Anomalous dynamics of cell migration

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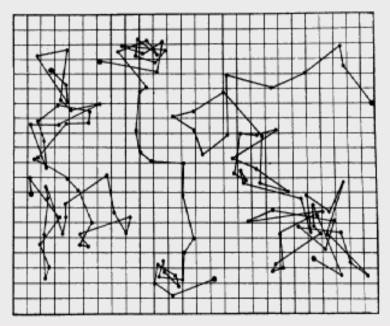
Outline

1. **Cell migration:** motivation and some biological details
2. **Experimental results:** statistics of cell migration
3. **Theoretical modeling:** fractional stochastic equation

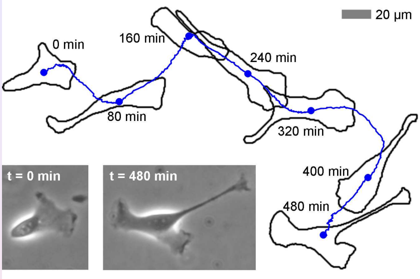
Brownian motion of migrating cells?

Brownian motion



Perrin (1913)

three colloidal particles, positions joined by straight lines



Dieterich et al. (2008)

single biological cell crawling on a substrate

Brownian motion?

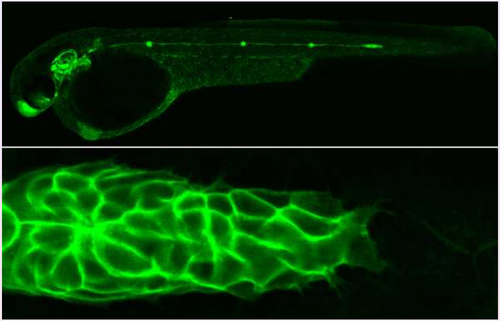
conflicting results:

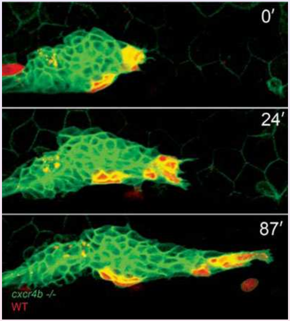
yes: Dunn, Brown (1987)

no: Hartmann et al. (1994)

Why cell migration?

motion of the *primordium* in developing zebrafish:





Gilmour (2008)

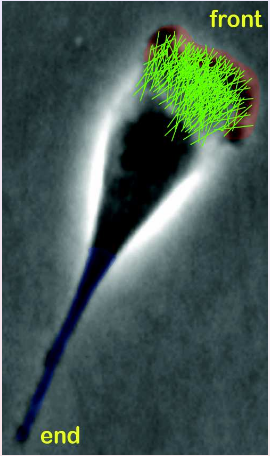
positive aspects:

- morphogenesis
- immune defense

negative aspects:

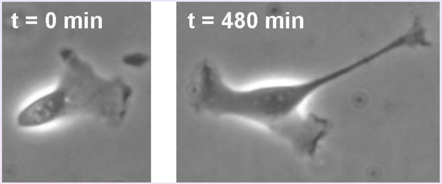
- tumor metastases
- inflammation reactions

How do cells migrate?



- **membrane protrusions and retractions** $\sim$ force generation:
  - lamellipodia (front)
  - uropod (end)
  - actin-myosin network
- formation of a **polarized state** front/end
- cell-substrate **adhesion**

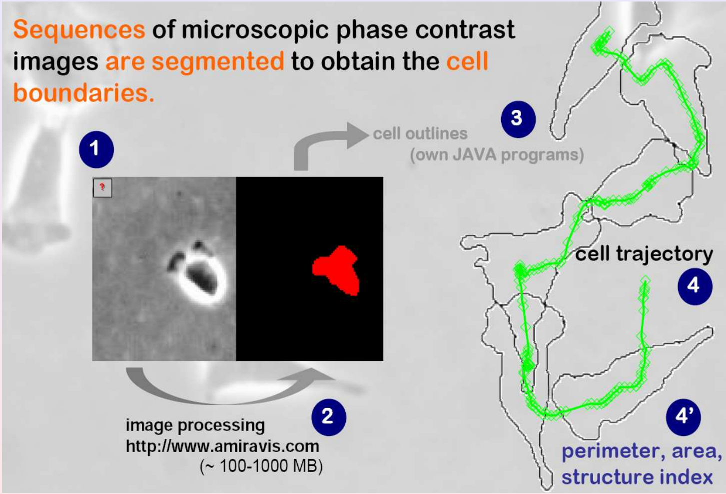
Our cell types and some typical scales



- renal epithelial MDCK-F (Madin-Darby canine kidney) cells; two types: wildtype (NHE^+) and NHE-deficient (NHE^-)
- observed up to 1000 minutes: here *no* limit $t \to \infty$!
- cell diameter 20-50μm; mean velocity $\sim$ 1μm/min; lamellipodial dynamics $\sim$ seconds

movies: NHE+: t=210min, dt=3min | NHE-: t=171min, dt=1min

Measuring cell migration



Theoretical modeling of Brownian motion

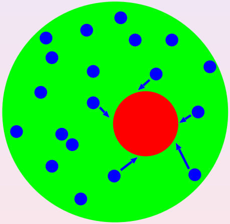
‘Newton’s law of stochastic physics’:

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

Langevin equation (1908)

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

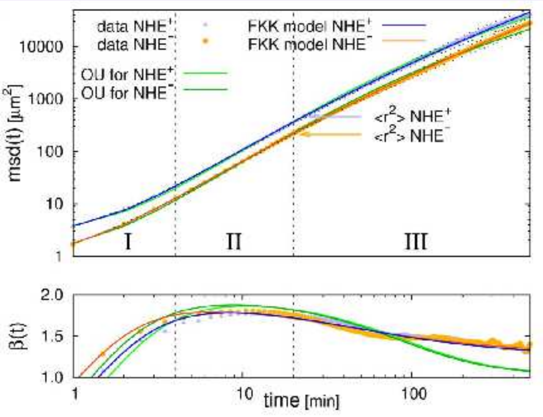
force decomposed into viscous damping and random kicks of surrounding particles



Application to cell migration?

