A systems approach to investigate GPCR-mediated Ras signaling network in chemoattractant sensing

Xuehua Xu, Wei Quan, Fengkai Zhang, and Tian Jin

Corresponding author(s): Tian Jin, NIAID, NIH

Review Timeline:
- Submission Date: 2020-08-19
- Editorial Decision: 2020-09-30
- Revision Received: 2021-10-28
- Editorial Decision: 2021-11-17
- Revision Received: 2021-12-01
- Accepted: 2021-12-07

Editor-in-Chief: Matthew Welch

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.)
Dear Dr. Jin,

Two reviewers have evaluated your manuscript titled: "A systems approach to investigate GPCR-mediated RasGAP activation and Ras adaptation in chemoattractant sensing". As you will see both reviewers expressed some reservation about the work and the novelty of the findings. While I agree with this to some extent, I do think that the use of the Simmune software to simulate signaling is very useful. In this context, I would like to invite you to consider publishing this work as a "Methods" paper for MBoC. This would give you the opportunity to provide more details about the model and how you select parameters.

Please let me know if this would be a viable option for you. I am happy to discuss in more details if you are interested.

Best wishes,

Carole Parent
Monitoring Editor
Molecular Biology of the Cell

Reviewer #1 (Remarks to the Author):

Previous studies have shown that Ras activation in response to cAMP stimulation of a GPCR (cAR1) in Dictyostelium exhibits adaptation. Theoretical considerations show that adaptation can arise from two main network topologies: incoherent feedforward loop and/or negative feedback loop. This paper reports the use of Simmune software to simulate signaling from a GPCR to Ras in potential networks capable of adaptation. Experimental profiles of G protein and Ras activation in Dictyostelium are provided, and fully recapitulate similar previously published results from this and other labs. The simulations involve hypothesized links between the G protein and Ras regulators that seem plausible but are not experimentally established. Parameters were chosen by trial and error to yield models that recapitulate the data. The simulations confirm previous theoretical work establishing that appropriate negative-feedback or incoherent-feed-forward networks can produce adaptation in outputs.

While the simulations recapitulate and confirm what is a quite intuitively plausible theoretical result, I do not understand what is novel in this paper. The findings are consistent with previous theory, and do not lead to any surprising result or significant advancement in our understanding of Ras activation in Dictyostelium. Furthermore, details about the model and its parameters could be presented better. This is a differential equation model, but no equations are presented (the absence of explicitly stated reaction constants in an equation also makes it hard to parse through the parameter table in the Supplement). The Supplemental Fig. 1 shows a 3D cell, but I don't see parameters that represent spatial processes (like length, diffusion) in the parameter table. The authors write: "To select the parameters of the molecules in each model, we first defined parameters based on earlier experiments and assumptions...", but do not clarify what parameters are experimentally constrained. I think that if suitably modified, this paper could be a tutorial to demonstrate the use of Simmune software to investigate biochemical networks, but is not suitable as a research contribution.

Reviewer #2 (Remarks to the Author):

There has been several studies addressing the adaptive response of Ras activity in Dictyostelium, however the model simulations have been conceptual and/or lacked comparisons between predictions from some of the possible molecular implementations. The present work by Xu et al tested three networks using their simulation platform and studied the nature of the adaptive response. At the heart of the model is the idea that Ga serves to activate GAP and Gbeta activates GEF (IFFLP) and also the idea that Ras negatively regulated RasGAP (NFBLB) which are both very attractive and worth obtaining model predictions.

