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University of Rochester
Spring 2023, Volume 21, Issue 2

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Journal of Undergraduate Research

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The Journal of Undergraduate Research (JUR) is dedicated to providing the student body with intellectual perspectives from various academic disciplines. JUR serves as a forum for the presentation of original research, thereby encouraging the pursuit of significant scholarly

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Letter from the Editors

In the fall, the Journal of Undergraduate Research celebrated its 20th year of publishing, twice per year, the original research of our student body. As we move past this milestone, turning our sights to the many years to come, we remain grounded in our mission to reflect the interdisciplinary and beautifully rich content of the research produced semester after semester.

The articles we receive affirm the belief that no question is too large for a passionate student to prod, examine, and add to. Whether it be mathematical proofs, our response to COVID, ocean acidification, or fusion in plasmas, the students at this University are keen to advance our collective knowledge. This is not an easy process, requiring iteration after iteration of hypothesizing, troubleshooting, and editing, all on top of a rigorous course load. It is inspiring to see the determination of our student researchers each year. This year is no different.

In this issue, we highlight eight articles that cover a diverse set of subjects, all of fascinating relevance to our world. Siddarth Seenivasa examines the nature of consecutive prime numbers and the gap lengths between them (pg. 57), Emily Han investigates the relationship between different parenting approaches and friendship quality in college students (pg. 50), and Fletcher Seymour details how our understanding of 'knowledge' has implications on the unity of science (pg. 34). Additionally, we had the pleasure of interviewing alumni, Dr. Francisco Ramirez-Valle and Dr. Kofi Mensah, who share their experiences and advice from their careers as physician-scientists.

Although it always goes without saying, we nonetheless express our deepest gratitude to our outstanding editorial board — our managing editors and content editors for their hard work ensuring our articles are of the highest quality — as well as our layout chair, Catherine Lan, and layout editors for assembling the journal design. Additionally, we want to thank Professor Dustin Hannum and his copy editing class for their efforts in reviewing our articles. Finally, we are ever grateful for the support of the Office of Undergraduate Research, Dr. Sina Ghaemmaghami and Ms. Ann Robinson, as well as our advisor Cat Crawford, without which this publication would not be possible.

It has been our honor to serve as the Journal's co editors-in-chief, to witness first-hand a semesterly renewal in the pursuit of truth, the power of collaboration, and the creativity and zeal to move our world forward through research. As we pass on the torch to Michael Christof and Priya Mandava, we eagerly await what will appear in the pages of future journals. To our readers, we hope you enjoy the result of the hard work done by our scholars, editors, and managers alike – the pages that sit before you today.

Sincerely,

Jocelyn Mathew & Ryan Hecker

Editors-in-Chief

Journal of Undergraduate Research

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Alumni Interview

Francisco Ramírez-Valle, M.D., Ph.D.

Senior Vice President
Head I Immunology and Cardiovascular Thematic Research Center
Bristol Myers Squibb

Kofi A. Mensah, M.D., Ph.D.

Executive Director I Immunology and Fibrosis Early Clinical Development
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Dr. Francisco Ramirez-Valle is Senior Vice President and Head of the Immunology and Cardiovascular (ICV) Thematic Research Center (TRC). In his position, Francisco is responsible for the discovery of novel targets for the treatment of autoimmune, inflammatory, and cardiovascular diseases, as well as the translational research and biomarker strategies to test these therapeutic hypotheses in clinical trials. Francisco started his career in the biopharmaceutical industry conducting early phase clinical trials across immunology and fibrosis. He enjoys drawing on clinical, scientific, and informatics expertise across the organization to identify and prioritize targets with the highest potential impact for diseases with unmet need. Francisco received MD and PhD degrees from NYU School of Medicine and was a resident in dermatology at the University of California, San Francisco. Francisco completed a postdoctoral fellowship in immunology in the laboratory of Jason Cyster, at UCSF. His key areas of interest include experimental medicine and the intersection of immunology with other therapeutic areas.

Dr. Kofi A. Mensah, MD, PhD is Executive Director of Immunology and Fibrosis Early Clinical Development at Bristol Myers Squibb. In this position, Kofi designs, develops, and oversees clinical trials and research plans in support of asset strategy, and also liaises with leadership of the Immunology and Cardiovascular Thematic Research Center (TRC) to define dose, schedule, indications, and patient selection. Kofi received his BS at the University of Rochester in Microbiology and Immunology. Kofi also received his MD and PhD degrees at U of R with his PhD in immunology under the direction of Edward Schwarz, PhD and Christopher Ritchlin, MD. His dissertation looked at immune system regulation of osteoclastogenesis in the context of inflammatory arthritis. He completed clinical fellowship in rheumatology and post-doctoral research in immunobiology at Yale University with research on pathogenic roles of B cells in rheumatoid arthritis. Kofi also completed the University of California San Francisco (UCSF) American Course on Drug Development and Regulatory Sciences. Key research interests include novel platforms for tackling autoimmune and inflammatory diseases that are refractory to current therapeutic approaches.

JUR: Could you briefly describe your journey to a research career, beginning from your time as a student?

Dr. Ramirez-Valle: I grew up in Mexico and always knew that I wanted to be a scientist; I had an opportunity to come to the US to live with some relatives in Texas in high school. I ended up winning a Bausch and Lomb Science award that actually got me to Rochester. I thought that I was going to be a PhD and that I would be an academic. But one of my early research experiences was with Doctor Tony Gaspari in the Department of Dermatology in the Medical Center. I saw postings for undergraduate research opportunities and his was one of them. That was the first time that I saw that you could be doing research with the intent of understanding dis-

ease in people. In that lab, we were going to his clinic and getting samples from his patients and bringing them back to the lab where we would [work with] those patient samples. It opened … my mind to the possibility that you could do research that was devoted to understanding human health with the intention of having new disease understanding and potentially new medications developed. And so that really changed my perspective of what I wanted to do with my research career. And instead of pursuing a PhD, I decided to pursue an MD PhD so that I would become a physician scientist. So that's in a nutshell how I got to my future career, but it was really that opportunity at Rochester that made that happen.

Dr. Mensah: My road to Rochester really began [because] I wanted to be a physician, but I was also very interested in science. When I was applying to college, I was looking at these undergrad programs where you have a combined ability to be admitted to medical school at the same time you're admitted to college. I interviewed at Rochester for the REMS program. [My favorite aspect] was that it was not accelerated so I didn't feel I was going to miss out on a full college experience and the medical school at Rochester had more of a holistic view of treating patients. As I was going through undergrad, that's when we had the first SARS pandemic. I was a junior, I was a Microbiology/Immunology major. At that time we were able to find out the cause of the virus, but then get it under control very quickly. A few years before that, they had first sequenced the human genome. And then that same year, 2003, was the 50th anniversary of the Watson/Crick model. So to me, all of that was happening around the same time. [We had] all these molecular tools available to quickly identify this new viral pathogen and avert an epidemic from becoming a pandemic, [but we weren't] really good at taking that information and applying it broadly in patient care. An opportunity arose to get a scholarship to go to Merck Research Labs [through] a program where they basically would pay for your last year of college, and then you would go and do research in their labs. I took that opportunity and did research in a laboratory that was looking at rheumatoid arthritis and osteoarthritis and differences in gene expression [between tissue samples]… We would get samples in and extract the RNA from those samples and then evaluate which genes were actually upregulated and downregulated, and then from that we were going to assess what could be novel therapies for these conditions. After that experience I basically decided, you know, as I was going to start medical school that what was really going to be important to me was combining patient care and research. And that's when I decided to [complete the MD/PhD).

JUR: Were there any times in your undergrad experience that made you think or have to rethink exactly what you originally had planned? Or was everything, in terms of your experience, pretty smooth sailing?

Dr. Ramirez-Valle: I don't think there's anything in life that's smooth sailing. Maybe one of the lessons that I've taken from my time in undergrad and beyond has always been that you prepare and plan for something and then deal with the changes that come. It never really is a straight line. And you know when? When I got to Rochester, I thought I was gonna be MD. I left wanting to be an in the PhD. But I think you know within, you know this research experience that I had in the dermatology department that also was very foundational for me. If I hadn't gone to that [dermatology] lab, I don't know if I would have ended up becoming a dermatologist myself. I was introduced to dermatology very early in my research career and from that moment on I knew that that was what I wanted to do; it was a research minded specialty [and allowed me to be] not just a physician but a physician scientist. The skin for me was an amazing organ… and tool to study almost anything that you wanted to study. The skin has a microbiome, it has a nervous system, it has epithelial mesenchymal interactions, it has stem cells, it gets cancer, and has an immune system. Any disease that you're interested in studying, you can study in the skin as a model, except for consciousness perhaps. For me that [experience] was really foundational and helped me say "I want to be a physician scientist and that uses [skin] as a model for understanding other areas of biology." It also made me realize that you come in with one idea and you modify as you go along.

Dr. Mensah: I think Francisco hit the nail on the head. You have to be adaptive to your plans because I think that's very hard to embrace in this career path because everything can seem very prescribed and regimented, meaning you do your four years of college, or maybe you do a Take Five, and then you go on to do something in between, and then you go to medical school, which has a fixed length of time. Or if you're doing an MD/PhD, you know that at the end of that you're going to have to apply to residency, and then after residency, maybe there's fellowship. Everything kind of has a next step that's already sort of laid out. We kind of fall into this thing where, if you don't get into residency, then it's sort of like, what do I do? Because that was supposed to happen next. Or if you don't get into medical school, what do I do? OK, maybe I'll do research here because that's an option that people do if they don't get into medical school right away. But at some point, you start realizing that not everyone has a straight line from point A to destination Z. As you go along speaking to mentors, a lot of people had a very somewhat unpredictable path, or a path where they had to seize an opportunity that presented itself. Sometimes that can be a bit nerve wracking, especially if you are in a field where there are some usual paths that people take. For me, that experience working in the labs at Merck, was very helpful because when I finished that experience and was starting medical

school. I went to go and speak to people in the Rheumatology department and in the Orthopedic department about getting involved in research that they were doing because, you know, I learned some techniques. I learned more about this disease area and I wanted to really understand this. Again, being a microbiology immunology major, the immune system was fascinating to me because. It sort of challenged the central dogma where you have one gene leading to one protein. To make a T cell receptor, or B cell receptor you don't start out with one gene for every single B cell or T cell receptor, there's VDJ recombination events that occur, which I thought was very fascinating. How is it that our body can sometimes mistake itself for foreign antigens, then lead to autoimmune disease? To me, that experience in the lab really let me know that there were ways to really answer these questions through research. And then, around that time there were people who paved the way for what you guys are doing, who were starting to form groups around people who are interested in MD/PhD careers. People like Deepak Sophie, who was one of the founding editors of the JUR. Joe Kadiyala, who was one of the founding editors. We're really interested in this idea of how we create forums for people interested in research in medicine. And that's kind of where the idea sort of came out of. For MVP people interested in MVP, the career path, so that helped me also because now I found other people who are interested other students at U of R who are interested in the same kind of career trajectories and it's easier to sort of talk about this with your peers sometimes than to talk about it with people who are established.

JUR: What makes a good mentor for you guys and what are some special experiences that you've had with your research mentors?

Dr. Ramirez-Valle: A good mentor is somebody who's interested in helping you do what you want to do, not what they think that you should do. Those were the best mentors that I've had, they've really taken the time to get to know me and understand my needs and my motivations and not just assume that their path is [the most] successful.

Dr. Mensah: I think for each experience just really trying to pay attention to what the various mentors have to impart to you is critical. Everyone has some little bit of information to provide. Again, like Francisco said, their definitions of success may not necessarily be the only definitions of success, but just take what each one has to impart to you as something to file away for drawing upon later on.

JUR: Were there any specific classes, professors, and experiences during undergrad that inspired you?

Dr. Francisco Valle: Definitely the research experience with Tony Gaspari and Alice Pentland, the chair of the department of dermatology. The whole department was very open to students and that's pretty unique to Rochester. I did a Take 5 in Italian cultural studies and had amazing Italian language professors. I did a whole year of Dante like comedy… I did a summer program in Ottawa; all of those were foundational experiences for me that really gave me a more well-rounded perspective on being a human being. I wasn't focused solely on science. I also understood a lot about religion and different cultures and countries and architecture and art languages and I think that was really instrumental for me to be where I'm at now.

Dr. Mensah: Yeah, I think that's one of the advantages of Rochester, a lot of schools had a core curriculum, but at Rochester there was a cluster system, and so designed your own plan. I think that really did help create a more well-rounded student. I turned two of my clusters into minors… I did Spanish, film, some art classes… I think that definitely helped provide a more well-rounded experience instead of focusing on science all the time. Professors that were helpful to me in the department where people like Marianne Courtney and Robert Marquee who were two, you know, very instrumental people in the microbiology department, and David Goldfarb, who was in cell biology, was also another person who was a good person to chat with about his research. As I was transitioning to medical school, I was able to go and start talking to some people in the clinical departments who were doing research in rheumatology, for example, or orthopedics. There are a lot of medical schools that are not geographically located so close to their undergraduate institution, so I think that was something we were lucky to have at Rochester.

Dr. Ramirez-Valle: I remember walking through a blizzard to get to the medical school because I had some of my classes there, and we were able to go out to classes along with grad students. That's pretty unique, too. So it was awesome.

JUR: Why did you choose to pursue both MD and PhD degree as opposed to just doing one of them?

Dr. Ramirez-Valle: For me I had come to Rochester thinking that I was going to get a PhD. My dad has a PhD in engineering and my entire life has always been very scientific minded. It was that experience (at Rochester) that really made me consider that you can improve human health by [conducting] research in a more clinically minded way. I also sort of recognized while I was going to the clinic to see these patients from whom we were getting biopsies, that we would then do our experiments on [the biopsies] in the lab. I got to talk to some of these patients and [hear] their reflections… It just made me very interested in human health. I've never given that much thought. But people really suffer from different kinds of diseases and it limits their quality of life. It felt like, if I'm going to study something, if I'm going to spend

my life doing something, it better be meaningful, and what could be more meaningful than making people feel better. That's kind of how I decided.

Dr. Mensah: For me, I was planning on the MD only part and as I had alluded to, just the series of events that were happening in the world around the time it has sort of made me think, you know, it's really important to understand the molecular underpinnings of disease because we can use that to develop new therapies. Now there's an option as you had mentioned where you can do the MD, maybe you can do a year out in between your second and third year and then when you go to residencies nowadays [where] they have some research programs in residency and then fellowships can also be research heavy. There was a path to be able to do research as a physician without getting a separate degree without being a PhD. But for me, especially after that experience at Merck, and our microbiology upper level courses where we actually took the same courses that the grad students were taking, it seemed like formal training in research methods and thinking like a scientist would actually be the better route than … trying to create research experiences that might be disjointed. I wanted a more formal research experience and I felt that getting a PhD in an MD PhD program would be the best way to do that.

Dr. Ramirez-Valle: Ultimately pursuing a PhD, pursuing an MD, pursuing an MD PhD is a personal decision and each one has their own values. Hopefully we can impart through this discussion today that you'll always have a lot of options regardless of which path you take in. It really depends on what you aim to do, and I know a lot of physicians who are great scientists and they didn't do a PhD. But I do think that there's a really strong value in having the PhD [to understand] how to ask questions in the lab, how to run assays, how to apply for grants, it just gives you a formal education on how to do it.

Another instance in which I had planned on something and then I ended up doing something completely different was how I got into pharmaceuticals. I did my MD/PhD, I did my residency, and I did a postdoctoral fellowship. All of that I did with the anticipation that I was going to be an academic, I was going to have a lab, I was going to do 20% clinical care and 80% research. I would have grad students. I would be applying for grants. I would be publishing papers. That's what I planned for, and then I finished my postdoc and I said, "Wait, is this really what I want to do? Do I really want to be writing grants all the time, living from paper to paper. That's an awesome life, and some people love it, and ultimately it fuels innovation and science. But I wanted to do something a little bit more applied; I wanted to really impact people's day-to-day; I wanted to come up with a cure for diseases. I wanted to take my patients with eczema and be able to treat them in a more significant way. I wanted to have better treatments for psoriasis, for atopic dermatitis, for blistering diseases and I realized that the only place in which you really develop drugs like that is in the pharmaceutical industry. That's kind of how I ended up making a transition from academics to industry. But again, that wasn't something that I had planned.

It was something that developed as I started to see what the research environment was like and by talking to people. I was able to meet a few people who made the transition from academics to industry. They described to me what they were working on and I thought, "Oh my God, that's exactly what I want to be doing!" And so unless you seek out connections, you'll never know. So have an open mind [while you are] making plans.

Dr. Mensah: Yeah, just like Francisco, I was not intending on going into industry. After doing my postdoc in Immunology, the thought was to start getting your grants, start your lab, get some students and pick your topic and start your academic career. Both of us were being set up for that by our mentors and by our respective institutions. And similar to Francisco, the thought was "Ok. How do you really apply this?" I've always been interested more in the translational side of research, how do you take observations from human disease, go back and study that to understand mechanisms and then take those understandings back to modify human disease (the bench to bedside paradigm).

Industry sort of came my way by happenstance. I happened to be at a rheumatology conference. There was a table that had representatives from industry to talk about what they did. I put my name down on the list and then I got called by someone asking if I wanted to join. Again, I was not really thinking about that as something I wanted to do, but I decided to just hear what they had to say. I was just speaking to another rheumatologist who had also recently joined that specific company, and that opened my eyes to the research that people could do as a physician scientist. So, I had done research in industry in a PhD lab doing very basic and translational research, but didn't quite have an idea how a physician scientist would do something in industry besides running a lab. Speaking to people at this other company was really helpful to me. I found more people who were also like minded, many of them have had their own labs in academia and decided to join industry because they wanted more applied experience. I went with this company which was called Celgene. And when I joined Celgene, the person who helped me transition was none other than Francisco Ramirez-Valle, who you've been speaking with! Francisco and I, actually just came from 2 meetings where we were discussing some ideas! So, it's really good to be in a place where people have a similar thought process about bringing new medicines to patients thinking about translational research. We have people to bounce ideas off of, someone to say "Hey, did

you think about it this?" I really enjoy being in that setting. It really goes back to something that we've been repeating over and over again: if I wasn't open minded about industry then I wouldn't be where I am right now. That was the right decision to make and that's what we're both encouraging all of you to kind of keep that open mind. It's about getting perspectives from different individuals because, the path that sort of laid out that most people take, you pretty much can close your eyes and walk that path. It's in talking to people who have done something that's not the typical path that really helps you decide if that [path] is right for you. So, if you really want to get a PhD but still do patient relevant research, you can do that. One of my PhD advisors is a PhD who's the head of the research arm of the Orthopedic center at Rochester and my PhD Co-advisor is a rheumatologist who does not have a PhD. It really comes down to which components do you feel are critical for what you think you want to do.

JUR: You both have been incredibly helpful, for people not only starting out in research, but also kind of in the middle of it and deciding what to do next. So now that you've reached this point in your career, is there anything that you would look back on and advise your undergrad self to do at the time?

Dr. Mensah: Yeah, I don't think I would change where I ended up. I think what I would have told my younger self is really to be open minded. I don't know necessarily if it would have made things happen any faster than they did. But that's something that I would have probably advised my younger self to just be a bit more attuned to.

Dr. Ramirez-Valle: Let yourself experience things and not be too frigid in the direction that you take. They [these experiences] all really led to where I am today, which I'm very happy with. If there's something that I would have done differently, [I would] maybe experience more things. I think that Take 5, that was an awesome opportunity for me because I was more well-rounded with all the different courses that I took and the opportunities that I had. If there's one thing I would have changed is that in my junior year I had the opportunity to go to [study abroad in Italy], but it was at the same time that a course in virology was being offered. So, I guess it was my senior year actually and I decided to take the biology course. You know, in retrospect, with everything that's happened, I would rather be living for six months in Italy than taking virology. So just appreciating that there's opportunities that you only have once living them is probably something that I would have liked to do a little bit more. But that said, everything that I did has brought me to where I am today!

