A first-pass statistical dashboard for categorizing diverse particle movement patterns

Riley Juenemann[1], Scott A. McKinley[1], Christine Payne[2], and Quinton Tran[2]

[1] Department of Mathematics, Tulane University, [2] Department of Mechanical Engineering and Materials Science, Duke University

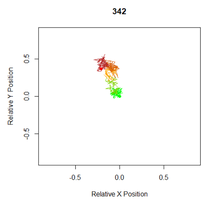
Introduction to Single Particle Tracking

In contrast to in vitro particle tracking experiments, wherein there are great controls on particle and environmental homogeneity, live cell (in vivo) tracking features tremendous diversity in particle movement. Determining what types and relative proportions of particle movement exist within a cell is important in determining whether heterogeneity in intracellular transport among cells has a genetic basis or if transport properties vary within each cell over its lifetime.

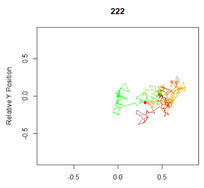
Objective: Develop a dashboard of statistics to categorize disparate behavior in heterogeneous populations.

Easy Ad Hoc Path Categorizations

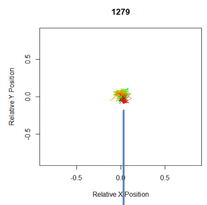
Start → End Time



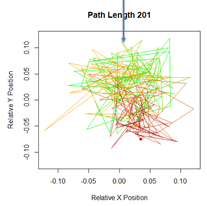
Directed Transport



Freely Diffusing



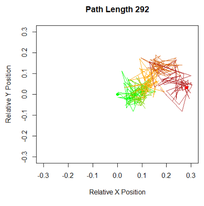
Stuck Diffusing



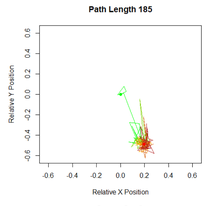
Tracker Error

More Difficult Ad Hoc Path Categorizations

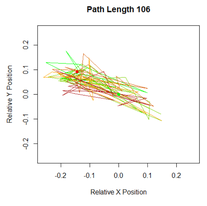
Start → End Time



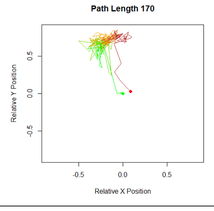
Winding



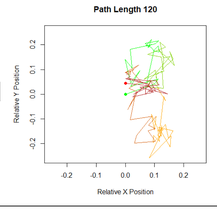
Switching



Pacing

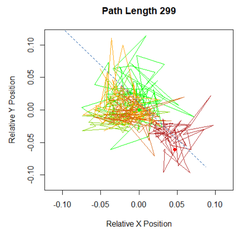


Uncategorized



A Combination of Statistical Measures Can Distinguish Between Movement Types

$\mathbf{D_{eff}}$ - used maximum likelihood estimation (MLE) on increment processes



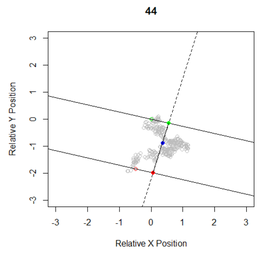
Determining Major and Minor Axes

- Projected points onto lines at angles between 0 and π
- Found the long direction (line at angle Θ with greatest range of points)
  - This axis is **major** direction
  - Transverse axis is **minor** direction
- Take the extent (standard deviation) for both directions ($\mathbf{SD_{major}}$, $\mathbf{SD_{minor}}$)

$\mathbf{AC_{major}}$ and $\mathbf{AC_{minor}}$ - correlation values for consecutive increments

Anchor Estimation

- Projected start and end point onto major axis to create a fictional moving anchor
- Computed distance to anchor and took the average for each path ($\boldsymbol{\delta_{anchor}}$)

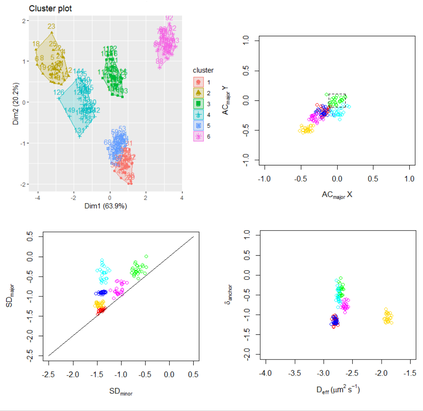


K-means clustering - an unsupervised machine learning algorithm, partitions the data into k clusters in a way that minimizes data variation

