Anomalous dynamics of cell migration

Peter Dieterich[1], Aleksei V. Chechkin[2], Roland Preuss[3], Otto Lars Lindemann[1], Rainer Klages[4], Albrecht Schwab[5]

[1] Institute for Physiology, Dresden University of Technology
[2] Institute for Physics and Astronomy, University of Potsdam
[3] Max-Planck-Institute for plasma physics, Garching
[4] Queen Mary University of London, School of Mathematical Sciences, London
[5] Institute for Physiology II, University of Münster

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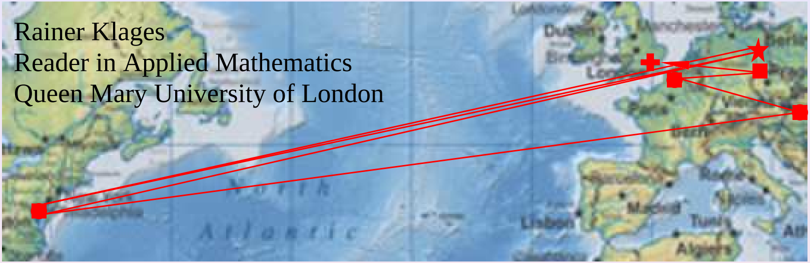
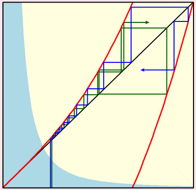
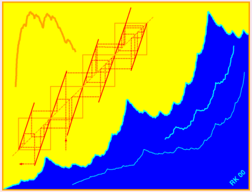
Queen Mary University of London

My own scientific foraging

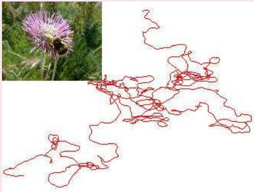




chaos



nonequ. stat. mech.



biology

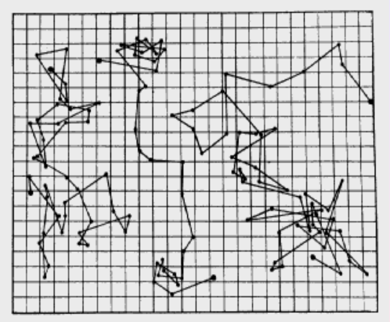
Outline

single cell migration:

1. **Experimental results:** statistical data analysis
2. **Theoretical modeling:** anomalous dynamics and its biophysical interpretation
3. **Lévy motion:** what is it, and search optimization - for cells
4. **Fluctuation relations:** experimental test of a theoretical model

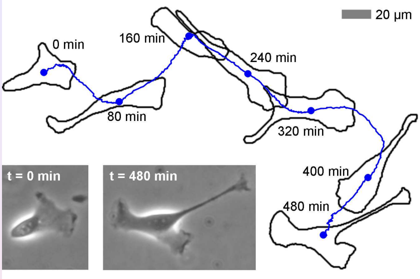
Brownian motion of migrating cells?

Brownian motion



Perrin (1913)

three colloidal particles, positions joined by straight lines



Dieterich et al. (2008)

single biological cell crawling on a substrate

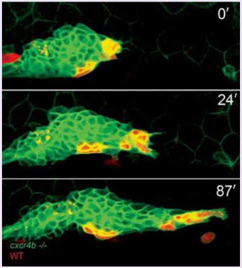
Brownian motion?

conflicting results:

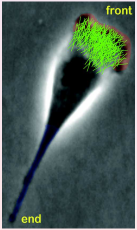
yes: Dunn, Brown (1987)

no: Hartmann et al. (1994)

Why and how do cells migrate?

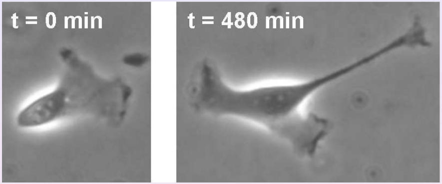


example:
motion of the primordium in developing zebrafish; collective cell migration
Lecaudey et al. (2008)



either via **membrane protrusions and retractions** or **blebbing**
here: no microscopic details
How does a cell migrate *as a whole* in terms of a **stochastic diffusion process**?

