Simulation-Based Study of Vesicle Motion

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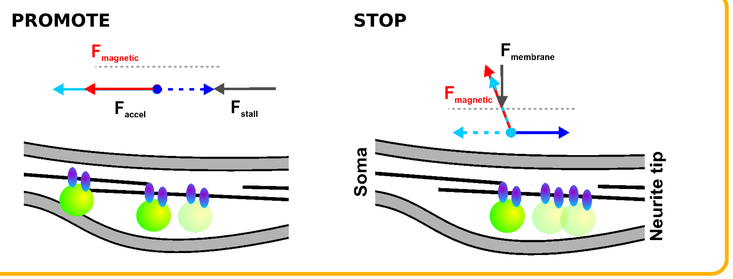
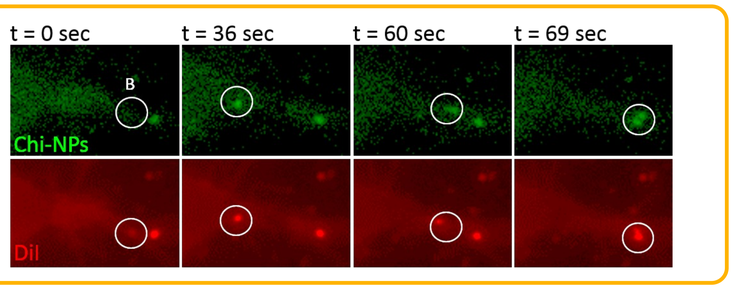
Transport of organelles and vesicles in neurons



Neurons translocate membrane compartments and proteins through organelles and vesicles within and throughout the cellular body. An impaired vesicle transport can lead to changes in cell signaling, misfolding in proteins, or neurodegeneration. Hence, the Kunze Lab developed cell assays for neurons that use magnetic nanoparticles within magnetic field gradients to modulate vesicle transport. Through the application of magnetic forces ($F_{magnetic}$), vesicles containing magnetic nanoparticles can be either accelerated (PROMOTE), stalled, or re-oriented (STOP). To better understand the underlying motility effects, we are developing a mathematical simulation toolbox to classify and predict force-mediated vesicle dynamics.

Time-lapse fluorescent microscopy images

We use time-lapse fluorescent microscope images as a data source for classifying vesicle dynamics in living systems:

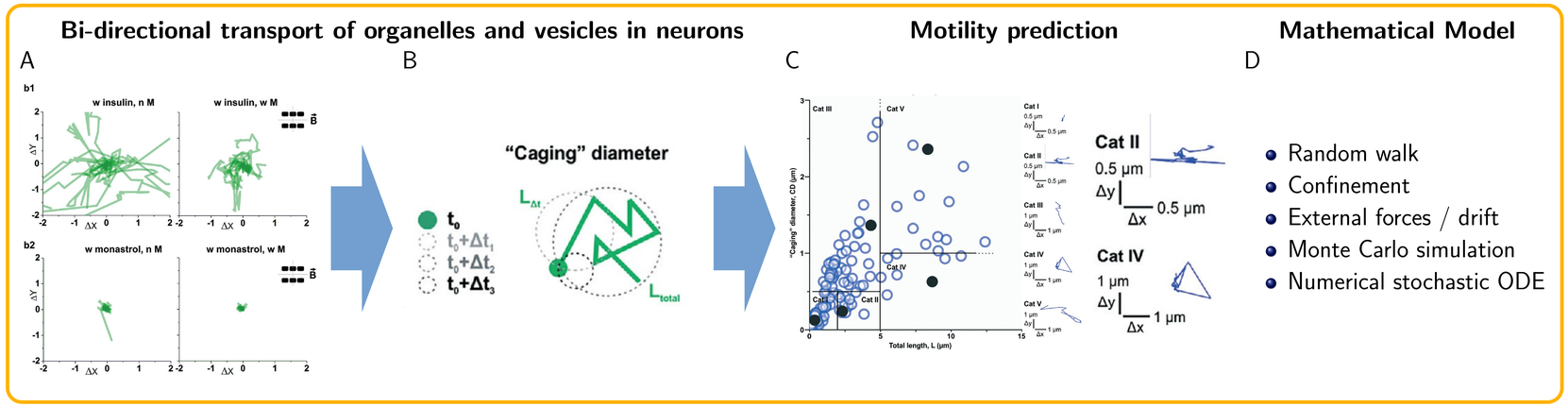


False-color fluorescent images show green-labeled lipid vesicles carrying red-labeled magnetic nanoparticles in primary cortical neurons grown ex vivo. Based on image segmentation and vesicle distribution over time, we extract trajectories of vesicles.

