Deformation of microtubules regulates translocation dynamics of kinesin

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Science Advances Vol. 7 Issue 42 13 Oct, 2021

21 Nov, 2022

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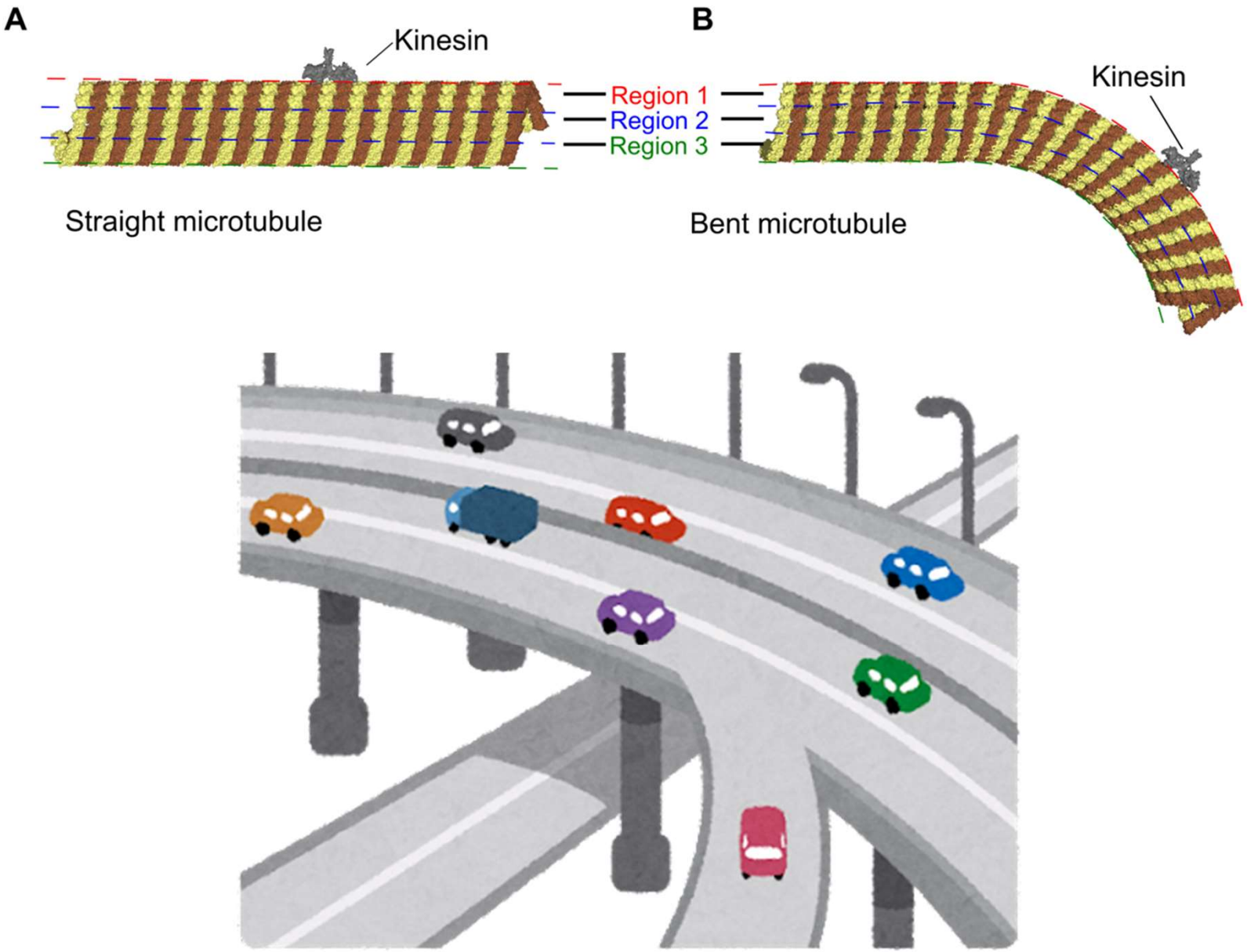

A
Kinesin
Region 1
Region 2
Region 3
Straight microtubule
B
Kinesin
Bent microtubule

- Microtubules, the most rigid components of the cytoskeleton, can be key transduction elements between external forces and the cellular environment. Mechanical forces induce microtubule deformation, which is presumed to be critical for the mechanoregulation of cellular events. However, concrete evidence is lacking.

- In this work, with high-speed atomic force microscopy, they unraveled how microtubule deformation regulates the translocation of the microtubule-associated motor protein kinesin-1, responsible for intracellular transport.
- Their results show that the microtubule deformation by bending impedes the translocation dynamics of kinesins along them.
- Molecular dynamics simulation shows that the hindered translocation of kinesins can be attributed to an enhanced affinity of kinesins to the microtubule structural units in microtubules deformed by bending.

- This study advances our understanding of the role of cytoskeletal components in mechanotransduction

- 細胞骨格の中で最も剛直な構成要素である微小管は、外力と細胞環境との間の重要な伝達要素になり得る。機械的な力は微小管の変形を誘発し、この変形が細胞内イベントの機械的制御に重要であると推測される。しかし、その具体的な証拠は乏しい。

- 本研究では、高速原子間力顕微鏡を用いて、微小管の変形が、細胞内輸送を担う微小管結合モータータンパク質であるキネシン-1の移動をどのように制御しているかを明らかにした。
- その結果、曲げによる微小管の変形が、それに沿ったキネシンの移動ダイナミクスを阻害することが明らかになった。
- 分子動力学シミュレーションの結果、キネシンの移動が妨げられるのは、曲げによって変形した微小管ではキネシンが微小管構造単位への親和性を高めていることに起因することが明らかになった。

