

# CYTOSQUELETTE

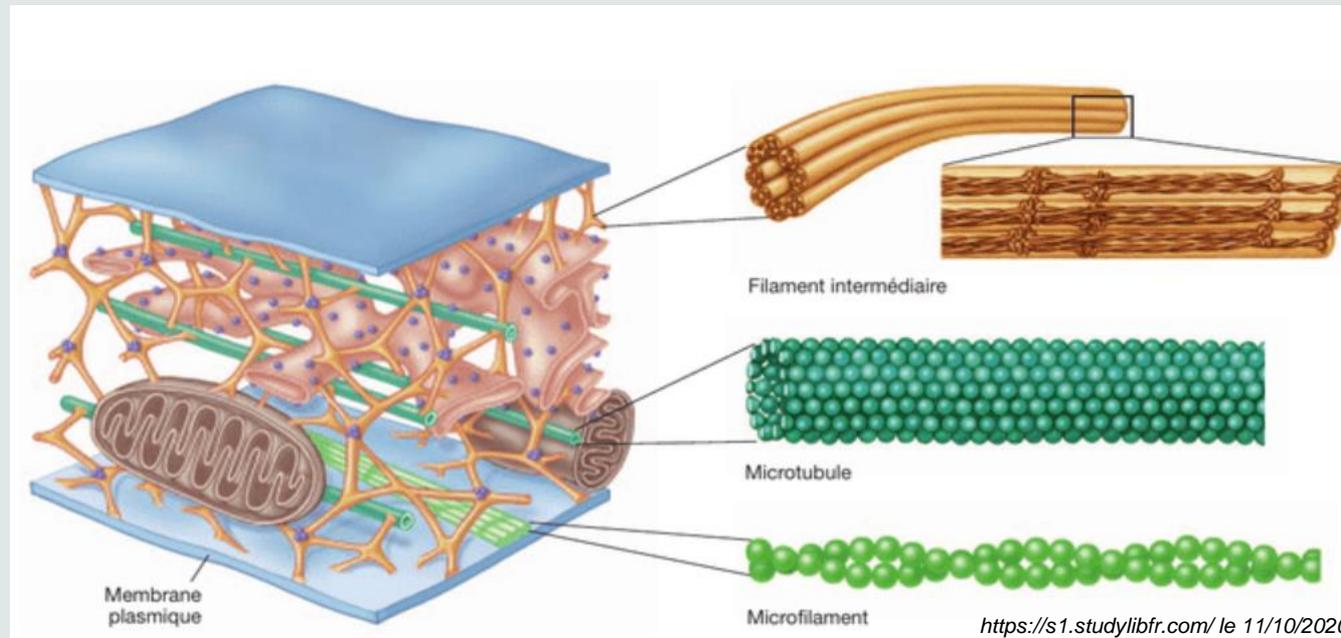
**PILON Antoine**

Laboratoire de Biochimie et Biologie Cellulaire

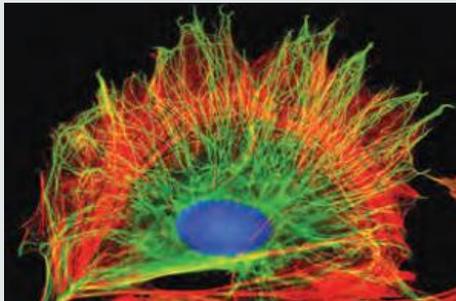
Inserm UMR-S-1193

Faculté de Pharmacie – Université Paris Saclay

# CYTOSQUELETTE



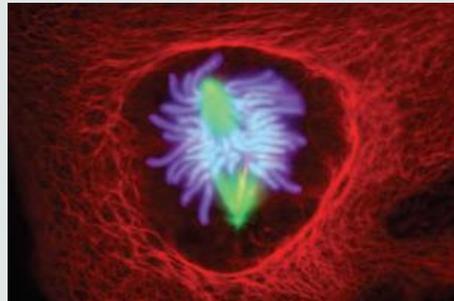
Microtubules ADN



Actine

10  $\mu\text{m}$

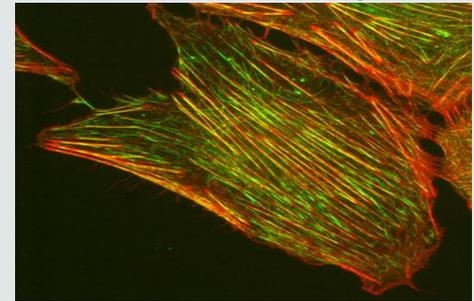
Microtubules ADN



Filaments intermédiaires

20  $\mu\text{m}$

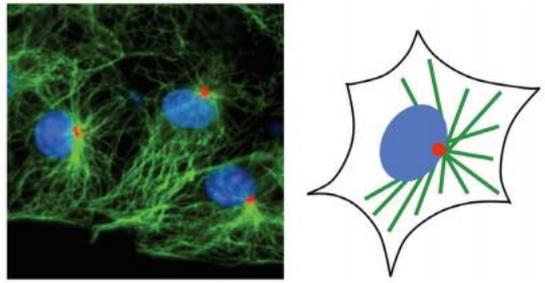
Actine Septine 2



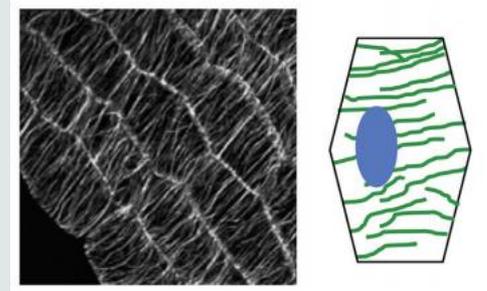
20  $\mu\text{m}$

# MICROTUBULES

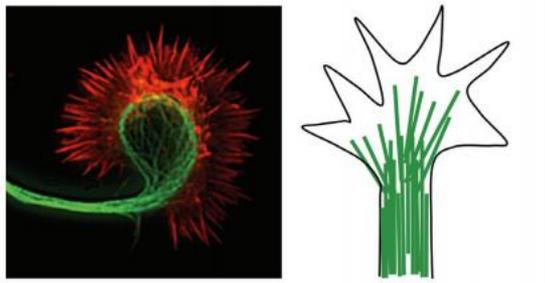
Cellule épithéliale en culture



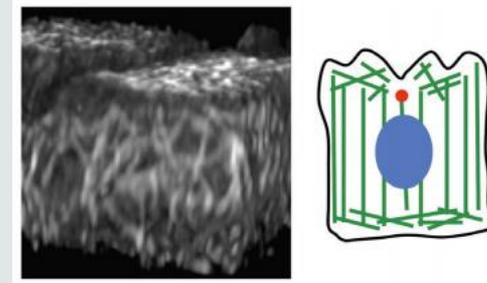
Cellule végétale



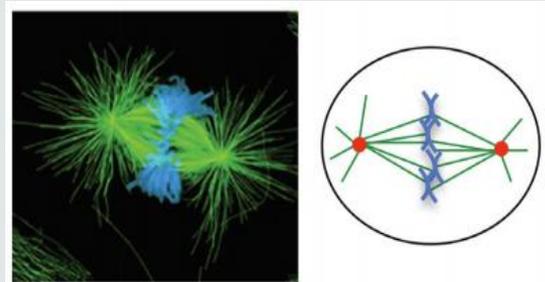
Neurone



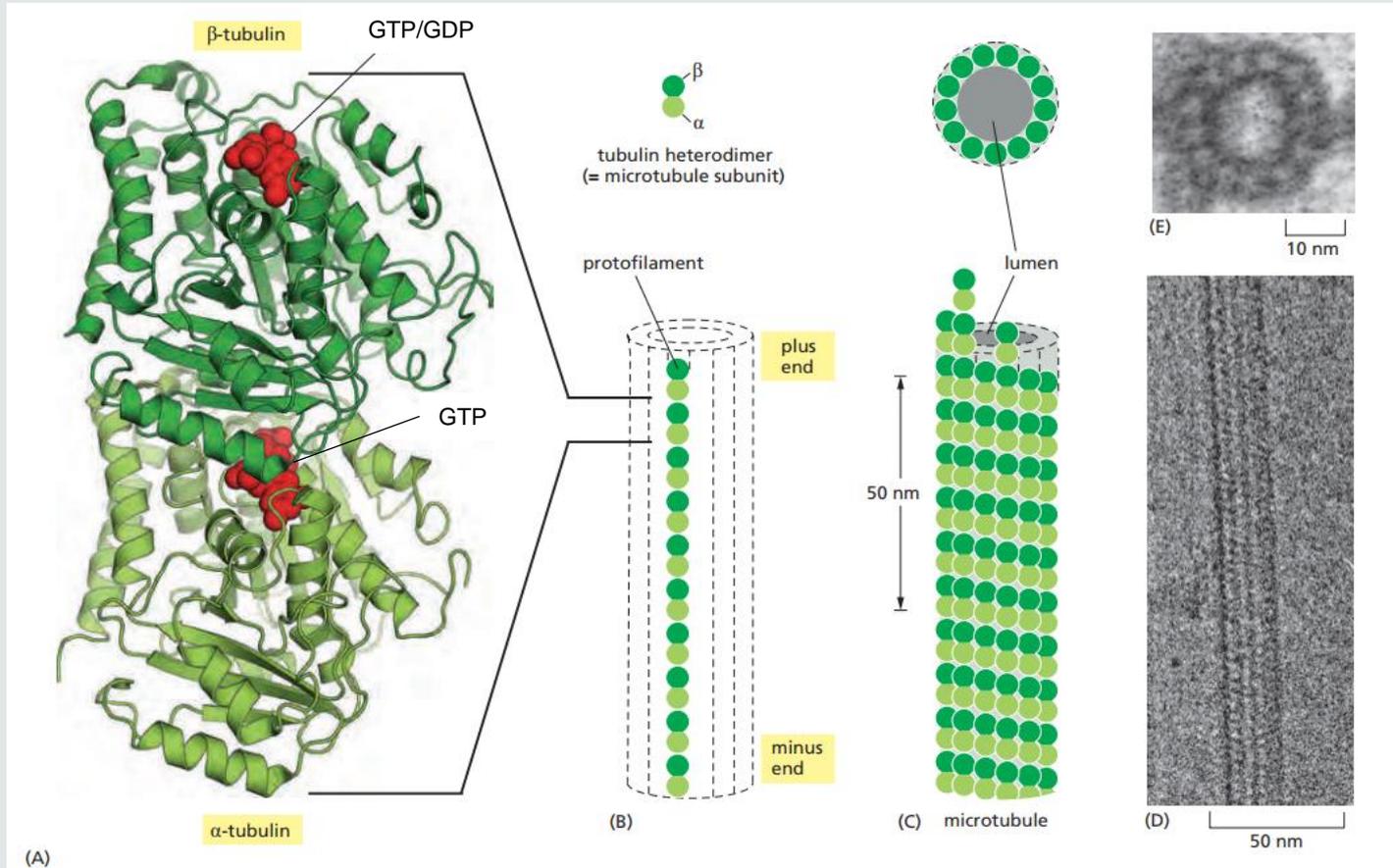
Cellule épithéliale polarisée



Mitose



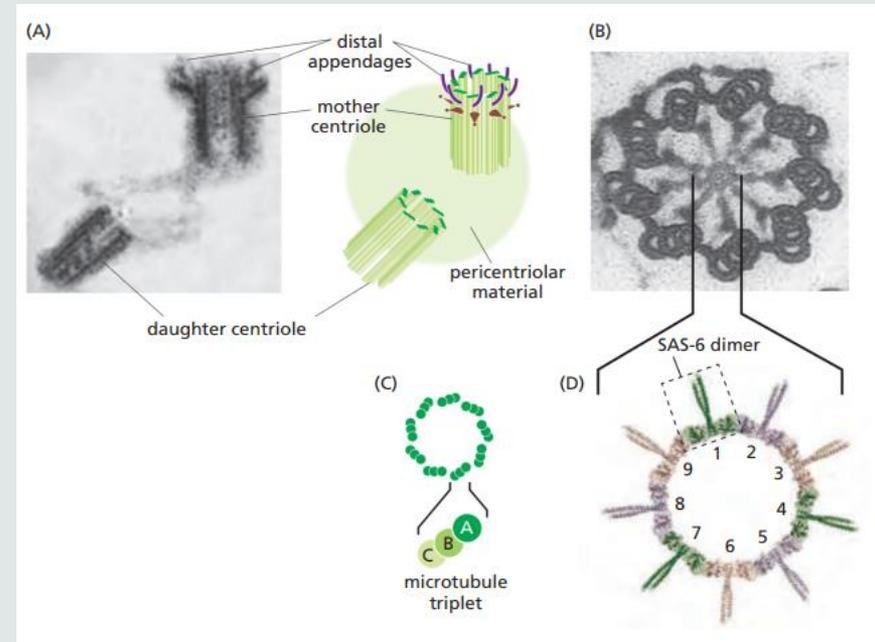
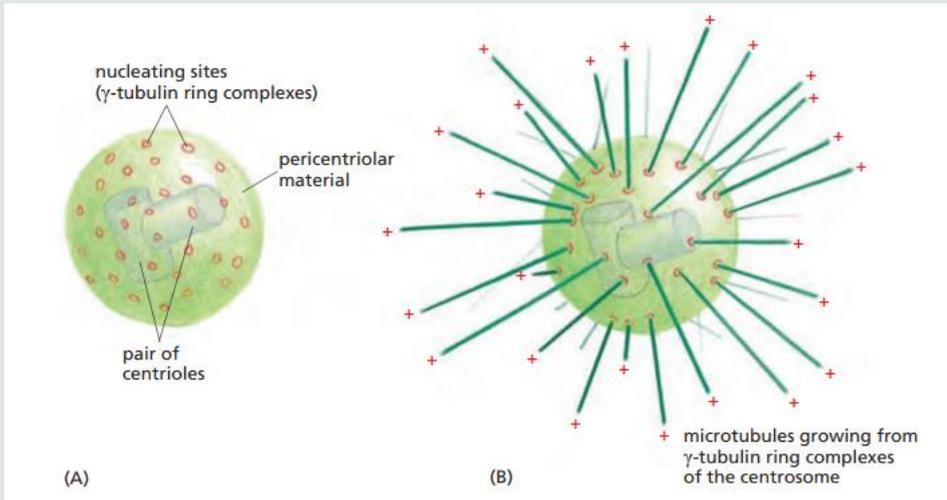
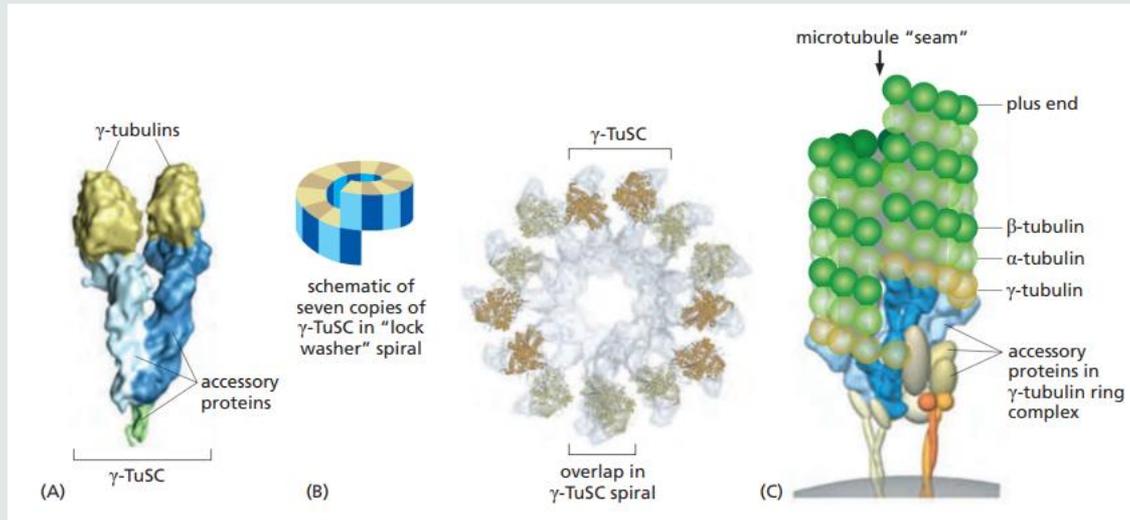
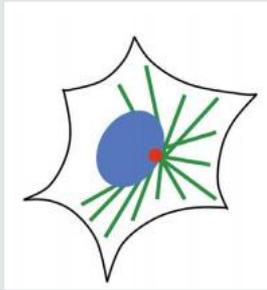
# Structure des microtubules



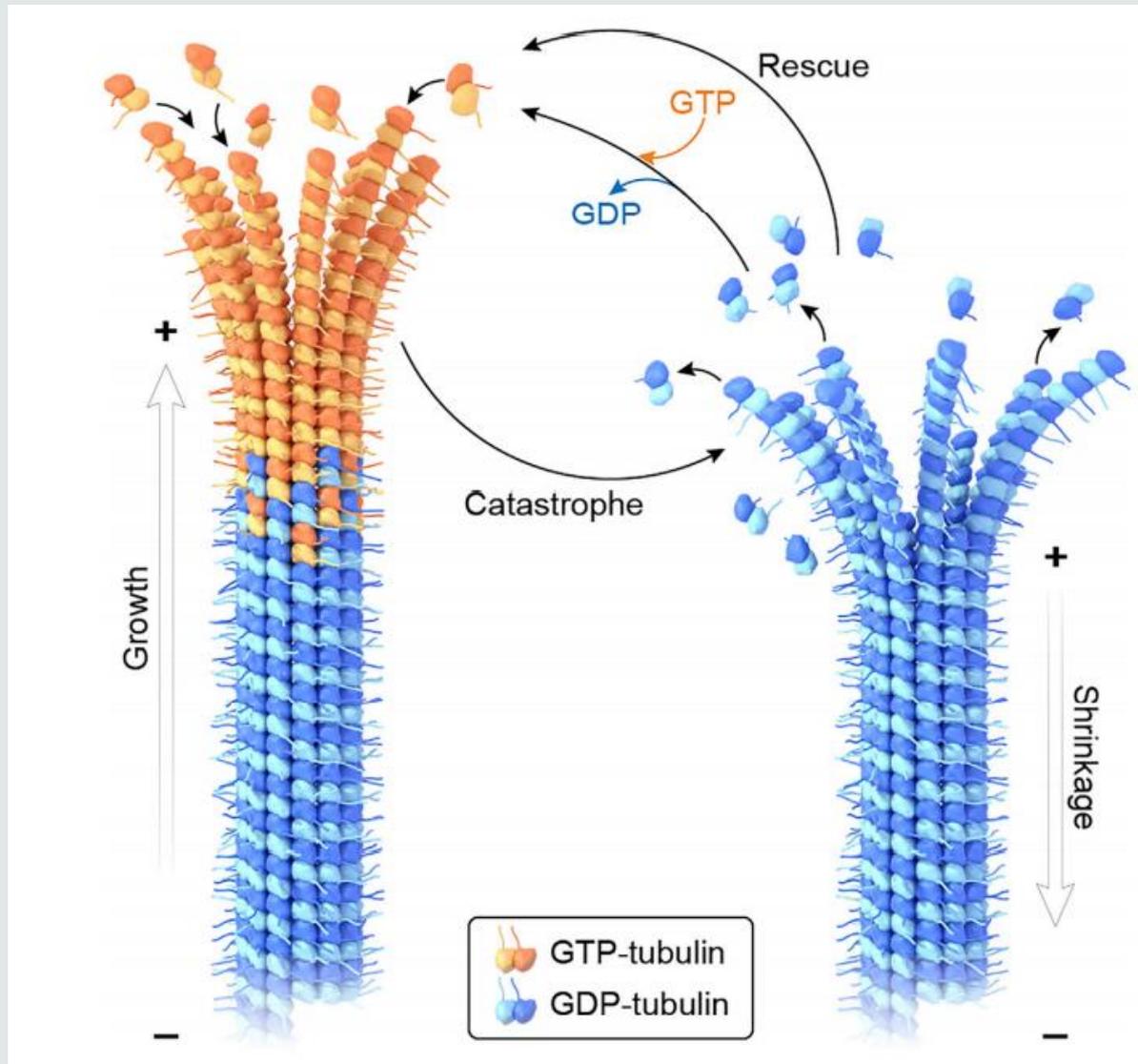
## Tubulines:

7 gènes alpha  
6 gènes bêta  
gamma-tubuline

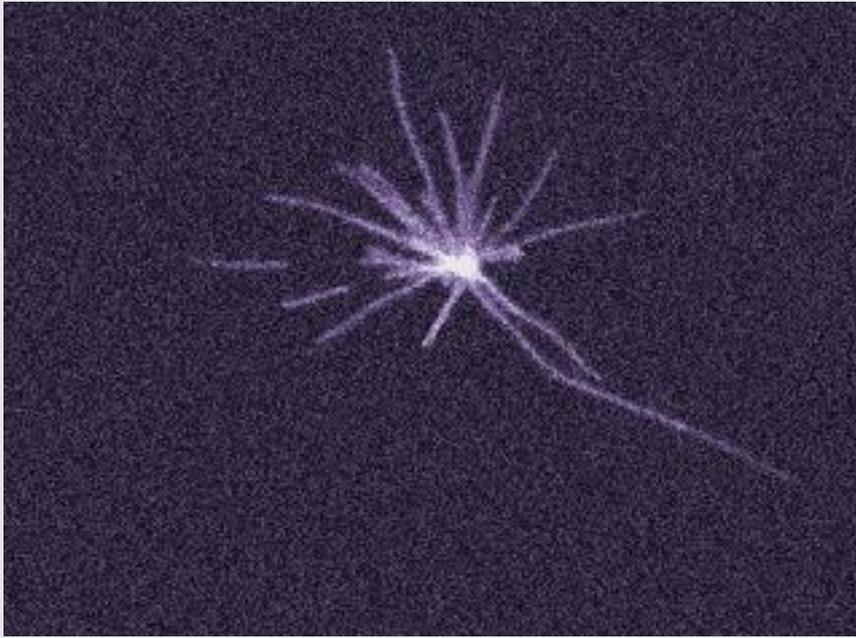
# Centrosome



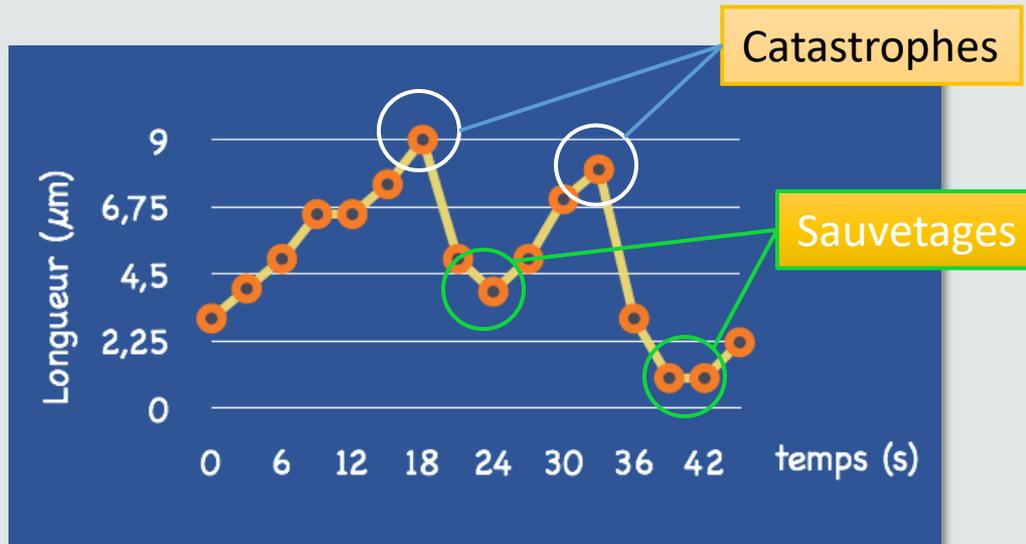
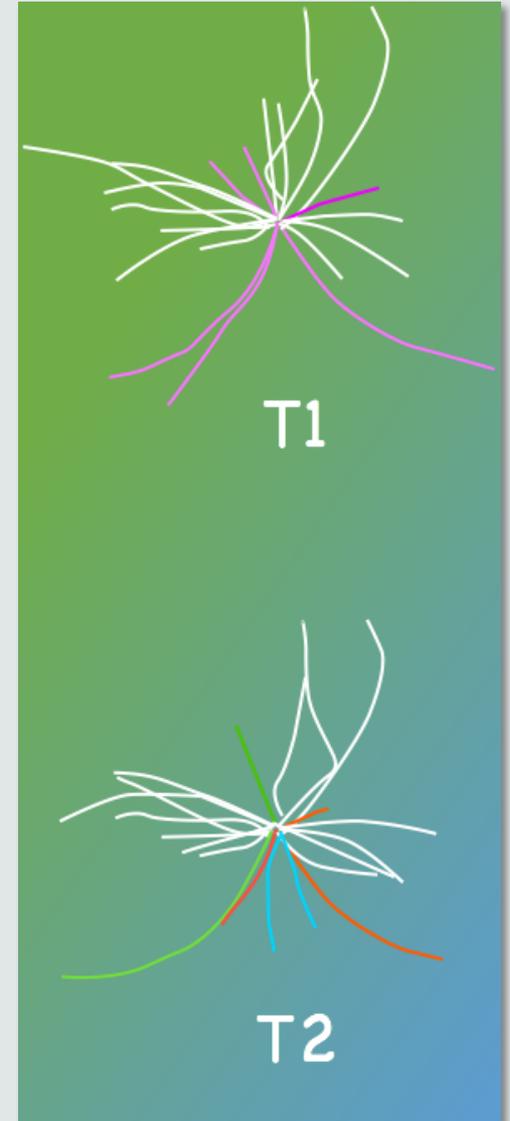
# Les microtubules forment un réseau dynamique



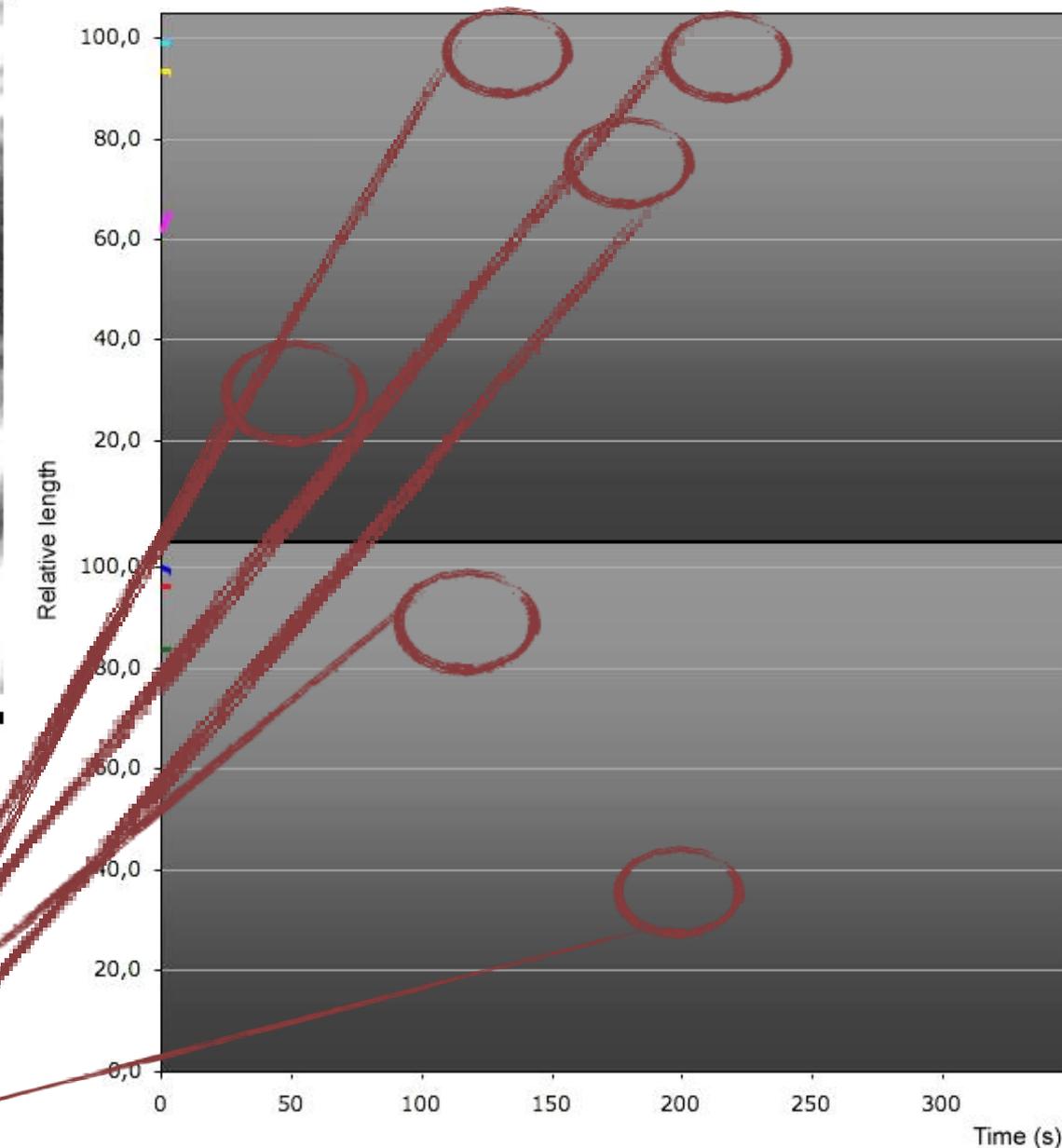
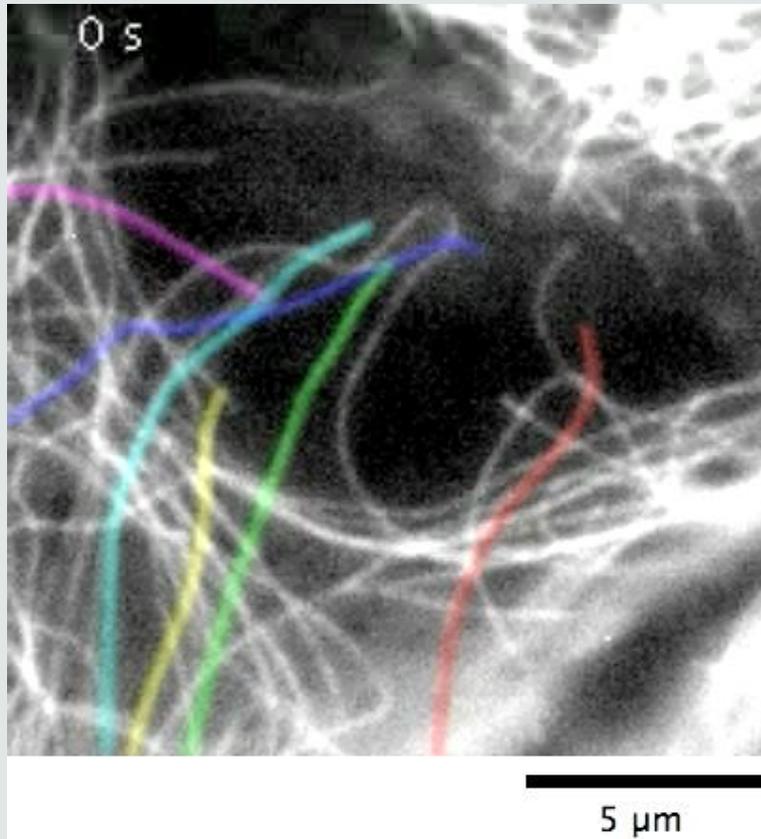
# Instabilité dynamique



Tubuline + GTP + centrosomes



# Instabilité dynamique



## Paramètres d'instabilité dynamique

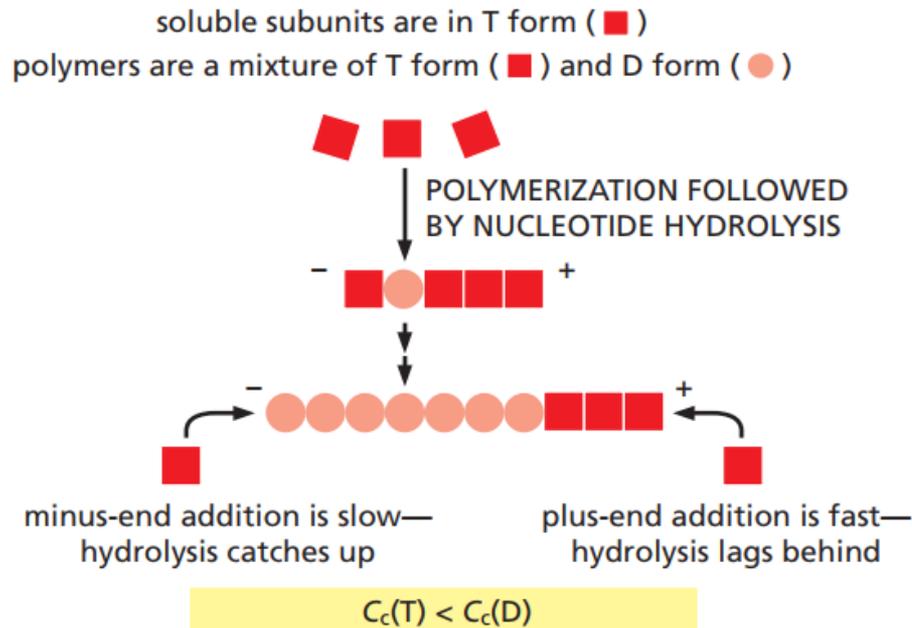
Vitesse d'assemblage

Vitesse de dépolymérisation

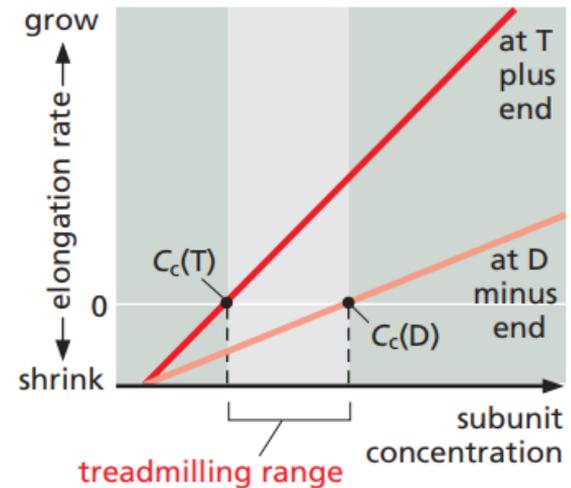
Fréquence des catastrophes

Fréquence des sauvetages

# Notion de concentration critique



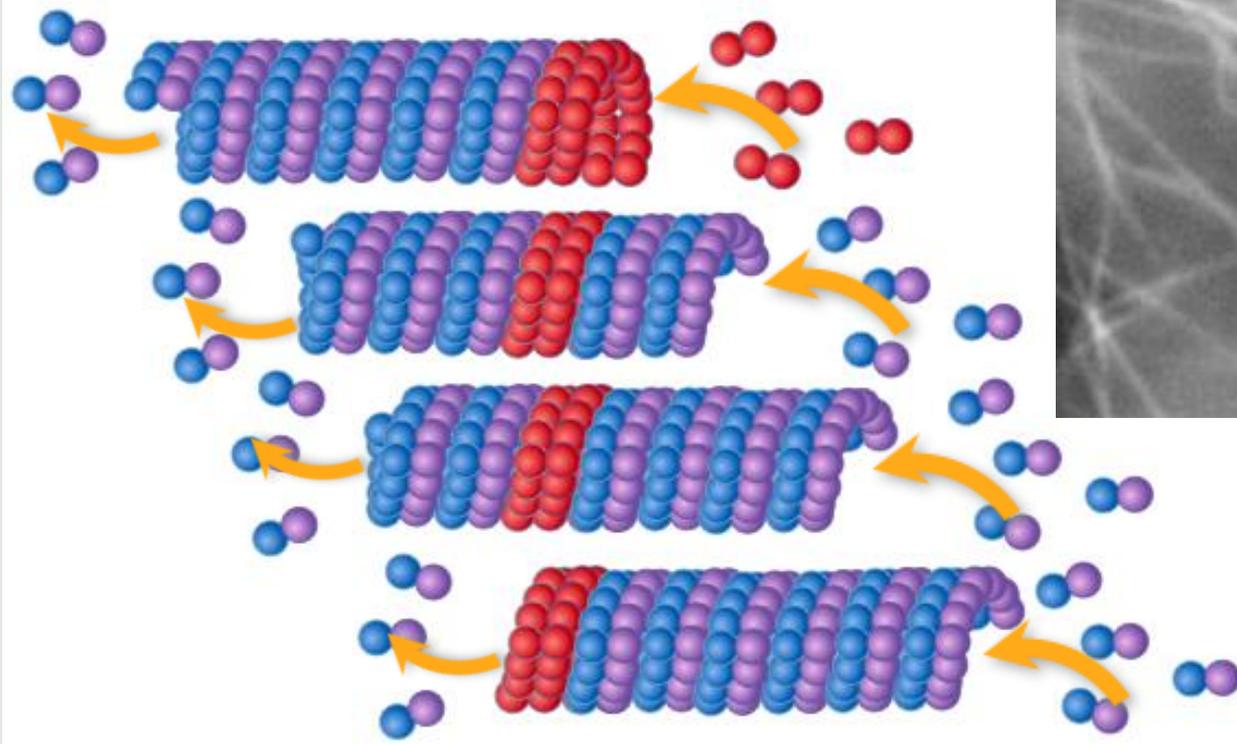
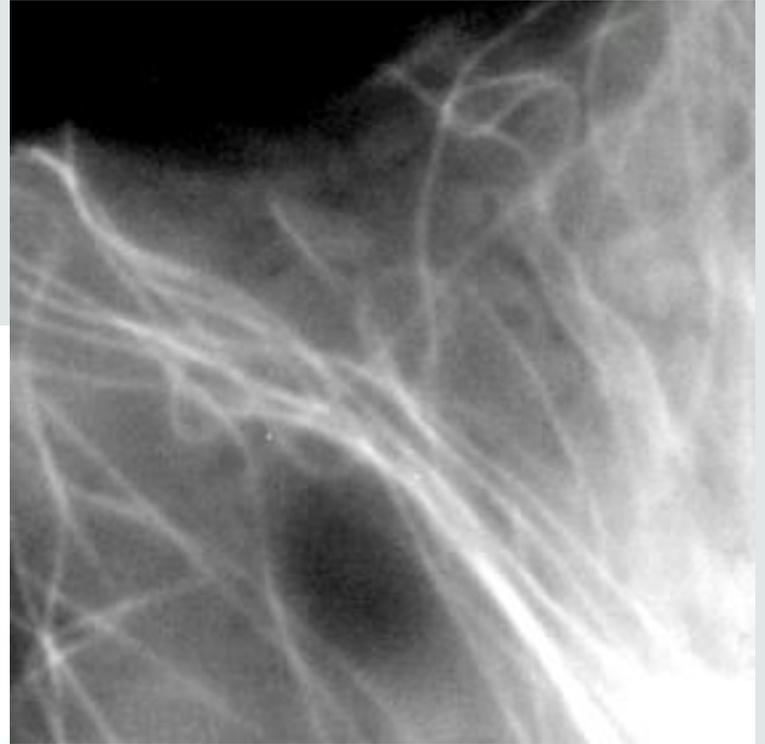
(A)



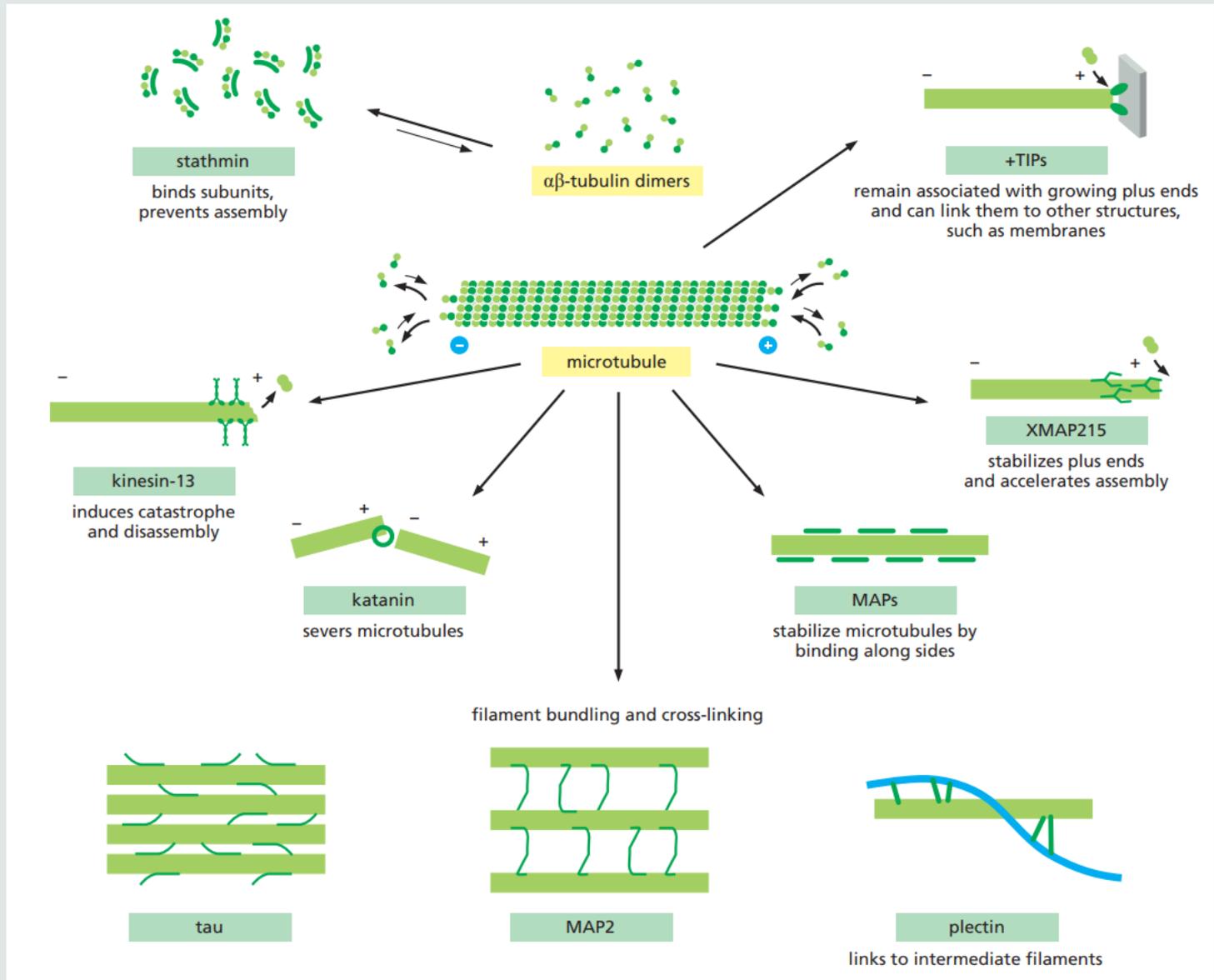
(B)

