Anomalous dynamics of cell migration

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Outline

1. **Cell migration:** motivation and some biological details
2. **Brownian motion:** theory in a nutshell
3. **Experimental results:** statistics of cell migration
4. **Theoretical modeling:** fractional stochastic equation
5. **Conclusions:** physical and biological interpretations?

Setting the scene

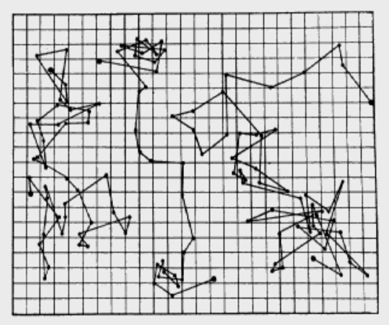
I. Cell migration

animation: **Brownian motion** vs. **cell migration**

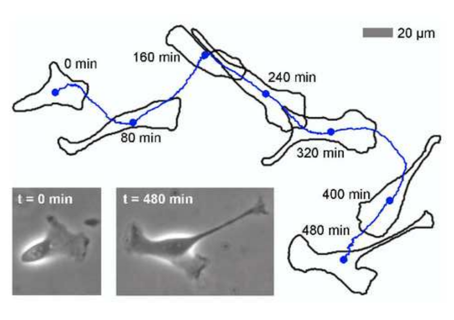
J. Ingenhousz (1785)
R. Brown (1827)

Brownian motion of migrating cells?

Brownian motion



3 colloidal particles of radius 0.53μm; positions every 30 seconds, joined by straight lines (Perrin, 1913)



single biological cell crawling on a substrate (Dieterich, R.K. et al., PNAS, 2008)

Brownian motion?

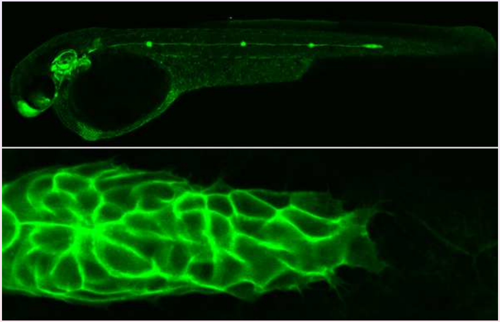
Brownian motion of migrating cells?

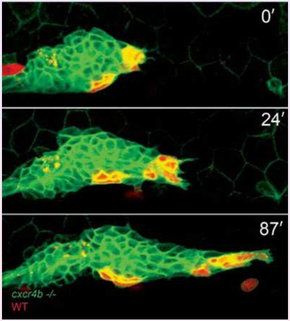
yes: Dunn, Brown (1987); Stokes et al. (1991)

not quite: Hartmann et al. (1994); Upadhyaya et al. (2001); T.-Norrelykke, Jülicher (2007); H.Takagi et al. (2008)

Why cell migration?

motion of the *primordium* in developing zebrafish (Gilmour, 2008):





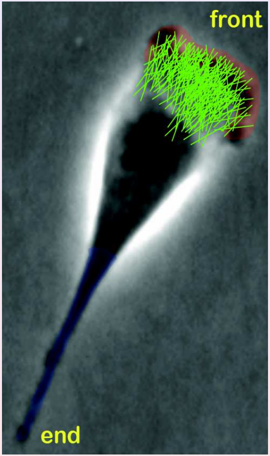
positive aspects:

- morphogenesis
- immune defense

negative aspects:

- tumor metastases
- inflammation reactions

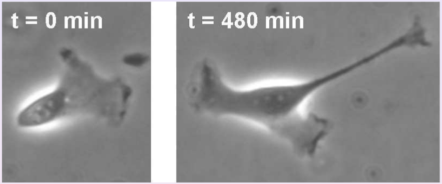
How do cells migrate?



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

note: here we do not study the *microscopic origin* of cell migration, which is a *highly complex process* involving a huge number of proteins and signaling mechanisms