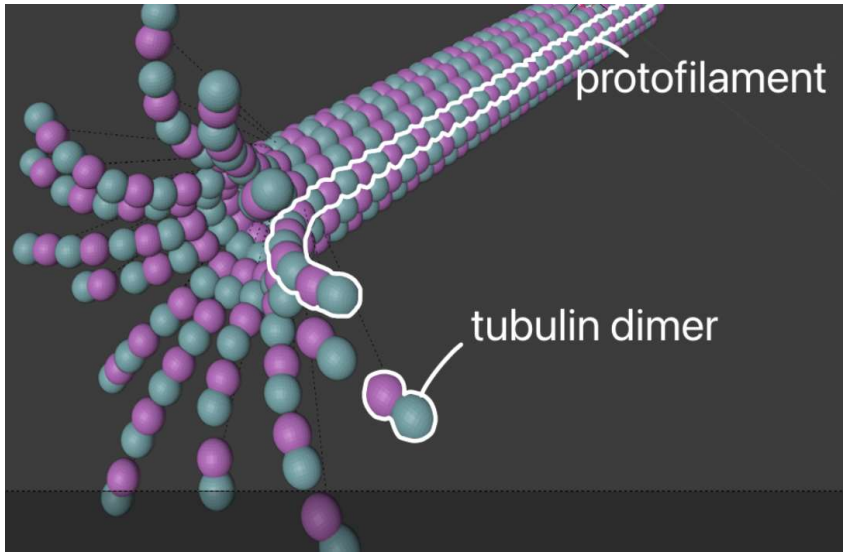
- この研究は、機械的伝導における細胞骨格の役割の理解を深めるものである

- 微管是细胞骨架中最坚硬的组成部分，可以成为外力和细胞环境之间的关键转导元件。机械力诱导微管变形，据推测这对细胞事件的机械调控至关重要。然而，目前还缺乏具体的证据。

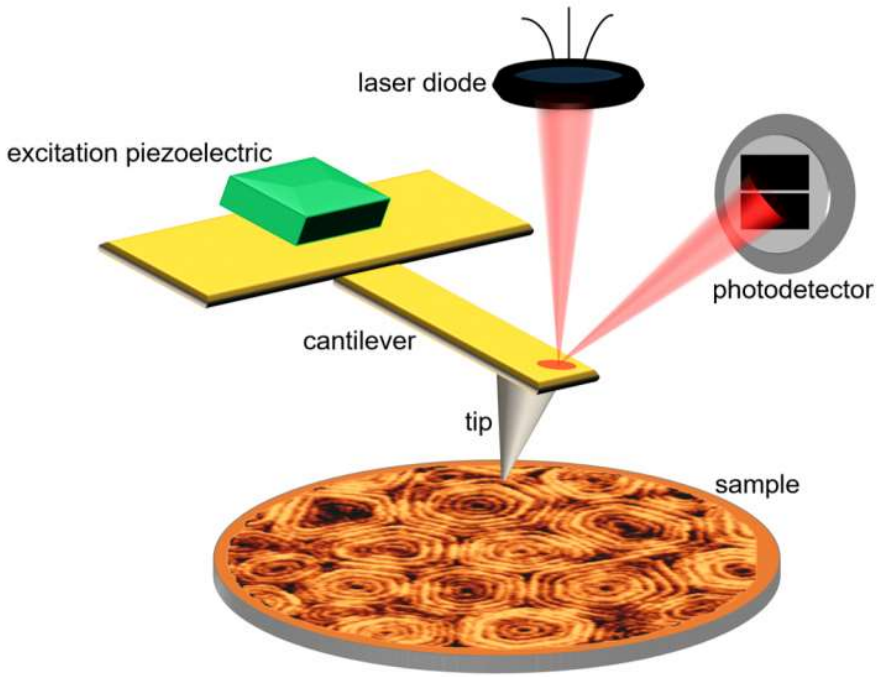
- 在这项工作中，利用高速原子力显微镜，他们解开了微管变形如何调节负责细胞内运输的微管相关运动蛋白kinesin-1的移位。
- 他们的研究结果表明，微管的弯曲变形阻碍了驱动蛋白沿微管的易位动态。
- 分子动力学模拟表明，驱动蛋白的转位受阻是由于在弯曲变形的微管中，驱动蛋白对微管结构单元的亲和力增强所致.

- 该研究推进了我们对细胞骨架成分在机械传导中作用的理解

- Living organisms are exposed to exogenous and endogenous forces and these forces affect their development and remodeling
- Microtubules are the most rigid cytoskeleton composed of protofilaments of tubulin dimers
- Microtubules are used as roads for the transport by kinesins and dyneins
- It was known that the deformation of microtubules affects kinesin-driven and dynein-driven transport
- However, it was unclear how the microtubule deformation regulates transport



- In this study, they investigated kinesin translocation along deformed microtubules using high speed atomic force microscopy (HS-AFM)
- They found that the bending of microtubules hindered the motility of kinesin
- They found that the retardation of kinesin translocation to be caused by both tension and compression
- Also, even along the central region of microtubule where neither tension nor compression is expected, kinesin slowed down
- They confirmed that this regulation of kinesin motility attributed to the altered affinity of kinesins to deformed tubulin dimers by molecular dynamics (MD) simulation
- These results suggest that the mechano-responsive role of microtubules in cellular mechanotransduction



Lorena Redondo-Morata (2018)

