Anomalous dynamics of cell migration

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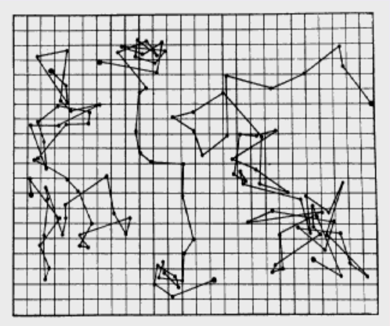
Outline

1. **Cell migration:** physical and biological motivation
2. **Experimental results:** statistical data analysis
3. **Theoretical modeling:** anomalous dynamics and its biophysical interpretation
4. **Summary and outlook**

Brownian motion of migrating cells?

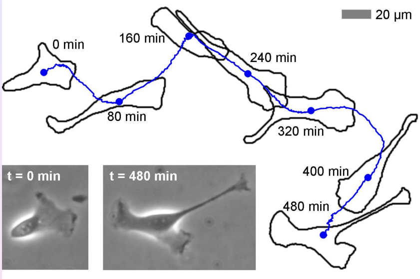
animation

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?

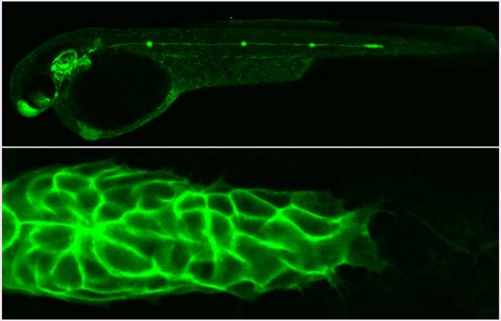
conflicting results:

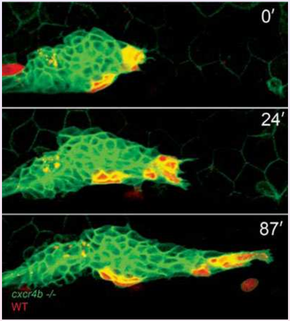
yes: Dunn, Brown (1987)

no: Hartmann et al. (1994)

Why cell migration?

motion of the primordium in developing zebrafish:





Lecaudey et al. (2008); here *collective* cell migration

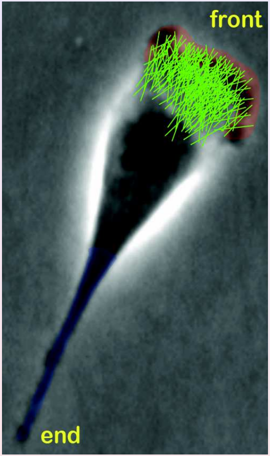
positive aspects:

- morphogenesis
- immune defense

negative aspects:

- tumor metastases
- inflammation reactions

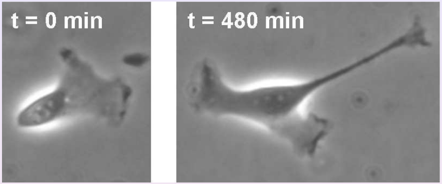
How do cells migrate?



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

Here we do **not** study the *microscopic origin* of cell migration; instead:
How does a cell migrate *as a whole* in terms of **diffusion**?

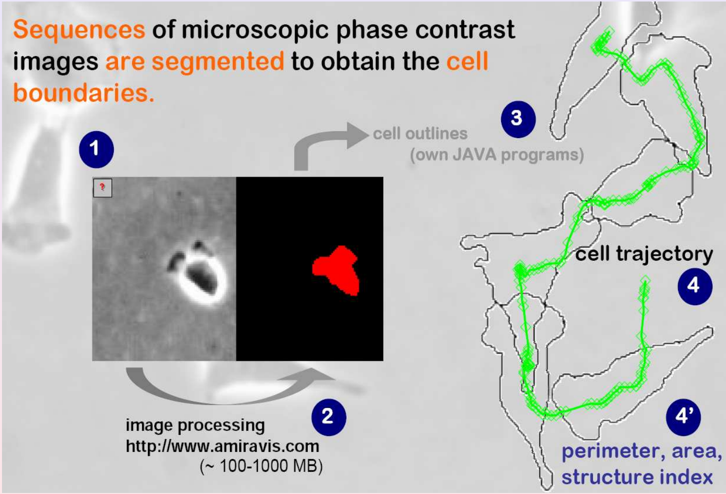
Our cell types and some typical scales



- 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

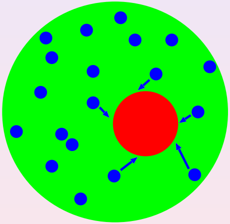
'Newton's law of stochastic physics':

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

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



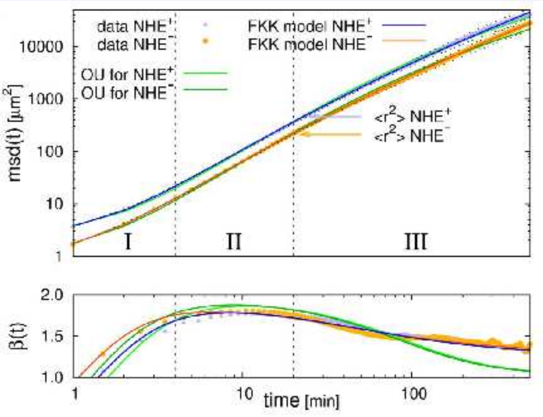
Application to cell migration?

but: cell migration is active motion, **not** passively driven!

cf. *active Brownian particles* (e.g., Romanczuk et al., 2012)