Effects of Ocean Acidification on Fish and Possibilities for Adaptation

Elizabeth Croyle '24, *Geobiology*
Advised by Chiara Borrelli, Department of Earth and Environemental Sciences

What is Ocean Acidification?

Climate change is the anthropogenic increase of greenhouse gasses in the atmosphere, particularly CO2 (carbon dioxide) that traps heat, increases the global temperature, and affects global weather patterns. Although most of the public is familiar with climate change and global warming, people are less familiar with the flipside--ocean acidification (OA). Atmospheric CO2 is increasing due to the burning of fossil fuels and large-scale land use changes, and the amount of CO2 dissolved in the surface ocean is increasing in tandem (Chivers et al., 2014, p. 1). CO2 reacts with H2O (water) to produce H2CO3 (carbonic acid), which then dissociates into HCO3- (bicarbonate) and H+ (Orr et al., 2005, p. 1). As more of these H+ ions build up, the pH decreases---so more atmospheric CO2 results in more CO2 and H+ in the ocean (Chivers et al., 2014, p. 1). Additionally, any free carbonates more readily bond with CO2, instead of Ca+, which causes a reduction in available CaCO3 (calcium carbonate), threatening calcifying organisms that depend on CaCO3 for their shells (Orr et al., 2005, p. 1). Ocean pH is normally around 8.1 (slightly basic), but since the industrial revolution, surface ocean pH has lowered by 0.1 units to 8.0 (Orr et al., 2005, p. 1). The pH is predicted to lower by another 0.3-0.4 units by 2100, which is roughly a 100-150% increase in [H+] (Orr et al., 2005, p. 1). This decrease corresponds to a pH of 7.7, pCO2 (the partial pressure of CO2) of 1000 atm, or CO2 of 1020 ppm (parts per million) (Di Santo et al., 2019, p. 2). Because many enzymes and other proteins can only function in a very particular pH,changing the pH of the environment is predicted to affect the physiological functions and survival of many fish. Although OA is about the increasing oceanic acidity, because of climate change, aquatic species will also have to deal with predicted ocean warming and hypoxia (Petit-Marty et al., 2021, p. 1). Hypoxia and OA often co-occur because decomposition of organisms uses O2 and produces CO2, which then reacts with H2O to produce more H+.

Overview of Experimental Designs

The current pCO2 level is around 400 µatm and the end of century prediction is around 1100 µatm under the Representative Concentration Pathway (RCP) 8.5 climatic model, which accounts for a faster rate than global trends (Di Santo et al., 2019, p. 2). A pCO2 (partial pressure of CO2) of 400 atm is equivalent to a pH of 8.0 and a pCO2 of 1000 atm is equivalent to a pH of 7.7 (Di Santo et al., 2019, p. 2). Experiments diffuse seawater tanks with CO2 to reach a desired pH for treatments, which is usually between a pH of 8.0-7.7, corresponding to a pCO2 of 600-1000 µatm, depending on how dramatic the treatment is intended to be (Chivers et al., 2014, p. 3). 600-700 µatm or ppm of CO2 is used for treating fish with mid-century (2050) conditions, corresponding to a decrease in pH of 0.14 units from current pH, which would be a pH of ~7.86 (Wittmann et al., 2013, p. 1). 900-1050 µatm or ppm of CO2 is used for treating fish with end-of-century (2100) conditions extrapolating from current CO2 emissions, and is equivalent to a decrease in pH of 0.3-0.4 units from current pH, which would be a pH of ~7.7-7.8 (Wittmann et al., 2013, p. 1). Experiments often use two or three different CO2 treatments: one representing current day levels as a control (pCO2 of 400 µatm), one representing mid-century levels (pCO2 of ~600-700 µatm), and one representing end-of-century levels (pCO2 of ~900-1050 µatm). Most experiments report their data in µatm of pCO2; however, some experiments use ppm of CO2 instead. The conversion between ppm of CO2 and µatm of pCO2depends on air pressure, water vapor partial pressure, temperature, and humidity. However, under normal humidity and temperature, they are roughly equivalent in amount of CO2 (difference of ~10-15 µatm) and pH (Ferrari et al., 2011, p. 2). To obtain fish, researchers either use wild-caught eggs and hatch them in the elevated pCO2 levels in the lab , catch adult or larvae fish and put them in elevated CO2 levels, or observe communities of fish in areas with a pCO2 > 400 µatm ,such as near CO2 seeps. In some experiments, elevated CO2 and decreased pH covary are both present to simulate future conditions, but this also means that the specific effects cannot be attributed to CO2 or pH (Dixson et al., 2010, p. 6). Some experiments only use either elevated CO2 or decreased pH to

simulate ocean acidification, disregarding the effect of increasing temperature. However, it is assumed that fish in both acidified and warmer waters will display a greater magnitude of negative consequences than if in only acidified or only in warmer waters (>~12°C).

Ocean acidification does not just affect acid-base regulation, it affects a plethora of physiological processes, including ion regulation, calcification rate, metabolic rate, protein synthesis, growth, muscle and heart function, and neural function, among others (Wittmann et al., 2013, p. 2). These processes are interconnected, carefully regulated, and conserved among fishes. Chemosensory, in particular olfactory, ability is crucial to detect predators under low visibility, since the fish can no longer rely on visual cues, and this ability is particularly impaired in fish when exposed to elevated CO2 conditions (Ferrari et al., 2011, p. 2). Additionally, ocean acidification is predicted to increase in concert with ocean warming, which will exacerbate the effects, so it is logical to assume that the negative effects discussed throughout this paper will be even worse than predicted (Wittmann et al., 2013, p. 5). Although there are both winners and losers in environments subject to OA conditions, fish--as a whole--will suffer behavioral and physiological drawbacks (Wittmann et al., 2013, p. 5).

Vulnerabilities of Fish to Ocean Acidification

Vulnerabilties within fish

Fishes are a diverse group of species, with complex niches and phylogenetic history, so OA does not affect all fish the same, nor will all fish adapt the same way to cope with the negative effects of OA. In particular, gregarious fish, strictly pelagic fish, benthic fish, fish with high oxygen consumption, and larvae fish seem to be more sensitive to the behavioral and physiological effects of OA. Gregarious fish--who rely on complex coordination with other individuals for survival--may suffer more from impairment in cognitive function and visual assessment due to high CO2 (Welch et al., 2014, p. 3). The location of fish species affects their exposure to CO2 levels, since deeper waters usually have higher levels of CO2 due to changes in density (Di Santo et al., 2019, p. 6). Compared to strictly pelagic fish, damselfish experience fluctuations in pCO2 when they exit their pelagic phase and return to the coral reef, where pCO2 can range from 431 to 622 µatm (Chivers et al., 2014, p. 2). So, coral reef fish--including damselfish--may be more resistant to CO2 changes than fish that are only pelagic and therefore are not yet adapted to fluctuating pCO2 concentrations. Benthic fish are predicted to move to deeper waters as the ocean temperature increases, but these deeper waters also usually have higher CO2 concentrations, which could also put these species at greater risk (Di Santo et al., 2019, p. 6). Therefore, fish face a tradeoff between escaping increasing temperatures and being exposed to acidification. Fish with very high rates of oxygen consumption, such as reef fish and active pelagic species, are more susceptible to CO2 changes due to high rates of gas exchange resulting in even lower blood pCO2 levels (Nilsson et al., 2012, p. 3). Therefore, differences in physiology, behavior, and location affect the vulnerability of fish between species.

Juveniles and larvae are especially sensitive to CO2 levels, since their developing anatomy, such as development of gills and ion regulation, and homeostasis mechanisms particularly suffer in high CO2 treatments (Nilsson et al., 2012, p. 3). For example, when juvenile spiny damselfish were tested in end-of-century CO2 conditions (pH of 7.9 or 8.0), they lost their innate avoidance of chemical alarm cues (skin extracts released upon mechanical damage), and were even attracted to them (Cripps et al., 2011, p. 2, Welch et al., 2014, p.1). Juvenile damselfish also suffered a reduction in olfactory preferences and behavioral lateralization, which are both key to predator avoidance and survival of juvenile fishes (Welch et al., 2014, p. 1). Not only are their regulation systems less developed, but they also rely on olfactory cues for settlement in times of low visibility and must navigate their way through predators from the reef to the open water (Dixson et al., 2010, p. 2). Settlement or settling is the movement of pelagic larvae to find a suitable benthic adult habitat while avoiding predators. Settlement is a very difficult transition with increased risk of mortality and starvation (Dixson et al., 2010, p. 6). So far in OA research, the knowledge of species vulnerable to OA mostly includes model organisms for these studies, such as damselfish, clownfish, anemonefish, and wrasse.

Vulnerabilities between fish and other taxa

The predicted level of pCO2 in the ocean by the end of the century is around 900 pm if current CO2 emissions are maintained and the oceanic pH is predicted to decrease by 0.3-0.4 units (Chivers et al., 2014, p. 1; Cripps et al., 2011, p. 1). In a comprehensive assessment carried out by Wittmann and Pörtner (2013) , 40% of the surveyed fish species were predicted to experience negative effects due to OA at only 500-650 pCO2 µatm, a very conservative pCO2 estimate for 2100 (p. 3). The authors have labeled fishes as having a high sensitivity to predicted OA levels--higher than corals, echinoderms, molluscs, or crustaceans--

since greater than 71% of the fish species studied were negatively affected (Wittmann and Pörtner, 2013, p. 5). When comparing species in terrestrial and aquatic systems, water breathers usually have lower plasma CO2 and HCO3- levels because CO2 has a higher solubility than O2 in water, and therefore changes in CO2 in the environment will have a larger impact on the CO2 gradients of their respiratory surfaces (Nilsson et al., 2012, p. 3). Throughout this paper, many behavioral and physiological negative effects on fish will be explained, but the specific reasons for why fish in particular are so vulnerable are unknown. One possible explanation for the range of observed and very detrimental behavioral effects on fish compared to other previously studied species (such as oysters, phytoplankton, and mussels) is that in fish behavioral changes are easier to observe, quantify, and connect to fitness and mortality. There could be behavioral changes in other previously studied species, but they would be very hard to observe definitively. A different explanation is that fish have a unique sensitivity to OA, and that this specific factor associated with this sensitivity (such as a chemical process, particular dependency, or regulatory system) has not been discovered or connected to OA yet. Regardless of the current uncertainties, a large portion of fish species are predicted to suffer from increasing effects of OA.

Behavioral Changes due to Ocean Acidification

The behavioral effects of ocean acidification on fish are usually measured by introducing innate chemical alarm cues (such as the scent of a predator) and quantifying how it affects feeding and movement, both of which are expected to decrease when chemical alarm cues are sensed. Alternatively, fish are exposed to alarm cues they have not experienced before, and it is recorded if they respond to them later. Additionally, behavioral lateralization is studied as a measure of learning and remembering chemical alarm cues. Behavioral lateralization is an innate preference for the right or left side; therefore, a decrease in lateralization is less preference for one side. Behavioral lateralization is thought to reduce decision-making time and is linked to both visual assessment and cognitive function, so a decrease in behavioral lateralization is indicative of impaired learning and assessment of visual cues (Welch et al., 2014, p. 3).

There are two proposed mechanisms affecting olfactory sensation and transmission: excitatory gamma-aminobutyric acid (GABA) transmission and an impaired olfactory system due to upregulation and downregulation of different genes. GABA is a major inhibitory neurotransmitter that serves a large role in sensing olfactory cues and making decisions using the information gained from it. It is suspected that elevated CO2 levels actually disrupt chemosensory signal transmission or transfer, not the development of the olfactory system itself (Dixson et al., 2010, p. 6). In other words, this impairment caused by increasing acidification is temporary or reversible if that acidification is removed or if a GABA antagonist, usually gabazine, is applied.

GABA-A and its effect on olfactory sensation

GABA-A is a crucial inhibitory neurotransmitter receptor in the brain, and has a high conductivity of Cl-(chloride) and HCO3- (bicarbonate) ions. One of the acid-base balance systems in fish develops an accumulation of HCO3-and reduces Cl- to prevent acidosis (Briffa et al., 2012, p. 4). When combined, the result is depolarization and excitatory GABAergic transmission (Nilsson et al., 2012, p. 1). The GABA system in fish is thought to be particularly susceptible to effects from OA due to fish having a much more permeable ion channel than mammals or other taxa (Nilsson et al., 2012, p. 3). Gabazine is a GABA-A antagonist and can repress the dramatic results of excitatory GABA transmission, and is often used in OA experiments (Nilsson et al., 2012, p. 2).

Adult damselfishes have innate responses to species specific cues, but they also typically learn to recognize the cues of specific predators they encounter (Chivers et al., 2014, p. 3). Fish exposed to high pCO2 (987 µatm, pH of 7.75) did not learn how to recognize these predators, and did not respond to the odors one or five days postconditioning (exposure to alarm cues from predator fish not previously seen by the damselfish), while fish kept under normal pCO2 (440 µatm, pH of 8.15) responded both one and five days postconditioning (Chivers et al., 2014, p. 3). When treated with a GABA-A antagonist (gabazine), the exposed fish showed an antipredator response, but could not repeat this effect (Chivers et al., 2014, p. 3). This response was not repeated because gabazine washes out quickly and only provides a short-term recovered response (Chivers et al., 2014, p. 3). Fish exposed to risk (predator odor) are expected to reduce feeding and activity (Chivers et al., 2014, p. 4). The fish in elevated CO2 without a gabazine treatment did not show a significant change in feeding strikes, while the fish given a gabazine treatment did show a significant reduction in the feeding strikes, particularly five days after the learning trial (Chivers et al., 2014, p. 5). When the fish were released back into the reef, a much higher proportion of the fish in the elevated CO2 gabazine treatment survived over the next 100

hours than those without the gabazine treatment (Chivers et al., 2014, p. 6). Therefore, end-of-century levels of CO2 (~1000 µatm pCO2) cause negative effects on predator learning and survival in the wild, and treatment with the antagonist of the GABA-A receptor reversed these effects (Chivers et al., 2014, p. 6).

Impaired olfactory sensitivity and transmission

Olfactory sensitivity is also affected by increasing ocean CO2 levels. When only the olfactory epithelium was isolated and in contact with seawater and elevated CO2, the sea bass needed up to five times greater concentrations of the odorants or needed to be ~50% closer to produce the same physiological response as the control bass (Porteus et al., 2018, p. 2). RNA sequencing was also used to look at differences between bass in current CO2 conditions (pCO2 of ~450 µatm, pH of ~8.0) and bass exposed to elevated CO2 (pCO2 of ~1000 µatm, pH of 7.7) for two days. Genes involved in glutamate receptors, synaptic plasticity, neurotransmitter reuptake, and olfactory receptors were downregulated while genes involved in bicarbonate transport were upregulated (Porteus et al., 2018, p. 2). This regulation pattern suggests that the fish could not correct for their decreased olfactory sensing and were possibly sending reduced amounts of olfactory information to higher brain centers (Porteus et al., 2018, p. 4). As a result, not only are the fish sensing less information, but they are also transmitting less olfactory information as well. Unlike the GABA mechanism (based on blood CO2 levels), this method is based on seawater CO2 levels. These two mechanisms could also work in tandem, which could continue to worsen effects on olfactory sensing and transmission.

Attraction to chemical alarm cues (CAC), decreased behavioral lateralization, and changes in reproductive behavior

When four juvenile damselfish species were exposed to elevated CO2 (700-800 ppm, pH of ~7.9-8.0) and the odor of injured conspecifics, they displayed either a less adaptive or not adaptive antipredator response (Ferrari et al., 2011, p. 4). A negative correlation was found between the severity of CO2 levels and an antipredator response--meaning that a higher CO2 level was associated with a decreased antipredator response (Ferrari et al., 2011, p. 4). Even a slightly worsened antipredator response can lead to considerable changes in survival with more elevated CO2 damselfish being subject to predation (Ferrari et al., 2011, p. 5). There was variation between the damselfish species, ranging from a 30% to 95% reduction in response.t is unknown what causes this difference, since the body size and life history of the damselfish were very similar (Ferrari et al., 2011, p. 6). When the olfactory preferences and behavioral lateralization of juvenile damselfish reared in high CO2 were tested in a different experiment, juveniles in 700 or 800 ppm CO2 spent more time with CAC and were even attracted to them (Welch et al., 2014, pp. 2). The fish also saw an overall decrease in lateralization, meaning that the fish in elevated CO2 concentrations did not have as much of a preference for their right or left side when compared to control fish, indicating a decrease in visual assessment and cognitive function (Welch et al., 2014, p. 2, 3). Larvae barramundi fish reared in elevated CO2 levels became attracted to unfamiliar and artificially generated sounds, which were ignored in control conditions (Rossi et al., 2018, p. 1). OA affects the processing of auditory and chemosensory cues. This experimental data suggests that fish in future OA conditions will become attracted to environmental cues that are not advantageous (Rossi et al., 2018, p. 1).

Similarly, when clownfish were reared from an egg in 1050 µatm CO2 (pH ~7.7), they became attracted to the cues of noxious stimuli and the odor of their parents, which were avoided in control conditions (Briffa et al., 2012, p. 3). At even higher CO2 levels of 1700 µatm, the larvae did not respond at all to any of the cues, indicating that a threshold (700 ppm CO2) for impairment may be present (Briffa et al., 2012, p. 3). They also exhibited increased risky behavior and consequently increased mortality (Briffa et al., 2012, p. 3). In a similar experiment using clownfish reared in high CO2 (900 ppm), they also exhibited an attraction to CAC, an effect that was almost completely reversed when treated with gabazine (Nilsson et al., 2012, p. 2). Interestingly, the chemosensory ability of newly hatched clownfish in elevated CO2 was not affected by acidification, possibly because embryos are normally exposed to pH and CO2 variation and are therefore more adapted to variation due to OA (Dixson et al., 2010, p. 6).

OA has also been observed to affect reproductive behavior in ocellated wrasse. Ocellated wrasse males consist of dominant males, who build nests, care for eggs, and attract females; satellite males, who cooperate with dominant males to drive away sneakers, but also secretly fertilize the eggs; and sneaker males, who release more sperm than the other males and do not cooperate or care for the spawn (Milazzo et al., 2016, p. 2). Courtship, competition behavior, male fertilization success, mating behavior, and other responses were measured in both elevated (pCO2 of 1100 µatm, pH ~7.7) and ambient CO2 (pCO2 of 400 µatm, pH ~8.0) areas

(Milazzo et al., 2016, p. 2). There were no differences in nest site visits, nest attractiveness, female spawning rate, number of eggs laid, time spent courting, or aggressive dominant male behavior (Milazzo et al., 2016, pp. 4–5). The number of pair spawns (female and dominant male) decreased, while the number of sneak spawns and satellite spawns remained approximately the same (Milazzo et al., 2016, p. 5). There was also a trend of lower satellite and sneaker male paternity as well as an increased dominant male paternity, contrary to the hypothesis that increased sperm competition would reduce dominant male reproductive success, which could possibly be due to effects on sperm mobility or other physiological differences (Milazzo et al., 2016, p. 5). Regardless, the results show that there are both winners and losers in elevated CO2 levels.

Reduced sensing of chemical cues in predatory fish

Although effects on prey behavior, such as with the damselfish), and their increased mortality have been researched multiple times, research into effects on predator behavior is less understood. When brown dottyback fish were exposed to elevated CO2 levels (either 600 µatm or 950 µatm, pH of ~8.0 or 7.9, respectively), they avoided water with prey odor--instead of being attracted--and exhibited higher activity and lower feeding activity levels (Cripps et al., 2011, p. 1). Sensory cues, especially chemical cues, are crucial for finding and capturing prey and responding to changes in food availability (Cripps et al., 2011, pp. 2, 5). The exact physiological mechanism causing this change is not known but is assumed to relate to changes at a cellular level, such as from acid-base regulation (Cripps et al., 2011, p. 6). However, hampered olfactory sensing and behavior seem to be more dramatic for prey than for predators, and therefore the mortality rates of prey are still predicted to increase (Cripps et al., 2011, p. 1).

