OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
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NAME: Chia, Nicholas Lee-Ping

eRA COMMONS USER NAME (credential, e.g., agency login): NICHOLAS\_CHIA

POSITION TITLE: Associate Professor of Surgery

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 |
| --- | --- | --- | --- |
| Georgetown University, Washington DC | B.S. | 06/2001 | Physics |
| The Ohio State University, Columbus, OH | Ph.D. | 06/2006 | Physics |
| Institute for Genomic Biology, University of Illinois, Urbana-Champaign, IL | Post-Doctoral Fellowship | 06/2011 | Biophysics |

**A. Personal Statement**

My role in the proposed project is that of Co-PI. I have a broad background in biophysics and theoretical biology, with specific training in the systems and computational biology approaches needed to make this project successful. I have always believed that the most interesting subject a physicist can study is life. From my undergraduate days in microscopy, when I developed a glass-only total internal reflection microscope from spare parts, to my present focus on understanding how we can model the microbial-host interface to create better tools for diagnosis and prevention, biology has been a constant. As PI of an R01 on the role of the microbiome in causing colon cancer, I have demonstrated my ability to manage a large, interdisciplinary project involving metabolic modeling, metagenomic sequencing, and human samples. In addition, in my position as Co-Director of the Microbiome Program at Mayo Clinic, I am ideally placed to ensure that this project receives the clinical, bioinformatics, and statistical support required. This work builds logically on my prior experience and interests, and the direction of Principal Investigator Dr. Leigh Greathouse will provide complementary expertise in using MBRA models to study the effects of dietary prebiotics on the microbiome; we have published and presented work on the microbiome together in the past. Below, I list 4 publications that exemplify my work in building and strengthening computational pipelines for clinical and basic research at Mayo Clinic; many recent publications from Mayo Clinic in the areas of Microbiology and Microbiome research have made use of these pipelines to generate novel findings. Of course, this proposal also requires expertise in microbiome bioinformatics, and representative publications in this area can be found in section C.

1. Jeraldo P, Kalari K, Chen X, Bhavsar J, Mangalum A, White BA, Nelson H, Kocher JP, **Chia N**. IM-TORNADO: A tool for comparison of 16S reads from paired-end libraries. PLOS One. 2014 Dec 15;9(12):e114804. PMCID: PMC4266640.
2. Sipos M, Jeraldo P, **Chia N**, Qu A, Dhillon AS, Konkel ME, Nelson KE, White BA, Goldenfeld N. Robust computational analysis of rRNA hypervariable tag datasets. PLoS One. 2010 Dec 31; 5(12):e15220. PMCID: PMC3013109.
3. Jeraldo P, **Chia N**, Goldenfeld N. On the suitability of short reads of 16S rRNA for phylogeny-based analyses in environmental surveys. Environ Microbiol. 2011 Nov; 13(11):3000-9.
4. Jeraldo P, Sipos M, **Chia N**, Brulc JM, Dhillon AS, Konkel ME, Larson CL, Nelson KE, Qu A, Schook LB, Yang F, Goldenfeld N, and White BA. Quantifying the role of neutral and niche processes in evolution, Proc Natl Acad Sci U S A.. 109, 9692-9698 (2012) PMCID: PMC3382495.
5. Jeraldo, P., Sipos, M., Chia, N., Brulc, J. M., Dhillon, A. S., Konkel, M. E., ... & Yang, F. (2012). Quantification of the relative roles of niche and neutral processes in structuring gastrointestinal microbiomes. *Proceedings of the National Academy of Sciences*, *109*(25), 9692-9698.
6. Sinha, R., Chen, J., Amir, A., Vogtmann, E., Shi, J., Inman, K. S., ... & Chia, N. (2016). Collecting fecal samples for microbiome analyses in epidemiology studies. *Cancer Epidemiology and Prevention Biomarkers*, *25*(2), 407-416.
7. Sipos M, Jeraldo P, Chia N, Qu A, Dhillon AS, Konkel ME, Nelson KE, White BA, Goldenfeld N. Robust Computational Analysis of rRNA Hypervariable Tag Datasets. PLoS One. 2010 Dec 31; 5(12):e15220. PMCID: PMC3013109
8. Multinu, F., Harrington, S. C., Chen, J., Jeraldo, P. R., Johnson, S., Chia, N., & Walther-Antonio, M. R. (2018). Systematic Bias Introduced by Genomic DNA Template Dilution in 16S rRNA Gene-Targeted Microbiota Profiling in Human Stool Homogenates. *mSphere*, *3*(2), e00560-17.

