BIOGRAPHICAL SKETCH

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NAME: Huang, Kerwyn Casey

eRA COMMONS USER NAME (credential, e.g., agency login): kchuang

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
California Institute of Technology, Pasadena, CA	B.S.	1998	Physics/Mathematics
Cambridge University, Cambridge, England	M.Phil.	1999	Physics
Massachusetts Inst. of Technology, Cambridge, MA	Ph.D.	2004	Physics

A. Personal Statement

I have a broad background in computational physics and biology, with specific training in the physical modeling of bacterial physiology. As a postdoctoral fellow at Princeton, I was trained in theoretical physics by Ned Wingreen, a condensed matter physicist-turned biophysicist, while immersed in the environment of the Molecular Biology department. This combination of training was critical for the development of my interest in biological self-organization, which I translated into a series of results related to bacterial cell division, membrane organization, mechanosensation, and cell shape determination. I was funded on these projects as the PI of an NIH K25 award, which allowed me to expand my interests and establish ties with the microbiology, systems biology, computational biology and biophysics communities through travel to conferences and subsequent collaborations. In recent years, my lab has developed a strong interest in applying these tools to complex microbial communities such as the intestinal microbiome. In collaboration with Justin Sonnenburg, we have developed a powerful experimental and computational framework for quantifying the spatial organization of the gut, which has revealed strong effects of diet on the structure of the community surrounding the mucus.

As PI on an NIH Director's New Innovator Award, I have been able to lay the groundwork for the proposed research at my current position at Stanford by developing computational tools and experimental synthetic biology tools that enable novel interdisciplinary studies of the role of physical forces in cellular organization. In addition, I have administered these awards (including staffing, research protections, and budget), collaborated with other researchers at Stanford and elsewhere, and have produced a number of peer-reviewed publications. Synthesizing my experiences, it is clear that successful projects require a realistic research plan, timeline, and budget, and the current application builds logically on my previous work in computational biology. In addition, these experiences have prepared me to educate undergraduates, graduates, and postdoctoral fellows, through classroom education and academic research. In particular, I have substantial experience mentoring graduate students and postdocs, with four of my postdocs having successfully acquired faculty jobs and others with prominent positions in industry. As Director of the Biophysics Program at Stanford, I am also responsible for the mentorship of ~60 graduate students. In summary, I have demonstrated my ability to carry out successful and productive research projects in an area of high relevance linking bacterial physiology and biophysics, and my expertise and experience will serve me well for carrying out the responsibilities required for this Sproposal.

Publications relevant to this proposal:

1. KA Earle[*], G Billings[*], M Sigal, J Lichtman, J Elias, MR Amieva, **KC Huang**[†], JL Sonnenburg[†], "Quantitative Imaging of Gut Microbiota Spatial Organization", *Cell Host & Microbe* **18** 1-11 (2015). PMCID: PMC4628835

2. ER Rojas, JA Theriot†, **KC Huang**†, "The response of *Escherichia coli* growth rate to osmotic shock," *PNAS* **111** 7807-7812 (2014). PMCID: PMC4040581.
3. JM Peters*, A Colavin*, H Shi*, TL Czarny, MH Larson, S Wong, JS Hawkins, CHS Lu, B-M Koo, E Marta, AL Shiver, EH Whitehead, JS Weissman, ED Brown, LS Qi†, KC Huang†, CA Gross†, "A Comprehensive, CRISPR-based Approach to Functional Analysis of Essential Genes in Bacteria," *Cell* **165** 1-14 (2016). PMCID: PMC4894308.
   *co-first authors.
   † co-corresponding authors.
4. G Auer, TK Lee, M Ranjendram, S Cesar, A Miguel, **KC Huang**†, D Weibel†, "Mechanical genomics: identification of regulators of bacterial cell stiffness," *Cell Systems* **2** 1-10 (2016). *Profiled in ACS Chemical Biology.* PMCID: PMC4967499.
   † co-corresponding authors.

