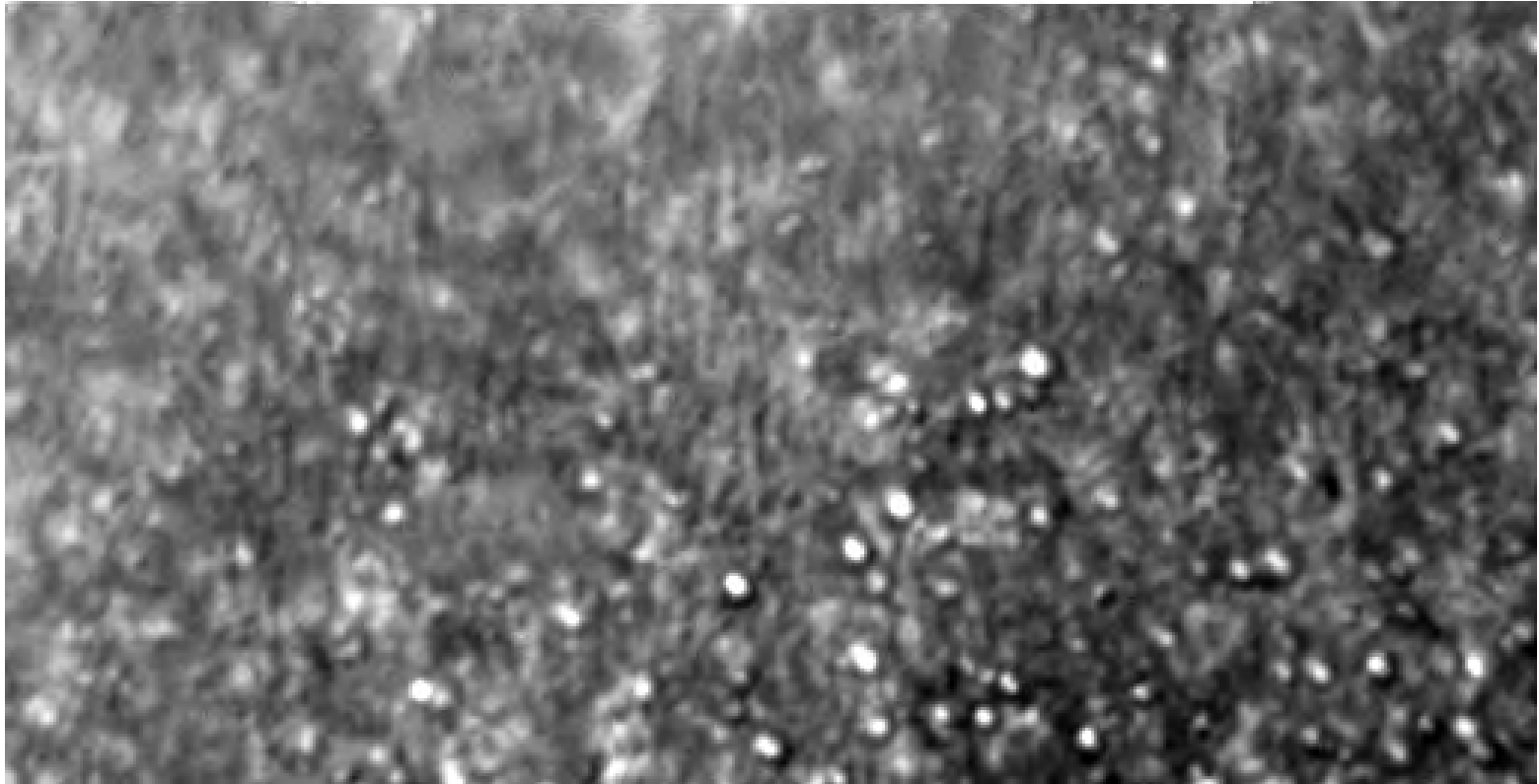


Fluid Physiology Networks in the Brain



Eberhard Bodenschatz
Max Planck Institute for Dynamics and Self-Organization, Göttingen

Venice: perfection of a fluid-based economy



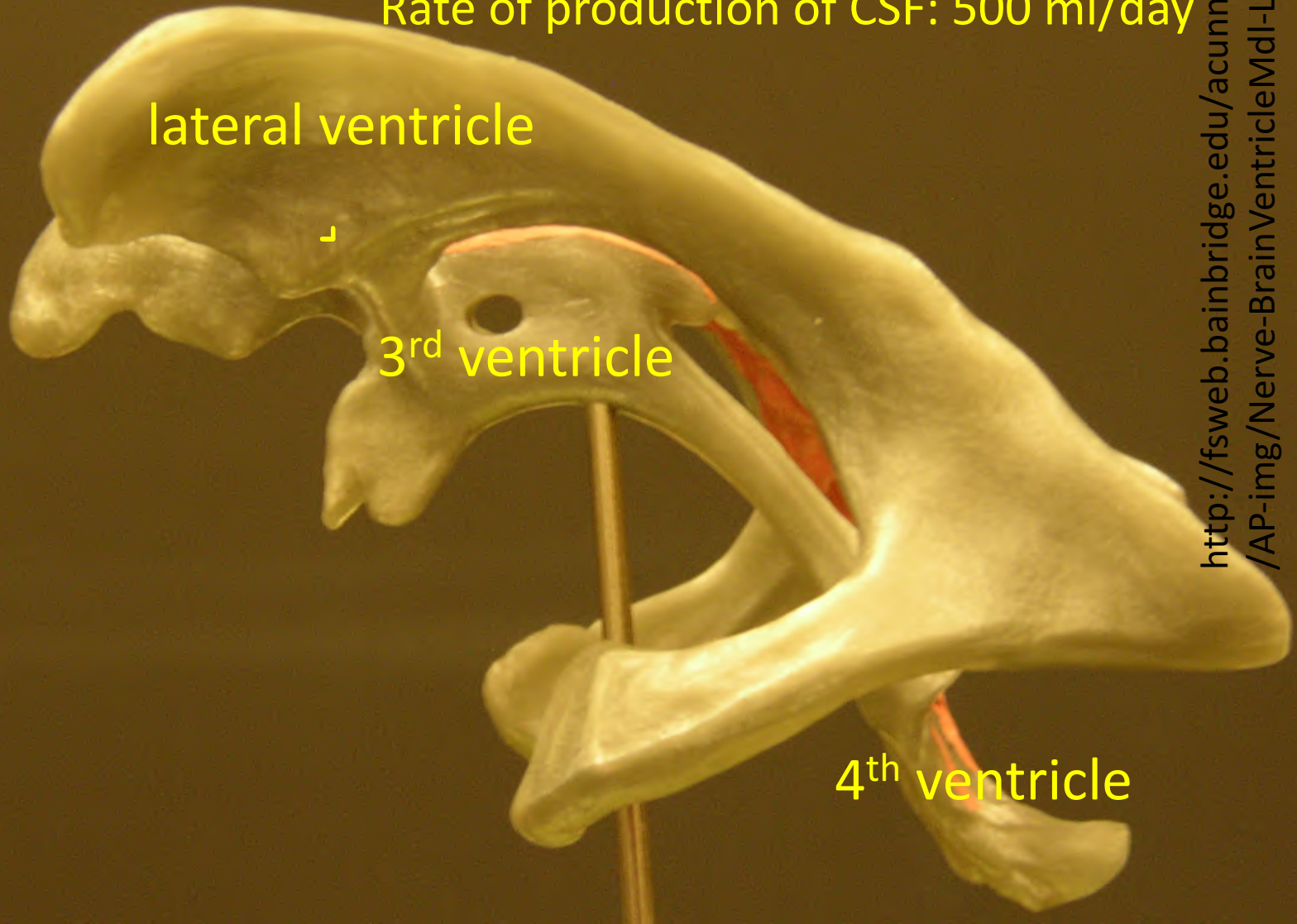
procurement
distribution
disposal

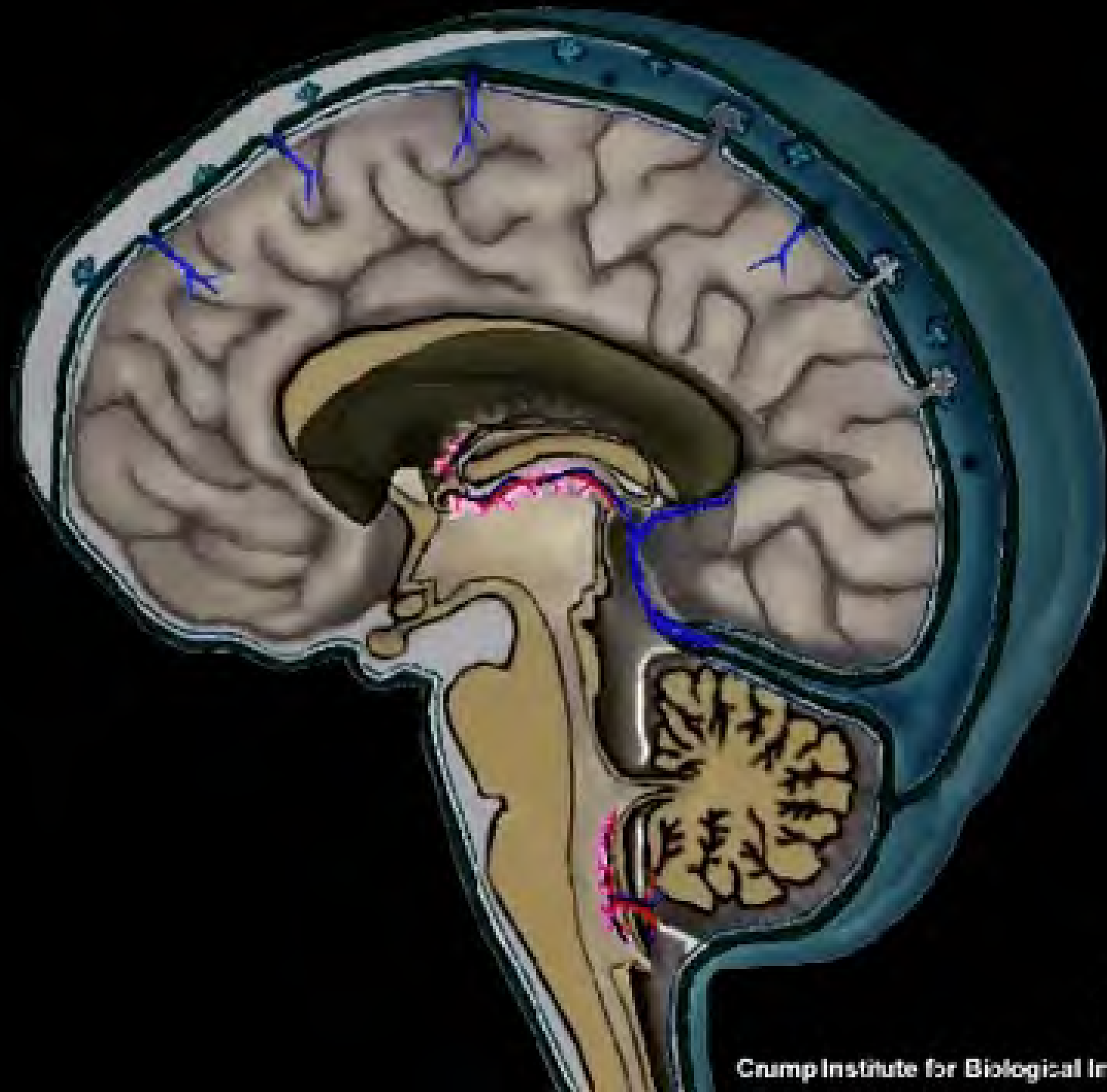
Human brain ventricles are fluid-filled

CSF: 125-150 ml

Turnover 3 to 4 times per day

Rate of production of CSF: 500 ml/day



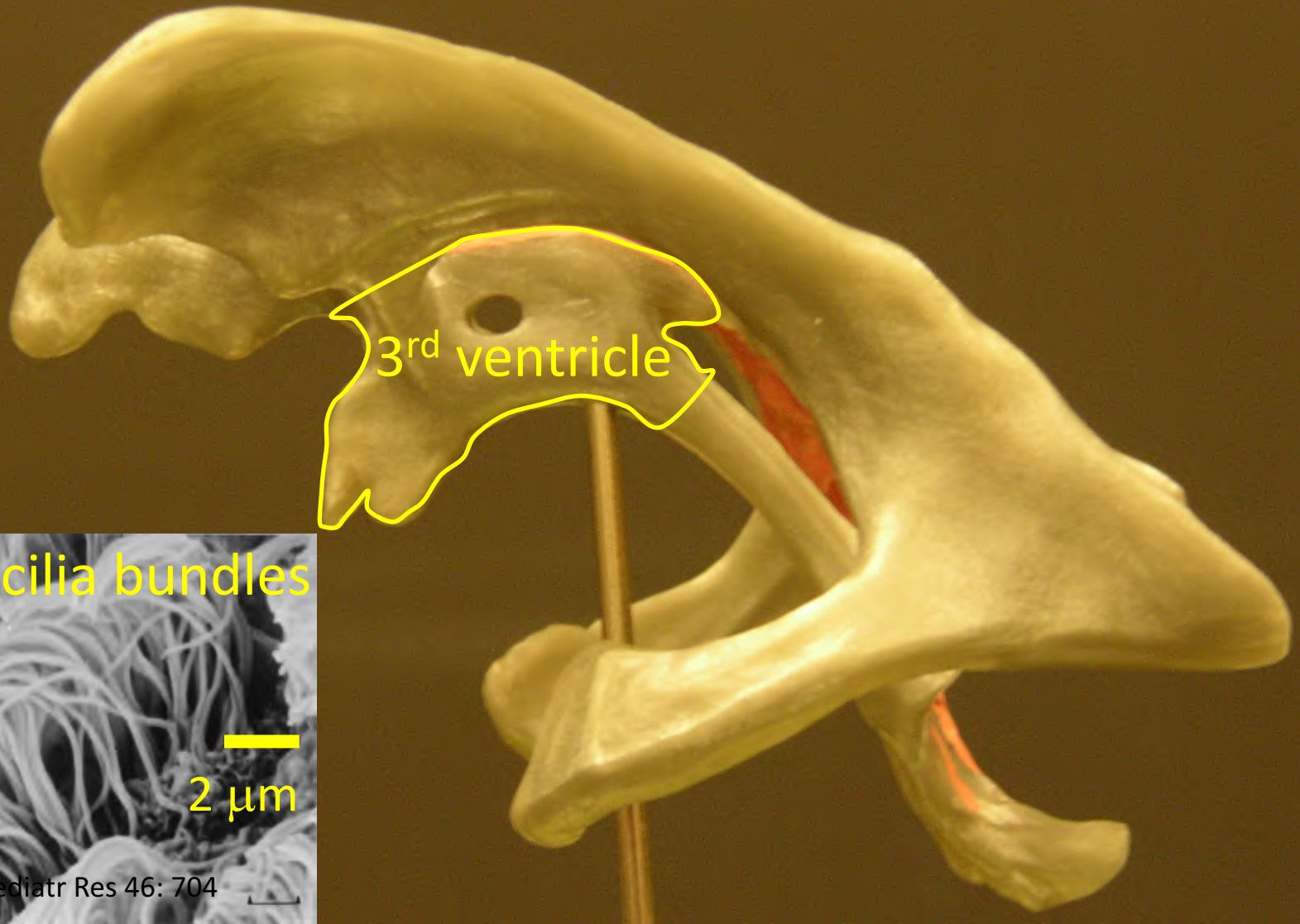


Composition of CSF

The brain produces roughly 500 mL of cerebrospinal fluid per day. This fluid is constantly reabsorbed, so that only 100-160 mL is present at any one time.