**B. Positions and Honors**

**Positions and Employment**

2006-2008 Postdoctoral Researcher under Nigel Goldenfeld and Carl Woese, University of Illinois at Urbana-Champaign, Champaign, IL

2011-2012 Senior Research Scientist, Institute for Systems Biology, Seattle, WA

2012-2014 Associate Consultant, Department of Surgery, Joint appointment in Health Sciences Research, Mayo Clinic, MN

2012-2018 Associate Director, Microbiome Program, Center for Individualized Medicine, Mayo Clinic, MN

2015-Present Senior Associate Consultant, Department of Surgery, Mayo Clinic, MN

2015-2018 Assistant Professor, Department of Surgery, Mayo Clinic, MN

2018-Present Associate Professor, Department of Surgery, Mayo Clinic, MN

**Honors**

2001 Awarded Fowler Fellowship by the Ohio State University Department of Physics

2006 Awarded the Alexander von Humboldt Fellowship for work in the area of Bioinformatics

**C. Contribution to Science**

My research career contains three key ingredients that relate to the success of this proposal, namely (1) creating new bioinformatics tools; (2) improving the accuracy of metabolic modeling, especially as regards the microbiome; and (3) designing theoretical models that predict biological reality. Specifically, I have:

1. **Created new bioinformatics tools to facilitate the analysis of sequence data**. My contributions to the field of bioinformatics date back to my Ph.D. in Statistical Physics, when I improved sequence alignment processes, and they continue to this day through my implementation of analysis pipelines for metagenomics analysis. Although Section A lists the most recent of these accomplishments, some others include:
2. **Chia N**, Bundschuh R. A practical approach to significance assessment in alignment with gaps. J Comput Biol. 2006 Mar; 13(2):429-41.
3. Li Y, **Chia N**, Lauria M, Bundschuh R. A performance enhanced PSI-BLAST using hybrid alignment. bioinformatics. 2011 Jan 1;27(1):31-7.
4. Yang F, **Chia N\***, White BA, Schook LB. Compression-based distance (CBD): a simple, rapid, and accurate method for microbiota composition comparison. BMC Bioinformatics. 2013; 14:136. PMCID:3660234.
5. **Chia N**, Cann I, Olsen GJ. Evolution of DNA replication protein complexes in eukaryotes and Archaea. PLoS One. 2010; 5(6):e10866. PMCID:2880001.

The bioinformatics tools I have helped create have been used in a wide variety of work, including studies focused on plant stress responses, the ubiquitination cascade, and assembly of the Chikungunya virus genome.

1. **Improved the accuracy of metabolic modeling approaches to studying the microbiome**. My second important contribution to science is in the field of metabolic modeling. By extending likelihood-based concepts from bioinformatics to the reconstruction of metabolic networks, I have helped generate more accurate metabolic modeling approaches (a-c). These skills and tools have allowed me to generate a global map of microbial metabolism and cross-feeding (d).
2. Benedict MN, Mundy MB, Henry CS, **Chia N,** Price ND. Likelihood-based gene annotations for gap filling and quality assessment in genome-scale metabolic models. PLOS Computational Biology. 10(10): e1003882.
3. Mundy, M., Mendes-Soares, H., & **Chia, N**. (2017). Mackinac: a bridge between ModelSEED and COBRApy to generate and analyze genome-scale metabolic models. *Bioinformatics*, *33*(15), 2416-2418.
4. Mendes-Soares, H., Mundy, M., Soares, L. M., & Chia, N. (2016). MMinte: an application for predicting metabolic interactions among the microbial species in a community. *BMC bioinformatics*, *17*(1), 343.
5. Sung, J., Kim, S., Cabatbat, J. J. T., Jang, S., Jin, Y. S., Jung, G. Y., **Chia, N** & Kim, P. J. (2017). Global metabolic interaction network of the human gut microbiota for context-specific community-scale analysis. *Nature communications*, *8*, 15393.
6. **Designed theoretical models to explain and predict diverse biological phenomena**. Finally, and in my opinion, most importantly, I have a history of producing models that provide important insights into the underlying biology of a wide variety of biological phenomena observed among microbes. Working under Nigel Goldenfeld and Carl Woese as a postdoc, I had the opportunity to use modeling parameters to predict biologically reasonable states and generate important predictions in a number of ecologic systems, as demonstrated by the publications below.

