Modeling myosin Va liposome transport through actin filament networks reveals a percolation threshold that modulates transport properties

Sam Walcott and David Warshaw

Corresponding author(s): Sam Walcott, Worcester Polytechnic Institute

Review Timeline:

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| Submission Date        | 2021-08-11 |
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Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. The original formatting of letters and referee reports may not be reflected in this compilation.)
1st Editorial Decision

September 19, 2021

RE: Manuscript #E21-08-0389

TITLE: "Modeling myosin Va liposome transport through actin filament networks reveals a percolation threshold that modulates transport properties"

Dear Sam: both reviewers and I enjoyed the manuscript. The reviewers have insightful questions and suggestions - please revise accordingly. Depending on revisions, I will decide if the manuscript needs to be sent to one of the reviewers for the second look, or can be accepted right away.

Sincerely,
Alexander Mogilner
Monitoring Editor
Molecular Biology of the Cell

Dear Prof. Walcott,

The review of your manuscript, referenced above, is now complete. The Monitoring Editor has decided that your manuscript requires minor revisions before it can be published in Molecular Biology of the Cell, as described in the Monitoring Editor’s decision letter above and the reviewer comments (if any) below.

A reminder: Please do not contact the Monitoring Editor directly regarding your manuscript. If you have any questions regarding the review process or the decision, please contact the MBoC Editorial Office (mboc@ascb.org).

When submitting your revision include a rebuttal letter that details, point-by-point, how the Monitoring Editor’s and reviewers’ comments have been addressed. (The file type for this letter must be "rebuttal letter"; do not include your response to the Monitoring Editor and reviewers in a "cover letter.") Please bear in mind that your rebuttal letter will be published with your paper if it is accepted, unless you have opted out of publishing the review history.

Authors are allowed 180 days to submit a revision. If this time period is inadequate, please contact us immediately at mboc@ascb.org.

In preparing your revised manuscript, please follow the instruction in the Information for Authors (www.molbiolcell.org/info-for-authors). In particular, to prepare for the possible acceptance of your revised manuscript, submit final, publication-quality figures with your revision as described.

To submit the rebuttal letter, revised version, and figures, please use this link (please enable cookies, or cut and paste URL):
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Authors of Articles and Brief Communications whose manuscripts have returned for minor revision ("revise only") are encouraged to create a short video abstract to accompany their article when it is published. These video abstracts, known as Science Sketches, are up to 2 minutes long and will be published on YouTube and then embedded in the article abstract. Science Sketch Editors on the MBoC Editorial Board will provide guidance as you prepare your video. Information about how to prepare and submit a video abstract is available at www.molbiolcell.org/science-sketches. Please contact mboc@ascb.org if you are interested in creating a Science Sketch.

Thank you for submitting your manuscript to Molecular Biology of the Cell. Please do not hesitate to contact this office if you have any questions.

Sincerely,

Eric Baker
Journal Production Manager
MBoC Editorial Office
mbc@ascb.org

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Reviewer #1 (Remarks to the Author):

The manuscript, "Modeling myosin Va liposome transport through actin filament networks reveals a percolation threshold that modulate transport properties," by Walcott and Warshaw is a theoretical and simulation paper examining the ability of the network geometry to control intracellular transport. The networks of actin filaments were randomly created and a Monte Carlo simulation was run with probabilities derived from prior higher resolution simulations that matched probabilities from experimental results. The exciting result was that, as the number of filaments increases, the number of transport avenues for the cargo goes through a phase transition to enable better transport and delivery of cargos. This was beautifully described and clear supported with several different simulations and analyses. The "connectivity" of the network was controlled by the network geometry and the size of the cargo, as larger cargos can connect more filaments due to their size. Overall, I found the manuscript excellent. It has an important result and was so clearly explained, that I am hopeful that people will not only learn what a percolated network is, but also be able to determine it for themselves and use this correct terminology for future work.