Cerebrospinal Fluid Substances

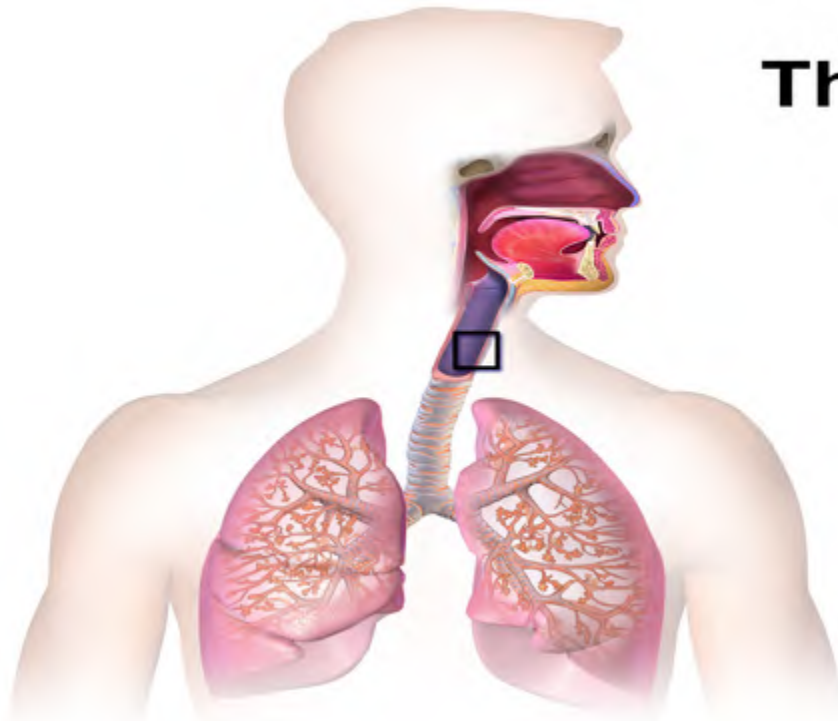
Water Content (%)	99
Glucose (mg/dL)	60
Sodium (mEq/L)	138
Potassium (mEq/L)	2.8
Calcium (mEq/L)	2.1
Magnesium (mEq/L)	0.3
Chloride (mEq/L)	119
Protein (mg/dL)	35; proteome: about 3,000 types, >1,000 belong to secretome



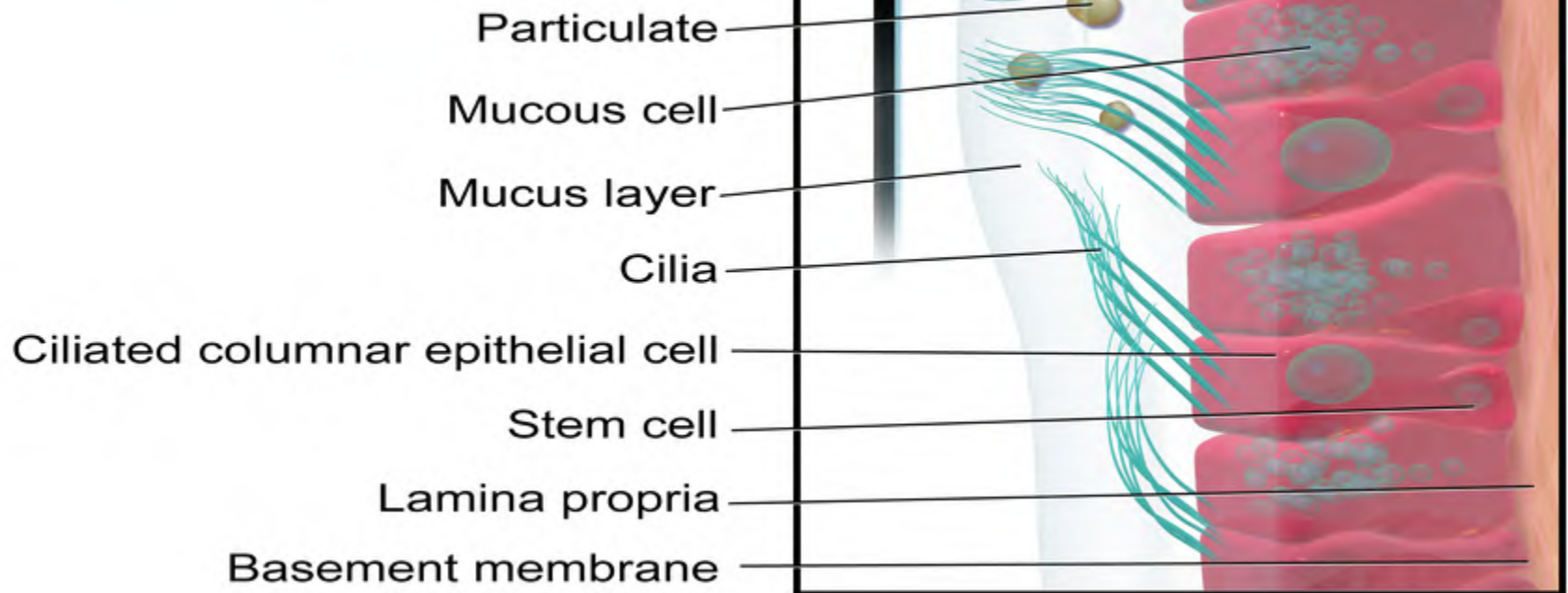
lined with cilia bundles

2 μm

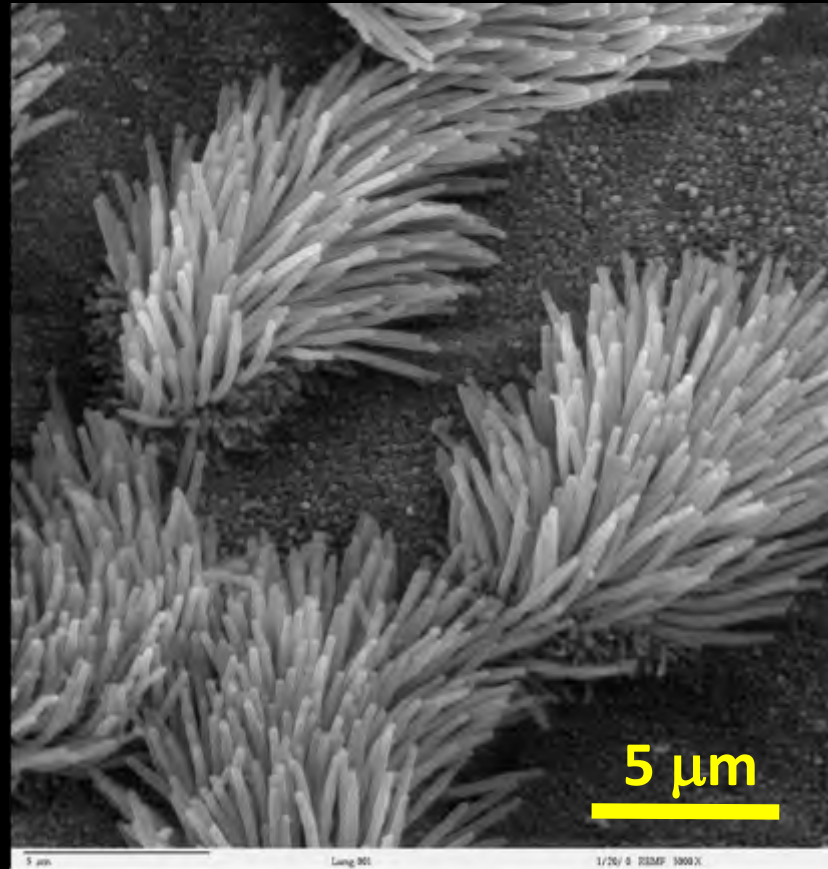
The Respiratory Epithelium



Movement of mucus to the pharynx



Cilia in the trachea



A R C H I V
F Ü R
ANATOMIE, PHYSIOLOGIE

UND
WISSENSCHAFTLICHE MEDICIN,
IN VERBINDUNG MIT MEHREREN GELEHRTEN

HERAUSGEGEBEN

VON

DR. JOHANNES MÜLLER,

ORD. ÖFFENTL. PROF. DER ANATOMIE UND PHYSIOLOGIE, DIRECTOR DES
KÖNIGL. ANATOM. MUSEUMS UND ANATOM. THEATERS ZU BERLIN,
MITGLIED DER KÖNIGL. ACADEMIE DER WISSENSCHAFTEN.

JAHRGANG 1836.

MIT FÜNFZEHN KUPFERTAFELN.

BERLIN.

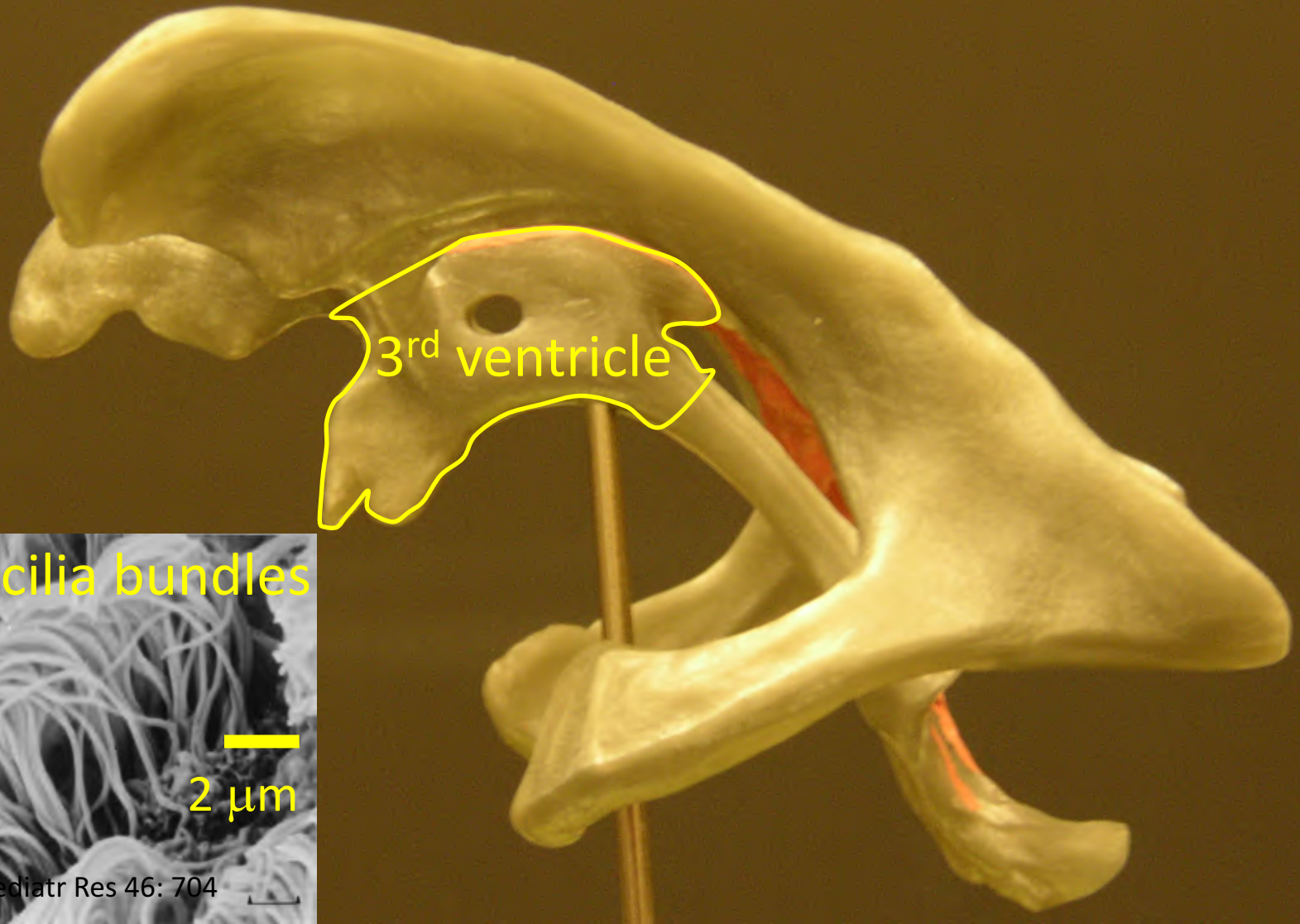
IM VERLAG VON G. EICHLER.

Flimmerbewegungen im Gehirn.

Von *Purkinje.*

Endlich ist es mir gelungen, die Wimperhaare und ihre Bewegungen auch in den gesammten Hirnhöhlen der Säugethiere zu entdecken. Nachdem ich schon im vorjährigen Sommer bei Untersuchung der Bergmannschen Chorden an feinen Schnitten des Epithelium eine den Flimmermembranen ähnliche Structur gefunden und somit ähnliche Function an diesem Epithelium vermuthet hatte, auch vielfach in dieser Hinsicht, jedoch vergebens, Untersuchungen angestellt, gelang es mir endlich (den 28. Mai) die Flimmerbewegungen an einem sehr wohl bewollten, ziemlich reifen Schaffötus und zwar den andern Tag nach dem Schlachten, etwa nach 30 Stunden, am Rande der Fimbria des gerollten Wulstes in der schönsten Activität zu entdecken. Nun waren sie auch ganz klar an allen Wandungen der Hirnhöhlen zu sehen, und

Die Wimpern sind verhältnissmässig lang zugespitzt (nicht lappig, wie sonst in der Luftröhre) und vibriren peitschenförmig; man unterscheidet auch eine Schichte von Körnern, in denen sie befestigt sind und die sehr leicht sich abstreift, ohne dass die Continuität des Epithelium verloren geht. Den andern Tag untersuchte ich ein Schöpsengehirn, wo sie eben auch leicht aufzufinden waren. Auch an einem ziemlich reifen Schweinefötus stellte sie Dr. Valentin sogleich dar. An einem viel frühern Schweinefötus war nichts zu unterscheiden: wahrscheinlich sind die Theile zu zart für unsere groben Werkzeuge. Ueberhaupt konnte ich schon bei diesen wenigen Untersuchungen sehen, dass die Wimperhaare der Hirnböhlen viel empfindlicher und zerstörbarer sind, als die irgend eines andern Gebildes. Eben so wenig konnte ich sie in dem Gehirn eines Sperlings, eines Karpfen wahrnehmen, woraus jedoch über ihre Nicht-



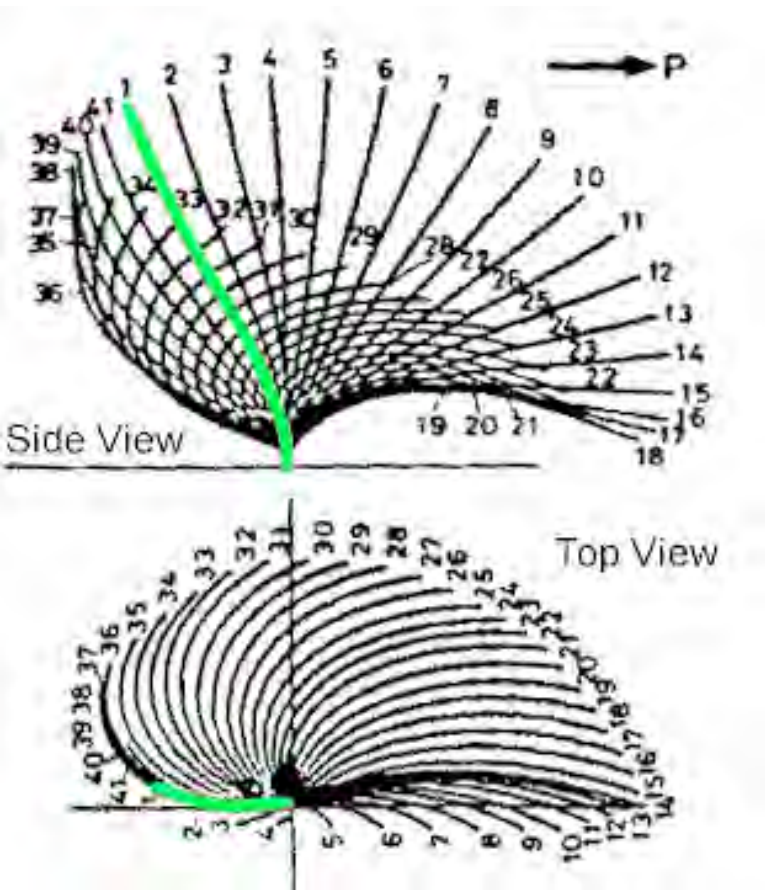
lined with cilia bundles

Cilia movement in the 3rd ventricle



slow motion movie

Cilia movement



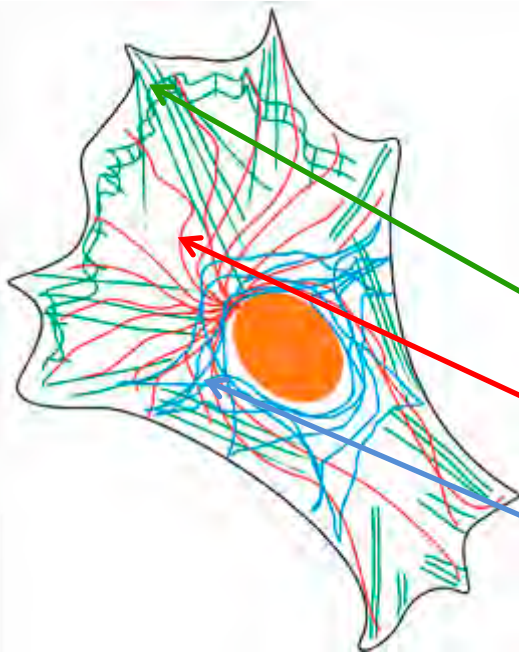
basics



What are microtubules?

Cells have to

- organize themselves in space and interact mechanically with their environment.
- rearrange their internal components as they grow, divide, and adapt to changing circumstances



CYTOSKELETON

Actin filaments

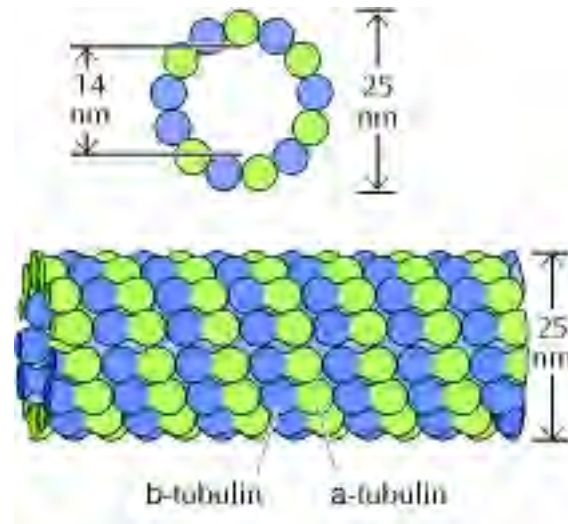
Microtubules

Intermediate filaments

microtubules

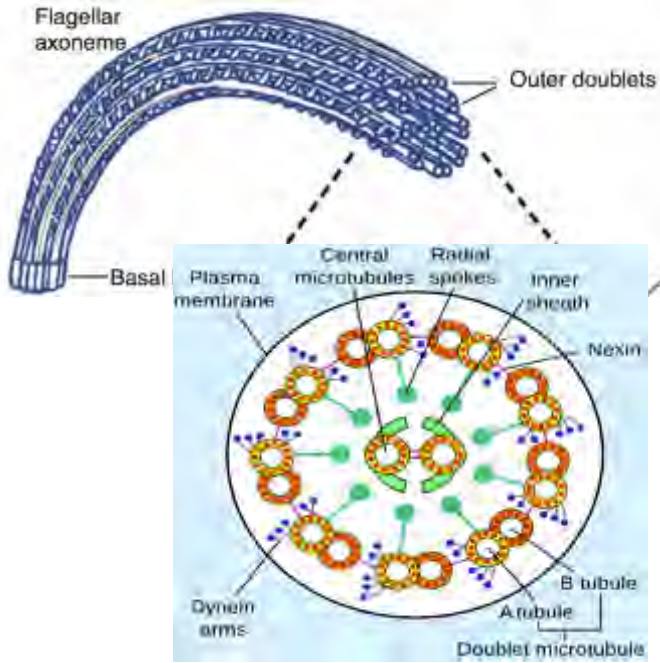


Microtubules are linear polymers of tubulin which is a globular protein. Tubulin is a dimer consisting of two polypeptides, α - and β -tubulin



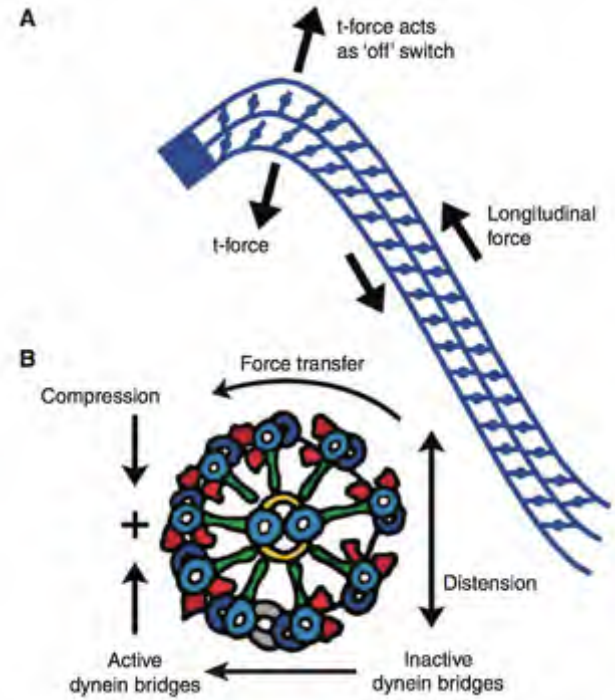
Microtubules are dynamic structures that undergo continual assembly and disassembly within the cell.

