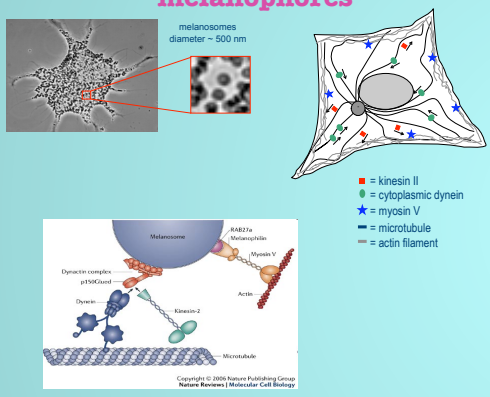
Anomalous diffusive behavior in intracellular transport mediated by molecular motors

Luciana Bruno[1,3*], Valeria Levi[2,3], Maia Brunstein[4] and Marcelo Despósito[1,3]

[1] Departamento de Física and [2] Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina. [3] CONICET, Argentina. [4]Laboratoire de Photonique et Nanoestructure, Route de Nozay, 91460 Marcoussis, France; *lbruno@df.uba.ar*

Abstract Intracellular transport of large cargoes, such as organelles, vesicles, or large proteins, is a complex dynamical process that involves the interplay of ATP-consuming molecular motors, cytoskeleton filaments, and the viscoelastic cytoplasm. In this work we investigate the motion of pigment organelles or melanosomes driven by molecular motors in *Xenopus laevis* melanocytes using a high-spatio-temporal resolution tracking technique. By analyzing the obtained trajectories, we show that the melanosomes mean-square displacement undergoes a transition from a subdiffusive to a superdiffusive behavior. A stochastic theoretical model, which explicitly considers the collective action of the molecular motors, is introduced to generalize the interpretation of our data. Starting from a generalized Langevin equation, we derive an analytical expression for the MSD, which also takes into account the experimental noise. By fitting theoretical expressions to experimental data we were able to discriminate the exponents that characterize the passive and active contributions to the dynamics. Then, our model gives a quantitative description of active transport in living cells with a reduced number of parameters.

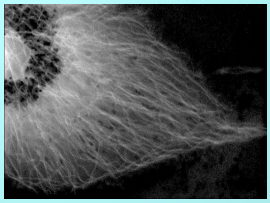
Motors involved in melanosome transport in *Xenopus* melanophores



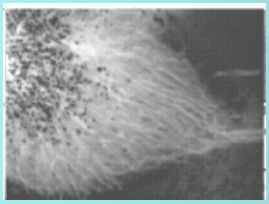
Methods

Microtubules are depolymerized with 10 μM nocodazol. Aggregation and dispersion are stimulated by treatment with **melatonin** and **MSH**, respectively and trajectories of melanosomes driven by myosin-V are recovered by using the pattern-recognition method [1].

To investigate the behavior of melanosomes when the activity of myosin-V motors ins inhibited, we used cells with **mutated myosin-V** which cannot attach to actin filaments.



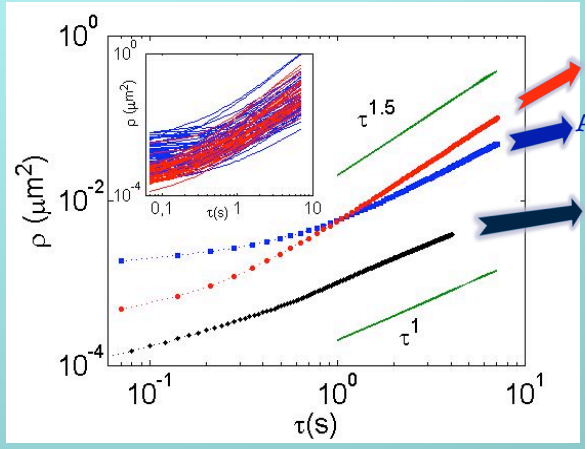
Melatonin
Aggregation



MSH
Dispersion

Trajectories

A representative trajectory recovered from a tracking experiment. The cell was stimulated with 10nM of MSH. Scale bar=0.5 μm. Myosin-V driven melanosomes were tracked during 70 s with 0.07s resolution.



$$\rho(\tau) = \left\langle \left[x(t+\tau) - x(t)\right]^2 + \left[y(t+\tau) - y(t)\right]^2 \right\rangle$$

Theoretical Approach

The modeling of anomalous diffusing stochastic processes has mainly been done within the framework of the generalized Langevin equation (GLE) approach.

$$m\ddot{X}(t) + m\int_0^t \gamma(t-t')\dot{X}(t')dt' = F(t) + \xi(t)$$

where $\gamma(t)$ is the dissipative memory kernel, $F(t)$ is an internal noise (related to the subdiffusive passive transport) while $\xi(t)$ is an external noise related to the active transport due to the action of the molecular motors.