High Speed Atomic Force Microscopy (HS-AFM)
高速原子間力顕微鏡

① Visualization of microtubules free from lattice defects with HS-AFM

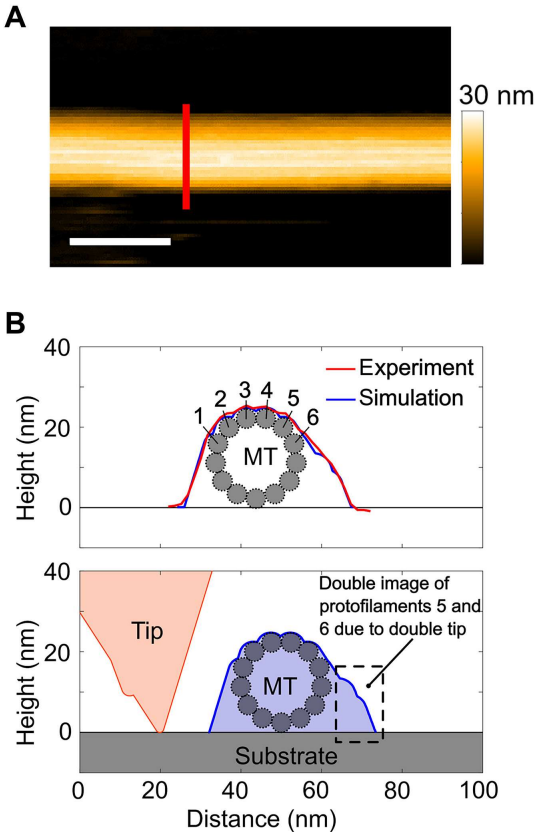
② Observation of kinesin translocation along straight and bent microtubules

③ Microtubule curvature-dependent behavior of kinesin translocation

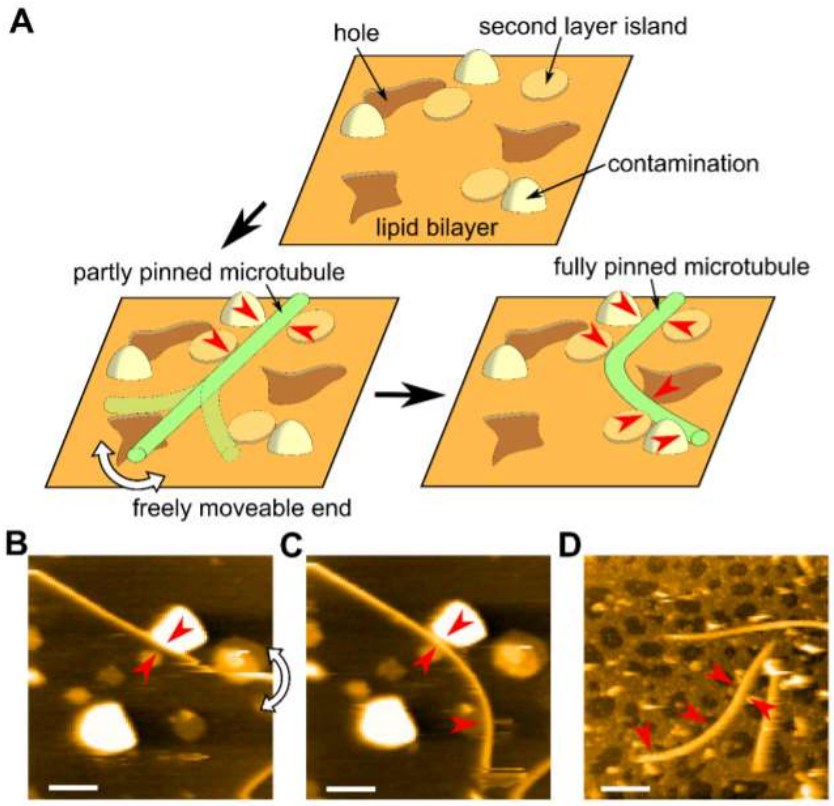
④ The effect of microtubule deformation on kinesin binding affinity

⑤ MD simulations of the effect of the microtubule deformation on the kinesin-tubulin interaction

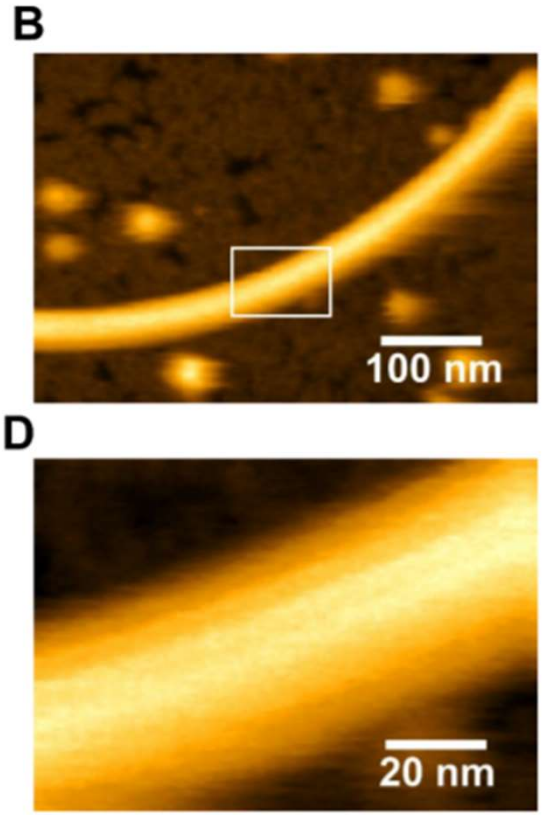
① Visualization of microtubules free from lattice defects with HS-AFM