Cilia structure



50nm

The internal cytoskeletal arrangement of a cilium is composed of nine doublet microtubules in a ring surrounding a pair of single microtubules.

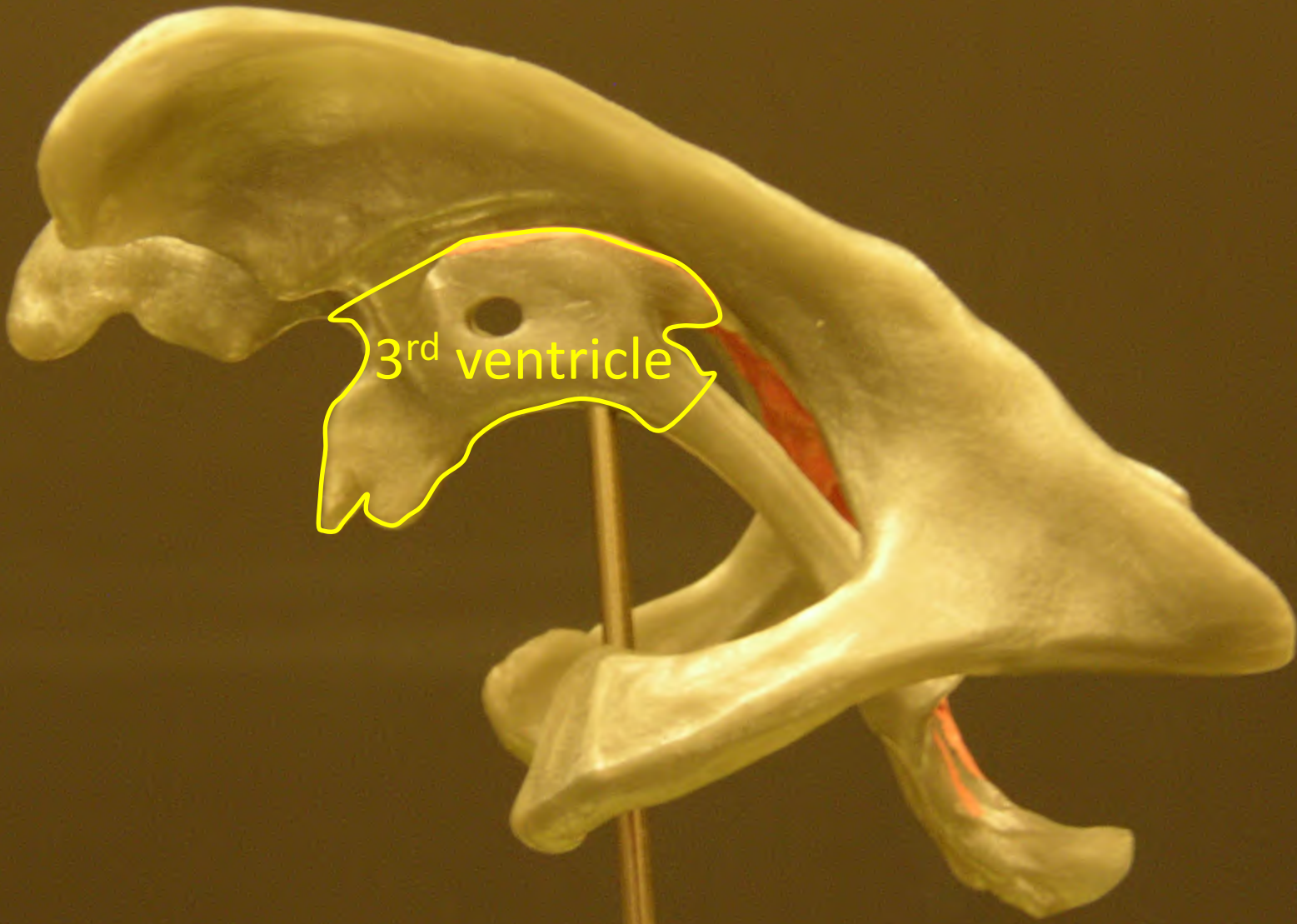


Dynein motor : ATP hydrolysis

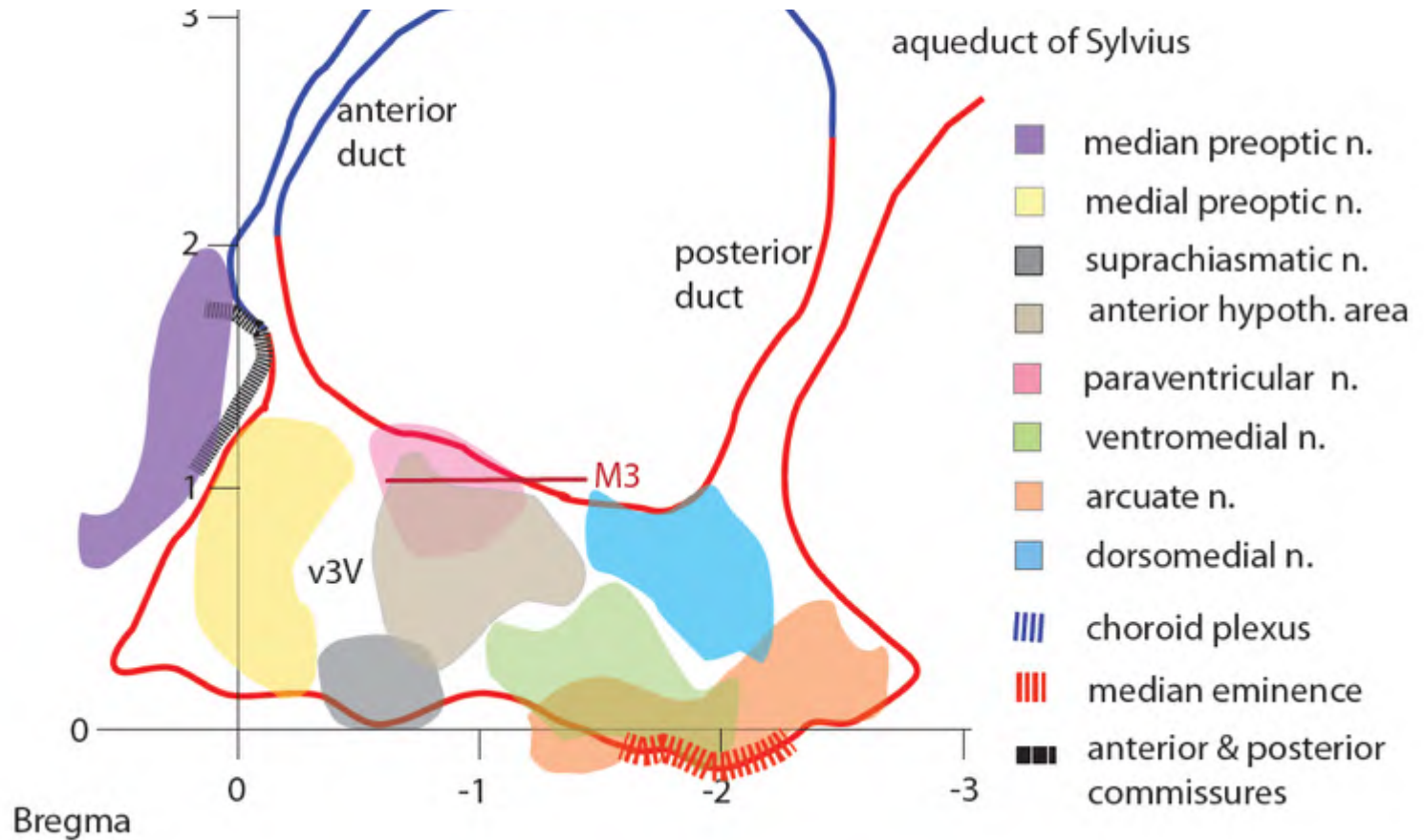


Linear movement along a microtubule

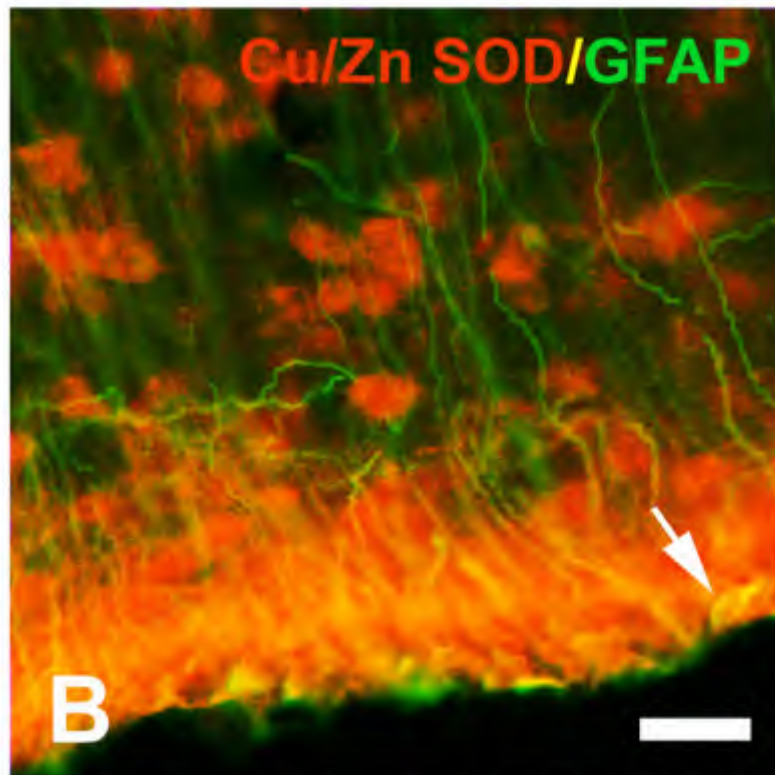
Return to the brain



- What is around the appendix of the 3rd ventricle



Tanycytes extend deep into the hypothalamus. It is proposed that their function is to transfer signals from the cerebrospinal fluid to the hypothalamic nuclei and vice versa.



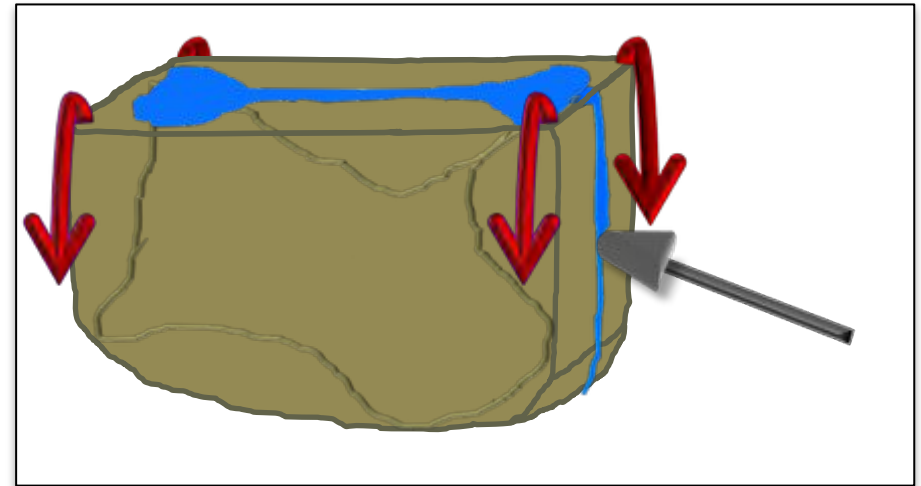
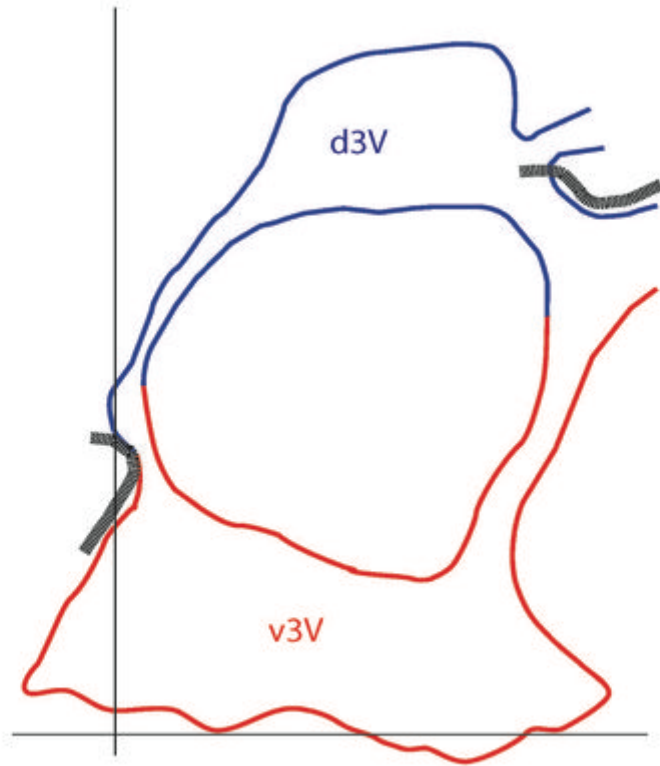
- junctions between the ependymal cells are permeable, CSF components diffuse from the ventricles into the central nervous system.

Peluffo et al. Journal of Neuroinflammation
2005 2:12 doi:10.1186/1742-2094-2-12

Flow may transport signals directionally

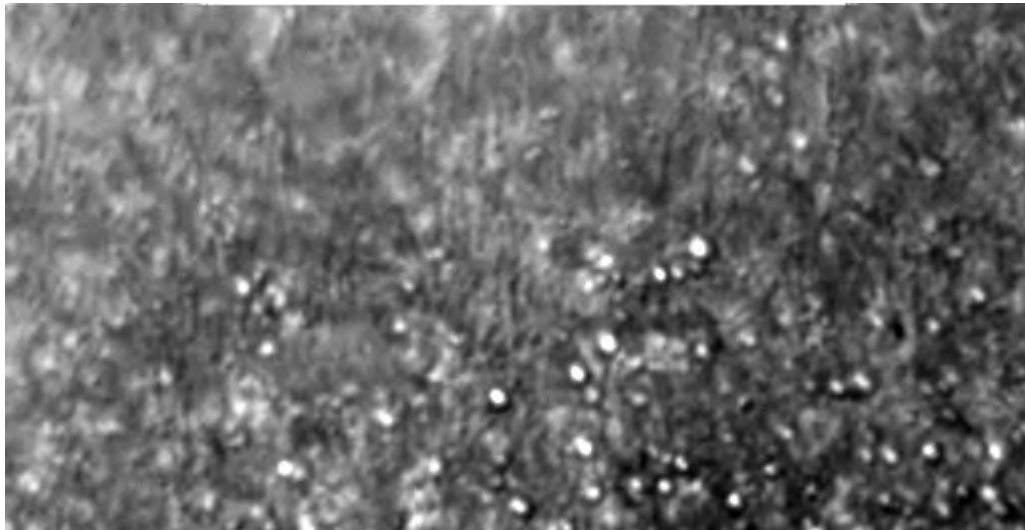
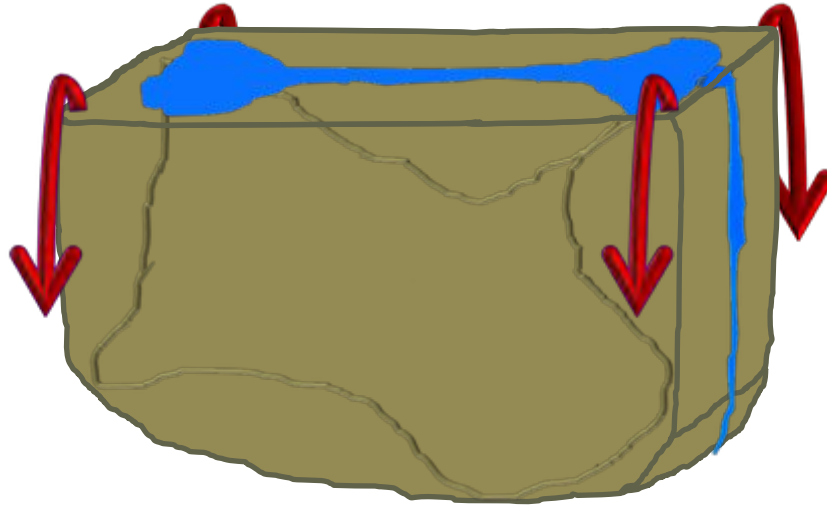
Fluid flow in the 3rd ventricle