Positive aspects of the manuscript:
1. Clear and important result about the network geometry and cargo affects on transport.
2. Clearly written manuscript that should allow young scientists to learn about these important concepts.
3. Very nice and clear figures and captions elucidating the concepts and results.
4. The authors used metrics that appear very useful for the community to continue to use to make comparisons between different data sets. We should all go back and reanalyze our transport data on networks to use these metrics.

Negative aspects of the manuscript:
I only had a few minor suggestions that I think will further increase the impact. No major issues detected.

Minor suggestions:
1. Figure 1, part A, in the first figure, the second, horizontal filament that is yellow in later frames of the simulation cartoon is not yellow in the first one with the cut-away sphere. Not sure if that was on purpose or not.
2. I was surprised that in the times when the trajectory becomes less directed, the alpha_MSD never goes to one. Do you think that is important, so that it is still super-diffusive. Or do you think that if you continued it would go to 1. If the alpha_MSD went to one, do you think that would be a problem for the transport. There is a brief discussion that at very high densities, the trajectories don't reach the edge. Do you think that "too diffusive" motion would result in never making it to the edge, or just taking way too long? None of this is essential, it is just a question I would ask the authors directly, if we were at a conference.
3. I really liked how the transport networks turned into vertex-edge networks, and how they inverted. What I mean by that is that edges in the vertex-network were at vertesxes in the real physical world. I wonder if that is a typically phenotype of proper vertex models. For instance, vertex models used for cell mechanics also seem to have this inversion and real-world consequences can be deduced from using the correct network. This made we think though, if I have a real work network, in an experiment or in a cell, and I turn it into a vertex network, can I predict which networks will be percolated and super critical?? This is something I think the authors should include - a way for experimentalists to take a picture of a network and predict the connectivity before running motors (or analyzing). Also, if you do that and instead of using the "number of filaments" which is specific to your system size and your cargo size, you relate it to a dimensionless number that includes both the filament density or perhaps the network meshsize AND the cargo size, could you come up with THE number that rules the entire thing? I am thinking like a physicist here, but it seems that coming up with one dimensionless parameter that can be checked from a SINGLE image of the network would be incredibly powerful. Again, I got this idea from vertex models of cells, which does have a single control parameter of this type. It can be found for any system of cells and it controls the mechanics.
4. Figure 6, A (B, C) can you make the y-axis clearer? What is "Pro. Of actin network"? Is it the proportion of the network that is accessible?
5. The authors found that size of the cargo was important, but only did it for two cargo sizes. It seems to be directly proportional. Do you think that will hold? Or will there be a size that is untenable, and the cargo will always stick?
6. For the power law fits in figures 4 and 7, did you give the fit equation? The best fit parameters? I may have missed it, but would be good to give those, so others can reproduce what you did exactly.

Reviewer #2 (Remarks to the Author):

This is a modeling study of actin-based liposome transport on a cell-size scale, performed for varying actin filament density and liposome size. To make computations practical, the authors coarse-grained their previously published detailed model (references 19, 20) by employing a multiscale strategy. Using the experimentally validated detailed model that resolves states of myosin motors bound to a liposome but is efficient only on short spatiotemporal scales, they inferred effective rate constants of the coarse-grain model formulated in terms of three liposome states. In this model, a liposome may either undergo a directed run along a filament, pause at an intersection of two filaments, or diffuse in the cytosol upon detaching from a filament; a pause may result in resuming transport along the same filament, switching tracks, or detaching from the filaments.
The main finding of the study is the existence of a critical actin density separating two modes of transport: directed runs along a single filament and random walks in the network. The latter arise for denser filament networks, as directed runs become interspersed with pauses, some of which result in switching tracks. The authors provide convincing arguments that the change of transport modes in their problem is akin to second-order percolation phase transitions describing sudden increases of network connectivity. They also showed that the critical actin density is inversely proportional to the liposome size, if the myosin motor surface density is independent of the liposome size.