Mean square displacement

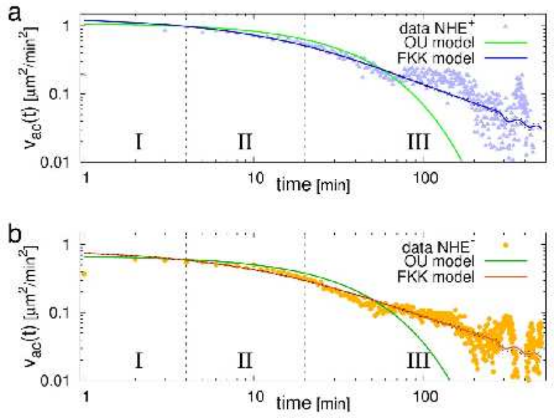
- $msd(t) := \langle[\mathbf{x}(t) - \mathbf{x}(0)]^2\rangle \sim t^\beta$ with $\beta \to 2\ (t \to 0)$ and $\beta \to 1\ (t \to \infty)$ for Brownian motion; $\beta(t) = d \ln msd(t)/d \ln t$



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

Velocity autocorrelation function

- $v_{ac}(t) := \langle \mathbf{v}(t) \cdot \mathbf{v}(0) \rangle \sim \exp(-\kappa t)$ for Brownian motion
- fits with same parameter values as $msd(t)$



crossover from **stretched exponential to power law**

Position distribution function

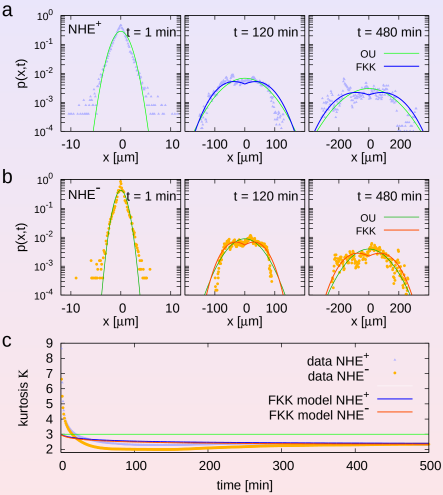
- $P(x,t) \rightarrow$ Gaussian $(t \rightarrow \infty)$ and kurtosis

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

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 $v_{th}^2 = kT/m$ 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)

What is a fractional derivative?

letter from Leibniz to L'Hôpital (1695): $\frac{d^{1/2}}{dx^{1/2}} = ?$

one way to proceed: we know that for integer m, n

$$\frac{d^m}{dx^m}x^n = \frac{n!}{(n-m)!}x^{n-m} = \frac{\Gamma(n+1)}{\Gamma(n-m+1)}x^{n-m};$$

assume that this also holds for $m = 1/2\ ,\ n = 1$

$$\Rightarrow \quad \boxed{\frac{d^{1/2}}{dx^{1/2}}x = \frac{2}{\sqrt{\pi}}x^{1/2}}$$

extension leads to the *Riemann-Liouville fractional derivative*, which yields power laws in Fourier (Laplace) space:

$$\frac{d^\gamma}{dx^\gamma}F(x) \leftrightarrow (ik)^\gamma \tilde{F}(k)$$

$\exists$ well-developed mathematical theory of **fractional calculus**, see Sokolov, Klafter, Blumen, Phys. Today 2002 for a short intro

Physical meaning of the fractional derivative?

- 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 $\kappa(t) \sim t^{-\alpha}$ generates *the same* $msd(t)$ and $v_{ac}(t)$ as the fractional Klein-Kramers equation

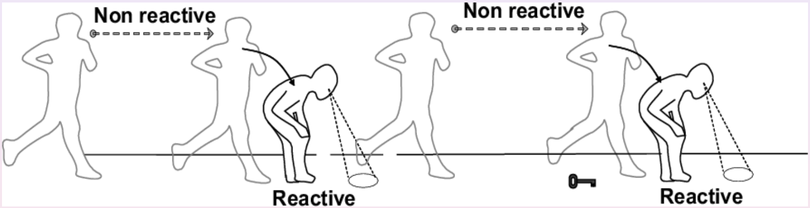
- fractional derivatives naturally model **power law correlations**:

$$\frac{\partial^\gamma P}{\partial t^\gamma} := \frac{\partial^m}{\partial t^m}\left[\frac{1}{\Gamma(m-\gamma)} \int_0^t dt' \frac{P(t')}{(t-t')^{\gamma+1-m}}\right] , \; m-1 \leq \gamma \leq m$$

- 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)

Biological meaning of the anomalous cell migration?

- results show *diffusion for short times slower* than Brownian motion while *long-time motion is faster*:
intermittent dynamics can minimize search times



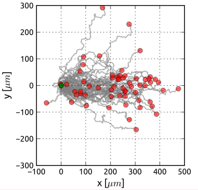
Bénichou et al. (2006)

- T-cells found to perform generalized Lévy walks by optimizing search efficiency (Harris et al., 2012)
relates to the *Lévy flight hypothesis* (Krummel et al., 2016; cf. also ASG 2015 at PKS)

Summary: Anomalous cell migration

- **anomalous dynamics:** superdiffusion with power law velocity correlations and non-Gaussian position pdfs for long times
- **theoretical model:** coherent mathematical description of experimental data by an anomalous stochastic process
- **temporal complexity:** different cell dynamics on different time scales
- **interpretation:** possible biophysical meaning of anomalous dynamics

Outlook



- new experiments on cell chemotaxis and verification of a generalized 2nd law-like relation: Dieterich et al. (2016)
- single vs. collective cell migration?
  - single cell motility controls glass and jamming transition Bi et al. (2016)
  - density dependence of cell migration: Allee effect Böttger et al. (2015)
- biological significance of anomalous diffusion? superdiffusion enhances colony formation of stem cells Barbaric et al. (2014)

References

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Anomalous Dynamics of Cell Migration
PNAS **105**, 459 (2008)