B. Positions and Honors

Positions and Employment

1995	Database Programmer, Cleft Palate Clinic of Children's Hospital of Michigan, Detroit, MI
1996-1998	Economic Analyst, First Quadrant Corporation, Pasadena, CA
1999-2004	Research Assistant, Massachusetts Institute of Technology, Cambridge, MA
2001-2004	Systems Administrator, Graduate Student Council of MIT, Cambridge, MA
2002-2004	Intern, NEC Laboratories America, Inc., Princeton, NJ
2004-2005	Research Associate, Princeton University, Princeton, NJ
2005-2008	Associate Research Scholar, Princeton University, Princeton, NJ
2008-	Assistant Professor of Bioengineering, Stanford University, Stanford, CA
2011-	Assistant Professor of Microbiology and Immunology, Stanford University, Stanford, CA

Other Experience and Professional Memberships

1995-1998	Dean's Tutor, California Institute of Technology, Pasadena, CA
1997-1998	Teaching Assistant, Optoelectronics, California Institute of Technology, Pasadena, CA
1998-2000	Member, Institute of Physics
2002-	Member, American Physical Society
2007-	Member, Biophysical Society
2008-	Member, American Society of Cell Biology
2009-	Member, American Society of Microbiology
2008-2010	Editor, PMC Biophysics
2010-	Editor, BMC Biophysics

Honors

1994-1995	National Merit Scholarship
1996-1997	H.J. Ryser Scholarship for Outstanding Mathematics Scholarship, California Institute of Technology
1996-1998	Goldwater Scholarship
1996-1998	Caltech Merit Scholarship
1998-1999	Churchill Fellowship, Cambridge University
1999-2001	Robert Stockbarger Fellowship, Massachusetts Institute of Technology
1999-2002	NSF Graduate Student Fellowship
2005	Helen Hay Whitney Fellowship
2008-2011	Frederick E. Terman Fellowship
2009-2014	NIH Director's New Innovator Award
2010-2012	Hellman Faculty Fellowship
2013-2018	NSF CAREER Award
2015-2016	Friedrich Wilhelm Bessel Award (Humboldt Foundation)

C. Contribution to Science

1. My early publications focused on the physical principles underlying the establishment of spatiotemporal organization in bacterial cells. Using reaction-diffusion and biophysical models, we introduced minimal

models explaining division site selection by Min oscillations and polar localization of cardiolipin in bacterial cells.

a. **KC Huang**, Y Meir, and NS Wingreen, "Dynamic structures in *Escherichia coli*: Spontaneous formation of MinE rings and MinD polar zones," *Proc. Nat. Acad. Sci. USA* **100,** 12724 (2003). *Selected for November 15, 2003 issue of Virtual Journal of Biological Physics.* PMCID: PMC240685.
b. **KC Huang,** R Mukhopadhyay, and NS Wingreen, "A curvature-mediated mechanism for localization of lipids to bacterial poles," *PLoS Comp. Biol.* **2** 1357 (2006). *Commentary in Science.* PMCID: PMC1635540.

2. A major challenge for testing hypothesized mechanisms of bacterial growth has been the importance of the mechanics, dynamics, and spatial architecture of the cell wall. The wide disparity between the length and time scales of the molecular machinery and those of growth precludes direct experimental investigation, and requires a computational model with the flexibility to address mechanisms involving spatial patterning, biochemical regulation, and both physical and immunological perturbations - while spanning time scales of seconds to hours. My group developed the first quantitative, 3D physical model of the cell wall that predicts the mechanical response of shape to PG damage and other perturbations.
   a. L Furchtgott, NS Wingreen, **KC Huang**, "Mechanisms for maintaining cell shape in rod-shaped Gram-negative bacteria," *Molec. Microbiol.* **81** 340-353 (2011). PMCID: PMC3134142.
   b. S Teeffelen, S Wang, L Furchtgott, **KC Huang**, Ned S. Wingreen, Joshua W. Shaevitz, and Zemer Gitai, "The bacterial actin MreB rotates and rotation depends on cell-wall assembly," *Proc Nat Acad Sci USA* **108** 15822-15827 (2011). PMCID: PMC3179079.