1) The results essentially show that all three networks (IFFLP only, NFBLB only and IFFLP+NFBLB) yield very similar response at the level of Ras activity. Conceptually this is not new and there are vast literatures out there that demonstrate this numerically or has given theoretical proof (reviewed in Adler and Alon, Current Opinion Sys Biol 8, 81-89). The authors should describe how their results fit into the current understanding of the core network structure essential for adaptive response in general.
The authors then test the IFFLP+NFBLB model to predict the outcome of RasGAP overexpression or hyperactivation. I find it strange that the authors did not compare the different outcome of the perturbation in the NFBLB network but rather chose to study IFFLP+NFBLB only. This is central in deciphering the actual network structure. From how the kinetics operate, one can imagine that IFFLP is the essential ingredient in the observed behavior and that the role of negative feedback is secondary. I feel this aspect can easily be checked by the model and discussed with respect to the following statement in p.10 "We found that the rasGAP- cell displayed unchanged dynamics att..... Ras-GTP remained at a fully activated level even before the cAMP stimulation, and cAMP stimulation could not further activate Ras signaling (Ras-GTP, blue curve in Figure 6A), demonstrating that receptor-induced inhibition of Ras is essential for a network to produce a transient and adaptive Ras signaling."

In the present state, this conclusion almost sounds trivial (required no simulations) as it is not comparing the possible routes of RasGAP and RAS regulation.

3) The work showed the response at the heterotrimeric G protein for an incremental increase in extracellular cAMP which I believe is novel. It is pity that the authors did not really go deep in the analysis as to what the fold-change response curve looks like for Gbeta-gamma dissociation. The fold-change response for the adaptive response has been analyzed for Ras (Takeda et al Science Signal Fig. 2) as well as PIP3 and cAMP (Kamino et al, PNAS 114, E4149; Fig .2E, Fig. 4E) which authors did not discuss.

4) I would like to see some discussion regarding the the work by Hans Othmer's and his colleague (PLoS Comput Biol. 2016 May; 12(5): e1004900) which have studied a detailed model with regard to Ras regulation.

5) Also, regarding the biological role of the adaptive response (p. 12 discussion), what would be some of the predictions with regard to how cells chemotax under these three different models? According to Nakajima et al, the adaptive response is capable of doing two things. One is the steady state responses that reads out spatial difference in the ligand concentrations with the help of globally diffusing inhibitory signal and localized activation kinetics. The other is the transient response which reads out temporal changes. According to Nakajima et al (reference in p.16), in wave chemotaxis, the cells essentially can determine the front based the so-called first-hit mechanism first proposed by Herbert Levine and others (Levine et al PNAS 103, 9761-) which again uses globally diffusing inhibitory signal and localized activation to detect time delay of the stimulus arrival between one end of a cell from the other. E. coli chemotaxis is based on negative feedback regulation by the two component system which uses to read out temporal changes. If negative feedback is important, is there something that one can related to these two roles that adaptation plays in Dicty? The unique feature of negative feedback based adaptation is that depending on parameter, one obtains damped oscillations. As far as I am aware there has not been clear demonstration of this without the help of secreted extracellular cAMP.
**Point by point**

**Reviewer #1 (Remarks to the Author):**

Previous studies have shown that Ras activation in response to cAMP stimulation of a GPCR (cAR1) in Dictyostelium exhibits adaptation. Theoretical considerations show that adaptation can arise from two main network topologies: incoherent feedforward loop and/or negative feedback loop. This paper reports the use of Simmune software to simulate signaling from a GPCR to Ras in potential networks capable of adaptation. Experimental profiles of G protein and Ras activation in Dictyostelium are provided, and fully recapitulate similar previously published results from this and other labs. The simulations involve hypothesized links between the G protein and Ras regulators that seem plausible but are not experimentally established. Parameters were chosen by trial and error to yield models that recapitulate the data. The simulations confirm previous theoretical work establishing that appropriate negative-feedback or incoherent-feed-forward networks can produce adaptation in outputs.

