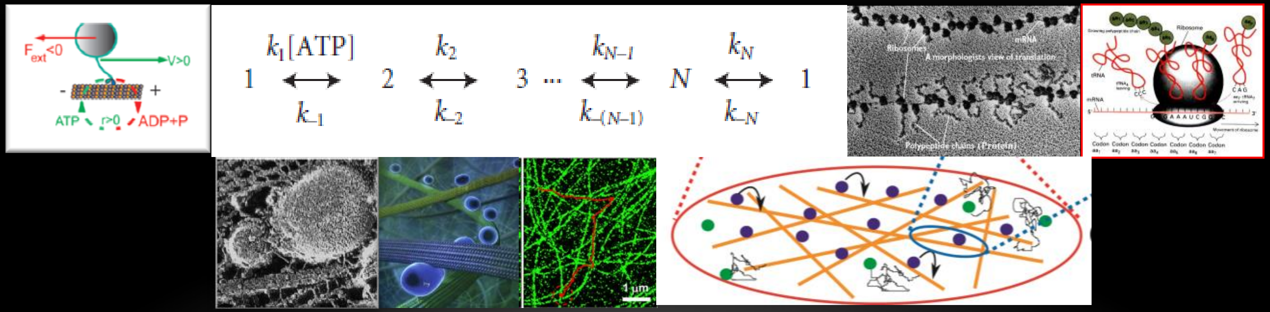
PHYSICS OF TRAFFIC IN THE SELF-ORGANIZED CYTOPLASM

PHYSIQUE DU TRAFIC DANS LE CYTOPLASME AUTO-ORGANISÉ DE LA CELLULE



Andrea Parmeggiani

Laboratory Charles Coulomb UMR5221 CNRS

University of Montpellier, France

&

Dynamique des Interactions Membranaires Normales et Pathologiques UMR5235 CNRS

Rencontres Scientifiques des Grands Causses, Millau 28/09-2/10 2015

THEORETICAL BIOLOGICAL PHYSICS… AND MORE

Theoretical Biophysics and Systems Biology (DIMNP)

O. Dauloudet (PhD, DIMNP and L2C), A. Raguin (PhD DIMNP and L2C, post-doc ICSMB Aberdeen), L. Ciandrini (DIMNP and L2C), A. Chesseron (DIMNP), O. Radulescu (DIMNP), J. Rambeau (post-doc, DIMNP), A. Naldi (Post-doc, DIMNP), G. Innocentini (post-doc, DIMNP)

Complex Systems and Nonlinear Phenomena (L2C)

J.-C. Walter (Post-doc L2C-LMGC), J. Dorignac, F. Géniet, J. Palmeri, M. Manna, V. Lorman, N. Crampé (Integrable Models)

Statistical Physics (L2C)

I. Neri (post-doc MPIKS Dresden), N. Kern

F. Turci (PhD L2C, post-doc U. Luxembourg), E. Pitard

B. Embley (PhD, U. Bangkok)

2 Master Programs in Montpellier:

Physics and Engineering of Living Systems

Biophysics, Structures and Systems

"External" Collaborators:

K. Kissa (DIMNP), P. Montcourrier (IRCM), P. Bomont (INM), M. Peter (IGMM), G. Cappello (U. Grenoble), P. Pierobon (I. Curie, Paris), C. Leduc (I. Pasteur, Paris), M. Manghi and N. Destainville (LPT, Toulouse)
E. Carlon (U. Leuven), C.M. Romano (U. Aberdeen, UK), C. Vanderzande (U. Hasselt, Belgium),
I. Pagonabarraga (U. Barcelona), I. Palacios (U. Cambridge), E. Peterman (U. Amsterdam, USA),
P. Pullarkat (Bangalore, India), F. Pedaci (CBS, Montpellier), …
J. Y. Bouet's team (LMGC, Toulouse), M. Nollmann's team (CBS, Montpellier)

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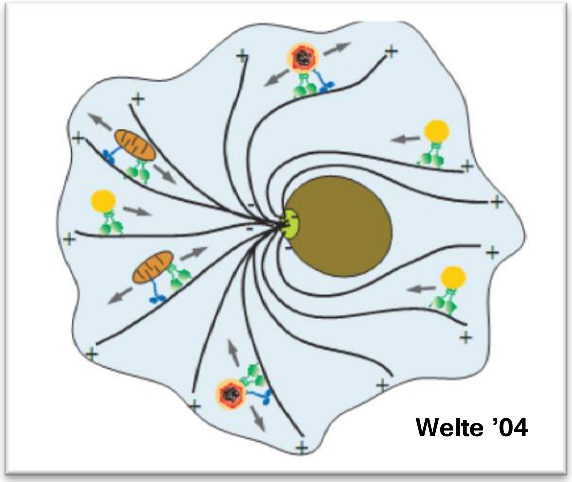
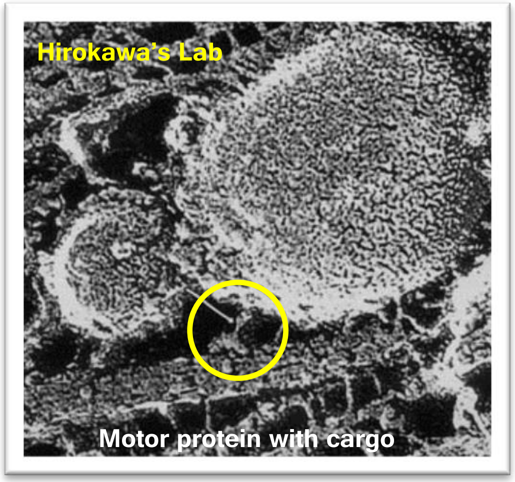
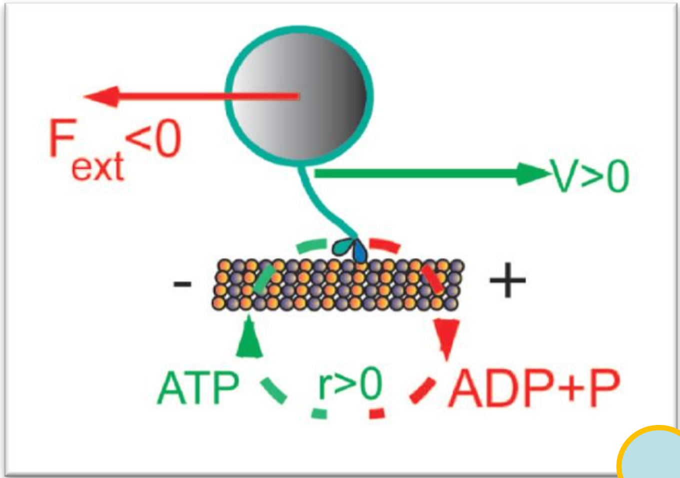
Motor proteins and (active) cytoskeletal transport



Cytoskeletal transport





Motor protein = molecular machine

Motor protein driven transport

- Long and short range delivery
- Targetting cargo in cytoplasm,
  nucleus <-> cellular membrane
- Organelle and cytoskeleton intracellular remodeling
- Transport and pathologies
- Quantitative knowledge

Novelties for (Bio)Physics:

- Processes far from equilibrium
- Nanoscopic size stochastic carriers
- Force production at molecular scale
- Very powerful engines
- Molecular motors (10 Hz-10 KHz)
- Collective, self-organized process
- Multimodal (different transporters)
- Multiscale (from nm to meters!)

OUTLINE

Studying aspects of the "Self-organizing Cytoplasm and Nucleoplasm" via transport phenomena in biology

- Active cytoskeletal transport driven by motor proteins
- Theoretical modeling approaches
- "Simple" examples playing with:
  - Intracellular effective viscosity (ie diffusion coefficient)
  - Filament organization
  - Large networks
- Conclusions

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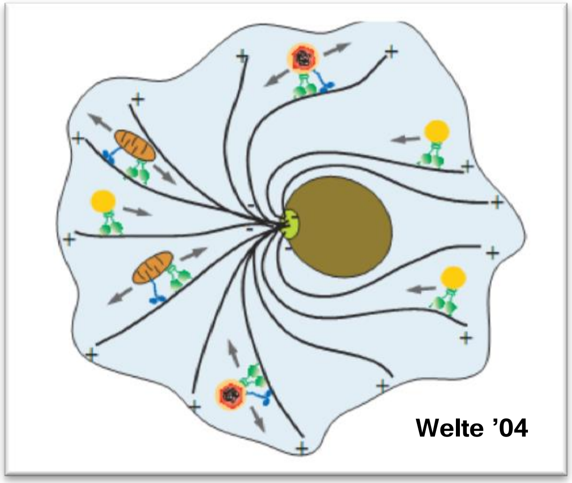
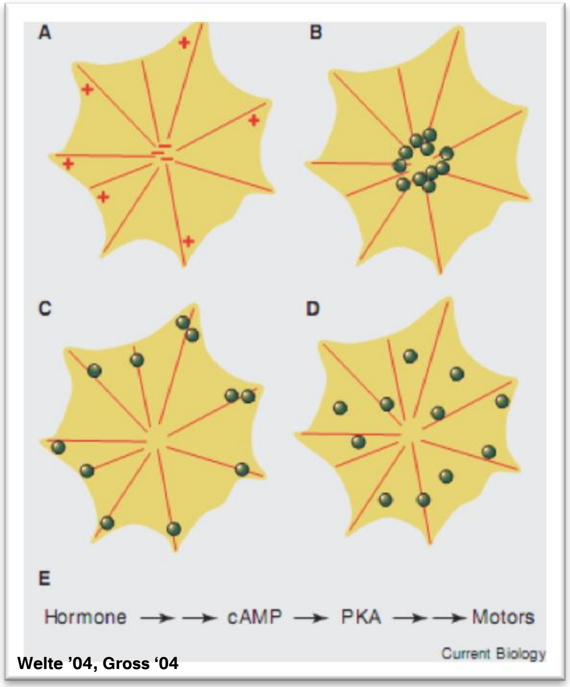


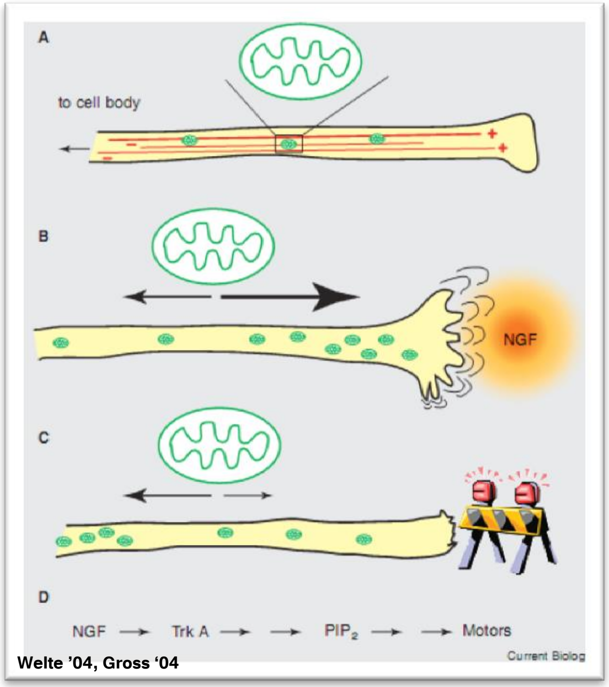
Cytoskeletal transport

Motor protein driven transport

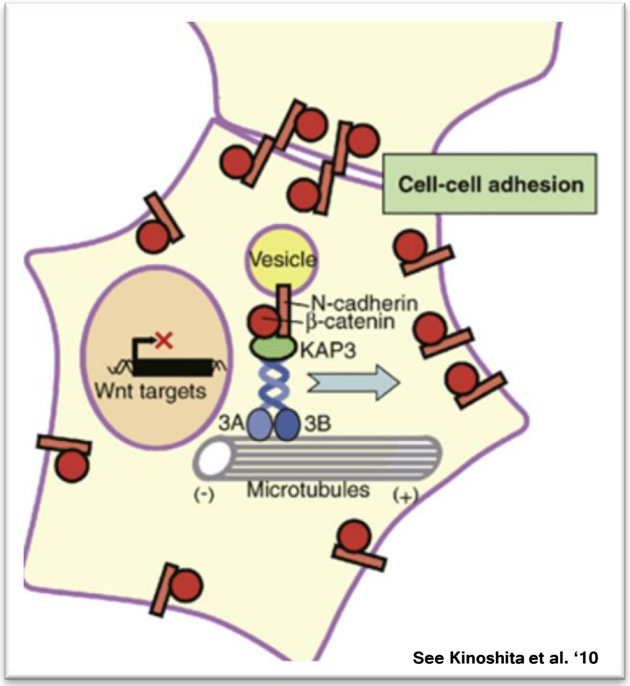
- Long and short range delivery
- Targetting cargo in cytoplasm, nucleus <-> cellular membrane
- Organelle and cytoskeleton intracellular remodeling for cellular functions (mitosis, motility, adhesion, differentiation, ...)