Pollution--and by extrapolation, OA--has the potential to affect behavior in three ways: 1) disrupting metabolic processes, which affects the rate at which the behavior can be performed, 2) harming the ability to gather and assess information and make decisions, and 3) hindering the ability to detect and avoid the polluted/affected areas (Briffa et al., 2012, pp. 1–2). All three of these effects have been documented in fish exposed to increased CO2 levels, specifically: GABA as a part of metabolism and the metabolic cost that comes with physiological stress, perceiving and making decisions about CAC (including decreased behavioral lateralization), and poor detection and even attraction to areas of high CO2 or high CAC. Changes in reproduction behavior and sensing environmental cues, particularly through olfactory means, have also been discovered, although further research needs to be conducted into adaptations and evolution to lessen these effects.

Physiological Changes due to Ocean Acidification

Although behavioral and physiological effects are often connected, physiological changes in the context of this paper are changes in primarily tissues, organs, and bones. It is worth noting that behavioral and physiological changes can be coupled, so some of the examples discussed could be connected to or cause behavioral changes. Decreased mineralization in calcifying organisms, which involves the accumulation and hardening of calcium carbonate, is commonly discussed as a negative consequence of OA. This effect occurs because OA decreases the amount of available calcium carbonate, since any free carbonate more readily bonds with CO2 (instead of Ca2+), which forms H2CO3. Although fish are not calcifying organisms (such as oysters and mussels), mineralization is still involved in skeletonization. Similar to previously discussed behavioral consequences, physiological changes are particularly detrimental in larvae fish due to their negative consequences on developmental processes involving tissue and organ function. Larvae fish also have less developed acid-base regulation systems, making them even more susceptible to changes in CO2 concentration.

Changes in Mineralization

Mineralization is usually discussed in reference to calcifying invertebrates, who have a reduction in shell formation under low pH (Di Santo et al., 2019, p. 1). Fish calcify internal skeletal elements, while invertebrates calcify external ones (Baumann et al., 2012, p. 1). Mineralization (more specifically, hydroxyapatite density) in the little skate increased in the cartilage of crura (modified pelvic fins) and jaws due to elevated CO2 but decreased in the pectoral fins due to increased temperatures (Di Santo et al., 2019, p. 1). Trends in mineralization changes differed in pCO2 of 1000 atm (equivalent to a pH of 7.7), elevated temperature of 15°C or 20°C (control was 12°C), and both pCO2 of 1000 atm and elevated temperature conditions (Di Santo et al., 2019, p. 4). A decrease in mineralization is more likely and could be due to less available energy for mineralization when in a more stressful environment (lower pH, higher temperature) (Di Santo et al., 2019, p. 5). There are a few plausible explanations for increased mineralization due to OA. The first is that CO2 affects Ca2+ deposition, which affects neuronal activity, and although cartilage is not heavily innervated, neuronal activity

could regulate calcium deposition, which affects mineralization and growth (Di Santo et al., 2019, p. 4). Another possibility is that skates increase their buffer capacity to prevent acidosis, which can increase phosphate concentration in blood and hydroxyapatite density (Di Santo et al., 2019, p. 5). It is most likely that changes in mineralization are the result of trade-offs between physiological processes involved in mineralization compared to acid-base and thermal homeostasis (Di Santo et al., 2019, p. 5). Increased jaw and crura mineralization could improve walking ability, mechanical jaw power, and swim speed, but may decrease walking speed (Di Santo et al., 2019, p. 5). It is difficult to predict the exact overall changes and trends in future conditions since mineralization differed in the three tested combinations of pCO2 and temperature, and further research needs to be done to provide scientific explanations of the results.

Larvae cobia (a tropical predator) reared in elevated CO2 had a significantly increased otolith size and density, which would increase the hearing threshold and range (Bignami et al., 2013, pp. 1, 2). Otoliths are part of the auditory and vestibular sense organs. The increased hearing ability is predicted to be advantageous for benthic species and disadvantageous for pelagic species (Bignami et al., 2013, p. 2). Benthic species usually have larger otoliths for increased vestibular sensitivity while pelagic species have smaller, and therefore lighter, otoliths for more mobile swimming (Bignami et al., 2013, p. 2). The otolith changes may be possibly from altered neurological function or ion changes (Bignami et al., 2013, p. 2). It is unknown how wild fish survival, dispersal, or diversity might change as a result, since increased otolith size could be beneficial for benthic species but detrimental for pelagic species.

Organ and Tissue Damage

Atlantic herring larvae in ocean acidification scenarios experienced a greater incidence of organ damage (kidney, pancreas, liver, and fins) and a reduction in growth rate, causing increased mortality rates since smaller and slower herring face higher rates of predation (Frommel et al., 2014, p. 7). It is suspected that available energy prioritizes acid-base regulation development, resulting in less energy left for growth (Frommel et al., 2014, p. 7). Atlantic cod were also reared in the same system and suffered severe organ damage at early developmental stages; however, they saw increased growth and no fin damage (Frommel et al., 2014, p. 9). Reduced early life growth and survival was also recorded in a similar experiment with inland silverside larvae, with these small changes in survival being able to affect fish populations (Baumann et al., 2012, p. 1). A negative correlation with CO2 concentration and larvae survival was statistically significant (Baumann et al., 2012, p. 1). The one-day post-hatch fish showed more malformations, possibly due to poorly developed acid-base and cardiorespiratory control (Baumann et al., 2012, p. 1).

Increased reproductive output and offspring size

Cinnamon anemonefish kept in elevated CO2 levels for nine months exhibited stimulated breeding activity, increased reproductive output, and larger clutches with smaller yolks (Miller et al., 2013, p. 1). Fish respond to stress by either reducing investment into current reproduction and saving it for future reproduction or by investing more in current reproduction and increasing offspring survival (Miller et al., 2013, p. 1). Some species invest more in reproduction and others invest more in acid-base regulation. Cinnamon anemone produced more eggs with less investment into each age, increasing reproductive output, providing evidence for different strategies to deal with OA. One possible reason for this result is a hormetic response to increased CO2, where the stressor speeds up or stimulates physiological reactions and performance (Miller et al., 2013, p. 7).

In conditions of elevated CO2 and temperature warming, larger California grunion larvae were less sensitive to changes in CO2 and pH and therefore had lower mortality rates (Johnson et al., 2022, p.1). This decreased sensitivity is possibly because larger offspring have a greater metabolism/potential energy that can cope with environmental stressors, such as increased CO2 or any of the other predicted competition effects (Johnson et al., 2022, p. 3). Additionally, mothers that produced more eggs also had less mass per egg, indicating a trade-off between egg mass and egg quantity (Johnson et al., 2022, p. 2). It is predicted that if the population evolved based on the current genetic variation, reproductive success will be ~90% of the current success (Johnson et al., 2022, p. 1).

Ocean Acidification as Contemporary Evolution—What We Know and What We Might Know Later

Review of natural selection and adaptation

Fitness is an individual's ability to successfully reproduce, and it increases with the addition of a beneficial mutation or adaptation. Whether or not a change is beneficial depends on the unique environmental and ecological pressures the individual

faces--if a mutation is beneficial and continues to be beneficial, then it will increase in frequency until it reaches fixation (Petit-Marty et al., 2021, p. 2). A mutation may be beneficial for one generation or population, but not for another. It is important to understand how fitness is connected to genotypes to make further predictions on the adaptive potential of fish to environmental change, such as OA (Petit-Marty et al., 2021, p. 2). Because multi-generation studies are not feasible for species with longer generation times, like fish, researchers use genetic studies to quantify variation in tolerance of OA (Johnson et al., 2022, p. 1). One of the first steps is identifying changes in gene expression in environments with OA, and upregulated genes are likely candidates for genetic changes in the future to improve efficiency or response (Petit-Marty et al., 2021, p. 2).

Candidate genes for adaptive selection to ocean acidification

Because OA modifies existing selection on individual variations, it is logical to assume that future adaptations that deal with the pressures of OA will focus more on genes or regions that will improve fitness and chances of survival. Transcriptome analysis of gonad tissue of a population of common triplefin at natural CO2 seeps (which have higher CO2 and therefore a lower pH of ~7.93-7.86) was compared to that of a control group (ambient pH of ~8.0) (Petit-Marty et al., 2021, p. 5). The fish from the seeps had a higher average level of gene expression and showed upregulation of 66 genes that were involved in maintenance of homeostasis, energy production, protein production, protein binding, actin, and signal transduction (Petit-Marty et al., 2021, p. 8). Males had higher values of gene expression overall, which was attributed to the sex-biased gene ophn1. This gene increases signal transduction and expression in males (Petit-Marty et al., 2021, p. 8). Almost half of the candidate genes also had SNPs (single nucleotide polymorphisms) and almost all of these were synonymous (resulting in no amino acid change) (Petit-Marty et al., 2021, p. 9). Therefore, it appears that mutations located in functional, rather than coding, regions may be more adaptive and plausible in an OA environment. If these alleles continue to be beneficial to the population, they could reach fixation in the future. Other probable candidate genes could be involved in controlling hemoglobin and oxygen transport, as these were identified as the main difference between sensitive and tolerant adult damselfish in CO2 conditions of 750 µatm (Schunter et al., 2018, p. 2). Additionally, adaptive mutations improving survival chances in conditions of OA are already present in populations under that stress, just like any other beneficial mutation for a stressor (Petit-Marty et al., 2021, p. 12).

GABA seems like a very promising mechanism for adaptive selection, since it is phylogenetically old and very conserved (Nilsson et al., 2012, p. 3). However, GABA itself may have limited plasticity, so adaptation can only resolve effects from OA to an extent since multiple mechanisms require adaptation (Welch et al., 2014, p. 3). Additionally, species relying heavily on the GABA system or other systems sensitive to changes in HCO3- or Cl- could suffer greater impairment under rising CO2 levels (Nilsson et al., 2012, p. 1). In other words, species heavily relying on or with heavily fine-tuned GABA are more at risk, since GABA's function flips from inhibitory to excitatory in higher acidity and has little room for future adaptation (Nilsson et al., 2012, p. 3).

Balancing selection is the selective process that maintains genetic diversity within populations (Petit-Marty et al., 2021, p. 2). Although balancing selection has not yet been documented in fish, it has been documented in other aquatic organisms and is likely important for long-term maintenance of adaptation or potential adaptation to changing environmental conditions (Petit-Marty et al., 2021, p. 12). It is logical to assume that offspring larger than the average size will be able to deal with OA more than smaller offspring because larger body size also means larger organs and acid-base regulation systems, which would give them the upper hand (Johnson et al., 2022, p. 1). In a study that looked at larvae size and potential evolutionary responses in California grunion, it seems that selection will drive them to produce increasingly larger offspring with higher fitness (Johnson et al., 2022, p. 2). Grunion reared in pCO2 of 1,650 µatm (pH = 7.6) for 14 days displayed a large enough amount of genetic variation in larvae size to suggest that the species has the capacity to evolve (Johnson et al., 2022, p. 2). When projection models were created for the year 2100 (81 years or 27 generations), mean larvae size was projected to increase by 20% (Johnson et al., 2022, p. 3). Directional selection is projected to offset the projected decline in reproductive success from OA by ~50% (Johnson et al., 2022, p. 4). It is currently unknown if other species will respond the same way, but increasing offspring size is a viable selection strategy that could occur in the present or in the future with more extreme OA conditions.

Possible transgenerational acclimation

Developmental and transgenerational plasticity have recently been explored as possible avenues

for adaptation to rising oceanic CO2 and acidity. Effective transgenerational plasticity, where the parent's environment affects expression in the offspring, could rescue or reduce negative effects on reproductive success, chemical sensation, lateralization, and acid-base regulation, creating a system where each progressive generation is better adapted for the increasing ocean acidification (Schunter et al., 2018, p. 2; Petit-Marty et al., 2021, p. 8). Transgenerationally CO2 exposed damselfish, when compared to acute and developmentally exposed, exhibited unique genetic recovery patterns in increased microtubule and decreased cytoskeleton pathways (Schunter et al., 2018, p. 5). Changes in regulation or expression are suspected to be from changes in methylation, affecting silencing and transcription (Schunter et al., 2018, p. 6). One important adaptive change was the upregulation of a K-Cl cotransporter, which removes intracellular Cl- and could reduce the excitatory action of GABA-A (Schunter et al., 2018, p. 5). This change indicates that there may be different responses to increases in CO2 over a short time frame rather than more gradual increases, and therefore slowing future trends in OA could help promote genetic recovery patterns. Across the treatment groups, all exhibited an upregulation in genes for glucose transporters, which would increase gluconeogenesis; subsequently, the constant rebalancing of gluconeogenesis and glucose homeostasis is predicted to be crucial to continue to adapt to changing OA conditions (Schunter et al., 2018, pp. 6-7). Unfortunately, so far transgenerational acclimation has not been observed to restore key sensory and behavioral traits in elevated CO2 conditions (Welch et al., 2014, p. 3). 700 ppm might represent a threshold for what biological adaptation can deal with, since individuals are more variable in these conditions than in higher CO2, but progressive acclimation could push the CO2 limit further (Ferrari et al., 2011, p. 5). The impact of transgenerational acclimation likely depends on the heritability of individual variation, which has yet to be researched and quantified (Welch et al., 2014, p. 3).

Future research could examine additional physiological mechanisms disrupting olfactory processes, contribution of CO2 as compared to pH to those disruptions, and how environmental changes can alter ontogenetic timing in olfactory development (Dixson et al., 2010, p. 6). Interestingly, some observations of populations in environments with higher acidification (such as volcanic seeps) show them thriving, rather than declining (Petit-Marty et al., 2021, p. 2). However, these ecosystems and observations are not common. Adjustment of their physiology, particularly gene expression, will be crucial for survival and adaptation (Petit-Marty et al., 2021, p. 2). Good candidates for future changes in gene expression are ones related to calcification, metabolism, acid-base regulation, stress responses, and behavior. Understanding how fast a species can change the expression of these genes (upregulate or downregulate) is crucial to predicting long-term negative effects on fitness and survival (Petit-Marty et al., 2021, p. 2). If CO2 emissions are significantly reduced by 2100 and CO2 levels reach only 500-700 ppm - instead of the currently predicted 850-1000 ppm--adaptation of behavioral and physiological responses might be possible, although species decline is still highly likely (Munday et al., 2010, p. 3). There is currently no comprehensive data predicting how dramatic this decline will be, how adaptation might offset it, and what the overall ecosystem effects might be. Some fish, including Atlantic herring, are a large part of commercial fishing, and will affect availability for human consumption (Nilsson et al., 2012, p. 3).

Conclusion

Performing tasks (such as avoiding predators, getting food, finding a mate) is dependent upon behaviors, and disruption of these behaviors or their connected physiological processes can influence individual fitness and overall population success (Briffa et al., 2012, p. 8). Furthermore, behavior plays a role in other ecosystem services and interrelated geochemical processes, such as mineralization, linking OA and ecosystem level effects (Briffa et al., 2012, p. 8). Inhibiting or reversing innate predator avoidance due to sensing of CAC increases mortality of larvae before they have a chance to reproduce, threatening population replenishment and causing population decline (Dixson et al., 2010, p. 5). Upregulation of genes in functional regions, contributing to either downregulation or upregulation, seems to be a good candidate for future adaptation, particularly of genes involved in homeostasis, energy and protein production, oxygen transport, acid-base regulation, and signal transduction. Contemporary acclimation in the form of intraspecific variation and transgenerational acclimation could result in changes to community composition, which could affect biodiversity at other levels (Ferrari et al., 2011, p. 6). However, it seems that there is a threshold (~700 ppm CO2) for how much adaptation can counteract reproductive decline due to ocean acidification (Munday et al., 2010, p. 3). Effects of ocean acidification on fish will vary within and between species, and although these effects are not completely elucidated, they will cause changes in community and ecosystem organization as trade-offs

between acid-base regulation and reproductive success become more apparent.

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About the Author

For my Geobiology course, I had the opportunity to write about any paleooceanographic topic. Climate change, and its increasing impending doom, is important in so much of ecology and evolutionary biology research. One of its effects is worsening ocean acidification, and I compiled research to predict if fish could combat some of these pressures with adaptation, or sadly not.

Investigating the Relationship Between Select Emergency Department Patient Characteristics and the Disposition of Emergency Department Patients Among Two South Korean Emergency Departments

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I. Overview

The purpose of this research project was to analyze a subset of patient characteristics from 1267 randomly selected medical records from South Korean emergency department (ED) patients to determine whether any characteristics correlated with a patient's ED disposition. Specifically, this analysis sought to investigate the hypothesis that a longer time spent in the ED is significantly associated with greater odds of the patient being admitted to the hospital. The variables in the multivariate analysis and best fit logistic regression model included a patient's sex, age, mental status, pain status, length of stay in the ED, disposition, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), body temperature (BT), and oxygen saturation. The results of this multivariate analysis found that only sex, injury, and SBP are significantly associated with a patient's disposition. These analyses are practically significant because they can help ED providers consider the patient's disposition at the beginning of the care timeline by prioritizing patient characteristics based on the likelihood that the characteristics can predict a patient's disposition.

II. Background

Emergency medicine (EM) is the practice of medicine that trains providers to assess, care for, and stabilize a generally diverse patient population in the pre-hospital setting[1]. EM is applied in the emergency department , the point of reception for patients seeking immediate medical evaluation for acute illnesses and injuries among otherwise potentially life-threatening conditions. Following the typical course of initial triage, evaluation, and stabilization in emergency care, a patient is assigned a disposition – in-hospital admission or discharge from the emergency department[2]. Because each patient presents to the ED with an individualized medical history and unique personal circumstances, a range of factors influence a patient's disposition. As a result, a main focus of ED quality assurance is recommending the most clinically appropriate disposition by weighing the burden of admission against the risk of discharge for every patient[3].

Worldwide, the utilization rate of emergency departments is increasing[4]. However, ED utilization is inconsistent across the board. Although a March 2021 report by the Department of Health and Human Services to Congress concluded that the ED utilization rate in the US remained relatively stable between 2009 and 2018, experiences vary across EDs and throughout different communities[5,6]. For example, COVID-19 significantly decreased ED utilization rates in the US. The Centers for Disease Control and Prevention (CDC) estimates that US EDs witnessed a 42% decrease in visitation rates when visit volumes from March 29 to April 25 of 2019 and 2020 were compared—a result of the US government's recommendations to stay home[7]. Some EDs surveyed by the American College of Emergency Physicians (ACEP) reported even greater ED visit volume drops, with some facilities experiencing a decrease of over 50%[7]. In 2022, some US emergency departments are witnessing increasing patient volumes, with one Shasta County, CA ED's volume up 30% to 40% compared to December 2021 with local hospitals urging patients to avoid the ED unless medically necessary, despite increasing referrals to the ED by primary care providers[8]. Evidenced by periods of unpredictability, the need for appropriate disposition of the emergency department patient has become increasingly important.

According to the Society of Academic Emergency Medicine (SAEM), "A good clinician thinks about patient disposition from the moment he or she enters the room"[2]. Although the best disposition for each patient is not always well-defined, thinking about patient disposition throughout the timeline of care can reduce patient time spent in the emergency department and improve patient satisfaction and ED efficiency[2]. Research on factors that may be associated with an increased likelihood of admission or discharge from the ED could further help providers determine the most appropriate disposition for an ED patient at the beginning of care.

This investigation will assess the relationship between select emergency department patient characteristics and their disposition to determine whether there is sufficient evidence to suggest that a patient's sex, age, injury status, or length of stay in the ED, among other characteristics, is associated with their disposition (i.e., admission or discharge). This research seeks to answer the following question: Which characteristics of emergency department patients, if any, are associated with inpatient hospital admission or discharge from the emergency department?

It is well understood that ED visitation rates vary by age, sex, race, and ethnicity, and that females, infants under 1 year of age and adults over 75 years of age, and non-Hispanic Black or African Americans have the greatest ED utilization rate. This may support hypotheses about these characteristics and others as they relate to a patient's disposition following their visit to the emergency department[9]. While age and sex are variables that will be considered in the analysis, it is primarily hypothesized that: A patient's length of stay in the emergency department is significantly associated with inpatient admission. Specifically, the longer a patient's stay in the emergency department, the more likely the patient is to be admitted to the hospital.

