10^{-6} \) even for very long Mts (\( L = 100\mu m \)), underlying the importance of lattice vacancies transforming a V-let into a \( V^{gap} \)-let. Another interesting observation is that in all three cases \( \langle \Delta z \rangle_{S/V} \approx \rho F^{2} \).

From Eqs \( \mathcal{B} \) we can derive criteria for the dominance of motor slack over the thermal slack. For instance using the values estimated from Fig 2 b,c for katanin for elastic constants from \( \mathcal{B} \) (\( F = 20p_{N}, \lambda = 1\mu m \)) and \( \mu = 8nm, L = 20\mu m \) we obtain \( \langle \Delta z \rangle /L = \rho /\rho_{c} \approx 0.25nm^{-1}, \rho_{c,v} \sim 1.2 \times 10^{-3}nm^{-1} \). For large enough motor densities the katanin action easily dominates over the thermal slack \( \langle \Delta z \rangle /L \approx 6 \times 10^{-4} \).

Being evolutionary specialized for MT deformation and degradation katanin is likely to be among the strongest slack generating motors. We suspect however that classical motors like dynein and kinesin might cause less pronounced but observable effects as well. While dynein is known to walk between several PFs, kinesin is very strictly following a single one \( \mathcal{B} \). Our theory suggest that dynein should induce moving S-lets, yet with quickly fluctuating signs which would diminish the effect considerably. A battery of many kinesins, however, walking over a MT region with many tubulin vacancies, would give rise to spatially stationary \( V^{gap} \)-lets blinking between "on" and "off" states. The theoretical and experimental exploration of these issues is an interesting future direction.

The authors acknowledge fruitful discussions with E. Frey, C. Heussinger, M.Bathe, O. Campos, J.F. Joanny and P.C. Nelson. I.M.K. acknowledges support by the Max-Planck Society.

[1] J. Howard, Mechanics of Motor Proteins and the Cytoskeleton, Sinauer Press (2001); L.A. Amos and W.G. Amos, Molecules of the Cytoskeleton, Guilford (1991).
[2] A. Kis et al. Phys. Rev. Lett. 89: 248101 (2002)
[3] F. Pampaloni et al. PNAS 103: 10248 (2006)
[4] R. Everaers, R. Bundschuh, and K. Kremer, Europhys. Lett. 29, 263 , (1995)
[5] C. Heussinger, M. Bathe and E. Frey, [cond-mat/0702097]
[6] L.J. Davis, D.J. Odde, S.M. Block, and S.P. Gross, Biophys. J. 82, 29162927 (2002)
[7] J.J. Hartmann et. al, Cell, Vol. 93, 277287; Movie at [http://valelab.ucsf.edu/images/mov-romhtsvkat.mov](http://valelab.ucsf.edu/images/mov-romhtsvkat.mov) with kind permission by R. Vale