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FIRST PERSON

First person – Amruta Vasudevan and Reshma Maiya

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping researchers promote themselves alongside their papers. Amruta Vasudevan and Reshma Maiya are two of the co-first authors on 'Transport of synaptic vesicles is modulated by vesicular reversals and stationary cargo clusters', published in JCS. Amruta is a PhD student in the lab of Dr Sandhya P. Koushika at the Tata Institute of Fundamental Research, Mumbai, India, investigating neuronal vesicular transport in the context of neuronal function and organismal behaviour. Reshma is a PhD student in the lab of Prof. Gautam I. Menon at The Institute of Mathematical Sciences, Chennai, India, modelling and performing theoretical studies of intracellular transport, specifically in neurons.

Amruta Vasudevan

How would you explain the main findings of your paper in lay terms?

A.V. & R.M.: Neuronal function requires the transport of cargo vesicles carrying important proteins and/or neurotransmitters from the cell body to synapses along neuronal processes. This transport depends on motor proteins, which actively carry vesicles along microtubule tracks. Neuronal processes are often very crowded, presenting numerous obstacles for moving cargo–motor complexes. We asked how this transport is modulated to avoid frequent 'traffic jams' along the process. We computationally modelled the neuronal process as a bundle of parallel tracks containing various obstacles, and the cargo–motor complex as individual moving particles. Our results show that the ability of moving particles to reverse their direction of motion is crucial to maintain transport in crowded systems. Removing reversals creates permanent 'traffic jams', causing all transport to come to a halt. This has implications for the progression of neurodegenerative diseases, as we observe that a reduction in reversals is associated with reduced transport in a nematode worm model of dementia and Parkinson's disease. We find that reversals help navigate crowded locations, as triggering reversals specifically at sites of obstacles leads to higher cargo flow in the system.

Were there any specific challenges associated with this project? If so, how did you overcome them?

A.V. & R.M.: We were interested in identifying factors that maintain transport of vesicles along crowded neuronal processes. As this is not a local phenomenon, it is a complex problem that has to account for several parameters. We also needed to develop a model that was extensively benchmarked to our experimental system, so that predictions from the model can be meaningful and validated *in vivo*. This being a collaboration between pure experimentalists and theorists, it took a while to understand the varied perspectives and practical considerations of both fields. An important aspect of this project was arriving at the correct set of parameter values to describe the simulations. As individual motor attachment and detachment rates to vesicles and microtubules are not available in our system, we developed a coarse-grained model with a set of parameters that reproduced macroscopic transport properties of synaptic vesicles in posterior lateral mechanosensory (PLM) neurons. The values taken by these parameters had to be provided from experimental measurements. In order to benchmark simulation parameter values to experiments, we had to come up with the right metrics for comparison between experiments and simulations. Furthermore, experimental data are noisy and much more variable, compared to data obtained from simulations. The comparisons between experimental measurements and simulations required a lot of standardisation of various experimental assays, using multiple transgenic lines expressing synaptic vesicle markers, different types of quantitative analyses, and trial and error to arrive at the appropriate simulation parameter values.

When doing the research, did you have a particular result or 'eureka' moment that has stuck with you?

A.V. & R.M.: There were a couple of such moments for us. The first was when our simulations predicted the occurrence of a completely jammed configuration that blocked all transport when reversals were removed. This was particularly striking as we did not observe such a drastic effect when track-switching events were disallowed. This suggested that reversals play a very important role in maintaining transport in crowded environments. A second moment that stuck with us would be when we identified a reciprocal trend between the

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Reshma Maiya

reversal rate/net anterograde current and the proportion of long-lived stationary clusters in the simulations, which we were then able to validate in our experimental system.

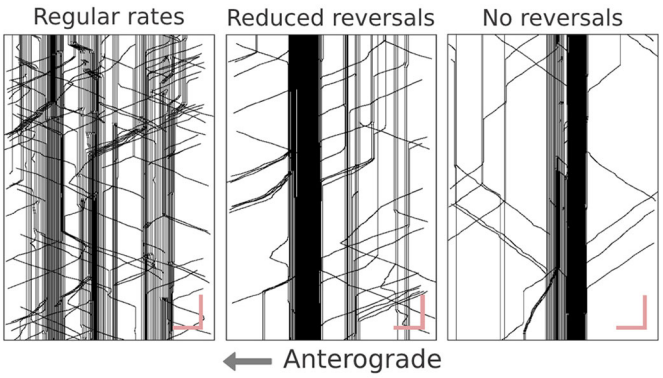
Why did you choose Journal of Cell Science for your paper?

A.V. & R.M.: The strength of this study is that it uses macroscopic observations from experiments to extensively inform simulations, and then uses this model to make experimentally infeasible perturbations and examine the effects. Although our model is an approximation of axonal transport in PLM neurons, it provides very useful insights that can be tested experimentally, making this a powerful tool with which to understand mechanisms that cannot be easily studied in the experimental context. This is a useful approach for experimentalists to adopt and we wanted to present it to the vast readership of cell biologists and other experimentalists associated with JCS. We thank the JCS editorial and review process for recognising the value of this work and accepting our paper.

Have you had any significant mentors who have helped you beyond supervision in the lab? How was their guidance special?

A.V.: Dr Sandhya Koushika, my PhD supervisor, has always been very understanding and patient as a mentor. She has trained me to think independently and develop my own projects. In addition to asking very interesting questions in neuronal cell biology, she believes in and adopts interdisciplinary approaches to address biological problems. I have always admired that and intend to carry that forward into all my future endeavours in academia.

R.M.: I am grateful to my PhD supervisor Prof. Gautam I. Menon for his patience and all the support during my PhD.



Representative kymographs from simulations run with regular, reduced rates of reversals and without reversals, showing decreased cargo flow and increased stationary cluster formation on reducing reversal rates.

What motivated you to pursue a career in science, and what have been the most interesting moments on the path that led you to where you are now?

A.V.: I have been interested in science from a very young age. However, the decision to pursue research came much later for me. I studied electrical engineering in university, and did not care much for biology until my later years in college. It was only then that my interests changed, and it occurred to me that biological research would be the most fulfilling future pursuit for me. So towards the end of my graduate studies, I decided not to sit for the university placement interviews and went on to be a junior research fellow in a research institute for a year to get some exposure. It was a very scary and unusual decision to take at the time, but ever since, I have not looked back. Working on this particular interdisciplinary project as part of my PhD has inspired me to transition into theoretical biophysics for my future research endeavours.

R.M.: I have always been interested in science. Coming from a biology background, courses in biophysics and complex systems during my PhD showed new ways of viewing and tackling questions in biology.

What's next for you?

A.V.: I intend to pursue research in theoretical biophysics and will be looking for postdoctoral opportunities in that field.

R.M.: I am currently looking for a postdoctoral position.

Tell us something interesting about yourself that wouldn't be on your CV.

A.V.: I love solving and designing cryptic crosswords, and generally love solving puzzles in all shapes and forms. Although I haven't been able to give this much time in the past couple of years, I hope to get back into it in the immediate future.

R.M.: I am an avid reader. I love travelling. Birdwatching is something that I picked up during the pandemic.

Reference

Vasudevan, A., Maiya, R., Venkatesh, K., Kumar, V., Sood, P., Murthy, K., Koushika, S. P. and Menon, G. I. (2023). Transport of synaptic vesicles is modulated by vesicular reversals and stationary cargo clusters. *J. Cell Sci.* **136**, jcs261223. doi:10.1242/jcs.261223