Each protofilaments are observed
The height is about 25μm

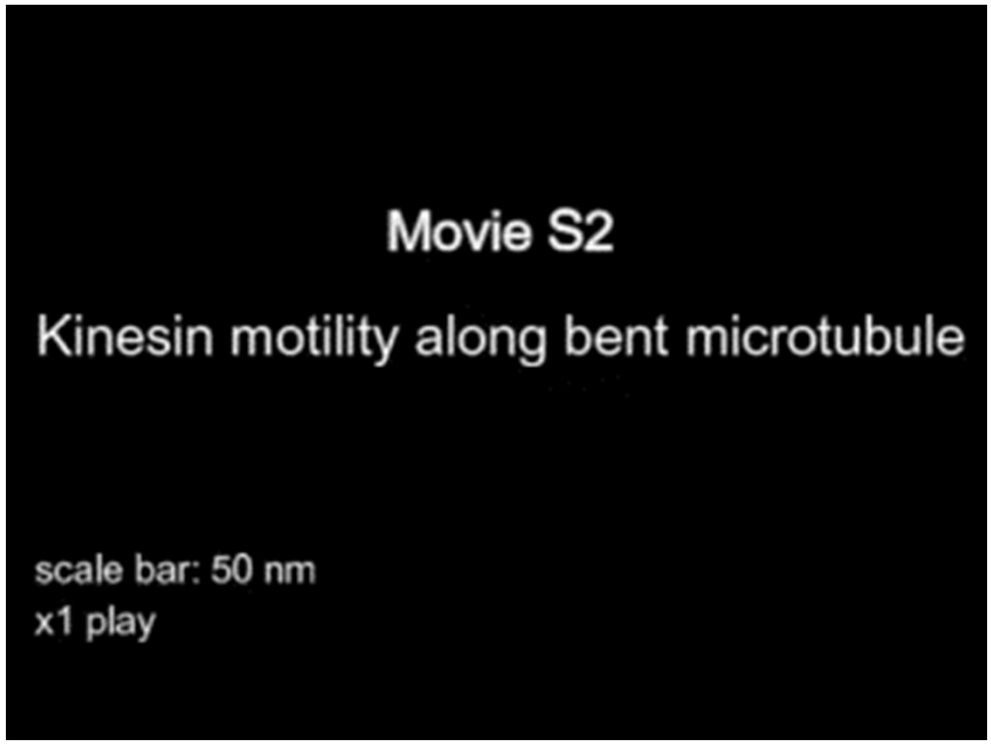


How to make bent microtubules



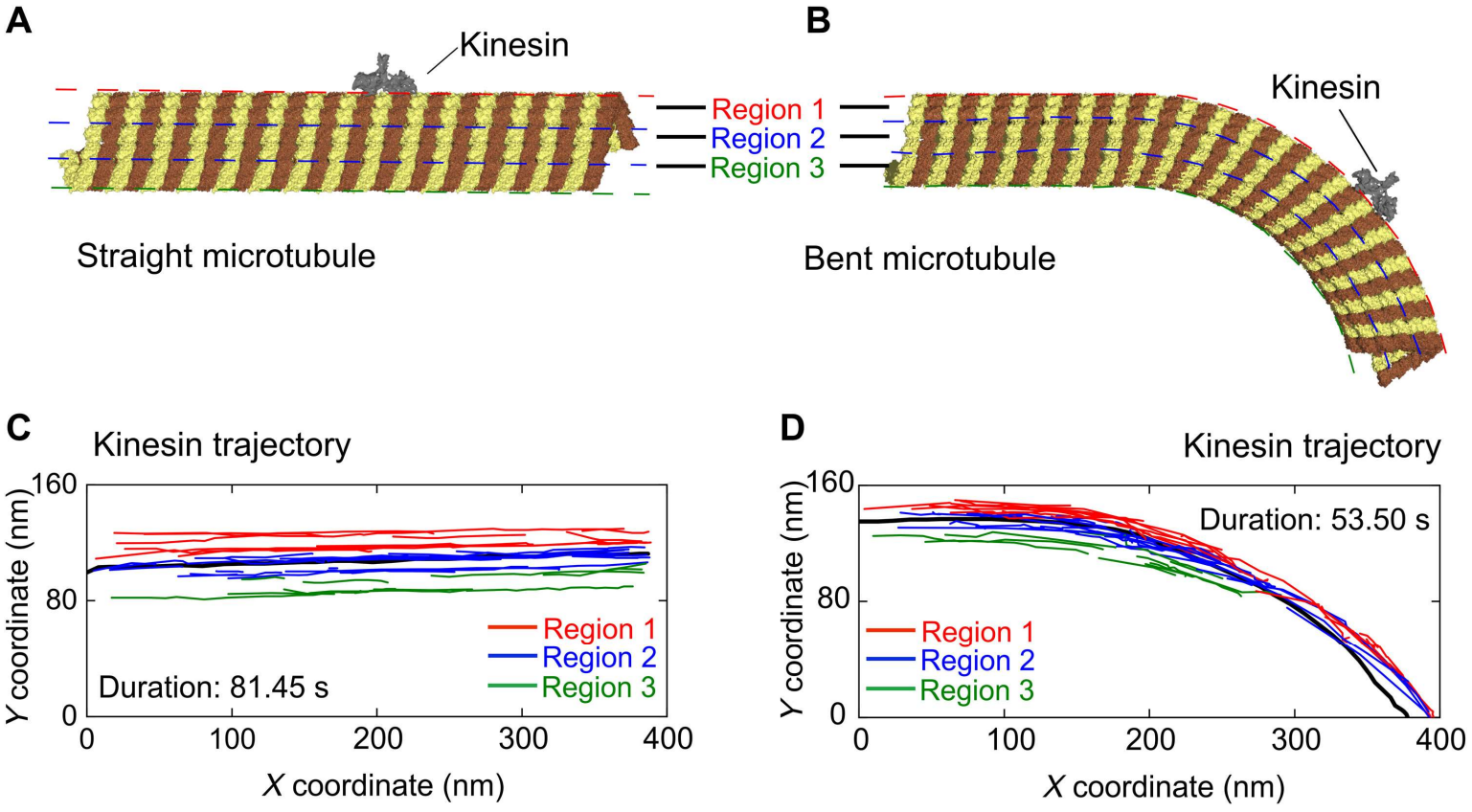
The microtubule did not have lattice defects

