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Agency Name:	National Science Foundation
Agency Tracking Number:	**2213103**
Organization:	
NSF Program:	CONDENSED MATTER & MAT THEORY
PI/PD:	Phillips, Michael
Application Title:	MPS-Ascend: Liquid-Liquid Phase Separation of Heteropolymers: Sequence Details and Coupling to Statistical Fluctuations

Review 1

Rating:

Very Good

Review:

Summary

In the context of the five review elements, please
evaluate the strengths and weaknesses of the proposal with respect to intellectual merit.

The PI and the sponsoring scientist intend to investigate the liquid-liquid phase separation of charged heteropolymers and the ability of such separated condensates to regulate protein expression.

Strengths:
* The proposed activities intend to address important questions (role of charge, regulation of chemical activity via structured separated phases) that are of interest to a wide range of disciplines, including polymer science, biochemistry, and biophysics.
* The proposed activities are based on a sound rationale, and they build on the prior work of the sponsoring scientist. However, some technical details were omitted in the proposal, which raises some questions (see weaknesses).
* The PI has a background in theoretical condensed matter physics and is well qualified to carry out the proposed activities under the supervision of the sponsoring scientist, who is an expert in this area.

* The PI has adequate resources at the university to carry out the proposed activities.

Weaknesses:
Many technical details were omitted in the proposal, which makes it unclear how certain tasks will be done:
* How will the PI model the first three terms in Eq. (1) that describe the entropy and fluctuations of counterions? No reference was provided.
* Why do charge-charge interactions in Eq. (2) not depend on the degree of ionization?
* How do the two-body short-range interactions in Eq. (2) depend on the degree of ionization?
* It seems that the effective free energy terms in Eq. (2) were derived assuming that the polymer configuration corresponds to the Gaussian chain. This assumption may not be true in the dense phase of the phase separation.
* It is unclear how the effects of salt concentration will be captured in Eqs. (1) and (2).
* Why does the effective 'chi' parameter describing the polymer-solvent interactions in Eq. (3) not depend on the degree of ionization?
* How will the kinetics of phase separation be modeled to probe the regime where the time scale of phase separation is comparable to the characteristic reaction times?
* How will Gillespie's simulations be done? Are they going to simulate both the phase separation of protein A and the chemical reactions in Eq. (4)?

Other comment:
* It seems that the degrees of ionization were assumed to be uniform throughout the heteropolymer chain. This is a good starting point, but in the future, this assumption may need to be relaxed to allow the degree of ionization to be position-dependent.

In the context of the five review elements, please
evaluate the strengths and weaknesses of the proposal with respect to broader impacts.

Strengths:
* The proposed educational activities are extremely strong and would have a big impact on the education and preparation of URM students at the University of Denver and beyond.
* The PI has proposed a number of innovative activities, including video games, sports, animations, machine learning tools that will appeal to the younger generations.
* The proposed new hands-on workshops will help URMs develop many important research skills.
* The PI has extensive experience with mentoring URMs and classroom innovations during his time as an instructor at the Central New Mexico Community College.
* The PI is a URM and will serve as a role model to URM students.
* The existing resources at the university (DEI, ESTEM) will enable the PI to reach a broad group of URMs.

Weaknesses:
none

Please evaluate the strengths and
weaknesses of the proposal with respect to any additional solicitation-specific review criteria, if
applicable

Strengths:
* The Fellowship would have a huge impact on the future career of the PI. It would help the PI's scientific development. It would further improve the PI's skills as an educator which are already extremely strong.
* In his previous role as an instructor at the Central New Mexico Community College, the PI has already demonstrated the ability to increase the representation of URM students in MPS fields. The proposed projects in connection with the host university will further increase the representation of URM students at the University of Denver and beyond.
* The proposed research is of very high scientific quality that will have an impact on a wide range of disciplines
* The sponsoring scientist is an expert in the field of the proposed research and has demonstrated the ability to successfully mentor postdocs and URMs.
* The PI has strong foundations in theoretical condensed matter physics and computational methods that will enable him to carry out the proposed interdisciplinary research.

Weaknesses:
none

Summary Statement

This is a very good proposal that intends to address important questions related to the phase separation of charged heteropolymers and their regulation of chemical activity, which will have an impact on many different fields. The lower rating is due to the omission of some technical details, which makes it

unclear how certain proposed activities will be carried out. The proposed educational activities will impact a number of URMs and will increase their preparation and participation in STEM fields.