The internal noise $F(t)$ is a zero-centered and stationary random force with correlation function

$$\langle F(t)\rangle = 0, \quad \langle F(t)F(t')\rangle = C(|t-t'|)$$

The memory kernel $\gamma(t)$ is related to the correlation function of the noise via the fluctuation-dissipation theorem $C(t) = kT\gamma(t)$

Assuming that the F-actin network has no global directionality, the external noise $\xi(t)$ is chosen as a zero-centered one. and stationary random force with correlation function

$$\langle \xi(t)\rangle = 0, \quad \langle \xi(t)\xi(t')\rangle = \Lambda(|t-t'|)$$

To describe the non-Markovian dynamics of an anomalously diffusing particle the memory effects through a long-time tail noise must be taken into account.
In particular, a power-law correlation function is usually employed to model the anomalous diffusion processes.

$$C(t) = \frac{C_0}{\Gamma(1-\lambda)}t^{-\lambda}, \quad 0<\lambda<1$$

$$\Lambda(t) = \frac{\Lambda_0}{\Gamma(1-\alpha)}t^{-\alpha}, \quad 0<\alpha<1$$

Results

The dynamics can be solved analytically. In the asymptotic regime, the mean square displacement leads to [2]:

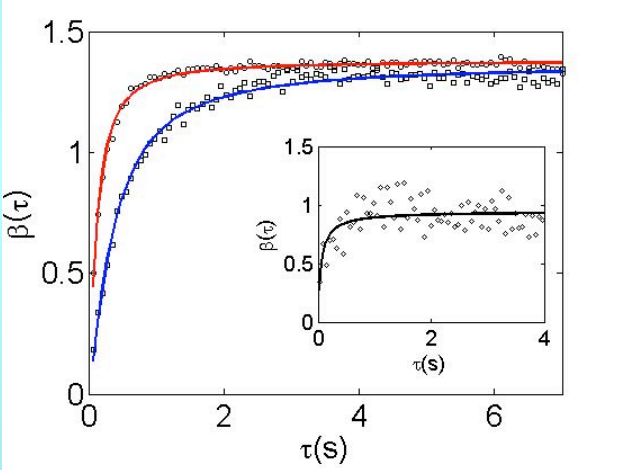
$$\rho(\tau) = \frac{2k_BT}{\gamma_o}\left(\frac{1}{\Gamma(\lambda+1)}\tau^{\lambda} + \varepsilon K_{\lambda,\alpha}\tau^{2\lambda-\alpha}\right) + 2\eta^2$$

$$K(\alpha,\lambda) = \Gamma(\alpha-2\lambda)\frac{\sin(\pi(\lambda-\alpha)) - \sin(\pi\lambda)}{\pi} > 0$$

Note that when $2\lambda-\alpha>1$ the behavior is **superdiffusive**. η is the magnitude of the tracking error. For mutants, $\varepsilon=0$.

Local Slope = $\beta(\tau) = \dfrac{\tau}{\rho}\dfrac{d\rho}{d\tau}$

$$\beta(\tau) = \frac{\frac{\lambda}{\Gamma(\lambda+1)}\tau^{\lambda} + \varepsilon(2\lambda-\alpha)K_{\lambda,\alpha}\tau^{2\lambda-\alpha}}{\frac{1}{\Gamma(\lambda-1)}\tau^{\lambda} + \varepsilon K_{\lambda,\alpha}\tau^{2\lambda-\alpha} + \gamma_0\frac{\eta^2}{2k_BT}}$$



	λ	α	ε	δ
Aggregation	0.96 +/- 0.04	0.58 +/- 0.08	202 +/- 38	41 +/- 8
Dispersion	0.98 +/- 0.03	0.58 +/- 0.10	83 +/- 13	4.0 +/- 0.6
Mutant M-V	0.94 +/- 0.04			0.06 +/- 0.01

Conclusion: The model predicts the observed crossover between subdiffusive to superdiffusive regimes, as well as it gives good estimates for the *in vivo* motor forces. Also, it enables us to determine a link between the macroscopic effective diffusion coefficient and the parameters in the microscopic scale

References:
[1] Levi, V., Serpinskaya, A.S., Gratton, E. and Gelfand, V. (2006) Biophys J 90, 318-27.
[2] Bruno, L., Levi, V., Brunstein, M. and Despósito, M. (2009). Phys. Rev. E 80, 011912