1. **Chia N**, Woese CR, Goldenfeld N. A collective mechanism for phase variation in biofilms. Proc Natl Acad Sci U S A. 2008 Sep 23; 105(38):14597-602. PMCID:2567205.
2. **Chia N**, Goldenfeld N. Dynamics of gene duplication and transposons in microbial genomes following a sudden environmental change. Phys Rev E Stat Nonlin Soft Matter Phys. 2011 Feb; 83(2 Pt 1):021906.
3. **Chia N**, Goldenfeld N. Statistical mechanics of horizontal gene transfer in evolutionary ecology. Journal of Statistical Physics. 2011 Apr; 142(6):1287-301.
4. **Chia N**, Golding I, Goldenfeld N. Lambda-prophage induction modeled as a cooperative failure mode of lytic repression. Phys Rev E Stat Nonlin Soft Matter Phys. 2009 Sep; 80(3 Pt 1):030901. PMCID:4038166.

In addition to having the basic ingredients necessary for accomplishing the work outlined in this proposal, I also have a history of successfully combining these approaches to advance our understanding of colorectal cancer (CRC) and other diseases.

1. **Applied microbiome, metabolic modeling, and evolutionary modeling approaches to improve our understanding of colorectal cancer (CRC).** My CRC work includes data-based studies both adenomas, CRC, and the microbiome. In addition, important advances in integrated multi-omics analyses focused on potential links between microbial metabolism and microbial metabolites.
2. Hale, V. L., Chen, J., Johnson, S., Harrington, S. C., Yab, T. C., Smyrk, T. C., ... & **Chia, N**. (2017). Shifts in the fecal microbiota associated with adenomatous polyps. *Cancer Epidemiology and Prevention Biomarkers*, *26*(1), 85-94.
3. Hale, V. L., Jeraldo, P., Mundy, M., Yao, J., Keeney, G., Scott, N., ... & **Chia, N**. (2018). Synthesis of multi-omic data and community metabolic models reveals insights into the role of hydrogen sulfide in colon cancer. *Methods*.
4. Hale VL, Jeraldo P, Chen J, Mundy M, Yao J, Priya S, Keeney G, Lyke K, Ridlon J, White BA, French AJ, Thibodeau SN, Diener C, Resendis-Antonio O, Gransee J, Dutta T, Petterson X-MT, Blekhman R, Boardman L, Larson D, Nelson H, **Chia N**, Sung J, Blekhman R, Boardman L, Larson D, Nelson H, Chia N. Distinct Microbes, Metabolites, and Ecologies Define the Microbiome in Deficient and Proficient Mismatch Repair Colorectal Cancers. Genome Med [Internet]. 2018 Jan 1;10(1):78.
5. Kim, M., Druliner, B. R., Vasmatzis, N., Bae, T., **Chia, N**., Abyzov, A., & Boardman, L. A. (2018). Inferring modes of evolution from colorectal cancer with residual polyp of origin. *Oncotarget*, *9*(6), 6780.
6. **Application of metabolic modeling approaches to studying the microbiome in other disease areas**. The skills I picked up as a Senior Research Scientists at the Institute for Systems Biology, before joining Mayo Clinic, have allowed me to accurately analyze metabolic data in a number of other microbiome studies as well, showing the broad applicability of these approaches across a number of disease settings.
7. Seto C, Jeraldo P, Orenstein R, **Chia N**, J DiBaise. Prolonged use of a proton pump inhibitor reduces microbial diversity: Implications for *Clostridium difficile* susceptibility. Microbiome. 2014 Nov 25;2:42.
8. Chen J, **Chia N**, Kalari KR, Yao JZ, Novotna M, Soldan MMP, Luckey DH et al. "Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls." Scientific Reports 6 (2016).
9. Kang SS, Jeraldo PR, Kurti A, Miller ME, Cook MD, Whitlock K, Goldenfeld N, Woods JA, White BA, **Chia N**, Fryer JD. Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. Mol Neurodegener. 2014; 9:36. PMCID:4168696.
10. Battaglioli, E., Hale, V., Chen, J., Jeraldo, P., Rekdal, V. M., Huq, L., ... & Kashyap, P. (2017). Prophylactic Fecal Microbial Transplant Restores Clostridium Difficile Colonization Resistance in a Dysbiotic Subset of Diarrhea Associated Human Microbial Communities Modeled in Germ Free Mice. Gastroenterology, 152(5), S348.