Methods used in the study are sound and well documented. All assumptions are clearly described. Results are intuitive.

My only concern relates to biological significance of the findings. The authors hypothesized that because the transition between the transport modes is sharp, both actin density and liposome size (and/or myosin motor characteristics) might be targets for regulation by the cell, such that the actin filament network could swiftly change from being tracks for cargo delivery to a sieve separating vesicles by size, to a barrier the organelles are tethered to by myosins. They point to insulin granules as an example: these granules, ready to be released, are tangled in the cortex, whose density might be lowered upon stimulation by glucose. These hypotheses might hold true, if the critical actin density were comparable to typical densities of polymerized actin in cells, but this is not the case.

The critical number of 60 filaments in the sphere with a 10-micron radius translates into the concentration of polymerized actin subunits of 60 nM. Indeed, the average length of the actin filament in the problem is \( \frac{(2/\pi)\times20}{0.005} = 2546 \) polymerized subunits. Multiplying this number by 60 and dividing by the sphere volume yield \( \frac{2546\times60/3}{(4/\pi\times1000/3)} = 36 \) subunits per micron\(^3\) = 60 nM. This density is more than two orders of magnitude lower than typical concentrations of polymerized actin in non-muscle cells, given that the total actin in these cells is in the range of 46-70 micro-Molar (cytoskeleton.com/qa/actin) and the fraction of F-actin is \( \sim 35-50\% \) (McGrath et al., Biophys. J. 75, 2070 (1998); Dominguez and Holmes, Annu. Rev. Biophys. 40, 169 (2011)). Thus, typical actin filament densities in cells appear to be so deep in the supercritical range, that nearly all actin should be depolymerized to reach the critical concentration. Could it be that the rate constants determining the fraction of pauses are in error?

My minor suggestions and comments are as follows:

Page 4, last paragraph: I was perplexed by a statement that the MSD scaling exponent for directed runs, that appeared to be uniform, was less than 2 in simulations and I remained mystified till I got to the Methods section and later Suppl. Mater., where I learned that the movement wasn't deterministic but rather consisted of two stochastic substeps. For readers like me, an explanation immediately following the statement would be beneficial.

Page 5, Figure 2: the snapshots in each panel appear to be redundant, particularly since the authors did not even mention how they chose these snapshots.

Page 11, Figure 7. The legend includes two references to Fig. 7.

The main text is nicely written but is not entirely free from typos and awkward phrases. Here are the few that I spotted.

Page 2: "... actin networks consisted of randomly placed filaments of varying number; (?) covering roughly ...".
Page 4: "Rate constants between states (?)..."; "... (linear distance between initial and final position(s)...)".
Page 6: "... then, most if not all, of the 100 targets...". Did you mean "... then most, if not all, of the 100 targets..."?

See also the caption of Figure 7 on page 11: "In the plot of accessible actin (bottom graph).", and on page 12: "...(e.g. fluid- to gel-like (reviewed in [33])..."; did you mean "...(e.g., the fluid- to gel-like transition reviewed in [33])..."?

There are multiple inconsistences and grammar/typographical errors in the Suppl. Mater.; perhaps the most substantial is in the definition of \( e^p \) (footnote #2 on page 1).
Response to reviews
S. Walcott and D. M. Warshaw

We thank both reviewers for their positive and constructive comments and their extremely careful reading of our manuscript. In fact, to address important common issues brought up by both reviewers, we added new analysis of how the estimation of the percolation threshold, $N_c$, for cargo transport through a random actin network can be generalized by an equation that scales $N_c$ with transport distance, $d_T$, and liposome radius plus myosin reach, $r_B$. This new analysis is presented in two new supplemental figures (S5 and S6), a new section of the supplement (Section 3.6, Calculating $N_c$ for infinite networks), and a new section of the Results (Actin network percolation threshold is dependent on both liposome diameter and travel distance). We hope this makes our findings more generalizable and biologically relevant.