III. Data Collection and Summarization

A. Data Collection

Before beginning this project, I sought to develop and investigate a research question within the field of emergency medicine research. I explored Kaggle and searched "emergency department dataset," and I found "Emergency Service – Triage Application", which is a dataset that was published in the peer-reviewed article titled "Triage accuracy and causes of mistriage using the Korean Triage and Acuity Scale" in PLOS One, an open access scientific journal that includes primary research from scientific and medical disciplines[10]. This dataset consists of 24 variables and N=1267 randomly selected medical records of adult patients evaluated at two South Korean EDs between October 2016 and September 2017. These records were sampled from one "local" ED and one "regional" ED based on several factors, including "patient visits per year, the presence of emergency nurses dedicated to triage only, and collection possibility of the selected variables"[4]. Both EDs are also urban academic medical centers.

The original study was a retrospective review that sought to "identify the accuracy of triage based on medical records and to evaluate the causes of mistriage"[4] Moon et al. evaluated the association of 24 select patient characteristics to determine if they are associated with mistriage. The triage decisions made by emergency nurses at the emergency departments were compared to triage decisions made by three selected triage experts, whose Korean Triage and Acuity Scales (KTAS) scores were compared for inter-expert agreement. The results of this study found the primary cause of mistriage to be the misapplication of the Numeric Pain Rating Scale to the KTAS. I determined that it would be pertinent to evaluate the relationship between several of these patient characteristics and the disposition of each patient to identify whether any statistically significant associations exist. I am specifically interested in investigating the relationship between a patient's length of stay in the emergency department and their likelihood of admission to the ED.

B. Potential Bias

There are several important considerations to evaluate potential biases within these data. Primarily, these data are randomly selected medical records from two emergency departments in South Korea from October 2016 through September 2017. A limitation of the original study, according to Moon et al., is that it did not reflect the entire original study period of October 2016 through September 2017, because the N=1267 randomly selected medical records were sampled from randomly selected dates during this time period. This limitation applies to the current investigation because these data are reflective of a limited time period and are even further limited given that the October 2016 to September 2017 range is not entirely reflected in the data. It may be difficult to generalize any associations found to other time periods if the original range includes data on a nonrepresentative sample of individuals visiting the ED for out of the ordinary reasons, such as injuries from war. However, there is no evidence to believe that visits to these EDs from October 2016 through September 2017 were due to such reasons.

Secondly, these data were collected from only two emergency departments in South Korea, both of which are urban academic medical centers assumed to be physically attached to a hospital. It is reasonable to suggest that differences exist in the patient populations of other emergency departments in the country, such as urban non-academic EDs, rural EDs, and free-standing emergency departments, which are not physically attached to a hospital and are often independently owned and operated outside of an established health system. Although Moon et al. stated that the two EDs were selected in part because they believed sufficient

patient data would be collected from them, it remains important to remember that these EDs are not representative of the status of emergency care or patient populations visiting the ED in South Korea. For example, rural EDs may see fewer motor vehicle crashes, but may see more pediatric patients with chief complaints typically characteristic of non-ED primary care visits in urban areas if access to a primary care provider in rural areas is limited.

Lastly, it is important to understand that differences in emergency care exist worldwide. As Moon et al. explains, different countries have different medical environments. Although the KTAS was adapted from the Canadian Triage and Acuity Scales (CTAS), it was ultimately standardized to fit the South Korean medical environment. In the context of this investigation, findings from this analysis should be contextualized within South Korea. Distinctions in findings from these data may only be made with other countries if similar investigations are carried out to reflect the medical environment of that country, while taking into consideration the general health and well-being of that population, and understanding that health risk factors of a population and how they compare to health risk factors for South Koreans.

Overall, this dataset serves as a good starting point for this analysis because of its completeness (i.e., minimal missingness) of its dataset and relatively large sample size. Specifically, out of all 1267 observations and 24 variables, 1487 out of 30,408 data points were missing. Further, out of all 1267 observations and of the 13 variables of interest, 909 out of 16,471 data points were missing. As a result, no more than 6% of the data is missing.

C. Data Summarization and Preliminary Analyses

This dataset consists of 24 variables. This investigation will analyze 13 of these variables, 12 of which will serve as predictor variables and 1 that will serve as the response variable (i.e., patient disposition). The variables that are included in this analysis are listed below, along with appropriate labels and how they are coded in the dataset for this investigation:

triage Dataset

Sex: Sex of the Patient (0: Female 1: Male)

Age: Age of the Patient (Years)

Injury: Is the Patient Injured? (0: Non-injury 1: Injury)

Mental*: Is the Patient Alert? (0: Not Completely Alert 1: Completely Alert)

Pain:** Is the Patient in Pain? (0: No Pain 1: Pain)

Length of Stay: Duration of ED Encounter (Minutes)

Disposition*:** Disposition of Patient (0: Discharge 1: Admission)

SBP: Patient's Systolic Blood Pressure (mmHg)

DBP: Patient's Diastolic Blood Pressure (mmHg)

HR: Patient's Heart Rate (Beats per minute)

RR: Patient's Respiration Rate (Breaths per minute)

BT: Patient's Body Temperature (Celsius)

Saturation: Patient's Oxygen Saturation

*In the original dataset, patients are coded as 1: Alert 2: Verbal Response 3: Pain Response 4: Unconsciousness. For this analysis, patients will be coded as 0: Not Completely Alert 1: Completely Alert.

**In the original dataset, patients are coded with 0s and 1s, not 1s and 2s as described in the original study. Upon looking at the data, it is apparent that the coding values are: 0: No Pain 1: Pain.

***In the original dataset, patients are coded as 1: Discharge 2: Ward admission 3: ICU admission 4: AMA discharge 5: Transfer 6: Death 7: OP from ED. For this analysis, patients will be coded as 0: Discharge 1: Admission. All other values will be considered missing since we are only interested in admission and discharge dispositions (not including against medical advice, AMA, discharge or ICU admission).

Summary statistics from Table 1 show that, on average, admitted patients were 9.33 years older than patients who were discharged. Notably, admitted patients spent an average of 14,810 more minutes in the emergency department than discharged patients. When taking into account likely outliers in the average, the median number of minutes spent by admitted patients in the emergency department remained 406 minutes higher than among discharged patients, indicating that admitted patients spent more time in the ED than discharged patients before being assigned an admission disposition. Alternatively, SBP, DBP, HR, RR, BT, and saturation values were similar between discharged and admitted patients.

Because this dataset has mostly complete information for all randomly selected medical records of patients that visited these EDs between October 2016 and September 2017, I decided to include 12 other patient characteristics in my analysis to see if some or all of the variables above are ultimately kept in the best-fit model for these data. To do this, I will build a regression model, perform model selection, and interpret the parameter estimates to suggest whether my hypothesis is correct and explain how unit increases in variables such as length of stay and SBP change the odds multiplicatively. However, it would be helpful to include some plots to model relationships of interest before testing my hypothesis.

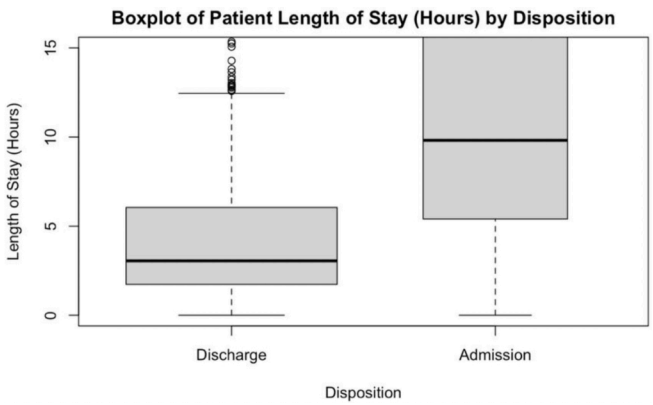
I created a new variable Length of Stay in hours in the dataset to be able to show a boxplot with a reasonable y-axis to compare the length of stay in the

Variable	Total Sample (N=1267)		Discharge (n=797)		Admission (n=373)	
Sex	--		--		--	
Male	661 (52.2%)		401 (50.31%)		205 (54.96%)	
Female	606 (47.8%)		396 (49.69%)		168 (45.04%)	
Age (years)	--		--		--	
Mean	54.52		51.00		60.33	
Median	57.00		52.00		64.00	
SD	19.73		19.72		18.57	
Range	16.00-96.00 (80.00)		16.00-95.00 (79.00)		16.00-96.00 (80.00)	
Injury	Non-injury 1023 (80.7%)	Injury 244 (19.3%)	Non-injury 612 (76.69%)	Injury 185 (23.21%)	Non-injury 335 (89.81%)	Injury 38 (1.02%)
Mental	Not Completely Alert 80 (6.3%)	Completely Alert 1187 (93.7%)	Not Completely Alert 24 (3.01%)	Completely Alert 773 (96.99%)	Not Completely Alert 30 (8.04%)	Completely Alert 343 (91.96%)
Pain	No Pain 553 (43.6%)	Pain 714 (56.4%)	No Pain 304 (38.14%)	Pain 493 (61.86%)	No Pain 200 (53.62%)	Pain 173 (46.38%)
Length of Stay (min)	--		--		--	
Mean	11016.10		7020.34		21831	
Median	274.00		183.00		589.00	
SD	80446.09		65173.58		112958.93	
Range	0.00-709510.00 (709510.00)		0.00-699303.00 (699303.00)		0.00-709510.00 (709510.00)	
Disposition	Discharge 797 (62.9%)	Admission 373 (29.4%)	--		--	
SBP (Missing=25)	--		--		--	
Mean	133.60		136.20		129.83	
Median	130.00		134.00		130.00	
SD	27.28		26.02		27.66	
Range	50.00-275.00 (225.00)		60.00-221.00 (161.00)		70.00-275.00 (205.00)	
DBP (Missing=29)	--		--		--	
Mean	79.78		80.52		78.71	
Median	80.00		80.00		80.00	
SD	15.15		14.19		15.57	
Range	31.00-160.00 (129.00)		36.00-130.00 (94.00)		40.00-154.00 (114.00)	
HR (Missing=20)	--		--		--	
Mean	83.96		83.07		85.63	
Median	82.00		80.00		84.00	
SD	16.64		15.40		18.34	
Range	32.00-148.00 (116.00)		48.00-145.00 (97.00)		32.00-148.00 (116.00)	
RR (Missing=22)	--		--		--	
Mean	19.51		19.22		19.98	
Median	20.00		20.00		20.00	
SD	2.02		1.87		2.04	
Range	14.00-30.00 (16.0)		14.00-30.00 (16.00)		16.00-30.00 (14.00)	
BT (Missing=18)	--		--		--	
Mean	36.58		36.55		36.66	
Median	36.50		36.50		36.50	
SD	0.55		0.50		0.64	
Range	35.00-41.00 (6.00)		35.00-41.00 (6.00)		35.80-39.80 (4.00)	
Saturation (Missing=697)	--		--		--	
Mean	97.02		97.36		96.83	
Median	98.00		98.00		98.00	
SD	4.35		4.95		3.40	
Range	20.00-100.00 (80.00)		20.00-100.00 (80.00)		68.00-100.00 (32.00)	

Table 1. Summary Statistics for Select Patient Characteristics from Total Sample and by Disposition

ED between discharged and admitted patients. I initially created a boxplot for the original variable length of Stay in minutes, however, I was unable to set a range that showed enough of either boxplot for a comparison. The summary statistics for this new variable are listed here:

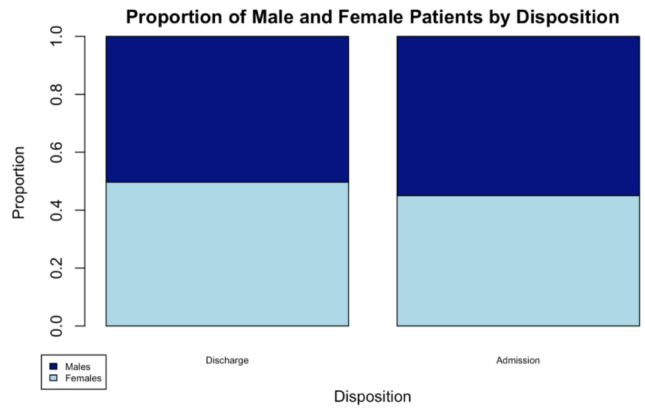
Length of Stay (Hours)	Mean	Median	SD	Range
	183.602	4.57	1340.77	11825.17



Plot 1. Side-by-Side Boxplot of Length of Stay (Hours) by Disposition

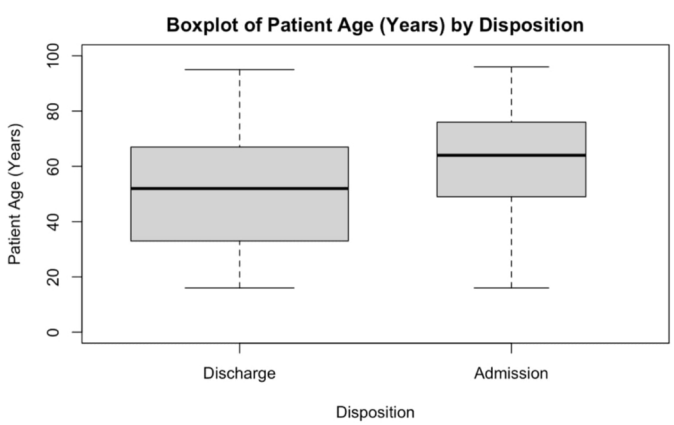
As we can see from the summary statistics for patient length of stay in hours and the plot above, it is difficult to create a side-by-side boxplot for any Length of Stay variable because of the magnitude of the difference in ED visit times between patients who are ultimately discharged and those who are admitted. It is difficult to assess the degree of overlap because the overall visible spread cannot be ascertained from looking at the plot above. Additionally, both boxplots appear to be right-skewed, indicating that substantially longer lengths of stay are more variable than shorter lengths of stay. Although the median number of hours spent by all patients is 4.57 hours, discharged patients are more likely to spend closer to 4.57 hours in the ED because the median number of hours spent in the ED for admitted patients is closer to 10 hours, as seen above. In R, I set *varwidth=TRUE* to show boxplots that are proportional to their respective sample sizes since 62.9% (797 patients) of all patients were discharged and therefore constitute the majority of the disposition data.

Visualizing the relationship between Sex and Disposition can also be helpful, along with the relationship between Age and Disposition, as seen below in Plots 2 and 3, respectively.



Plot 2. Stacked Barplots of Patient Sex by Disposition

The stacked barplots above indicate a relatively even split between male and female patients who were discharged and admitted. It appears that a slightly greater proportion of males than females were admitted, whereas the proportion of male and female patients is about the same. Referencing Table 1, more male than female patients were discharged and admitted. These small differences in proportions suggest that this is likely a result of randomly sampling more males than females (52.2% vs. 47.8%) in the original study.



Plot 3. Side-by-Side Boxplot of Patient Age by Disposition

The side-by-side boxplots above indicate that the median age for admitted patients is greater than the median age for discharged patients. Referencing Table 1, the median age for admitted patients and discharged patients is 64 years and 52 years, respectively. The boxplots also appear to overlap significantly.

Lastly, it is helpful to investigate the relationships between the patient characteristics in Table 1 and the response variable, Disposition. Below, Table 2 presents the results of two sample t-tests and Chi-squared tests to evaluate any potential statistically significant relationships at the $\alpha = 0.05$ level.

Variable	Statistical Test	P-Value
Sex	Chi-squared	0.1383
Age	T-Test	3.482e-14***
Injury	Chi-squared	1.252e-07***
Mental	Chi-squared	0.0001321***
Pain	Chi-squared	6.298e-07***
Length of Stay (Min)	T-Test	0.00473**
Disposition	--	--
SBP	T-Test	0.0001592***
DBP	T-Test	0.03894*
HR	T-Test	0.01335*
RR	T-Test	6.392e-10***
BT	T-Test	0.003663**
Saturation	T-Test	0.1943

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Table 2. Results from T-Tests and Chi-squared Tests on Table 1 Variables

The results of running two-sample t-tests and Chi-squared tests on these patient characteristics suggest that most of the variables from Table 1 are significantly associated with Disposition; however, these tests do not indicate the direction of the association. The strongest associations are seen for Age, Injury, Mental, Pain, SBP, and RR, while moderately strong associations are seen for Length of Stay (Min) and BT and marginally strong associations are seen for DBP, and HR. Sex and Saturation were not found to be significantly associated with Disposition. Therefore, my analysis will include each of the variables above in a binary logistic regression model after identifying the model of best fit by evaluating each model using backward, forward, and stepwise selection. I will also include an interaction term between SBP and Age, as evidence from scientific literature suggests the burden of hypertension increases with age[11].

IV. Analysis and Results

A. Model Selection

To select the best subset of variables for modeling whether a patient's disposition is associated with their length of stay in the emergency department, backward, forward, and stepwise selection methods will be carried out to determine if they each produce the same model with the same variables and same AIC score, or if one selection method produces a more efficacious model with different variables and a lower AIC score relative to the others.

After running each of the model selection methods, it was found that each method produced similar models with the same AIC of 375.8. However, the forward and stepwise regression models dropped BT, RR, and Saturation from the model. Since the backward elimination model is generally preferred, we can choose to rely on the following binary logistic model it produces below, which keeps all of the original variables that it was given:

$$\underset{logit}{p}(p) = \log\left(\frac{p}{1-p}\right) = -8.302 + 0.7798_{Sex1} - 1.046_{Injury1} + 0.000002014_{Length\ of\ stay_min} - 0.04145_{Age} - 0.07233_{SBP} + 0.03758_{DBP} + 0.01263_{HR} + 0.06349_{RR} + 0.3847_{BT} - 0.04920_{Saturation} + 0.0006441_{Age*SBP}$$

Interpreting this model at baseline without taking into consideration any values for the parameters in our model, we are able to conclude that when a patient's sex is *female* and the patient is presenting to the emergency department *without an injury*, the odds of a patient being admitted to the hospital are exp(-8.302) = 0.0002480202902 times the odds of being discharged. In its current form, this odds ratio suggests that being an uninjured female that presents to the ED confers a protective effect, which in this case means that an uninjured female is more likely to be discharged than admitted since admission to the emergency department was defined as a success in our model. Alternatively, this odds ratio can be inversed and interpreted as 1/0.0002480202902 = 4031.928192. An interpretation with this odds ratio allows us to conclude the inverse of our initial interpretation, which in this case would be that when a patient's sex is *female* and the patient is presenting to the emergency department *without an injury*, the odds of a patient being discharged from the hospital are 4031.928192 times the odds of being admitted to the hospital. While the actual meaning of the odds ratio stays the same, there may be a preferred way of interpreting the result.

We can further interpret this model by examining the β coefficients for each variable in the model. For example, we can suggest that when a patient's sex is *male*, the odds of a patient being admitted to the hospital are exp(0.7798) = 2.181036015 times the odds of being discharged compared to when a patient's sex is *female*, holding Injury, Length of Stay (Min), Age, SBP, DBP, HR, RR, BT, Saturation, and Age*SBP constant. We can follow suit with this style of interpretation to suggest the following about the other variables in our model:

For Injury

When a patient presents to the emergency department with an injury, the odds of a patient being admitted to the hospital are exp(-1.046) = 0.3513403033 times the odds of being discharged compared to when a patient presents to the emergency department without an injury, holding all other variables in the model constant.

For Length of Stay (Min)

For each 1 minute increase in the length of time spent in the emergency department, the odds of being admitted to the hospital compared to being discharged change multiplicatively by exp(0.000002014) = 1.000002014, holding all other variables in the model constant.

For Age

For each year added to a patient's age, the odds of being admitted to the hospital compared to being discharged change multiplicatively by exp(-0.04145) = 0.959397304, holding all other variables in the model constant.

