The microtubule lattice - a brief historical perspective

Denis Chrétien, Charlotte Guyomar

▶ **To cite this version:**

Denis Chrétien, Charlotte Guyomar. The microtubule lattice - a brief historical perspective. Biology of the Cell, 2023, 115 (5), pp.e202300004. 10.1111/boc.202300004 . hal-03984704

HAL Id: hal-03984704
https://cnrs.hal.science/hal-03984704

Submitted on 12 Jun 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Check for updates

Received: 9 January 2023 | Revised: 30 January 2023 | Accepted: 1 February 2023

DOI: 10.1111/boc.202300004

Biology of the Cell

COMMENTARY

The microtubule lattice: a brief historical perspective

Denis Chrétien | **Charlotte Guyomar**

Univ Rennes, CNRS, IGDR (Institut de génétique et développement de Rennes)–UMR 6290, F-35000 Rennes, France

Correspondence
Charlotte Guyomar, Univ Rennes, CNRS, IGDR (Institut de génétique et développement de Rennes)–UMR 6290, F-35000 Rennes, France
Email: charlotte.guyomar@univ-rennes1.fr

Funding information
French National Research Agency, Grant/Award Numbers: ANR-16-C11-0017-01, ANR-18-CE13-0001-01

Abstract

At first glance, the structure of a microtubule is simple. Globular α- and β-tubulin subunits form constitutive heterodimers that align head-to-tail in protofilaments. In the most common configuration, 13 protofilaments associate laterally with a slight longitudinal stagger that results in a left-handed 3-start helix featuring lateral associations between tubulin subunits. This seemingly straightforward description is actually based on almost half a century of research aimed at understanding how tubulin dimers interact within the microtubule lattice. But while we start to have a good overview of their architecture in vitro, our knowledge of microtubule-lattice organization in vivo is nowhere near to being complete.

In 1974, Amos and Klug analyzed diffraction patterns in transmission electron microscope images of negatively stained axoneme doublet microtubules (Amos & Klug, 1974) (Figure 1a). The authors suggested that tubulin dimers in the complete, 13-protofilament A-subfiber share heterotypic lateral interactions (α-β, β-α), while those in the incomplete, 10-protofilament B-subfiber share homotypic ones (α-α, β-β). They thus named these lattices after the A and B microtubules in the axoneme doublet. An A-lattice configuration for the organization of microtubules with 13 protofilaments and a 3-start helix was highly attractive, as it allows them to be fully helical, thereby enabling helical growth as occurs with other biological polymers such as actin filaments.

In 1978, Crepeau and colleagues used negative staining to analyze the organization of tubulin dimers in zinc-induced tubulin sheets and in open sheets at the ends of regular microtubules (Crepeau et al., 1978). The authors were able to differentiate between the α- and β-tubulin monomers in these two-dimensional tubulin assemblies, and proposed B-lattice interactions in microtubules assembled in vitro. In 1993, Song and Mandelkow confirmed that microtubules assembled in vitro are predominantly organized according to a B-lattice (Song & Mandelkow, 1993) (Figure 1b). They used kinesin motor-domains, which bind every tubulin dimer and thus highlight how tubulins are organized in the microtubule lattice. They showed that these domains follow helical paths compatible only with the B-lattice, as they involve homotypic lateral interactions. The authors then used this method to confirm that microtubules in both the A- and B-subfibers of the axoneme are organized according to a B-lattice, thereby demonstrating that if microtubules are built with 13 protofilaments and a 3-start helix, they must include at least one A-lattice seam (Song & Mandelkow, 1995). Concomitantly, Chrétien and Wade used the emerging method of cryo-electron microscopy of vitreous specimens to show that the microtubule lattice reacts to different protofilament and/or helix start numbers via an overall skew of the constituent protofilaments (Chrétien & Wade, 1991). This prompted the authors to propose that microtubules could be composed of mixed AB-lattices having a variable number of seams (Wade & Chrétien, 1993).

Demonstration of a mixed-lattice organization in microtubules assembled in vitro was first provided by Kikkawa and colleagues in 1994 (Kikkawa et al., 1994) using metal-shadowing of freeze-etched samples (Figure 1c), and this was further confirmed by Sosa and Milligan (Sosa & Milligan, 1996) on microtubules observed by cryo-electron microscopy and reconstructed in 3D by back-projection. Since then, several

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2023 The Authors. *Biology of the Cell* published by Wiley-VCH GmbH on behalf of Société Française des Microscopies and Société de Biologie Cellulaire de France.