Trajectory features

A single vesicle trajectory is a collection of T points, $\vec{x}_1, \ldots, \vec{x}_T$, with length $L = \sum_{i=1}^{T-1} \|\vec{x}_{i+1} - \vec{x}_i\|_2$. For a sliding window of size t, we define a local caging diameter CD_i as the smallest radius of a ball centered at $\vec{x}_i$ containing all $t-1$ subsequent trajectory points: $CD_i = \max_{k<t} \|\vec{x}_{i+k} - \vec{x}_i\|_2$. The average caging diameter of a trajectory is then simply $\overline{CD} := \mathbb{E}_i\{CD_i\}$.

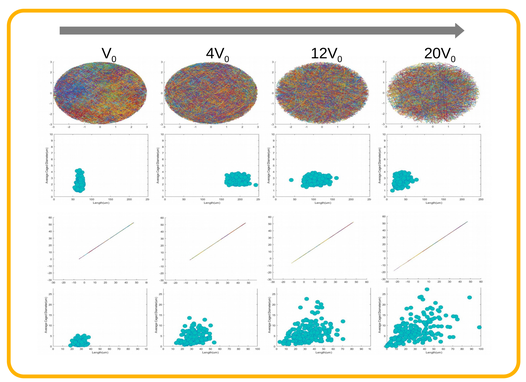
Methodology: Classifying vesicle motility based on caging diameter and total traveled length characteristics



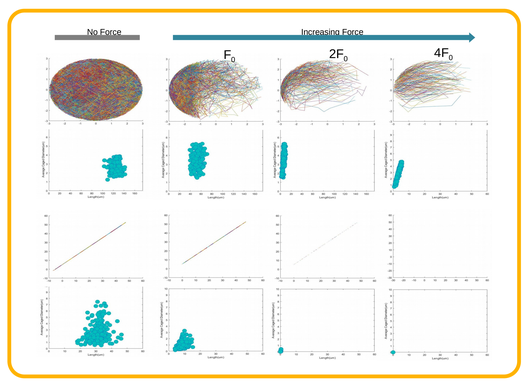
Schematic shows the work flow for predicting vesicle dynamics in living neurons based on random-walk with a confined space. For the confined space a circular surface and a tube were selected to project confined vesicle motion into the two-dimensional space. (A) Center plots of trajectories of vesicles exported from experimental data. (B) Caging diameter computation and extraction of total traveled length within a constant time frame is used in (C) to categorize vesicle motility into five motion patterns. (D) Mathematical framework comprises random walk in confined space with and without a force parameter to predict vesicle motility for future force-mediated experimental cell assays, solved as a combination of Monte Carlo simulation and numerical solution of ODE (forward Euler).

Results: Vesicle motility depends on simulation speed and force

Circular and linearly confined random walks exhibit characteristic differences in trajectory features. Another important phenomenon we notice in our simulations is that when we apply force on the vesicles, both the average caging diameter and the total traveled length decrease. This matches with what we find in data of real trajectories from neuronal cell vesicles.



Simulated trajectories of vesicles with corresponding caging diameters and total traveled length: **Top:** in a large-space, loose confinement, dominated by diffusion; **Bottom**: in a small-space, strict confinement over a long distance. An increase in vesicle moving velocity shows distinct clusters of vesicle motion pattern.



Force-mediated vesicle motion of simulated trajectories. **Top left**: Loose confined diffusion pattern without any force impact. **Top right**: Computational trajectories with increasing force impact. **Bottom left**: Strict confined motion pattern of vesicles without force impact. **Bottom right**: Motion pattern shows strong stalling effect as force increases.

Conclusions

We have successfully simulated vesicle motion under magnetic forces. Given the nature of trajectories and current features, however, K-Means clustering does poorly at identifying proper clusters.

References

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