Looking at the 3rd ventricle using flat-mounts

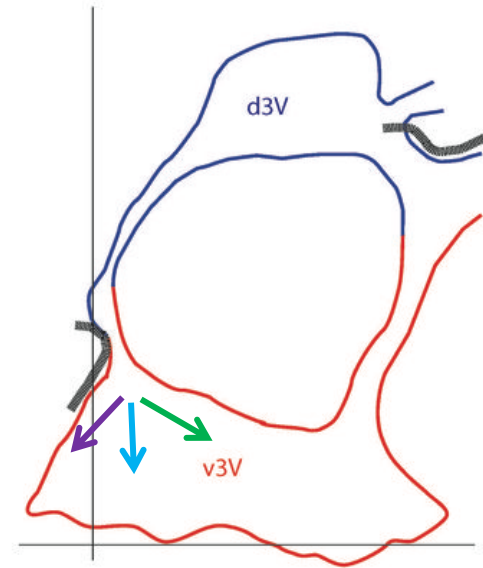
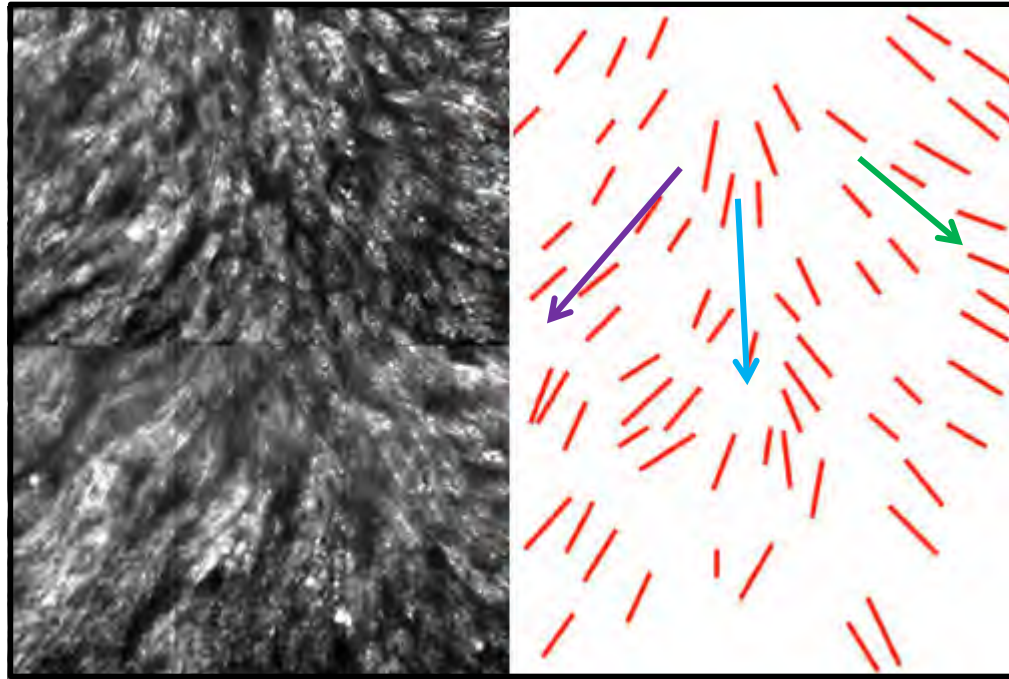


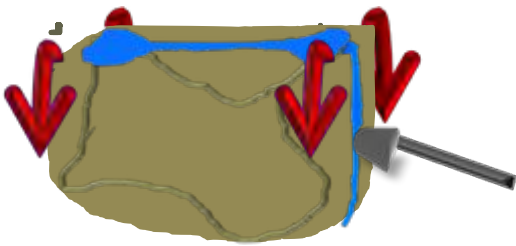
ventral part of the 3rd ventricle
is flattened

open book



Cilia beating and flow correlate at v3V entrance





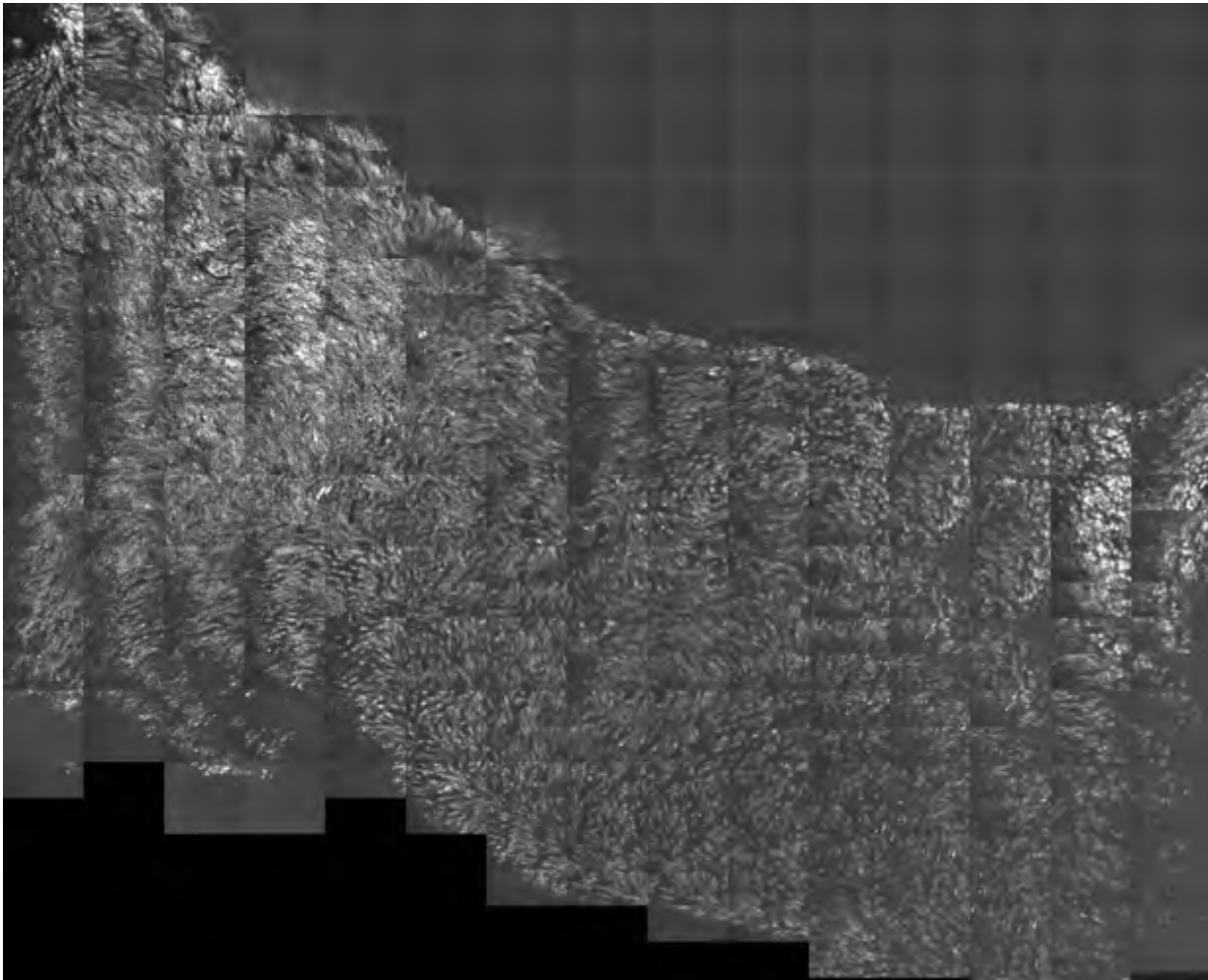
preparation



50 fps, 500 frames/movie



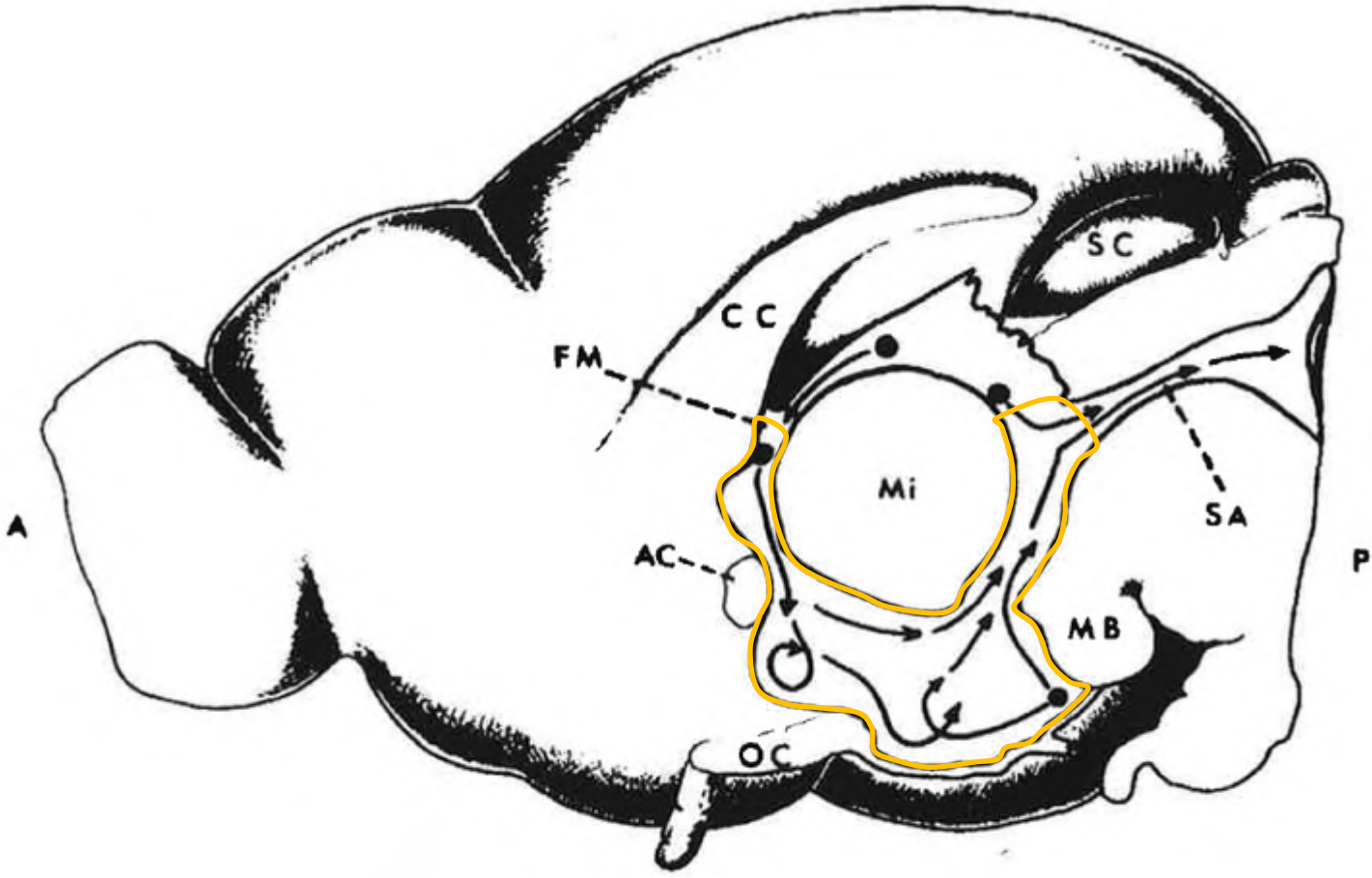
Mosaic of all regions



Ciliary Movement in the Rat Cerebral Ventricles: Clearing Action and Directions of Currents

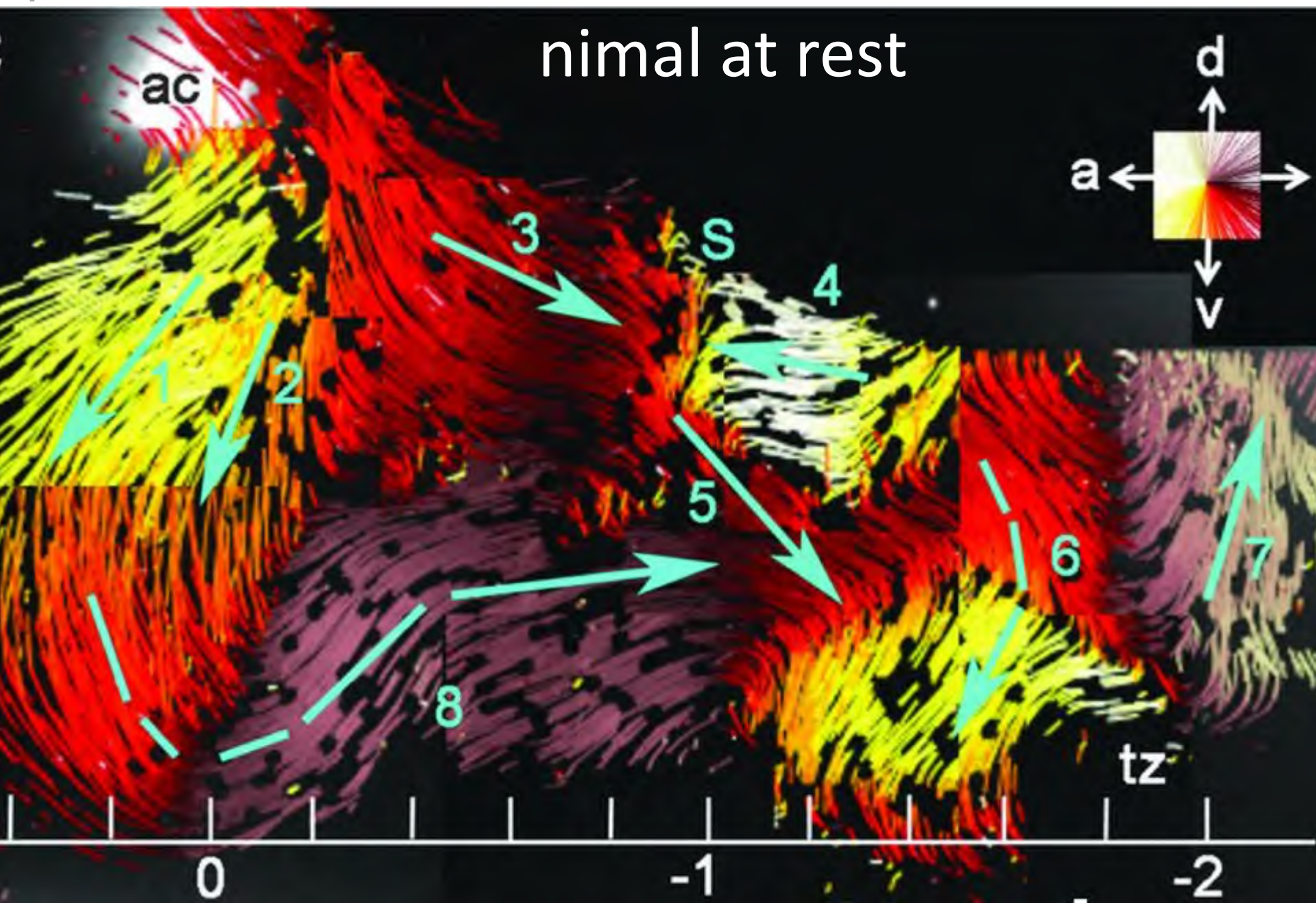
Robert S. Cathcart III B.A., W. Curtis Worthington Jr. M.D. DOI:

<http://dx.doi.org/10.1097/00005072-196410000-00003> 609-618 1 October 1964

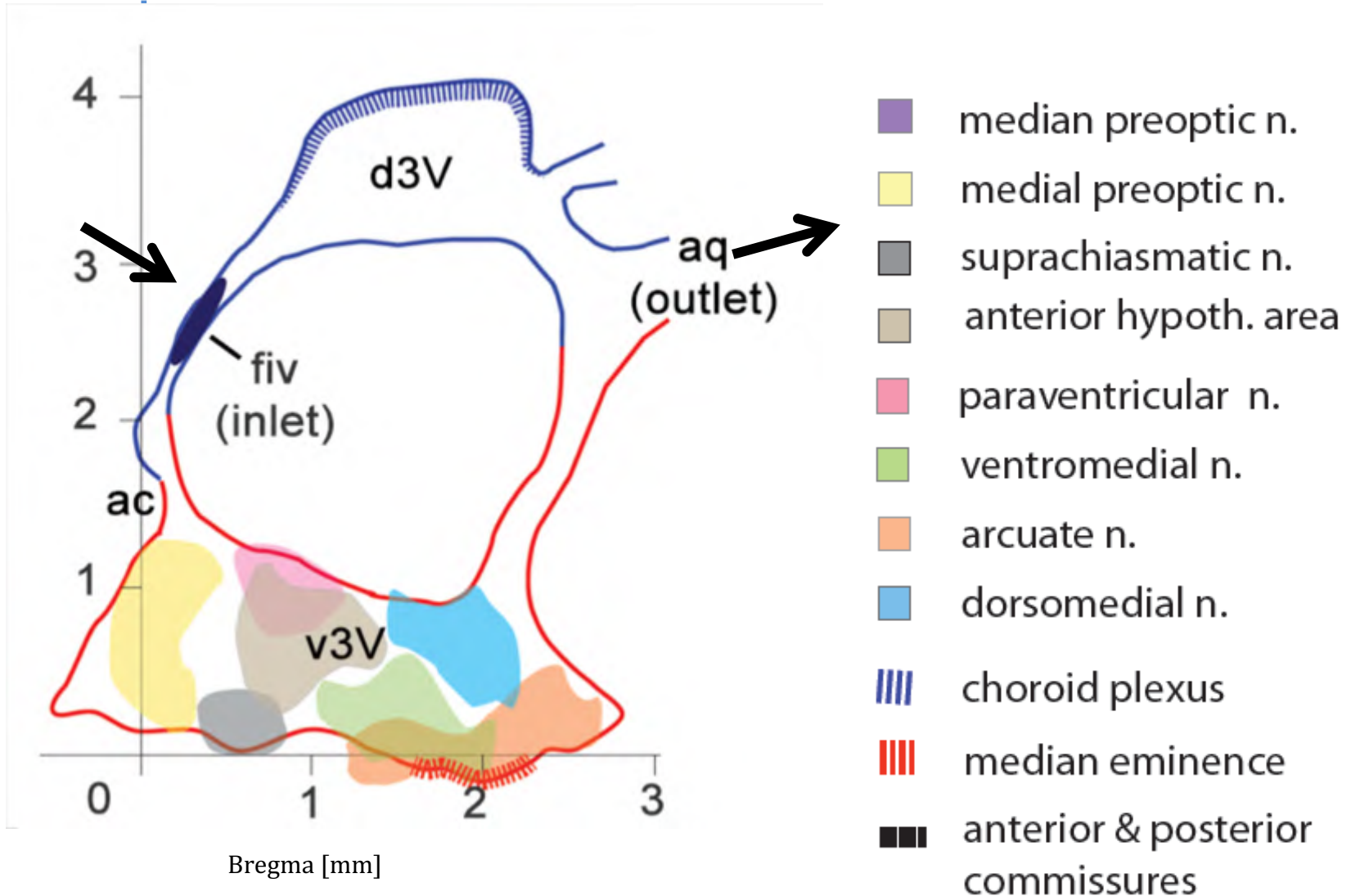


Third Ventricle

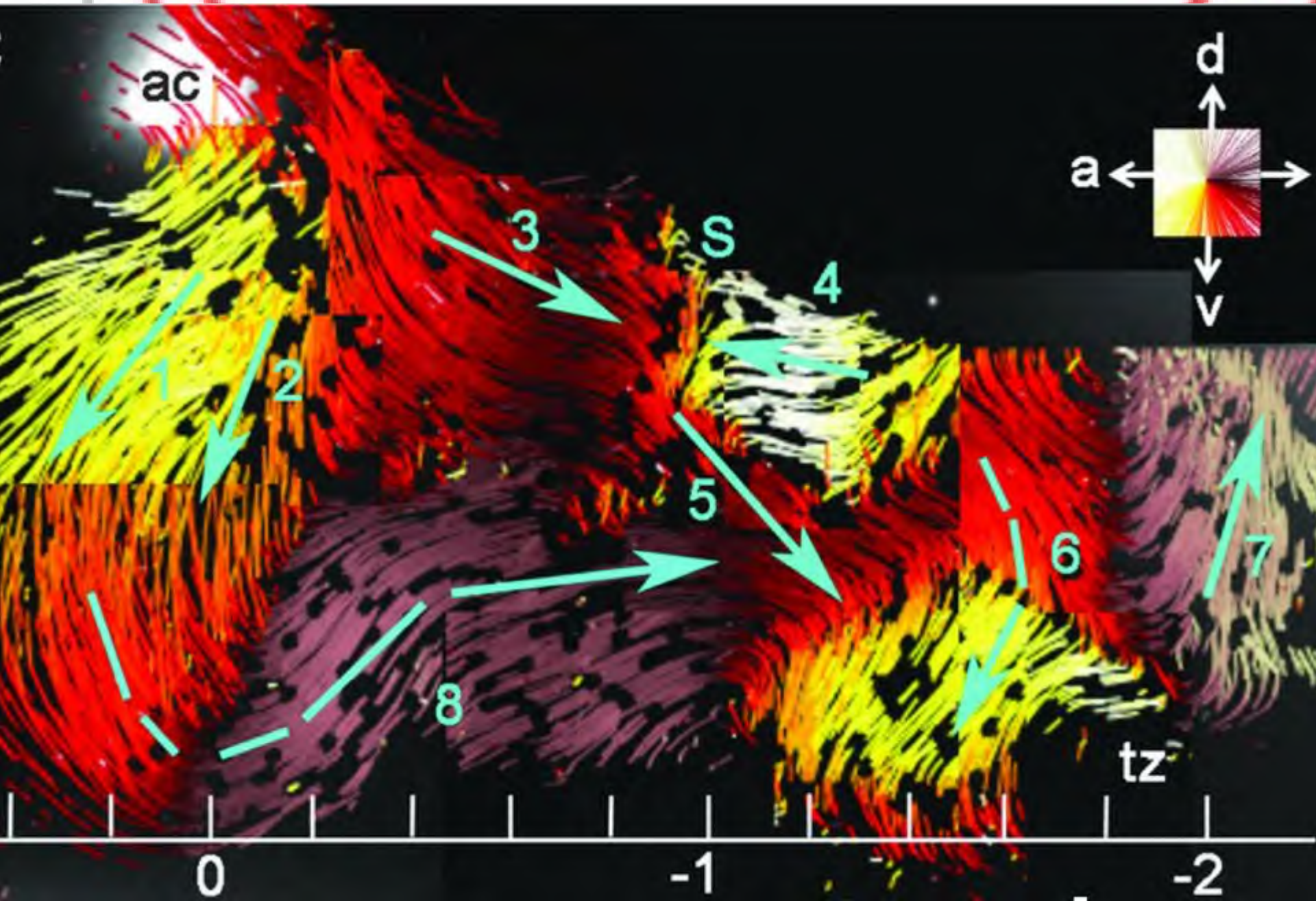
flow pattern



Architecture of the 3rd ventricle and nearby hypothalamic nuclei



Movement by particle tracking in flat-mounts of the 3rd ventricle



animal at rest

ac

a

b

c

1

2

3

4

5

6

7

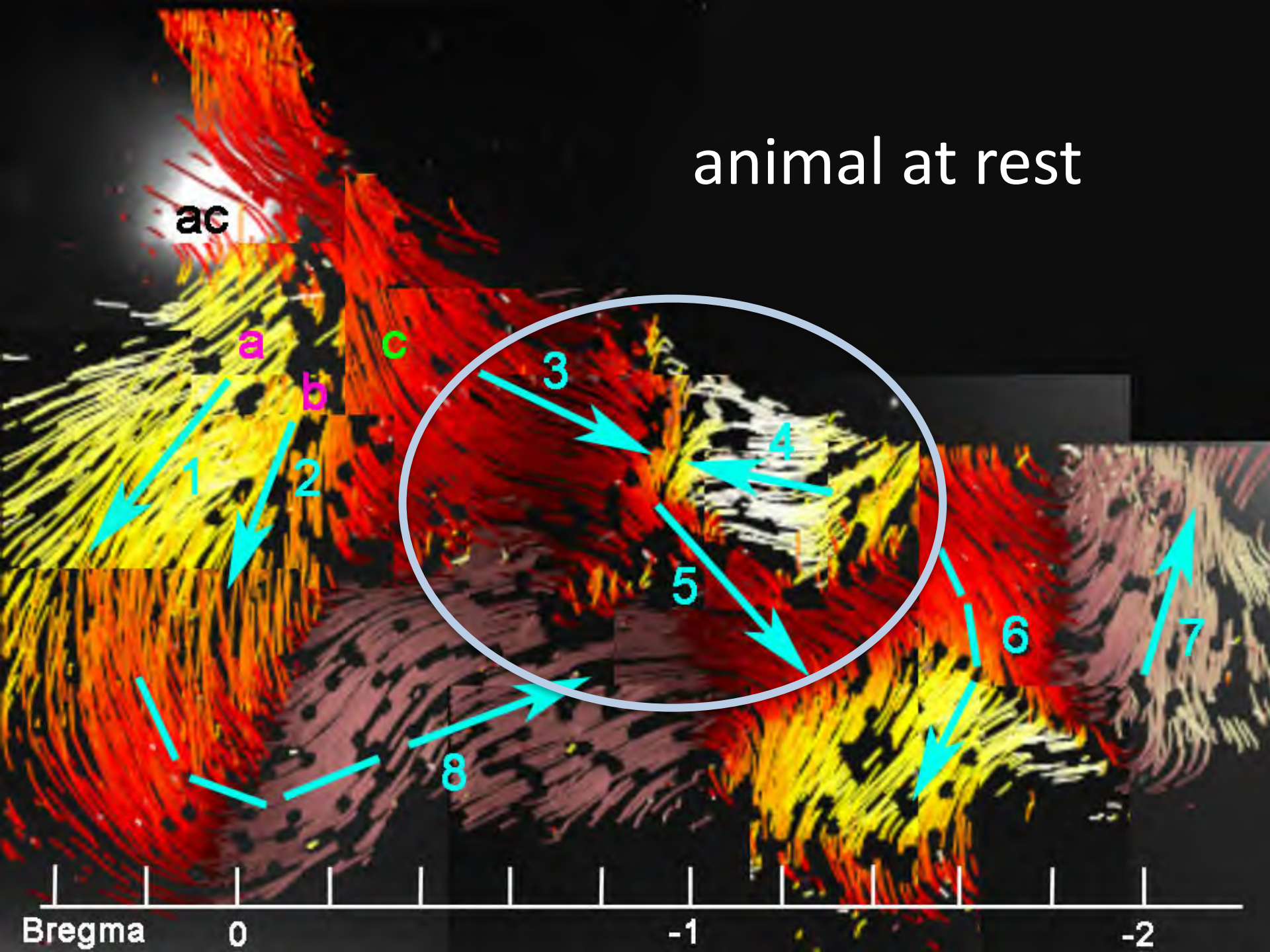
8

Bregma

0

-1

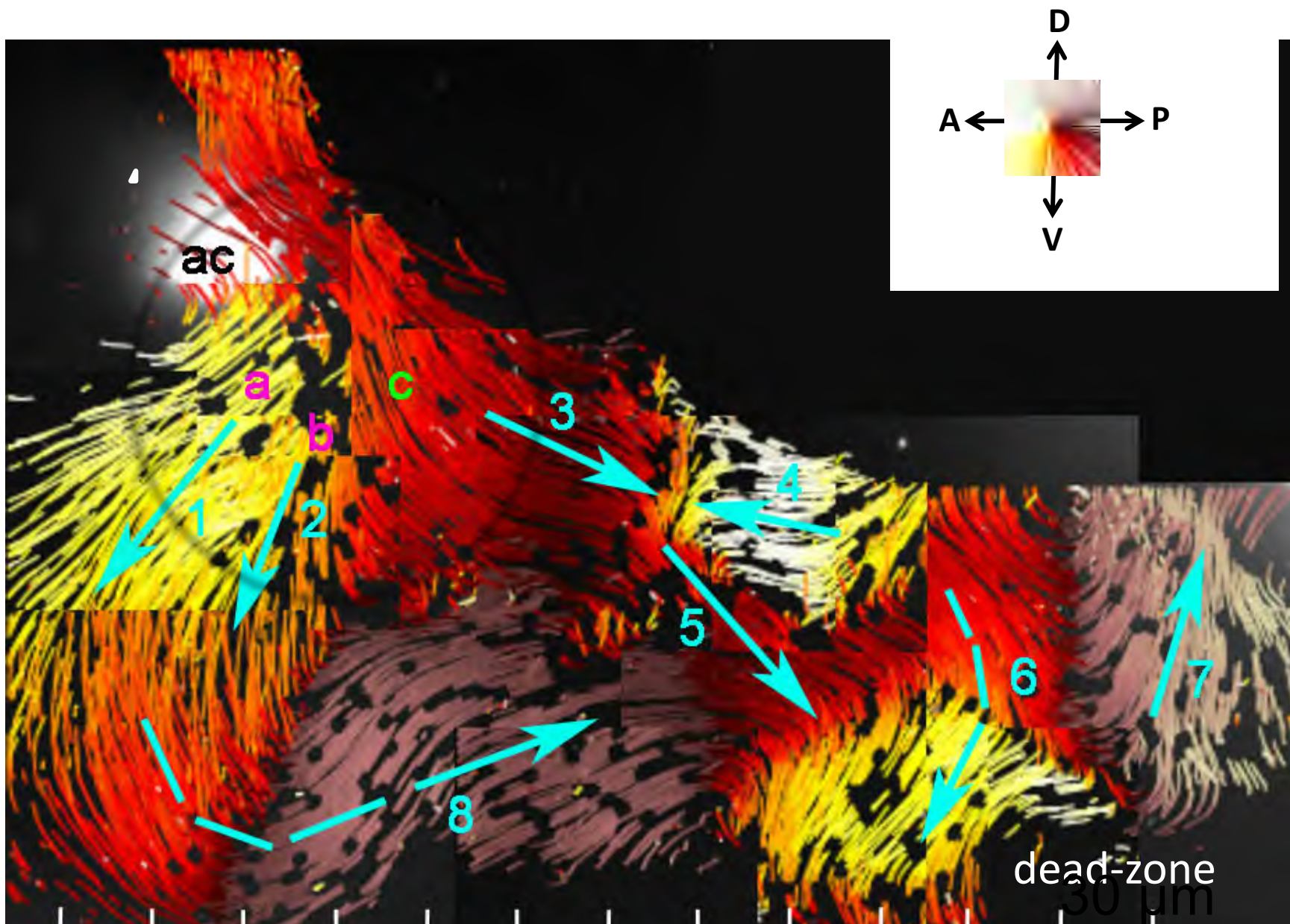
-2



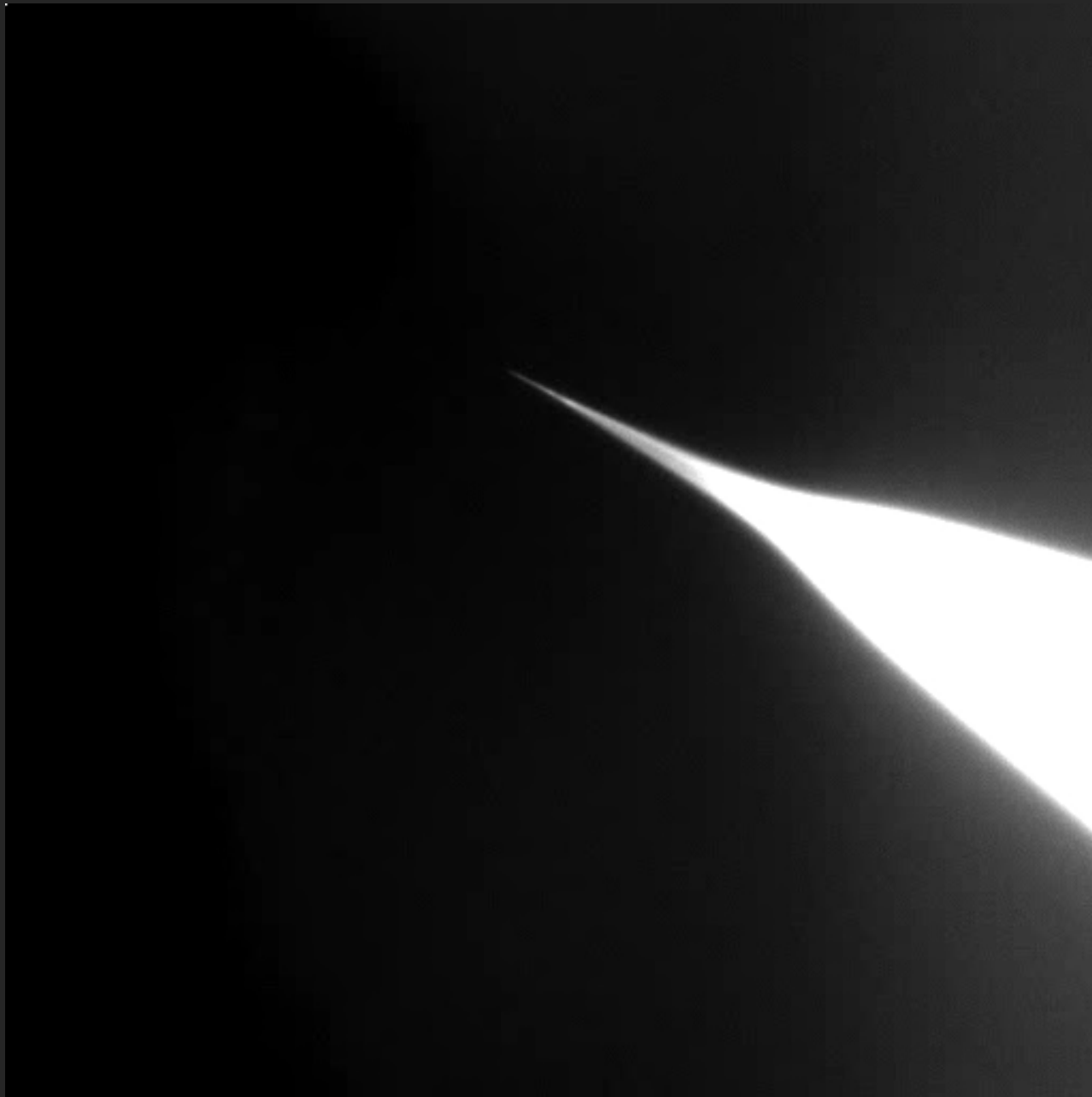
animal is active

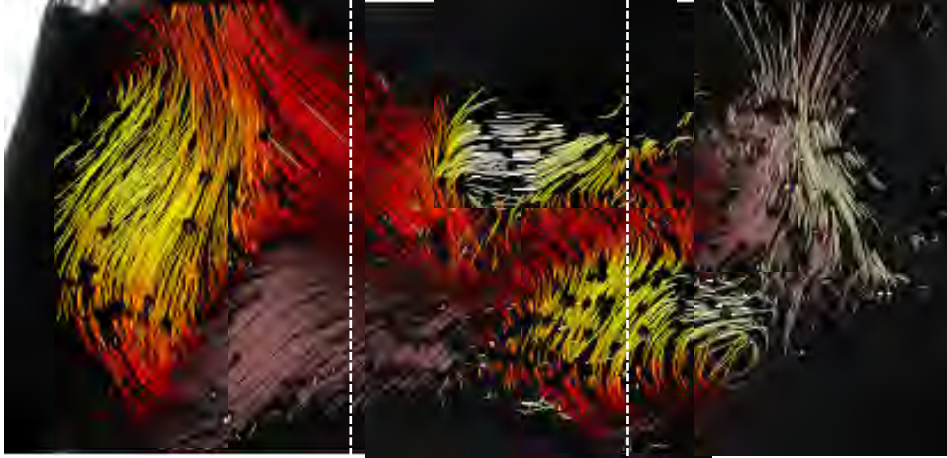
Change in topology → change in transport

Movement by particle tracking in flat-mounts of the 3rd ventricle



Direct observation of movement of 70 kD FITC- dextran

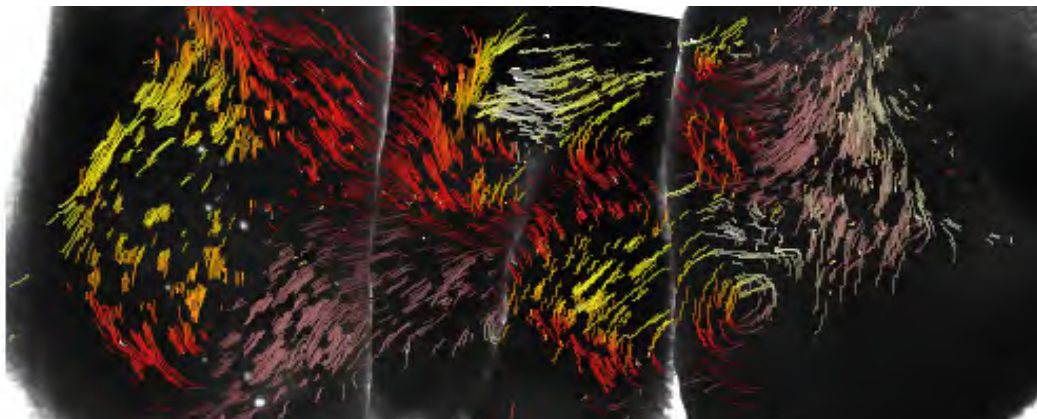




intact
wall



separate after
cutting



recombined

Cilia in the brain: going with the flow

Joshua J Breunig, Jon I Arellano & Pasko Rakic

Cilia are increasingly appreciated regulators of brain homeostasis. Several recent studies examine the cellular and molecular mechanisms of their biogenesis and orientation in ependymal cells.