For  $C_c(T) < C < C_c(D)$   
 treadmilling occurs

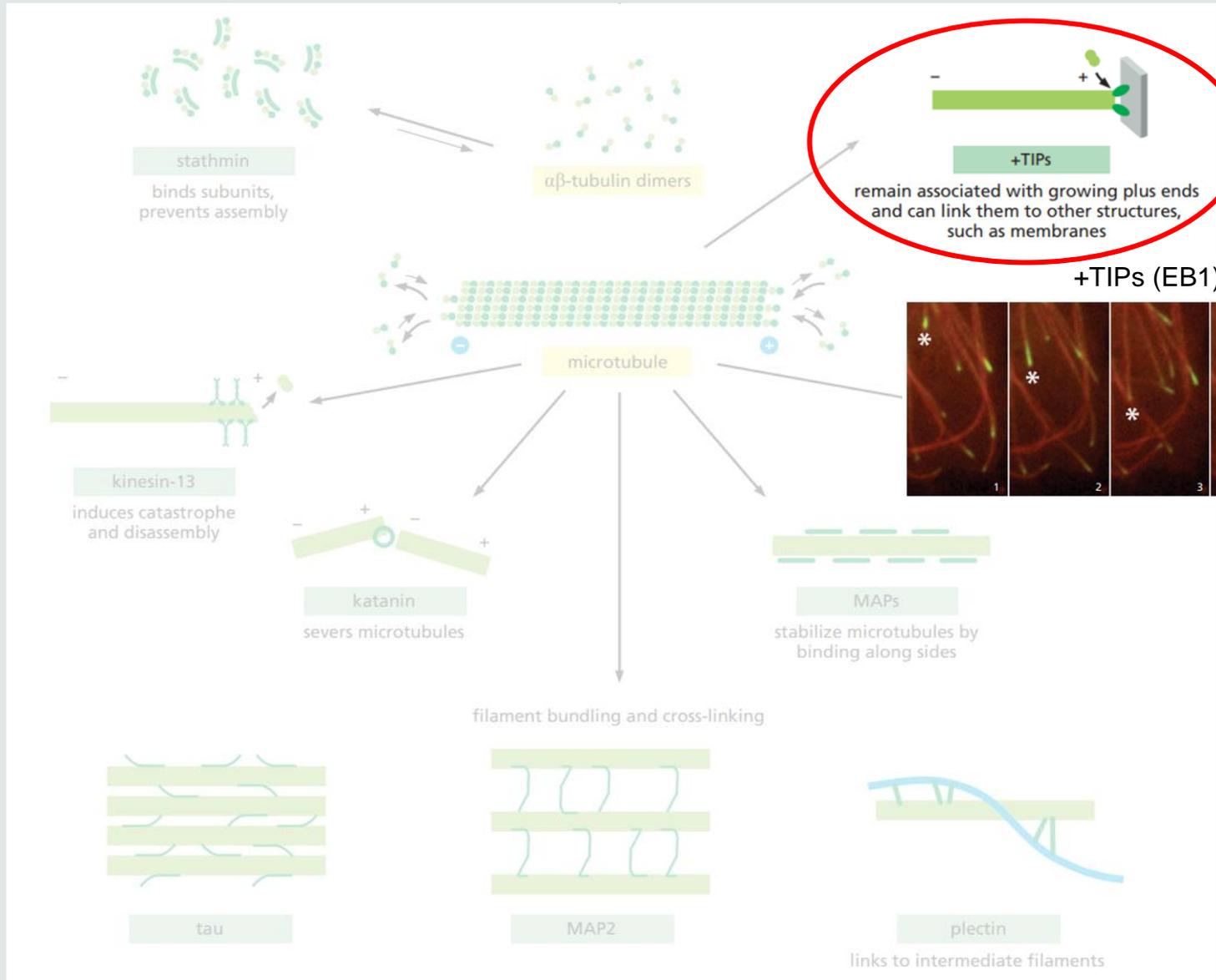
# « Treadmilling »



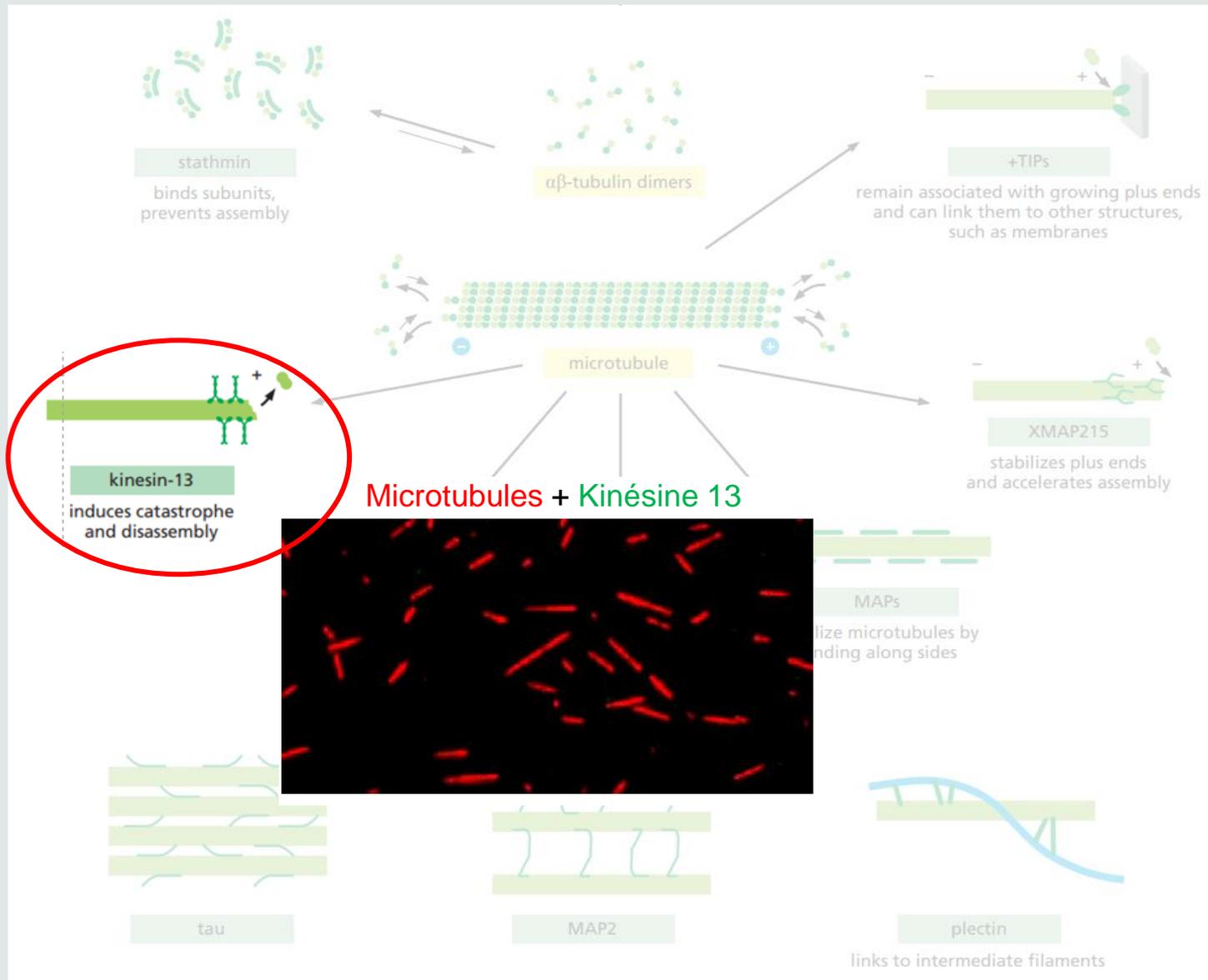
# Protéines associées aux microtubules



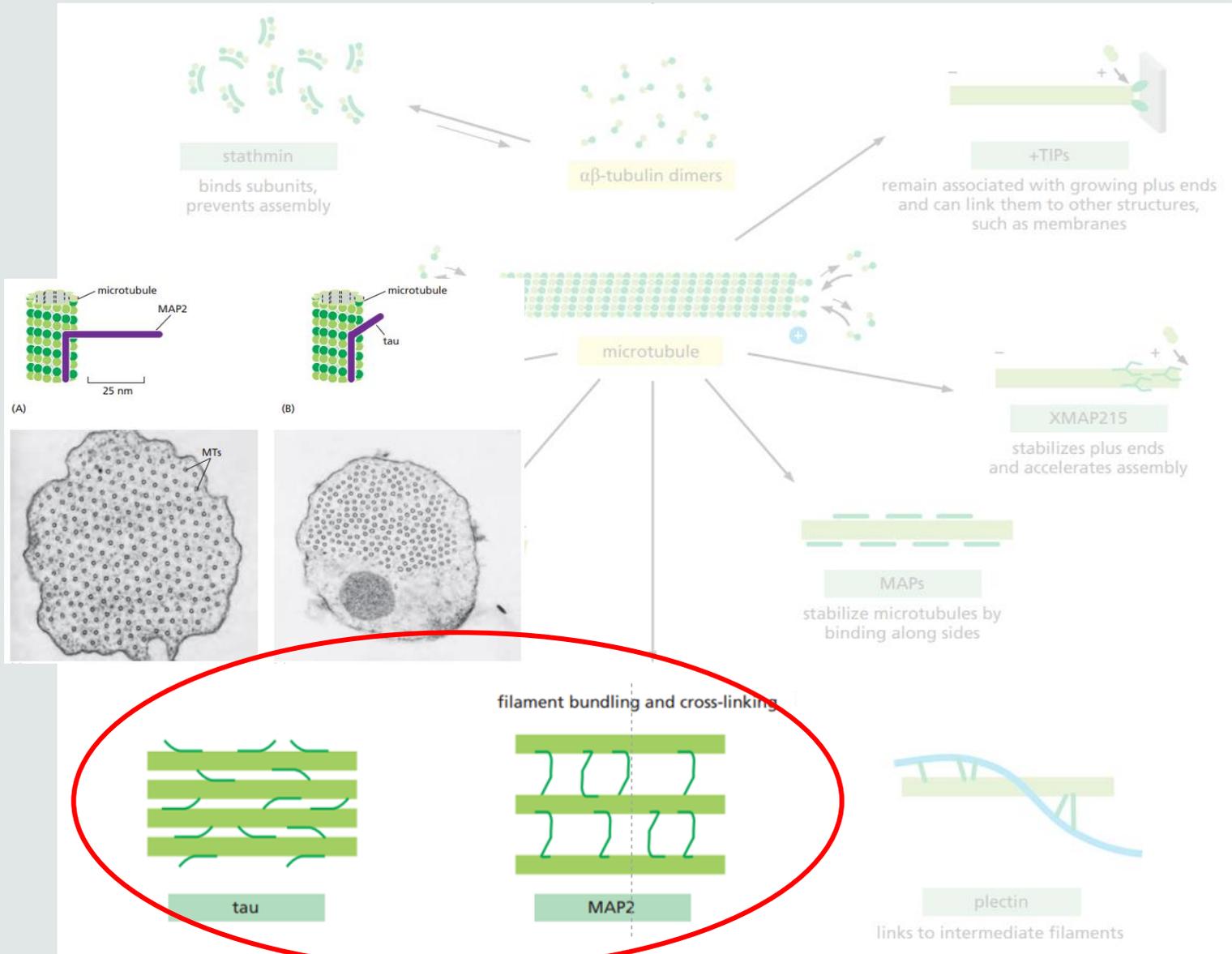
# Protéines associées aux microtubules



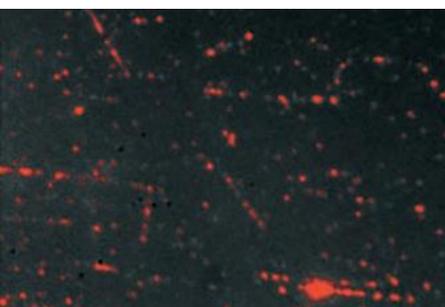
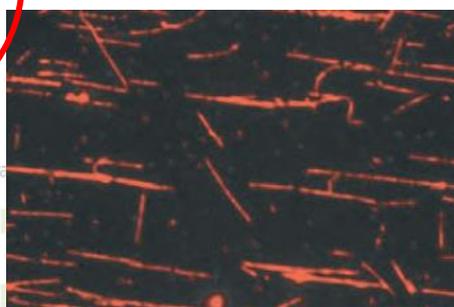
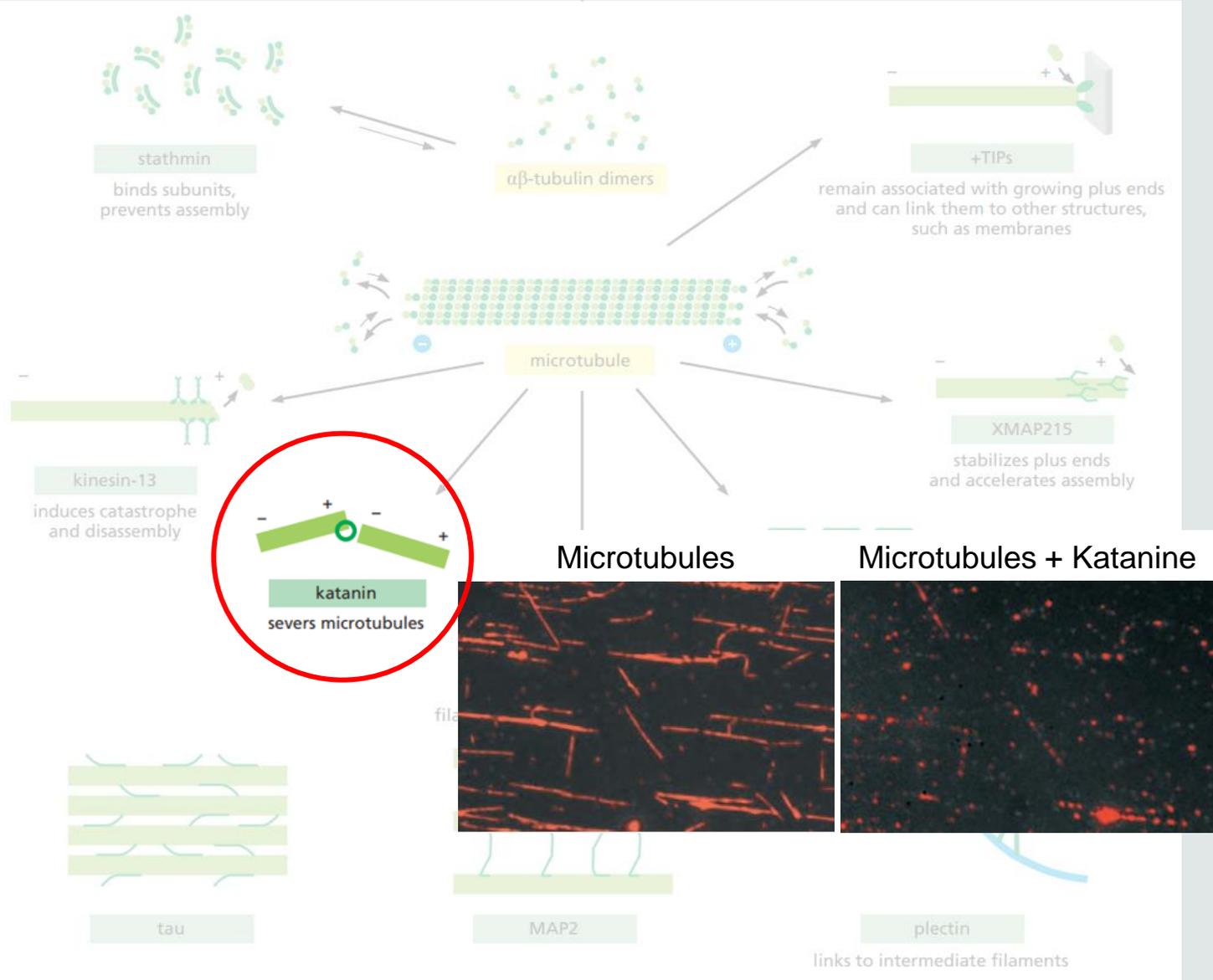
# Protéines associées aux microtubules