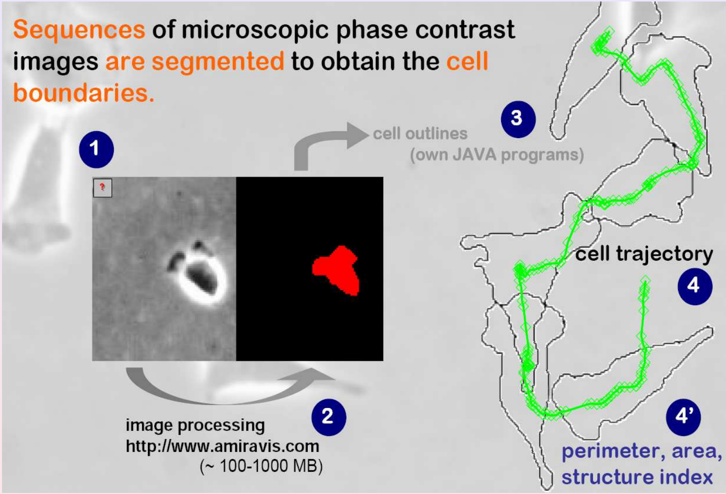
Our cell types and some typical scales



- 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

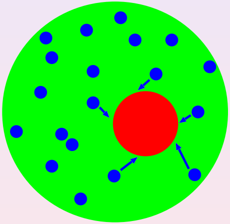
'Newton's law of stochastic physics':

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

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



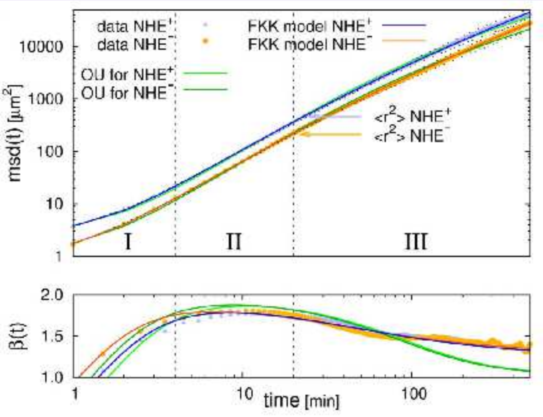
Application to cell migration?

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

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

Mean square displacement

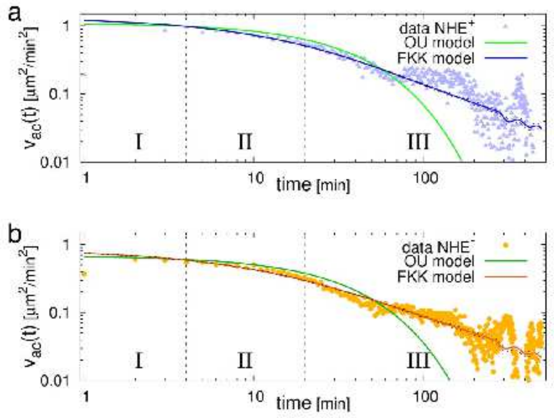
- $msd(t) := \langle[\mathbf{x}(t) - \mathbf{x}(0)]^2\rangle \sim t^\beta$ with $\beta \to 2\ (t \to 0)$ and $\beta \to 1\ (t \to \infty)$ for Brownian motion; $\beta(t) = d \ln msd(t)/d \ln t$



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

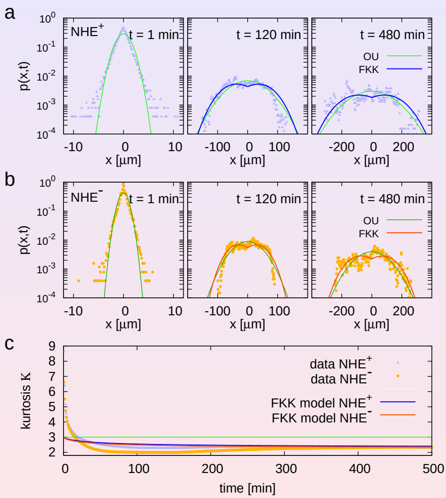
- $P(x,t) \to$ Gaussian $(t \to \infty)$ and kurtosis

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

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* and v_{ac} as the fractional Klein-Kramers eq.

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

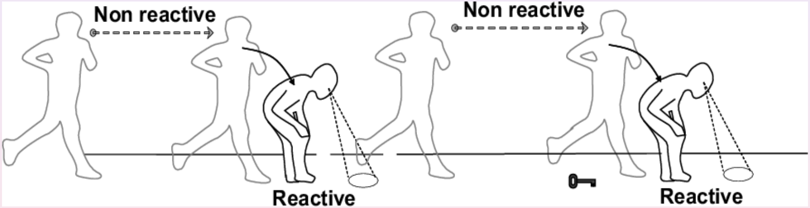
$$\frac{\partial^\gamma P}{\partial t^\gamma} := \frac{\partial^m}{\partial t^m}\left[\frac{1}{\Gamma(m-\gamma)} \int_0^t dt' \frac{P(t')}{(t-t')^{\gamma+1-m}}\right] \; , \; m-1 \le \gamma \le m$$

- 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)

- anomalous dynamics observed for **many different cell types** by at least 10 different groups

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)

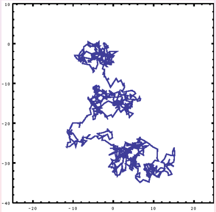
• question about optimal search strategy related to the **Lévy flight hypothesis**; for cells: see Krummel et al. (2016)

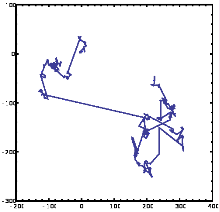
Optimizing the success of random searches

famous article by Viswanathan et al., Nature **401**, 911 (1999):

- question about *"best statistical strategy to adapt in order to search efficiently for randomly located objects"*
- random walk model leads to **Lévy flight hypothesis:**

Lévy flights provide an *optimal search strategy* for *sparse, randomly distributed, immobile, revisitable targets in unbounded domains*





Brownian motion (left) vs. **Lévy flights** (right)

- big debate about the **validity of this hypothesis**!