Evolution is frugal and often recycles old designs to derive new functions. For example, cilia, which are akin to flagellae used by single cell organisms such as algae or bacteria to swim in the ancient Cambrian sea, have been preserved through millennia, only to assume totally different functions in mammals. There are two main types of cilia in the mammalian brain, primary cilia and motile cilia. Choroid plexus (ChP) cells and radial glia/astroglial lineage cells have primary, nonmotile cilia. Indeed, their function in radial glia during development was obscure, and only in the past decade did we learn that these forgotten organelles are essential for tissue function and homeostasis^{1,2}. Notably, neural precursor/progenitor primary cilia appear to regulate Shh signaling during development and in pathological conditions such as medulloblastoma³⁻⁵. Many neuroscientists were surprised to learn that neurons also contain primary cilia. It has been speculated that they could be vestiges of the primary cilia present on embryonic radial glia and the truth is that little is known of their possible function⁶. In contrast, ependymal cells, lining the lateral ventricle surface, harbor the motile variety of cilia on their apical surface (Fig. 1a,b). These hair-like bundles of microtubules beat in a coordinated mode and are believed to facilitate the circulation of cerebrospinal fluid (CSF), although little is known about the proper development of

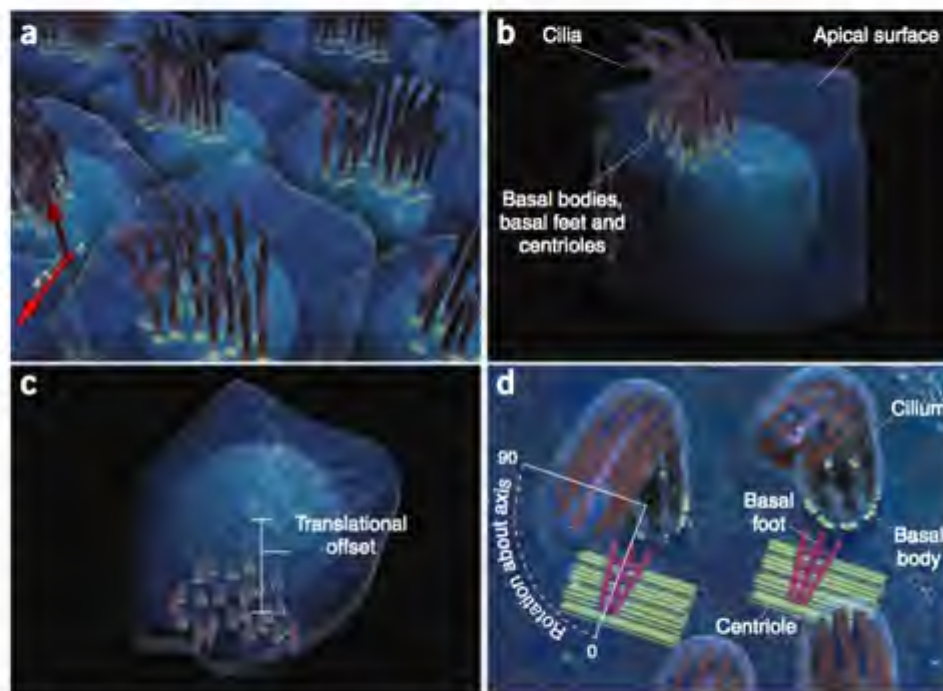
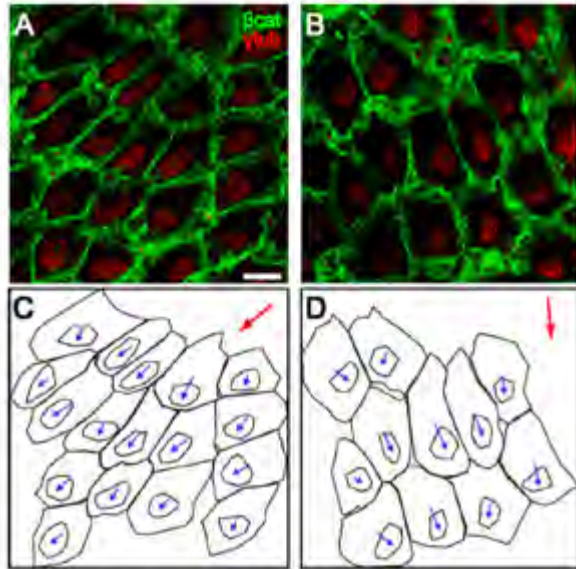


Figure 1 Representation of motile cilia translation and rotational orientation on the surface of ependymal cells. (a) Three-dimensional rendering of the surface of ventricular zone ependymal cells displaying their gross polarity and the directionality of cilia bundles. Arrow indicates apical basal plane perpendicular to CSF flow/PCP plane. (b) Individual ependymal cell showing motile cilia bundle on the apical surface. Ciliary axonemes arise from basal bodies (yellowish green) docked on the apical surface. (c) View of the apical surface of the ependymal cell showing the translational polarity of the cilia bundle that is established by the offset from the center of the apical surface often seen in wild-type ependymal cells⁹. (d) Higher magnification view of the apical surface displaying the rotational plane of the cilium based on the orientation of the basal foot (90° of a possible 360° shown). The basal foot, which is observed in close approximation to the basal body, correlates with the plane of beating of individual cilia^{8,9}. Underneath this is the centriole.

Definition:

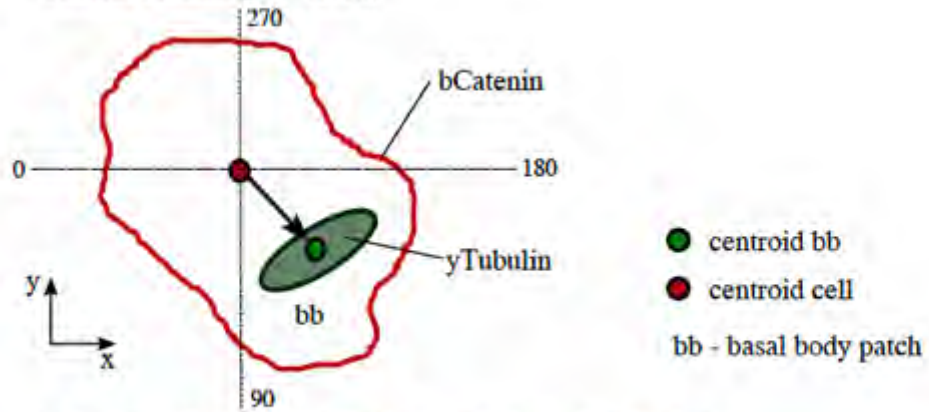
Translational polarity within the planar cell polarity



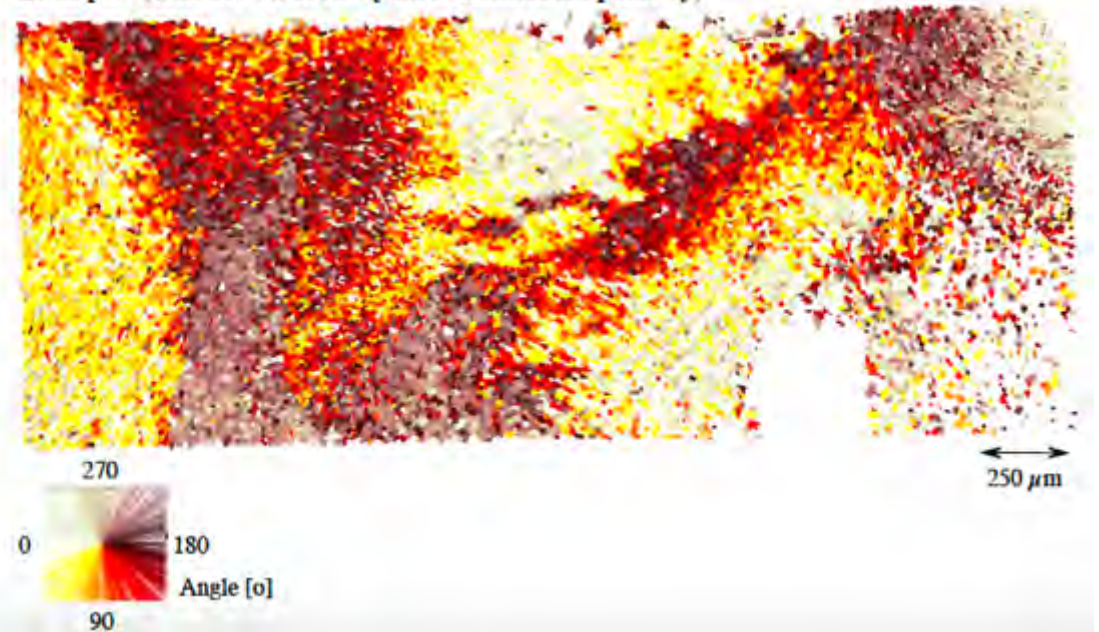
beat - betaCatenin
 ytub - gammaTubulin
 red arrow - flow direction
 blue arrow - translational polarity

[Mirzadeh et al. J Neuroscience 2010.]

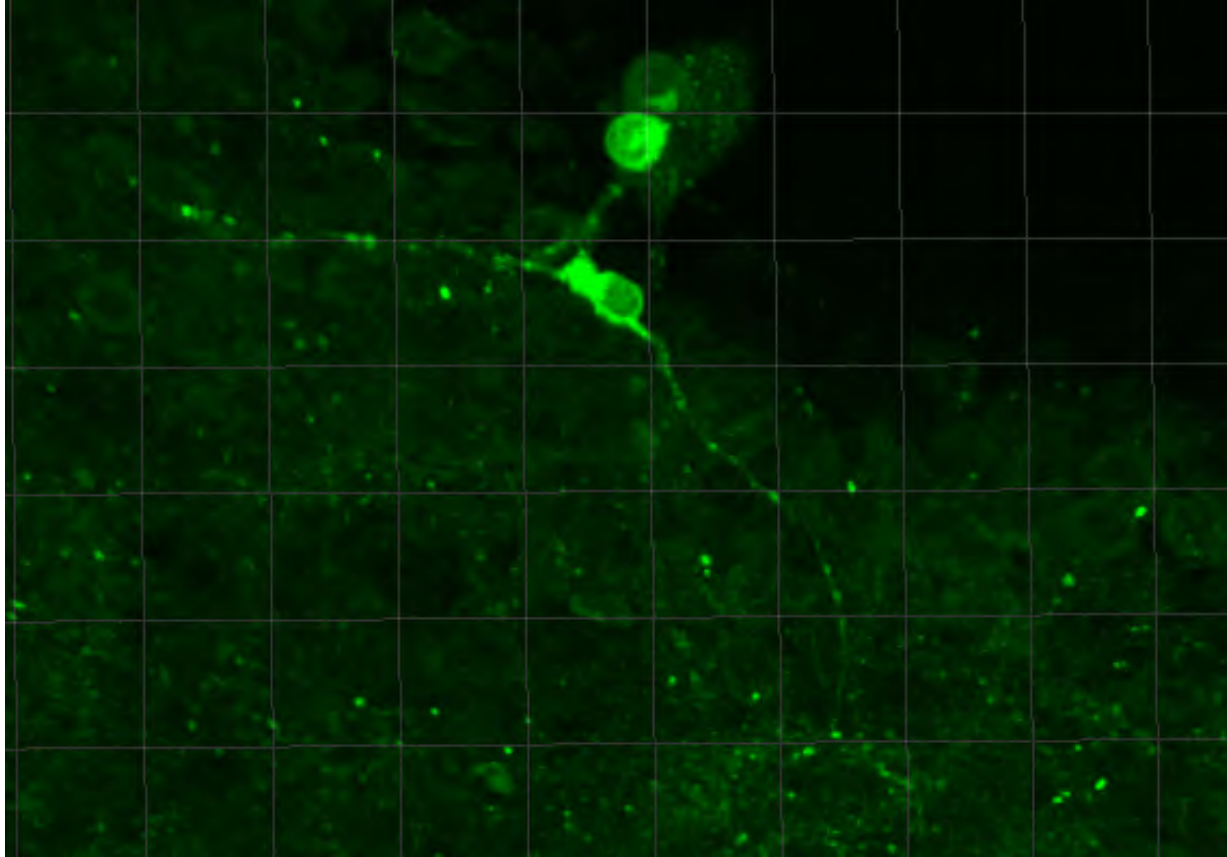
Sketch: (Staining reversed)



Example: (cells are colored by its translational polarity)



Neurons on the v3V?



Fluid dynamics takes part in the neurophysiology of the body





Shoba Kapoor

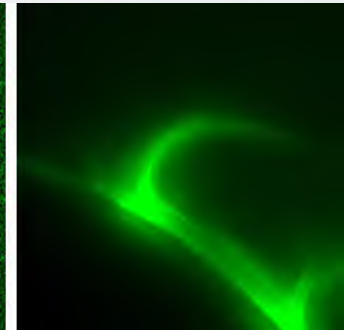
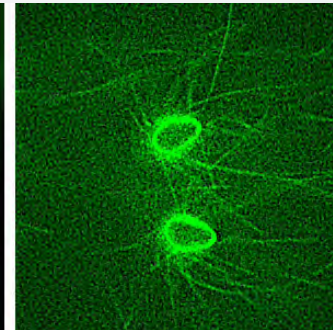
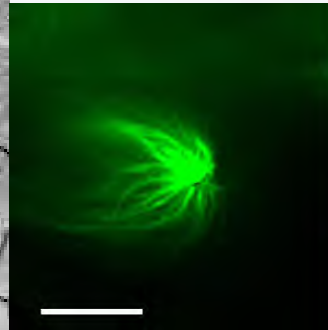
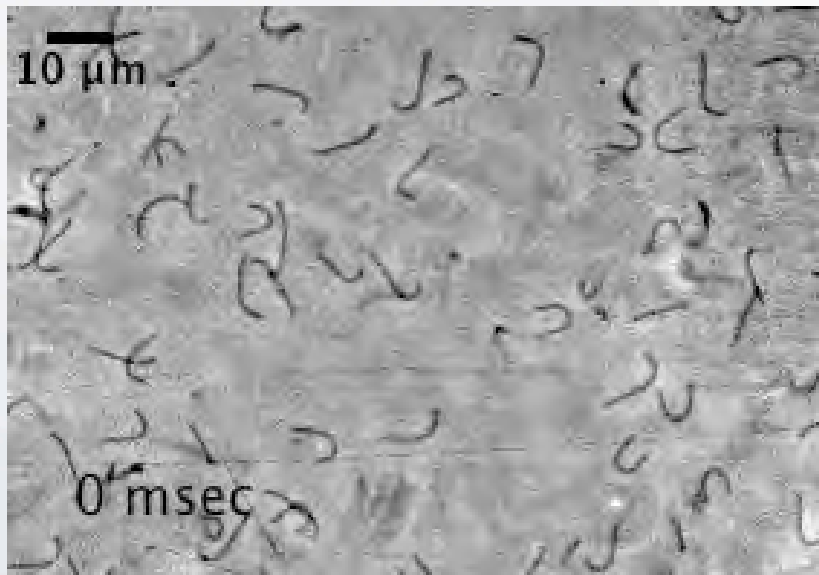
Faubel, R., Westendorf, C., Bodenschatz, E. and Eichele, G., "Cilia-based flow network in the brain ventricles". *Science*, July 2016, Vol. 353(6295), 176 pp.