Pigmentation in melanocytes



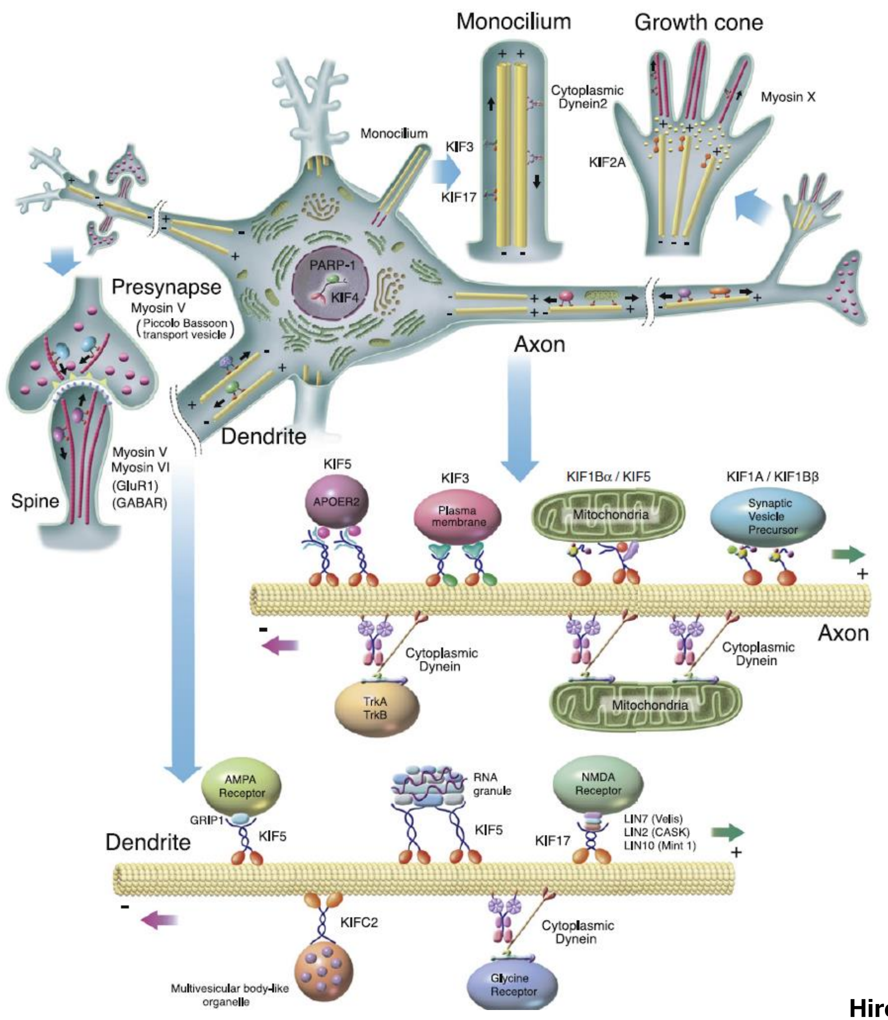
Mitochondria localization in neurite growth



Addressing adhesion complex at the cell periphery

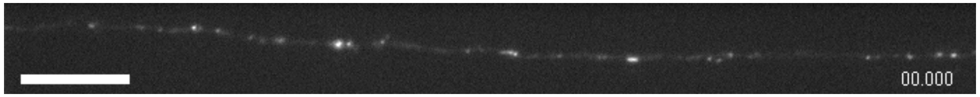
Axonal transport and neurodegenerative diseases

Transport defects and traffic jams ↔ neurodegenerative pathologies

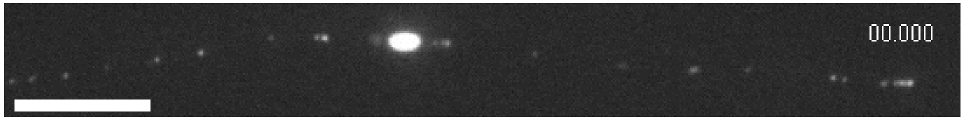


Hirokawa 2010

Figure 3. Intracellular Transport in Neurons
Various KIFs transport membranous organelles anterogradely in axons and dendrites, whereas cytoplasmic dynein 1 and KIFC2 transport retrograde cargos. In neuronal cilia, anterograde transport is performed by KIF3 and KIF17, while retrograde transport is performed by cytoplasmic dynein 2. In short-range transport, such as transport in the pre- and postsynapses and growth cone filopodia, the myosin family proteins function as the molecular motors.



Cargo movements within a single larval axon



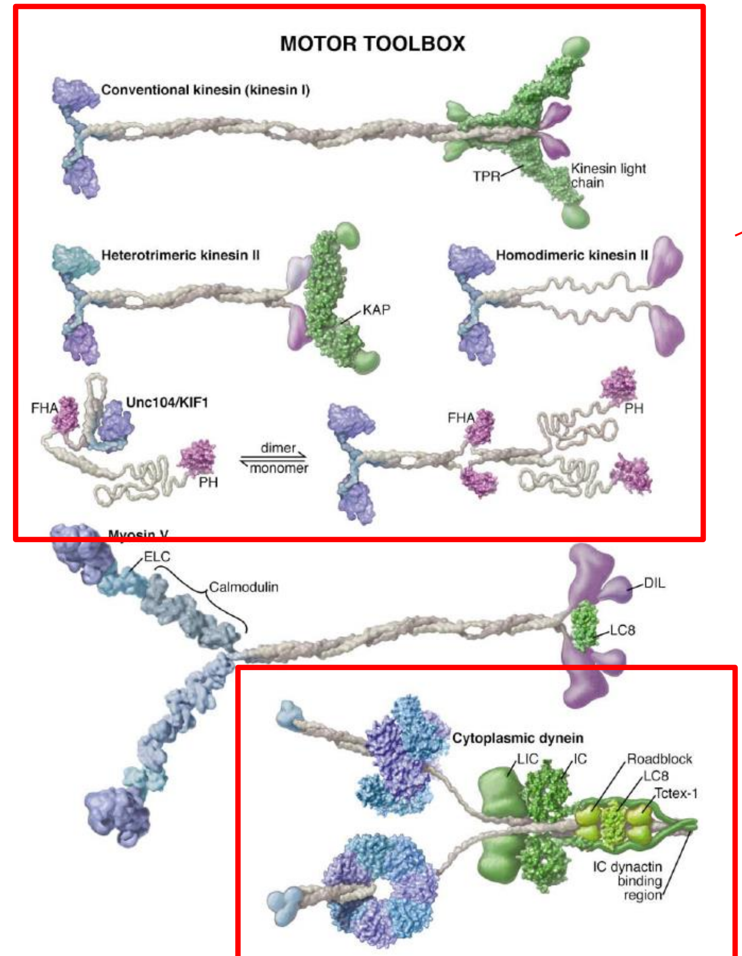
Cargo movements disrupted by expression of pathogenic polyQ proteins within a single larval axon

Gunawardena 2004

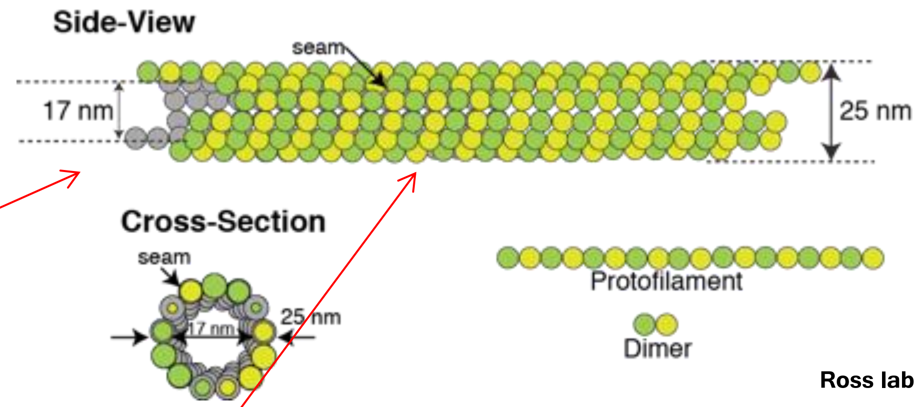
Complexity:

- Type of transporters
- Type or cargo
- Cargo-transporters regulation
- Cytoplasm and Cytoskeleton organization and dynamics
- Multiscale transport, delivery and aggregation of matter

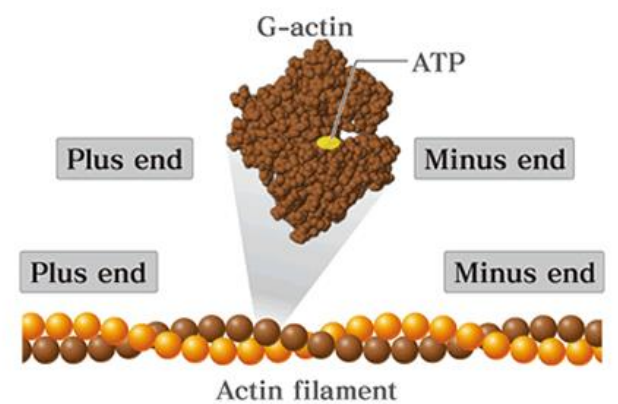
Motor proteins and cytoskeletal filaments



« The motor protein toolbox », R. Vale 2004



Ross lab



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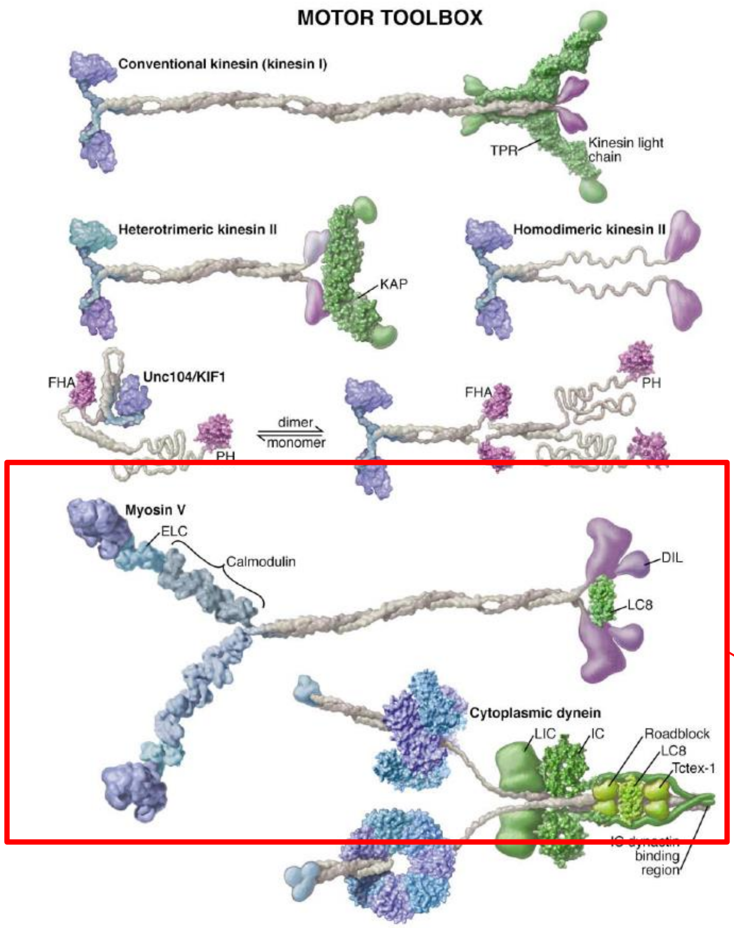
Motor proteins and cytoskeletal filaments



