Anomalous dynamics of cell migration

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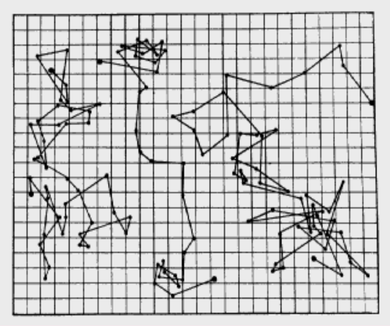
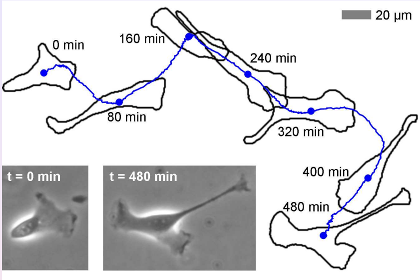
Brownian motion of migrating cells?

Brownian motion



Perrin (1913)

three colloidal particles, positions joined by straight lines



Dieterich et al., PNAS (2008)

single biological cell crawling on a substrate

Brownian motion?

conflicting results:

yes: Dunn, Brown (1987)

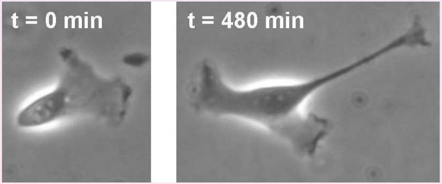
no: Hartmann et al. (1994)

Our cell types and how they migrate

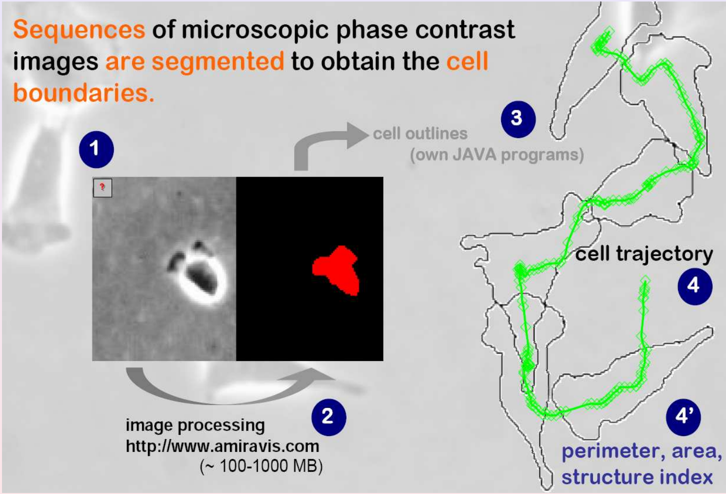
MDCK-F (Madin-Darby canine kidney) cells

two types: wildtype (NHE^+) and NHE-deficient (NHE^-)

movie: NHE^+: t=210min, dt=3min



Measuring cell migration



Theoretical modeling of Brownian motion

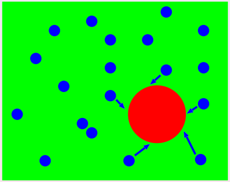
'Newton's law of stochastic physics':

$$\dot{\mathbf{v}} = -\kappa \mathbf{v} + \sqrt{\zeta}\,\xi(t)$$

Langevin equation (1908)

for a tracer particle of velocity **v** immersed in a fluid

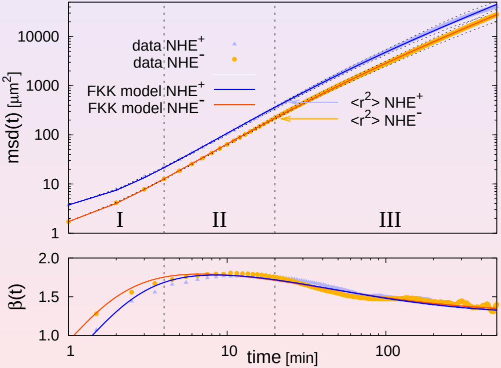
force decomposed into viscous damping and random kicks of surrounding particles



Application to cell migration?

Mean square displacement

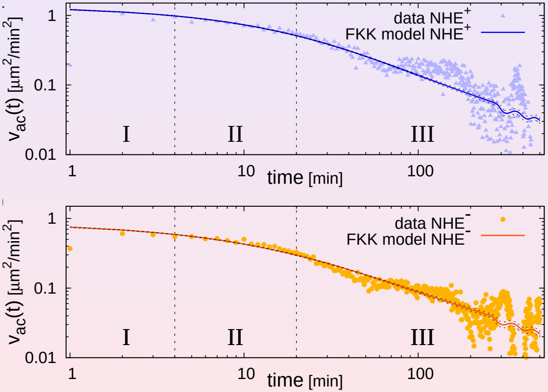
- $msd(t) := <[\mathbf{x}(t) - \mathbf{x}(0)]^2> \sim t^\beta$ with $\beta \to 2\ (t \to 0)$ and $\beta \to 1\ (t \to \infty)$ for Brownian motion; $\beta(t) = d \ln msd(t) / d \ln t$
- *solid lines:* (Bayes) fits from our model



anomalous diffusion if $\beta \neq 1\ (t \to \infty)$; here: **superdiffusion**

Velocity autocorrelation function

- $v_{ac}(t) :=< \mathbf{v}(t) \cdot \mathbf{v}(0) > \sim \exp(-\kappa t)$ for Brownian motion
- solid lines: fits from our model; same parameter values as $msd(t)$



