Correlation between speed and turning naturally arises for sparsely sampled cell movements

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Abstract

Mechanisms regulating cell movement are not fully understood. One feature of cell movement that determines how far cells displace from an initial position is persistence, the ability to perform movements in a direction similar to the previous movement direction. Persistence is thus determined by turning angles between two sequential displacements; it can be characterized by an average turning angle or persistence time. Recent studies found that a cell's average speed and turning are negatively correlated, suggesting a fundamental **cell-intrinsic program** whereby cells with a lower turning ability (i.e., larger persistence time) are intrinsically faster (or faster cells turn less). By simulating correlated or persistent random walks (PRWs) using two different frameworks (one based on von Mises-Fisher (vMF) distribution and another based on Ornstein-Uhlenbeck (OU) process) we show that the negative correlation between speed and turning naturally arises when cell trajectories are sub-sampled, i.e., when the frequency of sampling is lower than the frequency at which cells make movements. This effect is strongest when the sampling frequency is on the order of magnitude with the typical cell persistence time and when cells vary in persistence time. For both vMF- and OU-based simulations of PRWs we could find parameter values (distribution of persistence times, speeds, and sampling frequency) that matched experimentally measured correlations between speed and turning for two datasets of T cell movement in vivo suggesting that such simple correlations are not fully informative on the intrinsic link between speed and persistence. Our results thus suggest that sub-sampling may contribute to (and perhaps fully explains) the observed correlation between speed and turning at least for some cell trajectory data and emphasize the role of sampling frequency in inference of critical cellular parameters of cell motility such as speed[1].