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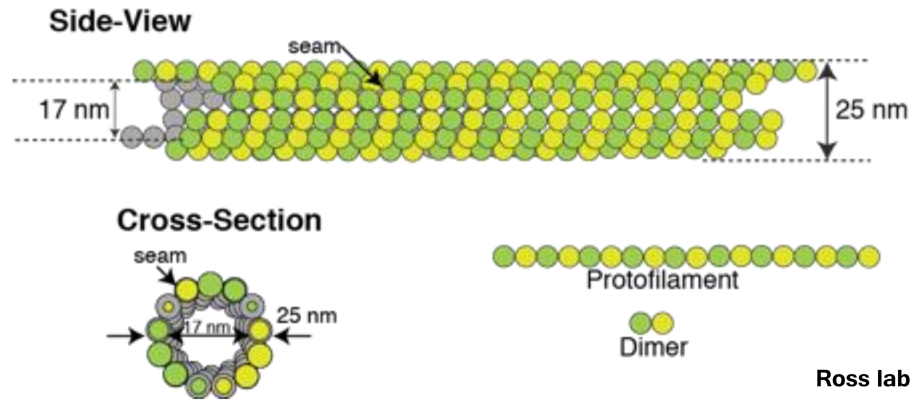

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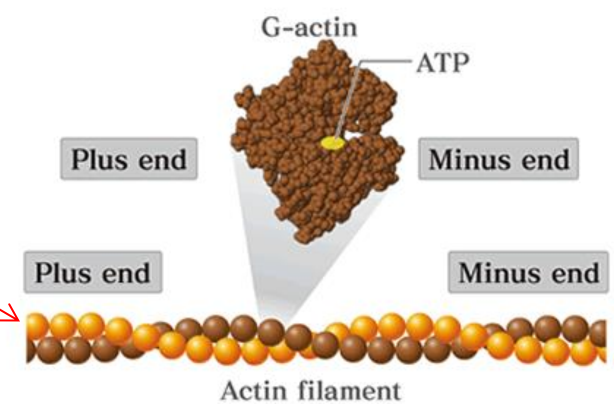

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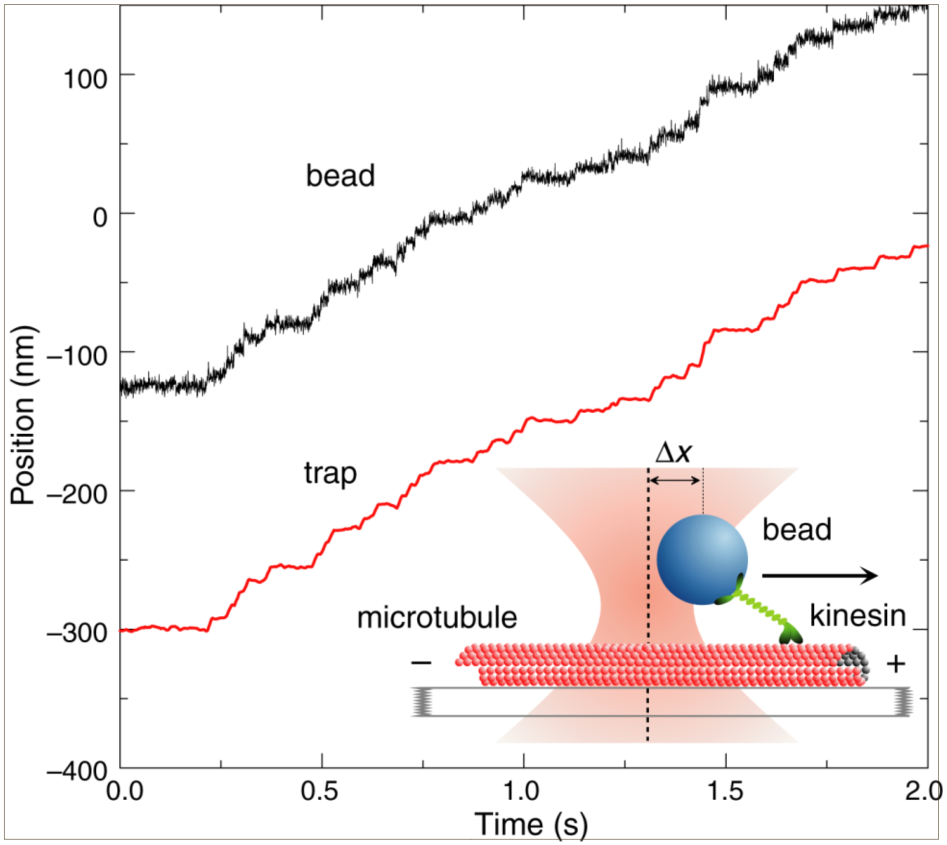
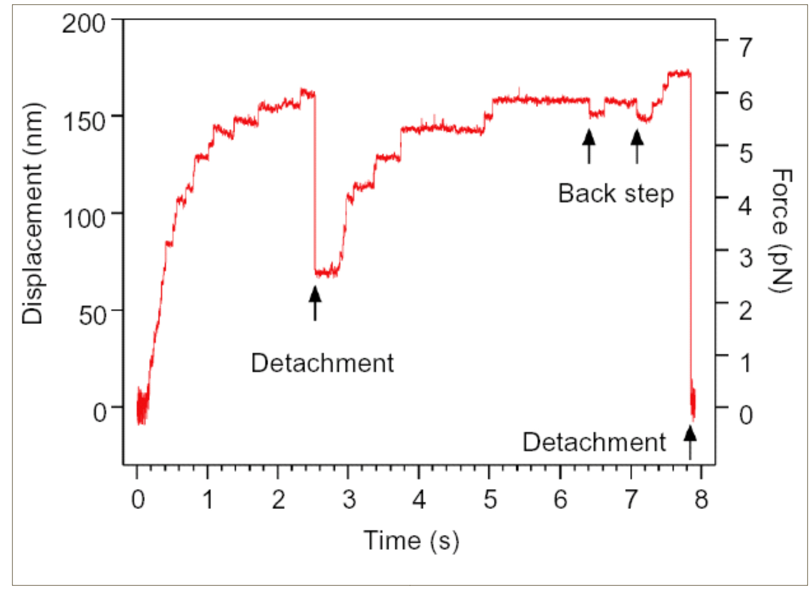
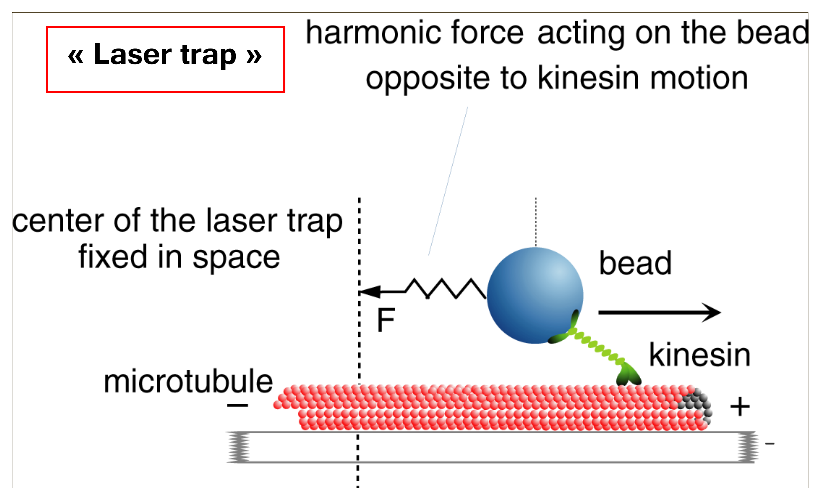
Laser tweezers and traps to measure single motor properties: conventional kinesin



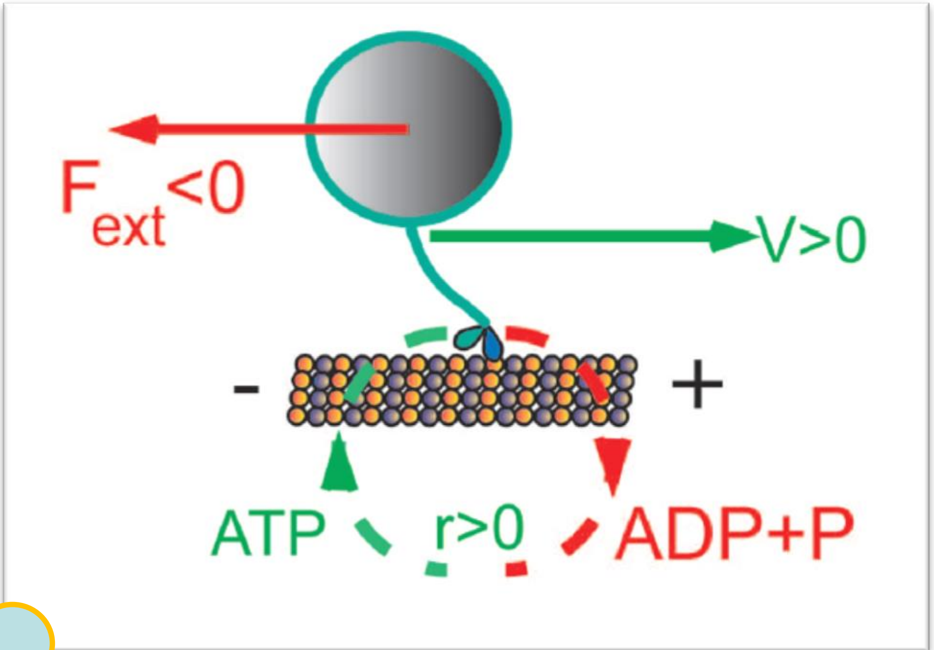
« Laser tweezer » (constant force) (Visscher et al., Nature ´99)



(Nishiyama et al., Nature ´02)



Motor proteins: some numbers



Motor protein = molecular machine

Speeds range : 10 nm/sec – few µm/sec

Force range : 1 pN – 6-7 pN

Mechanochemical cycle rate = 10 Hz – 1000 Hz

Step length: 5 nm – 36 nm

1 ATP molecule/step ~ 15-20 kT
(~ 60-80 pN*nm = 60-80*10^{-21} J)

Thermodynamic efficiency: 50 % to 80%

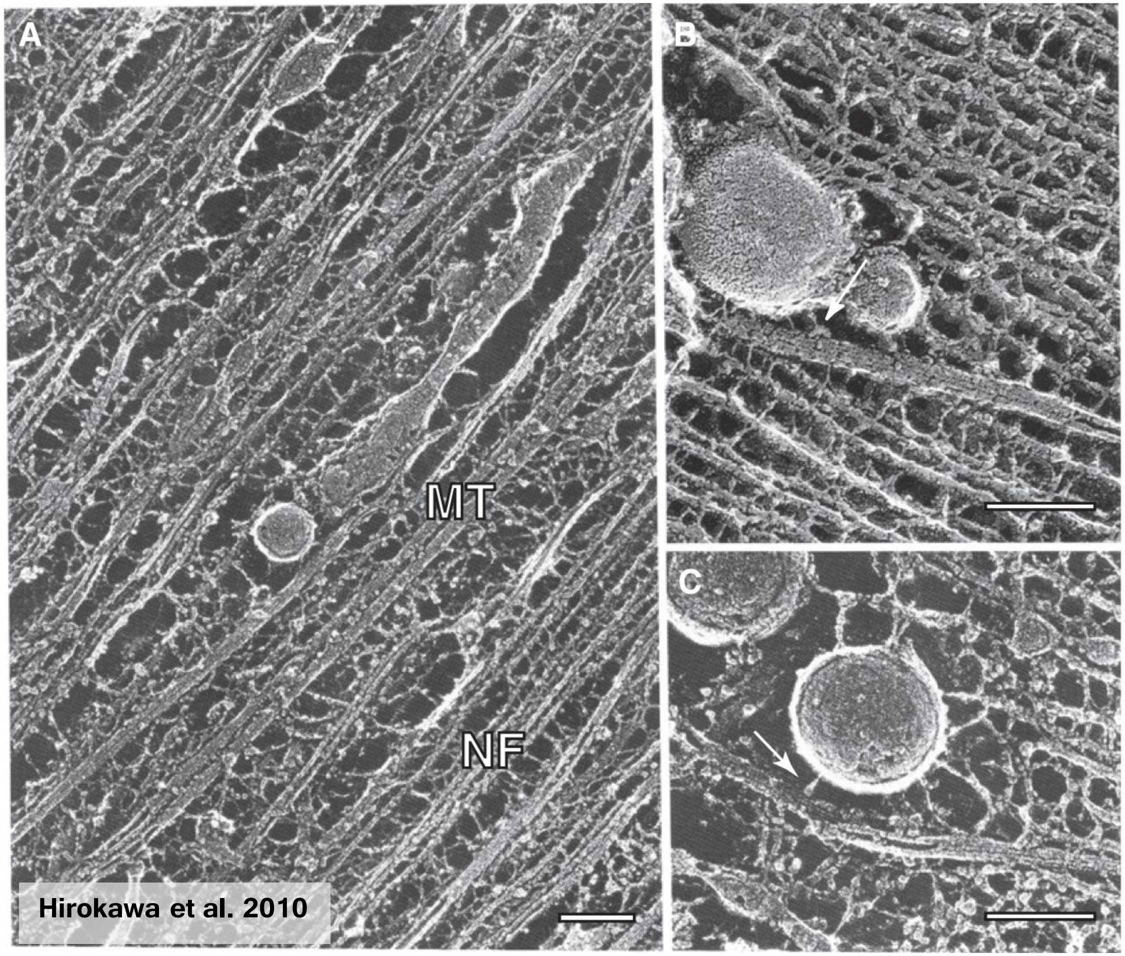
Processivity: from tens to hundrends steps without detachment