While the simulations recapitulate and confirm what is a quite intuitively plausible theoretical result, I do not understand what is novel in this paper. The findings are consistent with previous theory, and do not lead to any surprising result or significant advancement in our understanding of Ras adaptation in Dictyostelium. Furthermore, details about the model and its parameters could be presented better. This is a differential equation model, but no equations are presented (the absence of explicitly stated reaction constants in an equation also makes it hard to parse through the parameter table in the Supplement). The Supplemental Fig. 1 shows a 3D cell, but I don’t see parameters that represent spatial processes (like length, diffusion) in the parameter table. The authors write: "To select the parameters of the molecules in each model, we first defined parameters based on earlier experiments and assumptions...", but do not clarify what parameters are experimentally constrained. I think that if suitably modified, this paper could be a tutorial to demonstrate the use of Simmune software to investigate biochemical networks, but is not suitable as a research contribution.

To address the reviewer’s concern regarding novelty, we added sentences to focus on the method of using Simmune without writing differential equations, which allows experimental biologists who have not mastered higher-level mathematics to build quantitative models and do simulations.

We thank the reviewer for pointing out the missing spatial parameters. We have added the length of the digital cells and diffusion constants to the table in the revised manuscript.

As suggested, we have modified the manuscript to be a method paper.

**Reviewer #2 (Remarks to the Author):**

There has been several studies addressing the adaptive response of Ras activity in Dictyostelium, however the model simulations have been conceptual and/or lacked comparisons between predictions from some of the possible molecular implementations. The present work by Xu et al tested three networks using their simulation platform and studied the nature of the adaptive response. At the heart of the model is the idea that Ga serves to activate GAP and Gbeta activates GEF (IFFLP) and also the idea that Ras negatively regulated RasGAP (NFBLB) which are both very attractive and worth obtaining model predictions.
1) The results essentially show that all three networks (IFFLP only, NFBLB only and IFFLP+NFBLB) yield very similar response at the level of Ras activity. Conceptually this is not new and there are vast literatures out there that demonstrate this numerically or has given theoretical proof (reviewed in Adler and Alon, Current Opinion Sys Biol 8, 81-89). The authors should describe how their results fit into the current understanding of the core network structure essential for adaptive response in general.

Amended as suggested. In the revised MS, we have added a new paragraph to discuss the core network structure for adaptive response and the characteristics of our three networks.

Many sensory systems in cells and organisms share a property called fold-change detection (FCD), which describes a system that is sensitive to the fold-change in the input signal and not to the absolute change (Goentoro et al., 2009; Kamino et al., 2017; Shoval et al., 2010). FCD systems have an identical dynamic response to signals with the same fold-change, and the response shows a transient increase followed by a perfect adaptation. The FCD property applies to a range of input signals and breaks down when signals are too weak or too strong. Previous models simulated fold-change responses for the adaptive responses at the signaling steps of Ras signaling (Takeda et al., 2012), PIP3 production, and cAMP production (Kamino et al., 2017). In our study, we included mechanisms regulating dissociation of heterotrimeric G-proteins, and our simulations showed that cAMP-induced G-protein dissociation/activation displays persistent and incremental increases, unlike the adaptive responses of Ras activation, PIP3, and cAMP production. Our simulations showed that cAR1-mediated Ras signaling modeled in each network generates transient responses followed by adaptation in response to cAMP stimuli ranging from $10^{-9}$-$10^{-4}$ M (Figure 4) and produces two transient responses upon two stepwise cAMP stimulations (Figure 6A, 6B, and 6C), indicating that each of the networks (IFFLP, NFBLB, or IFFLP+NFBLB) displays the characteristics of a fold-change detection (FCD) system. Two types of gradient sensing models of eukaryotic cells have been proposed: one is spatial sensing, where a cell detects the spatial difference of stimuli between its front and back (Parent and Devreotes, 1999); another is temporal sensing, used in bacterial chemotaxis, in which a cell senses temporal changes in stimuli (Levine et al., 2006). Our simulations showed that our models generate directional responses to stimuli with spatial changes. Our adaptation models can generate directional responses but without spatial amplification at the signaling steps, including ligand/GPCR, G-protein activation, Ras-GTP, active RasGEF, and active RasGAP, between the front and back regions in response to gradients of different concentrations and/or steepness. Amplification of the directional difference at the receptor level thus likely occurs downstream of the Ras activating signaling steps. In the future, we will investigate how the models respond to stimuli with temporal changes and spatial-temporal changes such as waves.

