Title: Biomolecular Structure, Dynamics and Function (BSDF)

List of participating disciplines/academic units/departments

- From College of Liberal Arts & Sciences
    - (1) Department of Physics and Optical Science
    - (2) Department of Biological Sciences
    - (3) Department of Chemistry
    - (4) Department of Mathematics and Statistics
- From College of Computing and Informatics
    - (5) Department of Bioinformatics and Genomics
- From College of Engineering
    - (6) Department of Mechanical Engineering and Engineering Sciences

Lead PI: Irina V. Nesmelova (Physics and Optical Sciences)

Co-Lead PIs: Andrew W. Truman (Biological Sciences)
Donald J. Jacobs (Physics and Optical Sciences)

Target category for the submission: Areas of Future Opportunity and Investment

Keywords: biomolecules, structural biology, biophysics, function, teaching

1. **Executive Summary**

The Biomolecular Structure, Dynamics and Function (BSDF) research area operates at the interdisciplinary interface of biology, chemistry, physics, mathematics and computing to provide mechanistic understanding of biological function at the molecular level. We have identified BSDF as a successful and impressive research area primed for future opportunity and investment.

Our vision is that the investment into infrastructure supporting BSDF research will enhance the BSDF group's research productivity, facilitate cross-disciplinary collaborations at UNC Charlotte, generate greater returns in grant money, attract and secure highly trained doctorate-holding research staff*, *and bring UNC Charlotte closer to its goal of becoming an R1-ranked university.

A distinct feature of R1 universities is a large number of faculty with BSDF expertise engaged in basic biomedical research. UNC Charlotte has the critical mass of faculty needed to transition to R1 status in this research area. However, the number of faculty alone is insufficient to grow to the next level. Our data analysis (in Supporting Materials) shows that all R1 universities, statewide and nationwide, share two essential attributes: in-house core facilities offering state-of-the-art equipment and large numbers of doctorate-holding research staff (postdoctoral associates and non-faculty research staff) that are engaged in research projects and grant proposals. Due to research needs, the largest concentration of doctorate-holding research staff and high-end instrumentation falls within the BSDF research area. The uniqueness of BSDF research is that it serves as the foundation to translational biomedical research and other applied areas. Other areas of excellence at UNC Charlotte impacted by BSDF research include plant biology, genome integrity, cancer therapeutics and nanomedicine. Moreover, BSDF faculty are well positioned to play a critical role in these specialized areas of excellence.

At UNC Charlotte, the BSDF research area correlates with both high-impact research and publications as well as high levels of funding due to its connection with the NIH-Wide Strategic Plan having a biomedical focus, and the National Science Foundation's Understanding the Rules of Life addressing fundamental questions in the life sciences. UNC Charlotte has invested in the BSDF research area by hiring new faculty, acquiring equipment, expanding lab facilities, and constructing the new science building slated to emphasize BSDF research. This institutional support has paid off in the following ways. Undergraduate students with research training in BSDF often continue their education in top-ranked R1 universities. Large numbers of graduate students from several graduate programs (Applied Physics, NanoScale Science, Biological Sciences, Mechanical Engineering, Bioinformatics) are supervised by BSDF faculty. Graduate level curriculum relevant to BSDF research is in place, and can be expanded using expertise of current faculty. Collectively BSDF faculty achieved about $35M in external funding with over 1,000 publications and more than 82,000 citations.

We nominate BSDF research as a *future area of opportunity and investment*. We will create convergence of BSDF faculty in collaborative projects to leverage collective expertise. The outcome will be enhanced research productivity while acquiring essential BSDF infrastructure. During UNC Charlotte's progress towards R1 status, recognition of BSDF and associated biomedical research impact will continuously grow at the national and international levels, setting BSDF for success as an emerging area of excellence.