For SBP

For each 1 mmHg increase in a patient's systolic blood pressure, the odds of being admitted to the hospital compared to being discharged change multiplicatively by exp(-0.07233)= 0.9302238713, holding all other variables in the model constant.

For DBP

For each 1 mmHg increase in a patient's diastolic blood pressure, the odds of being admitted to the hospital compared to being discharged change multiplicatively by exp(0.03758) = 1.038295057, holding all other variables in the model constant.

For HR

For each 1 beat per minute increase in a patient's heart rate, the odds of being admitted to the hospital compared to being discharged change multiplicatively by exp(0.01263) = 1.012710095, holding all other variables in the model constant.

For RR

For each 1 breath per minute increase in a patient's breathing rate, the odds of being admitted to the hospital compared to being discharged change multiplicatively by exp(0.06349) = 1.06554883, holding all other variables in the model constant.

For BT

For each 1 degree Celsius increase in a patient's body temperature, the odds of being admitted to the hospital compared to being discharged change multiplicatively by exp(0.3847) = 1.469173503, holding all other variables in the model constant.

For Saturation

For each 1 percent increase in a patient's oxygen saturation, the odds of being admitted to the hospital compared to being discharged change multiplicatively by exp(0.04920) = 0.9519907125, holding all other variables in the model constant.

For Age*SBP

We are interested in knowing whether the interaction model gives a better fit than the simpler model lacking the interaction term. To do this, we can run a partial Chi-squared test and evaluate the corresponding p-value for significance. We get a p-value of 0.09133, which is not less than $\alpha = 0.05$, so this interaction term is not statistically significant. As a result, we do not have enough evidence to justify including this interaction term in our model, despite the knowledge that SBP generally increases with age, so we can remove this term from our model and ultimately get:

$$logit(p) = \log\left(\frac{p}{1-p}\right) = -8.302 + 0.7798_{Sex1} - 1.046_{Injury1} + 0.000002014_{Lengthofstay_min} - 0.04145_{Age} - 0.07233_{SBP} + 0.03758_{DBP} + 0.01263_{HR} + 0.06349_{RR} + 0.3847_{BT} - 0.04920_{Saturation}$$

Table 3 presents the parameter estimates and their associated p-values, for reference. We can also look at the confidence interval of the parameter estimate and see if it includes 0 to determine if the estimate is statistically significant. Statistically significant estimates have CIs that do not include 0.

Parameter	Estimate	95% Confidence Interval	P-value
Intercept	-8.302	(-39.1092055795934, 23.3795203803425)	0.60067
Sex1	0.7798**	(0.2454191275058, 1.3317187466473)	0.00480**
Injury1	-1.046**	(-1.7212877241186, -0.4129998362923)	0.00164**
Length of stay_min	0.000002014	(-0.0000005477554, 0.0000047617527)	0.12816
Age	-0.04145	(-0.1345877215136, 0.0487307771982)	0.37193
SBP	-0.07233*	(-0.1313251155084, -0.0167556778377)	0.01290*
DBP	0.03758.	(-0.0017793494598, 0.0784985004017)	0.06554.
HR	0.01263	(-0.0069943560137, 0.0325393788217)	0.20887
RR	0.06439	(-0.2335669097985, 0.3638861923722)	0.67066
BT	0.3847	(-0.3223740737783, 1.1066581106944)	0.28780
Saturation	-0.04920	(-0.2277111633292, 0.0995907051994)	0.55841

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Table 3. Parameter estimates and their associated p-values from the resulting logistic regression model

B. Evaluating the Initial Hypothesis

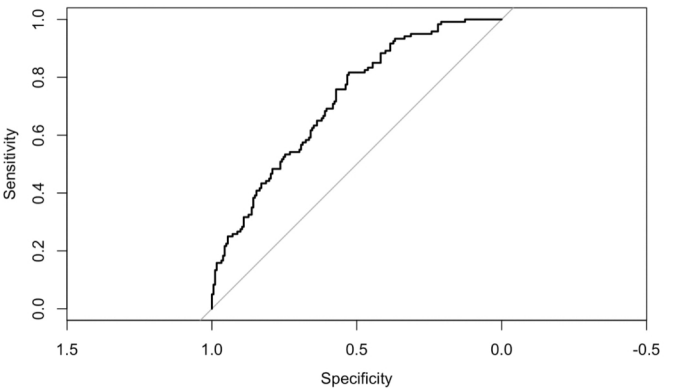
I initially hypothesized that a patient's length of stay in the emergency department is significantly

associated with inpatient admission, and that the longer the length of a patient's stay in the emergency department, the more likely the patient is to be admitted to the hospital. Preliminary analyses involving two-sample t-tests suggested that a patient's length of stay in the ED is associated with a patient's disposition. However, these tests did not suggest a direction of association, and this analysis was done before identifying a logistic regression model that would take all of the variables of interest into account. Now that we have a model that includes a patient's length of stay in the ED in conjunction with other variables, we can test the hypothesis that the length of stay has an effect on a patient's disposition and, more specifically, higher odds of admission with increased time spent by using a normal approximation (Wald) test. Here, we look at the p-value associated with our variable of interest and see if it is statistically significant. Observing a p-value of 0.12816 > 0.05, we have insufficient evidence to suggest that a patient's length of stay in the ED is significantly associated with a patient's disposition once including this variable in a multivariate analysis.

However, it is worthwhile to see if a patient's length of stay in the ED is significantly associated with their disposition in a more naïve model or one that only includes this variable. Constructing this model, we get a p-value of 0.263803, which is even greater than the p-value we observed for a patient's length of stay in the ED when it was included in a multivariate analysis. We can conclude that although a preliminary analysis suggested that length of stay in the ED may be significantly associated with disposition, these results suggest otherwise. Ultimately, we did not find sufficient evidence to support our original hypothesis that longer lengths of stay in the ED are associated with greater odds of inpatient admission. This conclusion is further supported by the odds ratio of 1.000002014, which is close to the null value of 1. We found this from our multivariate model for each additional 1 minute increase in the length of time spent in the emergency department.

C. Evaluating Model Fit

We can visualize the trade-off between our model's sensitivity and specificity by plotting an ROC curve.



Plot 4. ROC Curve of Resulting Model

At first glance, the ROC curve above suggests that this model does not predict patient disposition well because the curve is not subjectively close to the top left-hand corner of the graph. Calculating an AUC score of 0.7191, we can say that this model is marginally acceptable and slightly better than what is considered the high end of a poor AUC score, which is considered to be between 0.5 and 0.7. Generally speaking, a model with an AUC between 0.7 and 0.8 is acceptable, between 0.8 and 0.9 is excellent, and greater than 0.9 is outstanding. Our initial assumption of the curve is supported by its AUC of 0.7191.

V. Discussion and Conclusion

Broadly, the goal of this investigation was to ascertain which patient characteristics, out of a pool of selected variables for a multivariate model, are associated with a patient's disposition from a sample of randomly selected medical records from patients presenting at two South Korean emergency departments from October 2016 through September 2017. I initially hypothesized that the length of time spent in the ED would be most strongly associated with a patient's disposition; alternatively, this variable was not found to be significantly associated with a patient's disposition in either the naïve or the multivariate model. As a result, I could not find sufficient evidence to suggest that longer times spent in the ED are significantly associated with inpatient admission. Although preliminary analyses suggested early dependencies between select patient characteristics and a patient's disposition, including length of time spent in the ED, model selection of a logistic regression model and the corresponding AUC score of its ROC curve showed that only Sex1, Injury1, and SBP are significantly associated with Disposition in the multivariate model.

Throughout this analysis, model selection proved to be somewhat challenging. Initially, I intended to include every variable from Table 1. However, I ran

into trouble when I tried using backward elimination for my model selection because my original *triage* dataset had observations with missing values for at least one of the variables I intended to include in the multivariate analysis. I discovered that I needed to use *na.omit* on the *triage* dataset, so I created a new dataset, *triage2*, to only include non-missing observations. R did not approve of missingness in my dataset, so I used *triage2* going forward. Following through with model selection, R returned another error that suggested I remove variables with only 1 unique value. After removing missing observations from *triage*, the variables Mental and Pain in *triage2* were left with only 1 unique value of 1, indicating that any patients that were coded as Not Completely Alert (0) for Mental and No Pain (0) for Pain were excluded from the new dataset because these patients' records had missingness that prevented them from being included. As a result, Mental and Pain were excluded in the multivariate model.

Overall, the results of this analysis carry relevant implications for research in the field of emergency medicine and providers in the emergency department. They suggest that there are many patient characteristics that ED providers need to consider through the course of their clinical care of ED patients. These characteristics may prove helpful in ascertaining a diagnosis for the patient, but they may also make a disposition decision more complicated, especially if the patient has unique risk factors. This analysis sought to determine if there are any particular patient characteristics that can be taken into account early on to help providers think about a disposition from the beginning of care. Each patient presents to the ED with a unique history, and hoping to predict a patient's disposition based on several factors alone is farfetched. Although only a few of the predictors in the model proved to be significantly associated with a patient's disposition, this model explained which characteristics are least associated with a patient's disposition. These findings can help providers narrow their list of considerations and allow them to prioritize characteristics that are somewhat likely to be associated with a patient's disposition.

The limitations of the results of this analysis are related to the method of data collection for the original dataset that was adapted for this investigation. The results of this analysis can only be generalized to the South Korean medical environment and, further, the standard and status of emergency care in South Korea. Although *triage* had a good sample size of N=1267 observations, the *triage2* dataset used for model selection had just 302 complete, non-missing observations. Additionally, medical records were sampled from a relatively short time period and only from urban academic medical centers, leaving out insight that might have been gained from patients visiting rural EDs. Regarding this analysis, a shortcoming is the inability to include the Mental and Pain variables due to missingness. Future research should seek to sample records from a more representative sample of EDs over a longer period of time.

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About the Author

A University of Rochester graduate, Alan Ardelean pursued a Bachelor of Arts in Epidemiology and Minor in Statistics through the HEAL program. As a undergraduate, Alan discovered his passion for emergency medicine research through the Emergency Department Research Associate program, through which he invited patients at the Strong Memorial Hospital ED to participate in novel local and multi-site clinical studies. Alan's clinical research experience in the ED encouraged him to pursue research in emergency medicine, and his STAT218 class supported his interest to do just that. Alan's advice to undergraduates interested in research is to take advantage of in-class research projects to explore personal interests and to ask questions, apply for research opportunities (even if they seem out of reach), and be persistent!

Knowledge: A Fringe Definition and Its Implications For the Unity of Science

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Part I: How we Understand "Knowledge"

"Knowledge" is commonly defined as person-held, evidence-supported beliefs or ideas that are of a propositional nature. It is acceptable to refer to yourself as having "knowledge" of the date of your mother's birth. This piece of information can be laid out and communicated by you as a factual proposition. If your mother really was born on that day and is generally regarded to have been born on that day, and you believe it to be so, you can be said to have knowledge of your mother's birthdate. Most will agree with this. Most will not agree with the notion that bacteria are capable of possessing "knowledge." The bacterium/its DNA does not really "know" how to construct the requisite proteins that allow it to survive within its environment; this just happens automatically via unconscious physical/biological processes. According to the common definition, "knowledge" must pertain to mental objects of a conscious propositional nature, so we cannot regard the bacterium or its DNA as possessing knowledge.

However, defining "knowledge" in this way is not without its difficulties. Consciousness, mental processing, and neural networks exist along a continuum, and it is difficult to determine a line of demarcation to separate knowledge from mere physical/biological phenomena that non-randomly produce advantageous outcomes. Reflecting upon it, we often drop the "propositional" part of our definition of knowledge. We routinely acknowledge the existence of practical or procedural knowledge in the way we speak. It is perfectly acceptable to say "I know how to speak English" or "I know how to play piano" despite knowledge of how to do these things being largely non-propositional and unconscious. Similarly, we do not regard knowledge as being an exclusively human phenomenon. It seems acceptable to regard the chimpanzee as "knowing" which one of his group-mates took his banana, or the dog as "knowing" where she buried her bone, or perhaps even the bird as "knowing" which direction is southward. We might start to feel uneasy when considering "knowledge" that lizards, fish, bugs, and worms might possess. But why? Can we articulate a reason? Or have we just reached the boundary of our loose heuristical conception of knowledge? Why shouldn't we regard comb-jellies, with their small primitive nervous systems, as capable of "knowing" what direction is 'away from pain?' Is it because they don't have a concept of pain? What is a 'concept' of pain? What if the reflexive capacity to move away from pain represents the rudiments of a 'concept' of pain?

Consider the slime mold Physarum polycephalum: It consists of a colony of unicellular organisms and doesn't even have a nervous system, yet by forming networks of interconnected vein-like tubes that transport signaling molecules, they are able to engage in an amazing feat of communication and coordination – navigating forests (and artificial mazes) optimally in order to locate and locomote to food sources (Boussard et al. 2021). Why shouldn't we regard the slime mold as "knowing" the layout of the forest or maze? Why shouldn't we regard it as "knowing" the optimal path to get to food? Perhaps we can argue that it is because the slime mold is not conscious, but given how little we understand about what consciousness is and what can possess it, that shouldn't be a viable option.

Alternatively, we can go forward with arguing that knowledge must be "of a propositional nature." However, that would require us to argue that, while knowing and being able to state your mother's birthday constitutes knowledge, the pianist's "knowledge" of how to play the etude and the dog's "knowledge" of where the bone is buried does not constitute knowledge. Neither is impossible to propositionalize; one could propositionalize these (and just about anything) so long as one possesses a sufficiently expressive language and isn't limited in how long a series of propositions can be. The reasons that the pianist and the dog are not able to propositionalize their information are (respectively): how to play the etude is a task largely relegated to regions of the pianist's brain that his communicating-self cannot access; the dog lacks the linguistic capacity to state the location of her bone in propositional form (though she might able be to communicate this information by leading her owner to the location of the bone). In other words, we will have to argue that knowledge is, at least partially, defined in terms of the ability of whoever/

whatever possesses the information in question to propositionalize and communicate this information.

While communicating information propositionally is extremely powerful – while also happening to be something humans have a virtual monopoly on – the question of what constitutes a proposition and the sheer diversity in forms of precise communication that exist suggest that a line of demarcation for knowledge on this basis might be arbitrary. Why must knowledge be propositional? If the bee can perform a waggle dance to communicate to its hive mates information regarding the specific location of a food source it has found, why should we not regard the bee as having knowledge? It seems we could just as easily contend that in order for something to be knowledge, whoever/whatever possesses the information in question must be able to perform a waggle-type dance to communicate that information. Also, why fixate on communication? Communication is ultimately an adaptation that evolved because it benefited the fitness of the individual that was able to communicate. Given that the ability to communicate is secondary to the fitness benefit that such an ability confers, why is it not knowledge when an individual organism successfully utilizes information that it possesses (but can't communicate) to benefit its own fitness? Questions like these should illustrate how narrow and arbitrary 'can be communicated as a proposition' is as a line of demarcation for knowledge. Viewing things from the perspective of "Information" can also further illustrate the arbitrariness of such a line.

Brief aside: "Information" can be defined as the amount of non-randomness in a system; how much "interesting" stuff a system contains; how much language would have to be used to describe all that is "interesting" in that system. Random clumps of matter are relatively low in information and high in entropy, while things like DNA, brains, and computers are relatively high in information and low in entropy. "Information" has a rigorous technical definition developed by mathematicians such as Claude Shannon (Shannon 1949). Here, I will use a non-rigorous definition that roughly corresponds to the colloquial use of "information," but with elements of the technical definition in mind.

From an information perspective, the same essential phenomenon characterizes the man playing the Chopin etude, the dog locating its hidden bone, and you communicating your mother's birthday as a verbal proposition — all involve information being stored in the brain (human or dog), then accessed and utilized to produce some non-random action. All have a physiological manifestation as a pattern of activation of a network of neurons. In each case, the information, including your mother's birthdate, no matter how it is abstractly represented in the mind, is stored in a particular pattern/network which gets turned into a behavior due to its integration with numerous other patterns/networks. From the perspective of information, all are astonishingly impressive feats of information processing, and the differences between them are either superficial or a matter of degree. Translating information regarding when your mother was born into a proposition and communicating it is just another use of information by the brain to create a non-random action. We may view the ability to communicate information as propositions as exceptionally complex and innovative, biologically speaking. We may also find that it differs from the ability to play the piano and the dog's ability to remember where the bone is buried in terms of the powers it confers over 'nature.' But one can just as easily construe this as a difference in degree of complexity, and the extent of integration with other information, rather than any hard categorical difference. For this reason, we should be cautious when using 'the-ability-to-communicate-as-a-proposition' as a line of demarcation for knowledge.

Part II: A Fringe Definition of "Knowledge"

It may be fruitful, now, to consider a definition of "knowledge" that is more deeply grounded in the regularities of nature, and less subject to arbitrariness and ego-centricism (though it may force us to expand the sphere of what constitutes "knowledge"). A brilliant and divergent way of conceiving of knowledge comes from physicist-philosopher David Deutsch, who more clearly identifies what is essential (and exceptional) about those things that we agree qualify as "knowledge." I paraphrase Deutsch's definition of "knowledge" as the following:

Knowledge: a concentration of reality's regularity captured in some physical structure as information that can be accessed and utilized by lifeforms, enabling them to persist non-randomly in the hostile entropic mess that is the universe (Deutsch 1997).

So, according to this definition there are three characteristics that something must have in order to be considered knowledge.

1. Captures reality's regularity in physical structure as information

2. Accessible and usable by living things

3. Can aid in living things' non-random persistence in the universe

To understand this definition, let us consider your knowledge of your mother's birthday. As previously discussed, this knowledge is information stored as a physical structure – a pattern of activation of a network of neurons in your brain. This information is accessible and usable by you; its integration with the rest of your brain allows you to consider this information when deciding whether it is time to buy mom a gift or communicate to your sister that your mom's birthday is coming up. This information allows you to interact non-randomly with the world in such a way that benefits you; it allows you to say happy birthday and give gifts to your mom on the right day of the year, promoting good relations between you and her, which may increase her willingness to lend you emotional support and assistance with child rearing, all of which is advantageous to your fitness. It goes without saying that there is much more to a mother's relationship with her adult children than is captured by this evolutionarily reductive example, but the dynamic is nonetheless at play. The reason that the information regarding your mom's birthdate advantages you in the world, and the reason you are able to receive this relationship boost with your mother at a non-random rate of success (and this is important), is that this information actually captures some regularity in reality. Not necessarily regularity regarding the age of your mother or when she was born (that would only matter if you wanted to take a time machine back to go witness your mother's birth and needed to punch in the right numbers) but regularity regarding certain aspects of your mother's and others' brain structures – those that determine an agreed upon understanding of when your mother was born. It's this capturing of reality's regularity in your own brain that can be called "knowledge."

I would like to take a moment to emphasize an indispensable aspect of this definition of knowledge: What makes knowledge useful, and what makes it so that it can allow life, complexity, and information to exist in a hostile entropic universe, is that the structure of whatever bears the knowledge reflects or captures some regularity that exists as part of a transcendent reality, which most take for granted as existing. With knowledge in its possession, allowing it to direct its action in a non-random manner, a living thing can then exploit the regularities of the world, which corresponds with the captured regularity that is its knowledge. This feature of knowledge is what defines its power and significance, providing an argument for its presence at every level of complexity.

Now, to revisit the notion that bacteria are incapable of possessing "knowledge," if we accept the Deutsch definition of knowledge, then the bacterium certainly possesses knowledge. Bacteriums' knowledge is not stored as a pattern of activation of a network of neurons, because it does not have neurons. All its knowledge is stored in its DNA. This information-dense molecule is the physical structure that bears the knowledge of how to construct proteins that constitute an organism optimally designed to live in a specific environment. The DNA is accessible and utilizable by the transcription apparatus inside the bacteria, which transcribes and translates the DNA sequences into proteins.The proteins then act together to form a bacterium capable of acquiring and processing resources, protecting itself from threats in the outside environment, regulating its own inner environment, and propagating copies of the DNA. These systems overcome the entropy and hostility of the bacterium's environment and enable the bacterium to act with non-random success. These systems exploit certain regularities in the environment and it is by their very structures that they do so. Thus, these structures capture regularities in the environment and constitute knowledge. And since the information for how to construct these structures are encoded in DNA, it captures this regularity and constitutes knowledge. It is through evolution that these structures and the sequences of DNA that code for them have come to capture the regularities of the environment. Evolution can be thought of as the process by which knowledge comes to be, and knowledge as the fundamental key to life.