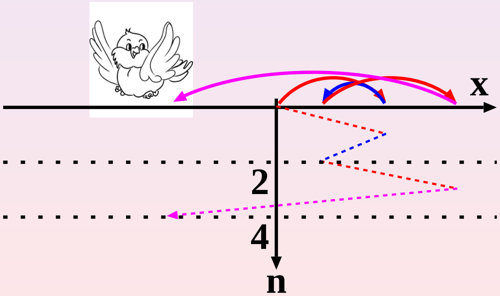
What are Lévy flights?

a random walk generating **Lévy flights**:

$x_{n+1} = x_n + \ell_n$ with steps of length $|\ell_n| = \ell$ to the left/right, sign determined by coin tossing; ℓ_n drawn from a Lévy α-stable distribution

$$\rho(\ell_n) \sim |\ell_n|^{-1-\alpha} \; (|\ell_n| \gg 1) \; , \; 0 < \alpha < 2$$

P. Lévy (1925ff)



- fat tails: larger probability for long jumps than for a Gaussian!

Properties of Lévy flights in a nutshell

- a Markov process *(no memory)*
- which obeys a generalized central limit theorem if the Lévy distributions are α-stable (for $0 < \alpha < 2$)
  Gnedenko, Kolmogorov, 1949
- implying that they are scale invariant and thus self-similar
- $\rho(\ell_n)$ has infinite variance

$$\langle \ell_n^2 \rangle = \int_{-\infty}^{\infty} d\ell_n \, \rho(\ell_n)\ell_n^2 = \infty$$

- Lévy flights have arbitrarily large velocities, as $v_n = \ell_n/1$
- position pdf given by the fractional diffusion equation

$$\frac{\partial f(x,t)}{\partial t} = K_\alpha \frac{\partial^\alpha f(x,t)}{\partial |x|^\alpha}$$

with Riesz fract. derivative $\sim -|k|^\alpha f(k,t)$ in Fourier space

Lévy walks

cure the problem of infinite moments and velocities by introducing an additional constraint:

- a **Lévy walker** spends a time

$$t_n = \ell_n / v \; , \; |v| = const.$$

  to complete a step; yields finite moments and finite velocities in contrast to Lévy flights

- Lévy walks generate anomalous (super) diffusion:

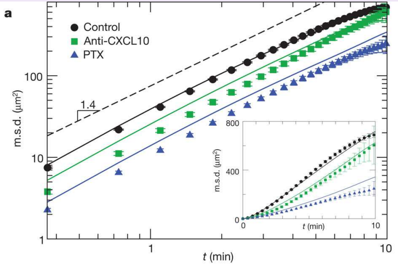
$$\langle x^2 \rangle \sim t^\gamma \; (t \to \infty) \text{ with } \gamma > 1$$

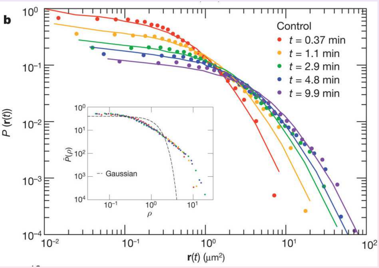
see Shlesinger at al., Nature **363**, 31 (1993) for an outline; Zaburdaev et al., RMP **87**, 483 (2015) for details

Generalized Lévy walks for migrating T cells

T.H. Harris et al., Nature **486**, 545 (2012):

• mean square displacement (for 3 different cell types) and position distribution function for T cells in vivo:





• T cell motility described by a generalized Lévy walk (Zumofen, Klafter, 1995)

• search more efficient than Brownian motion

• pdf not Lévy: how does the result fit to the Lévy hypothesis?

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)

experiments: test this theory for murine neutrophil chemotaxis

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 significance of anomalous dynamics for optimizing search; cf. *Lévy flight foraging hypothesis*
- **second law-like** relation for cell chemotaxis

Outlook

- single vs. collective cell migration?

  single cell motility controls glass and jamming transition Bi et al. (2016), or not Giavazzi et al. (2017)

- significance of *anomalous* diffusion for collective phenomena?

  superdiffusion enhances colony formation of stem cells Barbaric et al. (2014);
  non-trivial phase transitions in models of *active* Brownian particles Fodor et al. (2016)

References

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