2) The authors then test the IFFLP+NFBLB model to predict the outcome of RasGAP overexpression or hyperactivation. I find it strange that the authors did not compare the different outcome of the perturbation in the NFBLB network but rather chose to study IFFLP+NFBLB only. This is central in deciphering the actual network structure. From how the kinetics operate, one can imagine that IFFLP is the essential ingredient in the observed behavior and that the role of negative feedback is secondary. I feel this aspect can easily be checked by the model and discussed with respect to the following statement in p.10

"We found that the rasGAP- cell displayed unchanged dynamics att..... Ras-GTP remained at a fully activated level even before the cAMP stimulation, and cAMP stimulation could not further activate Ras signaling (Ras-GTP, blue curve in Figure 6A), demonstrating that receptor-induced inhibition of Ras is essential for a network to produce a transient and adaptive Ras signaling."
In the present state, this conclusion almost sounds trivial (required no simulations) as it is not comparing the possible routes of RasGAP and RAS regulation.

We appreciate the reviewer’s pointing out that we can compare outcomes of different models with various inputs using Simmune simulations. In our current manuscript, we focused on the method of using Simmune to build quantitative models and do simulations by showing some examples. Our revised manuscript emphasizes the protocol of using the software package, which allows experimental biologists who may not have mastered higher-level mathematics to build quantitative models and do simulations without writing differential equations. In the future, we and others will apply Simmune to do in-depth and comprehensive studies comparing different models using various stimulations, as suggested by the reviewer.

3) The work showed the response at the heterotrimeric G protein for an incremental increase in extracellular cAMP which I believe is novel. It is pity that the authors did not really go deep in the analysis as to what the fold-change response curve looks like for Gbeta-gamma dissociation. The fold-change response for the adaptive response has been analyzed for Ras (Takeda et al Science Signal Fig. 2) as well as PIP3 and cAMP (Kamino et al, PNAS 114, E4149; Fig .2E, Fig. 4E) which authors did not discuss.

We thank the reviewer for pointing out the novelty of our result showing the response at the heterotrimeric G-protein for an incremental increase in response to cAMP stimuli. As suggested, we have added the following sentences to the discussion:

“Previous models simulated fold-change responses for the adaptive responses at the signaling steps of Ras signaling (Takeda et al., 2012), PIP3 production, and cAMP production (Kamino et al., 2017). In our study, we included mechanisms regulating dissociation of heterotrimeric G-proteins, and our simulations showed that cAMP-induced G-protein dissociation/activation displays persistent and incremental increases, unlike the adaptive responses of Ras activation, PIP3, and cAMP production.”

4) I would like to see some discussion regarding the work by Hans Othmer's and his colleague (PLoS Comput Biol. 2016 May; 12(5): e1004900) which have studied a detailed model with regard to Ras regulation.

Amended as suggested. We have added the following sentences regarding Chang and Othmer’s detailed model on Ras regulation.

“A previous study proposed a molecular mechanism controlling RasGEF to regulate Ras activity in a model, in which Gα-GTP recruits RasGEF from cytosol to cell membrane and then free Gβγ activates RasGEF (Cheng and Othmer, 2016). Because the regulatory mechanism of RasGEF has not been determined, we simply defined that free Gβγ serves as RasGEF that interacts with Ras to convert Ras-GDP to Ras-GTP in our current models. To study the regulation of RasGAP, we incorporated different activating mechanisms of RasGAP, which are by Gα2-GTP alone (IFFLP), Ras-GTP alone (NFBLB), or both Gα2-GTP and Ras-GTP (IFFLP+NFBLB).”