Viscous force of a cargo of 1 µm size (25-50 times the motor size) in water at maximal speed:

$6\pi\eta rv \sim 0.02$ *pN!*

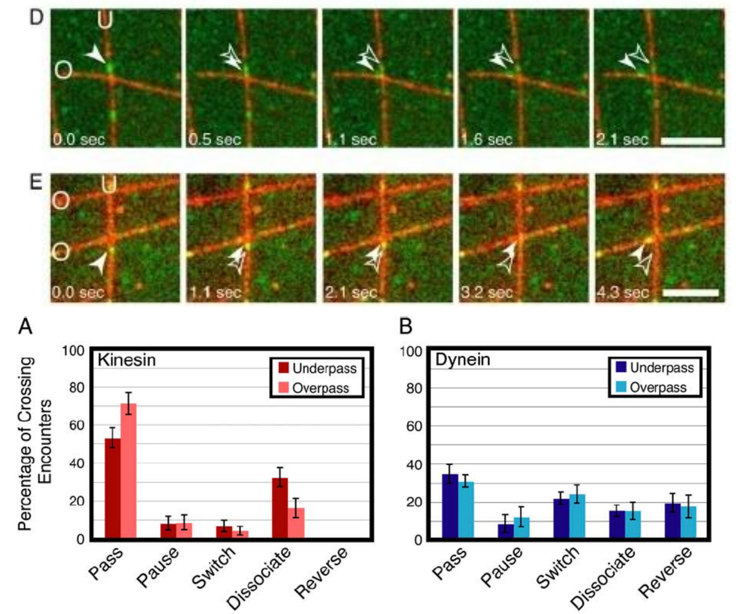
Motor proteins can work in highly viscous environments

Complexity of cytoplasm at small scale: exemple of the neurite

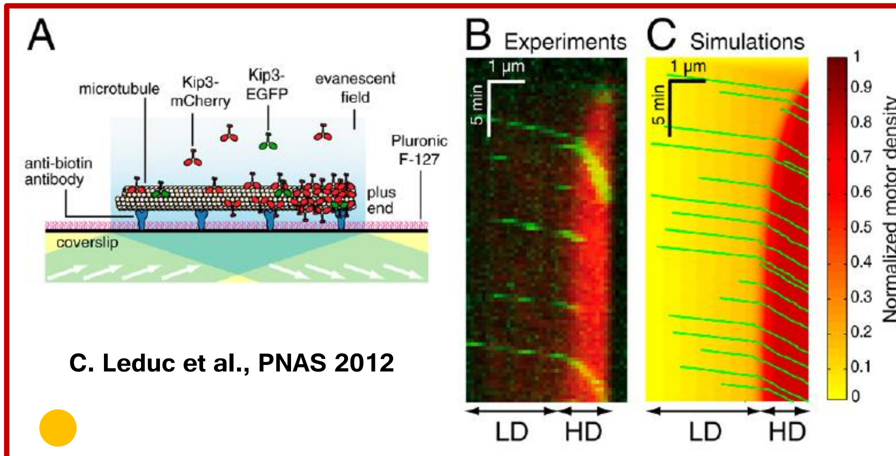


High force produced by the motor is necessary to face high viscous forces

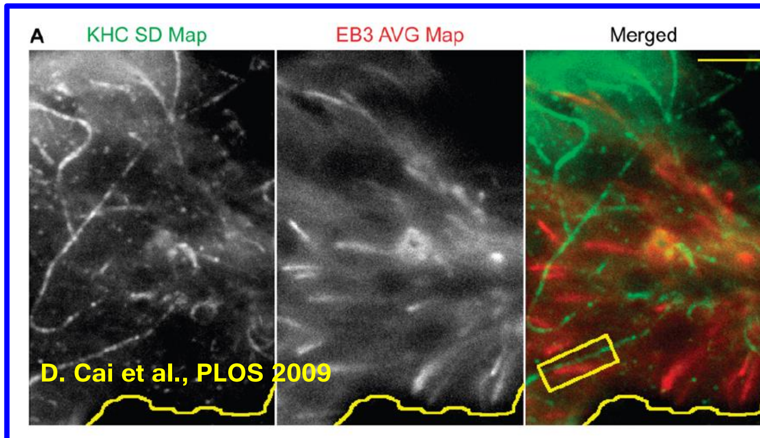
Quantitative detection and analysis are available

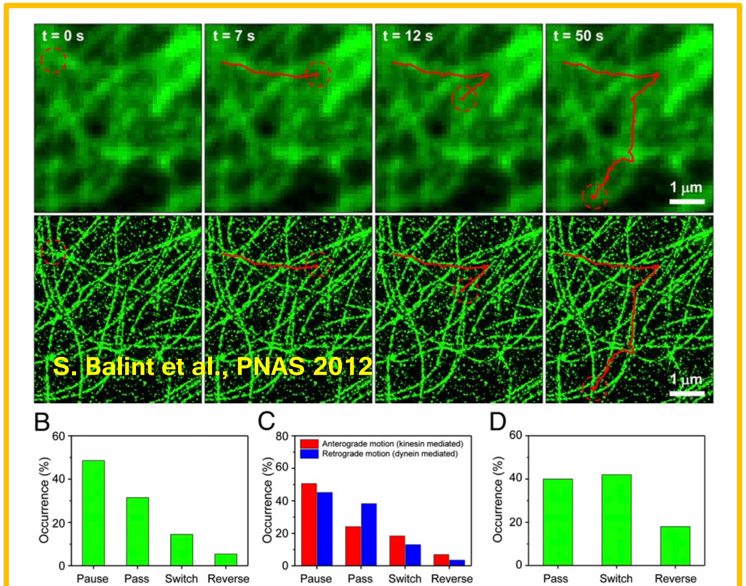


J. F. Ross et al., Biophys. J. 2008



C. Leduc et al., PNAS 2012

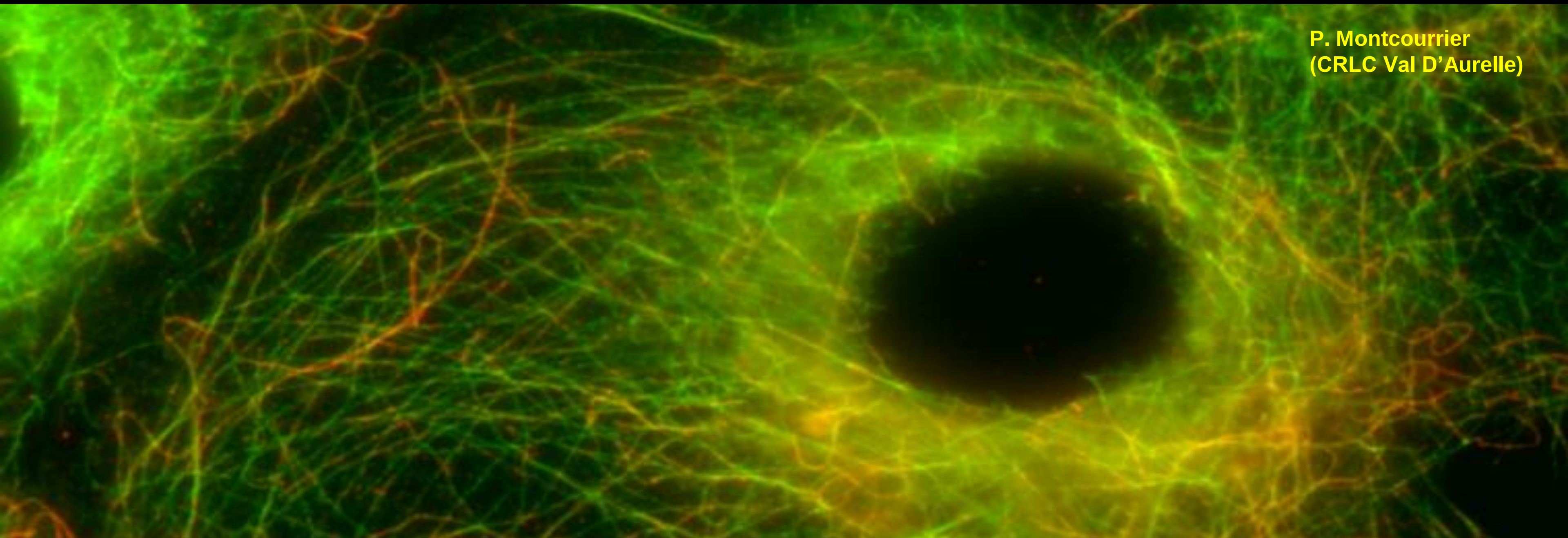




Methods (superresolution, single molecule) :

- **Fluorescence correlation spectroscopy and microscopy**
- **Single Particle Tracking, FIONA**
- **PALM-STORM**
- **STED**
- **...**

Intracellular “road-network”: structural complexity of the cytoskeleton

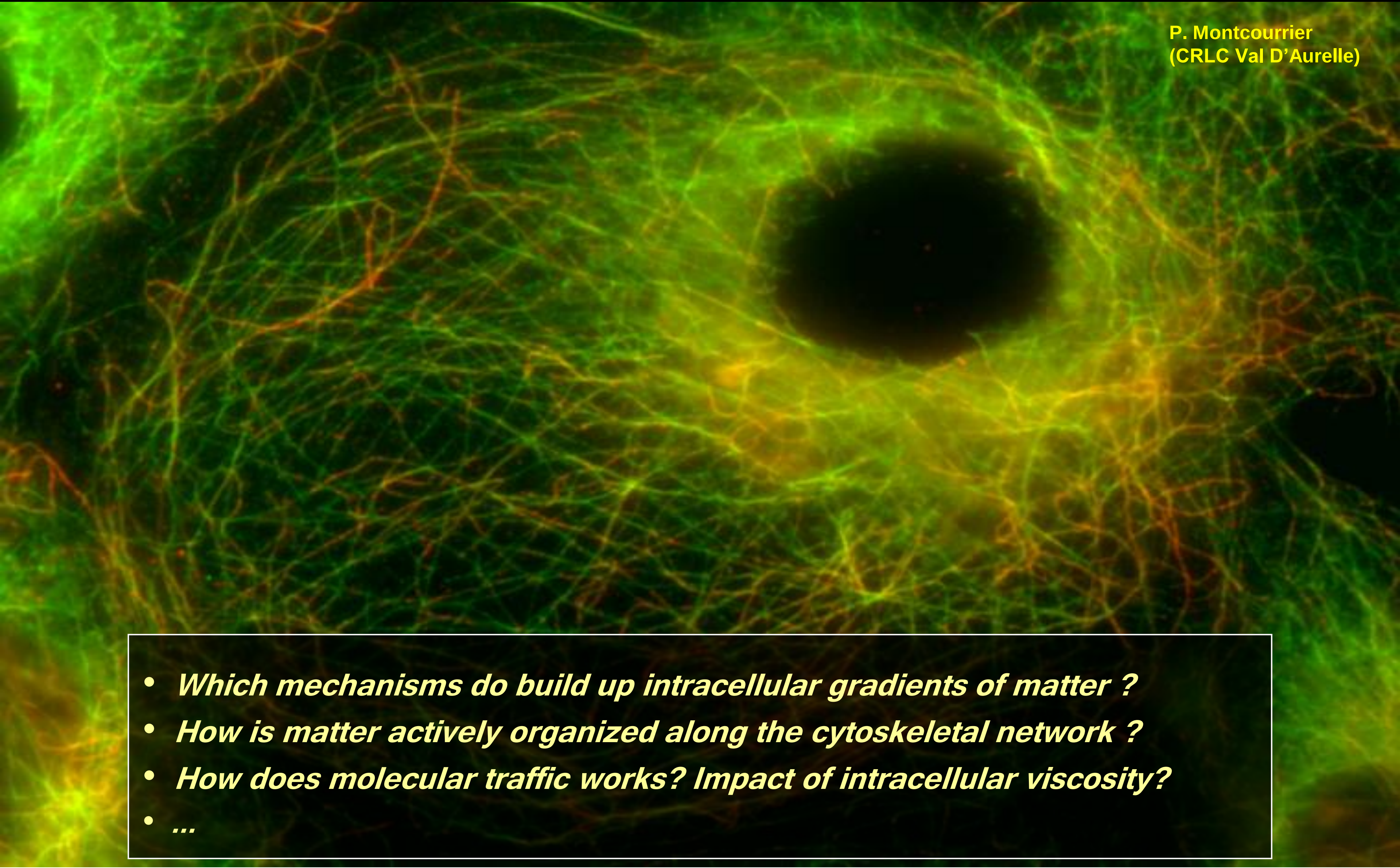


P. Montcourrier
(CRLC Val D’Aurelle)

“Rough” estimate for an “average cell” route system:

- **the total length of polymerized actin or microtubules : ~ half a meter**
  (scaling 10 nm up to 1 m: several time the French highway or the entire SNCF networks) squezed in the Paris city center)
- **lower bound for the number of filaments: ~5 10^3**
- **number of crossings between filaments : ~5 10^3 – 10^7**
- **in neurons such molecular highways can be several meters long!**
  (scaling 10 nm up to 1 m: the entire French road network)

Intracellular “road-network”: structural complexity of the cytoskeleton



- *Which mechanisms do build up intracellular gradients of matter ?*
- *How is matter actively organized along the cytoskeletal network ?*
- *How does molecular traffic works? Impact of intracellular viscosity?*
- *...*

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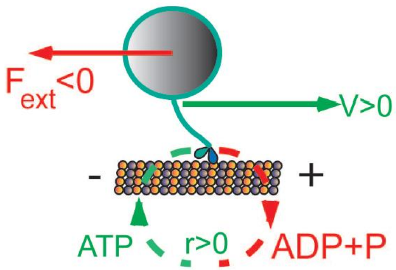
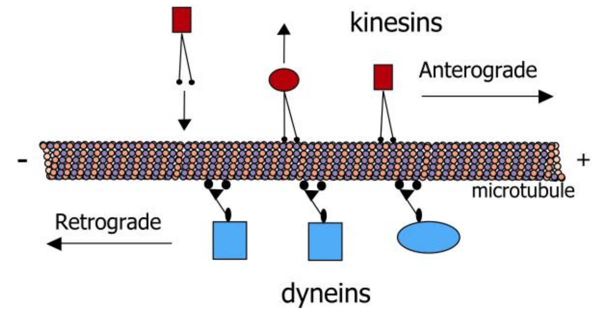
Our perspective (at DIMNP and L2C):
Multiscale modeling of cytoskeletal transport



Single motor protein properties

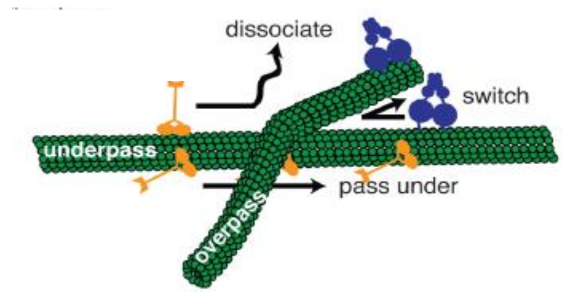


Collective transport on single filaments

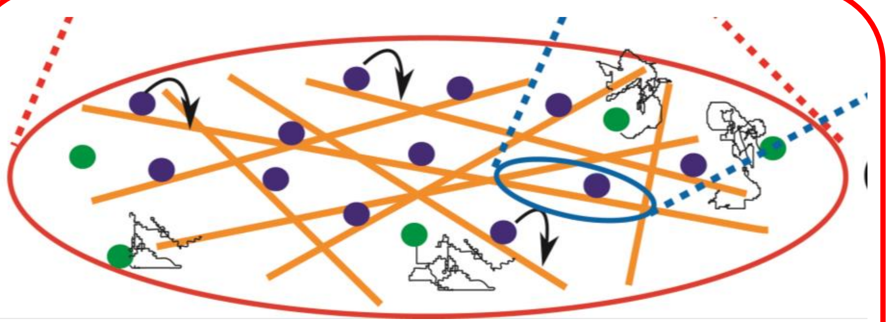
Biophysics
Biology
Medicine

Statistical mechanics
Stochastic processes
Non-linear physics

Applications



Collective transport on single junctions



Collective transport on networks

Man-made transports on networks also provide interesting examples and applications

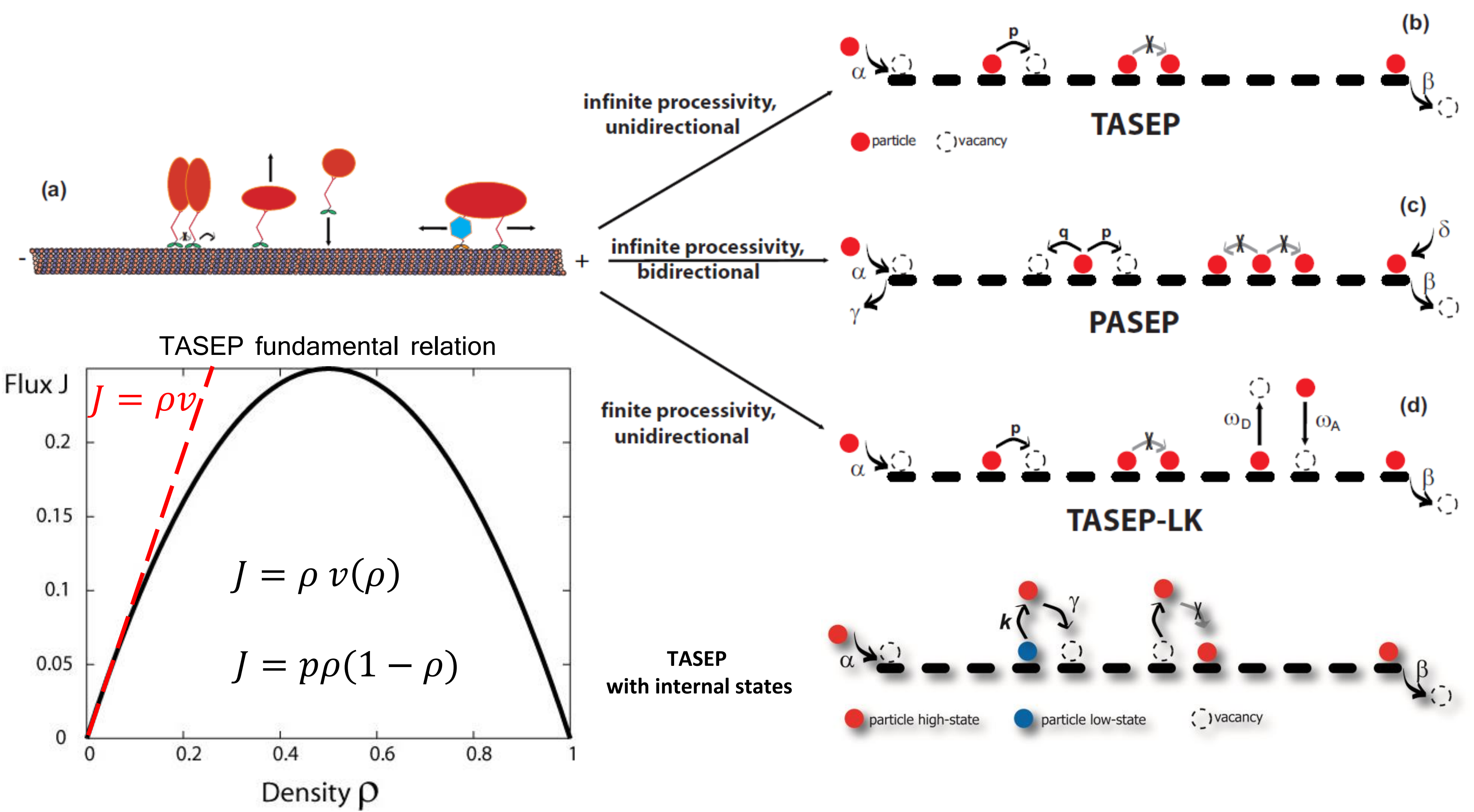
http://cbhg.org

- Traffic of vehicles, pedestrians, animals (logistics, environmental impact, migratory events)
- Power distribution grids
- Routing information on networks
- Electronic transport on q-dots linear chains and graphene-like structures, spintronics
- Anomalous low-dimensional heat conductivity on grids

Generalization of the Linear Transport Laws (Kirchoff-like) with interacting particles

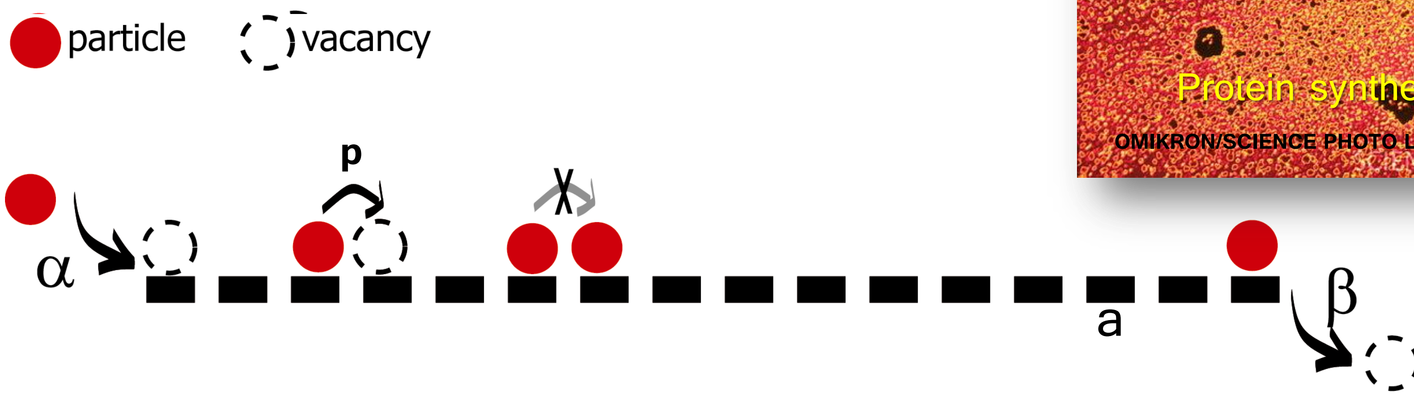
a “granular” flow of individual mobile entities → interactions → non linearities → novel phenomena?