2. **Evidence of Strength and Excellence**:

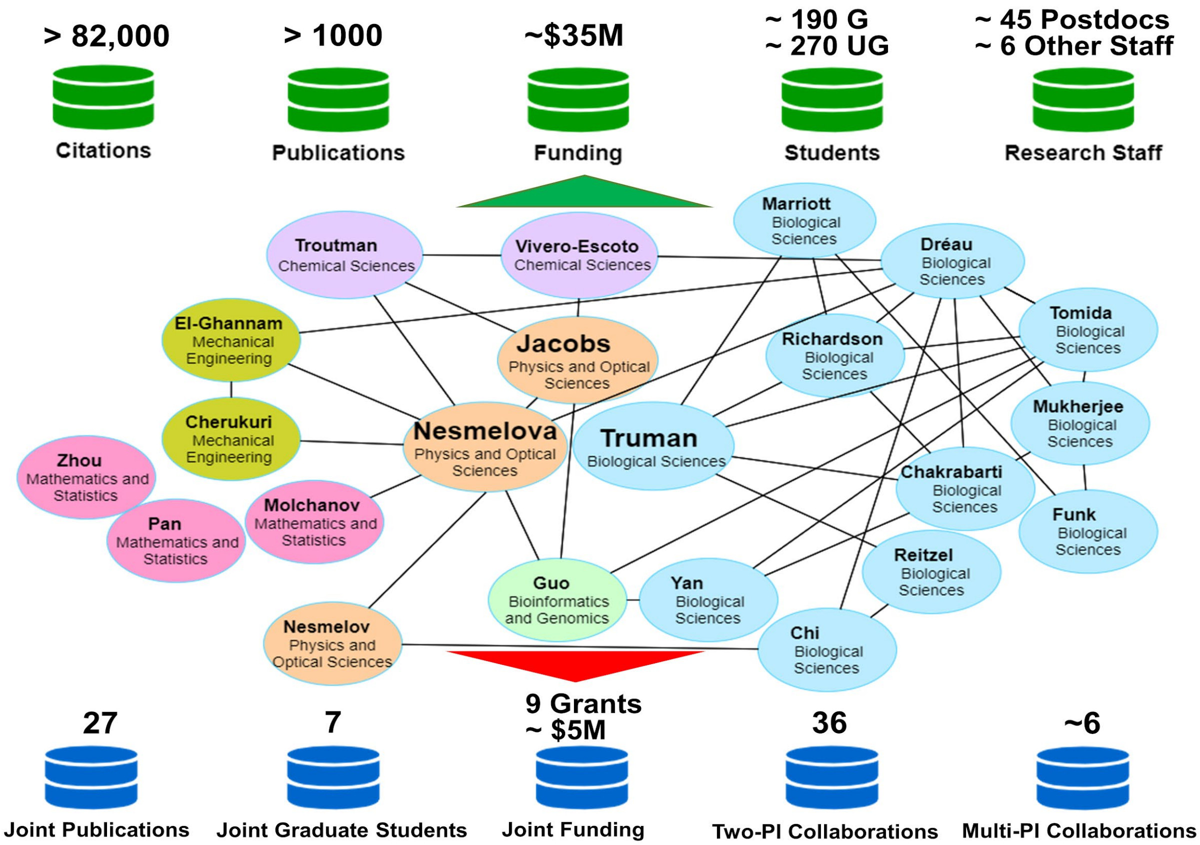


Figure 1. The evidence of success and collective impact of the BSDF group. Top: Meta data reflecting net contributions. Middle: A collaborative map of the BSDF group. Bottom: Meta data showing the outcomes of collaborative research.

The research outcomes of 22 faculty in the BSDF group are impressive. Per capita numbers of citations and publications are at the level of an R1 research university. We attribute the publication rate and increased funding success in recent years partly to a highly collaborative nature of our group. In the near future, we anticipate the growth of existing and emergence of new collaborations, and the increase of multi-PI projects. Awards, media announcements, editorial and grant panel service, are listed in CVs.