Philosophers might balk at the above notion (in no small part simply for the way it sounds), but by reserving the term "knowledge" for our own conceptual, propositional realm, we deprive ourselves the opportunity to grasp a fundamental pattern that manifests itself across the full continuum of complexity, a continuum to which we belong. Lifeforms of all different complexities are nodes of information that capture and concentrate reality's regularities in their physical structure. Let us think of knowledge as that which allows life to interact with and navigate reality with non-random success, whatever corner of reality life finds itself in; let us think of it as that which enables the adaptation to and persistence in a hostile, entropic world. Doing this helps us see that humans are not exceptional because of the belief that we supposedly do something different from what the rest of life does; we are exceptional because we do the same thing that the rest of life does to such an extreme extent. We pursue and acquire knowledge with such elaborateness, flexibility, and rapidity that it may represent a true biological innovation. Though we are not the sole bearers of knowledge and com-

plexity, as far as we can tell, we are its pinnacle bearers.

Part III: What are "Models"?

I now wish to consider the term "model," define it, and explain how it fits into Deutsch's conception of "knowledge." "Model," in its most concrete sense, refers to man-made physical structures that represent something that actually exists (or can exist) in reality. Common examples include scale versions of construction or engineering projects that convey visual appearance or proof of concept. A model usually bears resemblances to the actual thing it represents, capturing relevant essential features while also making certain simplifications or idealizations. They are often used for educational purposes to help us visualize something when it is difficult or expensive to construct that thing in reality.

Out of this concrete physical "model" comes the idea of a theoretical model. A theoretical model uses the physical "model" as its defining metaphor. The theoretical model, rather than being constructed in some physically presentable fashion, is constructed abstractly in the mind using logical, mathematical, theoretical, and conceptual objects. These types of models, like the physical models, are meant to resemble or approximate aspects of reality. They are abstract so that they can be generalizable to specific situations and commonly involve some degree of simplification or idealization. They serve as tools to help us make sense of and predict things, and perhaps even give us a glimpse into the nature of reality. Constructing and developing theoretical models is an essential aspect of science, perhaps the point of the whole endeavor.

Another understood (but slightly less common) use of the term "model" is in the context of cognitive science. "Mental models" share many common elements with physical models and theoretical models. They are constructions of the mind that represent things in reality, helping us perceive, think about, and behave adaptively in the world. Mental models are constantly in action, whether consciously or not, in all types of tasks that we engage in. When we are manipulating objects in space, we are referencing our implicit mental models for how objects like those behave in various situations. When we interact with our fellow humans, we unconsciously reference mental models for how fellow humans act and think in order to interpret and predict their behavior. Mental models are often more sophisticated than we are able to articulate. They are what underlie our intuitions.

There is much in common between each of these uses for the word "model." In defining knowledge, we referred to the physical informational "structures" that capture reality's regularity. I will define "model" as referring to these structures. I believe this is reasonable because in the three original definitions of "model," models refer to something that captures aspects of reality's regularity for the benefit of our understanding (which contributes to our non-random success in navigating the world). I will assume, for the examples of each of the original three definitions of "model" above, that physical, theoretical, and mental structures all ultimately have some physical basis that defines what regularity they capture and knowledge they bare. Some might take issue with this, but barring some platonic realm of thought, scientific theories ultimately exist as structures in the brains of those who understand them, the computers that run them in their mathematical form, and the networks of clever people whose collective understanding defines the "model." To reiterate, a "model" is an actual physical thing that contains a concentration of information, that captures reality's regularity in its structure, and can be accessed and utilized to act non-randomly in the world. Models are where knowledge lives.

In defining a "model" in terms of the definition of "knowledge," it follows that the most basic information-dense structures of life (like DNA) are models of the regularities that exist in the environments of the organisms that possess these structures. In order for the organism to effectively survive in its environment, to react non-randomly with it, its physical form must be such that it exploits certain regularities in the environment. Insofar as the particular structure of an organism exploits these regularities, it can be said that the organism "captures" regularity out in the environment. Insofar as DNA is knowledge of how to create structures of particular forms, it too can be said to capture that regularity of the environment. System theorists Conant & Ashby are responsible for a theorem showing that "Every good regulator of a system must contain a model of that system" (Conant & Ashby 1970). This theorem plays nicely with my point: Every living organism can be thought of as a regulator of a system; a system containing all the environmental factors which the living organism comes into contact with; factors that must be kept at bay, exploited, or controlled such that the homeostasis of a mini environment (the body) within the greater environment can be maintained and the organism's DNA can be allowed to persist and propagate. In order for the organism to successfully regulate the system in the particular way that is beneficial to its survival, it must have access to some model bearing the relevant knowledge of the system. In the case of simple life, such as single

cell organisms, the organism itself (by virtue of its very structure) and the DNA (by virtue of its relationship to the organism) are models that capture knowledge about the environment. Only those organisms that bear the proper knowledge will be able to regulate their system such that they persist inside of it. Those that do not bear such knowledge will fail at this and will be overcome by entropy, while those that manage this successfully will come to capture the regularities of their environments. They will possess knowledge pertaining to the factors of consequence to their survival that they interact with, and can thus be considered models of those aspects of the environment, but not necessarily the ecosystem at large.

The neurological systems that govern behavior and cognition are just another much more complex and interesting adaptive feature that contribute to an organism's ability to regulate its environment and preserve and propagate its DNA. Thus, this feature also involves use of models. The cognitive science concept of a "mental model" roughly corresponds with this feature, though I believe any non-human creature with a brain or nervous system that is capable of learning should also be thought to make use of mental models. The physical basis for these models are networks of neurons rather than sequences of DNA. Brains and neural networks are more dynamic and flexible than DNA, and can acquire knowledge much more rapidly. Brain/neural models are shaped, altered, and allowed to die based on direct feedback from the environment. Good outcomes will reinforce the model; bad outcomes will allow the model to degrade and die. This pseudo natural-selection/evolutionary process can happen within an individual organism's lifetime. Genetic evolution, on the other hand, unfolds over a much longer timescale as genetic alterations occur at random, are mostly unhelpful, and the shaping of traits by selection occurs over many generations. Nervous systems and brains represent an extremely powerful ability – being able to produce rapid knowledge-containing models that an organism can utilize in response to novelty and changes in the environment. This is why such systems evolved. Creatures with large, sophisticated nervous systems/brains acquire knowledge more rapidly because they are more dynamic and flexible in a changing, hostile world.

Models made out of brain matter/neural networks come to bear knowledge as after generating them, we apply them as we interact with and navigate the world. We experience the outcome of using those models to predict and perceive, and depending on what the outcome is like, the model will be reinforced or allowed to degrade. Models also undergo an alteration and integration with other models over time and in response to new situations. This capacity to unconsciously construct, develop, and refine these neural/brain models in response to novel situations we encounter (also known as learning) is something we share with other highly intelligent creatures such as great apes, corvids, and octopi. An example of this would be a child learning how to use wooden blocks to build a standing structure, or learning how to solve a shape-fitting puzzle. The rules regarding the "human-scale" physics that determine how these objects behave in various situations are eventually understood after many encounters with these objects in these various situations. As a toddler plays around with the blocks, she develops an implicit mental model for how they work. Unbeknownst to her, she is constantly testing this model with many instances of trial and error. Think of the trope of a toddler trying to fit the square peg into the round hole. She eventually comes to understand the physical characteristics of these objects, including behaviors regarding the normal capabilities of the objects. Understanding represents the successful development and refinement of a model. The model allows the girl to produce approximate, but useful, predictions. After the model is acquired and used regularly, it will recede into the realm of effortless intuition until she encounters a situation that violates a prediction made by the model. Perhaps in high school physics class she sees, in a seeming feat of magic, a spinning bicycle wheel dangling by a rope attached to its center yet staying perpendicular to the ground, in which case the model is undermined, demanding revision or replacement.

Part IV: "Models" in Science

It is interesting to consider the ways in which this unconscious building of intuitional models (which help us make sense of our environment) actually resembles certain steps of the scientific method. The generation of models made out of networks of neurons is analogous to the creative formulation of scientific theories. The use of these cognitive models as a kind of perceptual, predictive software that influences our actions and behavior is analogous to the derivation of testable predictions or hypotheses from these scientific theories. The reinforcement of models that work, their integration with other networks that model other things, and degradation of those that do not work, is analogous to accepting scientific models based on experimental results and their integration into broader scientific models, or their nullification and discarding. The invention of science as a tool/process represents an act of deep introspection. It

amounts to making explicit our implicit process for generating cognitive models, and making formal our informal 'empirical' proclivities. This process of "create, test, observe" has existed since the most primitive means of knowledge acquisition. For most of its existence, it has been engaged in by its practitioners without any conscious awareness of the process. Furthermore, it has only ever been directed towards objects and phenomena that exist tangibly in a creature's immediate environment. However, thanks to humans' astonishing cognitive and linguistic capacities, people were able to invent science; people were able to abstract the general algorithm from behind the implicit modeling of these empirically observable phenomena and formalize/standardize these processes, making them explicit and able to be communicated. This vastly increased the integration between people's formerly private journeys of knowledge acquisition, allowing for the greater social system to take part in a collective journey (but not too collective). This process, with grounding in math and logic (the axioms of which seem to be similarly derived from simple regularities that we can apprehend just by playing with wooden blocks) as well as social norms and institutions that "incentivise" adherence to the process, brought a greater deal of precision and rigor to bear on the human modeling of reality and acquisition of knowledge. With this species-wide collaboration and increase in the sharing of ideas, the process has vastly augmented our modeling and knowledge acquisition ability, along with our ability to adapt to and dominate novel environments. Prior to science, humans had already proliferated across most types of terrestrial environments on the planet and established some degree of regulatory dominion over these processes. With science, we can now thrive on virtually every surface of the Earth, as well as underground, underwater, and in the upper atmosphere; the great expansion of the scope and domain of what we can model has made for a great expansion in the places we can travel to and survive in. The tools of science, by allowing us to perceive the unimaginably big and the unimaginably small, lead to a better and wider array of models which give us an unparalleled ability to understand and exploit reality's regularities and survive in the universe. It is from the knowledge captured by these models that we have figured out how to build better insulated buildings to keep us alive in the cold, bunkers to keep us alive under 30 feet of dirt, submarines to keep us alive underwater, and space stations to keep us alive in the stratosphere. This is not to mention everything else that these models have allowed us to build (i.e., communications devices, computers, biomedical technology, and bioengineering). Insofar as life is all about building models to acquire knowledge, and science represents life's current maxima of the capacity to achieve that end, and humans are its only users, we can admit that there are some respects in which humans excel beyond all other forms of life.

DNA, nervous systems/brains, cognitive replicas, and scientific theories are all models. The scientific method is also a model given that it is a cognitive/mental model regarding a process for how to successfully acquire knowledge about reality. It tells us how to go about modeling so as to capture regularity in the world; essentially, by formulating standardized abstract models that can be communicated explicitly, shared and accessed by a greater social system, and then subjecting those models to a pseudo-evolutionary process to determine which ones yield the greatest powers to navigate reality, which should reveal which models capture the most of reality's regularity. The scientific method is also like other models in that it too has a physical basis in the world. It exists as neural structures in the minds of individual people who grasp its theories, as well as the web of interconnected minds that make up the scientific community. Science, as a model that captures regularity about how to generate models, has been very successful – so perhaps the scientific method itself captures some of reality's regularity, and bears its own sort of knowledge.

However, there is the possibility that better models for how to model can be created. And even if science is the best model for how to model, this does not mean that having a model for how to model (the scientific method) is sufficient to allow humanity to survive and thrive for all of time. Perhaps there are other more fundamental/essential structures that science must be embedded in. As prevalent as science and its fruits are, most, if not all, of sense-making in nature and among humans is still handled by implicit mental/cognitive modeling; our sense of ethics (though it may be informed by science) seems largely relegated to implicit models employed by our intuition.

I began this section by talking about how DNA can be thought of as a model of the organism and environment in which it lives, given the knowledge that it embodies. Now I wish to briefly mention larger scale systems like webs of interacting individuals/communicating minds as viable knowledge bearers, perhaps possessing a much greater capacity for knowledge than individual organisms. The ant colony, the beehive, the wolf pack, the chimpanzee troop, human societies, markets, and civilizations can all be thought of as modeling certain aspects of reality which they inhabit. A human

society may capture knowledge of how to create and distribute manufactured products like pencils, for instance, but that does not necessarily mean that individuals in that society capture this knowledge; it is captured by a delicate network of people and their interrelations in a market (Read 1958). We can perhaps draw an analogy here: an individual neuron captures knowledge of how to be a neuron; it does not capture knowledge of how to be a structure that can recognize your mom's face; that takes a network of neurons. An individual person's brain might capture an immense amount of knowledge (by human standards), but they do not capture the knowledge of how to be the immensely successful online retail and technology company Amazon. That would require a more complicated structure – a network of people working on different things, communicating, coordinating, with the sum total of decisions that far exceed what one person can handle.

Part V: Natural "Kinds"

Reality, in addition to having an aspect of generality (common patterns, relationships, regularities), can also be thought of as having an aspect of particularness. This can be thought of as the tangible stuff that we come into contact with; whatever medium that "the general" lives inside, or manifests itself through; whatever is front and center that we (as particular creatures) live amongst and are always in contact with; the aspect of reality which we touch. Our major problem, as model generating creatures, is that there is so much particularity that we simply do not have the cognitive resources to apprehend all the information, nor knowledge, that can be perceived or extracted from the particular. This is why we seek the general: to capture the common regularities that live inside the particular that we face, in order to construct models that we can then use to exploit and navigate the world of the particular. It is generalizable regularity (which is just knowledge) that allows us to navigate the particular without having to take in the entire incomprehensible cacophony of particularity that reality presents us with. Apprehension of "kinds" is one of the simplest and most fundamental ways that we arrive at generalizable abstracted regularities.

A "kind" might have a similar meaning to words such as 'schema,' 'category,' 'class,' 'type,' or 'form.' Philosopher Richard Boyd refers to "kind" as the regularity that actually exists "'out there'" amongst the set of properties shared by a set of things (which he calls Homeostatic Property Clusters) (Boyd 1999). I will draw on Boyd's work and define a "kind" as the regularity (reflective of reality's regularity) captured by cognitive models that abstract away particularity and extrapolate out commonality from a set of perceived or theoretically understood objects that bear some similarities to each other. "Kinds" save us time, energy, and risk by giving us a way of understanding, categorizing, and making sense of each novel particular thing we encounter. This keeps us from having to invest excess resources in understanding and generating models for each new individual particular thing we encounter (though, we sometimes must do this anyways). Instead of doing that, we can investigate just until we determine which "kind" best describes the novel thing at hand, then apply our existing model for that "kind" of thing to the novel thing. This helps us prioritize perceiving the most useful regularities, while avoiding the extra resource cost to parse through excess particularity to perceive regularities that are less useful given our situation. Sometimes the thing at hand does not fit any of our models for "kinds." If it is consequential enough, we may realize this and revise a "kind" or generate a new "kind" to account for this new thing. Think of the toddler who is learning to categorize animals. Eventually he will stop calling every medium-sized, four-legged mammal a "doggy" and start identifying other "kinds" of things that resemble "doggy", such as "cat," "fox," or "hyena." "Kinds" are often perfectly adequate for helping us to understand novel things and navigate the world; we're better off in this respect than if we had to apprehend each new thing we encountered from scratch. This represents a cognitive ability that pervades not only our intuitive understanding of the world but our formal scientific and philosophical understanding as well.

"Kinds" as a concept give us the metaphysical language we need to make generalizations. Generalizable propositions and theories are abstracted out from many instances of the particular. To cover over a range of things, these generalizable propositions must make reference to "kinds" of things in order to express the generalizable relationships (to capture the regularity) that we need in order to predict and conduct science. "Kinds" thus feature quite heavily in science and serve as the basic building blocks of scientific models. One might go so far as to say that one of the primary goals of both science and philosophy is to identify the fundamental or "Natural" "kinds" of things. As discussed previously, useful models capture some of reality's regularity (knowledge) and this is demonstrated by the extent to which the model (its knowledge) confers upon the user, the power to interact with reality non-randomly so as to overcome entropy. It happens that some models allow us to predict the behavior of certain aspects of reality with startling reliability. This can empower us

-ena concerning an immensely complex system. We have a better chance of capturing useful regularities regarding this aspect of reality by taking this approach, as opposed to attempting to understand it in terms of one field (least of all physics).

While "piecemeal approach" is a passable label, it is not quite correct to characterize contemporary science as representing a "divide and conquer" strategy, as there is an astonishing degree of overlap and integration among the scientific fields (the explanation above should provide encouraging evidence for this). Scientific fields are not as neatly assigned to certain levels of reality as Putnam & Oppenheim suggested (1958). Povich and Craver (2017) point out the difficulty in doing this given the mosaic of many different localized hierarchies of mechanistic levels. Additionally, many scientific fields tend to span multiple levels of analysis in terms of which entities and phenomena they are concerned with and what methodological tools they draw from (Darden & Maull 1977). The flipside of this is that fields overlap a great deal, and share some commonality in their domain. While this might occasionally pose difficulties related to workplace "politics," it may serve to maximize our access to knowledge about a complex system that we wish to understand. Philosopher Sandra D. Mitchell calls this an "integrated plurality of scientific models" (2002).

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About the Author

My name is Fletcher Seymour. I am a Philosophy Major (who also enjoys taking Economics and Biology courses). I am fascinated by the diversity of methods and perspectives offered by different fields, and enjoy research that brings many disciplines to bear on a single topic. I undertook my research project on the Unity of Science because I wanted a framework that would help me conceptualize the underlying connections and commonalities between different fields of knowledge. Much to my delight, my research allowed me to identify some of the patterns that I had been noticing throughout my studies.

Investigating the effect of early reperfusion conditions in reactive oxygen species generation by reverse electron transfer in mitochondrial complex I, using a mitochondrial model

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Abstract

The metabolite succinate is known to accumulate during tissue ischemia/hypoxia (i.e., during heart attack). Upon reperfusion, succinate is rapidly metabolized, and is thought to drive a burst of reactive oxygen species (ROS) generation by mitochondria, which trigger events leading to cell death. Controversy surrounds the source of ROS in early reperfusion, with one model suggesting that reverse electron transfer (RET) in respiratory complex I (Cx-I) is a source, driven by succinate reducing the coenzyme Q pool. However, evidence for Cx-I RET is largely based on artificial experimental systems, involving exposure of isolated mitochondria to large concentrations of succinate, poorly modeling the conditions of early reperfusion. Notably, some conditions seen in early reperfusion would be predicted to inhibit Cx-I RET ROS (e.g., high NADH drives Cx-I forwards, which should inhibit reverse activity of the complex). Herein, we hypothesized that Cx-I RET ROS may be an artifact of such conditions. Thus, various experimental perturbations were applied to isolated mitochondria to model early reperfusion, with measurement of ROS generation using the fluorescent probe PHPA. Conditions included: (i) A high concentration of NADH. (ii) A high concentration of lactate. (iii) A mildly acidic pH. (iv) A non-zero concentration of ADP (buffered by a creatine/creatine phosphate system). These studies revealed that even the presence of high lactate and NADH, acidic pH and engaging phosphorylating respiration in mitochondria by supplying a steady-state concentration of ADP, mitochondrial ROS generation still occurred via Cx-I RET, although to a smaller extent than seen under artificial conditions. Thus, we conclude that the conditions of early reperfusion, despite theoretically being unfavorable for Cx-I RET ROS, nevertheless were permissive for ROS generation via this mechanism.

