Anomalous dynamics of cell migration

P. Dieterich[1], R. Klages[2,3], R. Preuss[4], A. Schwab[5]

1 Institute for Physiology, Dresden University of Technology
2 Institute of Theoretical Physcs, Technical University of Berlin
3 School of Mathematical Sciences, Queen Mary University of London
4 Center for Interdisciplinary Plasma Science, MPI for Plasma Physics, Garching
5 Institute for Physiology II, University of Münster

Department of Physics, FU Berlin
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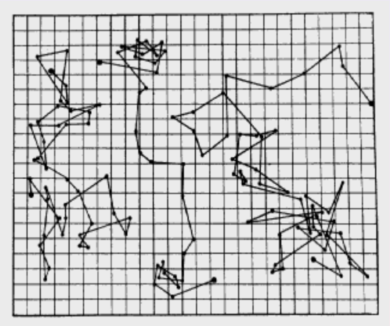
Outline

1. **Cell migration:** physical and biological motivation
2. **Experimental results:** statistical data analysis
3. **Theoretical modeling:** anomalous dynamics and its biophysical interpretation
4. **Fluctuation relations** for cell migration under chemical gradients

Brownian motion of migrating cells?

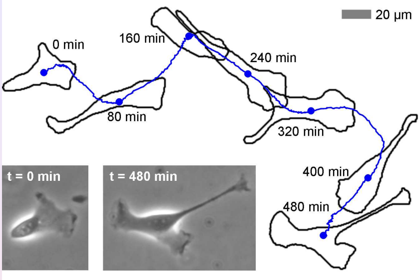
animation

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?

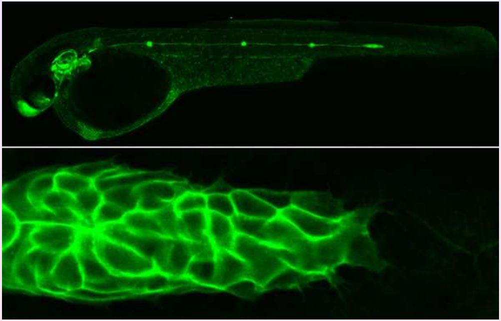
conflicting results:

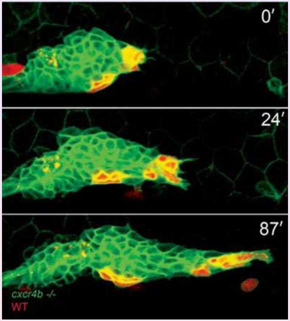
yes: Dunn, Brown (1987)

no: Hartmann et al. (1994)

Why cell migration?

motion of the primordium in developing zebrafish:





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

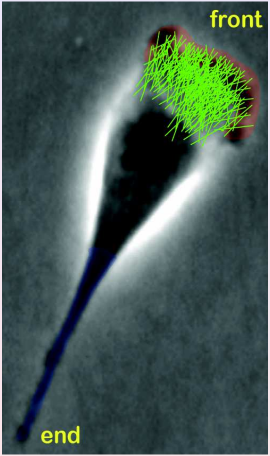
positive aspects:

- morphogenesis
- immune defense

negative aspects:

- tumor metastases
- inflammation reactions

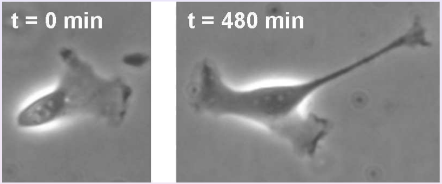
How do cells migrate?



- **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**?