In the following response, which we hope meets with the reviewers’ satisfaction, we have repeated edited versions of the reviewers’ comments (in plain type), our response (in italics) and changes to the manuscript (in bold).

Reviewer 1

Minor suggestions:

1. Figure 1, part A, in the first figure, the second, horizontal filament that is yellow in later frames of the simulation cartoon is not yellow in the first one with the cut-away sphere. Not sure if that was on purpose or not.

   In figure 1 (and associated movie, S7), actin filaments become yellow when liposomes engage. In the first panel, all liposomes are engaged with the same actin filament. In the second panel (t=15s), liposomes are engaged with two filaments, including the second, horizontal filament. In the third panel (t=30s), liposomes engage with a third filament, at the left, nearly obscured by the cut away sphere.

   We have added a sentence to the caption noting that an actin filament turns yellow once engaged by the liposome: “In both A and B, actin filaments turn yellow once engaged by a liposome.”

2. I was surprised that in the times when the trajectory becomes less directed, the $\alpha_{MSD}$ never goes to one. Do you think that is important, so that it is still super-diffusive. Or do you think that if you continued it would go to 1. If the $\alpha_{MSD}$ went to one, do you think that would be a problem for the transport. There is a brief discussion that at very high densities, the trajectories don’t reach the edge. Do you think that “too diffusive” motion would result in never making it to the edge, or just taking way too long? None of this is essential, it is just a question I would ask the authors directly, if we were at a conference.
There are a couple issues raised here: 1) why doesn't $\alpha_{MSD}$ go to 1?, and: 2) if $\alpha_{MSD}$ goes to 1, would that be a problem for transport?

For the first issue, as the reviewer points out, many of the trajectories don’t reach the edge in the 100s simulation at high density. I expect that if we ran the simulations for longer, say 200s, $\alpha_{MSD}$ would decrease towards 1 at the higher densities and more of the liposomes would make it to the edge. Additionally, over relatively long times scales, the trajectories appear diffusive; over short time scales, they appear directed. Thus, the $\alpha_{MSD}$ might always be a bit above 1, since fitting the whole trajectory results in a weighted average of directed ($\alpha_{MSD} = 1.8$) and diffusive ($\alpha_{MSD} = 1$) motion.

For the second issue, we chose to make our 3D actin networks as random and isotropic as we could. Thus, over sufficiently long times and long distances, we would expect all transport to be random. In a cell, we expect that actin networks for transport might have some average directionality to bias transport in a particular direction.

Based on the reviewer’s last sentence, we have not added text to explicitly address these issues in the revised manuscript. However, we have added a paragraph to the last section of the Discussion that clarifies that our analysis and simulations apply to random actin networks.

3. I really liked how the transport networks turned into vertex-edge networks, and how they inverted. What I mean by that is that edges in the vertex-network were at vertexes in the real physical world. I wonder if that is a typically phenotype of proper vertex models. For instance, vertex models used for cell mechanics also seem to have this inversion and real-world consequences can be deduced from using the correct network. This made us think though, if I have a real work network, in an experiment or in a cell, and I turn it into a vertex network, can I predict which networks will be percolated and super critical?? This is something I think the authors should include - a way for experimentalists to take a picture of a network and predict the connectivity before running motors (or analyzing). Also, if you do that and instead of using the ”number of filaments” which is specific to your system size and your cargo size, you relate it to a dimensionless number that includes both the filament density or perhaps the network meshsize AND the cargo size, could you come up with THE number that rules the entire thing? I am thinking like a physicist here, but it seems that coming up with one dimensionless parameter that can be checked from a SINGLE image of the network would be incredibly powerful. Again, I got this idea from vertex models of cells, which does have a single control parameter of this type. It can be found for any system of cells and it controls the mechanics.