Review 2

Rating:

Very Good

Review:

Summary

In the context of the five review elements, please
evaluate the strengths and weaknesses of the proposal with respect to intellectual merit.

This is an interesting and easy-to-read proposal that plans to develop improved sequence-specific analytical models for intrinsically disordered regions in the context of biomolecular condensate formation and biological noise. The general background is well motivated and the PI is an outstanding environment to complete the work, but concerns were noted regarding the need for the work, the criterion for success, and the applicant's qualifications to complete the proposed research.

Strengths
- This is a well-written proposal on an important and timely topic
- The general research question and background is well motivated
- The PI is in the perfect environment to pursue the proposed research, and Dr. Ghosh is uniquely qualified to advise the PI on the proposed project
- The second aim is extremely creative and the focus on small-number fluctuations is (in my opinion) a really overlooked and important area in the context of biological function with respect to phase separation

Weaknesses
A first concern is the PI's background. It appears the PI has no real background in either biophysics, polymer physics, or gene regulation. Given these are the main areas of interest, the absence of any preliminary data (which might otherwise not be a big deal) has left me wondering how achievable the actual work is? I recognize that switching fields is challenging, but I was left wanting some sort of confirmatory evidence that the work could actually be achieved; the absence of a track record and preliminary data makes that hard for me to evaluate. That said, the short time that the PI has been with the host offers some explanation for this weakness.

For aim 1. While the general area of interest is an important one, a question I was left wondering is what would the real impact of this work be? I say this not to imply it wouldn't be impactful, but I didn't feel like the importance was well articulated. To play Devil's advocate, both the PI's host (Gosh) and others (Chan, OShea) have developed sequence-specific models for polyampholyte phase separation and single-chain behavior. Despite the fact these models have been available for some time, their use and application have been quite limited. Maybe that's because they don't work well, but this is not articulated. My more general concern is that specific use cases for why the more advanced models are needed were not provided. They probably exist, but the grant mostly motivates based on the fact that current models make some limiting assumptions. I, as a reader, have no way to understand how "bad" those assumptions really are in terms of the knowledge gap they create. This could be mitigated by showing examples where the current state of the art fails and a new approach is needed, but this was not provided. To summarize this concern; it was hard for me to evaluate how necessary the proposed research would be given it’s unclear how much of an improvement these new models would provide and, more generally, what benefit these models truly provide in the proposed area of study.

For aim 2. While I like this idea a lot, the aim itself felt relatively unfocused. The authors reference the Klosin paper, and describe the simplicity of the model, but, despite its simplicity, the model does work and explains the experimental data (at least phenomenologically, if not mechanistically). As such, the motivation for a sequence-specific model was not totally clear to me. Again, as with aim 1, it was unclear what the ‘problem’ with the state-of-the-art is, and how the proposed research would fundamentally shift the needle in terms of the question of biological noise.

For both aims. In general, it was not clear to me what 'success' would look like. The ideas are extremely interesting but felt a bit like "we'll play around with a few things and see what we get". For example, in Aim 2, even if a network where noise increases with LLPS is found (as per the aim's hypothesis) how would this be tested to see if this is a physiologically accessible regime?

As a final note, however, some of these concerns are mitigated by the fact the PI has only recently switched fields, and while some concerns regarding the project are raised, the PI should be commended for writing such a clear proposal in an area that they have only just switched into. This does give me some confidence that even though there are some weaknesses (as discussed) the PI clearly has the ability and creativity to carve out a niche and many of my concerns would, I suspect, be addressed during the proposed work. My concerns do not chiefly stem from issues with the research or the ideas but are more grantsmanship concerns.

In the context of the five review elements, please
evaluate the strengths and weaknesses of the proposal with respect to broader impacts.

The real strength of this proposal is in the absolutely outstanding broader impacts. Clear, well-defined projects are articulated and the PI's broad background and training, while raised as a point of concern in terms of Intellectual Merit, is a huge strength here.

Strengths
The PI has an outstanding track record of STEM mentorship across multiple institutions and is incredibly well qualified to drive the proposed activities given this background.

The PI's proposed outreach and work are clearly defined, achievable, and the combination of being from an underrepresented group himself coupled with his own career path through multiple different fields and institutions affords a level of credibility within under-represented communities that would be challenging for most other scientists to obtain.