Introduction

Ischemia-reperfusion (IR) injury, better known as a heart attack, is one of the leading causes of hospitalization and death in the United States and around the world[1]. Therefore, it is a primary concern to identify causes of damage during IR injury so they can be targeted.

During reperfusion, i.e., return of oxygen flow to the heart, it is believed that generation of reactive oxygen species (ROS) is among the main sources of injury. ROS are radical species containing oxygen that may engage in various unintended reactions, resulting in negative effects in excess[2]. Chouchani et al. proposed that succinate accumulation during ischemia due to anoxic conditions is responsible for the burst in ROS[3]. Milliken et al. described a mechanism for injury wherein the burst in ROS generation at reperfusion causes opening of the permeability transition (PT) pore, leading to mitochondrial damage and subsequent cell death[4].

The current consensus is that most of the ROS generation on the onset of reperfusion can be attributed to reverse electron transfer (RET) in Complex I (Cx-I) of the electron transport chain (ETC)[5]. During ischemia, succinate accumulates because the ETC is not functional under anoxic conditions. Upon reperfusion, the built-up succinate would reduce a pool of coenzyme Q, causing electrons to flow into Cx-I in reverse direction, opposite to normal respiration. The electrons then reduce oxygen in a non-controlled manner, generating ROS. This theory is backed up by experiments by Lambert and Brand, where ROS generation in isolated mitochondria respiring on high concentrations of succinate was inhibited by rotenone, a commonly used Cx-I inhibitor[6]. However, those experiments fail to consider a number of conditions in early reperfusion that could alter the propensity of RET ROS. Namely, the experimental conditions had no NADH, no lactate, normal pH, and no ADP. The pyruvate + malate used as respiratory substrates in another experiment[7] serve the role of NADH sources, but were never added with succinate, so the added effect is not known.

Here, we hypothesize that Cx-I RET ROS may be an artifact of unrealistic experimental conditions (succinate +/- rotenone) and will not occur in conditions designed to mimic early reperfusion. We

measured ROS generation in conditions of high NADH, high lactate, acidic pH, and steady-state ADP, which are some conditions predicted to be present at reperfusion. NADH, like succinate, is a substrate for oxidative phosphorylation; without oxygen, it will also build up in the mitochondria. Since NADH cannot be directly added to the medium and introduced into the mitochondria (because it does not cross the mitochondrial membrane), we instead implemented a pyruvate + carnitine system[8] that can generate NADH inside the mitochondria. Lactate is expected to accumulate at the end of ischemia and be present at reperfusion due to anaerobic respiration that occurs in anoxic conditions, ending in lactic fermentation. With the increase in lactate and ATP hydrolysis, the environment in early reperfusion is also expected to become more acidic. Finally, without oxidative phosphorylation, there must be a build-up in ADP because it cannot be converted into ATP. More specifically, from metabolomic data by Milliken et al.[9], it seems that there is a decrease in both ATP and ADP levels during ischemia. ATP has a more significant decrease, so the ATP:ADP ratio overall decreases.

Methods

Unless otherwise stated, all chemicals and other reagents were obtained from Sigma, St. Louis MO.

Mitochondrial isolation

C57BL/6J mice of both sexes were anesthetized using tribromoethanol (Avertin). The mouse heart was excised and placed in "isolation solution 1" (KCl 100 mM, Tris 50 mM, EGTA 2 mM). After rinsing with fresh solution 1 to wash away blood and fat, the heart was then transferred to a weigh boat and chopped with a razor blade into chunks. After removing more fat, the tissue was rinsed a few times, and chopped until fully macerated. Following more washes with solution 1, it was drained and the tissue was transferred to a conical tube with 15 mL of "isolation solution 2" (solution 1 with BSA 0.5% m/v, $MgCl_2$ 5 mM, proteinase 2.1 U/mL, ATP 1 mM). The proteinase was added to disrupt fibers in muscle cells and free mitochondria previously trapped in them. The mixture was kept on ice for 3 min with frequent mixing and its content was homogenized with an IKA "Tissumizer" device set at 21,000 rpm (around 10 passes) to break cells open, then was kept on ice for 3 min, again with mixing. To remove residual fat and connective tissue, the mixture was divided into two 50 mL centrifuge tubes, topped up with solution 1, and spun at 600 x g, for 5 min at 4ºC. Then, mitochondria were isolated by spinning the supernatant at 10,000 x g, for 10 min at 4ºC. The pellets were washed with solution 2 to wash away residual BSA, then resuspended in 1 mL solution 1, transferred to a microcentrifuge tube, and spun at 10,000 x g, for 5 min at 4ºC. This was followed by resuspending the pellets in 0.5 mL solution 1, combining the pellets, and spun again at 10,000 x g, for 5 min at 4ºC. Finally, the resulting pellet was resuspended in 150 µL solution 1 and kept on ice and away from bright light until use. Mitochondrial protein content was determined using the Folin-Phenol reagent (Lowry assay).

Mitochondrial ROS measurements and buffers

For measuring ROS generation, the fluorescent probe para-hydroxy-phenyl-acetic acid (PHPA), which detects H_2O_2, was added to all assays. The assays were run in a spectrofluorometer, using acrylic cuvettes, while stirring with a small paddle attached to a motor. The excitation/emission wavelengths used corresponding to PHPA fluorescence were 320 nm/410 nm, respectively. Readings were taken for 0.5 s every 2 s, and the PMT voltage was set to "Medium". To calibrate each run for fluorescence, 1 nmol of H_2O_2 was added at the end of each run (see below).

Mitochondrial respiration buffer (MRB) used in the assays was composed of the following: KCl 120 mM, sucrose 25 mM, $MgCl_2$ 5 mM, KH_2PO_4 5 mM, EGTA 1 mM, and HEPES 10 mM, pH 7.4. For the experiments with the creatine/creatine phosphate (Cr/PCr) clamp system, the MRB was modified so concentration of KCl was decreased to 80 mM, to compensate for the sodium added as creatine phosphate disodium, and concentration of HEPES was increased to 30 mM, to buffer possible pH changes in presence of Cr and PCr. The solutions were prepared in bulk, their pH was adjusted to 7.4 or 6.8 as appropriate, then they were separated into 6-10 mL aliquots and kept at -20ºC for further use. Each aliquot underwent at most 2 freeze-thaw cycles (meaning they were thawed and used 2 days) to guarantee freshness of the components.The Cr/PCr ratios for the experiments were determined assuming $K_{eq}=150$[10] for the following reaction:

$$ADP+PCr \rightleftharpoons ATP+Cr$$

In other words, $K_{eq}=[ATP][Cr]/[ADP][PCr]=150$. Three conditions with corresponding ATP:ADP ratios were prepared: 3000/1 (extreme excess of ATP), mimicking state 4 respiration where relatively little ADP is present; 60/1 (anoxic conditions), where the ATP:ADP ratio is decreased due to ATP breakdown, mimicking early reperfusion; and 145/1, an intermediate level. Creatine monohydrate, phosphocreatine disodium, and sodium

chloride were added as solids according to Table 1, so that creatine species overall (Cr + PCr) were at 20 mM, and total sodium concentration was therefore at 40 mM. At the ADP concentration of 150 µM, the PCr/Cr ratio essentially dominated the equilibrium, so there was no need of adding ATP.

Condition	ATP:ADP ratio	PCr/Cr ratio	PCr (mM)	Cr (mM)	NaCl (mM)
State 4-like	3000/1	19/1	19	1	2
Intermediate	145/1	1/1	10	10	20
Anoxic	60/1	2/5	5.7	14.3	28.6

Table 1. Conditions for creatine/phosphocreatine clamp experiments. ATP:ADP ratio, and the concentrations of creatine monohydrate, phosphocreatine disodium, and sodium chloride needed for such. Total concentration of creatine species was set to 20 mM, and total sodium to 40 mM.

Experimental conditions for mitochondrial model

The ROS measurement assays were run in acrylic cuvettes, with total volume of 600 µL (volume of MRB added, not counting individual additions). Components were added to the assays as concentrated stocks, most 100X. The ROS measurement by para-hydroxyphenylacetic acid (PHPA), which measures H_2O_2 concentration more specifically, requires horseradish peroxidase (HRP) and superoxide dismutase (SOD) to generate a signal; their concentrations in the assay were 2 U/mL and 80 U/mL, respectively. Fat-free bovine serum albumin (FFBSA, assay concentration 0.16%) was added to all assays to increase mitochondrial stability and performance. PHPA dissolved in EtOH was also added to all assays, at an assay concentration of 0.0152 mg/mL. These components were all added to medium prior to beginning the measurements. Mitochondria were added at 0.5 mg/mL immediately preceding measurements, following the protein content measurement performed after isolation.

For the conditions simulating early reperfusion, most components were also added before measurements, in their respective runs. The assay concentrations were the following: lactate was 30 mM, creatine kinase was 15.5 U/mL, and ADP was 150 µM. As mentioned above, creatine and creatine phosphate were present in the buffer preparations, and the pH was already adjusted according to the appropriate conditions.

Succinate was added to the assay for a final concentration of 4 mM, while pyruvate and carnitine, where appropriate, were added for a final concentration of 5 mM each. Rotenone was added for a concentration of 3.3 µM, S1QEL for a concentration of 1 µM, and S3QEL for a concentration of 3.3 µM. Notably, for earlier assays, S3QEL 1 µM was added instead, which proved to be insufficient to observe any effect of this inhibitor. Finally, 1 nmol H2O2 was added as 1 µL of H_2O_2 1 mM to solution.

Calculating ROS rates and statistical considerations

From the fluorescence time traces, the slopes of the curve after each addition should correspond to rates of ROS generation. However, they first had to be calibrated because H_2O_2 fluorescence could vary by condition and other uncontrollable factors (such as heart condition, impurities, etc). For that, the 1nmol H_2O_2 additions were used; 1 nmol of ROS corresponds to the jump in fluorescence in absorbance units (A.U.). This ratio can be used to convert a fluorescence slope (A.U./min) to ROS generation rates (nmol H_2O_2/min). Finally, the protein content (controlled to 0.3 mg per assay) was taken into consideration to allow for replicability, making the final ROS generation rate measured as nmol H_2O_2/min/mg protein. Statistical significance for differences in data was determined via a two-tailed t-test, with $p < 0.05$.

Results

S1QEL is a specific inhibitor of RET

The first early reperfusion condition we considered was presence of NADH, by addition of pyruvate and carnitine [ref pyr carn system]. However, in previous experiments[6], the inhibitor used against RET ROS is rotenone, which inhibits Cx-I electron flow both forward and reverse. This stops RET ROS generation, but also inhibits flow from NADH to the rest of the ETC, causing buildup of NADH and subsequent generation of ROS in a different site of Cx-I from RET, namely the flavin site[11] (Figure 1B).

S1QEL is a family of commercially available inhibitors proposed to stop reverse electron flow to ROS in Cx I, while allowing for forward electron flow and respiration. When S1QEL 1.1 is added to mitochondria with succinate, the inhibition (Fig. 1C) is comparable to that of rotenone (Fig. 1D), as can be seen in Figure 1E.

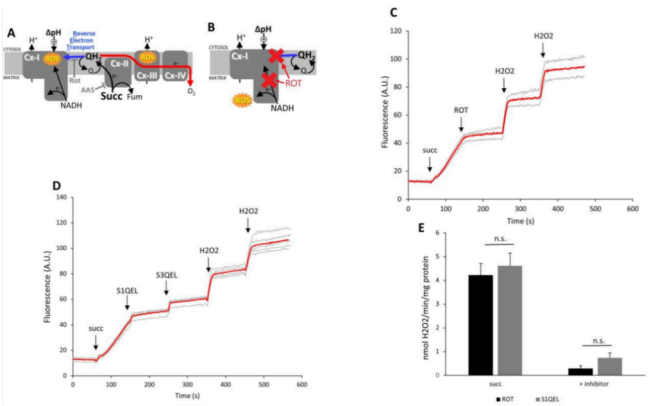

Figure 1. Comparison of S1QEL, specific inhibitor of RET ROS, versus rotenone (ROT), which inhibits Cx-I electron flow in both directions. S3QEL was also used, with the goal of inhibiting ROS at Complex 3 of the ETC, but its specificity is unclear. (A) Diagram of electron flow and reactions in the ETC, with hypothesized sites of ROS generation in Cx-I and Cx-III. (B) ROS generation at the flavin site of Cx-I, following inhibition by ROT. (C and D) Time trace of ROS generation by addition of succinate followed by (C) 3.3 μM ROT (N = 3) or (D) 1 μM S1QEL followed by S3QEL (N = 5). (E) S1QEL has comparable inhibition of ROS to ROT. Statistical significance determined by two-tailed t-test, $p < 0.05$.

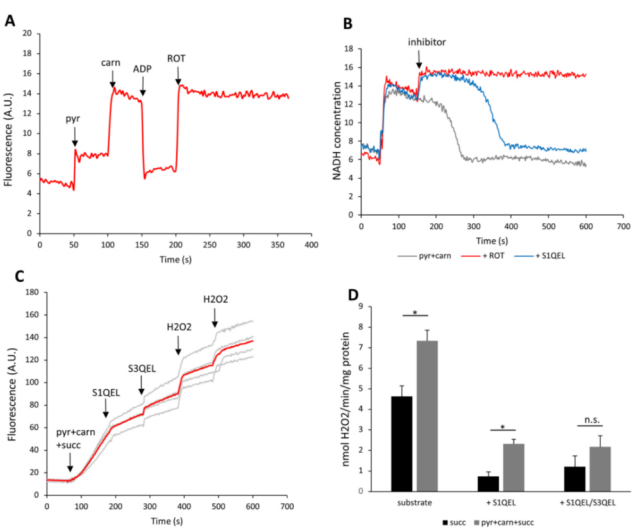

Figure 2. Generation of NADH by pyruvate and carnitine. (A) NADH is generated when pyruvate and carnitine are added. ADP depletes NADH by generating electron flow through the ETC, while rotenone causes it to build up by inhibiting forward flow. (B) S1QEL does not impede electron flow and eventual consumption of NADH, while rotenone does so. S1QEL is allowing forward electron flow. (C) Time trace of ROS generation for pyruvate + carnitine (NADH source) and succinate (N = 4). (D) Rates of ROS generation for pyr+carn+succ condition. Statistical significance determined by two-tailed t-test, $p < 0.05$. One asterisk denotes statistically significant difference.

NADH increases ROS generation, including non-RET ROS

In order to determine the effect of [NADH] on RET ROS, it was first necessary to test the system for generating NADH in mitochondria. As shown in Figure 2A, the addition of pyruvate alone resulted in an increase in steady state level of NADH (measured by its autofluorescence). The further addition of carnitine raised NADH higher, due to the release of acetyl-CoA inhibition of pyruvate dehydrogenase[8]. Confirming the response of [NADH] to mitochondrial respiratory state, addition of ADP resulted in oxidation of the NAD pool. Finally, addition of rotenone to inhibit Cx-I elevated the signal to its maximal level. Overall, the combination of pyr+carn resulted in complete reduction of the NADH pool. The NADH generating system was used to confirm the role of S1QEL in allowing for forward electron flow in Cx-I. Its addition generated a similar trace to NADH without inhibitor, while adding ROT generated an anomalous response due to buildup of NADH (Fig. 2B). ROS generation for mitochondria respiring on pyr+carn (NADH) in addition to succinate (Fig. 2C) was increased compared to ones respiring solely on succinate (Fig. 2D). Notably, the ROS production in the presence of S1QEL (that is, non-RET ROS) was also increased.

Lactate does not effectively influence CxI RET ROS

Lactate is a key component thought to accumulate during ischemia. As the product of anaerobic processing and fermentation of glucose, it makes sense that it would be produced when oxygen flow to the heart is blocked. Considering its historical role as a fatigue agent, and more recently its regulatory and signaling properties[12], it is important to observe its impact on ROS during early reperfusion. One possible function of lactate on ROS is as pyruvate source (Fig. 3A), leading to increased NADH levels, due to not being a fully oxidized carbon species. In our experiments, ROS generation in mitochondria respiring on pyruvate, carnitine, and succinate in the presence of lactate (Fig. 3B) was very similar to ones without lactate (Fig. 3C).

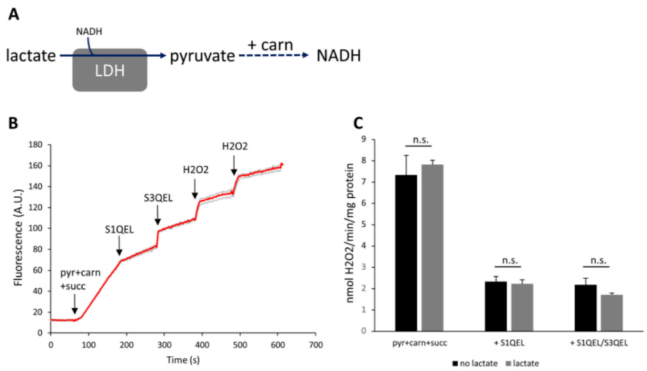

Figure 3. Effect of lactate on ROS generation. (A) One hypothesis for the effect of lactate on ROS generation, as a source of pyruvate leading to NADH. (B) Time trace for ROS generation by pyruvate, carnitine, and succinate in the presence of 30 mM lactate (N = 2). (C) Lactate does not significantly alter ROS generation or its sources. Statistical significance determined by two-tailed t-test, $p < 0.05$. One asterisk denotes statistically significant difference.

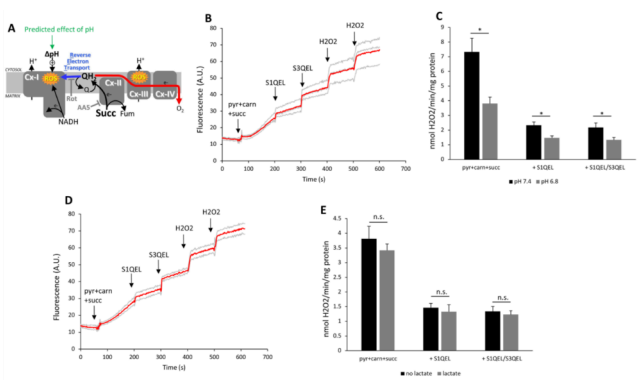

Figure 4. Effect of acidic pH on ROS generation. (A) Acidic pH may alter ROS generation by modifying the proton gradient (and thus membrane potential); according to Lambert and Brand, an increase in membrane potential should increase ROS [ref Brand]. (B) Time trace of ROS generation by pyruvate, carnitine, and succinate in pH 6.8 (N = 4). (C) Acidic pH decreases ROS generation significantly by around 40%. (D) Time trace of ROS generation by pyruvate, carnitine, and succinate in pH 6.8 and presence of lactate (N = 2). (E) Lactate has little effect in ROS at pH 6.8, similarly to pH 7.4. Statistical significance determined by two-tailed t-test, $p < 0.05$. One asterisk denotes statistically significant difference.

Acidic pH decreases ROS overall

During ischemia and onto early reperfusion, the pH is predicted to decrease due to the production of lactate from fermentation, in addition to ATP hydrolysis. Acidic pH has been suggested to increase ROS in the ETC by increasing membrane potential, which has been shown to correlate with ROS[13]. It is worth noting that the membrane potential only increases if the matrix pH remains relatively stable. For mitochondria at pH 6.8, we would expect ROS to increase overall.

In our mitochondrial model, ROS generation for pyr+carn+succ at pH 6.8 (Fig. 4B) seems to be lower compared to the one at pH 7.4 (Fig. 4C). This result does take the lower fluorescent response of the probe into consideration, as evidenced by the lower fluorescence increase upon addition of 1 nmol H_2O_2.