Theoretical approach: Asymmetric simple exclusion processes (ASEP) as minimal models for active collective transport



TASEP
Totally Asymmetric Simple Exclusion Process

Motors = particles



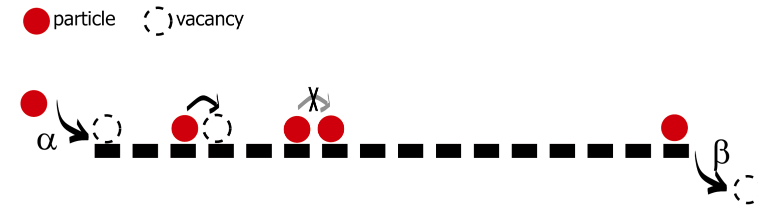
- Periodic binding sites
  with lattice size „a“
- Directed stochastic motion
- No double occupancy
- Boundary controlled

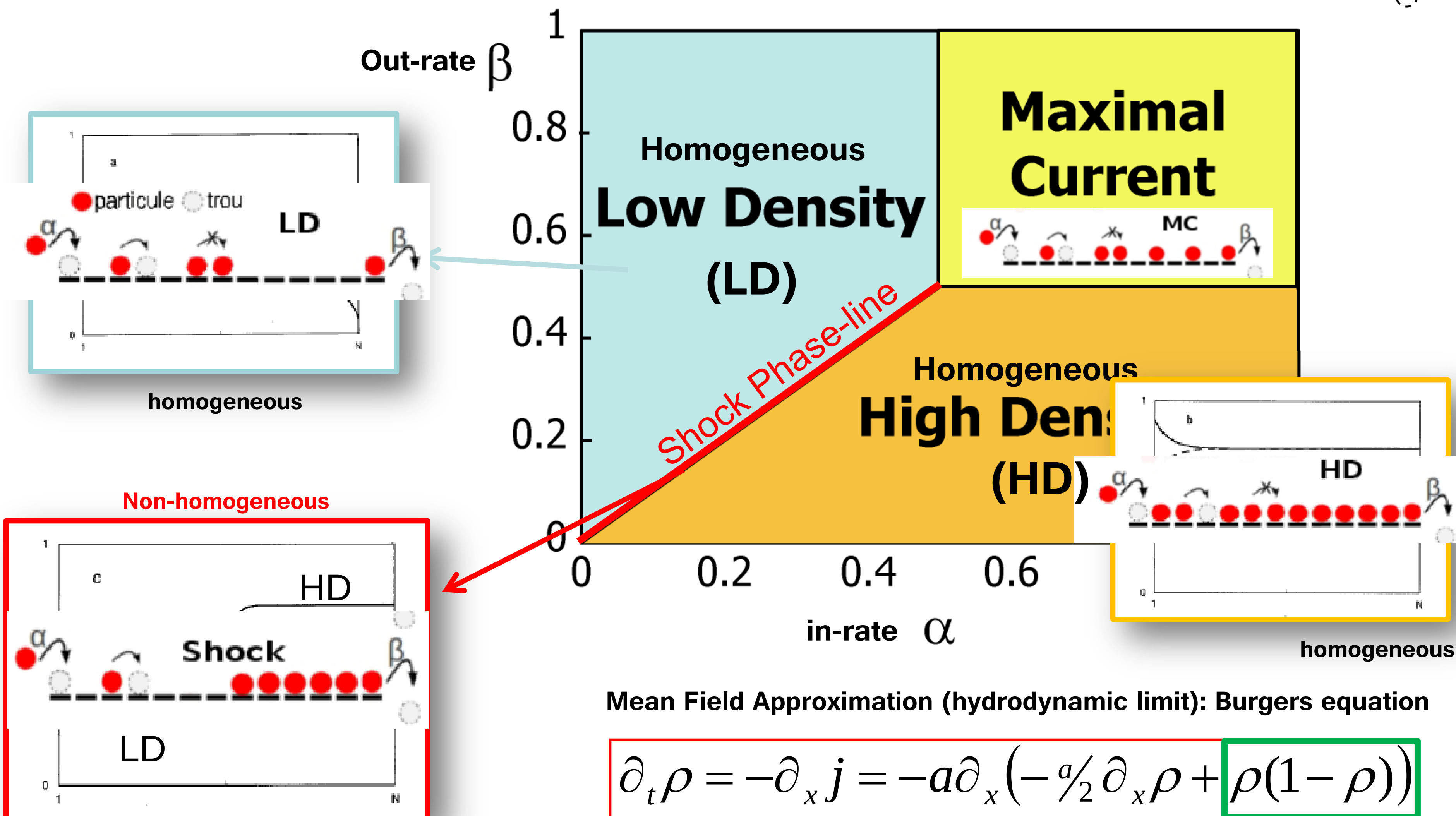
Totally Asymmetric Simple Exclusion Process: TASEP

(McDonald et al. ’68)

Non-linear problem developing a many-body open hierarchy of correlators. Impacts in: probability theory, traffic sciences, non-equilibrium statistical mechanics, field theory, mathematical physics, biological physics, animal collective behavior, …

TASEP phase diagram





Density shock performs a random walk with α–β dependent rate through all lattice **(Kolomeisky et al. '98)**

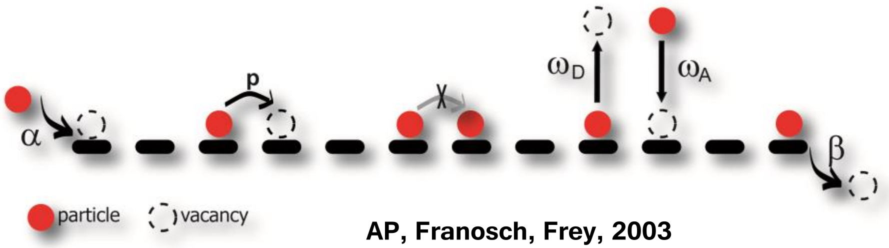
Mean Field Approximation (hydrodynamic limit): Burgers equation

$$\partial_t \rho = -\partial_x j = -a\partial_x\left(-{}^{a}\!/_{2}\,\partial_x \rho + \rho(1-\rho)\right)$$

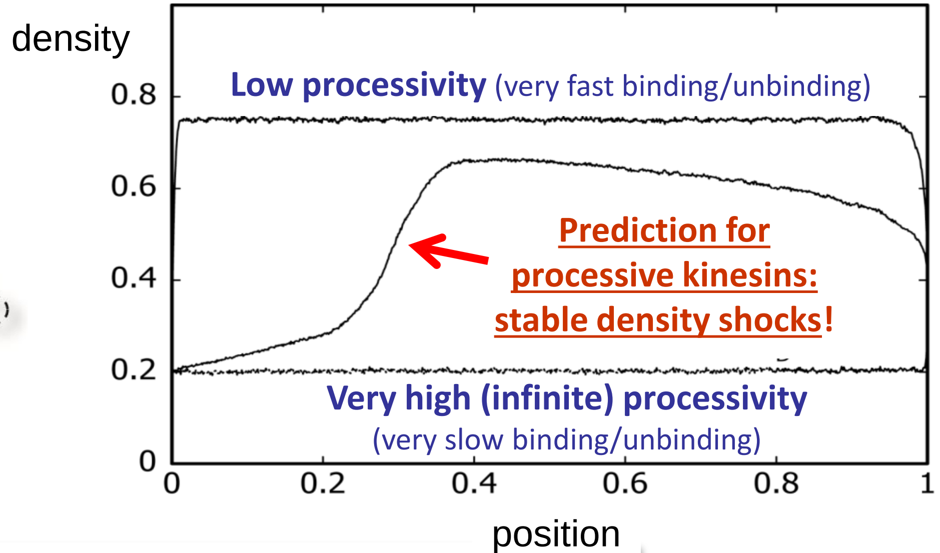
$$\rho(0) = \alpha,\ \ \rho(1) = 1\text{-}\ \beta \qquad \text{for } a = 1/L \to 0$$

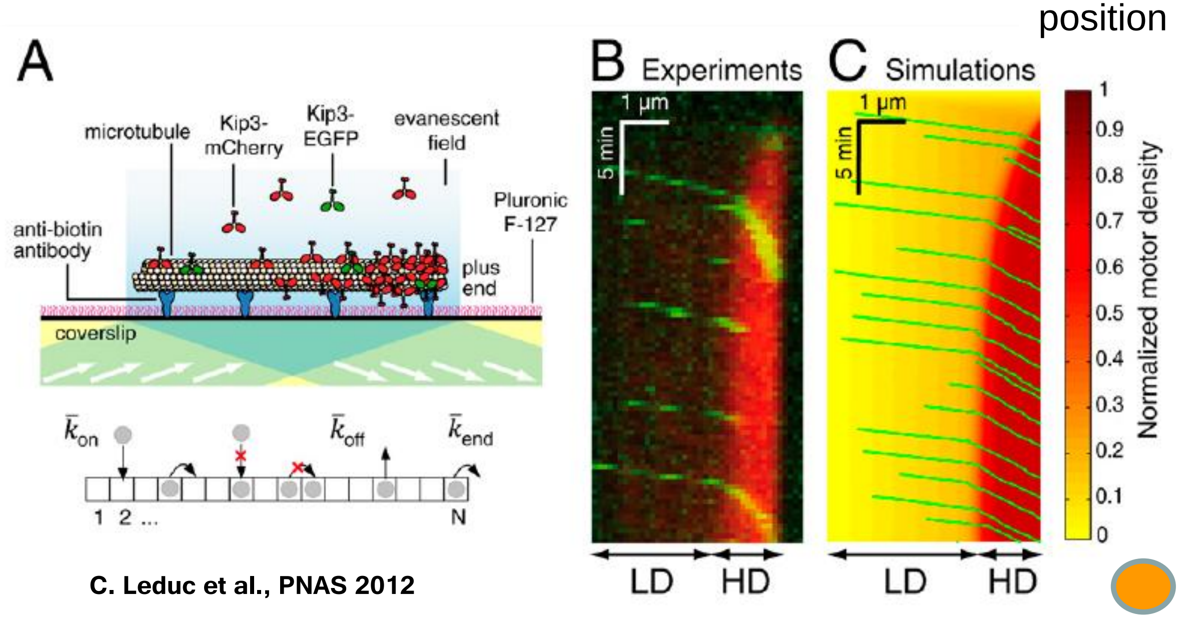
Exclusion Processes can provide qualitative and quantitative knowledge

TASEP-LK



AP, Franosch, Frey, 2003





C. Leduc et al., PNAS 2012

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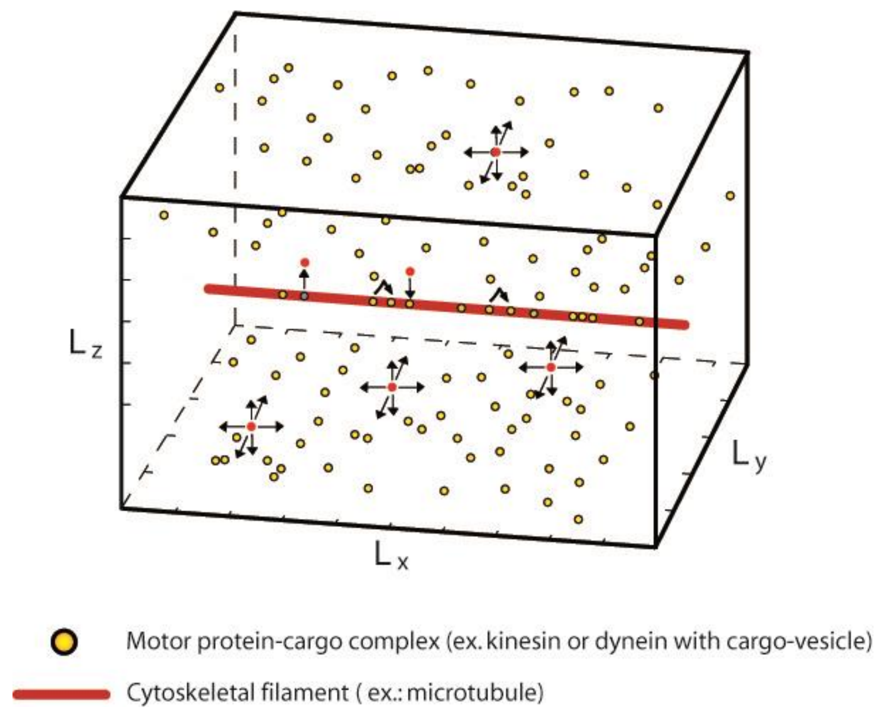
Role of cytoplasmic viscosity in a compartment

TASEP-LK (finite processivity)



- TASEP+LK on filament coupled with 3D diffusion
- New characteristic time: diffusion time in volume

Model Parameters (in water)