Correlation between speed and turning easily arises in subsampled trajectories

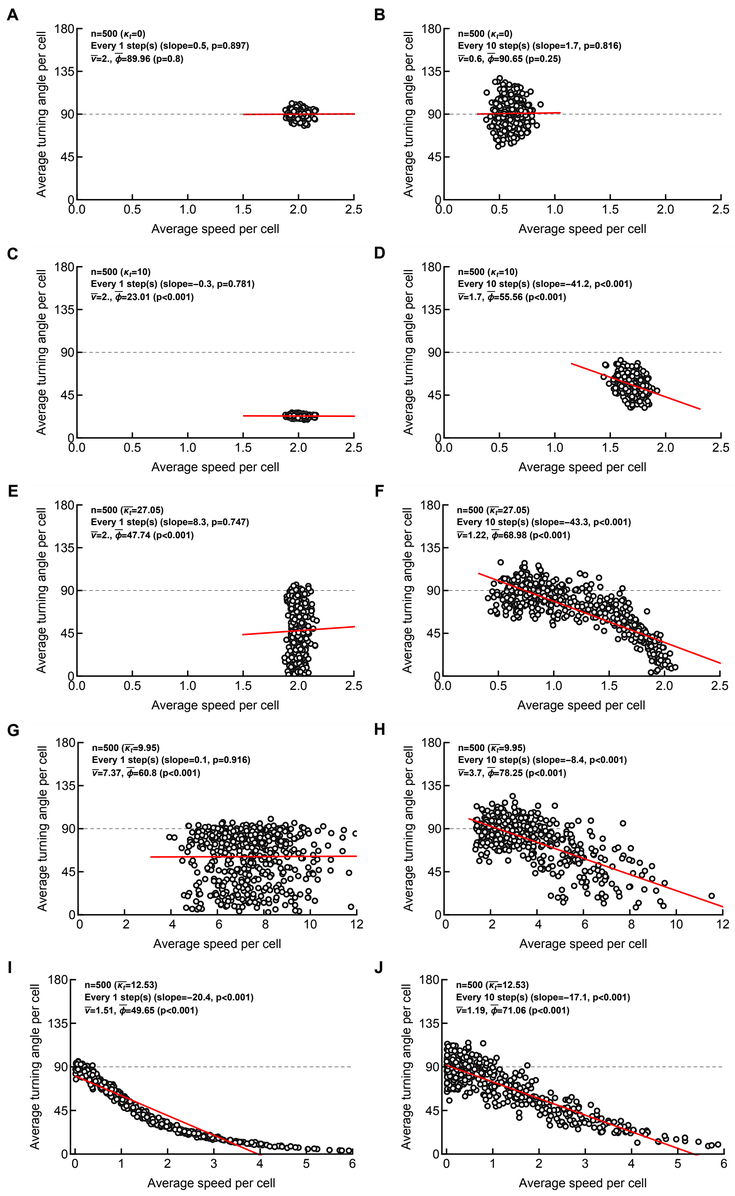

Figure 1. We simulated movement of 500 cells using a vMF distribution (eqn. (1)) assuming i) Brownian walk ($\kappa_t \to 0$, A-B), ii) persistence for forward movement being identical for all cells ($\kappa_t = 10$, C-D), iii) heterogeneity in cells' persistence of movement (κ_t was sampled from a lognormal distribution with $\mu = 0.2$ and $\sigma = 2$, E-F), iv) independent heterogeneity in cells' persistence and speed movement (κ_t and $\bar{r}$ were sampled from a lognormal distribution with $\mu = 0$ and $\sigma = 2$ for κ_t and with $\mu = 2$ and $\sigma = 0.2$ for $\bar{r}$), v) a direct relationship between cells' persistence ability defined by κ_t and cells' intrinsic movement speed ($\bar{r} = \ln(1 + \kappa_t)$, with κ_t following a lognormal distribution with $\mu = 1$ and $\sigma = 2$, I-J). The resulting trajectories were sampled either every step (A, C, E, G, I) or every $k = 10^{\text{th}}$ step (B, D, F, H, J). Each panel contains information on the average speed for all cells ($\bar{v}$), average turning angle for all cells ($\bar{\phi}_t$), and the result of linear regression of the average speed per cell and average turning angle per cell (denoted as "slope" and shown by red line) with p value from the t-test. We also test if the average turning angle of cells in the population is different from 90° (Mann-Whitney test). Note different scales in A-F and G-J due to higher speeds of cells in simulations in G-J.

Correlation between speed and turning angle depends on sub-sampling frequency

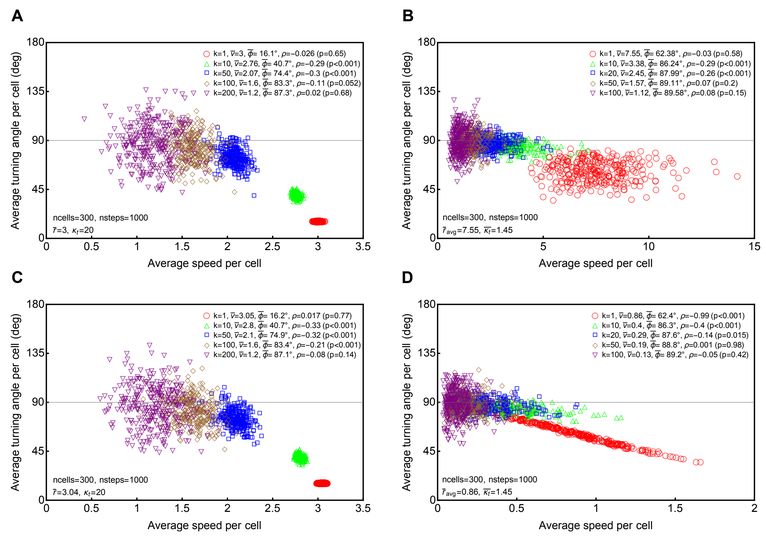

Figure 2. We simulated 300 cells each with 10^3 steps using a vMF distribution (eqn. (1)) and sampled every k^{th} movements (k is indicated on individual panels). In panels A-B we assume that speed and concentration parameter κ_t of the vMF distribution are uncorrelated, and in panels C-D, speed is determined by κ_t via $\bar{r} = \ln(1 + \kappa_t)$. In panels A and C we assume that every cell have the same persistence defined by $\kappa_t = 20$ and same speed defined by $\bar{r} = 3$. In panels B and D we assume that every cell in the population has a different κ_t which was drawn from a lognormal distribution with $\mu = 0.2$ and $\sigma = 0.5$). In panel B, every cell has a random speed determined by $\bar{r}$ in the Pareto distribution ($\bar{r}$ was drawn from a lognormal distribution with $\mu = 2$ and $\sigma = 0.2$), and in panel D speeds are directly determined by κ_t as $\bar{r} = \ln(1 + \kappa_t)$. Average speed $\bar{v}$ and average turning angle $\bar{\phi}$ for all cells are indicated on the panels, and statistical significance of the correlation between speed and turning angle per cell was determined using Spearman rank test (with the correlation coefficient ρ and p-values are shown on individual panels).

