Christopher Mathy - PhD Candidate

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Integrating protein biophysics with systems biology.
- Protein engineer trained in experimental biochemistry and biophysics of proteins, and techniques for measuring their quantitative functions in cells.
- Computational biologist with a background in large-scale analysis of interaction networks and omics data, as well as computational protein modeling.
- Vision: Advancing the design of proteins for precise activity in cells by understanding the systems-wide effects of protein mutations.

EDUCATION

PhD in Bioengineering	UC San Francisco and UC Berkeley	2022
BS in Bioengineering, with honors	Stanford University	2016

PUBLICATIONS

Peer-reviewed:

1. Perica, T*, Mathy, CJP*, Xu J, Jang GM, Zhang Y, Kaake R, Ollikainen N, Braberg H, Swaney DL, Lambright DG, Kelly MJS, Krogan NJ, & Kortemme T. (2021). Systems-level effects of allosteric perturbations to a model molecular switch. ***Nature***, 599, 152–157.

   * denotes equal contribution.

2. Baker JJ, Mathy CJP, Schaletzky J. (2021) A proposed workflow for proactive virus surveillance and prediction of variants for vaccine design. ***PLOS Computational Biology***, 17(12), e1009624.

3. Bouhaddou M, Memon D, Meyer B et al. [including Mathy CJP] (2020). The Global Phosphorylation Landscape of SARS-CoV-2 Infection. ***Cell***, 182(3), 685–712.e19.

4. Gordon DE, Jang GM, Bouhaddou M et al. [including Mathy CJP] (2020). A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. ***Nature***, 583(7816), 459–468.

Pre-prints:

Mathy CJP, Mishra P, Flynn JM, Perica T, Mavor D, Bolon DNA*, Kortemme T*. (2022). Complete mutational mapping of a GTPase switch in vivo reveals novel allosteric regulation. In bioRxiv (p. 2022.04.13.488230). https://doi.org/10.1101/2022.04.13.488230

* denotes co-corresponding author.

Additional works:

Mathy CJP (2016). Engineering the NK1 Fragment of the Human Hepatocyte Growth Factor for Dual Use as a Potent Agonist and a Gene Therapy Delivery Vehicle. ***Stanford Digital Repository.*** Senior Undergraduate Thesis, http://purl.stanford.edu/kw533qg7356

AWARDS

2018 - 2021	Byers Family Discovery Fellow, UC San Francisco ($6000)
2019	Best Poster, Quantitative Biosciences Consortium Retreat, UC San Francisco
2016	Top 10 team nationwide, NIBIB/VentureWell Design by Biomedical Undergraduate Teams Challenge

INVITED TALKS

2021-11-11	Integrating biophysics and high-throughput systems biology to uncover new models of GTPase switch function. *Special Guest Speaker, Pathology Advanced Translational Research Unit (PATRU)*. Emory University School of Medicine Department of Pathology and Laboratory Medicine.
2021-08-09	Conformational switching constrains the mutational tolerance of novel allosteric sites in the GTPase

Gsp1. *Annual RosettaCon Protein Design Conference*. RosettaCommons, virtual conference.

2021-04-07 Integrating biophysics and systems biology to uncover new models of GTPase switch function. *19th Annual National Graduate Student Symposium*. St. Jude Children's Research Hospital, Memphis, TN.

2020-01-28 Integrating biophysics and systems biology to understand mutations of the GTPase Ran/Gsp1. *Signaling Across Scales Symposium*. Quantitative Biosciences Institute, UC San Francisco.

2018-10-27 Mapping molecular properties of Gsp1 point mutants to cellular phenotype. *Bioengineering Retreat.* UC Berkeley - UC San Francisco Graduate Group in Bioengineering.

POSTER PRESENTATIONS

2021-10-14 Mathy CJP, Mavor D, Flynn JM, Perica T, Mishra P, Kelly MJS, Kortemme T, Bolon DN. Conformational switching constrains the mutational tolerance of novel allosteric sites in the GTPase Gsp1. UC Berkeley – UC San Francisco Bioengineering Retreat.

