

Avi I. Flamholz Ph.D.

POSTDOCTORAL SCHOLAR · CALTECH DIVISION OF BIOLOGY & BIOLOGICAL ENGINEERING

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Summary

I am excited when physical and mathematical principles help explain the behavior and evolution of cells, organisms and ecosystems. When possible, I strive to connect theory and laboratory experiments to real-world environments. I am focused on Earth's carbon cycle and working towards quantitative understanding of the metabolic rates of spatially-structured microbial communities in 3D environments like soils.

Education

University of California, Berkeley

PHD, MOLECULAR AND CELL BIOLOGY

Berkeley, CA

2013 - 2019

- Dissertation: "Analysis and Reconstitution of a Bacterial CO₂-Concentrating Mechanism"; Advisor: Prof. David Savage

Princeton University

B.S.E., COMPUTER SCIENCE

Princeton, NJ

2003 - 2007

- Graduated *magna cum laude*, certificate in Applied & Computational Mathematics; Thesis advisor: Prof. Kai Li

Professional Experience

- 2021- **Jane Coffin Childs Memorial Postdoctoral Fellow**, Dianne Newman & Rob Phillips Groups, Caltech
- 2020 **Postdoctoral Scholar in Biology & Bioengineering**, Dianne Newman & Rob Phillips Groups, Caltech
- 2014-2019 **NSF Graduate Research Fellow**, David Savage Group, UC Berkeley
- 2013-2014 **Graduate Student Researcher**, David Savage Group, UC Berkeley
- 2012-2013 **Founding Technical Lead**, Via Transportation, New York City
- 2010-2012 **Pre-doctoral Researcher**, Ron Milo Group, Weizmann Institute for Science, Israel
- 2007-2010 **Software Engineer II**, Google, New York City

Awards & Honors

- 2023 **Burroughs Wellcome Fund**, Careers at the Scientific Interface Award (starting 2024)
Caltech Center for Environmental Microbial Interactions, CEMI Travel Award
- 2022 **Western Photosynthesis Annual Meeting**, Best Talk Award
- 2021 **Jane Coffin Childs Memorial Foundation**, Postdoctoral Fellowship
- 2020 **Caltech Center for Environmental Microbial Interactions**, CEMI Pilot Award
- 2015 **UC Berkeley MCB Department**, Travel Award
- 2013 **National Science Foundation**, Graduate Research Fellowship
- 2007 **Princeton University Department of Computer Science**, Department Service Award
Elected to Sigma Xi, Research Honors Society

Publications

^{*}equal contribution, ⁺mentored undergraduate, [^]mentored graduate student

IN PREPARATION

Flamholz AI, Blikstad C, Dugan EJ, Fischer WW, Savage DF. *CO₂ fertilization of heterotrophic growth*.

IN SUBMISSION

Flamholz AI, Goyal A, Fischer WW, Newman DK, Phillips R. *The proteome is a terminal electron acceptor*. Submitted to Science.

Flamholz AI, Goldford J., Larsson EM, Jinich A, Fischer WW, Newman DK. *Annotation-free prediction of microbial oxygen utilization*. In review at mSystems. bioRxiv preprint doi:10.1101/2024.01.16.575888

Eshel G, **Flamholz AI**, Shepon A, Milo R. *Carbon budget and grassland needs of grassfed beef*. Submitted to PNAS.

PUBLISHED

Goyal A, **Flamholz AI**, Petroff A, Murugan A. *Closed ecosystems extract energy through self-organized nutrient cycles*. PNAS. 2024; 120: e2309387120. doi:10.1073/pnas.2309387120

Wang RZ[^], Nichols RJ, Liu AK, **Flamholz AI**, Artier J, Banda DM, Savage DF, Eiler JM, Shih PM, Fischer WW. *Carbon isotope fractionation by an ancestral rubisco suggests biological proxies for CO₂ through geologic time should be re-evaluated*. PNAS. 2023; 120: e2300466120. doi:10.1073/pnas.2300466120

Commentary by Sven Kranz in PNAS.