We thank the reviewer for this excellent suggestion. Therefore, we have added new analysis and presentation that address this issue. Based on this analysis, we find that in random actin networks the percolation threshold, $N_c$, scales as $N_c \propto (d_T/r_B)^{0.9}$, where $d_T$ is the transport distance and $r_B$ the liposome radius plus motor reach. Therefore, the dimensionless parameter of interest is $d_T/r_B$. This is not surprising, because $N_c$ is a geometric property of a network, so that a given actin network with a liposome would have the same $N_c$ if we increase or decrease the size of everything, in proportion. The nearly linear scaling arises from the fact that filament separation scales as $d_T/N$, so that the tug of war probability, or number of edges per vertex, $z$, scales as $r_B$/filament separation = $N r_B/d_T$. The weak non-linearity arises because the critical $z$ value is a weakly decreasing function of $r_B/d_T$.

The one caveat to this analysis is that it applies to random actin networks. Actin networks with some orientation bias, or with branching proteins or cross-linking proteins that promote specific orientations might have a different scaling law.
The generalized equation that the reviewer suggests is derived in the new section of the supplement (3.6), and associated two figures (S5 and S6) with the findings of this analysis presented in a new paragraph of the Results (Actin network percolation threshold is dependent on both liposome diameter and travel distance).

4. Figure 6, A (B, C) can you make the y-axis clearer? What is ”Pro. Of actin network”? Is it the proportion of the network that is accessible?

*Based on context, we presume that the reviewer meant the horizontal axis in writing “the y-axis.” We apologize for the confusion. The reviewer has correctly interpreted the axis label, it is the same as the vertical axis in Fig. 6D.*

*We have changed the label of the horizontal axes in Fig. 6A,B, and C to be “accessible proportion of actin network”*

5. The authors found that size of the cargo was important, but only did it for two cargo sizes. It seems to be directly proportional. Do you think that will hold? Or will there be a size that is untenable, and the cargo will always stick?

*We answer this question in two parts — first, will the critical actin density, \( N_c \), always vary in inverse proportion to the cargo size in the model? Second, will the critical actin density, \( N_c \), always vary in inverse proportion to the cargo size in reality?*

*The new analysis addresses part 1. As mentioned in our response to point 3, we find that in random actin networks the percolation threshold, \( N_c \), scales as \( N_c \propto (d_T/r_B)^{0.9} \). So, we expect the approximately linear scaling to hold.*

*For the second question, we expect that \( N_c \) will no longer be proportional to cargo size for 1) large cargo; and 2) dense networks. In the former case, large cargo generally have more motors than smaller cargo and are more easily deformable. Therefore, sufficiently large cargo will likely undergo deformations that violate assumptions of our detailed model that the cargo is not deformable. In the latter case, in sufficiently dense networks where pore size is comparable to cargo diameter, steric interactions between cargo and actin become important and cannot be neglected (as they are in our coarse-grained model), so we assume that cargo will get stuck and the network will act as a “barrier.”*

*As described above, the generalized equation for \( N_c \) is derived in the new section of the supplement (3.6), and associated two figures (S5 and S6). We discuss it in a new paragraph of the Results (Actin network percolation threshold is dependent on both liposome diameter and travel distance).*

6. For the power law fits in figures 4 and 7, did you give the fit equation? The best fit parameters? I may have missed it, but would be good to give those, so others can reproduce what you did exactly.
We have added the best-fit power laws to the figure captions of figures 4 and 7.
Reviewer 2

My only concern relates to biological significance of the findings. The authors hypothesized that because the transition between the transport modes is sharp, both actin density and liposome size (and/or myosin motor characteristics) might be targets for regulation by the cell, such that the actin filament network could swiftly change from being tracks for cargo delivery to a sieve separating vesicles by size, to a barrier the organelles are tethered to by myosins. They point to insulin granules as an example: these granules, ready to be released, are tangled in the cortex, whose density might be lowered upon stimulation by glucose. These hypotheses might hold true, if the critical actin density were comparable to typical densities of polymerized actin in cells, but this is not the case.