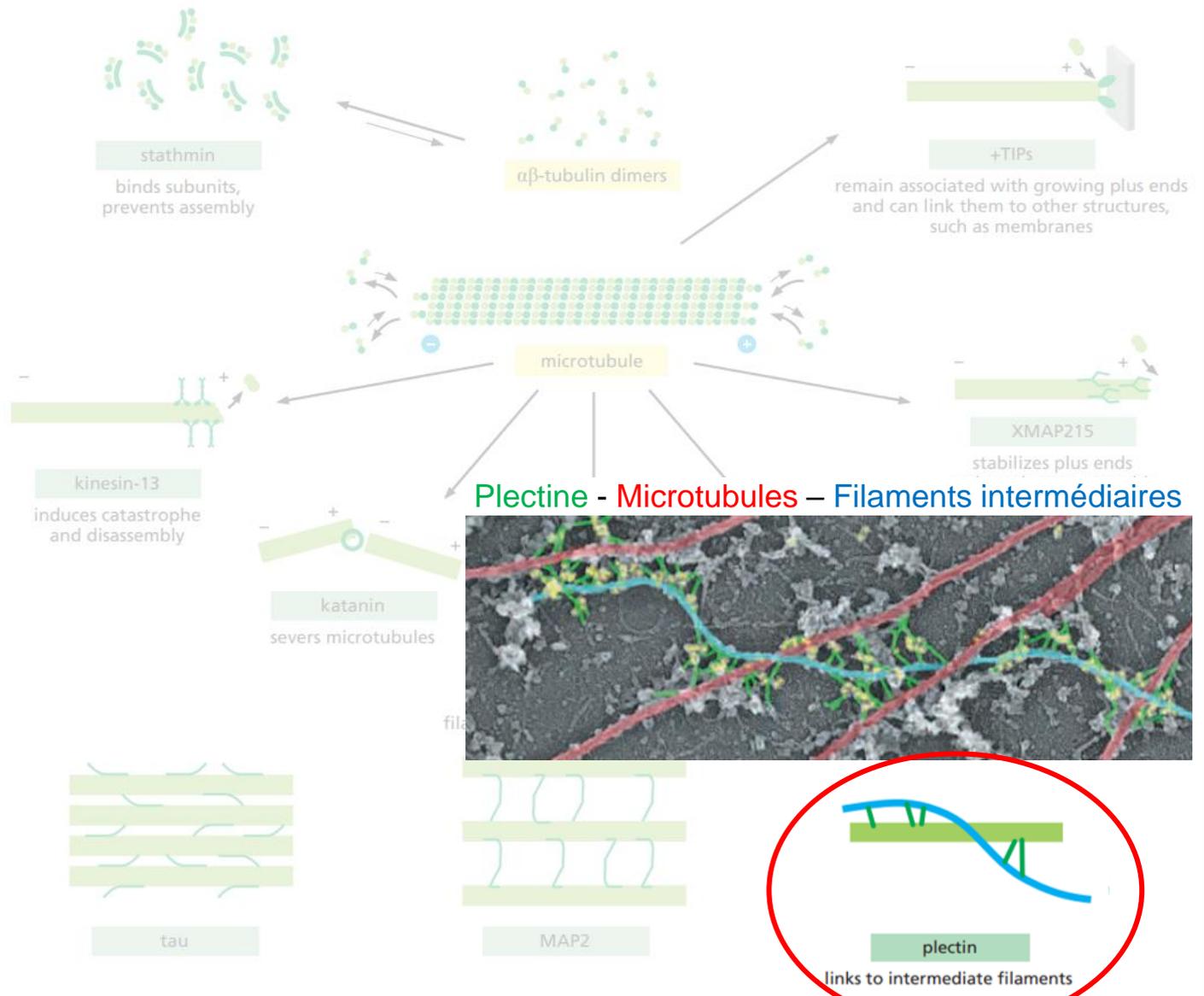
# Protéines associées aux microtubules



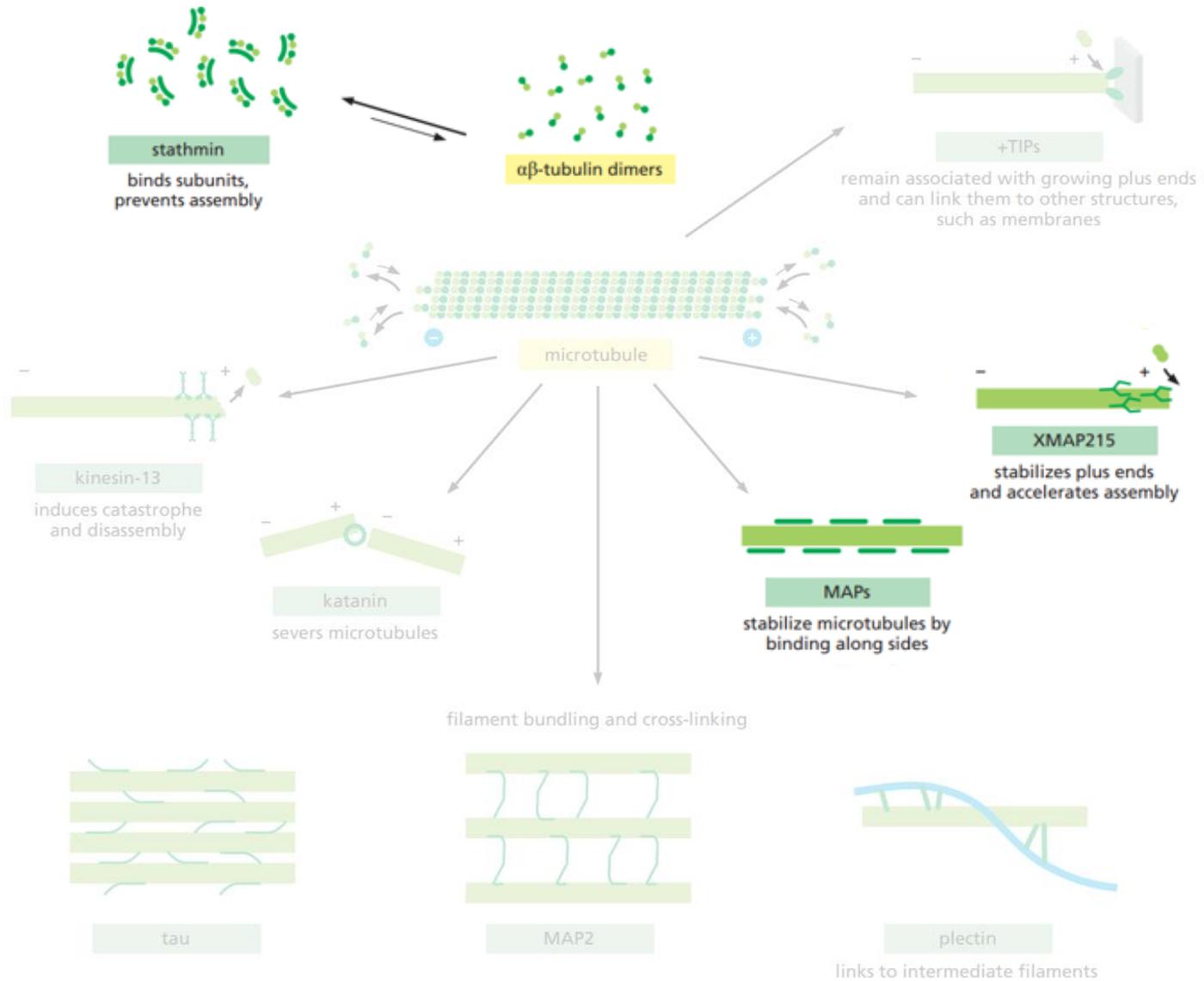
# Protéines associées aux microtubules



# Protéines associées aux microtubules

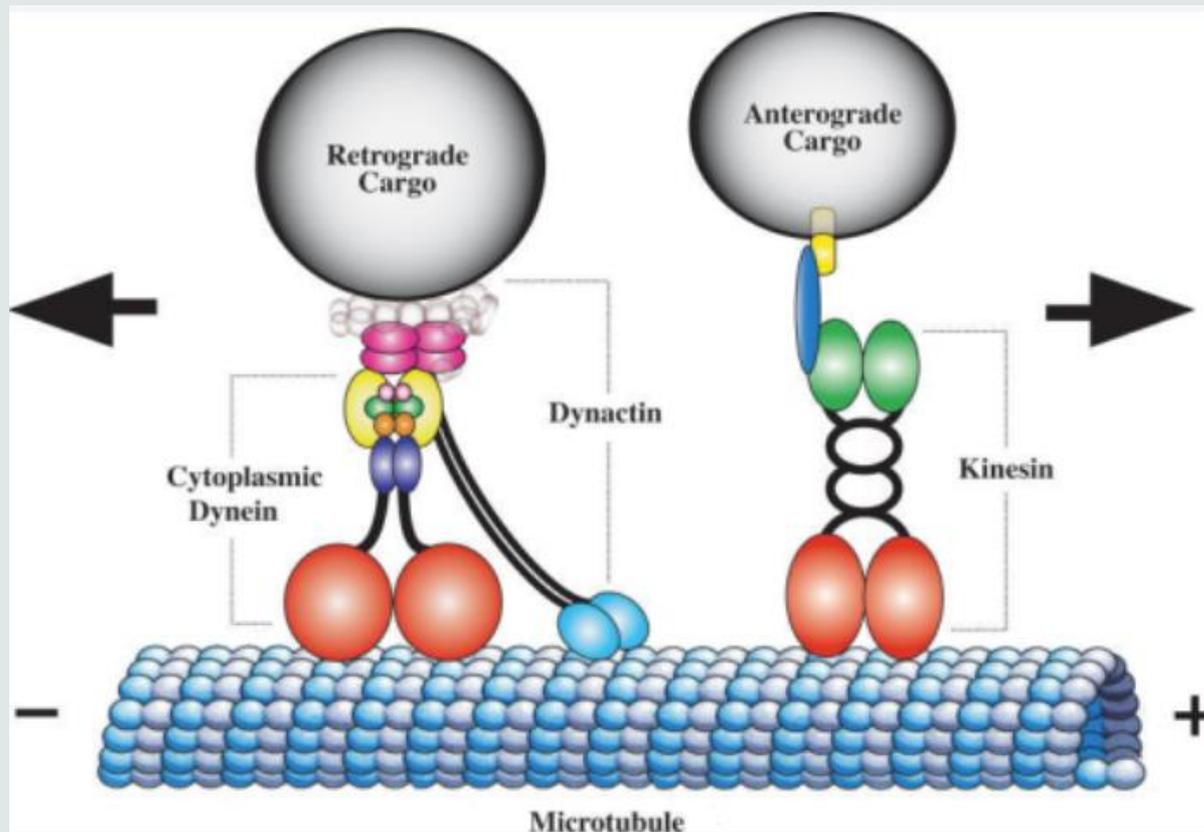


# Protéines associées aux microtubules



# Protéines associées aux microtubules

## Moteurs moléculaires

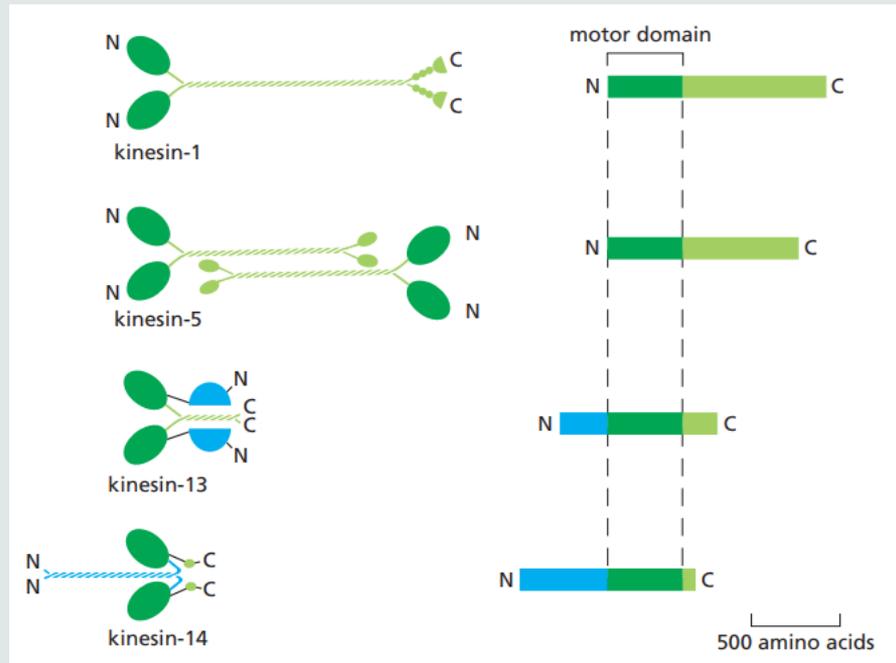


# Kinésines

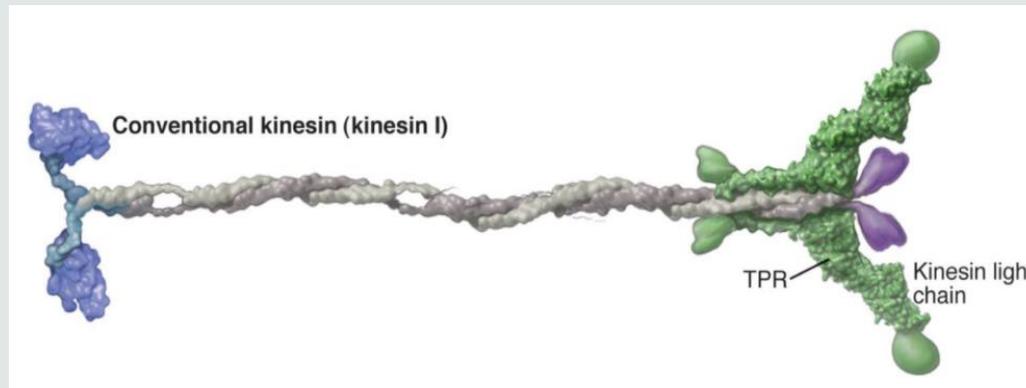
## Kinésines:

~50 gènes codent des moteurs spécialisés dans des transports différents

- Organisation du cytoplasme : mouvement et/ou maintient en place des organites (mitochondries, RE...)
- Trafic vésiculaire
- Transport (protéines, ARN ...)
- Assemblage des cils et flagelles (croissance)
- Organisation de voies de signalisation
- Formation du fuseau mitotique et mouvement des chromosomes

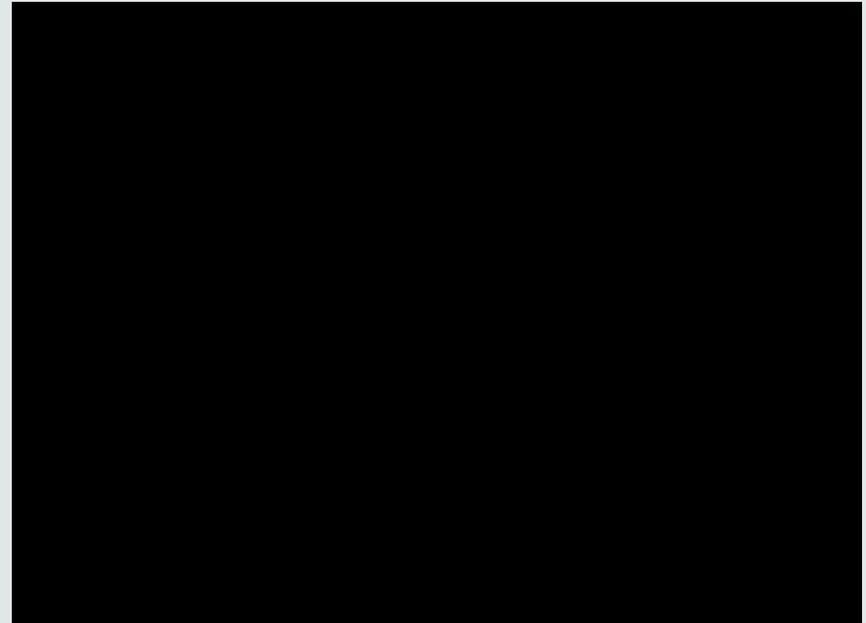
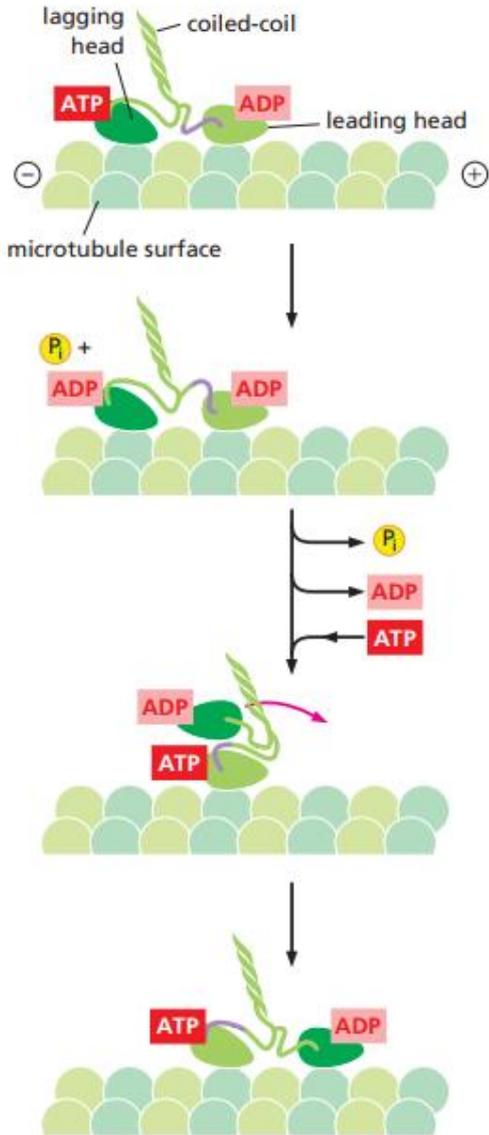


Alberts et al. in *Molecular Biology of the cell*, 6<sup>th</sup> edition, Garland Science



# Kinésines

## Déplacement grâce à l'hydrolyse d'ATP

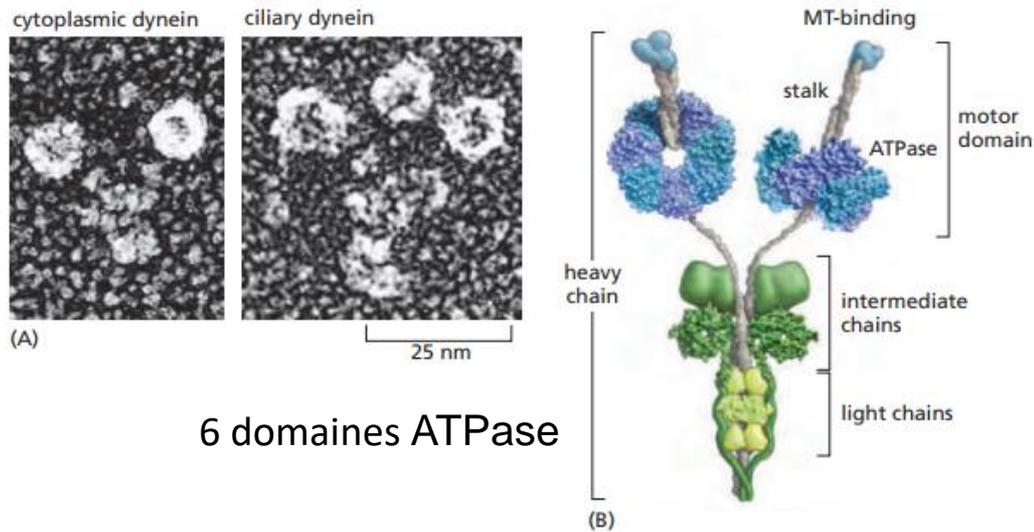


D'après « The inner life of the cell » Xvivo & Harvard Medical School

- Tête motrice + ATP : liaison forte
- Tête motrice + ADP : liaison faible
- Hydrolyse de l'ATP et libération du  $P_i$  : détachement
- Echange ADP/ATP : changement de conformation

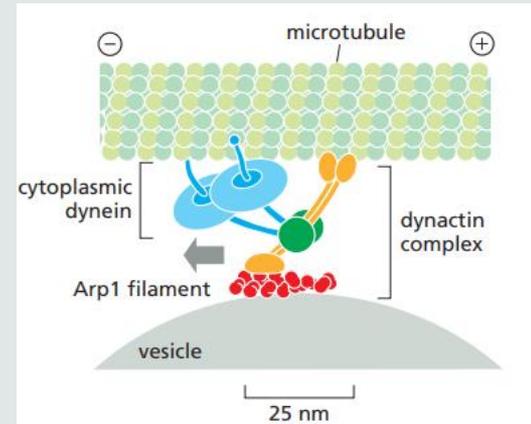
➡ Avancée d'un pas (8nm)

# Dynéines



6 domaines ATPase

*Alberts et al. in Molecular Biology of the cell, 6<sup>th</sup> edition, Garland Science*

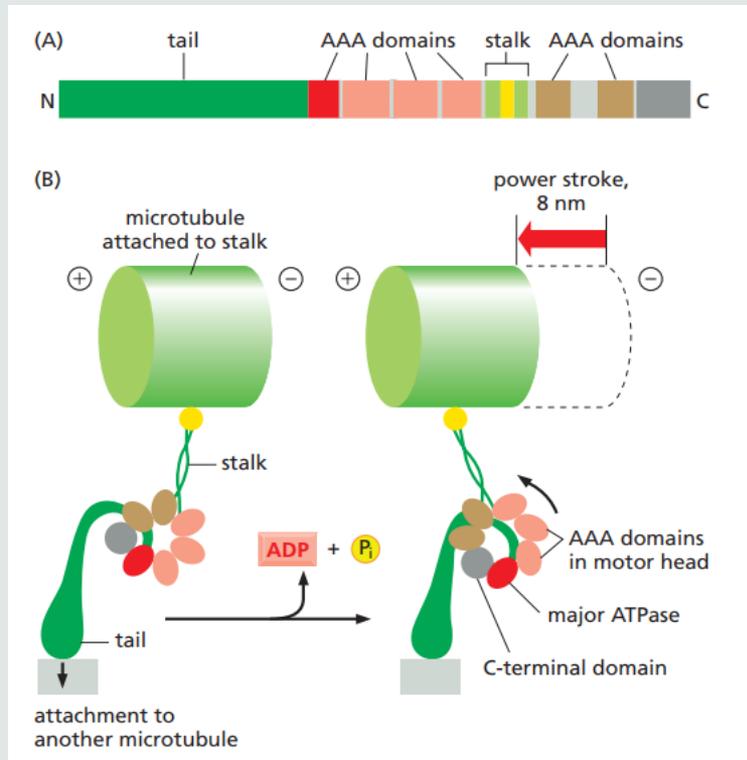


Association à la Dynactine

Dynéines:

- Dynéine cytoplasmique
- Dynéine ciliaire/ flagellaire
  
- Mouvement des organites et des vésicules membranaires
- Courbure des cils et flagelles
- Transport de protéines
- Voies de signalisation

# Dynéines

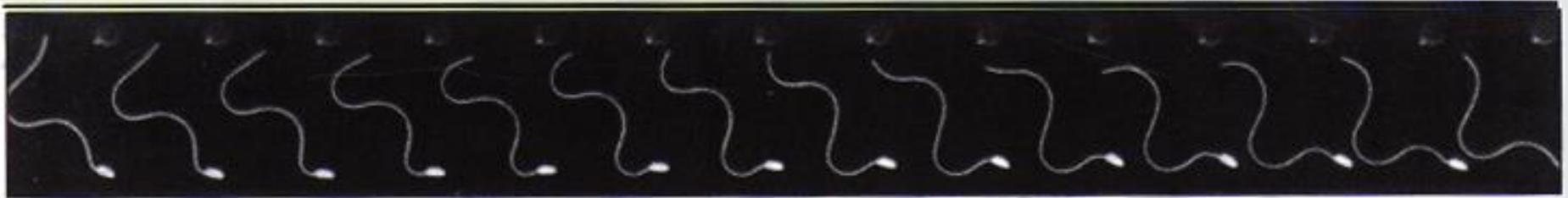


Pas variables 8 à 32 nm

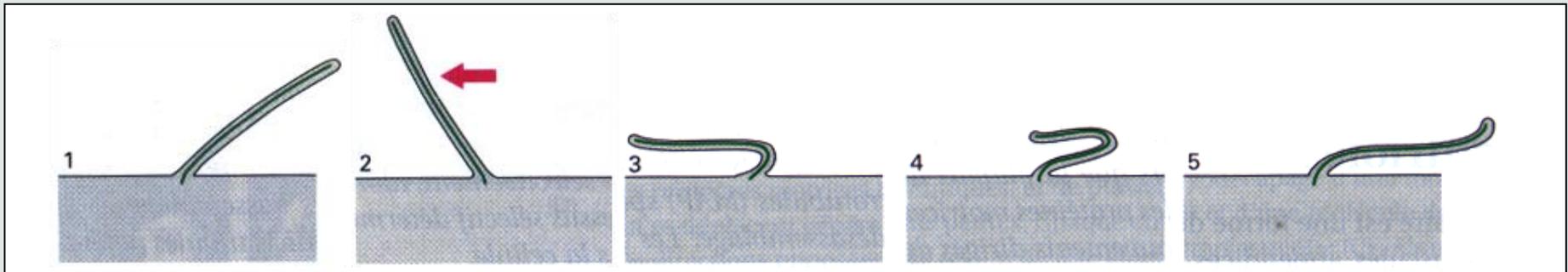
# Cils et flagelles

*Battements : Deux mouvements différents*

Flagelle

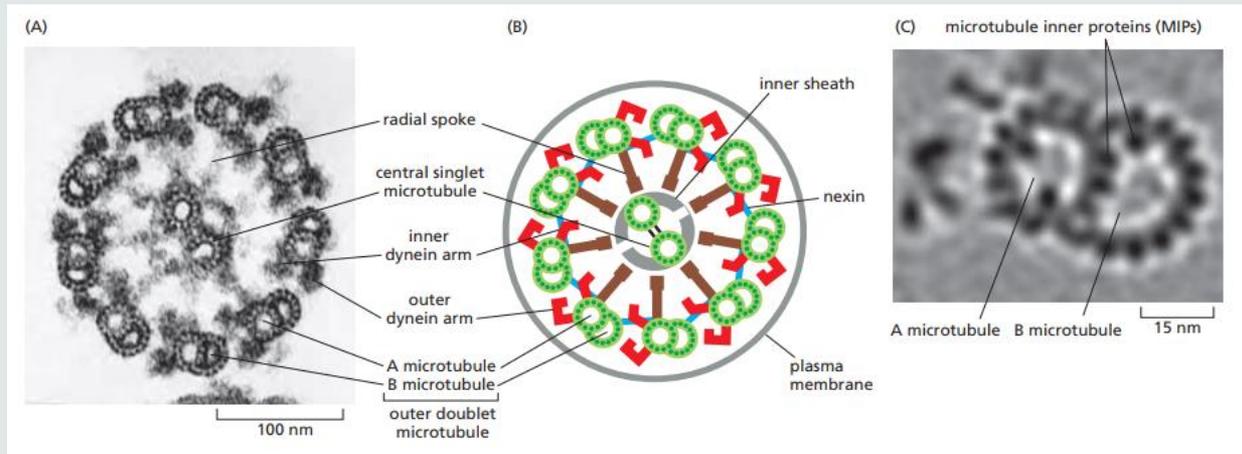


Cil

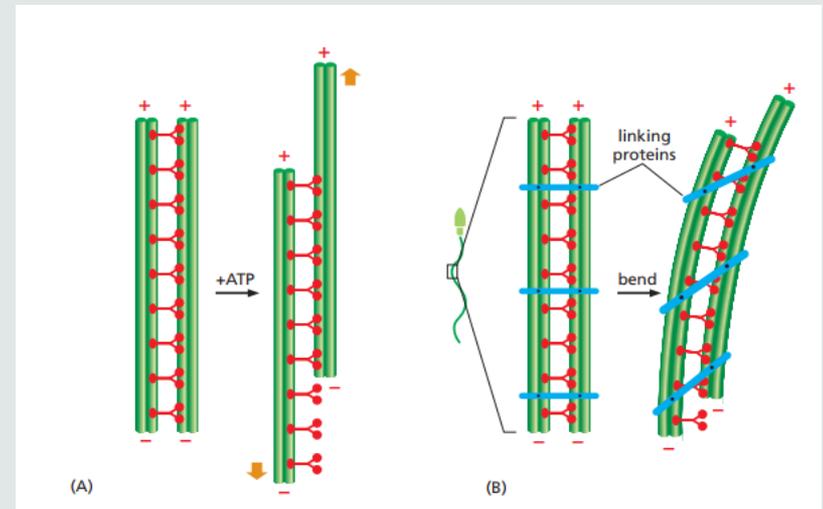
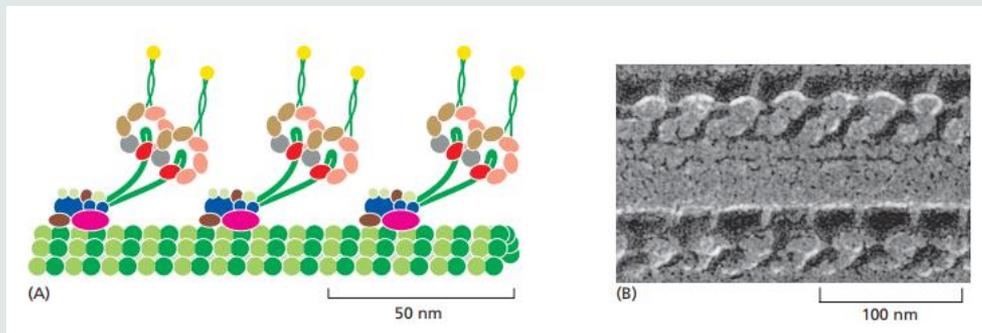