Validated on Simulated Data

$$dX(t) = -\frac{\kappa}{\gamma}(X(t) - Z(t))dt + \sqrt{2D}dW(t)$$

X - particle position
Z - anchor location
κ - spring constant (assuming Hooke's Law)
γ - drag coefficient
D - diffusivity
W - Brownian motion

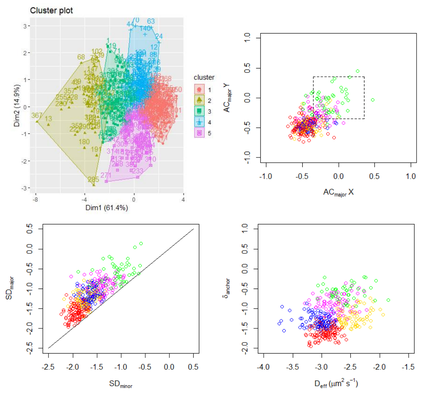


Path Categorizations via Dashboard:

Freely Diffusing
Stuck Diffusing
Directed Transport
Tracker Error (Candidates for Individual Inspection)
Subdiffusing
Skating

Re-emergence of the Ad Hoc Categories in Live Cell Data

Path Categorizations via Dashboard:



Freely Diffusing
Stuck Diffusing
Directed Transport
Tracker Error (Candidates for Individual Inspection)
Subdiffusing

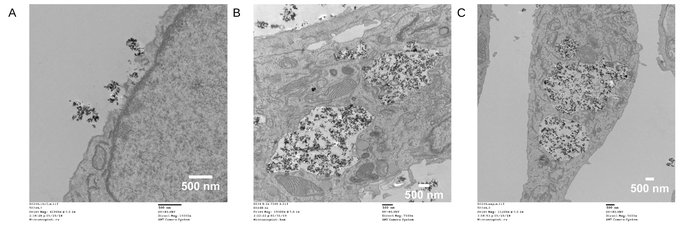
Data was generated in the Payne lab, using fluorescence microscopy with COOH modified polystyrene nanoparticles in HeLa (model human) cells.

Conclusion

The categories that we assumed were there in our ad hoc analysis actually emerged from the algorithm. Even better, a category we were unsure about at first became more clear: tracker error. Given data sets, we now have an automated categorization system that will help us identify which cells have more directed transport and which cells have more diffusive transport.

Future Application – TiO_2 Nanoparticles

Titanium dioxide (TiO_2) nanoparticles (NPs) are used as white pigments in consumer products. Previous work in the Payne lab has shown rapid internalization of TiO_2 NPs into enlarged lysosomes (3-5 μm).[2] We apply this dashboard to better understand movement of enlarged lysosomes relative to standard lysosomes in A549 (human lung) cells.



Internalization of TiO_2 NPs incubated with TiO_2 NPs (800 mg/mL, T-25 flasks) observed by TEM.[2] A. A549 cells were Cold-binding (4°C for 10 min) B. 1 hour incubation at 37°C C. 24 hour incubation at 37°C

Literature Cited

1. Culver–Hanlon, T.L.; Lex, S.A.; Stephens, A.D.; Quintyne, N.J. & King, S.J. (2006). A microtubule-binding domain in dynactin increases dynein processivity by skating along microtubules. *Nature Cell Biology, 8*, 264-270.
2. Jayaram, D. T.; Kumar, A; Kippner, L. E.; Ho, P.; Kemp, M. L.; Fan, Y. & Payne, C. K. TiO_2 nanoparticles generate superoxide and alter gene expression in human lung cells. *RSC Advances* (2019), In review.
3. Smith, J.D. & McKinley, S.A. *Bull Math Biol* (2018) 80: 2088.
4. Warren, E. A. K. & Payne, C. K. (2015). Cellular binding of nanoparticles disrupts the membrane potential. *RSC Advances*, 5(18), 13660–13666.

Acknowledgements

Thank you to my advisors Scott McKinley and Christine Payne. Special thanks to the National Institutes of Health R01GM122082-01 for funding my research.