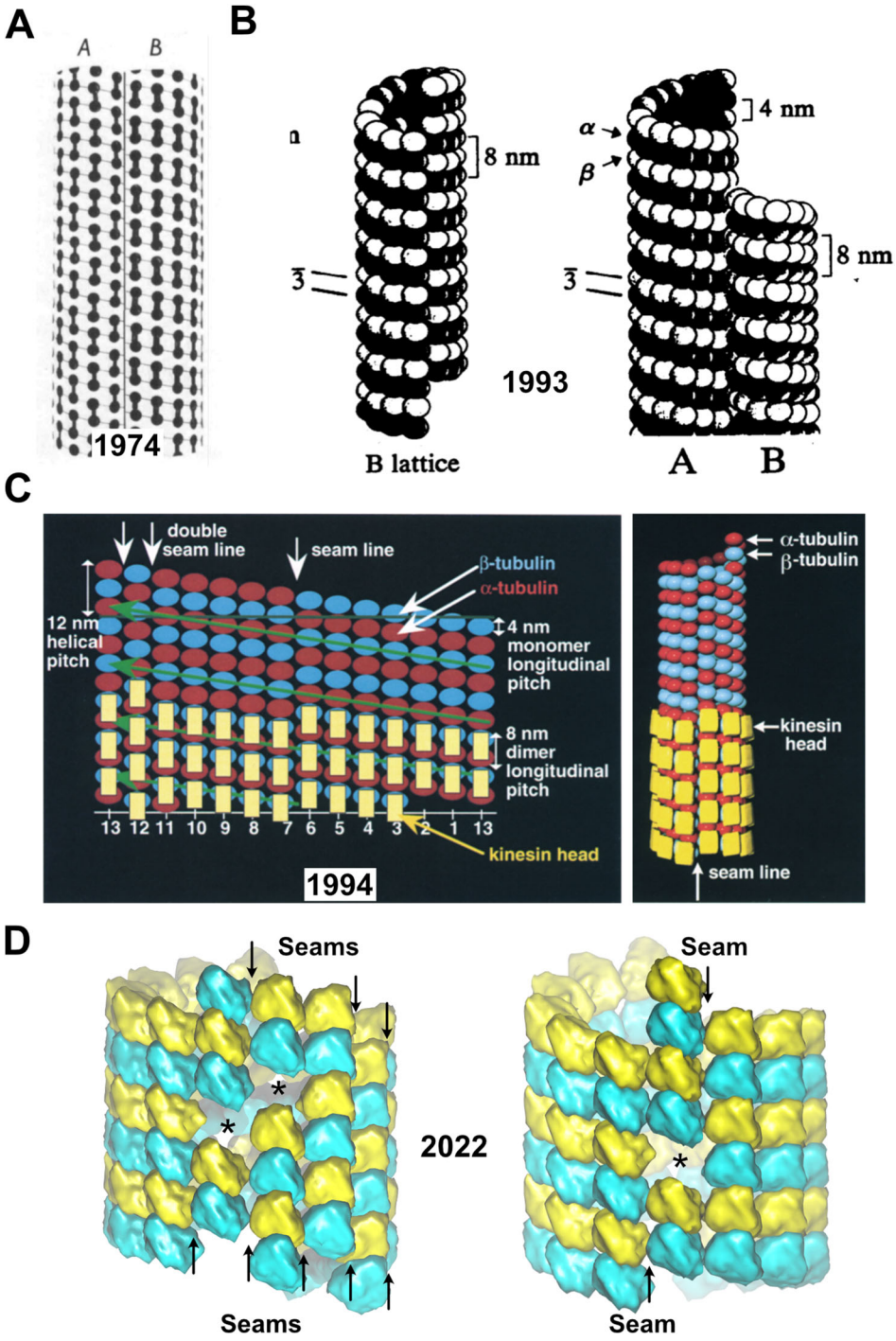

FIGURE 1 Evolution of microtubule lattice models over time. (a) A- and B-lattice models for the organization of the $\alpha\beta$-tubulin heterodimer in the A- and B-subfibers of the axoneme were introduced in 1974. The A-lattice was considered to be the preferred configuration for cytoplasmic microtubules. Reprinted from Figure 14 of ©1974 Amos and Klug. Originally published in *Journal of Cell Science*. https://doi.org/10.1083/jcb.127.6.1965 1974. (b) In 1993, it was demonstrated that the B-lattice actually predominates in microtubules assembled in vitro (left), as well as in the A-subfiber of the axoneme (right). This implied that 13-protofilament microtubules assembled according to a 3-start helix must contain at least one A-lattice seam. Adapted from Figure 5 of ©1993 Song and Mandelkov. Originally published in *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.90.5.1671 1993. (c) In 1994, it was demonstrated that multiple A-lattice seams occur in vitro (left), and that the B-lattice organization containing at least one seam is present in *in cellulo* microtubules (right). Adapted from Figure 5 of ©1994 Kikkawa *et al*. Originally published in *Journal of Cell Biology*. https://doi.org/10.1083/jcb.127.6.19651994. (d) In the current issue of *eLife*, results obtained from cryo-electron tomograms of microtubules assembled in vitro show that the number and location of seams varies within individual microtubules, with gaps (*) occurring inside the lattice (left). Microtubules assembled in Xenopus egg cytoplasmic extracts organize preferentially according to a B-lattice with a single seam (right); however, the seam location does vary within individual microtubules. Adapted from Figure 4 (left) and 8 (right) of ©2022 Guyomar *et al*. Originally published in *eLife*. https://doi.org/10.7554/eLife.83021 2022.