# Cils et flagelles

## Organisation de microtubules dans les cils et flagelles

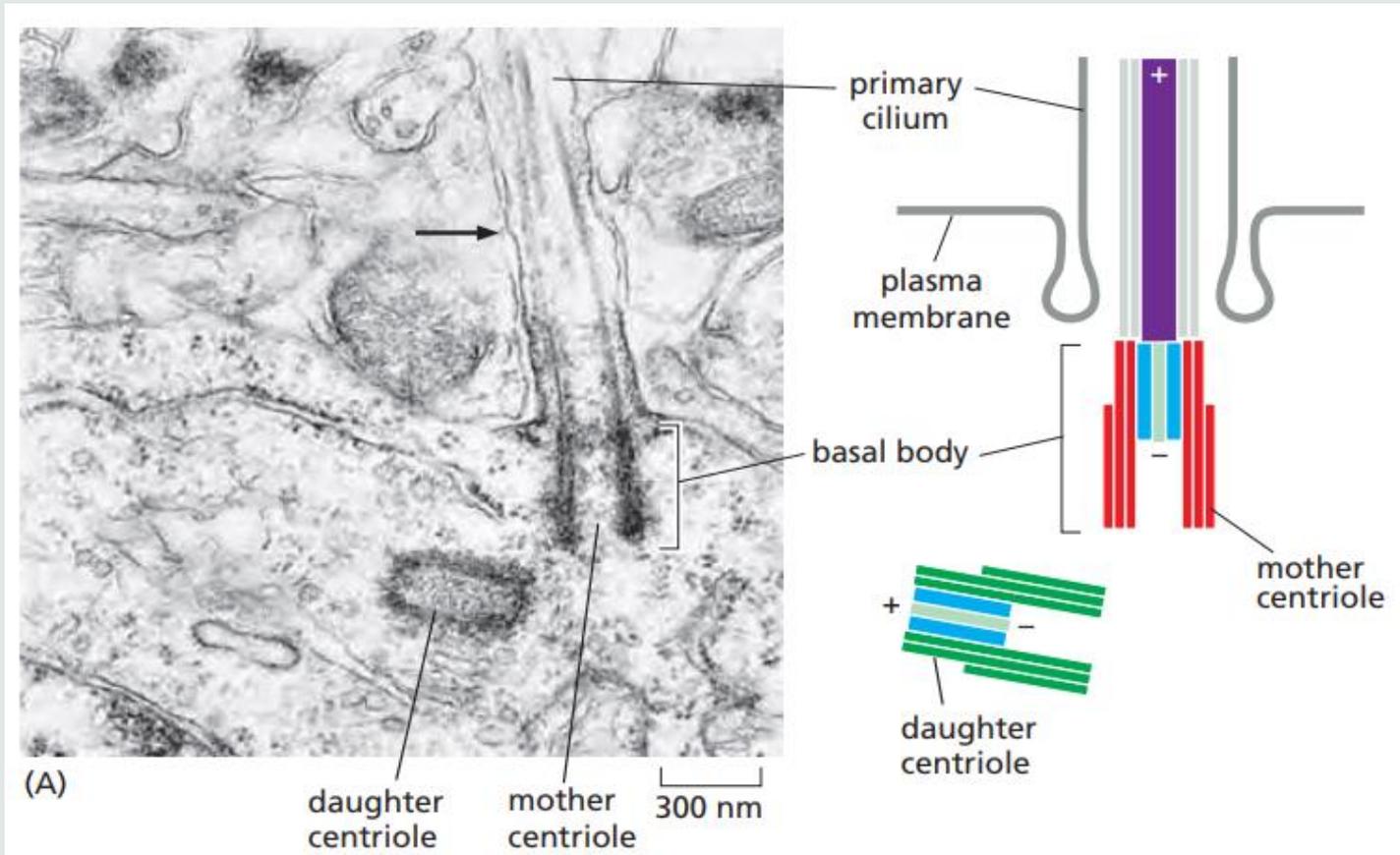


## Rôle des dynéines



# Cils et flagelles

## Formation des cils et flagelles



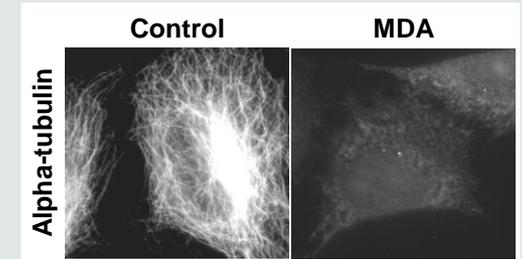
# Ciblage pharmacologique des microtubules

## *Bref historique :*

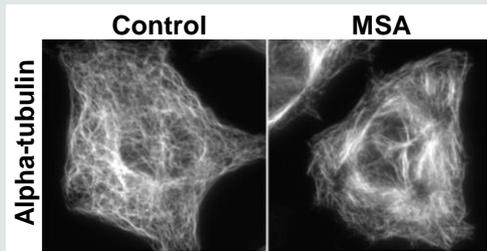
- Colchicine : 1<sup>er</sup> MTA identifié
- Vinca-alcaloïdes (vimblastine, vincristine) :  
Utilisés dans certains lymphomes et tumeurs solides depuis les années 60
- Taxanes (taxol®, taxotère®) :  
Utilisés en première intention dans les cancers de l'ovaire, du sein, de la vessie, de la prostate, du poumon depuis les années 90
- Nouvelles molécules (Epothilone, Eribuline, Maytensine...) :  
Mises sur le marché depuis une dizaine d'années

# Ciblage pharmacologique des microtubules

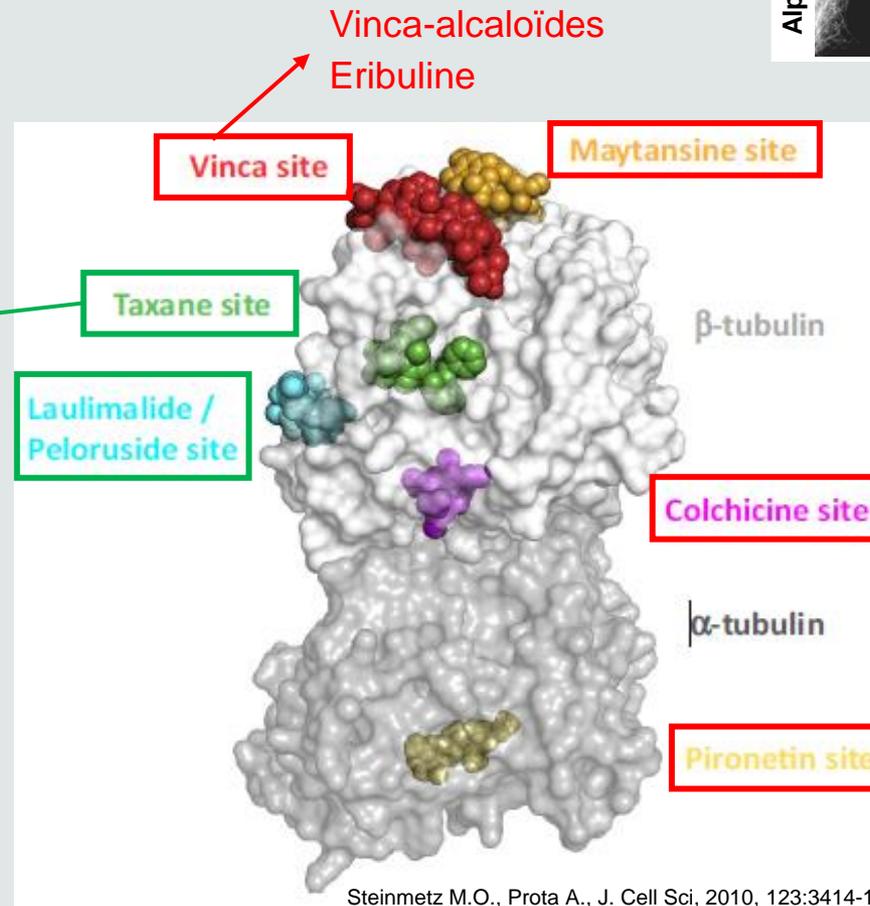
## Agents déstabilisateurs (MDA)



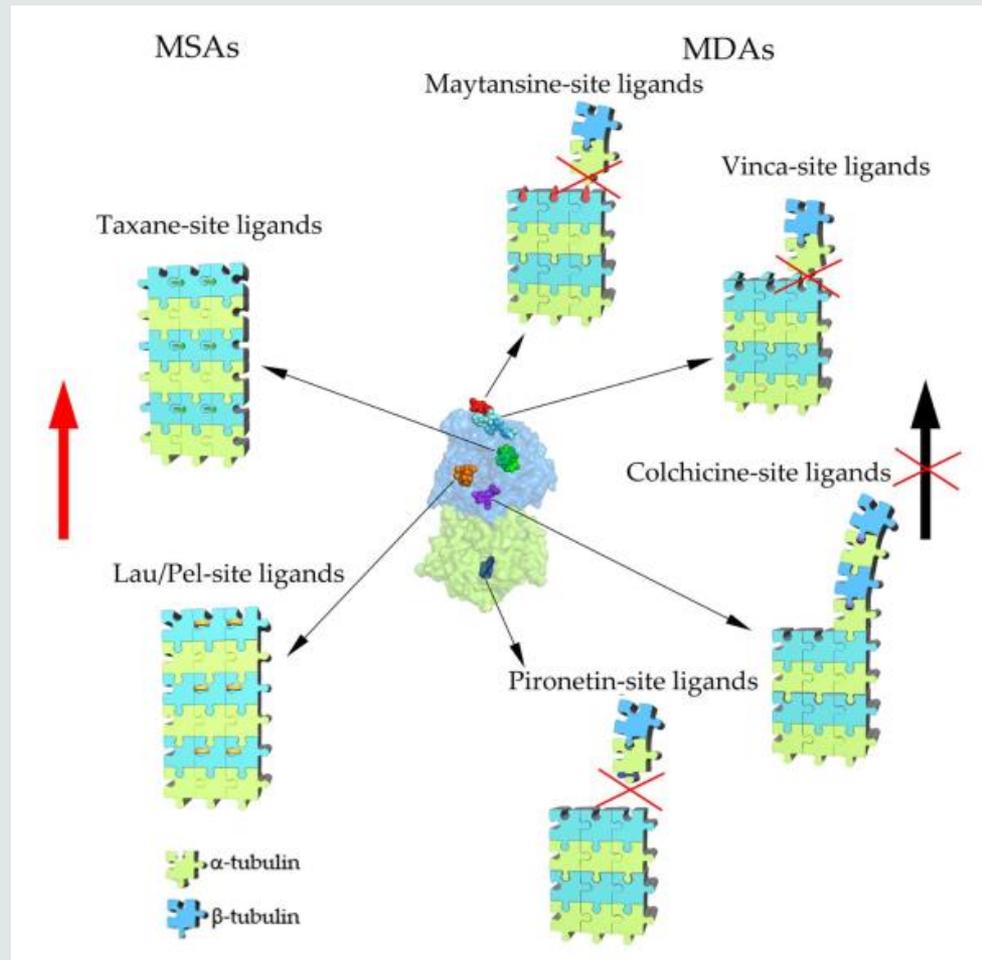
## Agents stabilisateurs (MSA)



Taxanes  
Epothilones

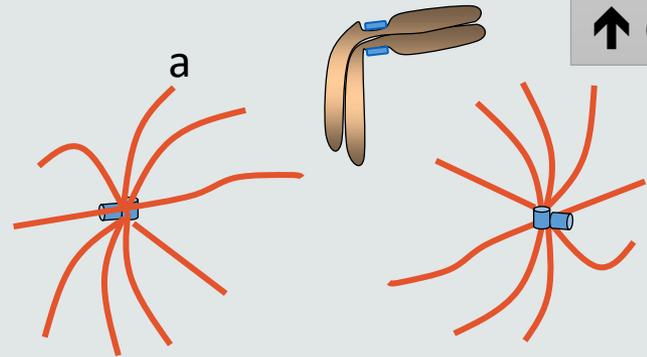
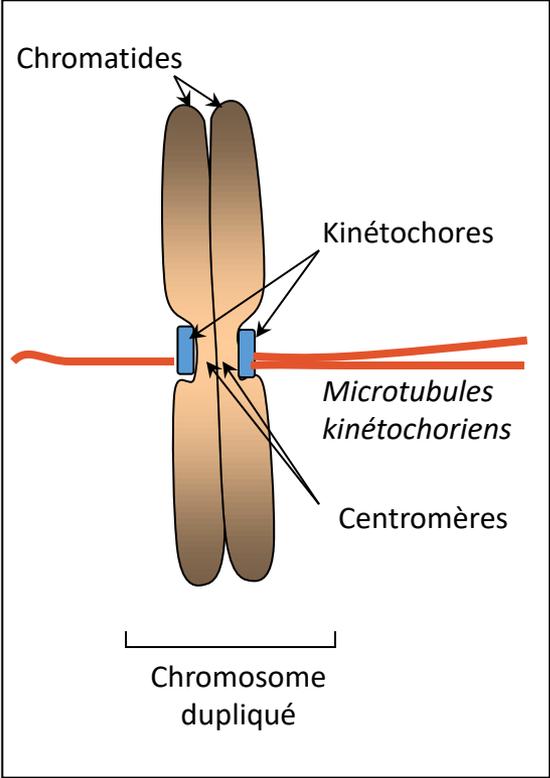


# Mécanisme d'action

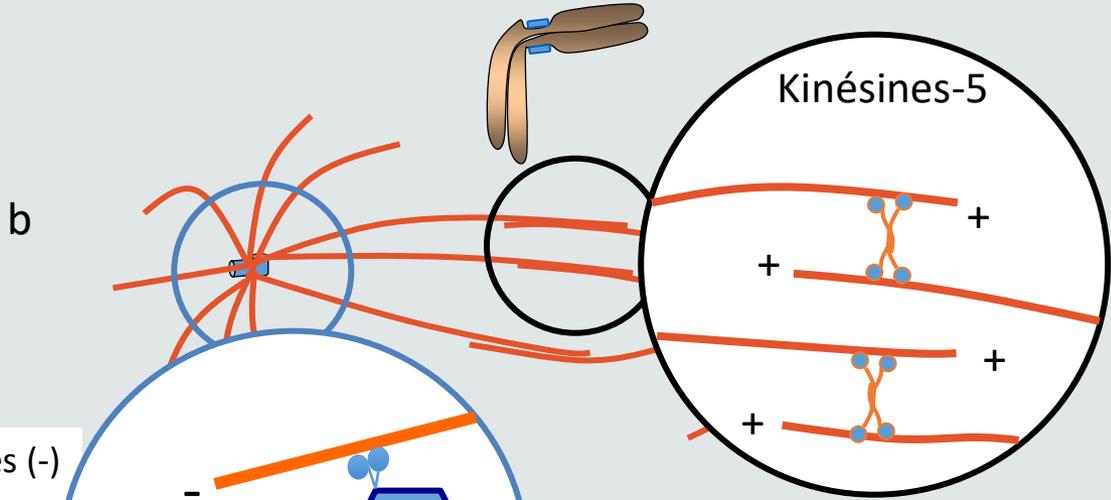


# Microtubules et mitose

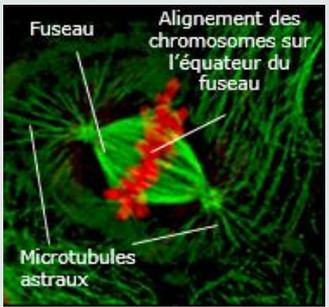
Accélération de la dynamique  
X4 à x10 par rapport à l'interphase:  
↑ catastrophes, ↓ sauvetages



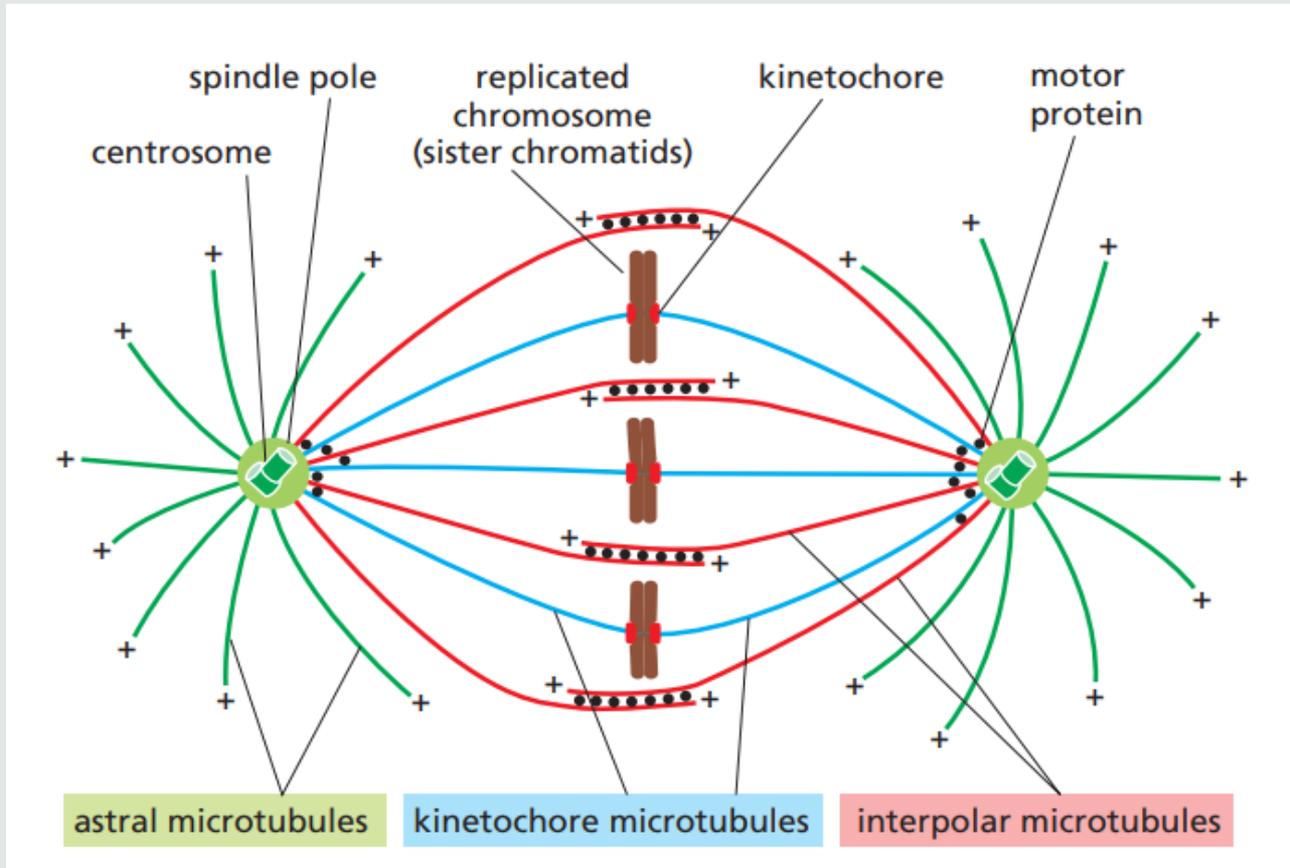
Treadmilling +++



Extrémités (-) libres

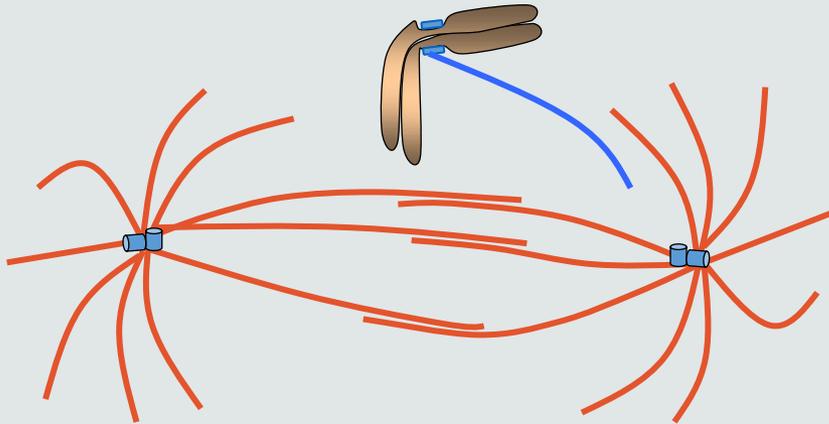


# Organisation des MTs pendant la mitose

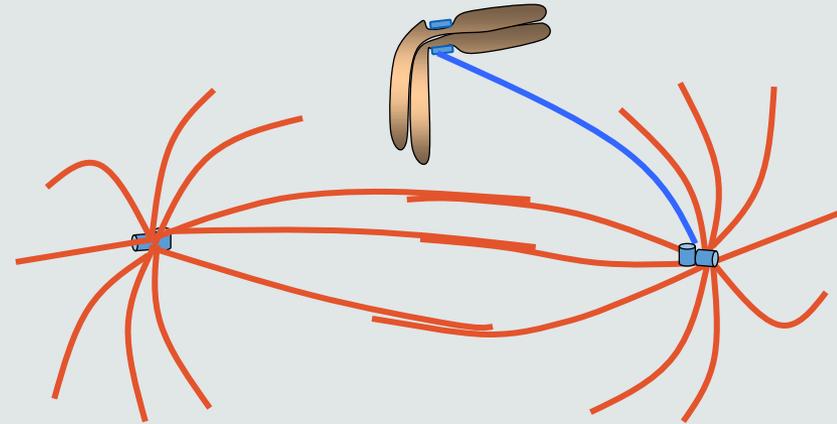


*Alberts et al. in Molecular Biology of the cell, 6<sup>th</sup> edition, Garland Science*