Collaborations. The BSDF research is highly interdisciplinary. Modern BSDF research requires state-of-the-art equipment, computer power, and in-depth expertise in their use. This is the driving force of collaborations within the BSDF group and with other faculty at UNC Charlotte in relevant research areas. A particular strength is that the BSDF group brings together the expertise in theory, computer modeling, and experiment. Below we highlight a few examples of active and productive collaborations.

Theory, modeling, and experiment. Molchanov and Nesmelova's groups developed a mathematical model for the anomalous protein diffusion near folding/unfolding transition, and now work on mathematical models for protein aggregation. Jacobs developed empirical models that fit calorimetry data, and quantify stability/flexibility relationships to inform protein design, and elucidate protein evolution. Jacobs collaborations with Nesmelova and Troutman focused on how mutations affect protein stability and function. Jacobs and Nesmelova published two papers together. Jacobs and Guo published jointly on homology modeling. The Guo and Jacobs groups apply molecular dynamics simulation and employ machine learning to glean mechanistic insights. Jacobs is collaborating with Vivero-Escoto to assess differences in morphology of porphyrin molecules as they aggregate in water.

Complementary experimental expertise. The BSDF expertise is fundamental to solving important biological questions, driving collaborations with faculty from Biology. Truman, Tomida, Chakrabarti, Richardson, Marriott and Yan comprise the *Genome Integrity Group* at UNC Charlotte (https://biology.uncc.edu/research/genome-integrity-group-0). Their strong collaboration seeks to understand how organisms respond to DNA damage at the molecular level. Mukherjee Marriott, Funk, Dréau, Nesmelova, Richardson and Truman collaborate in the area of *Cancer Biology* in developing new therapeutics based on manipulating protein-protein interactions. Reitzel, Chi and Truman currently collaborate on the molecular mechanisms behind day-night cycles in marine organisms. Troutman, Vivero-Escoto, Nesmelov and Chi are currently collaborating on work to engineer and purify enzymes that have the potential to produce a biological glue that is twice as strong as any currently known adhesive. El-Ghannam, Nesmelova, and Dréau collaboration focused on slow drug release systems for solid cancers.

Contribution to student education and research training. Collectively the BSDF group trained ~190 graduate and ~270 undergraduate students. The BSDF research area creates an integrative research environment. Faculty collaborations naturally involve students from different disciplines training them for cross-disciplinary research careers. Nesmelova-Dréau, Nesmelova-Jacobs, Chi-Reitzel, Richardson-Yan are a few examples where two faculty co-supervise a graduate student. Current curriculum offers several interdisciplinary courses cross-listed by different departments and/or programs (NANO/PHYS/OPTI/CHEM/BIO/ME).

Future progression of the BSDF research area. BSDF researchers apply a variety of biological and biophysical methods to gain a molecular level insight into a biological system. Although our group brought in ~$35M research grant money, many of our key experiments cannot be completed on campus, and a large portion of this money is spent on experiments at facilities of external R1 universities. Outsourcing limits our research capabilities because it is expensive, facilities have limited amounts of time available to outside users, and some samples are not stable for long storage and travel. Core facilities with shared equipment on campus (NMR spectroscopy and x-ray, mass spectrometry, electron microscopy and imaging) is a signature feature of R1 universities and will also create opportunities to hire doctorate-holding Research Staff, such as postdocs and research staff who will oversee high-end equipment and train students to use it. We will engage research staff in our research projects and grant proposals to increase productivity. Our group has considerable experience training postdoctoral researchers and acquiring shared equipment (Nesmelova led the effort of successful NIH S10 proposal - Microscale Thermophoresis) through federal funding. Established core facilities with technical support will eliminate reviewers' skepticism on the suitability of our research environment. The foundational nature of BSDF and its connection to other specialized areas of excellence gives BSDF a unique position to achieve R1 status by leveraging prudent institutional investments. To this end, Nesmelova, Truman and Jacobs will create BSDF community awareness to promote pairwise and multi-investigator collaborations that especially includes equipment grants.