Box volume $V = L_x L_y L_z = 10\times 1\times 1\,\mu m^3$

Filament length $L_f = 8\,\mu m$

Motor concentration

$c_m = tens\ of\ nM \ \ (6 \rightarrow 250\,\mathrm{mtrs})$

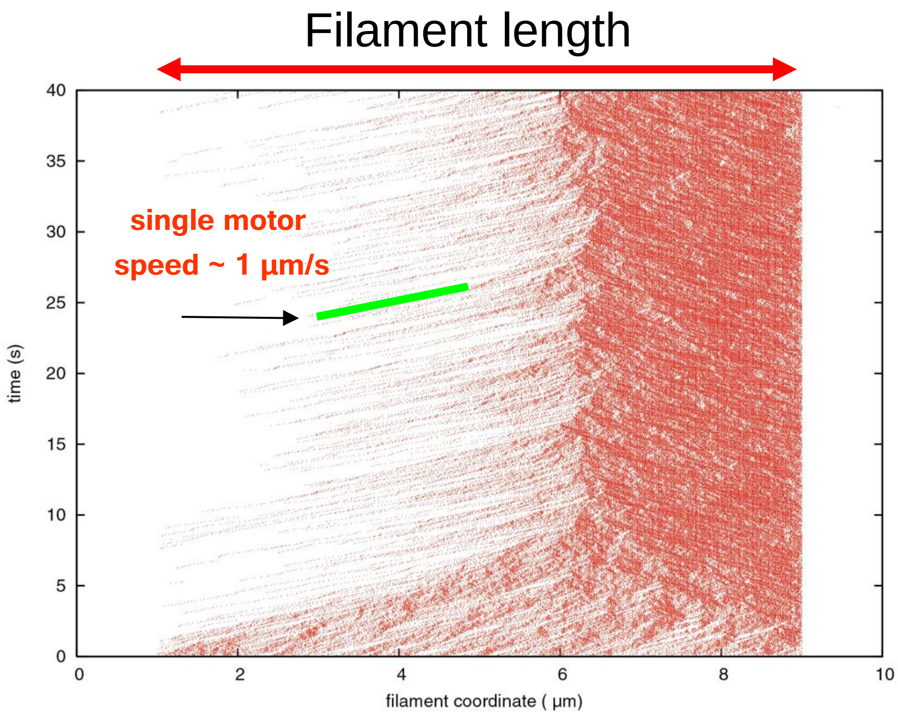
$\omega_{diff} \sim 10^6 s^{-1} \ \ (=1)$ >> $\omega_{step} = 0.0001\,\omega_{diff}$ >> $\omega_{\det} = 0.01\,\omega_{step}$

Diffusion rate (water) — Stepping rate — Detachment rate

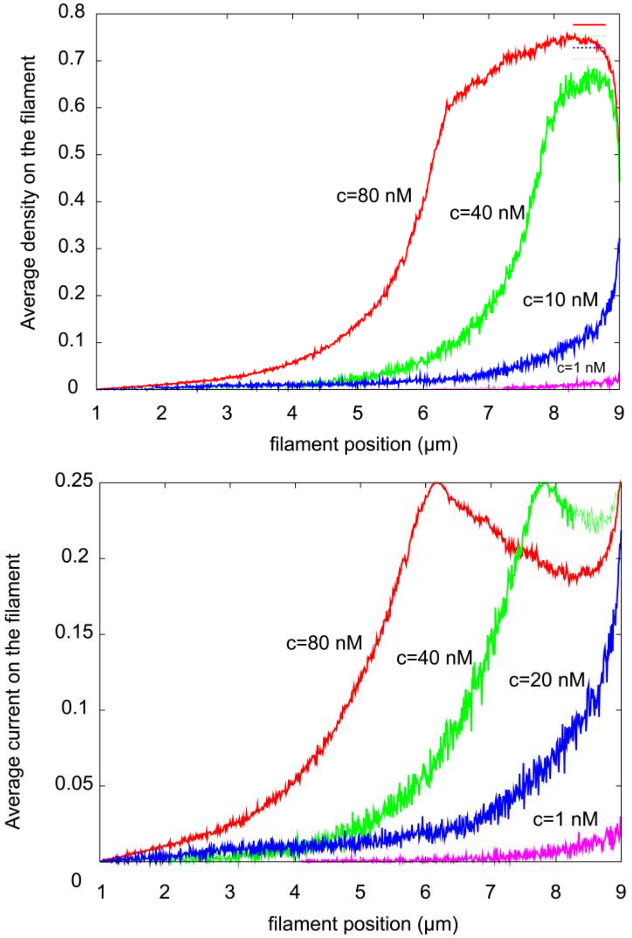
TASEP on the filament coupled with (3D) diffusion in the cytoplasm via LK and related models:

Klumpp and Lipowsky PRL 2001, Smith and Simmons, Biophys. J. 2001, Nedelec et al. PRL 2001, Klumpp et al., Biophys. J. 2005, Parmeggiani 2007…, Ciandrini et al. 2014, Dauloudet et al. in preparation

Monte Carlo simulation results (in water): concentration gradients and traffic jams along the filament



Kymograph reveals traffic jams and show that these are localized in space



Density jams along the filament

Monte Carlo simulation results: stochastic dynamics in watery vs cytoplasmic medium

- Proteins + cargo from 10 nm of hydrodynamic radius
- Cytoplasm effective viscosity ~ 10-100 times water viscosity

ω_{diff} (water) 100 times faster than ω_{diff} (cytoplasm)

•Two regimes : 1) Water (less viscous) -> "fast" diffusion (~ 1 μs)
2) Cytoplasm (more viscous) -> "slow" diffusion (~ 100 μs)

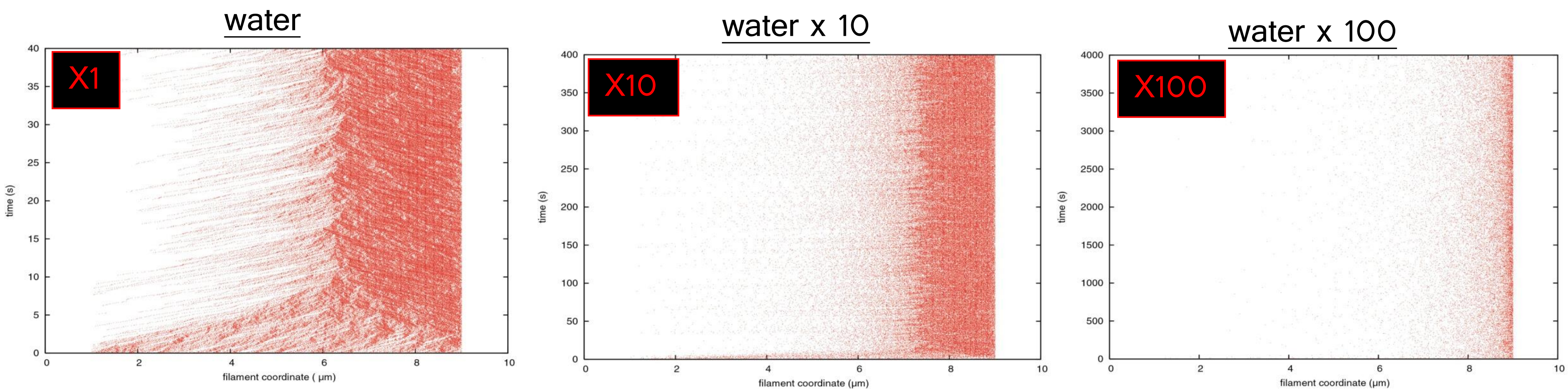
Water vs. Cytoplasm

•Traffic jams appear with fast diffusion (Dimensionality and geometry also matter!!!):

longitudinal diffusion *vs.* ***transversal diffusion***

(destroys concentration gradients) *(contributes to populate the filament by LK)*

Kymographs and Womain Walls : role of the medium (effective) viscosity



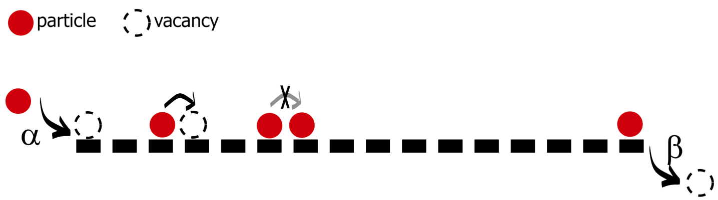
- In cytoplasm 3-dim concentration gradients are built without jams! (cytoskeletal filaments are "traps" of high affinity for processive motor proteins - AP (2009). Traffic and Granular Flow'07)
- In physiological conditions cytoplasm-like characteristics suggest that traffic jams are naturally prevented
- Other key parameters/determinants:
  - the ratio between "accessible-sites" on microtubules and the motor-cargo complex concentrations ("finite resources")
  - microtubule length and spatial organization (Ciandrini et al. 2014, Dauloudet et al. in preparation)
  - single active cargo mechanochemical transduction (ex.: motors with internal states or collective motors, Ciandrini et al. 2014)

OUTLINE

Studying aspects of the "Self-organizing Cytoplasm and Nucleoplasm" via transport phenomena in biology

- Active cytoskeletal transport driven by motor proteins
- Theoretical modeling approaches
- "Simple" examples playing with:
  - Intracellular effective viscosity (ie diffusion coefficient)
  - Filament organization
  - Large networks
- Conclusions

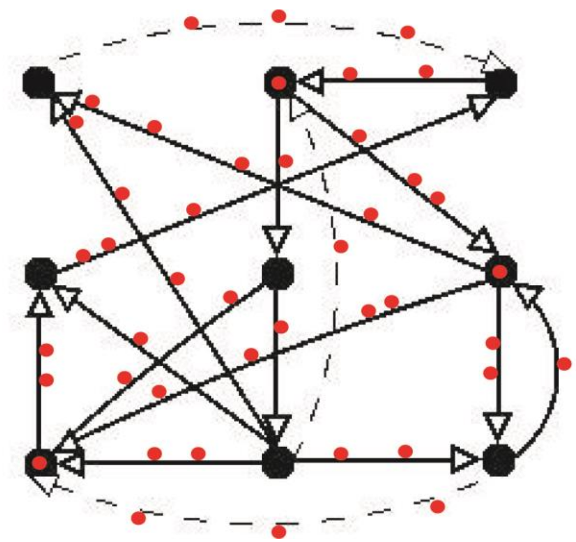
Transport on simple and complex topologies

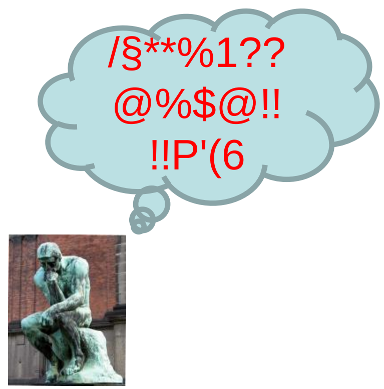


Mean Field Approximation (hydrodynamic limit): Burgers equation

$$\partial_t \rho = -\partial_x j = -a\partial_x\left(-\tfrac{a}{2}\partial_x \rho + \rho(1-\rho)\right)$$

$$\rho(0) = \alpha,\ \ \rho(1) = 1 - \beta \qquad \text{for } a = 1/L \to 0$$

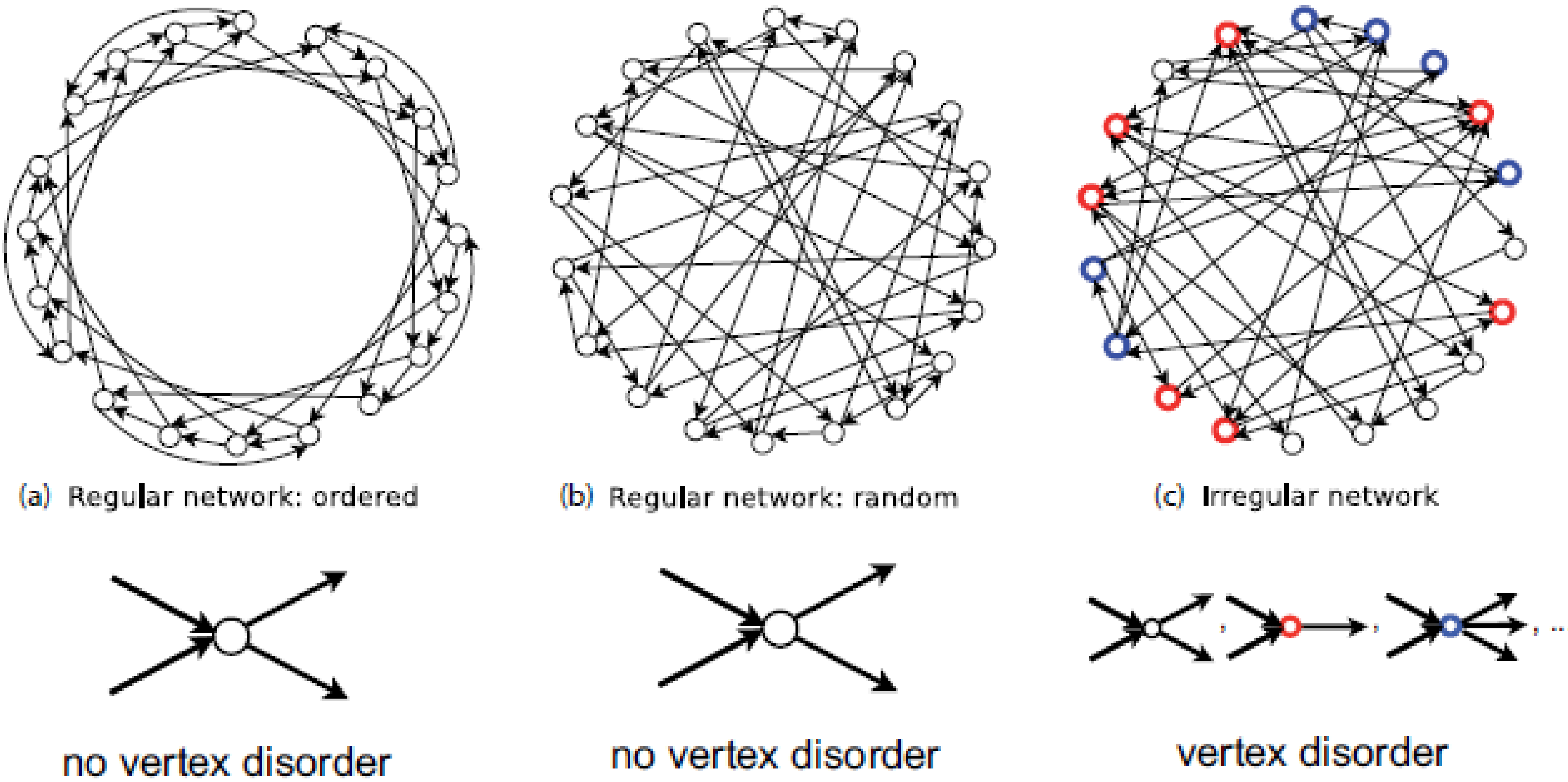




?