2019-10-05 Mathy CJP, Perica T, Xu J, Zhang Y, Ollikainen N, Jang G, Kaake R, Swaney D, Kelly MJS, Krogan NJ, Kortemme T. Allosteric coupling between interfaces and the nucleotide binding site of the small GTPase Gsp1 influences cellular processes. Quantitative Biosciences Consortium, UCSF. *Received Best Poster Award*

2019-06-02 Mathy CJP, Perica T, Zhang Y, Ollikainen N, Xu J, Jang G, Kaake R, Swaney D, Kelly MJS, Krogan NJ, Kortemme T. Targeted mutational perturbations of the small GTPase Ran reveal how pleiotropy is encoded in a model molecular switch. *Protein Science* (Vol. 28, pp. 200-201). Annual Protein Society Meeting.

2018-08-09 Mathy CJP, Perica T, Zhang Y, & Kortemme T. Biophysical analysis to map molecular properties of Gsp1 point mutations to their cellular scale phenotypes. Annual RosettaCon Protein Design Conference.

2018-02-21 Mathy CJP, Perica T, & Kortemme T. Mapping of molecular-level perturbations to systems-level phenotypes in Gsp1/Ran, a highly conserved protein switch. Biophysical Society Annual Meeting.

2017-10-07 Mathy CJP, Perica T, & Kortemme T. Mathematical modeling of Gsp1, a protein switch, to map mutations to phenotypic perturbations. UC Berkeley – UC San Francisco Bioengineering Retreat.

2016-05-24 Mathy CJP, Engineering the NK1 Fragment of the Human Hepatocyte Growth Factor for Dual-Use as a Potent Agonist and a Gene Therapy Delivery Vehicle. Stanford Bioengineering Honors Poster Fair.

2016-04-07 Baisiwala S, Mathy CJP, Moahi K, & Malavé C. Gel-Aid, Redefining Wound Packing: An Absorbent Removable Hydrogel. Stanford Tau Beta Pi + IEEE Engineering Showcase.

2015-10-24 Mathy CJP, Lim S, & Cochran JR. Internalization Study of the NK1 Fragment of the Human Hepatocyte Growth Factor. Symposium of Undergraduate Research and Public Service at Stanford University.

2013-08-29 Mathy CJP, Lim S, & Cochran JR. Development of Reporter Cell Assay for Engineering Human Hepatocyte *Growth Factor. Summer Research Experience for Undergraduates Poster Fair at Stanford University*

TEACHING

2021 Teaching Assistant, UCSF Biophysics 219: Computational Protein Design. Prepared exercises on computational protein modeling in Rosetta. Led a project group which successfully predicted the binding affinities of mutations in the SARS-CoV-2 Spike protein with the ACE2 receptor using ΔΔG calculations in Rosetta. Prepared lectures for first year UCSF graduate students, including the topic of protein design for therapeutic applications.

2018 Certificate, Science Teaching Effectiveness Program for Upcoming Professors (STEP-UP) workshop, UC San Francisco. 16-hour program on evidence-based teaching strategies that support student-centered learning in the college classroom, with an emphasis on supporting diverse learners.

2016 Teaching assistant, BIOE 131: Ethics in Bioengineering, Stanford University.

2014 - 2016 Personal tutor for middle- and high-school aged students in the San Francisco Bay Area.

SERVICE & OUTREACH

2021 - 2022 Co-President, UC Berkeley - UCSF Graduate Group in Bioengineering Association of Students. Non-voting member of the graduate program Executive Committee, advocating for student issues.

2020 - 2022 Admissions Committee, UC Berkeley - UCSF Graduate Group in Bioengineering Association of Students. Performed holistic admissions review for 70 applicants to the graduate program alongside faculty and 9 other PhD students.

2020 - 2021 Specialist, Rapid Reviews COVID-19 (MIT Press). Screened and pitched preprints for review and publication at Rapid Reviews COVID-19, an open-access overlay journal based at UC Berkeley.

2018 - 2019 Volunteer Educator, UCSF Science & Health Education Partnership. Taught scientific lessons in collaboration with teachers at local area elementary schools.