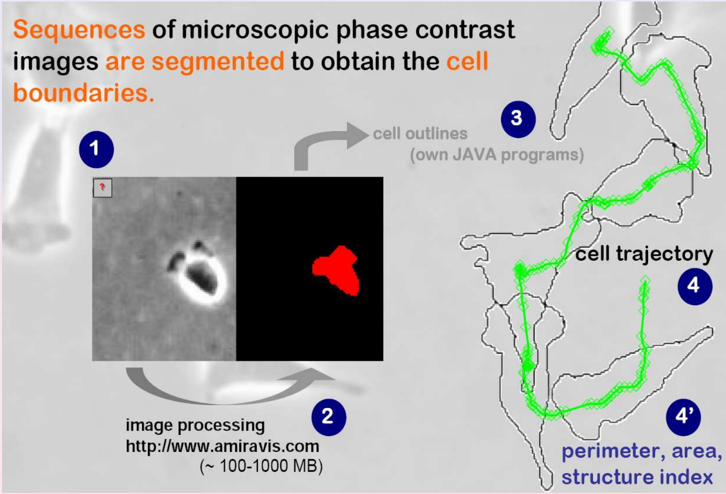
Our cell types and some typical scales



- 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

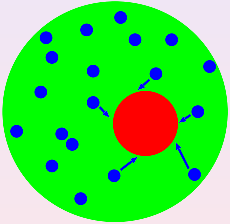
'Newton's law of stochastic physics':

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

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



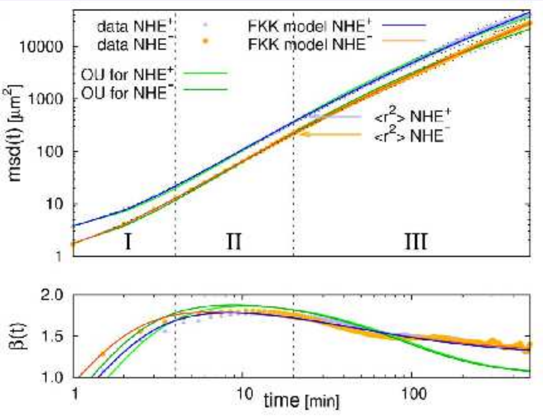
Application to cell migration?

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

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

Mean square displacement

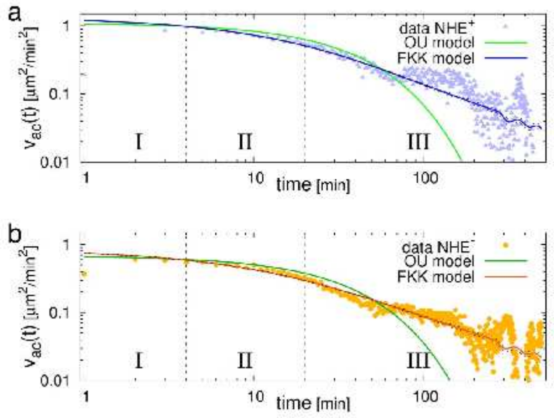
- $msd(t) := \langle[\mathbf{x}(t) - \mathbf{x}(0)]^2\rangle \sim t^\beta$ with $\beta \to 2$ $(t \to 0)$ and $\beta \to 1$ $(t \to \infty)$ for Brownian motion; $\beta(t) = d \ln msd(t)/d \ln t$



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

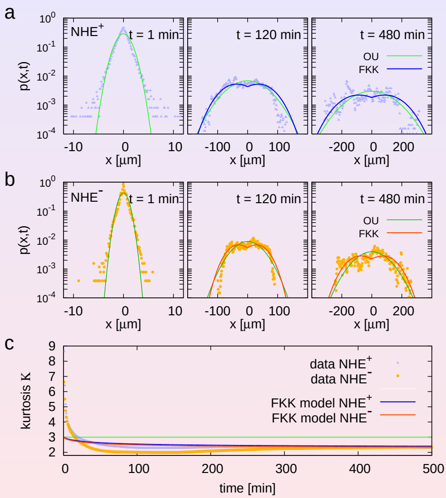
- $P(x,t) \to$ Gaussian $(t \to \infty)$ and kurtosis

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

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

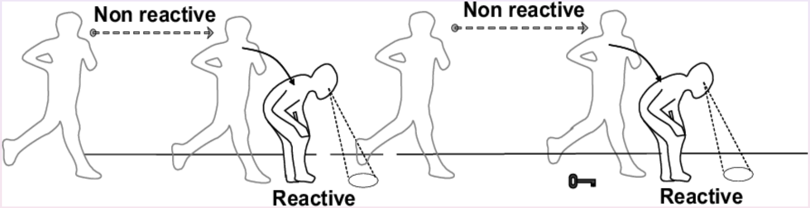
- fractional derivatives naturally model **power law correlations**:

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

- 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)

Motivation: Fluctuation relations

Consider a (classical) particle system evolving from some initial state into a nonequilibrium steady state.
Measure the probability distribution $\rho(\xi_t)$ of *entropy production* ξ_t during time t:

$$\ln \frac{\rho(\xi_t)}{\rho(-\xi_t)} = \xi_t$$

Transient Fluctuation Relation (TFR)