1768322x, 2023, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/boc.202300004 by Université De Rennes 1 BU Campus Beaulieu - Bât. 40, Wiley Online Library on [12/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

examples of mixed lattices have been documented (Debs et al., 2020; des Georges et al., 2008), including our recent study (Guyomar et al., 2022). We reveal another complexity in microtubule-lattice organization: not only can microtubules contain several seams, but their numbers and locations can vary *within* individual microtubules (Figure 1d, left). We find that microtubules assembled in vitro are composed of mixed, discontinuous AB-lattices with a preferred B-lattice organization. But what is the situation inside cells? Indeed, very few studies have addressed this question. While cellular microtubules are predominantly constructed from 13 protofilaments, numerous exceptions have been noted in different cell types and organisms (reviewed in Chaaban & Brouhard, 2017; Chrétien & Wade, 1991). Beyond the known diversity in protofilament numbers, our knowledge about microtubule-lattice organization in cells remains quite limited. The first study addressing this open issue was carried out by Kikkawa and colleagues (Kikkawa et al., 1994), who found single seams in cellular microtubules by using kinesin motor domain decoration after lysis with detergent (Figure 1c, right). However, they did not exclude the possibility that the analyzed microtubules contained several seams, as observed in in vitro-assembled microtubules. In a second *in cellulo* study, McIntosh and colleagues used a similar decoration strategy and analyzed lysed cells by cryo-electron tomography (McIntosh et al., 2009), concluding that the B-lattice organization was clearly favored in their preparations.

In our recent study (Guyomar et al., 2022), we performed an extensive analysis of microtubules assembled in *Xenopus*–egg cytoplasmic extracts. We confirm that microtubules are preferentially organized with 13 protofilaments, a 3-start helix, a B-lattice configuration, and one seam. But we also find that protofilament and/or helix start number transitions occur, as do changes in seam location along individual microtubules (Figure 1d, right). These observations are in line with recent studies revealing that tubulin exchange is not restricted to microtubule ends, but also occurs within the microtubule shaft (Gazzola et al., 2023, reviewed in Théry & Blanchoin, 2021). They also suggest that the intrinsic dynamic instability of microtubules could be intimately tied to the structural instability of their lattice, a property that could be exploited by proteins such as those that interact with their growing plus-ends (see the Ideas and speculation section in Guyomar et al., 2022). Since only a few cell types have been investigated so far, we expect that microtubule-lattice organization will turn out to be even more heterogeneous, depending for instance on the organism, cell type, or stage of the cell cycle.

Although half a century ago cytoplasmic microtubules were proposed to be helical polymers, we must now view them as imperfect tubular crystals. This structural heterogeneity, added to the many tubulin genes and a plethora of post-translational modifications, heightens the mosaicity of the microtubule lattice (reviewed in Roll-Mecak, 2019). As a result, we must reconsider the conventional view of the microtubule structure, and we expect further revelations about their functions in the coming years.

ACKNOWLEDGMENTS

Denis Chrétien and Charlotte Guyomar are supported by the French National Research Agency (ANR-16-C11-0017-01 and ANR-18-CE13-0001-01). The authors are grateful to Juliana Berland (http://jbedit.com/en/) for editing our manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Denis Chrétien https://orcid.org/0000-0001-8261-4396
Charlotte Guyomar https://orcid.org/0000-0001-9766-3932

REFERENCES

Amos, L.A., & Klug, A. (1974) Arrangement of subunits in flagellar microtubules. *Journal of Cell Science*, 14(3), 523–549. https://doi.org/10.1242/jcs.14.3.523

Amos, L., & Klug, A. (1974) Arrangement of subunits in flagellar microtubules. *Journal of Cell Science*, 14(3), 523–549.