crossover from **stretched exponential to power law**

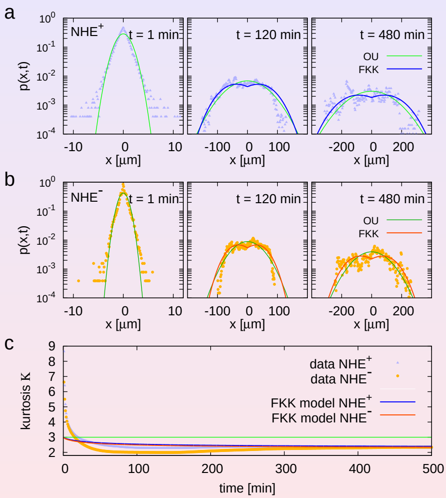
Position distribution function

- $P(x,t) \to$ Gaussian $(t \to \infty)$ and kurtosis

$$\kappa(t) := \frac{<x^4(t)>}{<x^2(t)>^2} \to 3 \ (t \to \infty)$$

for Brownian motion (green lines, in 1d)

- *other solid lines:* fits from our model; parameter values as before



crossover from peaked to broad **non-Gaussian distributions**

The model

- **Fractional Klein-Kramers equation** (Barkai, Silbey, 2000):

$$\frac{\partial P}{\partial t} = -\frac{\partial}{\partial x}[vP] + \frac{\partial^{1-\alpha}}{\partial t^{1-\alpha}}\kappa\left[\frac{\partial}{\partial v}v + v_{th}^2\frac{\partial^2}{\partial v^2}\right]P$$

with probability distribution $P = P(x, v, t)$, damping term κ, thermal velocity $v_{th}^2 = kT/m$ and Riemann-Liouville fractional (generalized ordinary) derivative of order $1-\alpha$
for $\alpha = 1$ Langevin's theory of Brownian motion recovered

- **analytical solutions** for $msd(t)$ and $P(x, t)$ can be obtained in terms of special functions (Barkai, Silbey, 2000; Schneider, Wyss, 1989)

- **4 fit parameters** v_{th}, α, κ (plus another one for short-time dynamics)

Possible physical interpretation

Physical meaning of the fractional derivative?

fractional Klein-Kramers equation is *approximately* related to the generalized Langevin equation

$$\dot{v} + \int_0^t dt' \, \kappa(t-t') v(t') = \sqrt{\zeta} \, \xi(t)$$

e.g., Mori, Kubo (1965/66)

with time-dependent friction coefficient $\kappa(t) \sim t^{-\alpha}$

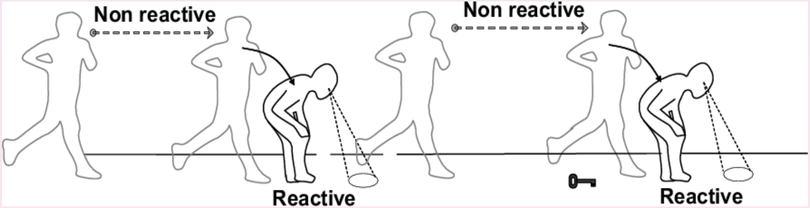
cell anomalies might originate from **glassy behavior** of the cytoskeleton gel, where power law exponents are conjectured to be universal (Fabry et al., 2003; Kroy et al., 2008)

Possible biological interpretation

Biological meaning of the anomalous cell migration?

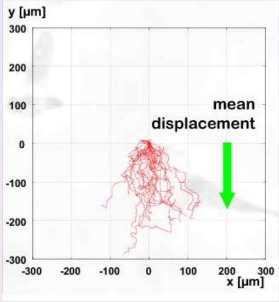
experimental data and theoretical modeling suggest *slower diffusion for small times* while *long-time motion is faster*

compare with intermittent optimal search strategies of foraging animals (Bénichou et al., 2006)



note: controversy about modeling the migration of foraging animals (albatros, bumblebees, fruitflies,...)

Outlook: cell migration under chemical gradients



new experiments on **murine neutrophils** under **chemotaxis**:

- linear drift in the direction of the gradient, $< y(t) > \sim t$
- $msd(t) - < y(t) >^2 \sim t^\beta$ with same exponent β as in equilibrium

$\Rightarrow \nexists$ fluctuation dissipation relation

modeled by the **fractional Klein-Kramers equation** with external force $F(x)$

$$\frac{\partial P}{\partial t} = -\frac{\partial}{\partial x}[vP] + \frac{\partial^{1-\alpha}}{\partial t^{1-\alpha}} \kappa \left[\frac{\partial}{\partial v} v - \frac{F}{\kappa m} \frac{\partial}{\partial v} + v_{th}^2 \frac{\partial^2}{\partial v^2} \right] P$$

Metzler, Sokolov (2002)

Thanks and literature

- **thanks** to A.V.Chechkin and E.Lutz for helpful discussions.
- **reference to this talk:**

P.Dieterich, R.K., R.Preuss, A.Schwab, *Anomalous Dynamics of Cell Migration*, PNAS **105**, 459 (2008)

- **as a general reference:**

R.K., G.Radons, I.M.Sokolov (Eds.)
Anomalous transport
(Wiley-VCH, 2008)