4. **Alignment with Regional and National Priorities.**

From UNC Charlotte's mission statement: *"to offer internationally competitive programs of research and creative activity, exemplary undergraduate, graduate, and professional programs".* The BSDF group trains large numbers of undergraduate and graduate students in research laboratories. BDSF faculty teach a range of classes that offer the chance for students to learn state-of-the-art technology (Biophysical Methods for Characterization Biomolecules, Advanced Protein Biotechnology, Computational Modeling and Molecular Evolution*).* Several of these courses provide training in effective proposal writing, useful for a range of scientific careers. Several of our faculty including Nesmelova and Chi are experts in 3D printing, and use this technology to print molecular models to aid student understanding of protein function. Chi's work in this teaching approach was recently highlighted by the *American Society of Microbiology*. We envision extending this approach to the general public by creating a hands-on "The Art of Proteins" exhibition at Discovery Place Science. This broader impact will allow children to 3D print their own protein and explore complex structures through virtual reality, while learning how and why scientists solve protein structures.

Students of BDSF faculty have accepted graduate or postdoc positions at top institutes such as Yale, Harvard, Vanderbilt, Max Planck Institute, UNC Chapel Hill, U. of Pennsylvania, Berkely, U. of Pittsburgh, U. of Michigan, NCSU, Georgia Tech, The Ohio State University, Dartmouth, Stanford, NIH and the CDC. Permanent job outcomes include academic faculty, *Scripps Research Institute*, biotech companies (*Merk, BASF, Plant and Food, Kintai Therapeutics, Diagomics*), Consulting (*Life Science Dynamics*), the US Patent office as well as Investment Banking (*Piper Sandler, Bank of America, Goldman Sachs*). BDSF students recently created the UNC Charlotte Career Ladder Program (https://biologycareerladder.wixsite.com/unccclp) to assist students in identifying and obtaining jobs after graduation.

Research within the BSDF group aligns with the ***National Science Foundation Big Ideas*** **– Understanding the Rules of Life.** "*Life on our planet is arranged in levels of organization ranging from the molecular scale through to the biosphere. There exists a remarkable amount of complexity in the interactions within and between these levels of organization and across scales of time and space.*" One of the goals is "to enable discoveries that will allow us to better understand such interactions and identify causal, predictive relationships across these scales -- so-called "rules" for how life functions.

NIH puts a significant emphasis on basic structural biology research naming it among the frontiers in fundamental science. NIHLBI, NIHGMS, NIAMS, NIEHS, NIDDK, NIAID, and NCI institutes, all have their own structural biology units focusing on elucidating protein structures, dynamics, and interactions. Funding of the fundamental research of protein structure and function is identified as a key area in the ***NIH-Wide Strategic Plan:*** *"Because the private biopharmaceutical sector funds only a limited amount of basic research, NIH-supported research serves as the world's leading source of foundational knowledge of relevance to both the public and private sectors of biomedicine."* Indeed, NIH has several study sections focusing exclusively on topics that are well represented within the BSDF research area, including four study sections called Molecular Structure, Dynamics, and Function. NIGMS institute with the largest budget of all NIH institutes funds only fundamental BSDF research. It is noted that several R01 and many R15 grants tied to UNC Charlotte have been awarded to BSDF researchers.