2017 - 2019 Retreat Committee, UC Berkeley - UCSF Graduate Group in Bioengineering Association of Students. Organized two annual scientific meetings with over 150 attendees.

2017 - 2019 Recruitment Committee, UC Berkeley - UCSF Graduate Group in Bioengineering Association of Students. Organized two annual visits for over 50 PhD program applicants.

2018 UCSF Center for Community Engagement Research Committee. Strategic planning and grant application review for partnerships between UCSF and community organizations.

2017 Volunteer Educator, Bay Area Scientists in Schools. Taught scientific lessons in collaboration with teachers at local area elementary schools.

MENTORSHIP

2019 Wilson Nieves Vasquez, UCSF Biophysics PhD Student. Supervised for 10-week rotation project using hydrogen-deuterium exchange to study the differences in GTPase conformations.

2019 Maru Jaime Garza, UCSF Biophysics PhD Student. Supervised for 10-week rotation project using 1-D ^{31}P-NMR to study the effect of partner binding on GTPase conformations.

2019 Christina Stephens, UCSF Biophysics PhD Student. Supervised for 10-week rotation project using computational protein modeling to examine how mutations impact GTPase conformational dynamics.

MAJOR RESEARCH EXPERIENCE

PhD Student Researcher PI: Tanja Kortemme, PhD UC San Francisco 2017 - Present
Thesis: Integrating biophysics and systems biology to uncover new models of GTPase switch function.

Projects:

1. Biophysical basis of cellular multi-specificity encoded in a model molecular switch. (published at Nature, co-first author)

This study probed the phenotypic effects of 55 point mutants to the GTPase switch Ran/Gsp1 in *S. cerevisiae* using high-throughput genetics and proteomics. Molecular characterization of the GTPase cycle and the switch's conformational equilibrium revealed novel allosteric pathways that perturb cycle kinetics. Integrating the systems and biophysical data allowed us to propose a novel paradigm for Gsp1 functional multi-specificity, whereby biological processes regulated by Gsp1 are differentially sensitive to perturbations to the kinetic parameters of the GTPase cycle. To our knowledge, this was the largest set of point mutants of a single gene studied using genetic interaction profiling and proteomics to date. I made fundamental contributions to the biochemical and biophysical assays as well as to the bioinformatics analysis of the systems-level data, and wrote the paper as a co-first author.

2. Mapping the fitness landscape of Gsp1 point mutants. (manuscript in preparation, first author)

In collaboration with Dr. Daniel Bolon's lab at UMass Medical School, we have measured the fitness effects of all point mutants in Gsp1 in S. cerevisiae using a pooled growth assay, employing a novel two-plasmid system that extends their lab's method for the study of essential genes. Unexpectedly, we observed a large number of positions where the majority of mutations had poorer fitness than that of STOP codon mutants, suggesting that these mutants have a functional dominant negative effect. I showed that although these mutations are enriched in one of the allosteric sites we have previously identified, they do not affect the kinetics of GTPase hydrolysis. Rather, they disrupt a precise network of residues that stabilize the GTP- and GDP-bound conformations to allow for effective switching. This result shows that quantitative fitness measurements from high-throughput mutagenesis assays can provide insight on classes of mutations with biochemical phenotypes that are hard to predict. Additionally, I computationally modeled the set of all possible point mutants using Rosetta, and showed that computational $\Delta\Delta G$'s of mutations in the protein core are predictive of poorer fitness in the growth assay.

3. Tuning the regulatory context of Gsp1 to efficiently screen phenotypes of novel variants. (on-going work)

I am taking an orthogonal approach to test the model proposed by Project 1, namely that mutational phenotypes in Gsp1 group according to the extent they perturb the hydrolysis or exchange rates, thus defining the primary dimensions of a functional landscape. To do this, I am precisely tuning the expression of the key regulators GAP and GEF which catalyze GTP hydrolysis and nucleotide exchange in cells. I am using transcriptional profiling by RNA-seq to characterize the phenotypes of yeast strains with altered GAP and GEF expression, and comparing their phenotypes to those of our previously characterized point mutant strains. My ultimate goal is to identify genes whose mRNA levels respond predictably to perturbations of the Gsp1 switch, and use these genes as markers for screening novel Gsp1 variants. This would represent a generalizable approach for engineering novel protein switches that operate predictably in the cellular context.