Flamholz AI, Goyal A. *Spotlight: Matching metabolic supply to demand optimizes microbial growth*. Trends Microbiol. 2023; 31, 769–771. doi:10.1016/j.tim.2023.06.003

Lammers NC, **Flamholz AI**, Garcia HG. *Competing constraints shape the nonequilibrium limits of cellular decision-making*. PNAS. 2023;120: e2211203120 doi:10.1073/pnas.2211203120

Flamholz AI^{*}, Dugan E⁺, Panich J, Desmarais JJ, Oltrogge LM, Fischer WW, Singer SW, Savage DF. *Trajectories for the evolution of bacterial CO₂-concentrating mechanisms*. PNAS. 2022;119: e2210539119. doi:10.1073/pnas.2210539119

Highlighted by Phys.org, Caltech News, & InnovativeGenomics.org.

Flamholz AI, Saccomano S, Cash K, Newman DK. *Optical O₂ Sensors Also Respond to Redox Active Molecules Commonly Secreted by Bacteria*. MBio. 2022; e0207622. doi:10.1128/mbio.02076-22

Chure G^{*}, Banks RA^{*}, **Flamholz AI**, Sarai NS, Kamb M, Lopez-Gomez I, Bar-On Y, Milo R, Phillips R. *Anthroponumbers.org: A quantitative database of human impacts on Planet Earth*. Patterns. 2022;3: 100552. doi:10.1016/j.patter.2022.100552

Highlighted in Wired, Phys.org, & ScienceDaily.

Noor E^{*}, **Flamholz AI**^{*}, Jayaraman V^{*}, Ross BL^{*}, Cohen Y, Patrick WM, Gruic-Sovulj I, Tawfik DS. *Uniform binding and negative catalysis at the origin of enzymes*. Protein Science. 2022;31: e4381. doi:10.1002/pro.4381

Special issue posthumously honoring Dan Salah Tawfik.

Goldford JE, George AB, **Flamholz AI**, Segrè D. *Protein cost minimization promotes the emergence of coenzyme redundancy*. PNAS. 2022;119: e2110787119. doi:10.1073/pnas.2110787119

Flamholz AI, Newman DK. *Microbial communities: The metabolic rate is the trait*. Current Biology. 2022;32: R215–R218. doi:10.1016/j.cub.2022.02.002

Beber ME, Gollub MG, Mozaffari D, Shebek KM, **Flamholz AI**, Milo R, Noor E. *eQuilibrator 3.0: a database solution for thermodynamic constant estimation*. Nucleic Acids Research. 2021;50: D603–D609. doi:10.1093/nar/gkab1106

Greenwald HD, Kennedy LC, Hinkle A, Whitney ON, Fan VB, Crits-Christoph A, Harris-Lovett S, **Flamholz AI**, Al-Shayeb B, Liao LD, Beyers M, Brown D, Chakrabarti AR, Dow J, Frost D, Koekemoer M, Lynch C, Sarkar P, White E, Kantor R, Nelson KL. *Tools for interpretation of wastewater SARS-CoV-2 temporal and spatial trends demonstrated with data collected in the San Francisco Bay Area*. Water Research X. 2021;12: 100111. doi:10.1016/j.wroa.2021.100111

Sender R, Bar-On YM, Gleizer S, Bernshtein B, **Flamholz AI**, Phillips R, Milo R. *The total number and mass of SARS-CoV-2 virions*. PNAS. 2021;118: e2024815118. doi:10.1073/pnas.2024815118

Crits-Christoph A, Kantor RS, Olm MR, Whitney ON, Al-Shayeb B, Lou YC, **Flamholz AI**, Kennedy LC, Greenwald H, Hinkle A, Hetzel J, Spitzer S, Koble J, Tan A, Hyde F, Schroth G, Kuersten S, Banfield JF, Nelson KL. *Genome sequencing of sewage detects regionally prevalent SARS-CoV-2 variants*. MBio. 2021;12: e02703–20. doi:10.1128/mBio.02703-20