② Observation of kinesin translocation along straight and bent microtubules



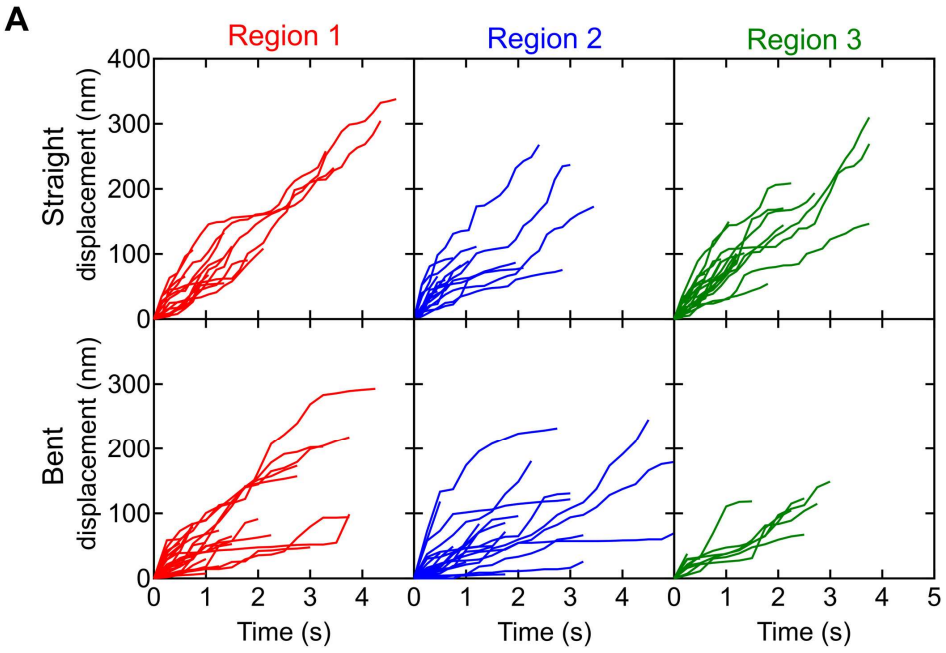
Kinesins on bent microtubules are slower