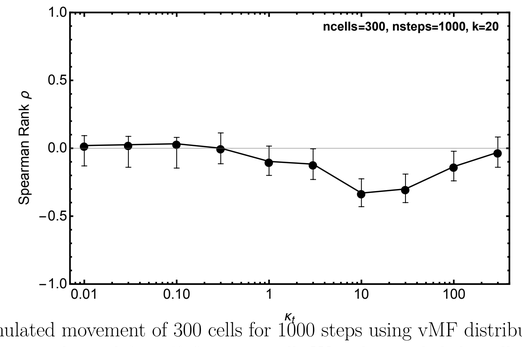

Figure 3. We simulated movement of 300 cells for 1000 steps using vMF distribution (eqn. (1)) assuming the same κ_t and speed ($\bar{r} = 2$) for every cell. We sub-sampled the cell trajectories with $k = 20$ and estimated the correlation between average speed and average turning angle per cell. Confidence intervals (95%) for the estimated Spearman rank correlation coefficient ρ were calculated using a bootstrap approach in the routine `SpearmanRho` in R package `DescTools`.

Cell cohorts with different speeds show different MSDs independently of the correlation between speed and persistence

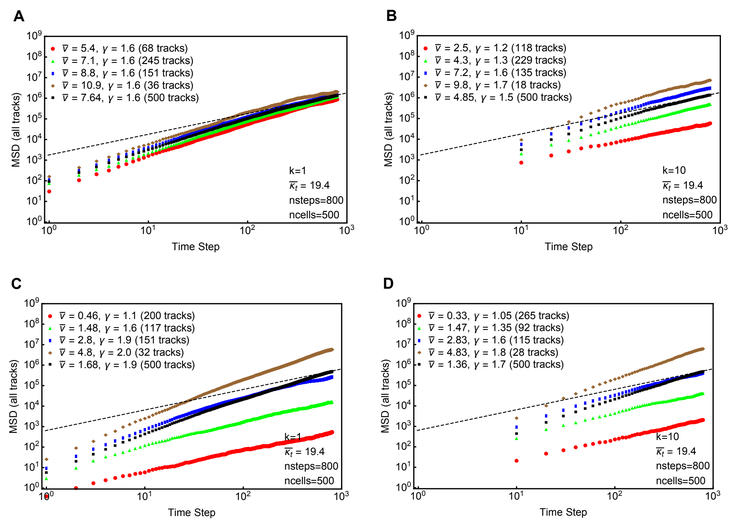

Figure 4. We simulated movement of cells assuming a correlated random walk characterized by the concentration parameter κ_t of the vMF distribution (see eqn. (1)) and an independent distribution of cell speeds (characterized by the mean $\bar{r}$ of the Pareto distribution, see eqn. (2); panels A&B) or when there is a direct correlation between κ_t and cell speed (panels C&D). We sampled the movement data either every step ($k = 1$, A&C) or every 10^{th} step ($k = 10$, B&D). In all simulations, the parameter κ_t, which dictates the average turning angle of a cell (i.e., persistence), is randomly drawn from a log-normal distribution with mean $\mu = 1$ and standard deviation $\sigma = 2$. The timestep indicates the regular intervals at which we simulated the cell positions, and MSD is dimensionless. In one set of simulations (A-B), we randomly draw $\bar{r}$ from an independent log-normal distribution with mean $\mu = 2$ and standard deviation $\sigma = 0.2$. In the Pareto distribution we set $\alpha = 3$ for every cell we calculated $r_{\min} = \bar{r}(\alpha - 1)/\alpha$. In another set of simulations, we let $\bar{r} = \ln(1 + \kappa_t)$ for every cell (C&D). Simulations were done with $n = 500$ cells for 800 timesteps. Four speed bins were considered from the distribution of average speed per cell and for each bin MSD was computed. We also include the MSD for all tracks together. To characterize the MSD we used the relation MSD $= ct^{\gamma}$ where $\gamma = 1$ suggests Brownian diffusion (denoted by a thin black dashed line) and $\gamma > 1$ suggests superdiffusion. The parameter γ was estimated for each MSD curve by linear regression of the log-log transformed MSD data.