- Claassens NJ, Scarinci G, Fischer A, **Flamholz AI**, Newell W, Frielingsdorf S, Lenz O, Bar-Even A. *Phosphoglycolate salvage in a chemolithoautotroph using the Calvin cycle*. PNAS. 2020;117: 22452–22461. doi:10.1073/pnas.2012288117
- Flamholz AI**, Dugan E⁺, Blikstad C, Gleizer S, Ben-Nissan R, Amram S, Antonovsky N, Ravishankar S, Noor E, Bar-Even A, Milo F, Savage DF. *Functional reconstitution of a bacterial CO₂ concentrating mechanism in Escherichia coli*. Elife. 2020;9: e59882.
- Commentary by Franklin & Jonikas in ELife, highlighted in Nature, Faculty Opinions.**
- Davidi D, Shamshoum M, Guo Z, Bar-On YM, Prywes N, Oz A, Jablonska J, **Flamholz AI**, Wernick DG, Antonovsky N, De Pins B, Shachar L, Hochhauser D, Peleg Y, Albeck S, Sharon I, Mueller-Cajar O, Milo R. *Highly active rubiscos discovered by systematic interrogation of natural sequence diversity*. EMBO Journal. 2020;39: e104081. doi:10.15252/embj.2019104081
- Flamholz AI**, Shih PM. *Cell biology of photosynthesis over geologic time*. Current Biology. 2020;30: R490–R494. doi:10.1016/j.cub.2020.01.076
- Bar-On YM, **Flamholz AI**, Phillips R, Milo R. *Science Forum: SARS-CoV-2 (COVID-19) by the numbers*. Elife. 2020;9: e57309.
- Highlighted in Small Things Considered.**
- Desmarais JJ[^], **Flamholz AI**, Blikstad C, Dugan EJ⁺, Laughlin TG, Oltrogge LM, Chen AW⁺, Wetmore K, Diamond S, Wang JY, Savage DF. *DABs are inorganic carbon pumps found throughout prokaryotic phyla*. Nature Microbiology. 2019;4: 2204–2215. doi:10.1038/s41564-019-0520-8
- Commentary by Price, Long & Forster in Nature Microbiology**
- Flamholz AI**, Prywes N, Moran U, Davidi D, Bar-On YM, Oltrogge LM, Alves R, Savage DF, Milo R. *Revisiting trade-offs between Rubisco kinetic parameters*. Biochemistry. 2019;58: 3365–3376. doi:10.1021/acs.biochem.9b00237
- Editor's Choice Award**
- Blikstad C, **Flamholz AI**, Oltrogge LM, Savage DF. *Learning to Build a β -Carboxysome*. Biochemistry. 2019. pp. 2091–2092.
- Jinich A, **Flamholz AI**, Ren H, Kim S-J, Sanchez-Lengeling B, Cotton CAR, Noor E, Aspuru-Guzik A, Bar-Even A. *Quantum chemistry reveals thermodynamic principles of redox biochemistry*. PLoS Comput Biology. 2018;14: e1006471. doi:10.1371/journal.pcbi.1006471
- Noor E, **Flamholz AI**, Bar-Even A, Davidi D, Milo R, Liebermeister W. *The protein cost of metabolic fluxes: prediction from enzymatic rate laws and cost minimization*. PLoS Comput Biology. 2016;12: e1005167. doi:10.1371/journal.pcbi.1005167
- Mangan NM^{*}, **Flamholz AI**^{*}, Hood RD, Milo R, Savage DF. *pH determines the energetic efficiency of the cyanobacterial CO₂ concentrating mechanism*. PNAS. 2016;113: E5354–E5362. doi:10.1073/pnas.1525145113
- Hood RD, Higgins SA, **Flamholz AI**, Nichols RJ, Savage DF. *The stringent response regulates adaptation to darkness in the cyanobacterium Synechococcus elongatus*. PNAS. 2016;113: E4867–E4876. doi:10.1073/pnas.1524915113
- Nadler DC, Morgan S-A, **Flamholz AI**, Kortright KE, Savage DF. *Rapid construction of metabolite biosensors using domain-insertion profiling*. Nature Communications. 2016;7: 12266. doi:10.1038/ncomms12266
- Oakes BL, Nadler DC, **Flamholz AI**, Fellmann C, Staahl BT, Doudna JA, Savage DF. *Profiling of engineering hotspots identifies an allosteric CRISPR-Cas9 switch*. Nature Biotechnology. 2016;34: 646–651. doi:10.1038/nbt.3528
- Davidi D, Noor E, Liebermeister W, Bar-Even A, **Flamholz AI**, Tummeler K, Barenholz U, Goldenfeld M, Shlomi T, Milo R. *Global characterization of in vivo enzyme catalytic rates and their correspondence to in vitro k_{cat} measurements*. PNAS. 2016;113: 3401–3406.
- Flamholz AI**, Phillips R, Milo R. *The quantified cell*. Molecular Biology of the Cell. 2014;25: 3497–3500. doi:10.1091/mbc.E14-09-1347
- Liebermeister W, Noor E, **Flamholz AI**, Davidi D, Bernhardt J, Milo R. *Visual account of protein investment in cellular functions*. PNAS. 2014;111: 8488–8493. doi:10.1073/pnas.1314810111
- Noor E, Bar-Even A, **Flamholz AI**, Reznik E, Liebermeister W, Milo R. *Pathway thermodynamics highlights kinetic obstacles in central metabolism*. PLoS Computational Biology. 2014;10: e1003483. doi:10.1371/journal.pcbi.1003483
- Noor E, **Flamholz AI**, Liebermeister W, Bar-Even A, Milo R. *A note on the kinetics of enzyme action: a decomposition that highlights thermodynamic effects*. FEBS Letters. 2013;587: 2772–2777. doi:10.1016/j.febslet.2013.07.028
- Flamholz AI**^{*}, Noor E^{*}, Bar-Even A, Liebermeister W, Milo R. *Glycolytic strategy as a tradeoff between energy yield and protein cost*. PNAS. 2013;110: 10039–10044. doi:10.1073/pnas.1215283110
- Commentary by Stettner & Segre in PNAS**