② Observation of kinesin translocation along straight and bent microtubules

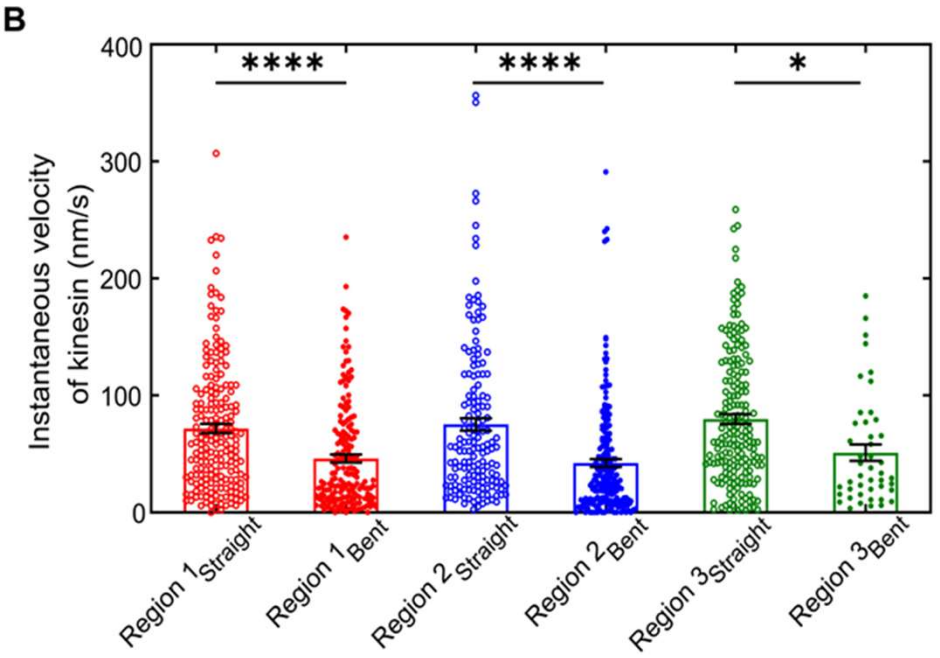


Mostly they ran along microtubules without sidestepping

② Observation of kinesin translocation along straight and bent microtubules

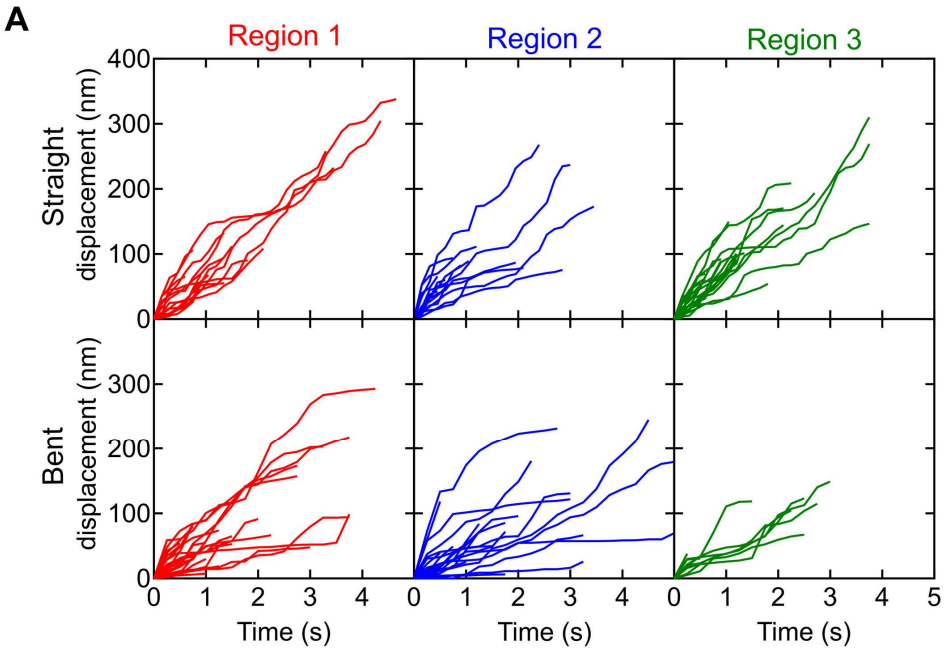


No significant differences among region 1,2 and 3 were found



Kinesins on bent microtubules are always slower

② Observation of kinesin translocation along straight and bent microtubules



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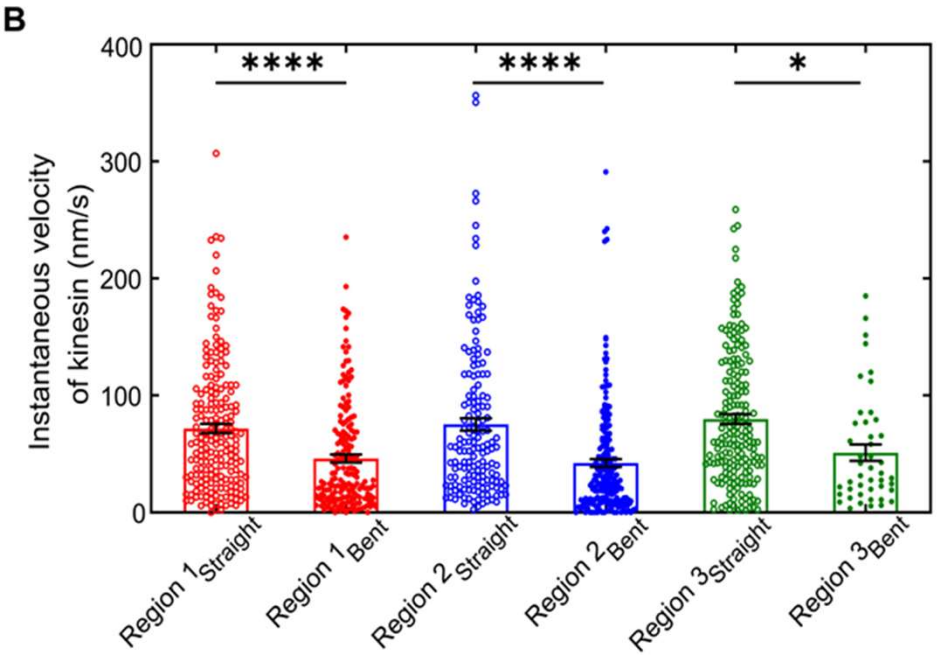
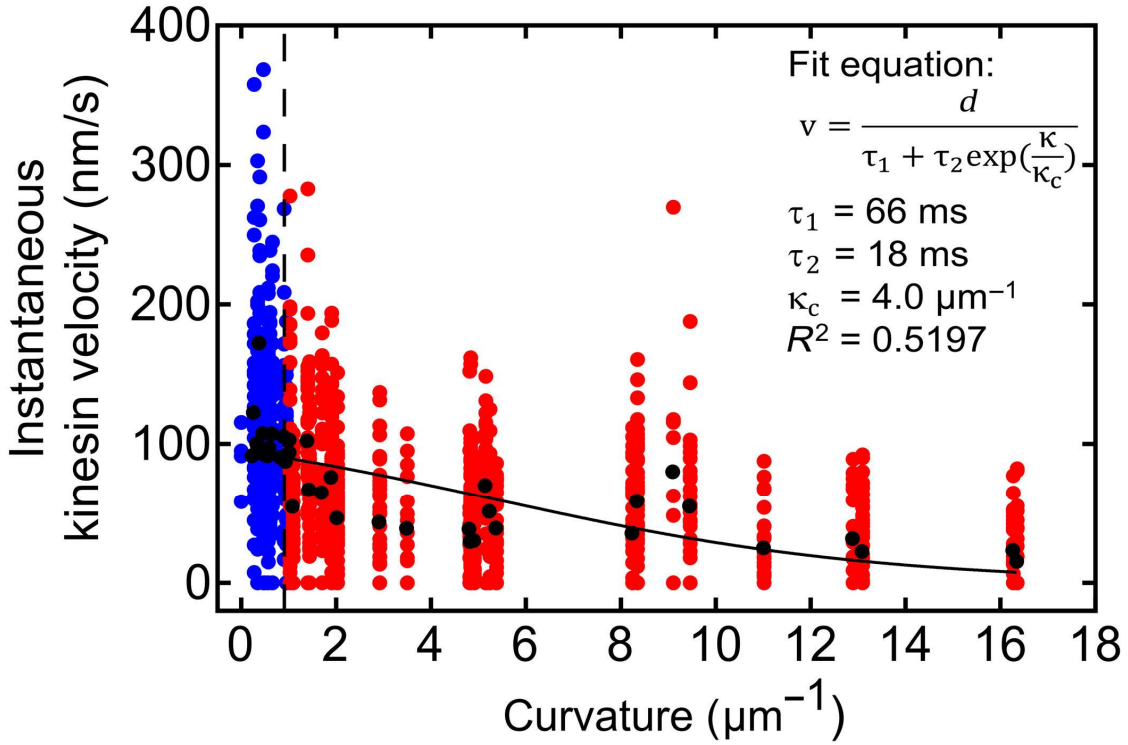