Methodology

To simulate persistent random walks (PRWs) using vMF process we choose turning angles (given in vector χ) and movement lengths r using probability distributions:

$$P(\chi|\mu, \kappa_t) = \frac{\kappa_t e^{\kappa_t \mu^T \chi}}{2\pi(e^{\kappa_t} - e^{-\kappa_t})}, \quad (1)$$

$$f(r|r_{\min}, \alpha) = \frac{\alpha r_{\min}^{\alpha}}{r^{\alpha+1}}. \quad (2)$$

Simulations with sub-sampled data can match experimentally observed correlations

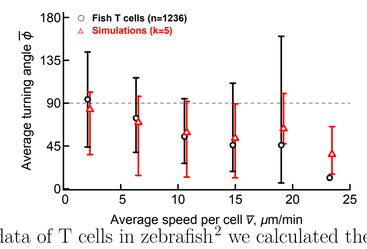

Figure 5. For cleaned data of T cells in zebrafish[2] we calculated the average turning angle and speed for every trajectory and plotted binned data. Note that the bin with the largest average speed had only one trajectory. We also performed simulations using vMF distribution (eqn. (1)) in which every cell has a defined persistence ability and speed, sub-sampled the resulting simulation data (every $k = 5$th step was used). To simplify calculations we assumed that this sampling frequency is 1min, calculated the average turning angle and average speed for every trajectory, and then binned these simulation data in the identical way to that of actual experimental data. Confidence intervals denote 2.5 and 97.5 percentiles of the data. Also note that while experimental data were collected in 2D by ignoring z-coordinates of the moving cells[2], our simulations were done in 3D.

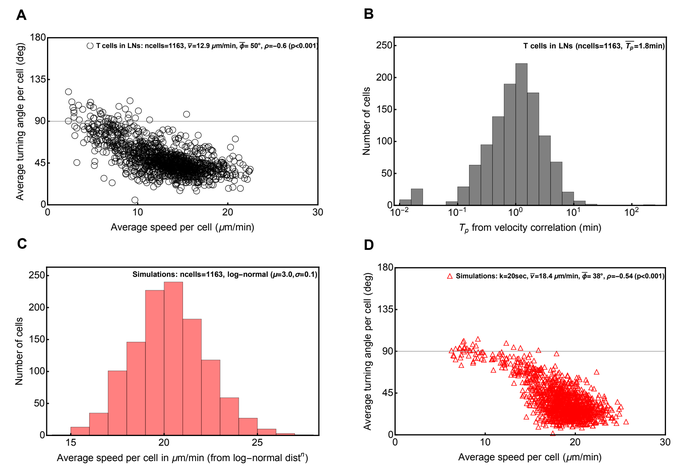

Figure 6. For each trajectory in the experimental data on movement of naive CD8 T cells in LNs[3,4] we calculated the average speed and average turning angle (panel A) or the persistence time from velocity correlations (panel B). We then simulated movement of cells using OU framework[5] by taking specific values of persistence time T_p for each cell in panel B and randomly assigning the speed of each cells from a lognormal distribution (panel C, $\mu = 3$, $\sigma = 0.1$). Cell movements were simulated every second and we sampled the resulting trajectories every $k = 20$ sec (panel D). The correlations observed experimentally or in simulations were evaluated using Spearman rank test (A&D) with p values from the test of the hypothesis $\rho = 0$ being indicated on individual panels.

Conclusions

1. Correlation between speed and persistence (turning angle or persistence time) arises naturally for cells undergoing persistent random walk when their trajectories are sub-sampled.
2. The impact of sub-sampling is strongest when sub-sampling frequency is on the order of magnitude with the typical persistence time of cells in the population.
3. Simulating cell movements with parameters chosen from in vivo experiments approximately reproduces the correlation between speed and persistence.

References

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