Chaaban, S., & Brouhard, G.J. (2017) A microtubule bestiary : Structural diversity in tubulin polymers. *Molecular Biology of the Cell*, 28(22), 2924–2931. https://doi.org/10.1091/mbc.E16-05-0271

Chrétien, D., & Wade, R.H. (1991) New data on the microtubule surface lattice. *Biology of the Cell*, 71(1–2), 161–174. https://doi.org/10.1016/0248-4900(91)90062-r

Crepeau, R.H., McEwen, B., & Edelstein, S. J. (1978) Differences in alpha and beta polypeptide chains of tubulin resolved by electron microscopy with image reconstruction. *Proceedings of the National Academy of Sciences of the United States of America*, 75(10), 5006–5010. https://doi.org/10.1073/pnas.75.10.5006

Debs, G.E., Cha, M., Liu, X., Huehn, A.R., & Sindelar, C. V. (2020) Dynamic and asymmetric fluctuations in the microtubule wall captured by high-resolution cryoelectron microscopy. *Proceedings of the National Academy of Sciences of the United States of America*, 117(29), 16976–16984. https://doi.org/10.1073/pnas.2001546117

des Georges, A., Katsuki, M., Drummond, D.R., Osei, M., Cross, R.A., & Amos, L.A. (2008) Mal3, the Schizosaccharomyces pombe homolog of EB1, changes the microtubule lattice. *Nature Structural & Molecular Biology*, 15(10), 1102–1108. https://doi.org/10.1038/nsmb.1482

Gazzola, M., Schaeffer, A., Butler-Hallissey, C., Friedl, K., Vianay, B., Gaillard, J., Leterrier, C., Blanchoin, L., & Théry, M. (2023) Microtubules self-repair in living cells. *Current Biology*, 33(1), 122–133. https://doi.org/10.1016/j.cub.2022.11.060

Guyomar, C., Bousquet, C., Ku, S., Heumann, J. M., Guilloux, G., Gaillard, N., Heichette, C., Duchesne, L., Steinmetz, M.O., Gibeaux, R., & Chrétien, D. (2022) Changes in seam number and location induce holes within microtubules assembled from porcine brain tubulin and in Xenopus egg cytoplasmic extracts. *ELife*, 11, e83021. https://doi.org/10.7554/eLife.83021

Kikkawa, M., Ishikawa, T., Nakata, T., Wakabayashi, T., & Hirokawa, N. (1994) Direct visualization of the microtubule lattice seam both in

1768322x, 2023, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/boc.202300004 by Université De Rennes 1 BU Campus Beaulieu - Bât. 40, Wiley Online Library on [12/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

vitro and in vivo. *The Journal of Cell Biology*, 127(6 Pt 2), 1965–1971. https://doi.org/10.1083/jcb.127.6.1965

McIntosh, J.R., Morphew, M.K., Grissom, P.M., Gilbert, S.P., & Hoenger, A. (2009) Lattice structure of cytoplasmic microtubules in a cultured mammalian cell. *Journal of Molecular Biology*, 394(2), 177–182. https://doi.org/10.1016/j.jmb.2009.09.033

Roll-Mecak, A. (2019) How cells exploit tubulin diversity to build functional cellular microtubule mosaics. *Current Opinion in Cell Biology*, 56, 102–108. https://doi.org/10.1016/j.ceb.2018.10.009

Song, Y.H., & Mandelkow, E. (1993) Recombinant kinesin motor domain binds to beta-tubulin and decorates microtubules with a B surface lattice. *Proceedings of the National Academy of Sciences of the United States of America*, 90(5), 1671–1675. https://doi.org/10.1073/pnas.90.5.1671

Song, Y.H., & Mandelkow, E. (1995) The anatomy of flagellar microtubules : Polarity, seam, junctions, and lattice. *The Journal of Cell Biology*, 128(1–2), 81–94. https://doi.org/10.1083/jcb.128.1.81

Sosa, H., & Milligan, R.A. (1996) Three-dimensional structure of ncd-decorated microtubules obtained by a back-projection method. *Journal of Molecular Biology*, 260(5), 743–755. https://doi.org/10.1006/jmbi.1996.0434

Théry, M., & Blanchoin, L. (2021) Microtubule self-repair. *Current Opinion in Cell Biology*, 68, 144–154. https://doi.org/10.1016/j.ceb.2020.10.012

Wade, R. H., & Chrétien, D. (1993) Cryoelectron microscopy of microtubules. *Journal of Structural Biology*, 110(1), 1–27. https://doi.org/10.1006/jsbi.1993.1001

How to cite this article: Chrétien, D., & Guyomar, C. (2023) The microtubule lattice: a brief historical perspective. *Biology of the Cell*, 115, 2300004. https://doi.org/10.1111/boc.202300004

1768322x, 2023, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/boc.202300004 by Université De Rennes 1 BU Campus Beaulieu - Bât. 40, Wiley Online Library on [12/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License