Statistical analysis and stochastic modelling of cell migration and bumblebee foraging

Rainer Klages[1,2]

[1] Max Planck Institute for the Physics of Complex Systems

[2] Queen Mary University of London, School of Mathematical Sciences

Advanced Study Group, Second Focus Week Meeting
6 November 2015

Outline

two parts:

1. **cell migration**
2. **bumblebee foraging**

in both cases:

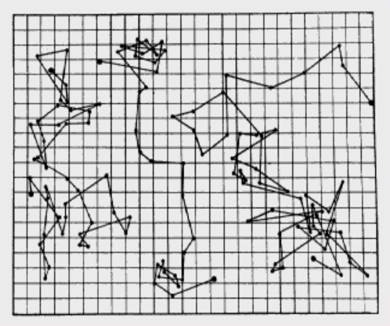
- motivation and experiment
- experimental results and statistical analysis
- theoretical stochastic modeling and summary

Part 1:

Cell Migration

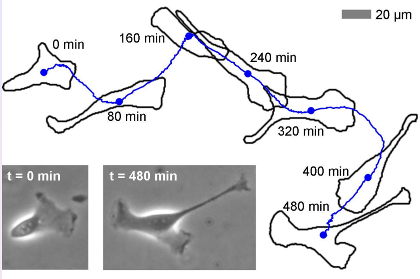
Brownian motion of migrating cells?

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)

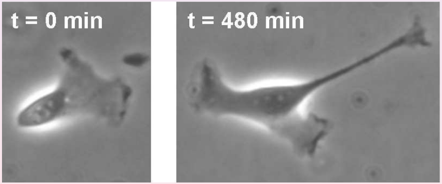
no: Hartmann et al. (1994)

Our cell types and how they migrate

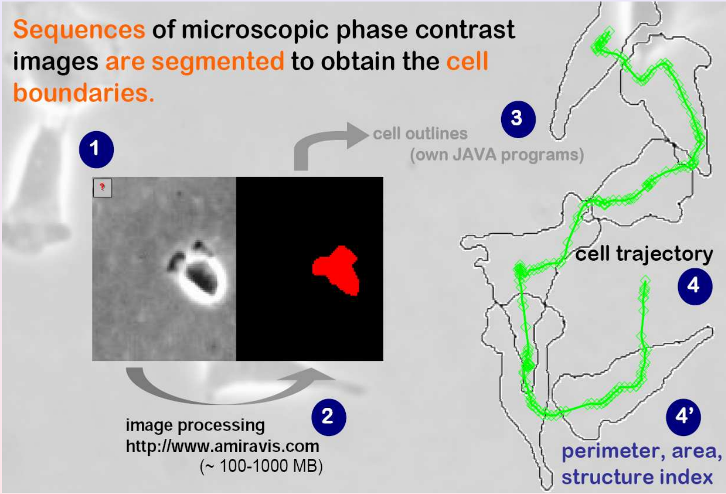
MDCK-F (Madin-Darby canine kidney) cells

two types: wildtype (NHE^+) and NHE-deficient (NHE^-)

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



Measuring cell migration



Theoretical modeling of Brownian motion

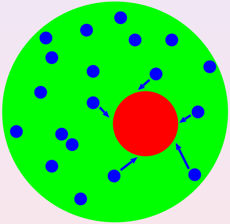
'Newton's law of stochastic physics':

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

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

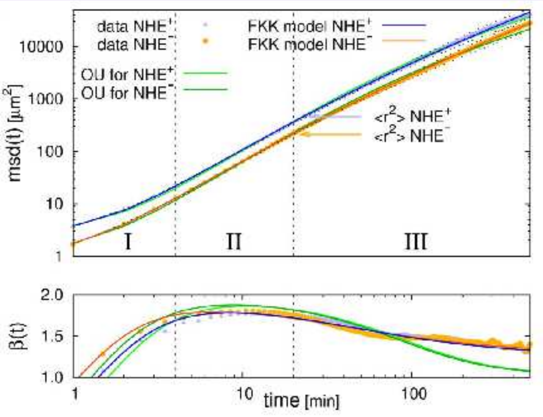


Application to cell migration?

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

Mean square displacement

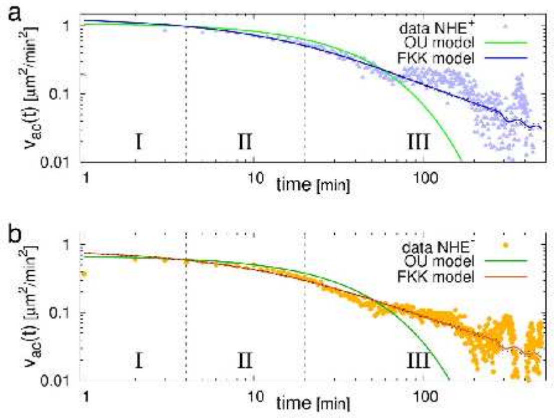
- $msd(t) := \langle [\mathbf{x}(t) - \mathbf{x}(0)]^2 \rangle \sim t^\beta$ with $\beta \to 2\ (t \to 0)$ and $\beta \to 1\ (t \to \infty)$ for Brownian motion; $\beta(t) = d \ln msd(t) / d \ln t$