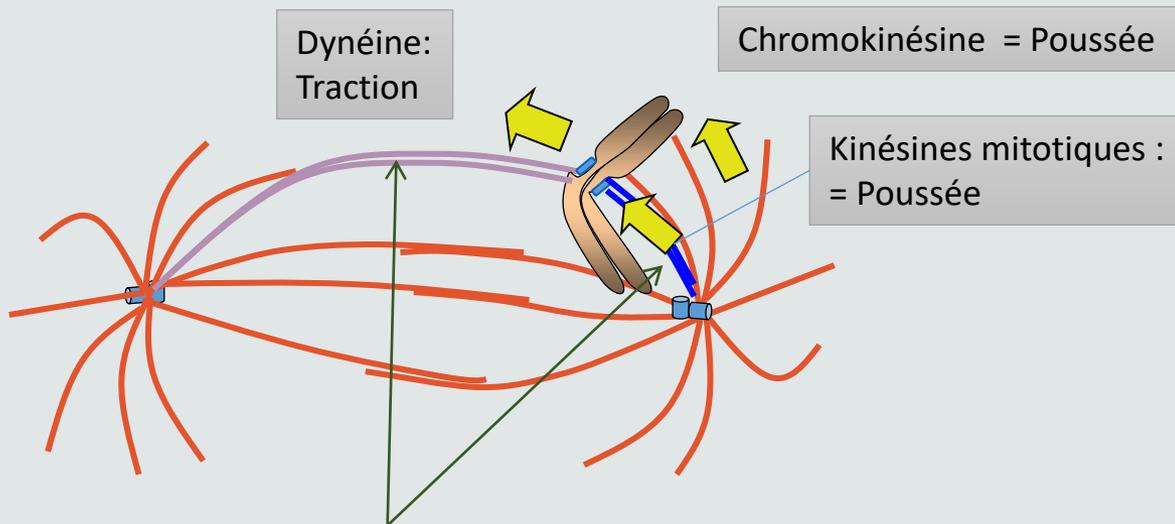
# Capture des chromosomes



Microtubules kinétochoriens +++

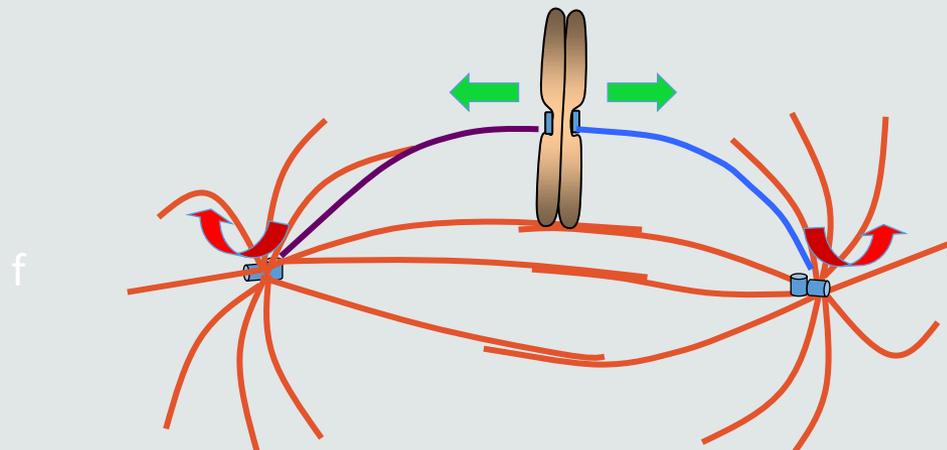
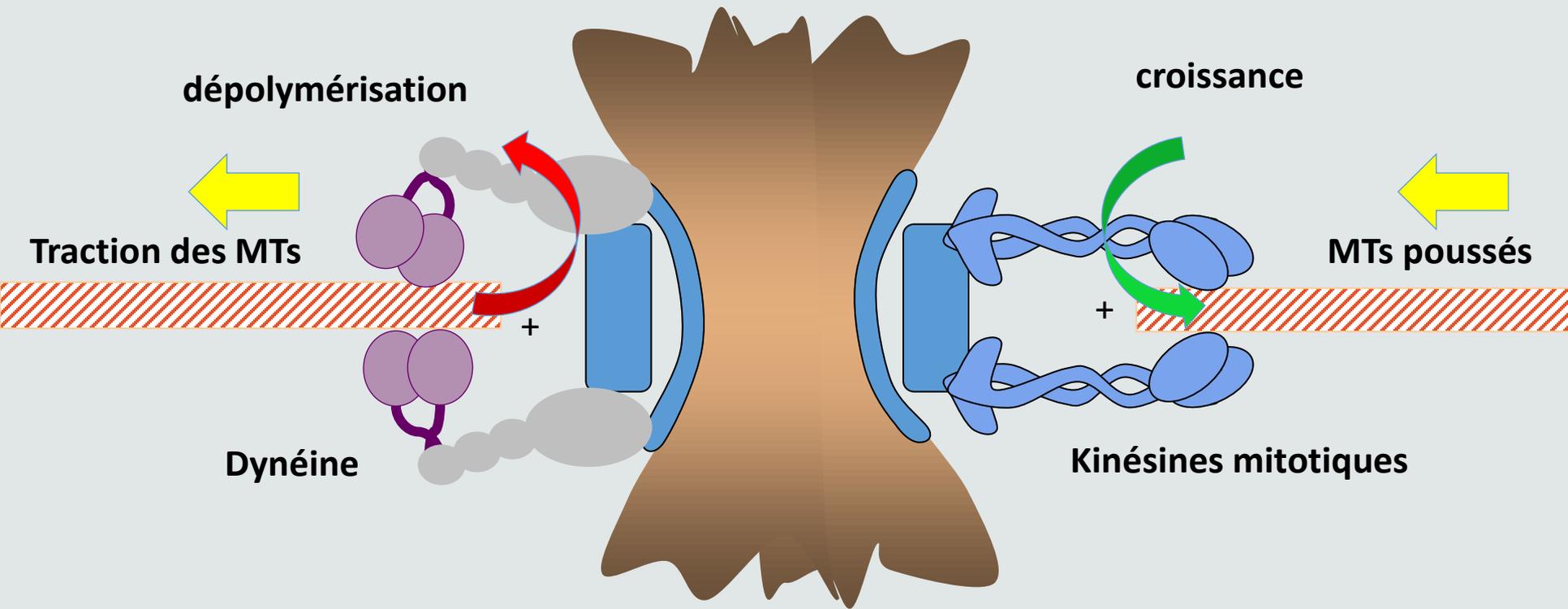


Microtubules interpolaire +



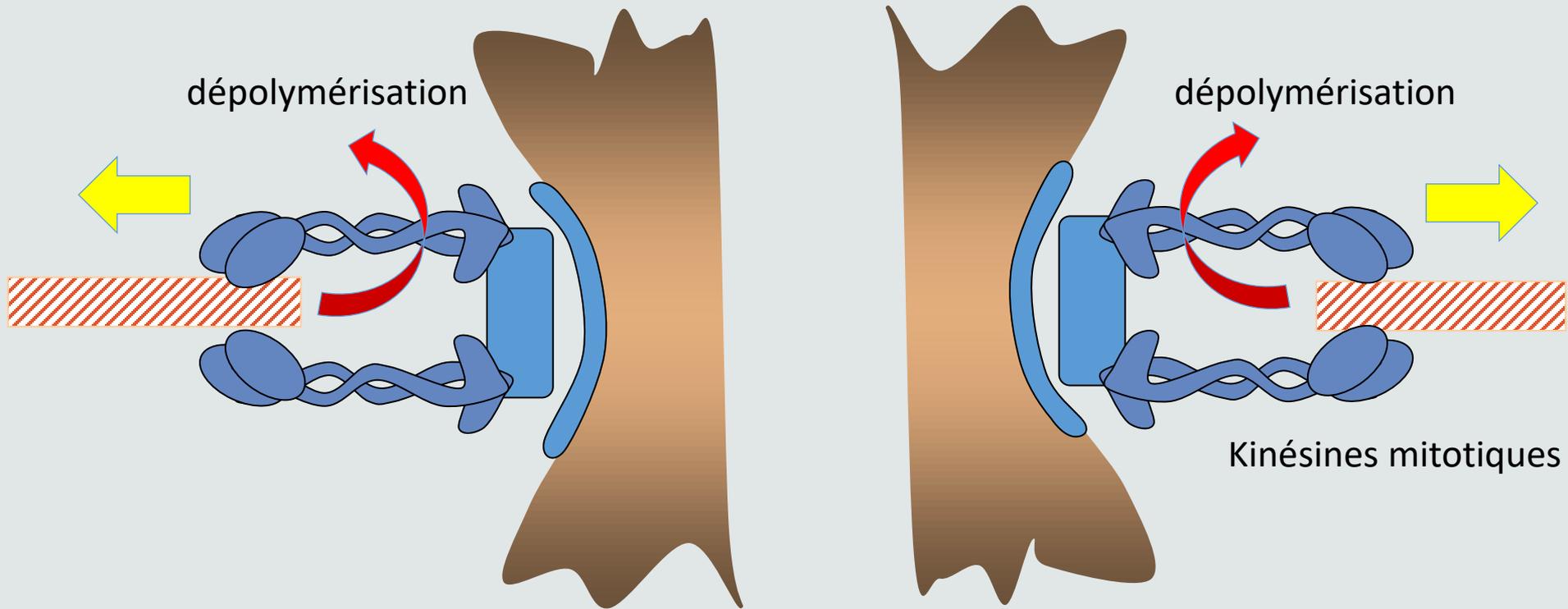
Fibres kinétochoriennes

# Alignement des chromosomes



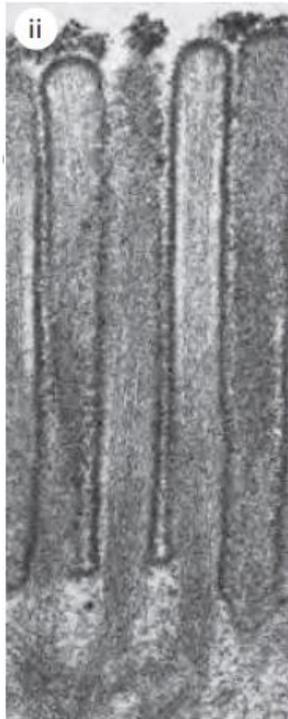
*Treadmilling des microtubules du fuseau  
= flux polaire de tubuline*

# Séparation des chromosomes en anaphase

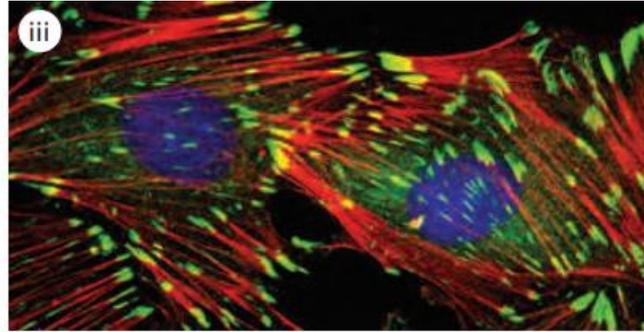


# MICROFILAMENTS

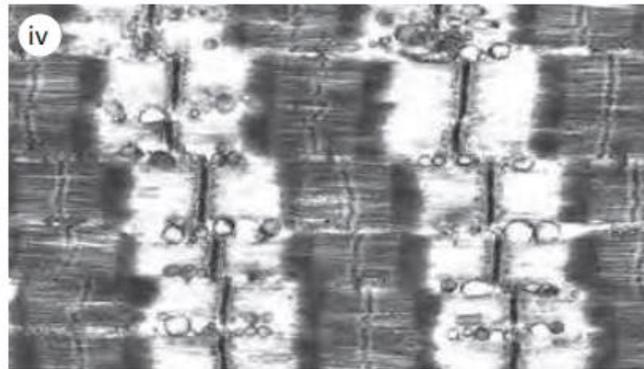
**Microvillosités**



**Fibres de stress**

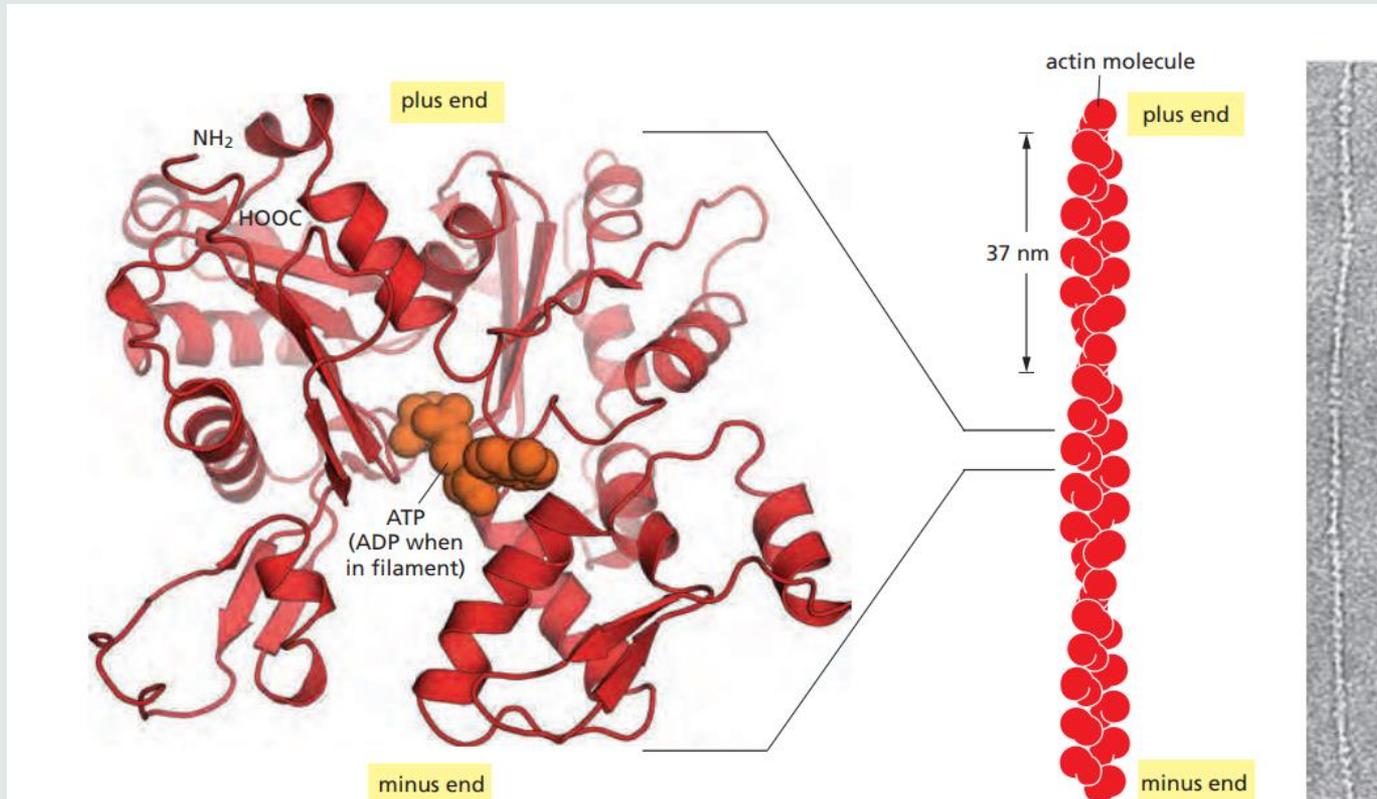


**Muscle strié**

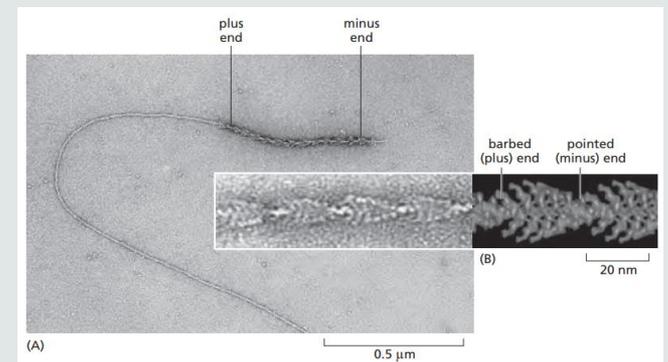


Micrographs courtesy of R. Craig (i and iv); P.T. Matsudaira and D.R. Burgess (ii); K. Burridge (iii).  
*Alberts et al. in Molecular Biology of the cell, 6<sup>th</sup> edition, Garland Science*

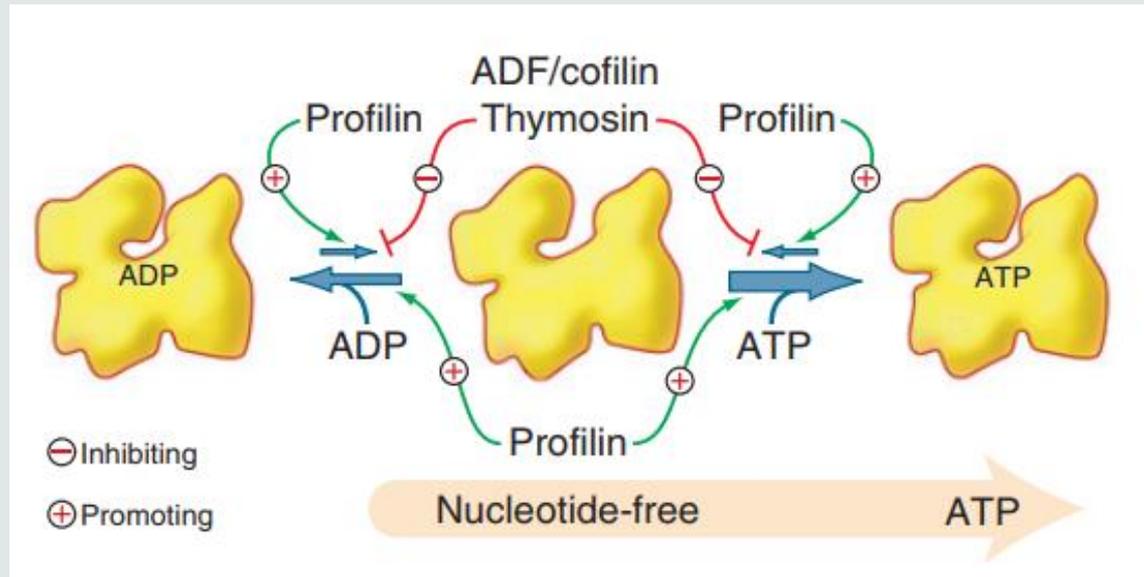
# Structure des microfilaments



Alberts et al. in *Molecular Biology of the cell*, 6<sup>th</sup> edition, Garland Science



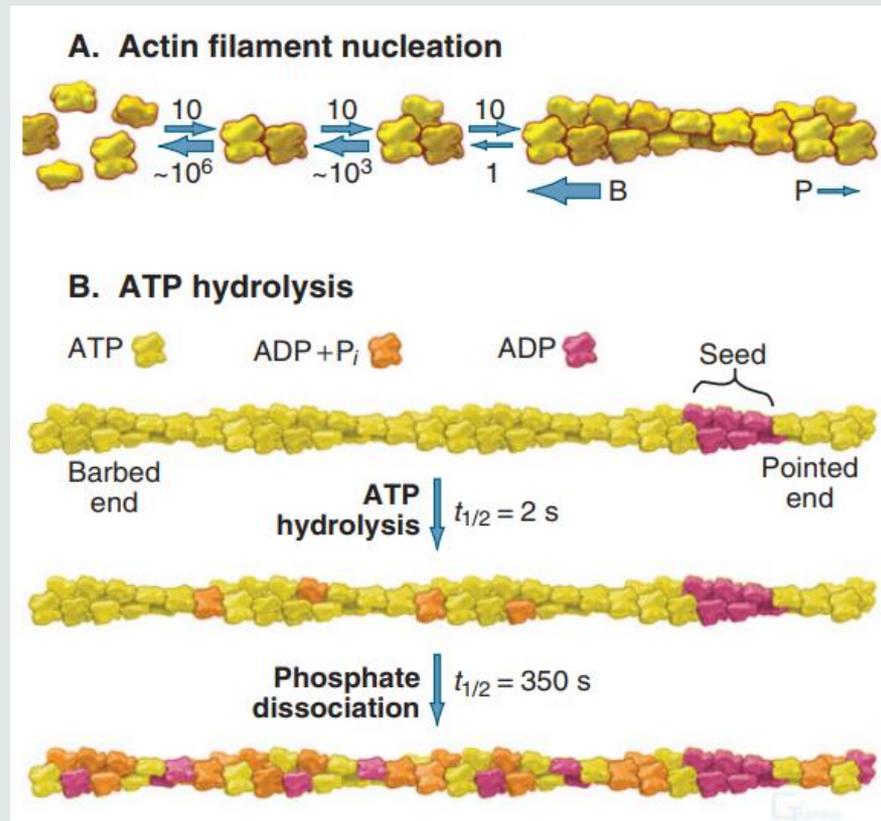
# Régulation des échanges nucléotidiques



Cell Biology third edition, T. Pollard, W. Earnshaw, Elsevier

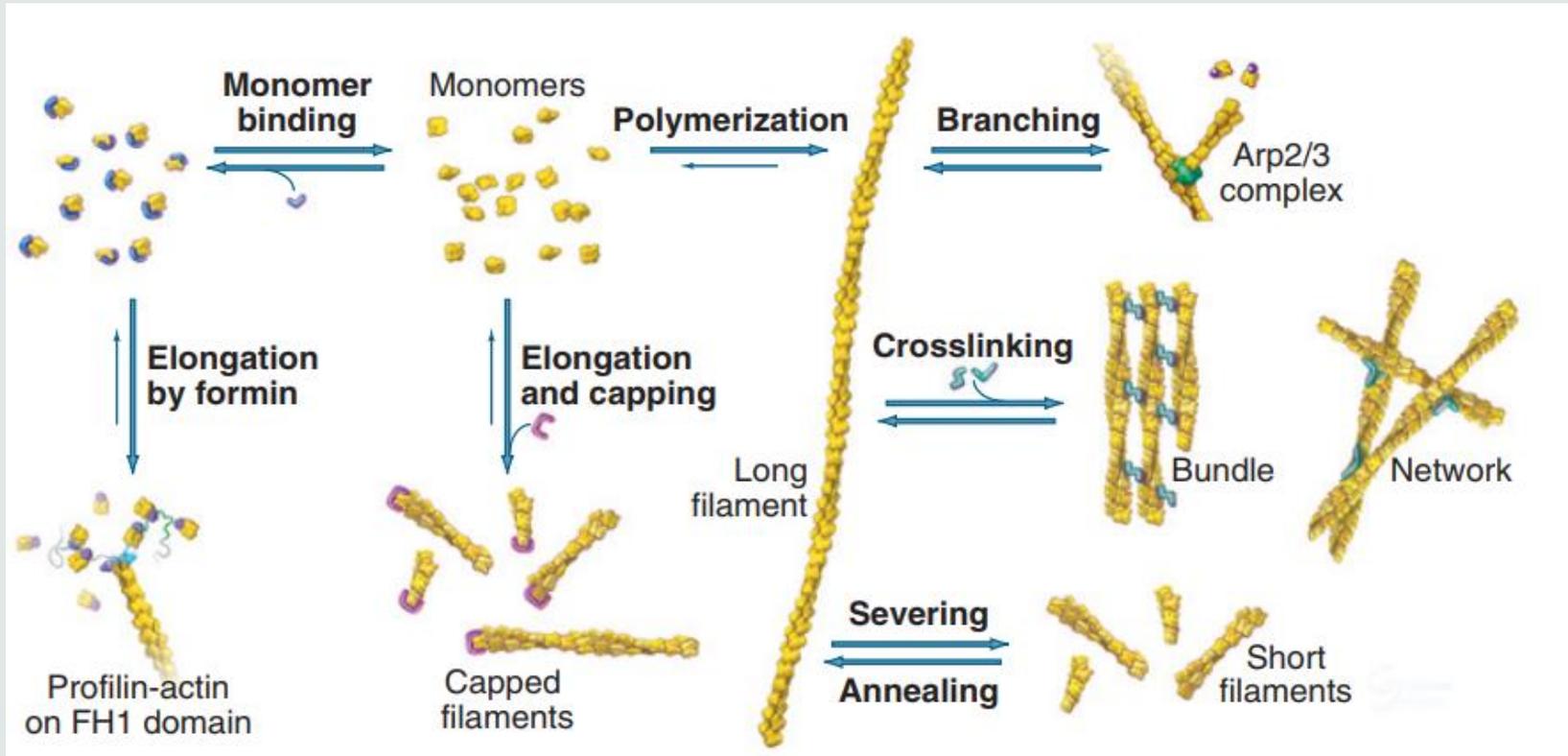
# Nucléation et croissance des microfilaments d'actine