5) Also, regarding the biological role of the adaptive response (p. 12 discussion), what would be some of the predictions with regard to how cells chemotax under these three different models? According to Nakajima et al, the adaptive response is capable of doing two things. One is the steady state responses.
that reads out spatial difference in the ligand concentrations with the help of globally diffusing inhibitory signal and localized activation kinetics. The other is the transient response which reads out temporal changes. According to Nakajima et al (reference in p.16), in wave chemotaxis, the cells essentially can determine the front based the so-called first-hit mechanism first proposed by Herbert Levine and others (Levine et al PNAS 103, 9761-) which again uses globally diffusing inhibitory signal and localized activation to detect time delay of the stimulus arrival between one end of a cell from the other. E. coli chemotaxis is based on negative feedback regulation by the two component system which uses to read out temporal changes. If negative feedback is important, is there something that one can related to these two roles that adaptation plays in Dicty? The unique feature of negative feedback based adaptation is that depending on parameter, one obtains damped oscillations. As far as I am aware there has not been clear demonstration of this without the help of secreted extracellular cAMP.

To address the reviewer’s question regarding to how these three models mediated chemotaxis, we added new results to the section “Simulated spatiotemporal dynamics of signaling events in response to cAMP gradients” and a section in the discussion, as follows.

“Simulated spatiotemporal dynamics of signaling events in response to cAMP gradients
We tested how each model performs in response to cAMP gradients (Figure 8). We tracked five signaling events upon exposure to a cAMP gradient (1 μM or 10^-6 M at the front and 0.5 μM or 0.5X10^-6 M at the back): ligand/GPCR, G-protein activation, Ras-GTP, RasGEF, and RasGAP, in both the front and back regions of the modeled cell. The results are shown in Figures 8A, 8C, and 8E. The dynamic profiles of ligand/GPCR, G-protein activation, and Ras-GTP in both the front and back regions are similar in all three models, and these profiles closely resembled those measured experimentally in real cells (Xu et al., 2005). Our simulations also predicted the spatiotemporal dynamics of active RasGEF and active RasGAP in the modeled cell in response to a cAMP gradient. We found that each of the three adaptation models showed increasing responses along the hierarchy of the five signaling steps, ligand/GPCR, G-protein activation, Ras-GTP, RasGEF, and RasGAP, in the front regions. However, the differences between the front and back regions for each signaling event were not significant in any of the three models under these stimulation conditions, indicating there was no significant spatial amplification at these signaling steps.

To further test our models in response to a much steeper cAMP gradient, we simulated the dynamic responses of a modeled cell exposed to 10 μM (10^-5 M) of cAMP at the front and 100 nM (10^-7 M) at the back (Figures 8B, 8D, and 8F). Our simulations showed that the dynamic patterns of each signaling step remained like those generated when the modeled cell was exposed to uniform stimuli (Figures 4A, 4B, and 4C) and a shallow gradient (Figures 8A, 8C, and 8E). We found that a stronger stimulus in the front region of the cell induced higher local responses in the front than in the back for ligand/GPCR, G-protein activation, Ras-GTP, active RasGEF, and active RasGAP. The steeper gradient induced increasing differences at each signaling step. Our simulations indicated that our adaptation models can generate directional responses but without significant spatial amplification at the signaling steps, including ligand/GPCR, G-protein activation, Ras-GTP, active RasGEF, and active RasGAP, between the front and back regions in response to gradients of different concentrations and/or steepness. Amplification of the directional information provided at the receptor level thus likely occurs downstream of the Ras signaling.”