5. Supporting Documents:

Name	Title	Expertise
Nesmelova	Associate Professor	Molecular structure/function, experimental biophysics, NMR spectroscopy.
Truman	Assistant Professor	Role of phosphorylation on molecular chaperone interactions, proteomics, CRISPR-CAS9.
Jacobs	Professor	Molecular modeling and simulation. Protein stability, binding, and allostery. Novel machine learning for molecular design.
Chakrabarti	Assistant Professor	RNA/mRNA structure-function and RNA-protein interactions in host-pathogen interactions and disease processes.
Cherukuri	Professor	Modeling dynamic behavior of materials.
Chi	Assistant Professor	Structure and function of proteins that regulate membrane trafficking.
Dréau	Professor	Protein-protein interactions in the tumor microenvironment.
El-Ghannam	Professor	Synthesis and characterization of delivery systems for biological molecules, drugs and cells.
Funk	Assistant Professor	Molecular mechanisms of neuroinflammation and neurodegenerative disease.
Guo	Professor	Computational tools and resources for studying protein-DNA interactions.
Marriott	Professor	Role of protein interactions in the immune response.
Molchanov	Professor	Theory of protein diffusion, folding, aggregation.
Mukherjee	Professor	Role of protein glycosylation in cancer.
Nesmelov	Associate Professor	Structural dynamic of myosin, FRET.
Pan	Assistant Professor	Statistical and machine learning methods for biomedicine.
Reitzel	Professor	Protein interactions in circadian rhythm of marine organisms.
Richardson	Professor	Molecular mechanisms of DNA repair and genome stability.
Tomida	Assistant Professor	DNA repair and cancer biology, protein-protein interactions within the pathways of DNA repair.
Troutman	Associate Professor	Molecular mechanisms of bacterial polysaccharides synthesis.
Vivero-Escoto	Associate Professor	Functionalizing nanoparticles, characterization and understanding of the interactions between nanoparticles and cells.
Yan	Professor	Role of phosphorylation in the DNA damage response.
Zhou	Assistant Professor	Statistical methodology of time data that commonly arise in epidemiological and biomedical studies.

Critical variables for increasing UNC Charlotte ranking towards R1 status.

Carnegie classification for research universities takes into account eight variables: STEM and non-STEM research expenditures, number of research faculty, number of doctorate-holding research staff (postdocs and other non-faculty), and number of doctorates granted in four categories: humanities, social science, STEM, and professional.

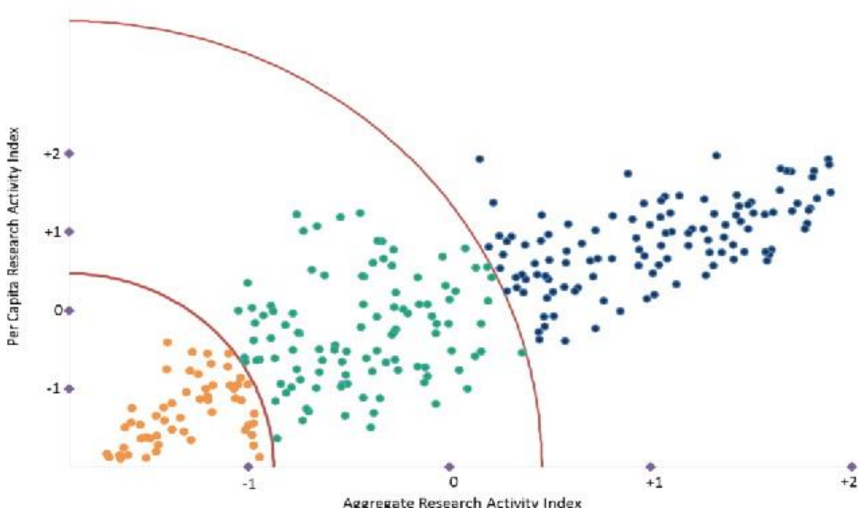


Figure 1. The principal component analysis[1], where the first principal component of per capita variables is plotted versus the first principal component of their aggregate version. Doctoral universities are classified as R3 (orange), R2 (green) and R1 (blue).

We analyzed the differential effects of investment on a particular Carnegie variable for UNC Charlotte using Shiny app (*https://rkspok.shinyapps.io/CarnegieClassifications/*).