The critical number of 60 filaments in the sphere with a 10-micron radius translates into the concentration of polymerized actin subunits of 60 nM. Indeed, the average length of the actin filament in the problem is \((2/\pi)*20\) micron, corresponding to \((2/\pi)*20/0.005 = 2546\) polymerized subunits per micron\(^3\) = 60 nM. This density is more than two orders of magnitude lower than typical concentrations of polymerized actin in non-muscle cells, given that the total actin in these cells is in the range of 46-70 micro-Molar (cytoskeleton.com/faqs/actin) and the fraction of F-actin is \(\sim 35 - 50\%\) (McGrath et al., Biophys. J. 75, 2070 (1998); Dominguez and Holmes, Annu. Rev. Biophys. 40, 169 (2011)). Thus, typical actin filament densities in cells appear to be so deep in the supercritical range, that nearly all actin should be depolymerized to reach the critical concentration. Could it be that the rate constants determining the fraction of pauses are in error?

We thank the reviewer for raising this point. We believe the central issue is that the critical density, \(N_c/volume\), depends on both cargo size and transport distance. As detailed in our response to Reviewer 1, we have added a new analysis to demonstrate that \(N_c\) scales as \(N_c = 1.8(d_T/r_B)^{0.9}\) for random actin networks.

Intracellular cargos vary in size from synaptic vesicles, which may be 40nm, to entire organelles or even the ER. Since we use the example of insulin granules in the paper, those are 200-350nm – perhaps a bit smaller than in our simulations. It is hard to know transport distance, but generally people argue that myoVa is a short-range transporter for insulin granules, moving them \(\sim 1\)μm. Thus, for insulin granules, we would expect the critical number of actin filaments to be, say, \(N_c = 1.8(1000\text{nm}/100\text{nm})^{0.9} = 14.3\) filaments. Then, \((2/\pi)*2\) microns is the length of actin filaments, and each has \((2/\pi)*2*2/0.005 = 509\) polymerized subunits, with the extra factor of 2 coming from the fact that each actin filament has two protofilaments. Multiplying this value by 14.3 and dividing by the sphere volume, we get 1740 subunits per \(\mu\text{m}^3\), or 2.9μM — a bit lower than, but of the same order of magnitude as the estimates provided by the reviewer of 15-35μM in non-muscle cells. We also note that our calculation applies to random actin networks, and actin networks with a polarity bias would likely favor directed motion (Lombardo et al. 2019). Therefore, we believe that our findings will have biological relevance.

We also note that the percolation threshold is a property of the actin network and does not depend on the rate constants in the liposome transport model.

The point that the percolation phase transition, \(N_c\), depends on both cargo size and transport distance is now explicitly raised in a new section of the Results (second to last section, titled “Actin network percolation threshold is dependent on both liposome diameter and travel distance”). We have added a section to the Discussion (second-to-last paragraph before the Methods) to present the calculation suggested by the reviewer and to discuss the points in our response, above.
My minor suggestions and comments are as follows:

1. Page 4, last paragraph: I was perplexed by a statement that the MSD scaling exponent for directed runs, that appeared to be uniform, was less than 2 in simulations and I remained mystified till I got to the Methods section and later Suppl. Mater., where I learned that the movement wasn’t deterministic but rather consisted of two stochastic substeps. For readers like me, an explanation immediately following the statement would be beneficial.

*Yes, there are two reasons that the MSD scaling exponent is not 2 – first, liposome trajectories are not straight lines, but rather spirals because of occasional short (31nm) steps; second, the model is stochastic both in terms of reaction times and step size.*

*We have added the following clarifying phrase at the location indicated:*

> **note that** \( \alpha_{MSD} < 2 \) **for directed motion because liposome trajectories are not straight lines, but rather spirals, and because the model is stochastic both in terms of reaction times and step size, see SM**

2. Page 5, Figure 2: the snapshots in each panel appear to be redundant, particularly since the authors did not even mention how they chose these snapshots.