3. There is a growing appreciation that the actin homolog MreB plays a central role in rod-shaped bacterial growth by coordinating the localization the wall synthesis machinery. Using novel 3D microscopy techniques and surface labeling, we determined that MreB segments were oriented predominantly as left-handed helices, and revealed an associated left-handed twisting during growth. Our simulations of cell growth quantitatively predicted that the wall twisted with the same handedness as the MreB pattern during elongation, demonstrating the power of coupled whole-cell simulations and quantitative mapping of growth. We have recently demonstrated that MreB preferentially localizes to regions of negative curvature, directing growth away from the poles and actively straightening locally curved regions of the cell. Taken together, our work demonstrates that MreB's generation of local heterogeneities in growth is critical for maintaining robust, uniform growth at the cellular scale.
   a. TS Ursell[*], E Trepagnier[*], **KC Huang**[†], JA Theriot[†], "Analysis of surface protein expression reveals the growth pattern of the Gram-negative outer membrane," *PLoS Comp Biol* **8** e1002680 (2012). P MCID: PMC3459847.
   b. S Wang, L Furchtgott, **KC Huang**[†], J Shaevitz[†], "Helical insertion of peptidoglycan produces chiral ordering of the bacterial cell wall," *PNAS* **109** E595-E604 (2012). PMCID: PMC3309786.
   c. T Ursell, J Nguyen, RD Monds, A Colavin, G Billings, N Ouzounov, Z Gitai, J Shaevitz, **KC Huang**, "Rod-like bacterial shape is maintained by feedback between cell curvature and cytoskeletal localization", *PNAS* **111** E1025-1034 (2014). PMCID: PMC3964057.

4. It remains mysterious how such a protein can detect geometry, exert forces on the membrane, and dictate cellular chirality. MreB and FtsZ are an ATPase and a GTPase, respectively, and the identity of the bound nucleotide has dramatic impact on the *in vitro* structure of filaments. To interrogate potential structural changes due to nucleotide hydrolysis, every atom matters, and hence one needs a technique at the appropriate scale. We have demonstrated through all-atom molecular dynamics (MD) simulations that GTP- and GDP-bound FtsZ dimers have different conformations and dynamics that drive constrictive force generation. Taken together, our studies explain the link between atomic-scale perturbations and cellular phenotypes, an ultimate goal of morphogenesis studies.
   a. J Hsin, A Gopinathan, **KC Huang**, "Nucleotide-dependent conformations of FtsZ dimers and force generation observed through molecular dynamics simulations," *PNAS* **109** 9432-9437 (2012). PMCID: PMC3948266.
   b. A Colavin, J Hsin, **KC Huang**, "Effects of polymerization and nucleotide hydrolysis on the filament properties of the bacterial actin homolog MreB", *PNAS* **111** 3585-3590 (2014). PMCID: PMC3948266.

5. For complex biological processes, the formation of protein complexes is a strategy for coordinating the activities of many enzymes in space and time. It has been hypothesized that growth of the bacterial cell wall involves stable synthetic complexes, but neither the existence of such complexes nor the consequences of such a mechanism for growth efficiency have been demonstrated. We used single-molecule tracking to demonstrate that the association between an essential cell-wall synthesis enzyme and the cytoskeleton is highly dynamic. This transient association allows the cell to buffer growth rate against large fluctuations in enzyme abundance, since any enzyme can contribute to multiple sites of synthesis.

    a. TK Lee, C Tropini, J Hsin, SM Desmarais, T Ursell, E Gong, Z Gitai, RD Monds†, **KC Huang**†, "A dynamically assembled cell-wall synthesis machinery buffers cell growth," *PNAS* **111** 4554-4559 (2014). PMCID: PMC3970539.
    b. C Tropini, TK Lee, J Hsin, SM Desmarais, T Ursell, RD Monds†, **KC Huang**†, "Principles of Bacterial Cell-Size Determination Revealed by Cell-Wall Synthesis Perturbations", *Cell Reports* **9** 1520-1527 (2014). PMCID: PMC4254626.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/kerwyn.huang.1/bibliography/45486784/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