Together, these contributions demonstrate that I possess the basic bioinformatics skill sets necessary to carry out the proposed project, including overseeing the integration of different data types; improving the accuracy and predictive ability of metabolic models; and successfully applying mathematical models to help address longstanding biological questions.

**Complete List of Published Work in MyBibliography**:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/nicholas.chia.1/bibliography/47744991/public/?sort=date&direction=descending>

**D. Additional Information: Research Support and/or Scholastic Performance**

## Ongoing Research Support

R01 CA179243 (N Chia) 06/05/2014 – 05/31/2019

*Microbial Metabolic Toxicity Drives Colon Cancer*

The aims of this application are to 1) build metabolic models reflective of the microbial production and consumption of potential toxins with special focus on the role of sulfate-reducing bacteria, methanogens, and microbial community structure, and 2) understand the role of microbially-produced metabolites in carcinogenesis in deficient and proficient mismatch repair colorectal cancer.

Role: PI

R01 AR56647 (R Patel) 09/01/14 – 08/31/19

*Metagenomic Analysis of Arthroplasty Failure*

The goals of this application is to understand the underlying microbial populations in prosthetic joint infections (PJIs) using next-generation sequencing methodologies to directly probe the environment in PJIs.

Role:  Co-investigator

Mayo Clinic & University of Minnesota Cooperation Program

(K. Khazaie & R Blekhman) 02/01/18 – 01/31/20

*Development of personalized microbiome-based treatment for colorectal cancer*

Our objective in this application is to build a systems-level, mechanistic understanding of the functional

interactions between tumor neoplastic mutations, standard of care treatments, and microbial factors (taxa,

genes, and functions) in colorectal neoplasia.

Role:  Co-investigator

## Completed Research Support (past 3 years)

Minnesota Partnership for Biotechnology and Medical Genomics (Baughn, A/Chia N) 2/1/2013-1/31/2015

Title: Functional Metabolomic Approach to Eradicate Tuberculosis

The goal of this project is to metabolically model the phenomena of bacterial persistence in tuberculosis using a combination of ‘omics technologies and molecular experiments.

Role: Co-PI

FP00078125 (K Beckman) 06/01/2014–05/31/2016

MN Partnership for Biotechnology & Medical Genomics

*Minnesota Microbiome Data Engine*

The goals of this project are to create a central data ‘engine’—a collaborative center for bioinformatics support for 16S rDNA, metagenomics, and metatranscriptomics analyses between the University of Minnesota and Mayo Clinic.

Role: Co-investigator

U01 AI89859 (N Lambert) 07/12/2010 – 06/30/2015

*Investigating Correlations Between the Nasal Microbiome and Immunity to LAIV*

The immune system plays an integral role in regulating the immune system. However, our understanding of this key interaction is limited. By introducing changes to the adaptive immune system and monitoring the microbiome longitudinally before and after, this project seeks to understand the interactions between the nasal microbiome and vaccines.

Role: Co-investigator

R21 AI125870 (Patel) 06/01/2016-05/31/2018

*Disappearance of rifampin resistance in MRSA foreign body osteomyelitis*

The goal of this grant is to study the kinetics of emergences and disappearance of rifampin resistance in *Staphylococcus aureus* in a rat model of foreign body osteomyelitis.

Role: Co-Investigator

U54DK 100227-5 (Lieske) 09/29/2013 – 06/30/2018

NIDDK

Improving stone disease treatment by accurate phenotyping and risk stratification.

The overall goals of the Mayo Clinic Urology O'Brien Research Center are to develop new diagnostic strategies in order to accurately phenotype patients and thus apply improved individualized management strategies. These goals are pursued via 4 interlinked multidisciplinary projects: 1) Develop and validate a comprehensive low-dose stone-characterization exam using clinical dual-energy CT techniques in order to predict stone fragility, and to develop new CT methods capable of detecting the earliest possible precursor lesions; 2) Determine factors that produce NL precursor lesions including Randall's plaques and tubular plugs; 3) Define specific factors that increase the risk of kidney stones and their recurrence, and develop clinical prediction tools to help clinicians identify high-risk patients; 4) Define environmental and genetic factors that influence oxalate transport and crystallization in a novel high throughput *Drosophila* model.

Role: Co-investigator