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

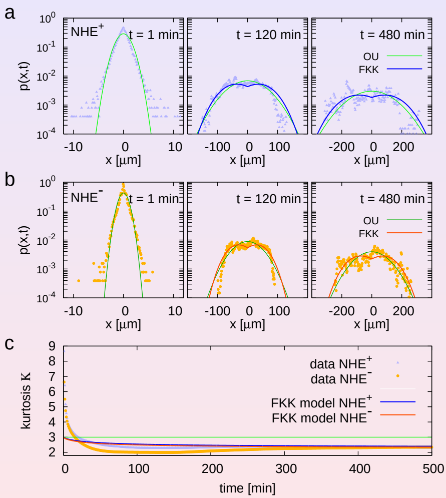
- $P(x,t) \rightarrow$ Gaussian $(t \rightarrow \infty)$ and kurtosis

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

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)

Possible physical interpretation

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

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)

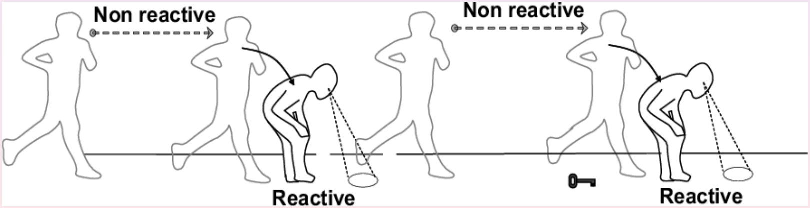
nb: anomalous dynamics observed for *many different cell types*

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,...)

Summary: Anomalous cells

- different **cell dynamics** on different **time scales** (cp. with Lévy hypothesis, which suggests scale-freeness)
- for long times cells crawl **superdiffusively** with power law decay of velocity correlations and non-Gaussian position pdfs
- stochastic modeling of experimental data by a generalized Klein-Kramers equation

Part 2:

Bumblebee Foraging

Motivation

bumblebee foraging – two very practical problems:

1. find food (nectar, pollen) in complex landscapes

2. try to avoid **predators**

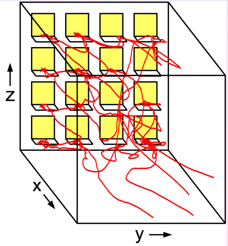
What type of motion?

Study bumblebee foraging in a *laboratory experiment*.

The bumblebee experiment

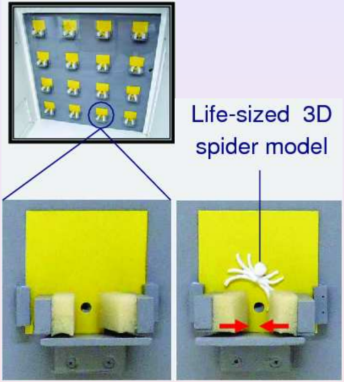
Ings, Chittka, Current Biology **18**, 1520 (2008):
bumblebee foraging in a cube of $\simeq$ 75cm side length

- artificial yellow flowers: 4x4 grid on one wall
- two cameras track the position (50fps) of a single bumblebee *(Bombus terrestris)*



- **advantages:** systematic variation of the environment; easier than tracking bumblebees on large scales
- **disadvantage:** no ‘free flight’ of bumblebees

Variation of the environmental conditions



safe and **dangerous**
flowers

movie

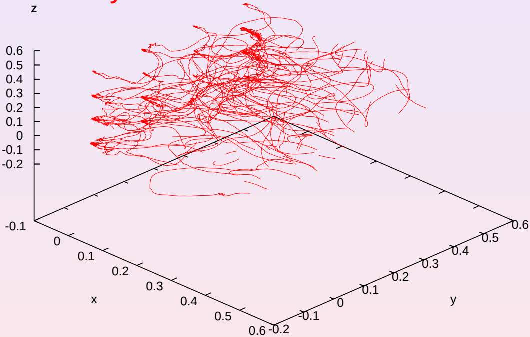
three experimental stages:

1. spider-free foraging
2. foraging under predation risk
3. memory test 1 day later

#bumblebees=30 , #data per bumblebee for each stage $\approx$ 7000

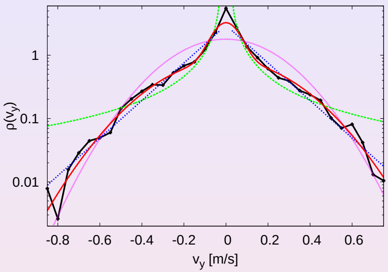
Bumblebee experiment: two main questions

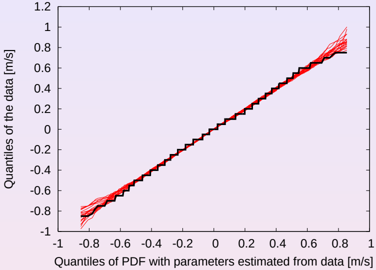
1. What type of motion do the bumblebees perform in terms of stochastic dynamics?