## Hydrolyse de l'ATP

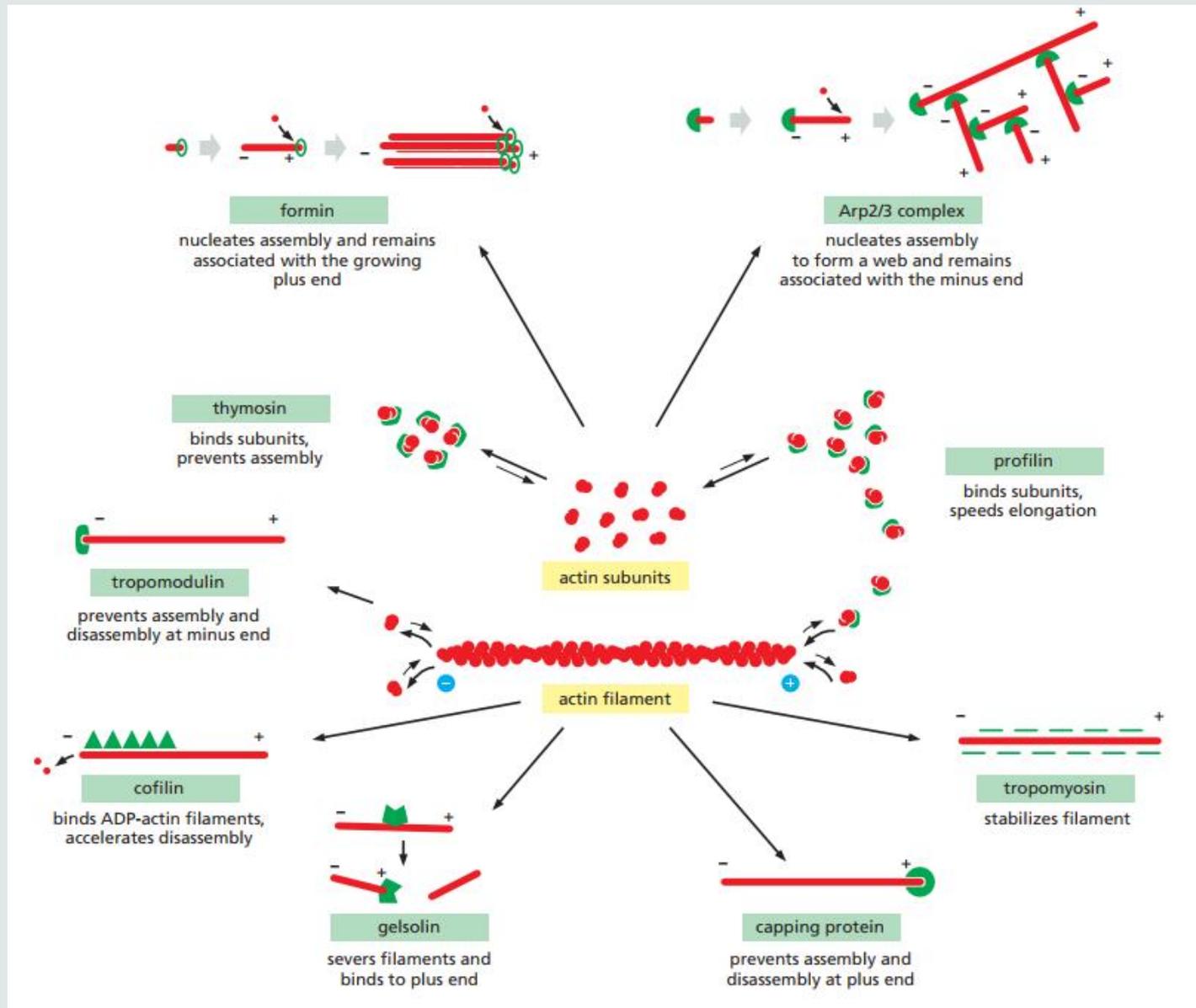


Cell Biology third edition, T. Pollard, W. Earnshaw, Elsevier

# Protéines de liaison à l'actine

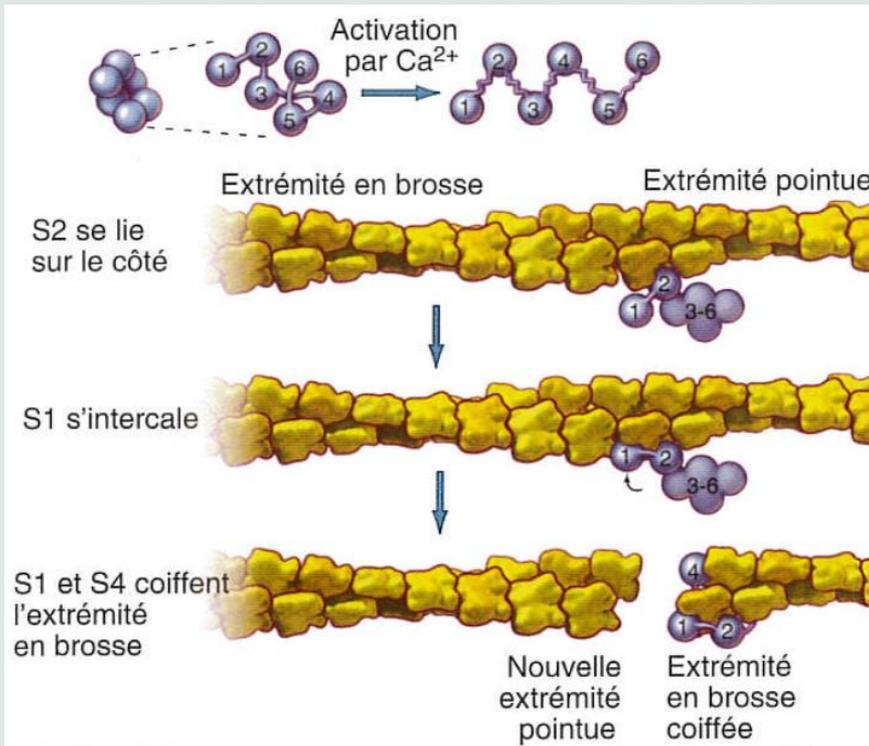


# Protéines de liaison à l'actine



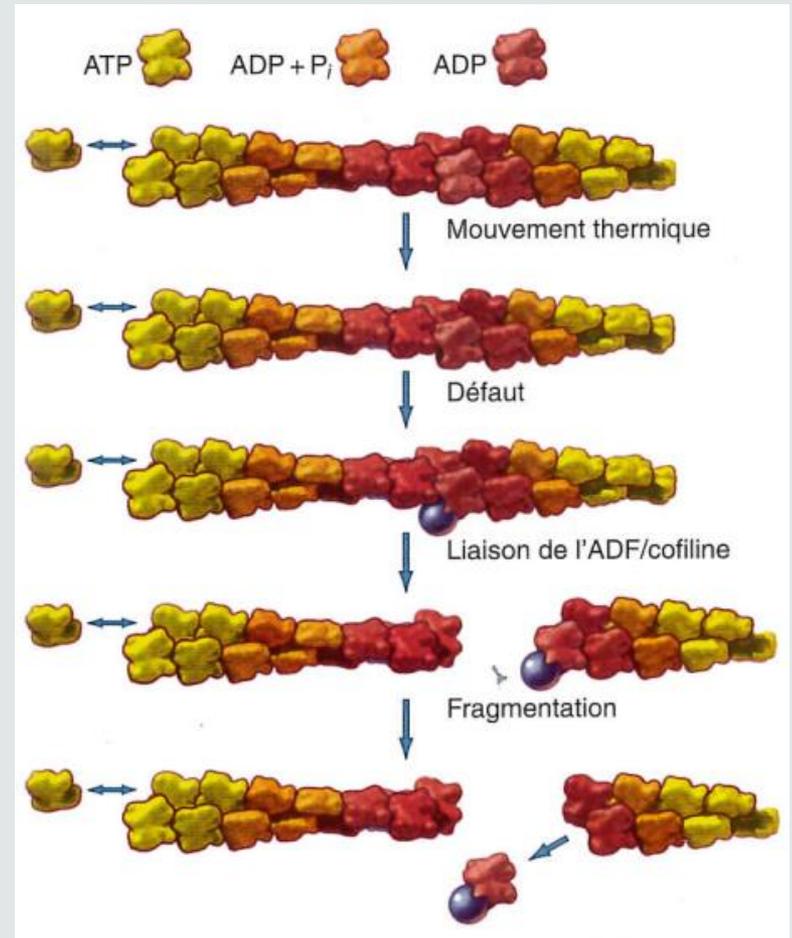
# Clivage des microfilaments

## Clivage et coiffage par la gelsoline



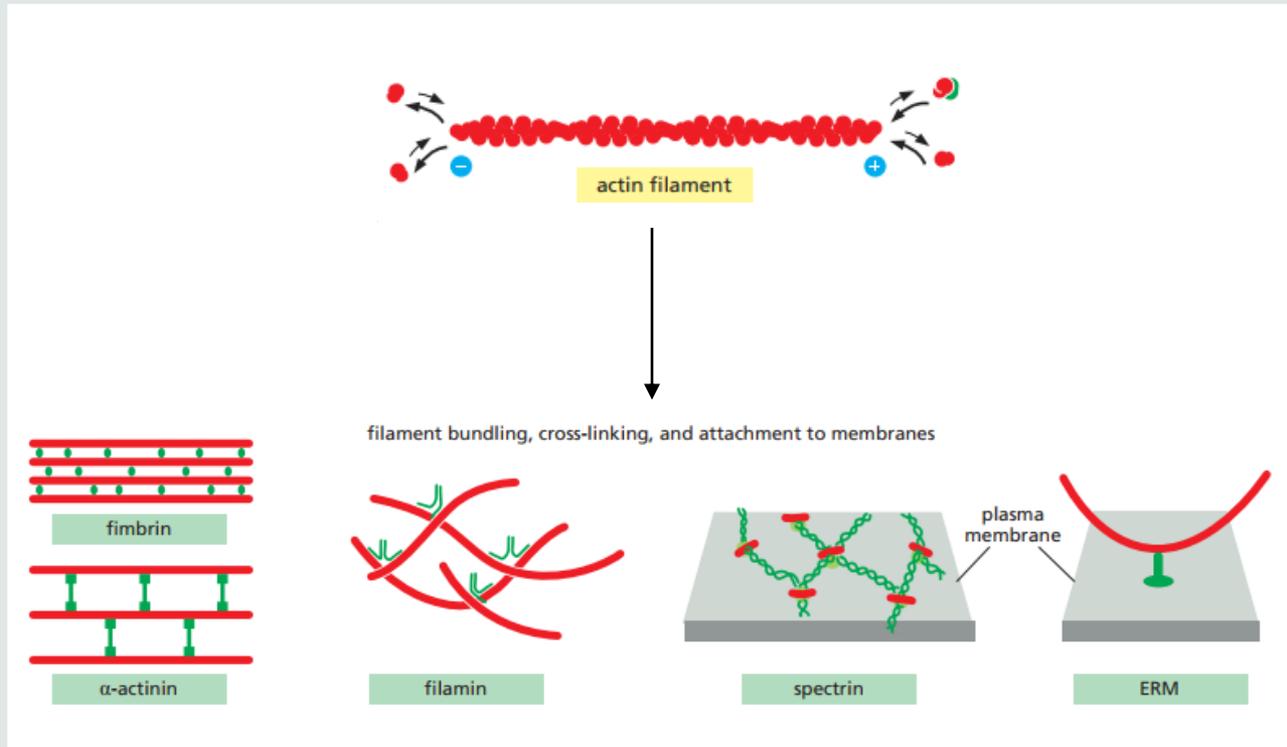
Biologie Cellulaire, T. Pollard, W. Earnshaw, Elsevier

## Clivage par l'ADF/cofiline



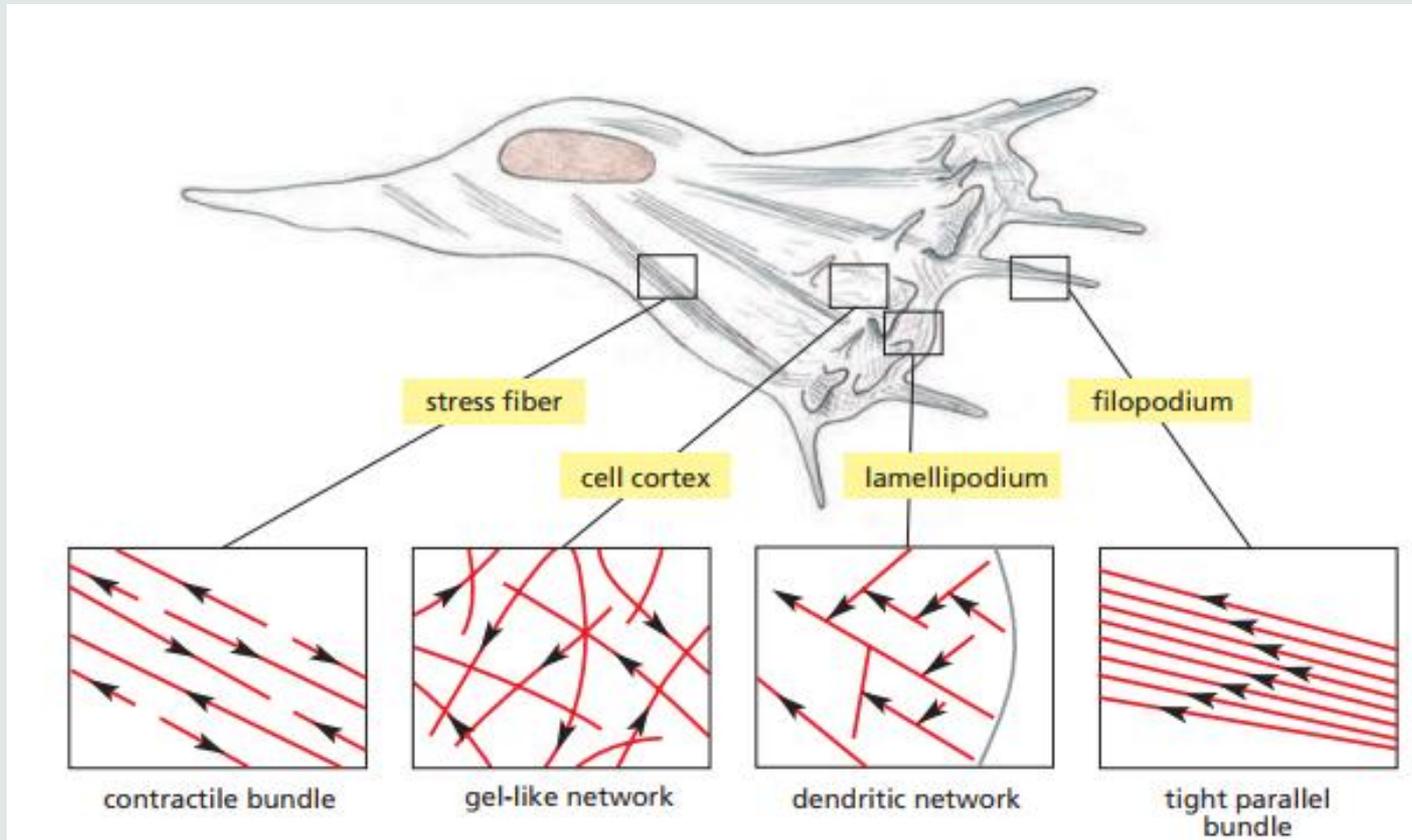
Biologie Cellulaire, T. Pollard, W. Earnshaw, Elsevier

# Protéines de liaison à l'actine



Alberts et al. in *Molecular Biology of the cell*, 6<sup>th</sup> edition, Garland Science

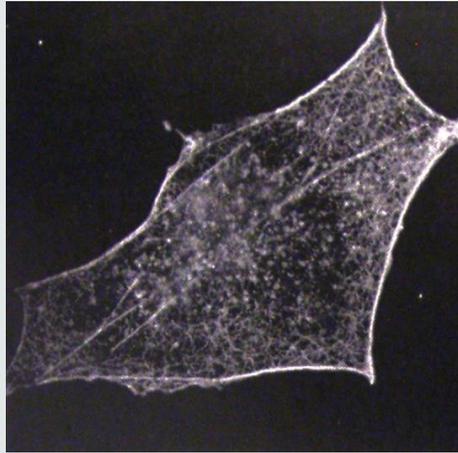
# Différentes organisations des microfilaments dans la cellule



