Advice for NSF CAREER proposal

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1. You win/lose reviewers on the first page of the research plan
   → Be extremely direct!
2. State of the field, what's missing, and how your proposal addresses it
3. Put the words into the reviewer's mouth
4. Include appropriate collaborators
5. Leverage existing PSU outreach programs for broader impacts and educational component
6. Underline and bold key points

2. State of the field, what's missing, and how your proposal addresses it

Extremely Direct

State of field
Whats missing
How to address

1. Objectives and Significance

The purpose of this CAREER proposal is to develop and apply theoretical tools to understand the origins of variable codon translation rates and their consequences for nascent protein behavior at the molecular level. An emerging paradigm for *in vivo* protein biophysics is that nascent protein behavior is a type of non-equilibrium phenomenon in which the kinetics of translation can govern the behavior of newly synthesized proteins (Fig. 1)[1]. The PI recently highlighted this in a *JACS* Perspective[1]. The recognition that the non-equilibrium nature of translation can determine nascent protein behavior is significant because it means that physical scientists have theoretical tools at their disposal to describe and understand this phenomenon. This work will utilize a range of theoretical methods (*i*) to understand the physical forces on the ribosome that cause altered codon translation rates; (*ii*) to determine how those variable codon translation rates coordinate co-translational folding; and (*iii*) to examine how alteration of codon translation rates alters protein function in the case of heterodimerization. Aspects of this research will be experimentally validated through two active collaborations. The integrated educational objective of this proposal will encourage and involve women and minority grade-school and high-school students in STEM education and research through outreach activities in the local community and through summer research positions in my lab. These underrepresented groups will learn core concepts in molecular biophysics and the role of high-performance computing in scientific research.

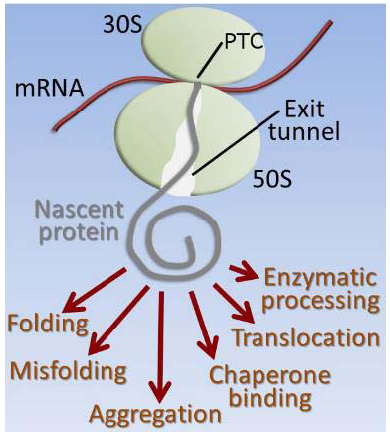

Figure 1. A range of nascent protein behaviors (orange) are affected by alteration of codon translation rates.

3. Put the words into the reviewer's mouth

3.1.2 Concluding remarks on Objective 1

The results from this multi-scale modeling study will quantify this novel form of allosteric communication within the ribosome-nascent-chain complex, identify the factors influencing the strength of this allosteric signal, and present a detailed molecular mechanism by which such forces can modulate codon translation rates. This type of tensile-force feedback may potentially be a common occurrence, as it is estimated that one-third of the *E. coli* cytosolic proteome co-translationally folds. The results from this work will lay the ground work for future research exploring that possibility.

4. Include appropriate collaborators

1.3 Methods: This proposal's objectives utilize a variety of methods in which we have expertise including coarse-grained molecular dynamics simulations[6–9], Metropolis Monte Carlo[8], chemical kinetic modeling[10,11] and Markov-state analysis of simulations[12]. One method we have not published on before is quantum mechanics/molecular mechanics (QM/MM) calculations – which we will use in Objective 1 to study peptide bond formation during translation. We have run test calculations demonstrating we can carry out such calculations on the ribosome (Fig. 6, below), however, we also have started a collaboration with Dr. Yihan Shao, a developer of the quantum mechanics package Q-CHEM[13] for over 10 years, who will co-advise one of my graduate students on the proper implementation, execution and interpretation of such calculations (see Dr. Shao's letter of support).

5. Leverage existing PSU outreach programs for broader impacts and educational component

5.4 Summer research for low-income, minority high-school students. I will enlist the help of minority high-school students to create the various simulation modules to be used on the Interactive Biomolecular Arcade system. Specifically, Penn State's Upward Bound Math and Science (UBMS) Program, in partnership with the Summer Experience in the Eberly College of Science (SEECoS), provides for minority high schools students to engage in research experience for two 3-hour sessions per week for six weeks. This time-frame (36 hours of total research time over the summer) is ideal for a high school student to create one to two modules by creating the biomolecular system in the easy-to-use NAMD software package as well as the 20-second power-point presentation that will serve as the introduction to the module. I have requested NSF funding to support rotation students in years one through three. In this way, I will both provide research experience to minority high-school students, build the platform for my other outreach activities, and encourage these underrepresented groups to continue their STEM education.

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