- Zelcbuch L, Antonovsky N, Bar-Even A, Levin-Karp A, Barenholz U, Dayagi M, Liebermeister W, **Flamholz AI**, Noor E, Amram S, Brandis A, Bareia T, Yofe I, Jubran H, Milo R. *Spanning high-dimensional expression space using ribosome-binding site combinatorics*. Nucleic Acids Research. 2013;41: e98–e98. doi:10.1093/nar/gkt151
- Bar-Even A, **Flamholz AI**, Noor E, Milo R. *Thermodynamic constraints shape the structure of carbon fixation pathways*. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 2012;1817: 1646–1659. doi:10.1016/j.bbabi.2012.05.002
- Noor E, Bar-Even A, **Flamholz AI**, Lubling Y, Davidi D, Milo R. *An integrated open framework for thermodynamics of reactions that combines accuracy and coverage*. Bioinformatics. 2012;28: 2037–2044. doi:10.1093/bioinformatics/bts317
- Bar-Even A, Noor E, **Flamholz AI**, Milo R. *Design and analysis of metabolic pathways supporting formatotrophic growth for electricity-dependent cultivation of microbes*. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 2012;1827: 1039–1047. doi:10.1016/j.bbabi.2012.10.013
- Flamholz AI**, Noor E, Bar-Even A, Milo R. *eQuilibrator—the biochemical thermodynamics calculator*. Nucleic Acids Research. 2012;40: D770–D775.
- Bar-Even A, **Flamholz AI**, Noor E, Milo R. *Rethinking glycolysis: on the biochemical logic of metabolic pathways*. Nature Chemical Biology. 2012;8: 509–517.
- Bar-Even A, **Flamholz AI**, Noor E, Milo R. *Thermodynamic constraints shape the structure of carbon fixation pathways*. Bioenergetics. 2012.
- Bar-Even A, Noor E, **Flamholz AI**, Buescher JM, Milo R. *Hydrophobicity and charge shape cellular metabolite concentrations*. PLoS Comput Biology. 2011;7: e1002166. doi:10.1371/journal.pcbi.1002166
- Huttenhower C, **Flamholz AI**, Landis JN, Sahi S, Myers CL, Olszewski KL, Hibbs MA, Siemers NO, Troyanskaya OG, Collier HA. *Nearest Neighbor Networks: clustering expression data based on gene neighborhoods*. BMC Bioinformatics. 2007;8: 1–13. doi:10.1186/1471-2105-8-250