Evans, Cohen, Morriss (1993); Gallavotti, Cohen (1995)

why important? of *very general validity* and

1. generalizes the Second Law to small systems in nonequ.
2. connection with fluctuation dissipation relations (FDRs)
3. can be checked in experiments (Wang et al., 2002)

Anomalous TFR for Gaussian stochastic processes

theory:

consider **overdamped generalized Langevin equation**

$$\boxed{\dot{x} = F + \zeta(t)}$$

with force F and Gaussian power-law correlated noise

$$< \zeta(t)\zeta(t') >_{\tau=t-t'} \sim (\Delta/\tau)^{\beta} \text{ for } \tau > \Delta \, , \; \beta > 0$$

that is external (i.e., no FDR):

- dynamics can generate **anomalous diffusion**, $\sigma_x^2 \sim t^{2-\beta}$ with $2 - \beta \neq 1 \; (t \to \infty)$
- yields an **anomalous work fluctuation relation**,

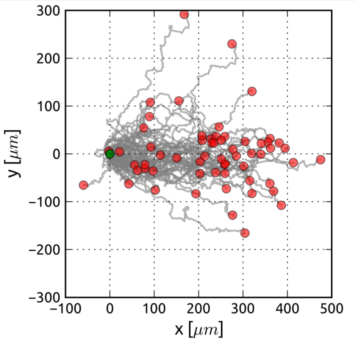
$$\ln \frac{\rho(W_t)}{\rho(-W_t)} = \mathbf{f}_{\beta}(\mathbf{t}) W_t$$

A.V.Chechkin, R.K. et al., J.Stat.Mech. L11001 (2012); L03002 (2009)

Cell migration under chemical gradients

experiments:

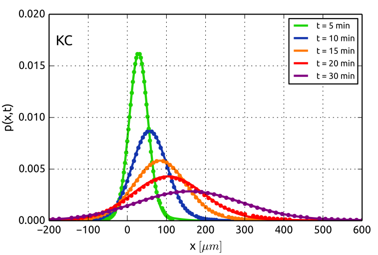
test this theory for chemotaxis of murine neutrophils:



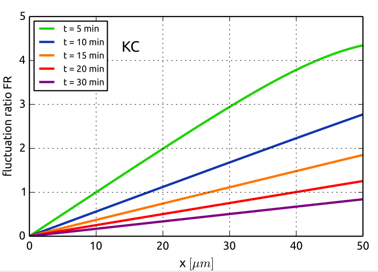
Dieterich et al. (submitted)

Anomalous fluctuation relation for cell migration

experim. results: position pdfs $\rho(x,t)$ are Gaussian



fluctuation ratio $R(W_t)$ is time dependent



$< x(t) > \sim t$ and $\sigma_x^2 \sim t^{2-\beta}$ with $0 < \beta < 1$: $\nexists$ FDR1 and

$$R(W_t) = \ln \frac{\rho(W_t)}{\rho(-W_t)} = \frac{W_t}{\mathbf{t}^{1-\beta}}$$

Dieterich et al. (tbp)

data matches to theory for persistent Gaussian correlations

Summary: Anomalous cell migration

- **experimental results:** MDCKF cells move *superdiffusively* 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
- **fluctuation relations:** generalized version derived theoretically and verified experimentally for chemotaxis of murine neutrophils

Outlook

- biological significance of anomalous diffusion?
  - superdiffusion enhances colony formation of stem cells (Barbaric et al., 2014)
  - cf. *Lévy hypothesis* that anomalous diffusion enhances search success? (Viswanathan et al., 1996)
- cross-link to active Brownian particles by non-trivial correlation decay (Fodor et al., 2016): importance of breaking FDR? (Volpe, RK, work in progress)
- single vs. collective cell migration?
  - single cell motility controls glass and jamming transition (Bi et al., 2016)
  - impact of velocity correlations on formation of nematic phases in interacting particle systems (Nava-Sedeno, Hatzikirou, RK, Deutsch, work in progress)

References

- P.Dieterich et al., PNAS **105**, 459 (2008)
- A.V. Chechkin, F.Lenz, RK, J. Stat. Mech. L11001 (2012)