4. Identifying structural determinants of allostery in Gsp1 using HDX-MS. (on-going work)

I am using hydrogen-deuterium exchange and mass spectrometry (HDX-MS) to identify differences in secondary structure stability in Gsp1 bound to GTP versus GDP. By performing this technique on a select set of mutants from Project 1, my collaborators and I hope to identify the pathway mediating the allosteric effects of these mutants.

5. Modeling the interaction between SARS-CoV-2 ORF6 and the human NUP98-RAE1 complex. (published in Nature and Cell)

In response to the COVID-19 pandemic, a consortium of labs at UCSF collaborated to map and characterize the host-pathogen interactome and the human proteome after SARS-CoV-2 infection. We observed a strong interaction between ORF6 and NUP98-RAE1, a known viral target to hijack host protein export. Using Rosetta, I computationally modeled the interaction between ORF6 and NUP98-RAE1 and proposed mutations to confirm the mechanism of interaction. My predictions were later confirmed experimentally by other groups (Miorin et al. Oct 23 2020 *PNAS*; Addetia et al. Aug 3 2020. *bioRxiv*).

Undergraduate Researcher PI: Jennifer Cochran, PhD Stanford University 2013-2016

Engineering the NK1 fragment of the human Hepatocyte Growth Factor for dual use as a potent agonist and a gene therapy delivery vehicle. (Submitted as Senior Thesis, and manuscript currently in preparation).

Engineered growth factors are powerful biological therapeutics in cancer treatment and wound healing. This study developed novel variants of the NK1 molecule with enhanced angiogenic potency, and also identified orthogonal mutations that tune the rate of internalization by the target cell independently of the angiogenic activity. Engineering internalization behavior of biologics could enable them to function as gene therapy delivery vehicles. I characterized the mechanism of internalization of NK1 using chemical targeting of endocytic receptors, FACS-based quantitation of internalized fluorescent protein fusions, and confocal microscopy. Additionally, I measured the angiogenic potency of novel variants using plate based assays. I helped write the manuscript as a second author.

Undergraduate Biodesign Team PI: Fan Yang, PhD Stanford University 2015-2016

Gel-Aid, a removable, alginate-based hydrogel for wound packing after surgical-site infections.

Year-long class project (four person team) on clinical needs-based biomedical device development. We partnered with clinicians to design, prototype, and validate a hydrogel-based solution for wound management. The translational potential of our invention was recognized by the University and we filed a provisional patent through Stanford University's Office of Technology & Licensing (May 27, 2016 U.S. Provisional Application No.: 62/342830). Additionally, we were recognized with an honorable mention (top 10 team, nationwide) at the 2016 NIBIB/ VentureWell Design by Biomedical Undergraduate Teams (DEBUT) National Challenge.

ADDITIONAL RESEARCH EXPERIENCE

PhD Rotation Student PI: Michael Keiser, PhD UC San Francisco 2017

Prediction of drug target proteins using a neural network trained on 3-dimensional fingerprints of small molecules.

Trained neural networks to predict protein target activation EC50 values using vectorized representations of small molecules drugs.

PhD Rotation Student PI: Adam P Arkin, PhD UC Berkeley 2016

Engineering a genetic circuit for proportional regulation of protein production.

Designed experiments for implementing proportional feedback control with genetic circuit components.

Undergraduate Researcher PI: John Löfblom, PhD KTH Royal Inst. of Tech., Stockholm, Sweden 2015

Characterization of VEGFR2-binding affibodies for biotherapy applications.

Purified six multivalent affibody proteins grown in *E. coli* and measured thermal stability using circular dichroism. Evaluated angiogenic potency using an ELISA-linked VEGFR2 phosphorylation assay.