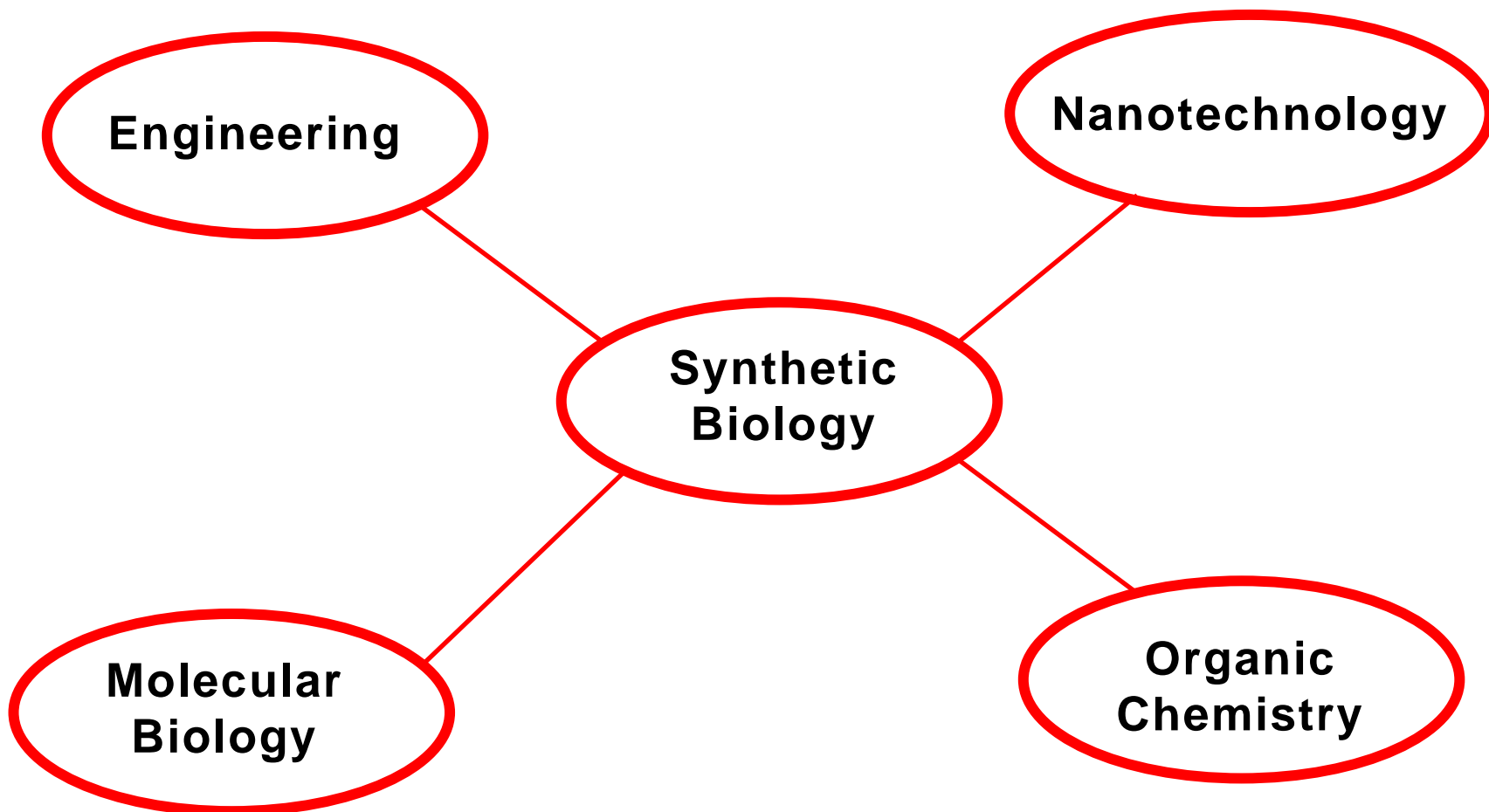
r. Christian Westendorf, Dr. Regina Faubel, Prof. Dr. Eberhard Bodenschatz, Prof. Dr. Gregor Eichele (von links).



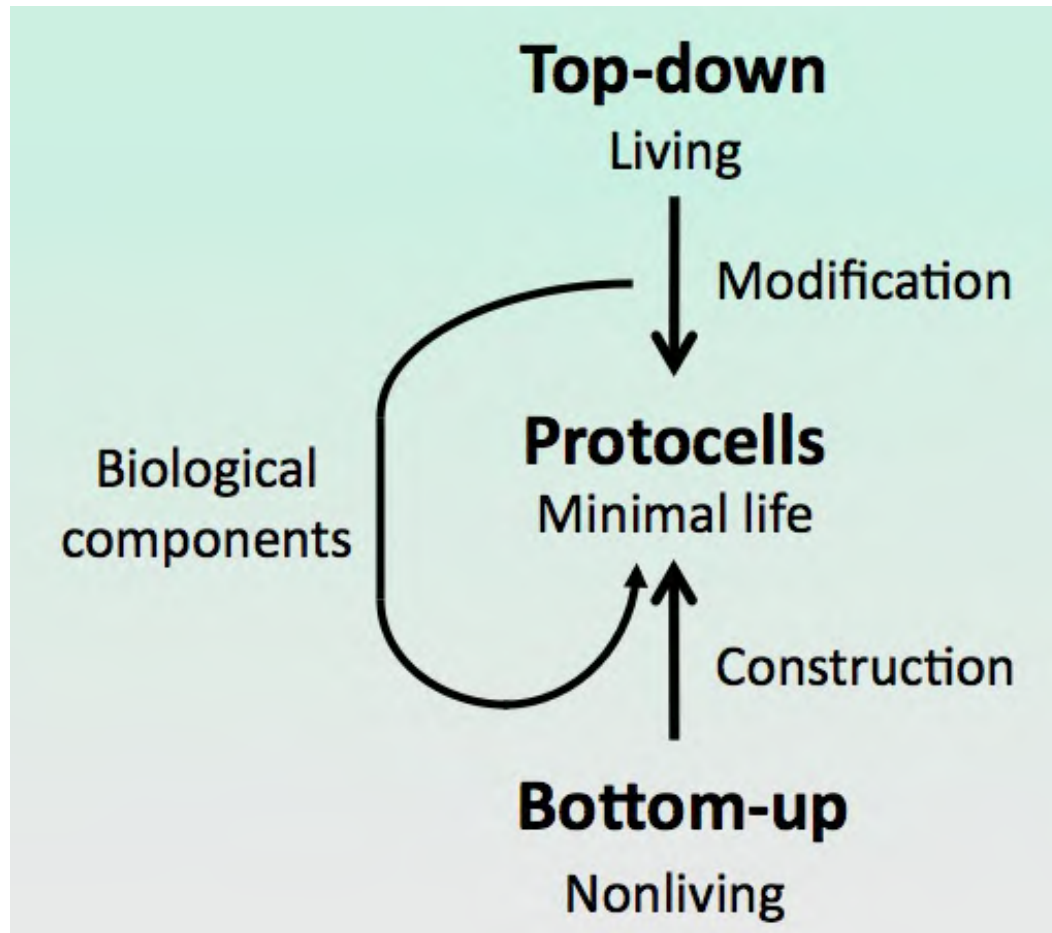
Biomimetic structures: Synthetic cilia

Isabella Guido, A. Gholami, A. Bae, C. Westendorf, E. Bodenschatz

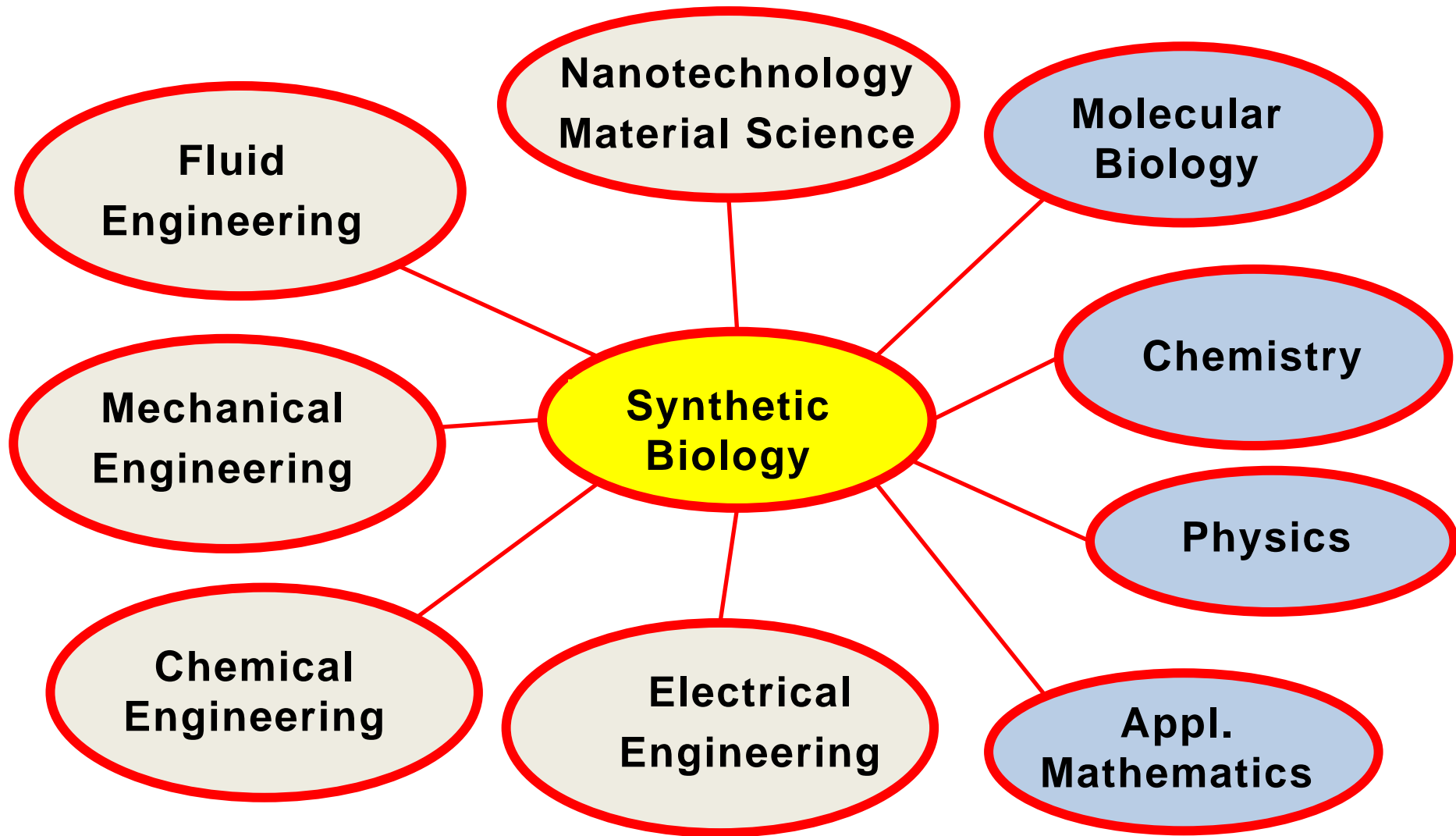




Two approaches

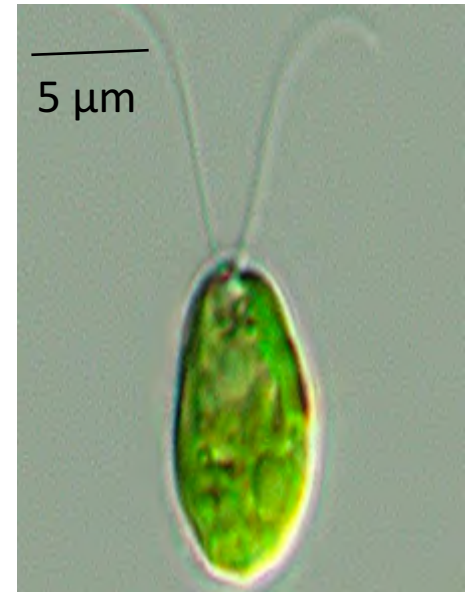
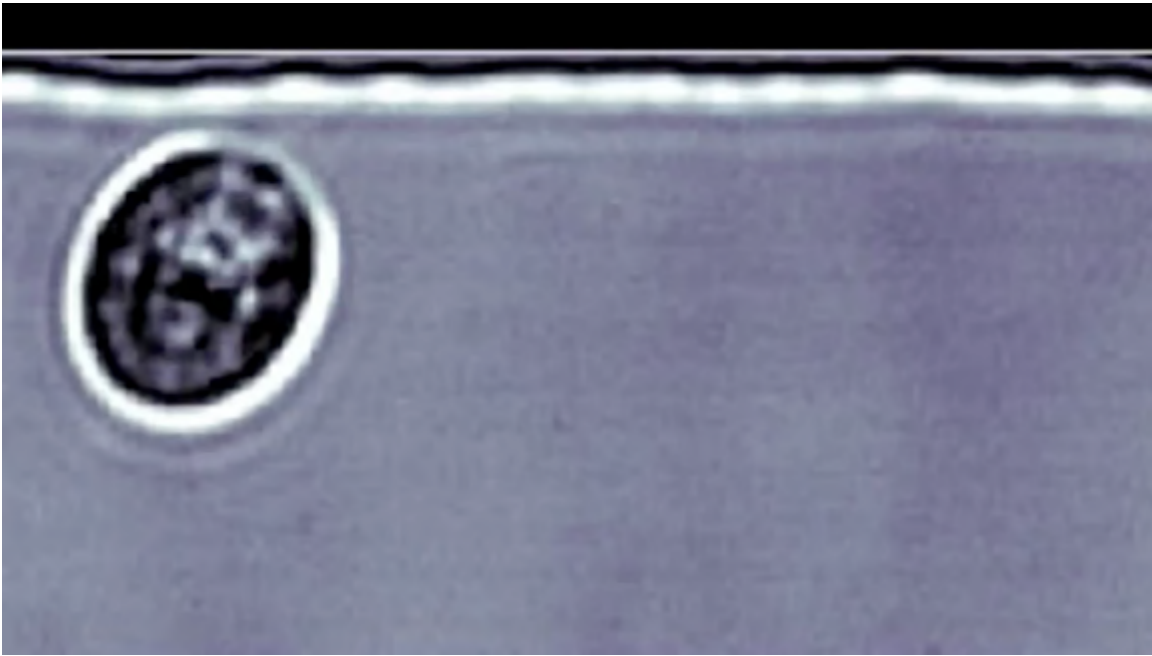