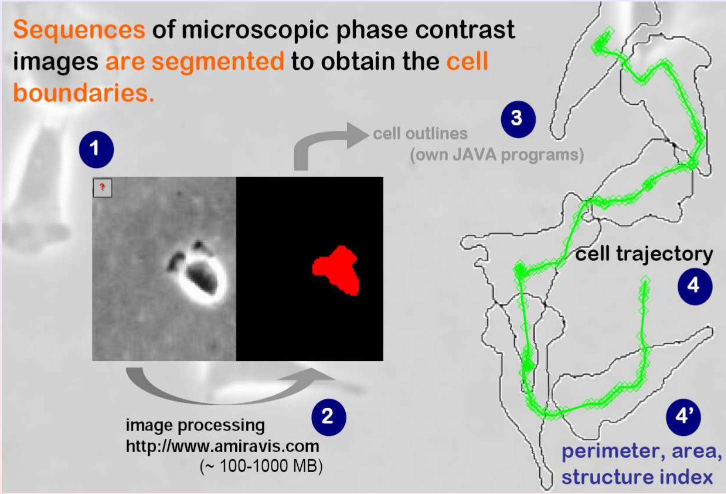
Our cell types and some typical scales



- 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

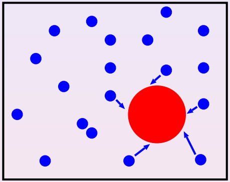


II. Brownian motion

The Langevin equation

microscopic understanding of Brownian motion: Einstein (1905)

simple theory suggested by Langevin (1908):



Newton's law for a particle of mass m and velocity $\underline{v}$ immersed in a fluid

$$m\dot{\underline{v}} = \underline{F}_d(t) + \underline{F}_r(t)$$

with total force of surrounding particles decomposed into *viscous damping* $\underline{F}_d(t)$ and *random kicks* $\underline{F}_r(t)$

suppose $\underline{F}_d(t)/m = -\kappa\underline{v}$ and $\underline{F}_r(t)/m = \sqrt{\zeta}\,\underline{\xi}(t)$ as *Gaussian white noise* of strength $\sqrt{\zeta}$:

$$\dot{\underline{v}} + \kappa\underline{v} = \sqrt{\zeta}\,\underline{\xi}(t)$$ **Langevin equation**

'Newton's law of stochastic physics': apply to cell migration?

Solving the Langevin equation

calculate three important quantities (in d dimensions):

1. the diffusion coefficient $D := \lim_{t\to\infty} msd(t)/(2dt)$

with *mean square displacement* $msd(t) :=< [\underline{x}(t) - \underline{x}(0)]^2 >$ over ensemble average $< \ldots >$; for Langevin eq. one obtains

$$msd(t) = 2dv_{th}^2 \left(t - \kappa^{-1}(1 - \exp(-\kappa t))\right)/\kappa$$

with $v_{th}^2 = kT/m$; note that $msd(t) \sim t^2$ $(t \to 0)$ and $msd(t) \sim t$ $(t \to \infty) \Rightarrow \exists D$

2. the velocity autocorrelation function $v_{ac}(t) :=< \underline{v}(t) \cdot \underline{v}(0) >$

for Langevin eq. one finds

$$v_{ac}(t) = v_{th}^2 \exp(-\kappa t)$$

Fokker-Planck equations and the like

3. the probability distribution function $P(x, v, t)$ (ff in one dimension):

• Langevin dynamics obeys (for $\kappa \gg 1$) the diffusion equation

$$\frac{\partial P}{\partial t} = D \frac{\partial^2 P}{\partial x^2}$$

solution for initial condition $P(x, 0) = \delta(x)$ yields *position distribution* $P(x, t) = \exp(-\frac{x^2}{4Dt})/\sqrt{4\pi Dt}$

• for *velocity distribution* $P(v, t)$ of Langevin dynamics one can derive the Fokker-Planck equation

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

stationary solution is $P(v) = \exp(-\frac{v^2}{2v_{th}^2})/\sqrt{2\pi} v_{th}$

- Fokker-Planck equation for position *and* velocity distribution $P(x, v, t)$ of Langevin dynamics is the Klein-Kramers equation

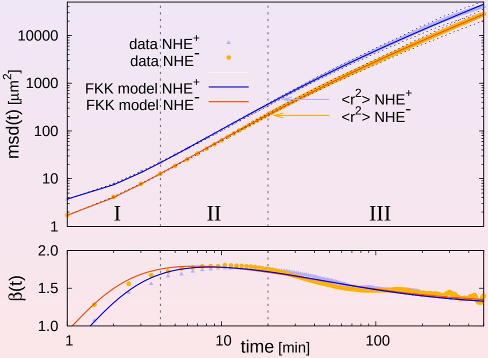
$$\frac{\partial P}{\partial t} = -\frac{\partial}{\partial x}\left[vP\right] + \kappa \left[\frac{\partial}{\partial v} v + v_{th}^2 \frac{\partial^2}{\partial v^2}\right] P$$

the above eqns. can be derived from it as special cases

III. Experimental results

Mean square displacement

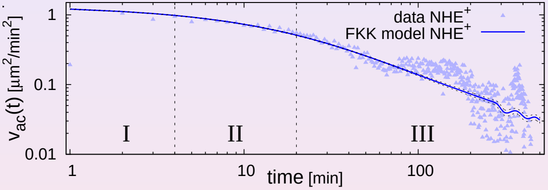
- $msd(t) := <[\underline{x}(t) - \underline{x}(0)]^2 >\sim t^\beta$ with $\beta \to 2$ $(t \to 0)$ and $\beta \to 1$ $(t \to \infty)$ for Brownian motion; $\beta(t) = d \ln msd(t)/d \ln t$
- *solid lines:* (Bayes) fits from our model