Kinesins on bent microtubules are always slower

③ Microtubule curvature-dependent behavior of kinesin translocation



Kinesins slow down in microtubule curvature-dependent manner

The shape of the graph is expected to reflect the exponential increase of the time for ATP/ADP cycle

④ The effect of microtubule deformation on kinesin binding affinity

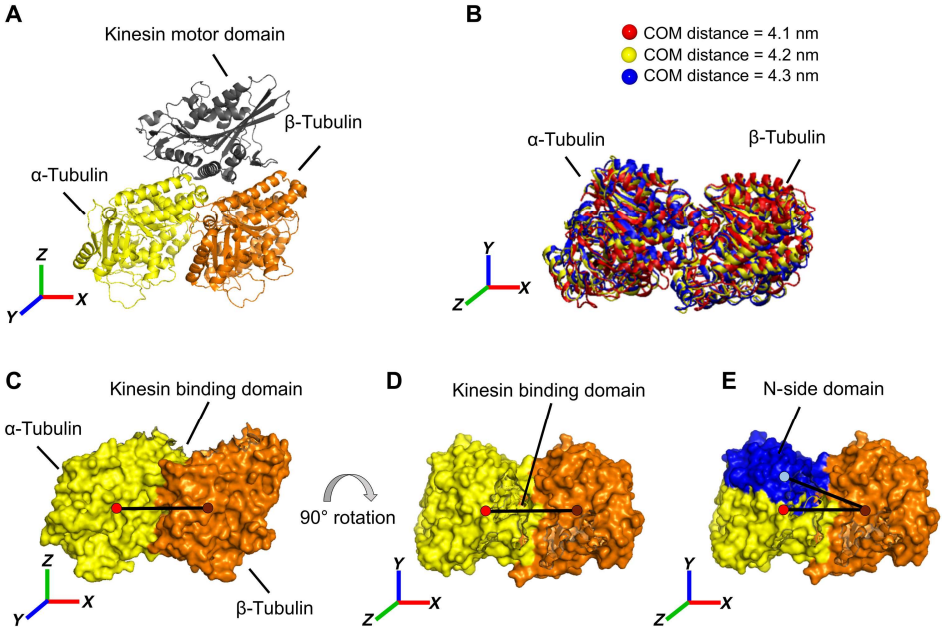
Table 1. Summary of the kinetic parameters. k_{on}, k_{off}, and K_d of kinesin binding to the straight and bent microtubules. The values are mean ± SE (see also data S4).

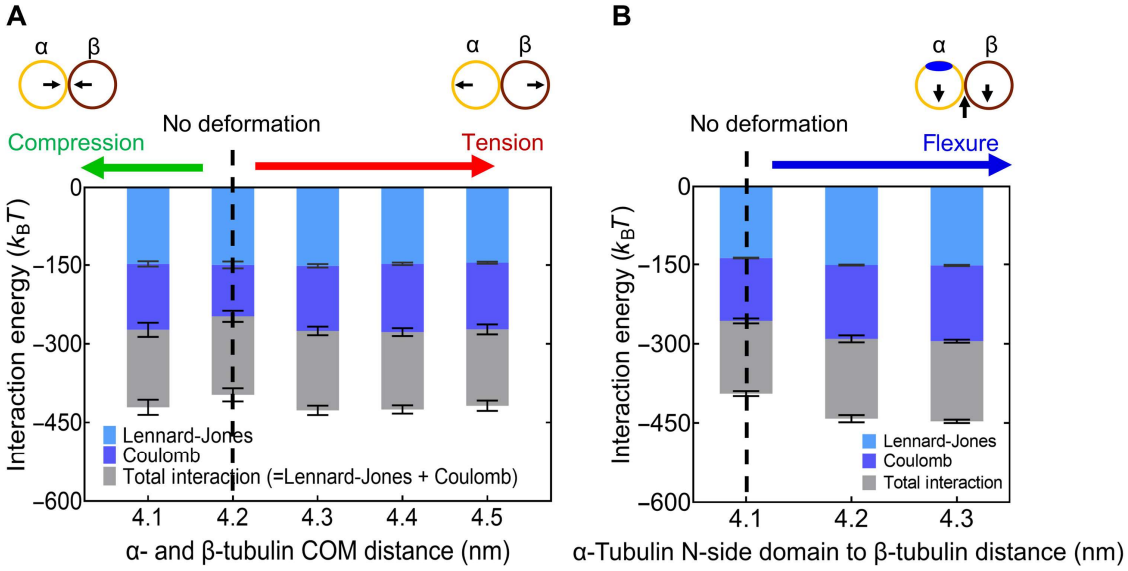
Microtubule feature	k_{on} ($M^{-1}\,\mu m^{-1}\,s^{-1}$)	k_{off} (s^{-1})	K_d (M μm)
Straight	39,026 ± 32	0.96 ± 0.12	$(2.46 \pm 0.31) \times 10^{-5}$
Bent	59,801 ± 186	0.61 ± 0.07	$(1.02 \pm 0.11) \times 10^{-5}$

$$K_d = k_{off} / k_{on}$$

Kinesins on bent microtubules are less likely to detach from microtubules

⑤ MD simulations of the effect of the microtubule deformation on the kinesin-tubulin interactions