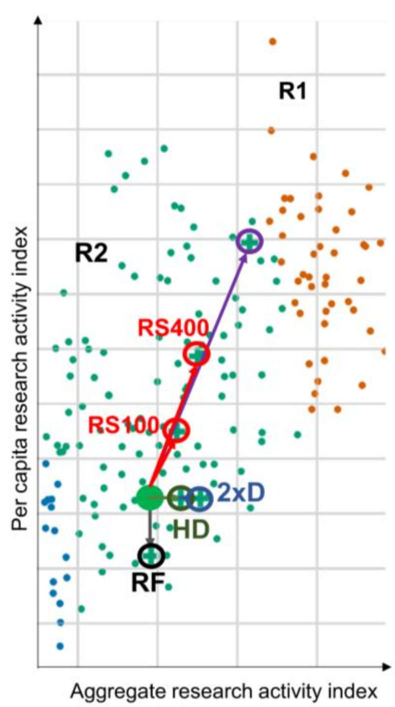
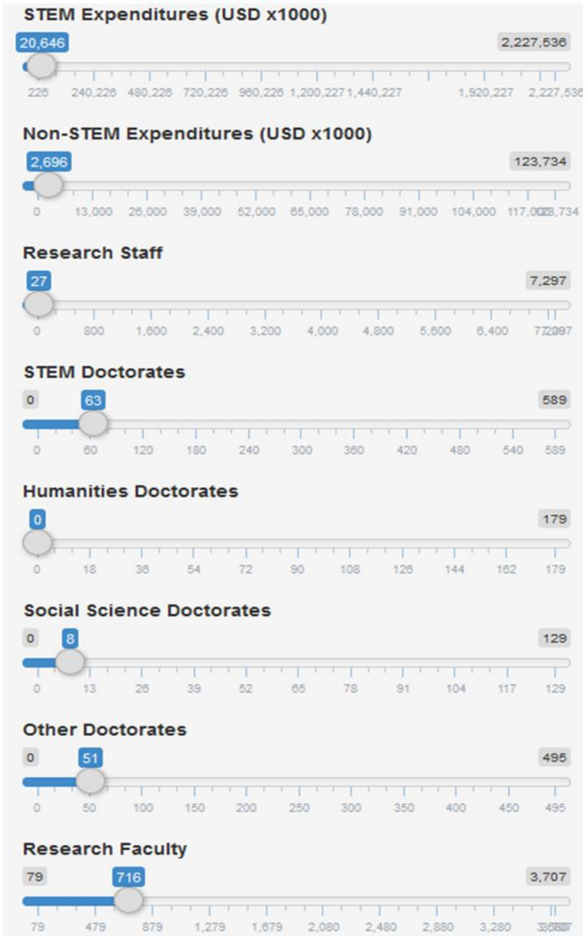


Figure 2. Effects of investment on a particular Carnegie variable for UNC Charlotte

Figure 2 magnifies part of the graph from Figure 1. Green circle indicates the position of UNC Charlotte. Surprisingly, increasing research faculty (RF, black circle) decreases UNC Charlotte's ranking, while adding two humanities doctorates (HD, grey circle) gives a similar effect as a two-fold increase in total number of doctorates we currently graduate (2xD, grey-blue circle). Remarkably, **UNC Charlotte's ranking is dependent mostly on the number of doctorate-holding research staff (RS).** The red circles demonstrate the effect of increasing RS from 27 to 100 and to 400. By increasing RS to 400 and increasing STEM and non-STEM expenditures by three-fold, UNC Charlotte reaches the R1 boundary (purple circle). For reference, UNC Greensboro, NCSU, and UNC Chapel Hill respectively have 18, 731 and 1034 research staff. UNC Charlotte current and projected numbers are given on the next page.

1. Kosar, R.; Scott, D. W. Examining the Carnegie Classification Methodology for Research Universities. *Stat Public Policy* **2018,** *5*.

Current status



Considered favorable scenario