Synthetic Biology Fluid-Transport Engineering

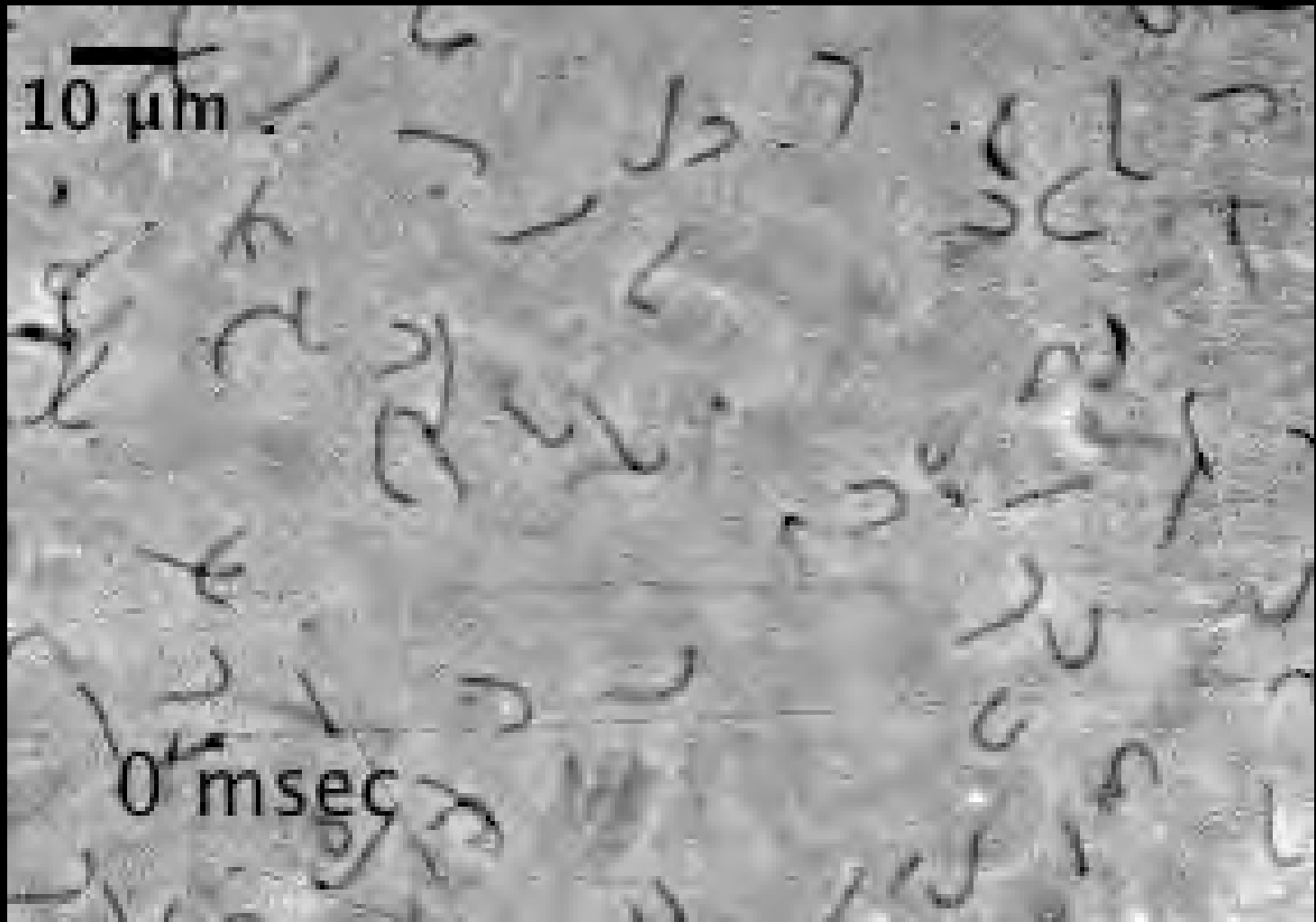


Chlamydomonas reinhardtii

green algae consisting of unicellular flagellates



**Swimming speed
58 micron/sec**

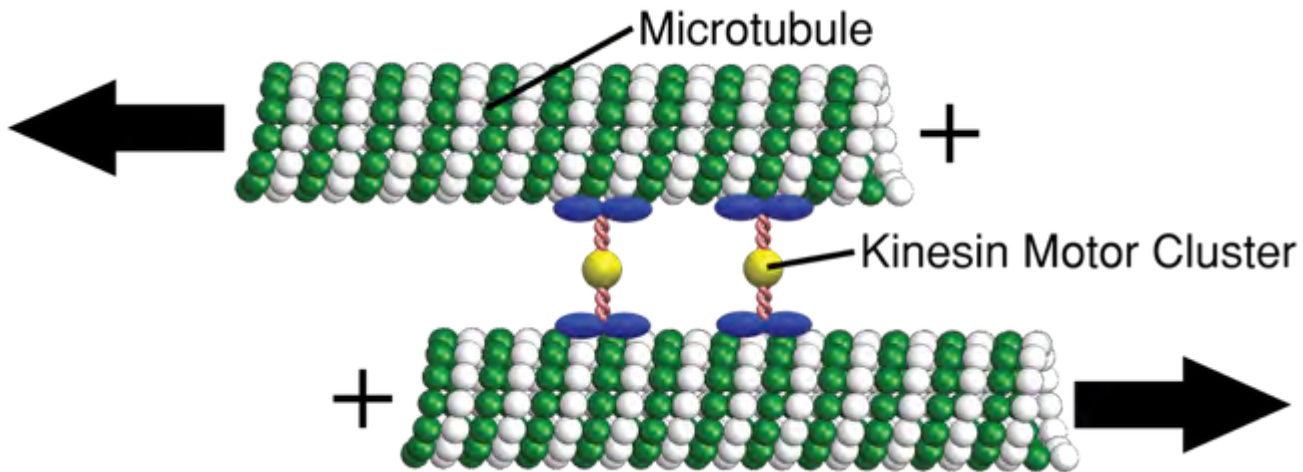
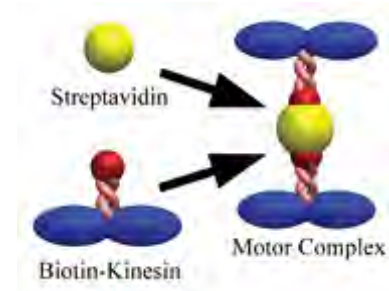
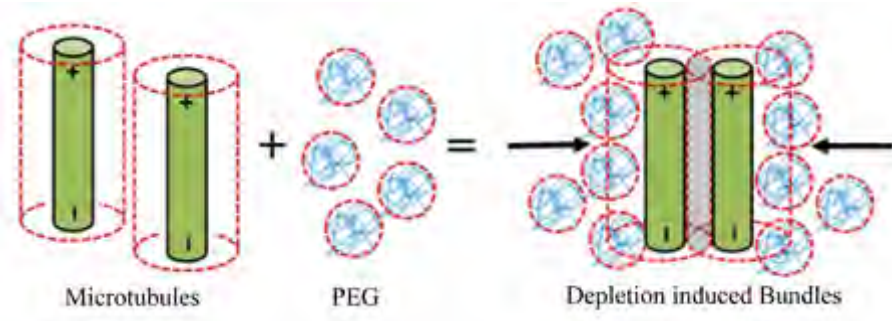


First step to carpets: axonemes attached from one side

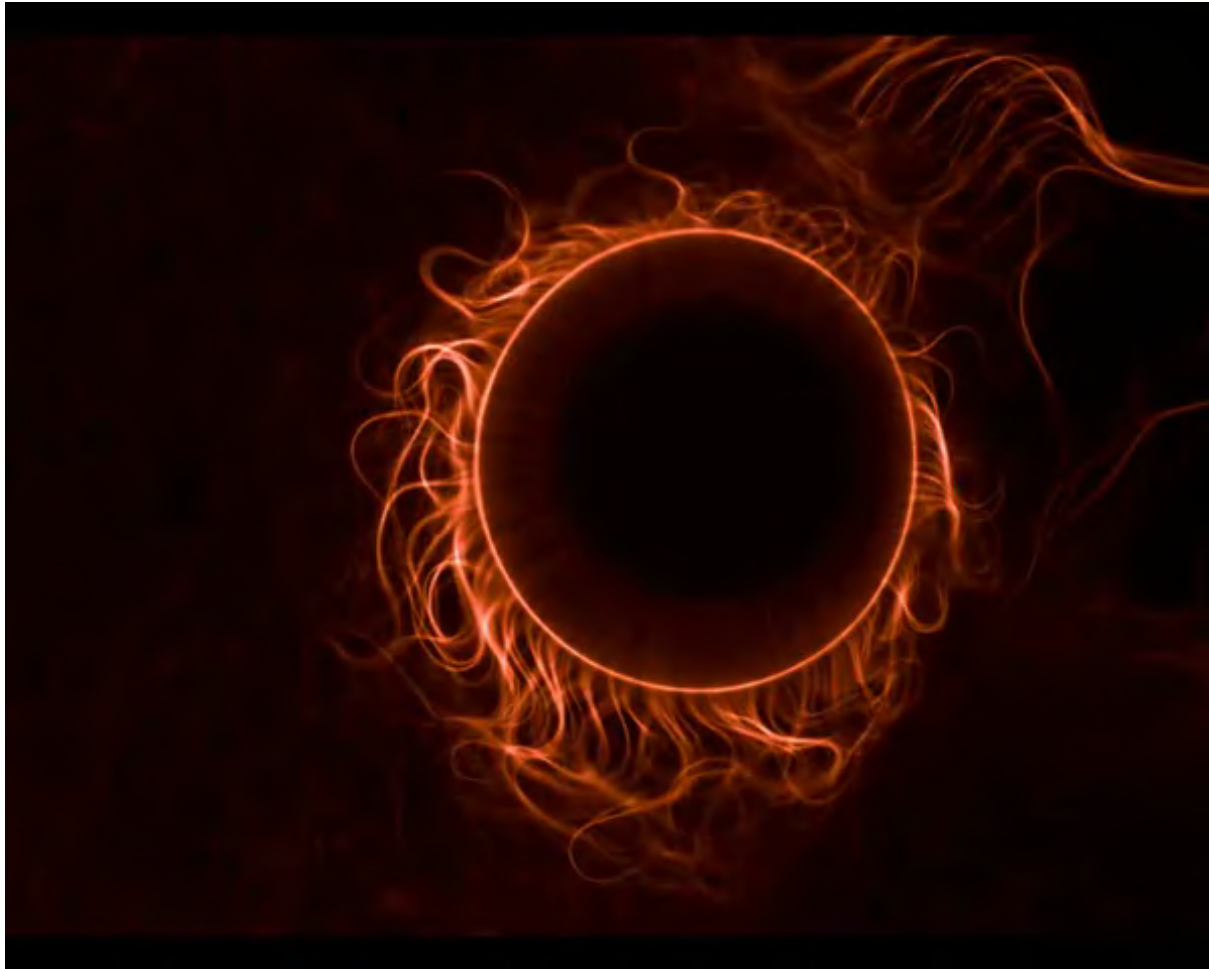
0 msec



Fully synthetic system: synthoneme

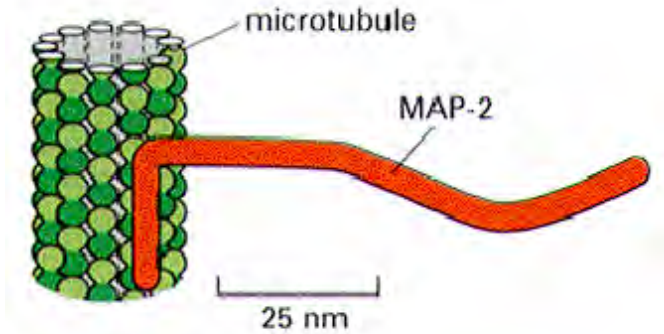


State of the art -

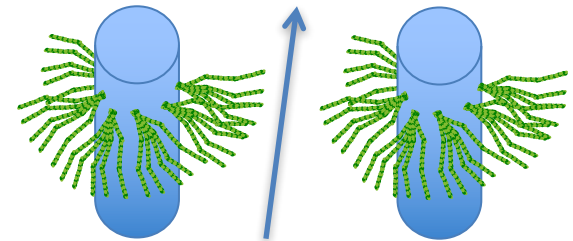
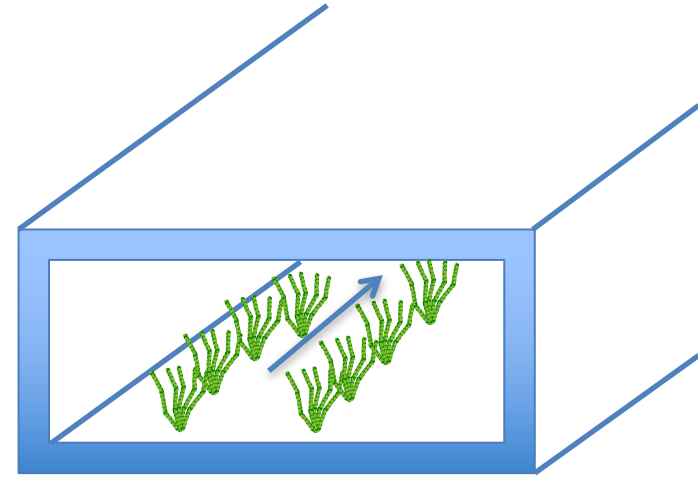


T. Sanchez, D. Welch, D. Nicastro and Z. Dogic, *Science* **333**, 456-459 (2011).

Other approach assemble microtubels attach motors



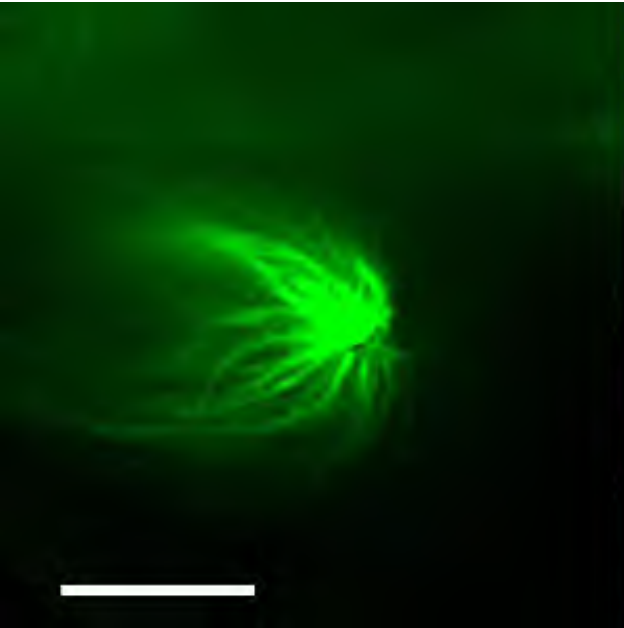
(B)



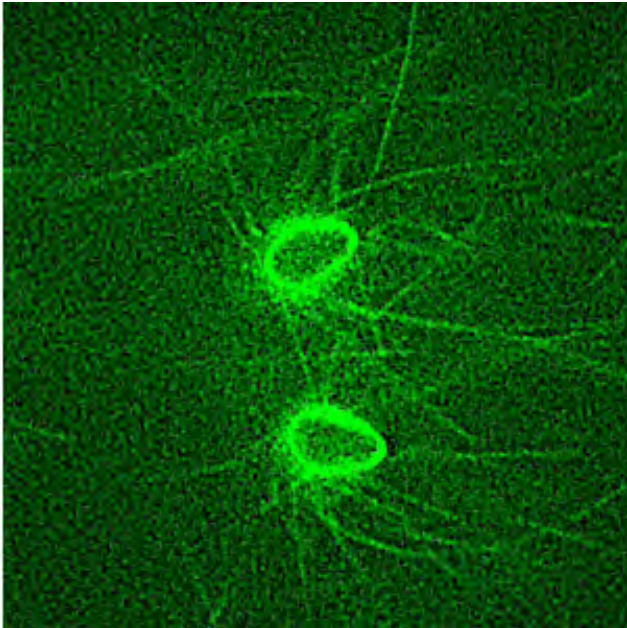
Microtubules bundles assembled on different surfaces



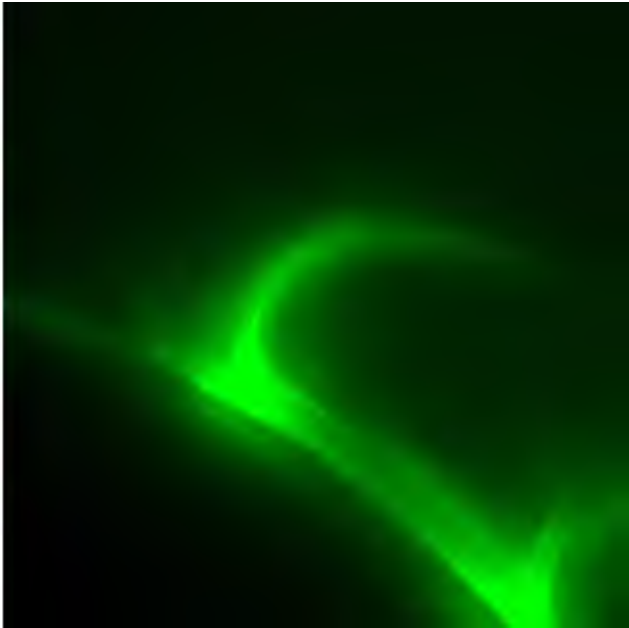
Nucleators adsorbed on the surface



Pillars

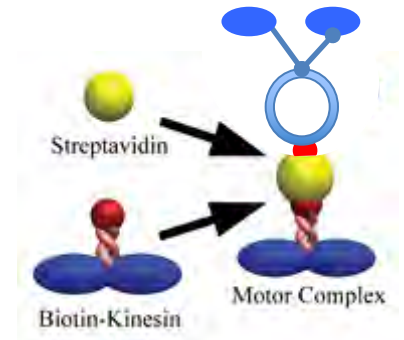
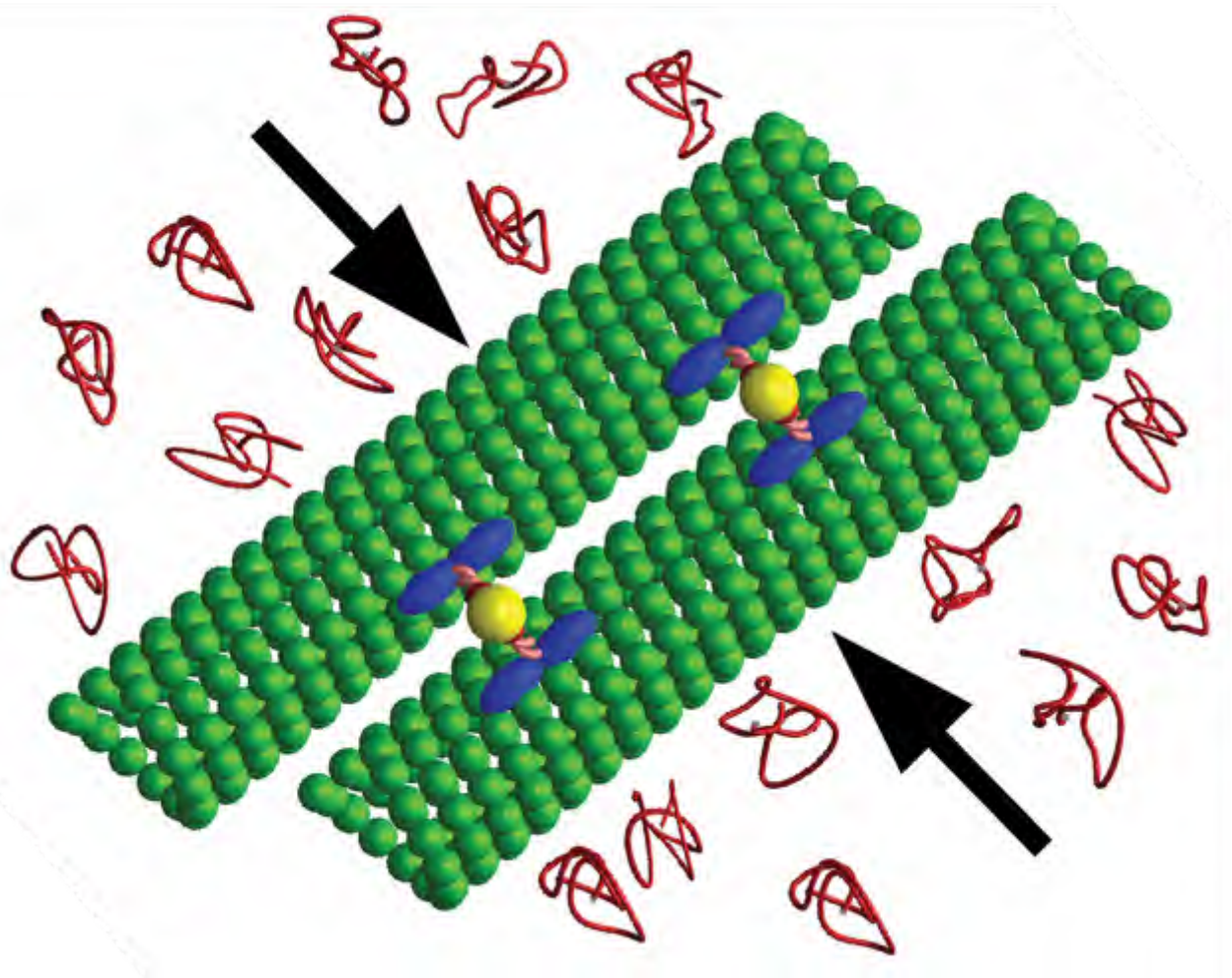


Boundary of microfluidic chamber



Scale bar 10 μm
Fps 100

Biomimetic systems



Summary

- Ciliated carpets give directional and locally driven flow in the brain
- Important for body functions?
- Artificial carpets would revolutionize fluid transport in small fluid systems and surfaces
- Can be used to build active matter ...