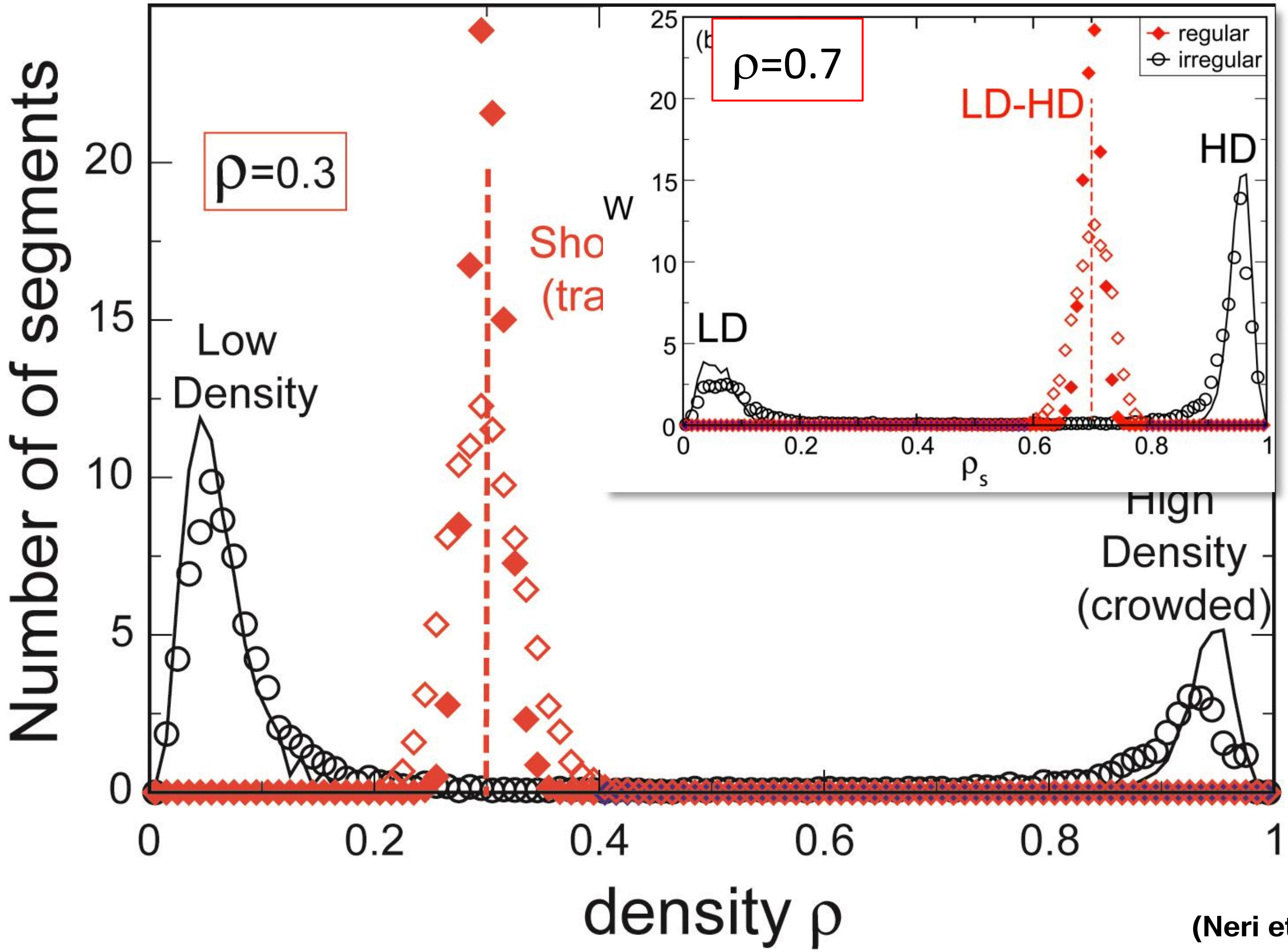
- ***Understanding the physical principles of intracellular transport (fluxes, traffic, regulation...)***
- ***Efficient method for large scale networks (comparable to the cytoskeleton size)?***
- ***Role of the network-cytoskeleton topology (regular, random, irregular, ...) ?***
- ***Role of transporter molecular properties (processivity, bidirectionality, ...)?***

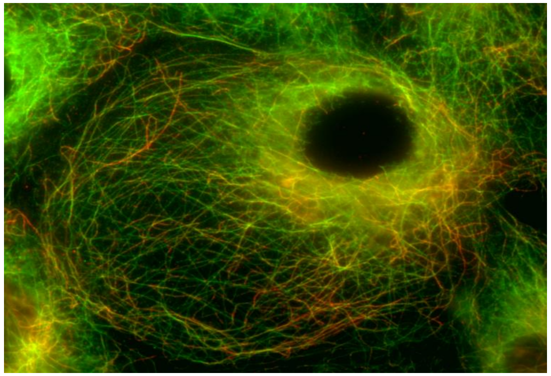
Mathematical complexity: Random networks as “toy” networks

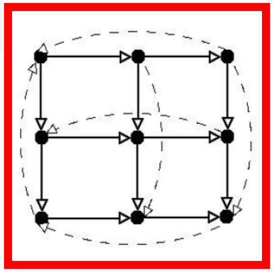


Role of the network/cytoskeleton connectivity?

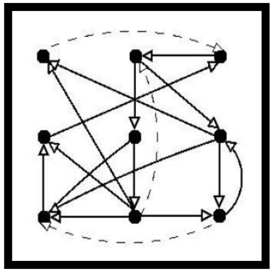
TASEP on regular vs. Irregular networks: distribution of densities of particles along the network







Regular
c=const.



Irregular
<c>=const

(Neri et al. PRL 2011, PRL 2013, NJP 2014)

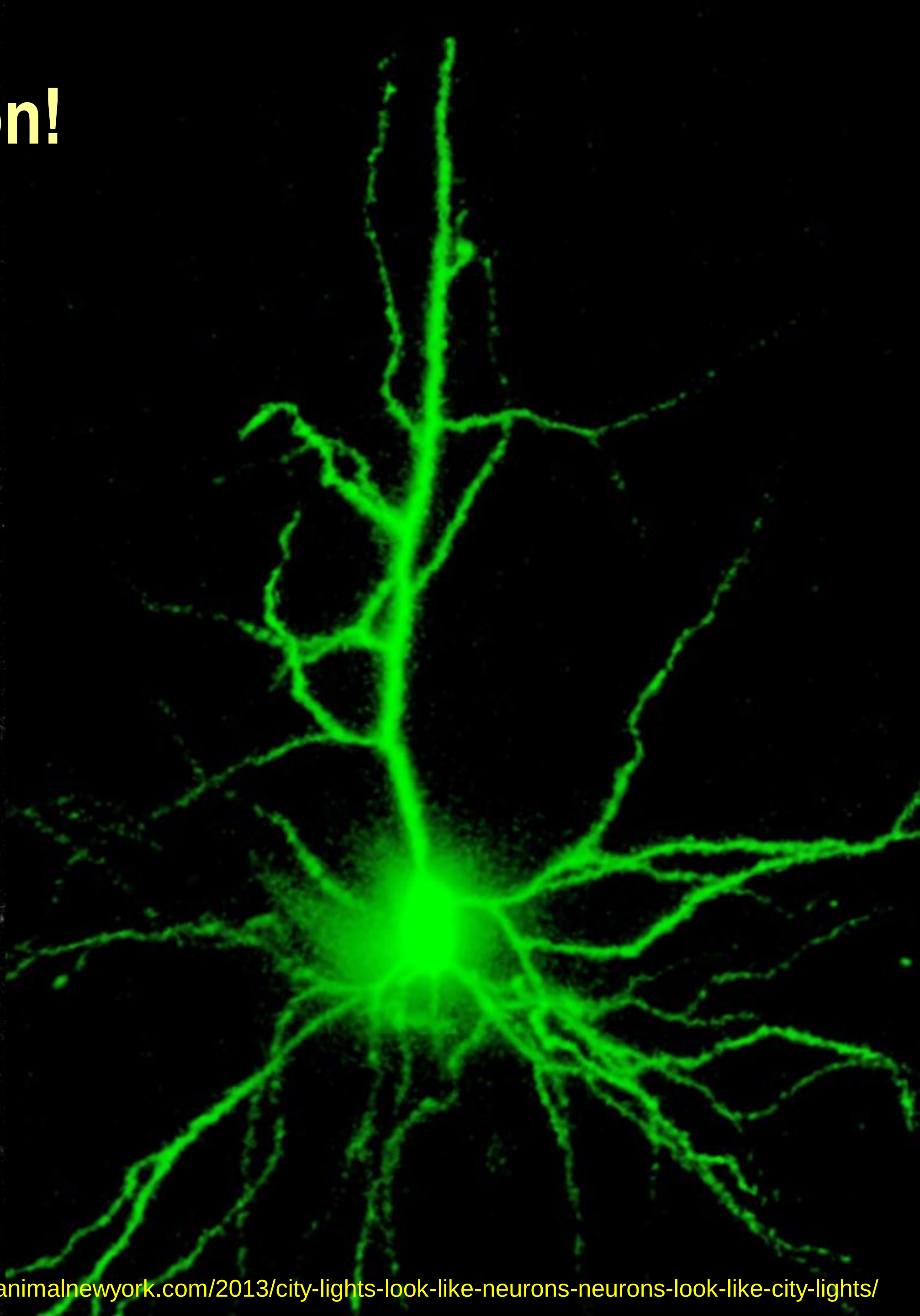
Irregular networks → density bimodality :
emergence of density heterogeneities between filaments
Preferential lanes for fast transport of individual cargoes?

CONCLUSIONS

- **General methods** :
  - numerical and analytical, from single motor properties to large scale networks
- **Multiscale coupled/phenomena**:
  - Finite diffusion coupled with network connectivity/topology and mesh size and molecular properties:
    - processivity, motor average speed, bidirectionality, motor protein internal dynamics
- **Multiscale emergence of matter heterogeneities**
  - Along the cytoskeleton and in the cytoplasm due to:
    - Cargo concentration and filament site availability
    - Filament length and organization
    - Cytoplasm properties: shape, effective viscosity and compartments
- **Robust mechanisms**
  - to build up cytoplasmic concentration gradients and avoid /modulate traffic jams/clustering in physiological conditions
- **Many open problems**
  - optimization principles, transport + filament dynamics, motor specificities and regulations (cargoes, targets), transport + aggregation, transport and membrane organization/activity, transport and cell mechanics, cytoplasmic streaming, …
- **Opening to nuclear biophysics:**
  - Analogies on macromolecular motions, but DNA as well as cytoskeleton conformation and remodeling factors need to be considered

http://itsnutsoutthere.blogspot.fr/2013/02/the-anatomy-of-traffic-jam.html

Thanks for your attention!



http://animalnewyork.com/2013/city-lights-look-like-neurons-neurons-look-like-city-lights/