It is extremely clear that the PI is truly a catalyst for STEM outreach and education to unserved groups in science. This, in my mind, far outweighs any weaknesses raised in Intellectual Merit.

Weaknesses
None of significance or importance noted

Please evaluate the strengths and
weaknesses of the proposal with respect to any additional solicitation-specific review criteria, if
applicable

The scientific ability and potential of the proposed Fellow

As discussed, this is where my main concern lines, not because I have any reason to believe the PI would be unable to complete the work, but, instead, because the proposal does not offer me strong evidence (based on track record and training) that he can. The PI's scientific output in his prior work is also relatively modest, but this should be offset by the strong track record in STEM outreach and education that has already been achieved.

The scientific quality of the research is likely to emerge from the Fellowship experience

Similar concerns as above, although the work from Dr. Ghosh's lab has consistently been of a very high caliber so I have no concerns about the final quality of any work, nor the caliber of his training.

The likely impact of the Fellowship on the future career of the Fellow;

The PI has a clear vision that aligns well with the NSF's broader impact goals of enhancing and improving STEM literacy in the general population. This funding opportunity would be absolutely transformative for the PI, offering him the fiscal independence to drive this vision in a real and tangible way while gaining scientific training in a field that is largely orthogonal yet complementary to his previous work.

The potential of the proposed Fellow and project to lead to increased representation of those underrepresented (Blacks and African Americans, Hispanics, Latinos, Native Americans, Alaska Natives, Native Hawaiians, and other Native Pacific Islanders) in MPS fields

Put simply, I cannot imagine a candidate who would be more qualified than the PI. As mentioned, the scientifically broad background while a possible weakness in terms of the specific project is an enormous strength here, and in combination with the excellent track record and strong future plans this is a remarkably good application from the perspective of having a real, meaningful impact on underrepresented groups in MPS fields.

The suitability and availability of the sponsoring scientist and other colleagues, as described in the sponsoring scientist statement, and the likely impact of the sponsoring scientist and the host institution on the professional and scientific development of the Fellow.

My concerns regarding the applicants' background are in many ways mitigated by the excellent environment provided by Dr. Ghosh. Having been familiar with Dr. Ghosh's work for some time, I can say with confidence we will provide the PI with an intellectually demanding yet supportive environment that will foster the necessary scientific development required for success in this project. More generally, the University of Denver has the resources necessary both for the proposed scientific work and the outreach projects proposed.

The data management plan is appropriate and well-articulated.

Summary Statement

This is a clear proposal from a candidate with a clear and unwavering dedication to STEM mentorship. Strong letters of support and an excellent proposed environment negate concerns regarding the applicant's background in the specifics of the proposed areas. While some questions regarding the details of the prosal (definition of success, expected outcomes, preliminary data) were raised, in this reviewer's mind these are more than made up from by the applicant's strong background in STEM education and clear and well-defined plan for future activities.

I rated this a Very Good because I could not say it was Outstanding in *all* respects, but (especially) given the solicitation-specific review criterion I would strongly endorse support of this proposal.

Review 3

Rating:

Very Good

Review:

Summary

In the context of the five review elements, please
evaluate the strengths and weaknesses of the proposal with respect to intellectual merit.

This proposal aims to build a theoretical framework describing the conformation and phase separation of charged polymers in solution, and to use this framework to investigate the coupling between polymer phase separation and gene expression.

In my opinion, the proposed research is interesting, creative, and well-motivated. If successfully realized and connected to biology (see below), the proposed research could provide the prospective fellow with a launching pad for an interesting long-term research program at the faculty level. The proposal does a good job explaining and motivating the background of the proposed research.

While the prospective fellow does not have an excellent track record in terms of productivity in research, it does appear to me that he has the required background and depth to successfully realize the proposed research. Also, the proposed mentor (with whom the prospective fellow is currently working as a postdoc) would play an important role in providing expertise and support. While, in general, it may be preferable for a fellow to use a fellowship to move to a different institution, the proposed arrangement seems to make sense in this case.

My biggest criticism of the proposal concerns the lack of detail and specificity in terms of the proposed research, the specific questions and sub-questions to be addressed, and the methods to be employed. While the proposal contains several passages concerned with methods and validation, they are far too vague and brief to be meaningful. If this was a grant proposal prepared by a faculty member, I would see this lack of specificity as a strong reason not to fund the proposal. However, since overall the proposal is very well formulated and rather creative, and the proposal is for a postdoctoral fellowship rather than for an independent grant, I am inclined to give the prospective fellow the benefit of the doubt here.