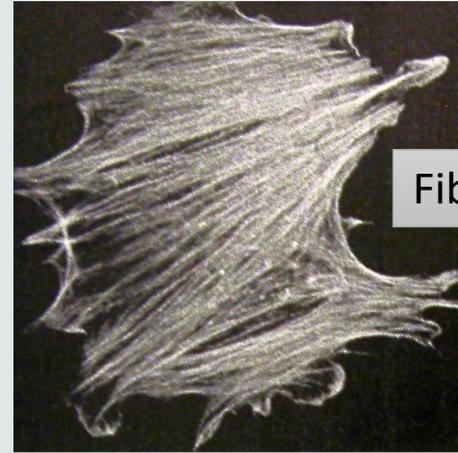
# Organisations des microfilaments

*Contrôle par les petites protéines G de la famille Rho*

Cellule au repos

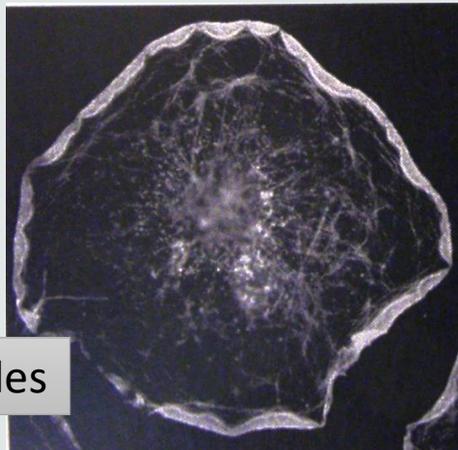


Rho



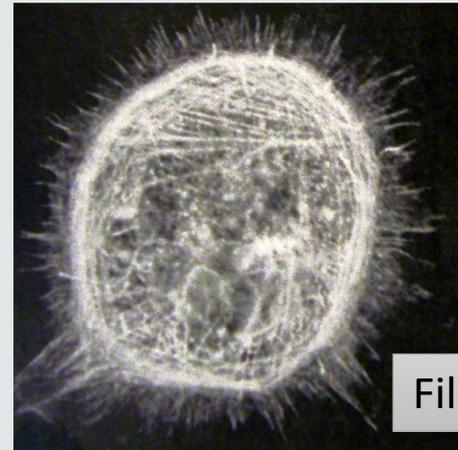
Fibres de stress

Rac



Lamellipodes

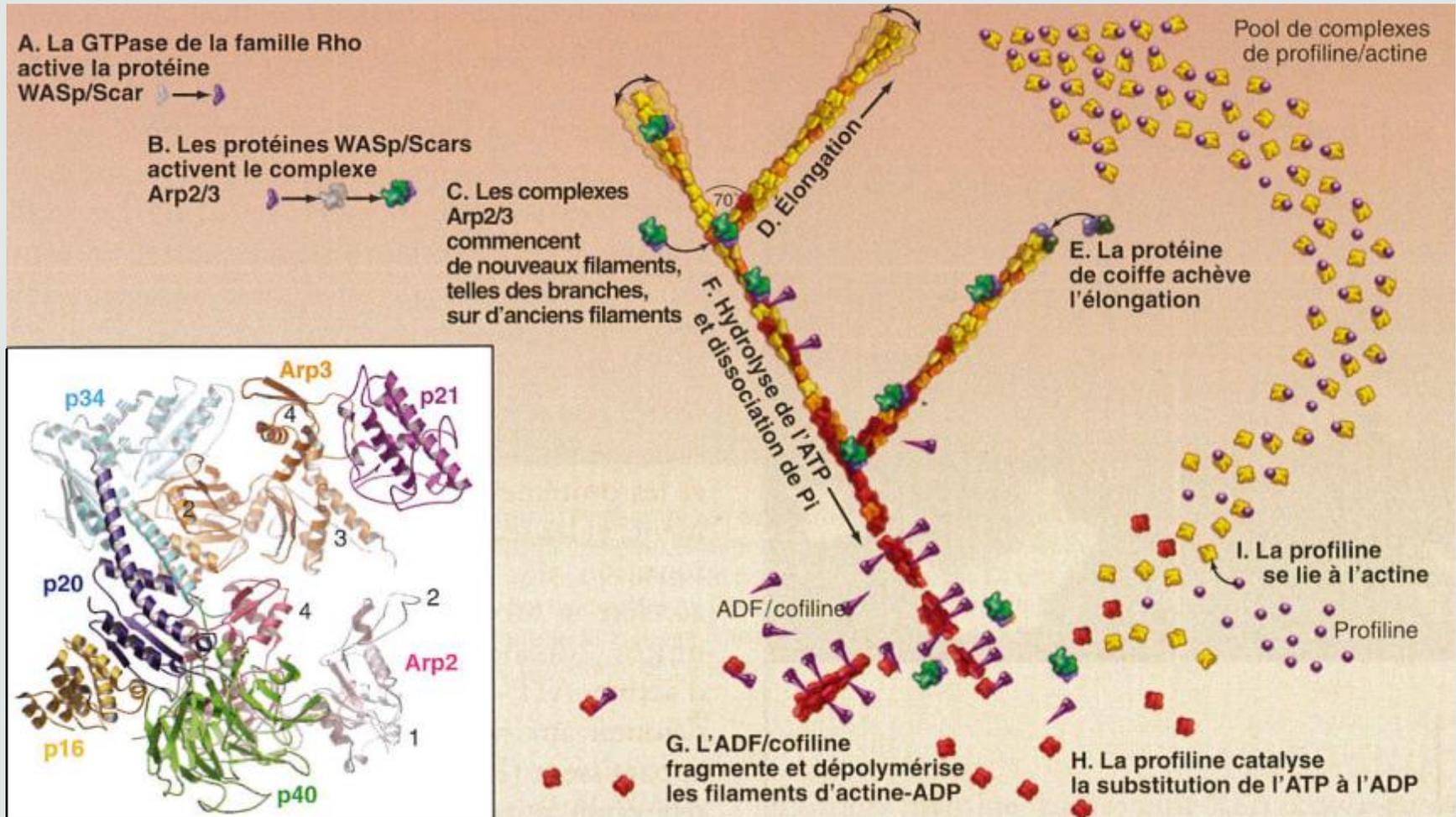
cdc42



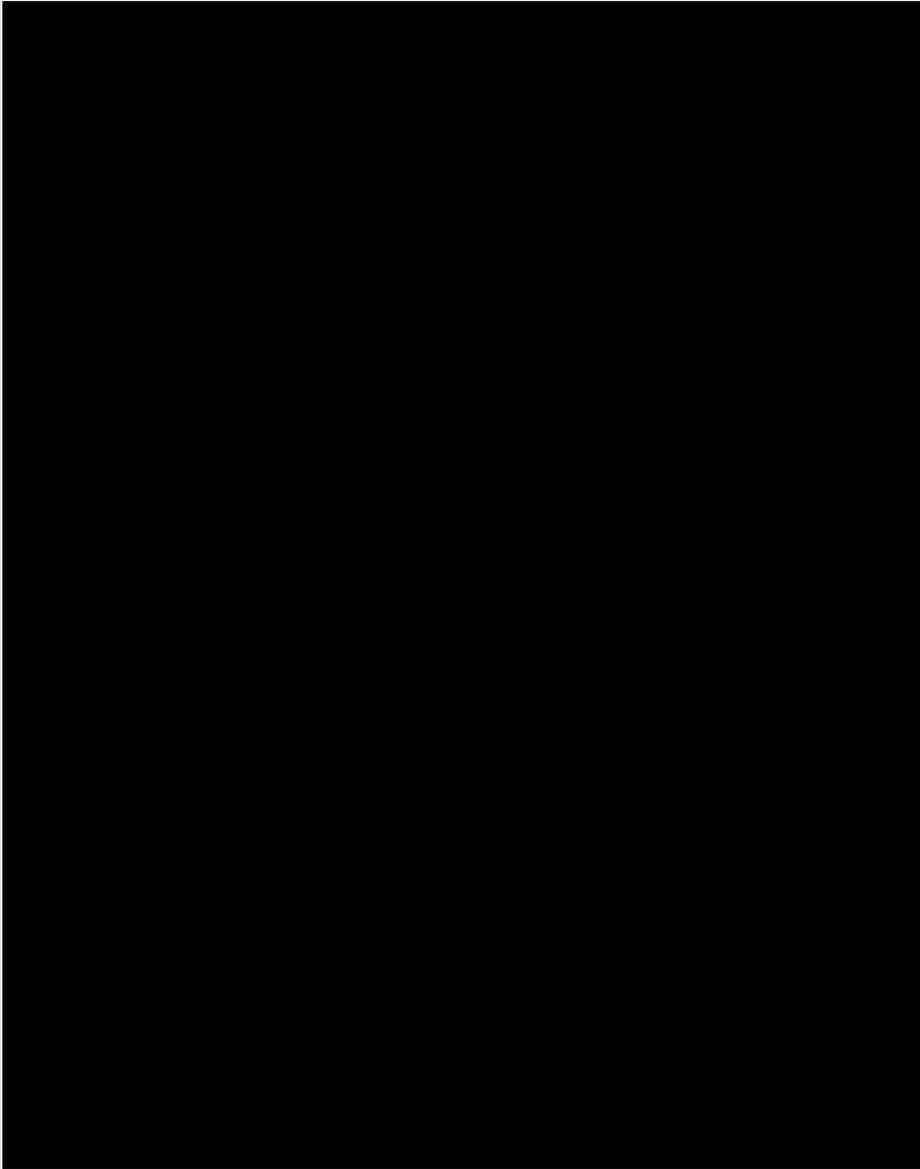
Filopodes

# Nucléation dendritique de l'actine

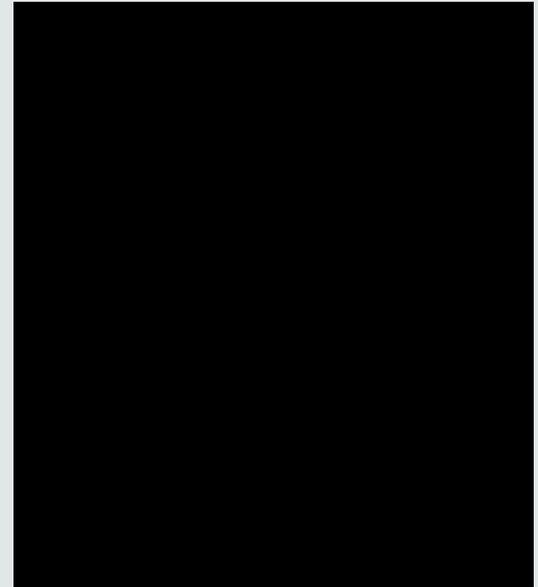
## Formation du lamellipode et migration cellulaire



Dynamique de l'actine-GFP dans une cellule  
en migration

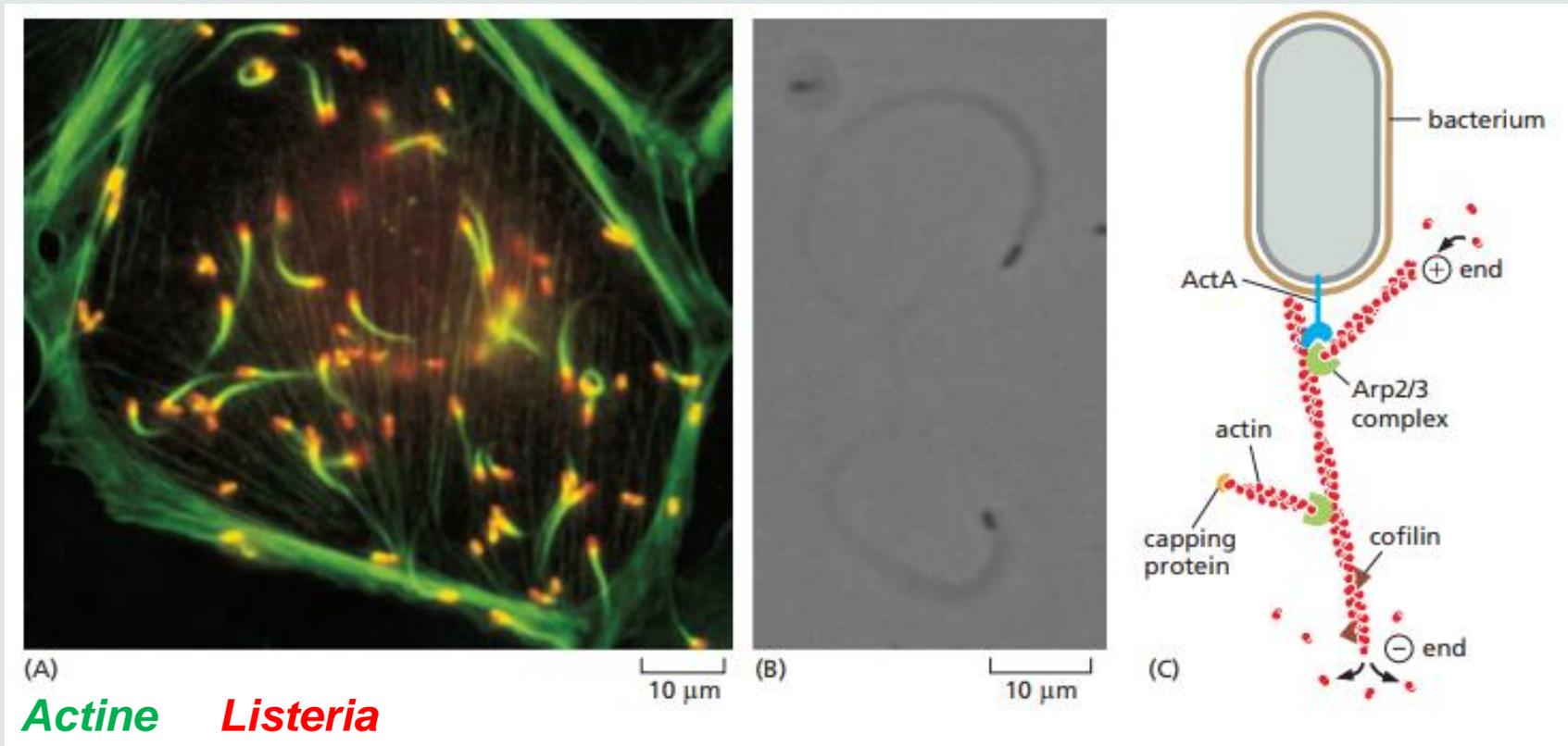


Dynamique de l'actine-GFP dans  
une cellule en cours d'adhésion

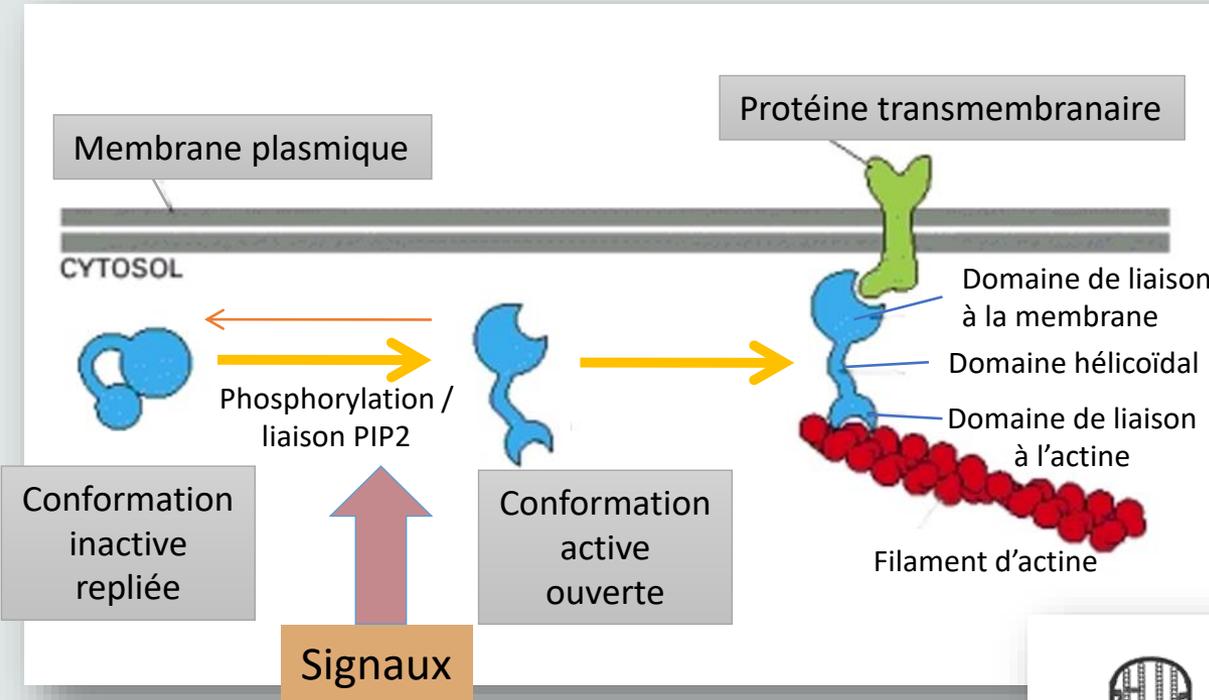


# Détournement des microfilaments par certaines bactéries

*Cellules infectées par Listeria monocytogenes*

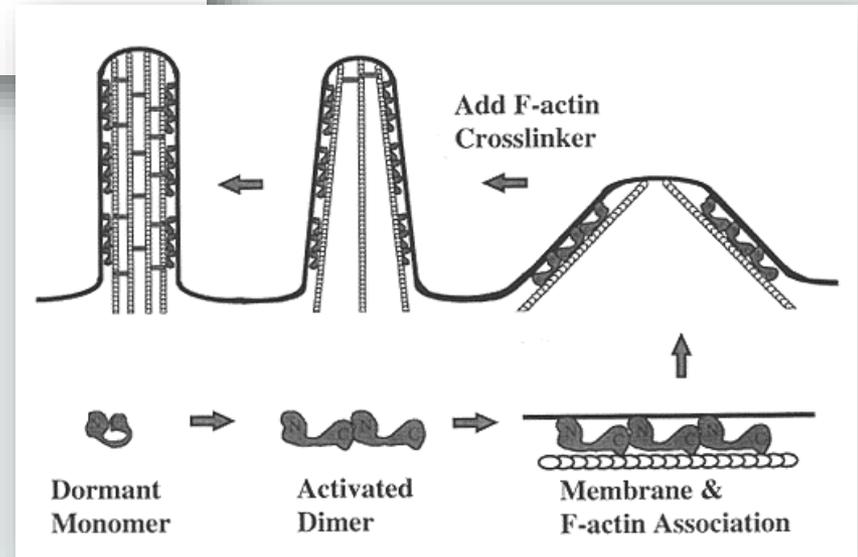


# Liaison des microfilaments à la membrane plasmique

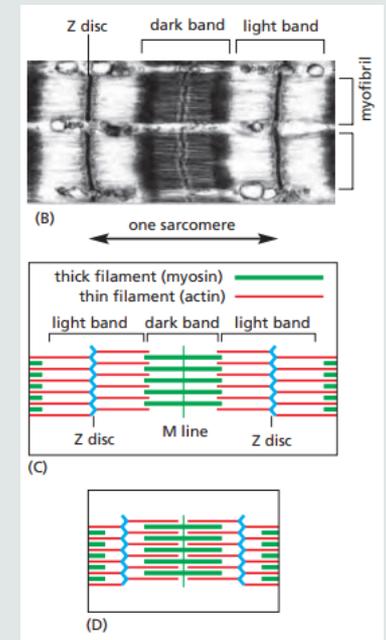
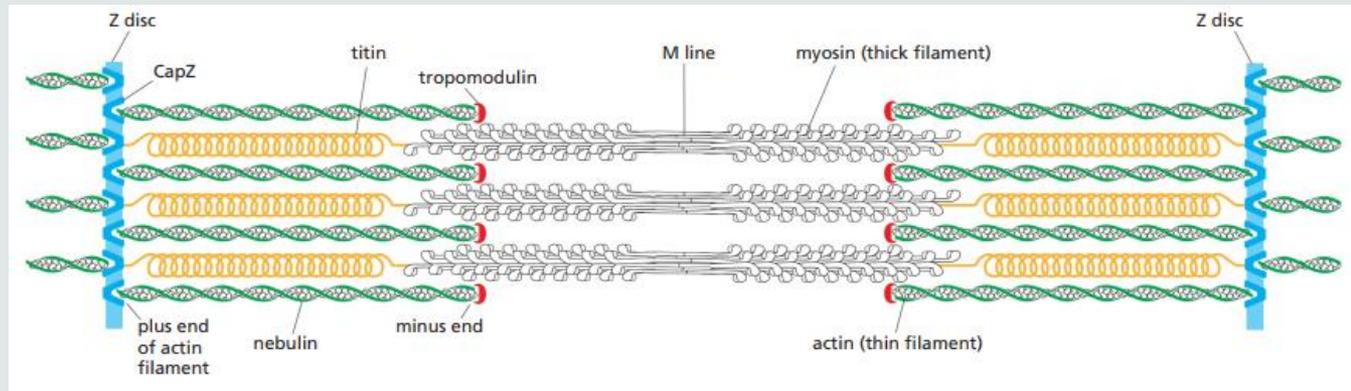
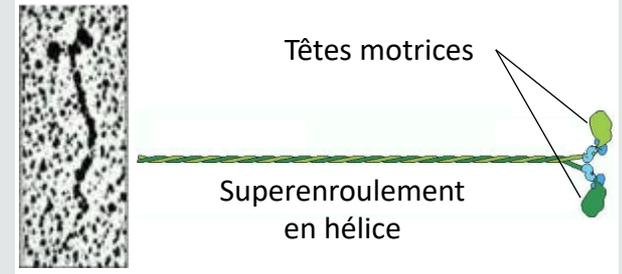
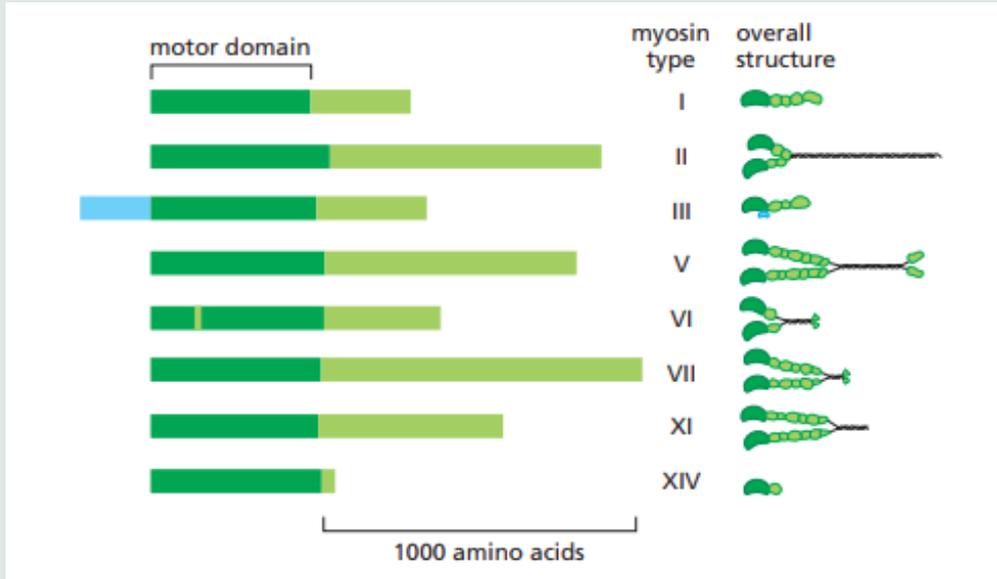


Protéines ERM :  
Ezrine, Radixine  
Moesine

Alberts et al., in *Biologie Moléculaire de la cellule*, 4<sup>e</sup> édition, Flammarion Médecine Sciences



# Myosines



# Myosines

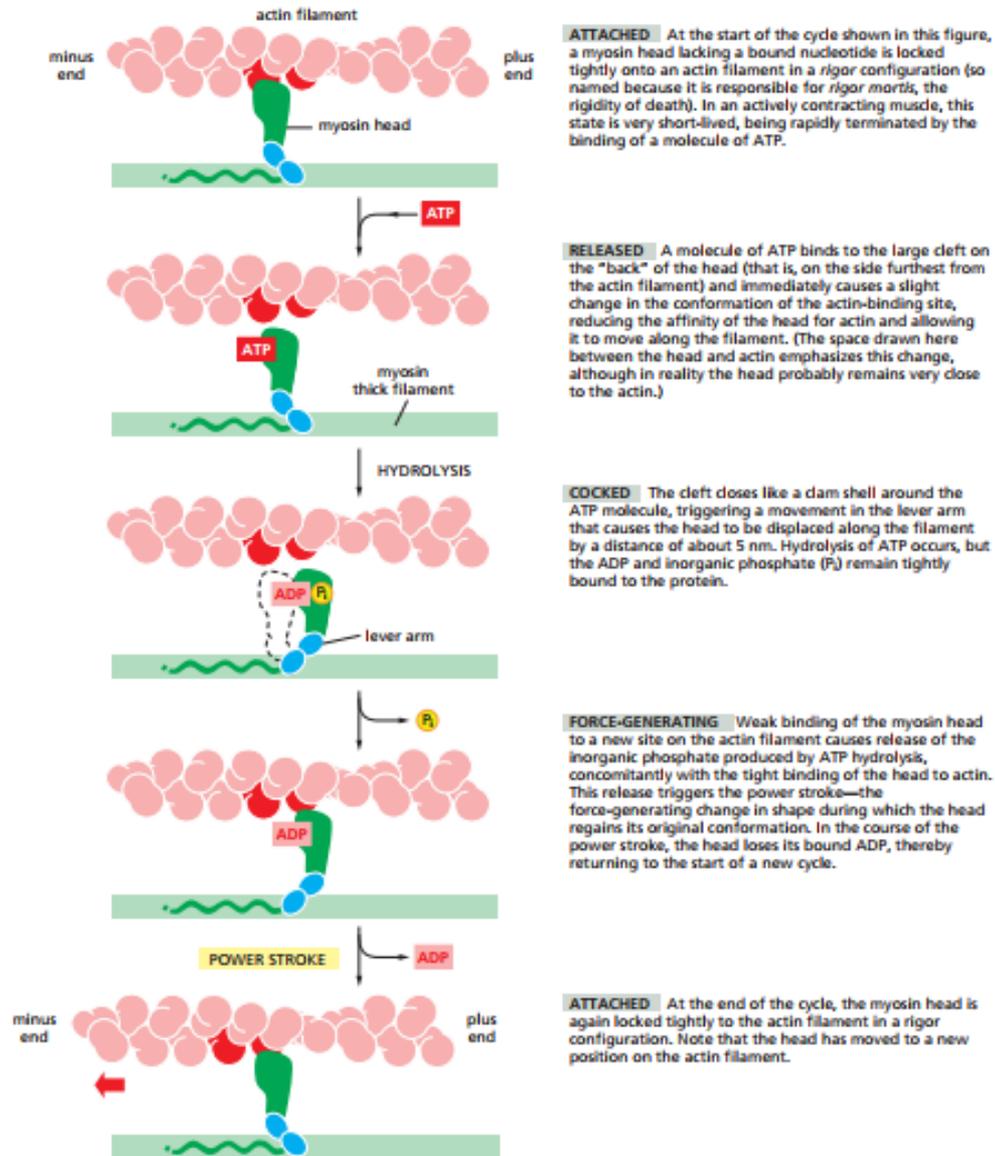


Figure 16-29 The cycle of structural changes used by myosin II to walk along an actin filament. In the myosin II cycle, the head remains bound to the actin filament for only about 5% of the entire cycle time, allowing many myosins to work together to move a single actin filament (Movie 16.3). (Based on I. Rayment et al., *Science* 261:50-58, 1993.)