*Sorry! We meant to indicate in the caption that each panel is a different trajectory from a single actin network. We wanted to show that, for small actin networks \((N = 1); \text{Fig. 2B})\, trajectories all are similar, while on dense actin networks \((N = 400, \text{Fig. 2C})\, trajectories are variable and consist of transport and tug of war states.*

*We have some text to the caption of Fig. 2, indicating that each panel shows a trajectory on the same actin network:*

> **In each plot, to show the variability of liposome trajectories, three liposome trajectories are shown on the same actin network. Only actin filaments engaged by the liposome are pictured.”**

3. Page 11, Figure 7. The legend includes two references to Fig. 7

*This was a mistake on our part with referencing the figures — the references should have been to figure 6.

*We have corrected these references to Fig. 6.*

The main text is nicely written but is not entirely free from typos and awkward phrases. Here are the few that I spotted.
We thank the reviewer for finding these. We have addressed each typo/awkward phrase.

4. Page 2: ”... actin networks consisted of randomly placed filaments of varying number; (?) covering roughly ...”.

Changed to “... actin networks consisted of a variable number of randomly placed filaments; covering roughly ...”

5. Page 4: “Rate constants between states (?)...”; “... (linear distance between initial and final position(s?)...”).

Changed to “Rate constants governing the transitions between states ...” and “...(linear distance between initial and final positions ...)”

6. Page 6: “... then, most if not all, of the 100 targets...”. Did you mean “... then most, if not all, of the 100 targets...”? 

Changed as suggested.

7. See also the caption of Figure 7 on page 11: “In the plot of accessible actin (bottom graph),” , and on page 12: “...(e.g. fluid- to gel-like (reviewed in [33])...”; did you mean “...(e.g., the fluid- to gel-like transition reviewed in [33])...”?

That sentence has been removed from the caption of Figure 7.
The parenthetical phrase on page 12 has been changed as suggested.

8. There are multiple inconsistencies and grammar/typographical errors in the Suppl. Mater.; perhaps the most substantial is in the definition of $e^p$ (footnote 2 on page 1).

We have gone through the supplement and corrected grammatical/typographical errors.

The particular note referenced by the reviewer now reads:

“Suppose that $x_i^s$ and $x_i^e$ are vectors to the start (minus end) and end (plus end), respectively, of actin filaments $i = 1$ and 2. $\hat{e}_i^s = (x_i^e - x_i^s)/||x_i^e - x_i^s||$ is a unit vector pointing along the $i$th filament, toward its plus end. $\hat{e}_i^p = (\hat{e}_1^p \times \hat{e}_2^p)/||\hat{e}_1^p \times \hat{e}_2^p||$ is a unit vector perpendicular to
both actin filaments. Then, $z = |(x_1^s - x_2^s) \cdot \hat{e}_r|$, and $\theta = \cos^{-1}(\hat{e}_{1r} \cdot \hat{e}_{2r})$."

2nd Editorial Decision

RE: Manuscript #E21-08-0389R

TITLE: "Modeling myosin Va liposome transport through actin filament networks reveals a percolation threshold that modulates transport properties"

Dear Prof. Walcott:

I am pleased to accept your manuscript for publication in Molecular Biology of the Cell.

Sincerely,
Alexander Mogilner
Monitoring Editor
Molecular Biology of the Cell

Dear Prof. Walcott:

Congratulations on the acceptance of your manuscript.

A PDF of your manuscript will be published on MBoC in Press, an early release version of the journal, within 10 days. The date your manuscript appears at www.molbiolcell.org/toc/mboc/0/0 is the official publication date. Your manuscript will also be scheduled for publication in the next available issue of MBoC.

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