In the context of the five review elements, please
evaluate the strengths and weaknesses of the proposal with respect to broader impacts.

The proposed research is broad and creative enough to provide a potential foundation for a faculty research program. This, to me, is one of the central strengths of this proposal. If executed successfully, it could play a central part in launching the awardee’s faculty career.

The proposal relates closely to ongoing research on liquid-liquid phase separation in cells. While many researchers are working on this topic now, it does appear to me that the proposed research would make a useful contribution to the field. I found the ideas in the proposal regarding stochastic gene expression to be interesting, if not fleshed out enough.

The proposal could have been much stronger if it had provided a clear path for how the proposed research will elucidate a set of specific biological problems, and if it contained a clear plan for how to develop collaborations with experimental biologists/biophysicists working on liquid-liquid phase separation in cells. I strongly encourage the prospective fellow to develop such collaborations, which could play a central role in making this research program competitive at the level of a faculty job search. If the prospective fellow manages to use the theoretical framework to be developed here to make interesting (specific!) biological predictions, this could be rather exciting.

Please evaluate the strengths and
weaknesses of the proposal with respect to any additional solicitation-specific review criteria, if
applicable

The prospective fellow provides a detailed engagement plan designed to broaden participation in the physical sciences through, for instance, the organization of workshops and the founding of a learning center. The prospective fellow has a good track record in this regard, having served as an instructor at a community college for four years. This should put the prospective fellow into an excellent position to contribute meaningfully to the outreach goals of the ASCEND program.

Summary Statement

This is an interesting and creative proposal that suffers somewhat from a lack of detail and specificity. The research is well motivated and, if successfully executed, could provide the foundation for an exciting independent research program at the faculty level. I recommend that the awardee works very hard to establish collaborations with experimental biologists/biophysicists, which would make this research program rather competitive for faculty job applications. I recommend that this proposal should be supported if at all possible.

Review 4

Rating:

Very Good

Review:

Summary

In the context of the five review elements, please
evaluate the strengths and weaknesses of the proposal with respect to intellectual merit.

This project aims to develop a theoretical model of so-called liquid-liquid phase separation (LLPS) phenomena in biological and material science systems and use the model to investigate interpay between phase separation and noise in gene expression circuits.

Strengths: The subject is of outstanding importance. The applicant and the host lab have the expertise necessary to make progress toward the stated goals of the project. The effect of LLPS on gene expression networks is a relatively unexplored subject.

Weaknesses: The proposed theoretical model of LLPS is somewhat simplistic and deals only with charge-charge interactions, which makes it a polyelectrolyte problem. The biological LLPS is much more complex, with hydrophobic interactions playing a major role. While recognizing the novelty of the study directed at elucidating an interplay between LLPS and gene expression noise, it was not clear from the project description which particular biological situation that study would address.

In the context of the five review elements, please
evaluate the strengths and weaknesses of the proposal with respect to broader impacts.

The Broader impact plan of the project progresses from engagement in established institutional programs to PI-driven workshops and learning centers.

Strengths: The plans are likely to be effective because of the PI’s background and because of the PI’s plan to commit a substantial fraction of the project's funds to the broader impact activities.

Weaknesses: Not really a weakness, but there seems to be too many different things that the PI is aiming to accomplish in 3 years. Focusing on fewer things (and describing them in greater detail) would have made this part of the project even stronger.

Please evaluate the strengths and
weaknesses of the proposal with respect to any additional solicitation-specific review criteria, if
applicable

The applicant has multi-disciplinary background, however the publication record is not exceptional.

The project is likely to produce several simple models of LLPS and its relation to gene expression noise. These results may form a basis for subsequent in-depth investigations.

This fellowship will very likely have a dramatic impact on the future career of the Fellow.

The Fellow and the project have great potential to increase representation of URG.

The sponsoring scientist is committed to help the Fellow in accomplishing their goals.

The Fellow is already at the sponsoring institution, hence the potential impact of new research environment is lost. Nevertheless, University of Denver and the host lab has all the resources necessary to aim professional and scientific development of the Fellow.

Summary Statement

This is a strong application that addresses a question of great biological importance and is well within scope of MPS. The applicant's institution is well suited for the proposed research and broader impact activities