Funded Research Proposals

- June 2023. *Predicting microbial CO₂ production in global soils*. **Burroughs Wellcome Fund** Careers at the Scientific Interface Transitional Fellowship.
- July 2021. *Developing bacterial biofilms as a model for predicting tissue metabolism*. **Jane Coffin Childs Memorial Foundation** Postdoctoral Fellowship.
- September 2020. *Experimental and theoretical approaches to studying the physiology of single cells in structured environments*. **Caltech Center for Emerging Microbial Interactions** Pilot Grant.
- May 2020. *Early detection of COVID-19 reemergence via wastewater surveillance of SARS-CoV-2* written with Profs. Kara Nelson & Jill Banfield's groups. **Innovative Genomics Institute at UC Berkeley** Rapid Response COVID-19 Research Grant.
- September 2018. *Mapping sequence-function landscapes to isolate improved Rubiscos* with Prof. David Savage. **National Science Foundation** award #1818377
- September 2013. *Interrogating Overflow Metabolism with Laboratory Evolution* **National Science Foundation** Graduate Research Fellowship

Presentations

SEMINARS AND CONFERENCE TALKS

- March 2023. *Engineering microbes to learn about the Earth: lessons for the global carbon cycle*
MIT Department of Earth and Planetary Sciences (Invited)
- March 2023. *The proteome is a terminal electron acceptor*.
Quantitative Physiology session at American Physical Society annual meeting in Las Vegas
- July 2022. *Using engineered bacteria to study the history of Earth's atmosphere*.
CCM10 Conference, Princeton University (Invited)
- May 2022. *Trajectories for the evolution of bacterial CO₂-concentrating mechanisms*.
Caltech Center for Emerging Microbial Interactions CEMInar monthly series
- March 2022. *Building a bacterial CO₂ concentrating mechanism*.
Western Photosynthesis Virtual Conference. "Best Talk" award.

July 2021. *Microbial energy conservation when O₂ is scarce*. Jointly delivered with Prof. Dianne Newman. Microbial Ecology and Evolution summer course, Kavli Institute for Theoretical Physics at UC Santa Barbara (Invited).

August 2020. *Building a bacterial CO₂ concentrating mechanism*. Online seminar. Department of Plant Biology at Australian National University, Canberra, Australia (Invited)

July 2020. *Building a bacterial CO₂ concentrating mechanism*. Online seminar. Department of Plant Biology at York University, York, United Kingdom (Invited).

December 2019. *An engineered E. coli fixes CO₂ from ambient air*. West Coast Bacterial Physiology Meeting, Asilomar, CA.

July 2018. *Rubisco: Why are you not better?* International Geobiology Course, Catalina Island, CA (Invited).

May 2017. *The cost of protein production*. Amyris Inc, Emeryville, CA (Invited).

January 2017. *Carboxysomes: What are they good for?* UC Berkeley MCB Department, Biochemistry, Biophysics & Structural Biology (BBS) Divisional Retreat

November 2013. *Thermodynamic Tradeoffs in Glycolysis* UC San Francisco Theory Lunch (Invited).

September 2013. *Thermodynamic Tradeoffs in Glycolysis* Metabolic Pathway Analysis Conference, Oxford, UK (Invited).

Teaching Experience

Sum. 2019	The Microverse , Introduction to microscopy & programming, Clubes de Ciencia	Monterrey, MX
Spring 2016	Biochemistry: Pathways, Mechanisms, and Regulation , Graduate Student Instructor	UC Berkeley
Sum. 2015	QB3 Python Programming Bootcamp , Teaching Assistant	UC Berkeley
Fall 2015	General Microbiology , Graduate Student Instructor	UC Berkeley
Fall 2011	English as a Second Language , Mesila program for refugees	Tel Aviv, Israel
Fall 2009	Introduction to Programming, 5th-8th Grades , Citizen Schools Volunteer	Brooklyn, NY
2005-2007	Head laboratory teaching assistant for intro courses , Dept. of Computer Science	Princeton

