**MSM U01 suggestions for new MSM Methodology challenges:**

1. Spanning Scales in Multiscale Modeling
2. Coarse-graining approaches bridging molecular dynamics and sub-cellular models.
3. Linking molecular fundamentals to cellular behavior in a more mechanistic way, to inform molecular interventions. Connection to omics data.
4. Linking cellular and tissue scales. Modeling heterogeneity of cell types and of the cell microenvironment. Developing sound homogenization methods that predict properties of disordered tissues.
5. Combining continuum based finite elements simulation methods (e.g., CFD, structural, and FSI) with particle based methods (e.g., DPD, MD) to cover the vast range of scales in biological processes. Common computational techniques with an emphasis on rigorous coupling in space and time.
6. Providing interfaces/meshing between high-level top-down phenomenological models of behavior with low-level bottom-up models of basic physiology.
7. Combining Data Analytics with Multiscale Modeling
8. Development, application, and uncertainty assessment of mechanism based, multi-scale models.
9. Multi-fidelity modeling via machine learning of multiscale biological systems. Physics/Biology-informed learning machines for discovering new models. Machine learning that takes into account physical principles, enabling inferences to be made in spite of noisy data.
10. Methods to predict regulation from principles (could be combined with inference from data). Understanding why cells are regulated, from an operational or dynamic perspective, will lead to predicting how cells are regulated.
11. Employment of cutting-edge deep learning techniques and development and validation of predictive models based on longitudinal data.
12. Integration of Experiment with Multiscale Modeling
13. Balancing the simplicity that models should bring with the complexity of biology through integration of biological data and hypothesis in multiscale modeling frameworks.
14. Strategies for experimental data generation and experimental design that are specifically generated for model development and validation.
15. Use of various imaging modalities to acquire dynamical data and to acquire realistic geometric information at various biological scales.
16. Developing heterogeneous multiscale methods to combine disparate descriptions (theories and models from different quantitative fields and biological and clinical data) into one process/simulation framework.
17. Enhancing communication (language and approaches) between experts in in engineering/ modeling approaches experimental biology.
18. Model Reproducibility and Sharing
19. Frameworks for defining and validating model reproducibility.
20. Improved methods of annotating and sharing biological knowledge, both experimental and computational).