Mean square displacement

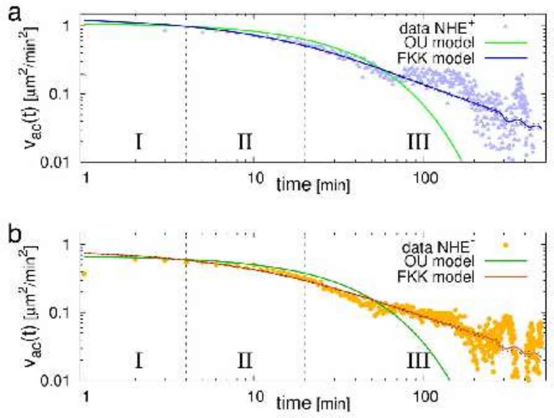
- $msd(t) := < [\mathbf{x}(t) - \mathbf{x}(0)]^2 > \sim t^\beta$ with $\beta \to 2$ $(t \to 0)$ and $\beta \to 1$ $(t \to \infty)$ for Brownian motion; $\beta(t) = d \ln msd(t) / d \ln t$



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
- fits with same parameter values as $msd(t)$



crossover from **stretched exponential to power law**

Position distribution function

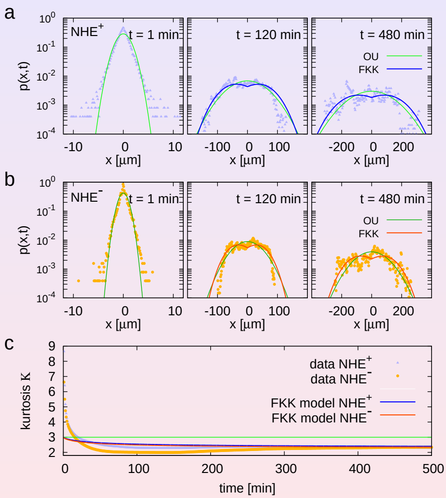
- $P(x,t) \rightarrow$ Gaussian $(t \rightarrow \infty)$ and kurtosis

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

for Brownian motion (green lines, in 1d)

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

note: model needs to be amended to explain short-time distributions



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} and Riemann-Liouville fractional derivative of order $1-\alpha$ defined by

$$\frac{\partial^\gamma P}{\partial t^\gamma} := \begin{cases} \frac{\partial^m P}{\partial t^m} & , \quad \gamma = m \\ \frac{\partial^m}{\partial t^m}\left[\frac{1}{\Gamma(m-\gamma)}\int_0^t dt' \frac{P(t')}{(t-t')^{\gamma+1-m}}\right] & , \quad m-1 < \gamma < m \end{cases}$$

with $m \in \mathbb{N}$; for $\alpha = 1$ ordinary Klein-Kramers equation recovered

4 fit parameters v_{th}, α, κ (plus another one for ‘biological noise’ on short time scales)

Solutions for this model

analytical solutions (Barkai, Silbey, 2000)**:**

- mean square displacement:

  $$msd(t) = 2v_{th}^2 t^2 E_{\alpha,3}(-\kappa t^\alpha) \to 2\frac{D_\alpha t^{2-\alpha}}{\Gamma(3-\alpha)} \ (t \to \infty)$$

  with $D_\alpha = v_{th}^2/\kappa$ and *generalized Mittag-Leffler function*

  $$E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k+\beta)} \ , \ \alpha \ , \ \beta > 0 \ , \ z \in \mathbb{C};$$

  note that $E_{1,1}(z) = \exp(z)$: $E_{\alpha,\beta}(z)$ is a generalized exponential function

- velocity autocorrelation function:

  $$v_{ac}(t) = v_{th}^2 E_{\alpha,1}(-\kappa t^\alpha) \to \frac{1}{\kappa\Gamma(1-\alpha)t^\alpha} \ (t \to \infty)$$

- for $\kappa \to \infty$ fractional Klein-Kramers reduces to a *fractional diffusion equation* yielding $P(x,t)$ in terms of a Fox function (Schneider, Wyss, 1989)

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)

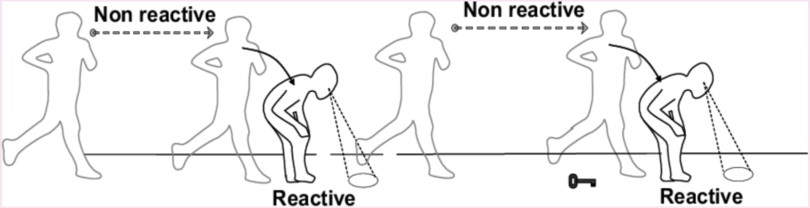
note: anomalous dynamics observed for *6 different cell types*

Possible biological interpretation

Biological meaning of the anomalous cell migration?

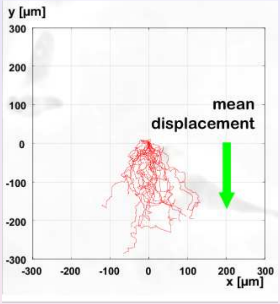
experimental data and theoretical modeling suggest *slower diffusion for small times* while *long-time motion is faster*

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)