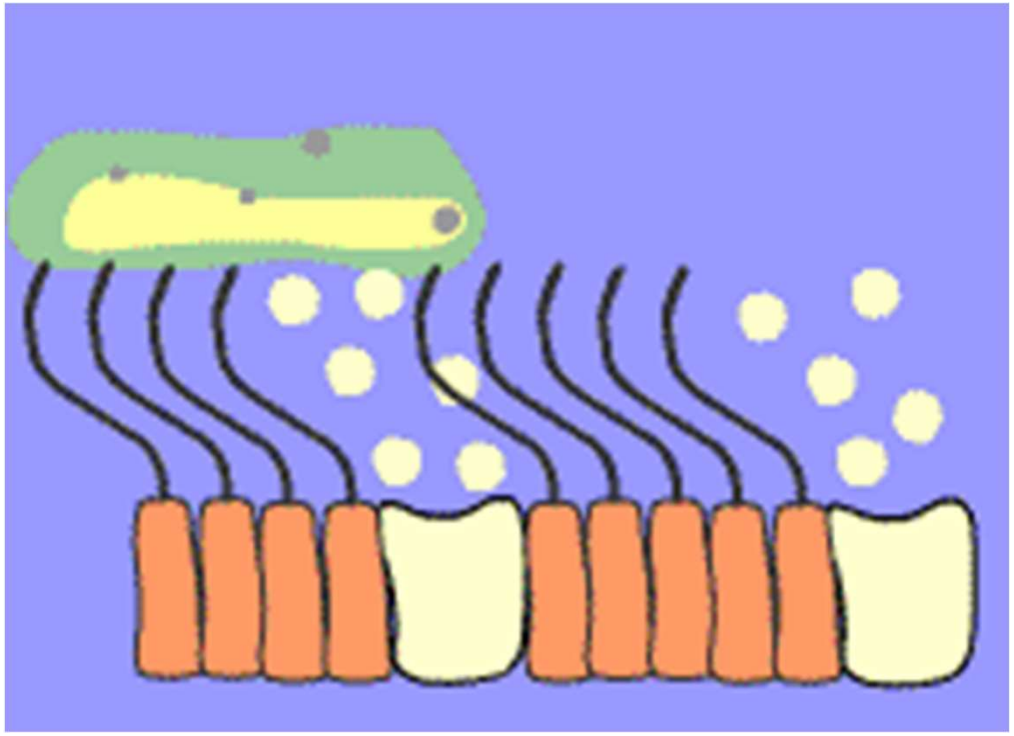
Molecular Dynamics simulation (MD simulation)
分子動力学シュミレーション

The interaction energy between a kinesin and a tubulin dimer is larger at deformed states

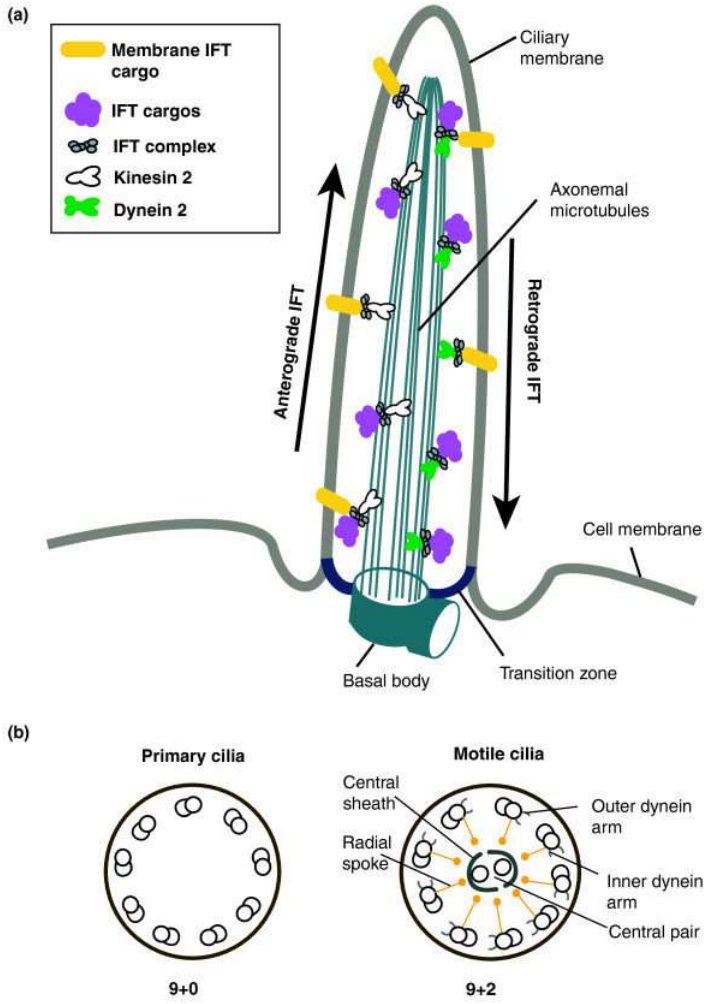
- They found that the bending of microtubules hindered the motility of kinesin
- They found that the retardation of kinesin translocation to be caused by both tension and compression
- Also, even along the central region of microtubule where neither tension nor compression is expected, kinesin slowed down
- They confirmed that this regulation of kinesin motility attributed to the altered affinity of kinesins to deformed tubulin dimers by molecular dynamics (MD) simulation

- This work offers evidence that microtubules can serve as a mechanosensor and can help to understand how microtubules regulate intracellular transport in adverse environments by absorbing mechanical forces
- This study can also help to understand the role of mechanical forces in regulating interactions between a microtubule and its associated proteins.
- They demonstrated for the first time how this altered affinity regulates intracellular transport
- It is expected to help to clarify the mechanism of some diseases related to impairment of intracellular transport
- A change in the interaction energy between microtubules and its associated motor protein by deformation of microtubules may offer itself as the starting point to an understanding of how microtubules serve as mechanotransducers in cells

- About motility traits of kinesins involved in IFT



TRAMS (2018)



Joseph Gleeson(2011)