“Two types of gradient sensing models of eukaryotic cells have been proposed: one is spatial sensing, where a cell detects the spatial difference between stimuli at its front and back (Parent and Devreotes, 1999); another is temporal sensing, used in bacterial chemotaxis, in which a cell senses temporal
changes in stimuli (Levine et al., 2006). Our simulations showed that our models generate directional responses to stimuli with spatial changes. Our adaptation models can generate directional responses but without spatial amplification at the signaling steps, including ligand/GPCR, G-protein activation, Ras-GTP, active RasGEF, and active RasGAP, between the front and back regions in response to gradients of different concentrations and/or steepness. Amplification of the directional difference at the receptor level thus likely occurs downstream of the Ras activating signaling steps. In the future, we will investigate how the models respond to stimuli with temporal changes and spatial-temporal changes such as waves.”
Dear Dr. Jin,

Thank you for providing a revised version of your manuscript titled: "A systems approach to investigate GPCR-mediated RasGAP activation and Ras adaptation in chemoattractant sensing" that you now wish to be published as a methods paper. I agree with comments from Reviewer 2 that your revised ms now provides more insight into the utility of the Simmune program to study signaling networks and simulate spatiotemporal dynamics. I did notice that one of the original co-author, Martin Meier-Schllersheim, was removed from the list of authors. Would you please comment on this? Furthermore, the web site for the Simmune Project notes that "most of the Simmune source code will be made available shortly". Is there are more recent release of the program? As suggested by Reviewer 2, you should include a URL that provides full access to the program. Finally, please have update Figure 8 to a higher resolution version.

I look forward to hearing back from you.

Sincerely,

Carole Parent
Monitoring Editor
Molecular Biology of the Cell

---------------------------------------------------------------

Dear Dr. Jin,

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): Link Not Available

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
Reviewer #2 (Remarks to the Author):

The revised manuscript addressed my concerns adequately. As a method paper, I believe it is almost necessary that the manuscript includes a link to a URL of the repository e.g. github etc for easy access to the program. Also, the authors should check that the new fig.8. It looks quite blurry when printed out.
Point by point

1. Martin Meier-Schllersheim, was removed from the list of authors. Would you please comment on this?

   Martin asked us to remove his name, and we did at his request and thanked him for developing Simmune and making it available to the public in the acknowledgment.

   After we received comments in October 2020, Martin suggested that we tried to scan parameters and determine the space of possible parameter values that define each model using SimAnalyzer, a new module in Simmune that has not been added to the URL of Simmune (https://bioinformatics.niaid.nih.gov/simmune/) and is not yet available to the public. The ability to scan parameters is a novel feature in Simmune and a step forward in quantitative modeling. This is an interesting attempt, which, if successful, would allow us to determine parameter space for each model and help us to determine which model is more likely to represent the real cell. Unfortunately, we have not been able to complete the task in a reasonable time frame. Not knowing when the task would be completed, I suggested, in October 2021, to submit the revised MS with current simulation results. Martin emailed us and asked to remove his name from the current MS because it does not include parameter scanning. We did at his request.

2. Furthermore, the web site for the Simmune Project notes that "most of the Simmune source code will be made available shortly". Is there are more recent release of the program? As suggested by Reviewer 2, you should include a URL that provides full access to the program.

   Simmune source code has not been made available to the public yet. The online official release of Simmune is https://bioinformatics.niaid.nih.gov/simmune/. The public can use Simmune using the URL as described in our manuscript. The current version consists of three modules: 1: The Simmune Modeler, 2: The Simmune Cell Designer, and 3: The Simmune Simulator. We described the usage of the three modules in the manuscript.

   Amended. We added the sentence “The URL to the online official release of Simmune is https://bioinformatics.niaid.nih.gov/simmune/” in the manuscript.

3. Finally, please have update Figure 8 to a higher resolution version.

   Amended. We provided a new Figure 8 with a higher resolution.
Dear Dr. Jin:

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

Congratulations!

Carole Parent
Monitoring Editor
Molecular Biology of the Cell

--------------------------------------------------------------------------------

Dear Dr. Jin:

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.

Within approximately four weeks you will receive a PDF page proof of your article.

Would you like to see an image related to your accepted manuscript on the cover of MBoC? Please contact the MBoC Editorial Office at mboc@ascb.org to learn how to submit an image.

Authors of Articles and Brief Communications 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.

We are pleased that you chose to publish your work in MBoC.

Sincerely,

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

--------------------------------------------------------------------------------