2. Are there changes of the dynamics under variation of the environmental conditions?

Velocity distributions: analysis





left: experimental **pdf of v_y-velocities** of a single bumblebee in the spider-free stage (black crosses) with max. likelihood fits of mixture of 2 Gaussians; exponential; power law; single Gaussian

right: **quantile-quantile plot** of a Gaussian mixture against the experimental data (black) plus surrogate data

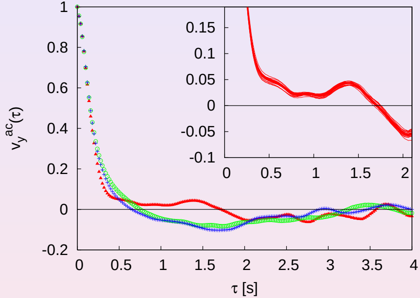
Velocity distributions: interpretation

- **best fit** to the data by a mixture of two Gaussians with different variances (quantified by information criteria with resp. weights)
- **biological explanation:** models spatially different flight modes near the flower vs. far away, cf. intermittent dynamics

big surprise: no difference in pdf's between different stages under variation of environmental conditions!

Velocity autocorrelation function ∥ to the wall

$V_y^{AC}(\tau) = \frac{\langle (v_y(t)-\mu)(v_y(t+\tau)-\mu)\rangle}{\sigma^2}$ with average over all bees:

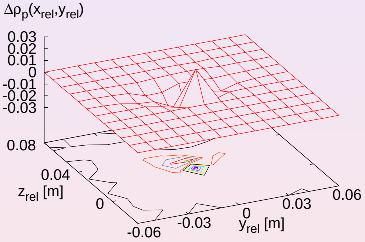


- plot: spider-free stage, predation thread, memory test
- **correlations change** from positive (spider-free) to negative (spiders)

⇒ all **changes** are in the **velocity correlations**, *not* in pdf's!

Predator avoidance and a simple model

predator avoidance as difference in position pdfs spider / no spider from data:

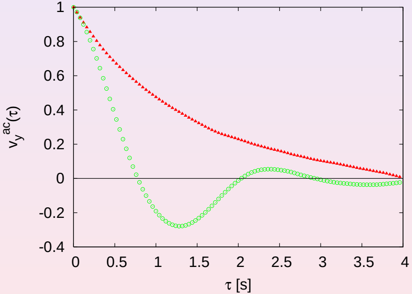


positive spike: *hovering*;
negative region: *avoidance*

modeled by Langevin equation

$$\frac{dv_y}{dt}(t) = -\eta v_y(t) - \frac{\partial U}{\partial y}(y(t)) + \xi(t)$$

η: friction coefficient,
ξ: Gaussian white noise



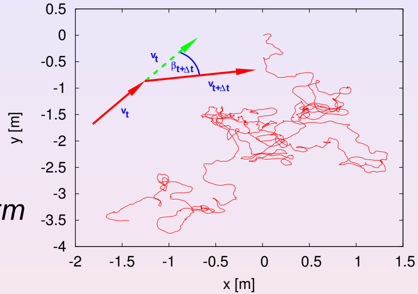
simulated velocity correlations with repulsive interaction potential U
bumblebee - spider off / on

Modeling free bumblebee flights

reorientation model:

describe 2d movement in comoving frame by

- speed $v(t) = const.$
- turning angle $\beta(t) = \xi(t)$ as random variable from *non-uniform pdf* modeling persistence



generalized model for bumblebee flights far away from flowers constructed from experimental data:

- $\beta(t) = \xi_v(t)$: power law correlated Gaussian noise
- $\frac{dv}{dt} = g(v(t)) + \psi(t)$: generalized Langevin equation with anti-correlated Gaussian noise

Summary: Clever bumblebees

- mixture of **two Gaussian velocity distributions** reflects spatial adjustment of bumblebee dynamics to flower carpet
- all changes to predation thread are contained in the **velocity autocorrelation functions**, which exhibit highly non-trivial temporal behaviour

  (**nb:** Lévy hypothesis *suggests* that all relevant foraging information is contained in pdf's)
- change of correlation decay in the presence of spiders due to **experimentally extracted repulsive force** as reproduced by generalized Langevin dynamics

Collaborators and literature

work performed with:

1. cells:

P.Dieterich, R.K., R.Preuss, A.Schwab, PNAS **105**, 459 (2008)

2. bees:

F.Lenz, T.Ings, A.V.Chechkin, L.Chittka, R.K.,
Phys. Rev. Lett. **108**, 098103 (2012)

F.Lenz, A.V.Chechkin, R.K., PLoS ONE 8, e59036 (2013)