Formal Mentorship

2022	Gia Han Vuong , Caltech CEMI-WAVE Summer Research Fellow in the Newman Lab	Caltech
2021	Elin Larsson , Rotation student in the Newman Lab - <i>joined for PhD</i>	Caltech
2019	Alejandra Zapata , UCB Transfers to Excellence Summer Research Fellow in the Savage Lab	UC Berkeley
2017	Edward Koleski , Rotation student in the Savage Lab	UC Berkeley
2017	Julia Borden , Rotation student in the Savage Lab - <i>joined for PhD</i>	UC Berkeley
2017-2020	Eli Dugan , Savage Lab technician - <i>now a PhD student at UCSF Tetrad Program</i>	UC Berkeley
2015-2017	Eli Dugan , Savage Lab Undergraduate Researcher	UC Berkeley
2016-2018	Allen Chen , Savage Lab Undergraduate Researcher - <i>now a PhD student at Caltech</i>	UC Berkeley
2015-2016	Sumedha Ravishankar , Savage Lab Undergrad Researcher - <i>now a PhD student at UCSD</i>	UC Berkeley
2015	Dylan McLung , Rotation student in the Savage Lab	UC Berkeley

Service and Outreach

2011-Present. *Maintain and develop eQuilibrator - the biochemical thermodynamics calculator*. With Elad Noor; 500-1000 students and researchers use eQuilibrator each month. equilibrator.weizmann.ac.il

Summer 2022. *Caltech PCC CEMI-WAVE summer research mentor*. Volunteer mentor for a summer program bringing Pasadena Community College students to Caltech for paid summer research.

Summer 2019. *Clubes de Ciencias, Monterrey, Mexico*. Volunteer teacher. Designed and co-taught “The Microverse” - a one-week course on microscopy and introductory programming for 20 students. With Alejandro Balderas of Tecnológico de Monterrey.

Summer 2019. *UC Berkeley Transfers to Excellence*. Volunteer mentor for a summer program bringing prospective transfer students to UC Berkeley for paid research internships.

2018. *Student representative to Graduate Admissions Committee*. UC Berkeley Department of Molecular and Cell Biology.

2017. *Student representative to “host-microbe interactions” Faculty Search Committee.* UC Berkeley Department of Molecular and Cell Biology.

2017-2019. *Primary organizer of annual 100-person campus-wide symposium “Photosynthesis, Carbon-Fixation and the Environment.”* UC Berkeley.

2017. *Student organizer of Biophysics, Biochemistry and Structural Biology divisional retreat.* UC Berkeley Department of Molecular and Cell Biology.

2013-2017. *Primary organizer of UC Berkeley Systems Biology Reading Group.*

PEER REVIEW

I have refereed papers for *ACS Synthetic Biology*, *Biophysical Journal*, *BioEssays*, *Cell*, *Current Opinion in Chemical Biology*, *ELife*, *Free Radical Biology and Medicine*, *mSystems*, *Nature*, *PLoS One*, *PNAS* and *Science*.

Advisors

B.S.E Junior Research Paper **Prof. Hilary Collier**, Princeton University, Department of Molecular Biology (now UCLA)

B.S.E. Senior Thesis **Prof. Kai Li**, Princeton University, Department of Computer Science

Pre-doctoral Research Mentor **Prof. Ron Milo**, Weizmann Institute for Science, Department of Plant and Environmental Sciences

PhD Mentor **Prof. David Savage**, University of California, Berkeley, Department of Molecular and Cell Biology

Postdoc Co-mentors at Caltech

Prof. Dianne Newman Divisions of Biology & Biological Engineering, Geological and Planetary Science

Prof. Rob Phillips Department of Physics, Division of Biology and Biological Engineering

Additional References

Woodward Fischer, Professor of Geobiology, California Institute of Technology

Hernan Garcia, Associate Professor of Physics, Genetics and Development, University of California, Berkeley

Niall Mangan, Assistant Professor of Engineering Sciences and Applied Mathematics, Northwestern University

Arvind Murugan, Assistant Professor of Physics, University of Chicago