P50GM107615-01 — Ferrell (PI) — 7/1/2013-6/30/2018
NIH
Systems biology of collective cell decision
This center grant will provide a systems-level understanding for cellular decision-making focusing on the interrelated processes of cell proliferation, migration, and differentiation. Particularly, we will be focusing on how to develop and validate models that range from molecular single cell mechanisms to collective cell behavior in bacterial communities.
Role: Co-Investigator

R01 GM105963 — Tian (PI) — 4/1/2014-3/31/2018
NIH
Molecular Insights into Membrane Curvature Recognition
Membrane remodeling is essential to many biological processes. The proposed study will determine the structural and molecular basis of membrane curvature recognition. In collaboration with Dr. Fang Tian at Pennsylvania State University, a structural biologist, Huang will perform molecular dynamics simulations of SpoVM and its interactions with a lipid bilayer to uncover the molecular origins of curvature sensitivity.
Role: Co-PI

5T32GM008294-27 — Huang (PI) — 7/1/2012-6/30/2017
NIH
Molecular Biophysics Training Program at Stanford
Training in the Biophysics Program centers on applying physical and chemical principles to solving and understanding biological systems. The Program coordinates all aspects of training Biophysics graduate students at Stanford. As part of the larger biomedical community at Stanford, Biophysics students are exposed to a broad range of biological problems for which biophysical understanding is lacking or for which new biophysical techniques are needed. The current focus on interdisciplinary research means that this Training Program occupies an essential and unique niche at Stanford.
Role: PI

Allen Discovery Center — Covert (PI) — 5/1/2016-4/30/2020
Paul Allen Foundation

Center for Multiscale Systems Modeling of Macrophage Infection
This center grant will interrogate the biophysical and genetic basis of macrophage infection by the pathogen *Salmonella enterica*. The center will focus on integration of cellular-scale modeling with single-cell transcriptomics and biophysical characterization of cell shape. Biological questions will involve antibiotic resistance and the progression of pathogenesis. Huang will particularly focus on measurements of cell growth and shape in a *Salmonella* knockout library, as well as technologies for quantifying the spatial organization of *Salmonella* in the context of the gut microbiota.

Internal award Huang (PI) 9/1/2014-8/30/2019
Stanford University
Imaging studies of collective behavior
This internal funding is intended to develop innovative research directions using imaging to study collective behavior. Current directions include: (1) spatial organization of the gut microbiome, (2) computational methods for quantifying gene expression within complex multicellular communities, (3) the role of adhesion in driving community organization, (4) bacterial responses to acute changes in environmental conditions.

Completed Research Support

1 DP2 OD006466 Huang (PI) 9/29/2009 – 6/30/2014
NIH
Engineering Cell Shape and Intracellular Organization

For this award, three design targets were pursued that leverage our expertise in biophysical modeling of cell shape to probe key features of cell growth: (1) exploration of the evolutionary origins of cell shape determination by transplanting foreign cytoskeletal elements between closely related bacteria, (2) programming of specific intracellular organizational phenotypes to dynamically reengineer cell shape, and (3) determination of the tension sensitivity of the growth machinery to elucidate potential feedback mechanisms for cell shape maintenance.
Role: PI

CAREER MCB-1149328 Huang (PI) 9/1/2012-12/31/2017
NSF
Virtual Microbe: Biophysical Modeling of Morphogenesis
We will develop general computational models for bacterial elongation of Gram-negative and Gram-positive rod-shaped cells, and for cell division in the round bacterium *Staphylococcus aureus*.
Role: PI

R01 GM086447 Supplement Xiao (PI) 4/1/2014-3/31/2016
NIH
Probing the Structure and Contraction Mechanism of the *E. coli* FtsZ-ring

For this supplement, my lab carried out Ultra Performance Liquid Chromatography muropeptide analyses of FtsZ GTPase mutants described in this proposal. In particular, we determined changes in glycan strand length and crosslinking, and used mass spectrometry where necessary to determine the identity of unknown muropeptide species.
Role: Co-PI