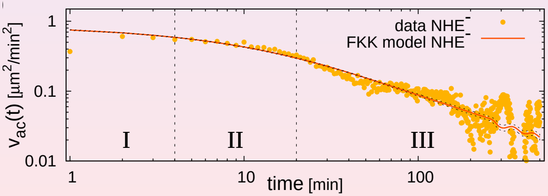


anomalous diffusion if $\beta \neq 1$: here superdiffusion for $t \to \infty$

Velocity autocorrelation function

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





$\Rightarrow$ crossover from stretched exponential to power law behavior

Position distribution function

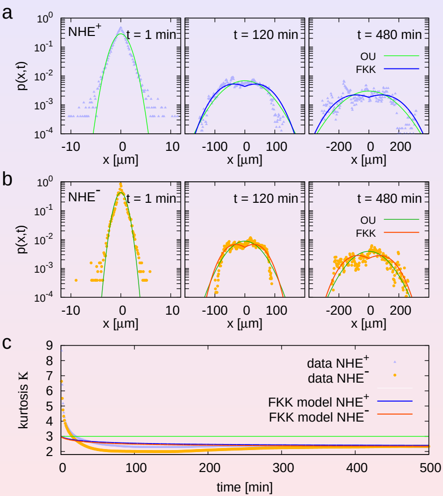
- $P(x,t) \to$ Gaussian ($t \to \infty$) and kurtosis

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

for Brownian motion (green lines, in 1d)

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

remark: model does not yet explain short-time distributions



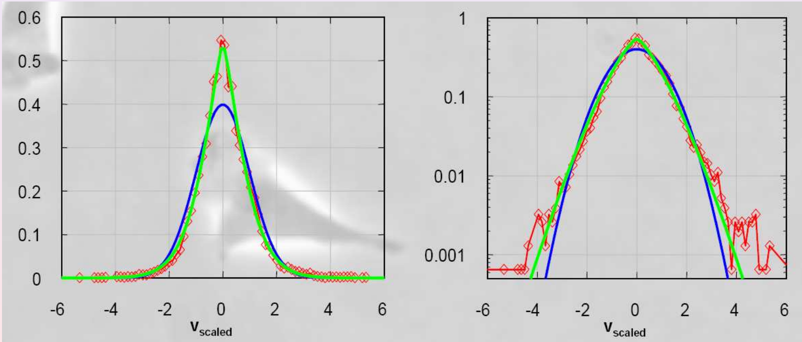
$\Rightarrow$ crossover from peaked to broad non-Gaussian distributions

Velocity distribution functions

$P(v) = \frac{1}{\sqrt{2\pi} v_{th}} \exp(-\frac{v^2}{2v_{th}^2})$ for Brownian motion;

fit by stretched exponential: $P(v) = c \exp(-\frac{b}{2}(\frac{v}{v_{th}})^a)$

linear plot semi-log plot



IV. Theoretical modeling

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

Fractional derivative

interlude – 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 $m = 1/2\,,\ n = 1$

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

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

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)

note:

3 fit parameters $v_{th}, \alpha \simeq 0.7, \kappa$ plus another one by adding "biological noise" of variance η^2 to *msd*,

$$msd_{noise}(t) := msd(t) + 2\eta^2 ;$$

mimicks measurement errors and cytoskeleton fluctuations

V. Conclusions

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; Lutz, 2001

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

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

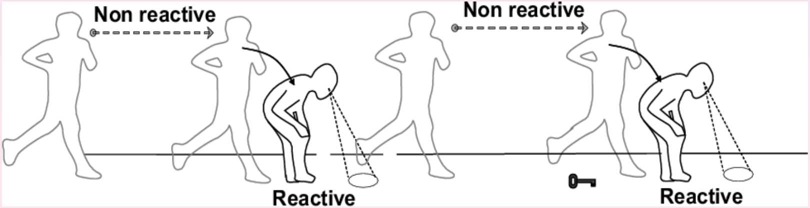
note: anomalous dynamics observed for *6 different cell types*

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: ∃ current controversy about *modeling the migration of foraging animals* (albatross, bumblebees, fruitflies,...)

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, July 2008)

see www.maths.qmul.ac.uk/˜klages for further information