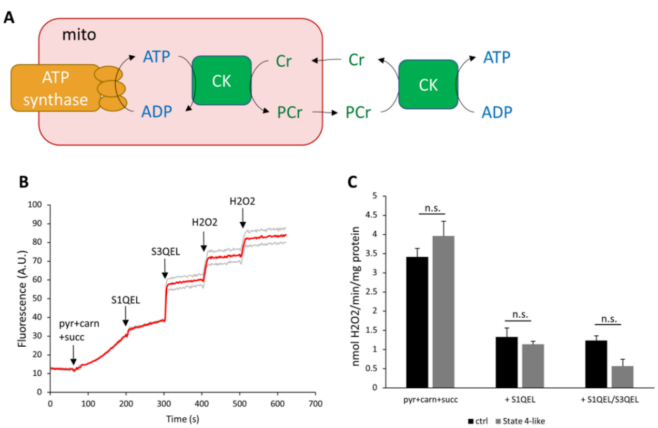

Figure 5. Creatine/Phosphocreatine (Cr/PCr) clamp system for steady-state supply of ADP. (A) mechanism of ADP regeneration by the Cr/PCr clamp system, based on creatine phosphokinase (CK). At an ADP concentration of 150 μM, the PCr:Cr ratio effectively determines the ATP:ADP ratio from the equilibrium. (B) Time trace for ROS generation in mitochondria with the Cr/PCr clamp system, with a PCr:Cr ratio of 19/1 (ATP:ADP ratio of 3000/1; N = 2), at pH 6.8 and presence of lactate. This condition simulates State 4 respiration, where most ADP has been converted to ATP via oxidative phosphorylation. (C) ROS generation for the "State 4-like" condition with the Cr/PCr clamp system is similar to a control without the clamp system. Statistical significance determined by two-tailed t-test, $p < 0.05$. One asterisk denotes statistically significant difference.

ATP/ADP ratio with steady supply of ADP influences Cx-I RET ROS

Lastly, the relative buildup of ADP during ischemia due to hydrolysis/degradation of ATP (evidenced by changes in the ATP:ADP ratio from normoxia to ischemia[9]) is predicted to affect ROS in the ETC,

because ATP synthesis will consume the electron flow that would otherwise leak, leading to ROS generation. Experimentally, however, addition of ADP by itself cannot accurately replicate conditions in the cell. That is because ADP/ATP levels are kept stable in the cell, but little such regulation exists in isolated mitochondria in vitro. What occurs instead is that, upon addition of ADP, ROS is completely depleted due to ATP synthesis. When ADP is fully consumed to form ATP, ROS shoots up to levels similar to conditions without ADP. This separation of phases is not accurate, thus undesirable.

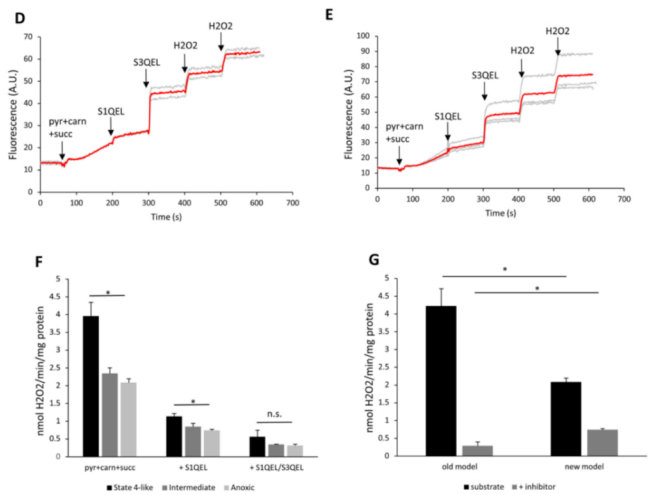

Figure 5. (cont) Time trace for ROS generation in mitochondria with the Cr/PCr clamp system,with a PCr:Cr ratio of (D) 1/1 (ATP:ADP ratio of 145/1; N = 2) at pH 6.6 and (E) 2/5 (ATP:ADP ratio of 60/1; N = 3) at pH 6.8, both in presence of lactate.. (F) The different Cr/PCr ratio conditions generate distinct ROS rates, as predicted from their correspondence to ATP:ADP ratios. (G) Comparison of ROS generation for the "old model" (succinate +/- rotenone) versus our new model (pyr+carn+succ +/- S1QEL). ROS overall is lower for the early reperfusion model, and the calculated percentage of RET is reduced from 93.2% to 64.3%. Statistical significance determined by two-tailed t-test, $p < 0.05$. One asterisk denotes statistically significant difference.

In order to maintain a consistent supply of ADP in isolated mitochondria, we implemented the creatine/creatine phosphate (Cr/PCr) clamp system based on creatine phosphokinase, which is naturally occurring in cells as a buffer and transport of the energy in ATP (Figure 5A). When creatine phosphate (PCr) is present, the ATP generated by oxidative phosphorylation can be converted into ADP and undergo phosphorylation again. Because the transphosphorylation reaction ADP+PCr⇌ATP+Cr is an equilibrium, the compounds can be manipulated to generate different equilibrium states. At [ADP] of 150 μM and total creatine species (Cr + PCr) concentration of 20 mM, the ratio PCr:Cr can effectively control the ATP:ADP ratio based on the equilibrium. Thus, we designed three conditions based on distinct ATP:ADP ratios. First, a 3000/1 ratio, mimicking State 4 respiration where ATP is abundant due to most ADP being phosphorylated. Second, a 60/1 ratio, which is the ratio predicted for ischemia based on an normal ratio at normoxia and the changes in ATP and ADP in ischemia (from metabolomic data by Milliken et al.[9]). Lastly, a 145/1 ratio, which is an intermediate state.

In mitochondria respiring on pyr+carn+succ, ROS generation for the State 4-like condition (Fig. 5B) was consistent with a control condition without the clamp system (Fig. 5C). Meanwhile, ROS production for the intermediate (Fig. 5D) and ischemic (Fig. 5E) conditions was greatly reduced, as predicted by the ADP regeneration from the Cr/PCr clamp system (Fig. 5F).

Finally, the new early reperfusion model developed here should be compared to the old model, from which the assumption of RET ROS as the main source of ROS in the onset of reperfusion was derived. While the old model consisted of mitochondria respiring on succinate, and ROS was inhibited by rotenone, our model has mitochondria respiring on NADH (from pyr+carn) and succinate, in the presence of lactate, pH 6.8, and steady ADP supply. From Figure 5G, we see that the ROS generation overall is reduced, and the contribution of the inhibitor to the ROS (indicating RET ROS) is decreased, from 93.2% in the old model to 64.3% in the new model.

Discussion

The central hypothesis of this work was that ROS generation via reverse electron transfer (RET) in Cx-I may be an artifact of experimental conditions (i.e., a high concentration of succinate and nothing else), and that the imposition of conditions mimicking more closely those seen in early reperfusion would abolish Cx-I RET ROS. The results presented in Figure 5G appear to partially disprove the hypothesis, since Cx-I RET ROS was still visible under IR-like conditions; on the other hand, ROS overall was reduced relative to the old model, and the contribution of RET ROS is smaller. Thus, the dogma that all ROS in early reperfusion is due to Cx-I RET ROS appears in need of reexamination.

Observations from results

It is worth noting that S1QEL and S3QEL were found to fluoresce at a similar wavelength to PHPA, which is why their addition caused small increases in fluorescence. Their addition without mitochondria

had the same effect, which indicates they are not causing bursts in ROS production.

The ROS increase in the presence of the pyruvate + carnitine system appears to be comprised of RET ROS, but also other mechanisms. The difference of ROS rates between the succinate and pyruvate + carnitine + succinate is 2.71 for the substrate condition, and 1.59 in addition to S1QEL. This suggests that RET ROS increased by 2.71-1.59 = 1.12, but the remaining increase should be attributed to a different mechanism. The addition of S3QEL did not significantly affect ROS, but it should be noted that its specificity for Cx-III ROS was not clearly observed in the experiments. An assay run with a stepwise addition of S3QEL (data not shown) demonstrated, for a 3.3 μM addition, 25% inhibition of total ROS for pyruvate + carnitine + succinate respiring mitochondria; however, when this concentration of S3QEL was added to similar conditions with prior addition of S1QEL, the 25% total ROS decrease was not observed. This could be due to a mild inhibitory effect of S1QEL on electron flow in Cx-I. Although it is claimed that the S1QELs can inhibit leakage of electrons to ROS without impacting overall "normal" function of the complexes, it is possible a mild effect on Cx-I would slow the respiratory chain and thus limit ROS generation from Cx-III, such that addition of a S3QEL would not have any effect.

The absence of effect of lactate in ROS (Figures 3C and 4E), despite its various roles in signaling and its character as a non-fully oxidized carbon species, could be attributed to some factors. First, the generation of pyruvate by reversal of LDH is generally energetically disfavored, and it consumes NADH, which would offset the generation of NADH by the pyruvate and carnitine system. Second, the pyruvate + carnitine system could be supplying maximal NADH in a way that lactate contribution is not significant; however, other assays performed with addition of lactate only instead of pyruvate or succinate resulted in no ROS whatsoever (data not shown), which may disprove the possibility of a minimal effect. It is also unclear at this stage whether lactate is actually getting inside mitochondria. It has been proposed [ref lactate phoenix] that lactate may enter mitochondria via monocarboxylate transporter 1 (MCT-1), but this transporter is normally found at the plasma membrane and evidence for its existence in mitochondria is no robust. Lastly, it is possible that lactate does not act on ROS at the ETC at all, despite its potential to do so.

For the ADP assays, the ADP concentration of 150 μM was chosen based on previous tests of ADP concentration, in the same ATP:ADP condition of 145/1 (data not shown). In these tests, increasing concentrations of ADP caused a decrease in ROS. The data corresponding to 150 μM ADP had an intermediate ROS generation without depleting it (which would make data impossible to analyze). When 1 mM ATP was added (and ADP was predicted to be very low based on the equilibrium), ROS was still depleted, perhaps because some of the ATP in excess was converted to ADP (data not shown), and this would place mitochondria in state 3 which lowers membrane potential and would be expected to lower ROS generation.

Patho-physiologic implications

The patho-physiological implication of the current data is that ROS generation during early reperfusion may not come exclusively from Cx-I RET, which has been dogma in the field for over a decade. Significant pharmacology efforts have been directed at suppressing ROS in early reperfusion, but if the source of ROS is different than that assumed by most in the field, then such efforts may need to be re-thought. Specifically, although we did not find evidence for a role of Cx-III in ROS generation in this system, we hypothesize this may be due to a complicated interaction between S1QEL and S3QEL effects in isolated mitochondria. The possibility is still present that some ROS in IR injury may originate from Cx-III, and so efforts to address ROS therapeutically should be directed at both sources, not just Cx-I RET.

Conclusion

ROS generation on the onset of reperfusion is a major source of damage during IR, and it has been assumed that RET ROS at Cx-I is the main source of ROS. With our new model, which takes into account, besides succinate, also NADH, lactate, acidic pH, and steady ADP, we have shown that its contributions to overall reperfusion are not as much as previously thought, and is subject to further investigation. This has major implications in the search for treatment and prevention of injury, as we may have to change our focus on drug targets.

Limitations and future directions

Our mitochondrial model for ROS generation at early reperfusion is comprehensive, but there are other possibly relevant factors that were not accounted for. At early reperfusion, it is known that calcium levels increase, but adding it to mitochondrial assays is a complex process that requires more time to work on. Besides, due to degradation of ATP and ADP during ischemia, adenosine nucleotides accumulate until reperfusion. These species could also have an effect on ROS in the ETC.

Finally, the role of S3QEL as a specific Cx-III ROS inhibitor was not clearly present from our assays; there seemed to be some other independent effect. This matter should be investigated further, so that the inhibitors used in the assays are proven to be reliable.

Acknowledgements

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About the Author

Caio had previous interest in pharmacology, and was drawn to it after taking the Signal Transduction class. With advice of course director Robert Freeman, he began his research in dr. Paul Brookes' lab in the summer after junior year.

Parental Behavior and Friendship Quality in College Students

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Advised by Jeremy Jamieson, Department of Psychology

Abstract

This study investigated the relationship between parental behavior and friendship quality in college students. Parental behavior was defined through parental monitoring and parental youth relationship, while friendship quality was defined through peer communication, alienation, and trust. Our work as part of a larger research study examining the relationship between academic processes and family background. College students from psychology classes (N=126) completed a survey measuring academic processes, perceived parental monitoring and parental-youth relationship, friendship quality, and psychological processes. Contrary to the current consensus, multiple regression analyses showed that parental monitoring led to greater peer communication and fewer peer alienation. In addition, moderation analyses indicated that parental monitoring had a greater effect on peer communication for male participants. Therefore, parental monitoring may be useful for college students in developing better peer communication, especially for male college students.

Introduction

The way parents care for their children influences their children's behavior through adolescence and into emerging adulthood. Emerging adulthood is an important moment, transitioning from childhood into adulthood. It is the first time adolescents are able to move away from their parents and make their own decisions. They are also straying from their existing social networks (i.e., childhood friends), having to create completely new social networks, which can be difficult. An adolescent's upbringing can affect the quality of these peer networks, specifically friendship networks, which further affects an emerging adult's psychological well-being. Friendship quality can often be assessed through distinct aspects of a friendship such as companionship and conflict resolution (Xia et al., 2021). As parenting styles are so important, particularly in how they affect emerging adults, the purpose of this study is to investigate how parenting styles affect friendship quality in college students.

There are four broad types of parenting styles: authoritative, authoritarian, permissive, and neglectful (Baumrind, 1967). Parents who fall under the authoritative parenting style have certain expectations but are willing to communicate with their children about said expectations (Baumrind, 1967). They can be strict and controlling but also warm and supportive. On the other hand, authoritarian parents are only controlling, (Baumrind, 1971) lacking the warmth that authoritative parents display (Baumrind, 1967). Lastly, permissive parents are warm and not strict, yet they allow their children to do anything they want and do not impose rules on them (Baumrind, 1967).

Contemporary research maps these three types through support and control. An example of a supportive parent would be someone who encourages a child to try new things, while a non-supportive parent would berate a child for their failures. Authoritarian parents are the most supportive as they encourage their child's independence and exploration (Baumrind, 1967). Support tends to have a positive effect on a child's development, resulting in fewer behavioral issues (Kuppens & Springer, 2019). In contrast, increased control can have a negative effect on a child's development, such as increased risk for depression (Kuppens & Springer, 2019). Control is broken down into psychological and behavioral control (Kuppens & Springer, 2019). Psychological control is where a child's thoughts and emotions are controlled, while behavioral control is when a child's actions are controlled. A parent may psychologically control their child by making them feel guilty, while a parent that utilizes behavioral control will discipline their child by determining who they can and cannot interact with. Authoritarian parents tend to be the most controlling (Baumrind, 1967), whether psychologically or behaviorally.

As shown above, these three parenting styles lead to different outcomes in children. When these three parenting styles were first proposed, authoritative parenting was said to have the most positive results in children, while authoritarian and permissive parenting were less effective (Baumrind, 1971). Contemporary research corroborates this fact. In a review of 116 studies, self-esteem in chil-

dren and adolescents were positively associated with authoritative parenting, while authoritarian parenting led to lower self-esteem (Pinquart & Gerke, 2019). These results were similar for both mothers and fathers and did not vary across cultures (Pinquart & Gerke, 2019). While Pinequart & Gerke (2019) did not look at emerging adults or friendship quality, it does corroborate Baumrind's (1971) results that authoritative parenting correlates with more positive outcomes compared to authoritarian parenting. Both of these studies inform our study hypothesis since higher friendship quality is also a positive outcome.

In a 2010 study done by Baumrind, Larzelere, & Owens (2010), the researchers gave participants of Baumrind's original study in the 1960s questionnaires assessing adolescent behavioral, emotional, and cognitive abilities. They compared these results to those from the 1960s and found that adolescents with authoritative parents were more competent and had fewer problems than adolescents with authoritarian parents (Baumrind, et al., 2010). Adolescents with permissive parents generally fell somewhere in the middle (Baumrind, et al., 2010). While they did not directly assess friendship quality, they did find that authoritarian parenting led to more prosocial adolescents. Prosocial behaviors are helpful in building and maintaining healthy friendships. Considering Baumrind, et al. (2010) shows that authoritative parenting leads to prosocial behaviors, it is likely that authoritative parenting styles also leads to higher quality friendships.

There have been studies that look at friendship quality in relation to specific aspects of parenting styles. Baumgardner & Boyatzis (2017) investigated the effect of parental control and warmth on friendship quality. They asked 237 undergraduates to report on their parents' psychological control and warmth, as well as asking them about their own relational aggression and friendship quality. The results were in line with Baumrind, et al. (2010) in that they found that the more controlling parents were, the lower the friendship quality of their child. What was unexpected was that Baumgardner & Boyatzis (2017) found that parental warmth did not lessen the negative effect of controlling parents on friendship quality. This might mean that although previous studies have found that authoritative parenting styles lead to more positive outcomes, authoritative and authoritarian parenting styles may actually lead to similar outcomes in terms of friendship quality. This is because the warmth factor of authoritative parents usually mitigates some of the negative outcomes of being high in control, but Baumgardner & Boyatzis (2017) suggests this is not in the case of friendship quality. Similarly, our study also used parental control and warmth as a proxy of the three parenting styles to contradict Baumgardner & Boyatzis (2017)'s results because we used parental warmth as a direct correlation variable to friendship quality rather than a moderator. We also asked students to specify a parent and/or legal guardian when answering study questionnaires. This expanded the analysis of parenting styles beyond traditional nuclear parents (i.e., mothers and fathers) as non-traditional parents/guardians also have an impact on emerging adults' outcomes.

We further looked at the effect of parental control on specific aspects of friendship quality. Oudekerk, et al. (2015) investigated how parental control influenced adolescents and emerging adults' relatedness and autonomy in friendships. They defined relatedness as less warmth and collaboration in a friendship. Participants at ages 13, 18, and 21 were asked to complete self-report questionnaires and nominate a close friend. What they found was that more parental psychological control at a younger age (age 13) predicted less autonomy and relatedness for adolescent friendships at age 18 (Oudekerk, et al., 2015). In addition, there was an indirect relationship between parental control at age 13 and autonomy and relatedness at age 21 (Oudekerk, et al., 2015). The more parental psychological control at age 13 predicted less autonomy and relatedness in romantic relationships at age 18, which in turn predicted less autonomy and relatedness of platonic friendships at age 21. Overall, this matches Baumgardner, et al.'s (2017) work as relatedness and autonomy are both specific aspects of friendship quality where more relatedness and autonomy lead to more intimate friendships (Oudekerk, et al., 2015). Both studies informed us that characteristics of the authoritarian parenting style, such as high control at a young age, are detrimental to friendship quality in later life. While Oudekerk, et al. (2015) only looked at some aspects of friendship, our study looked at friendship quality more generally and at emerging adults from all time-points between the ages 18-21, not just at two time points within emerging adulthood. Looking at all ages rather than just two in addition to looking at friendship quality in general gave a more comprehensive account of the relationship of parental control and friendship quality during emerging adulthood.

We built upon these existing pieces of research by examining all aspects of friendship quality and parenting styles of all possible parental figures/legal guardians, not just traditional mothers and fathers. Our independent variable was parental

control and support because as previous research studies above have shown, parental control and support are central to the three main parenting styles (i.e., authoritative, authoritarian, and permissive). This study focused on behavioral control. Our dependent variable was friendship quality. College students ages 18-21 completed self-report questionnaires on an online platform about their parents' behaviors and how they felt about their friends. In-line with previous research, we hypothesized that more parental control would lead to a lower friendship quality while more parental warmth will lead to a higher friendship quality with gender as a moderator where parental warmth and friendship quality will have a stronger relationship for boys (Miljkovitch et al., 2021).

Method

Sample Size Estimation

Based on post hoc power analyses for multiple regression, our targeted sample size is 42 for a target power of 0.80, two predictors, and an observed R^2 of 0.20 (p=0.05) as informed by previous research. With our sample size of 122 and an observed R^2 of 0.20, we well exceeded the power of 0.80 as we had a power of 0.99. We will be ending data collection after two weeks after the study has been posted on SONA due to time constraints.

Participants

126 university students (72.2% women; 45.2% non-White) were recruited from the Rochester, NY area through the SONA, a platform where psychology students can find research studies to participate in for credit. There were no exclusion criteria, and participants received psychology class credit for participating. Gender is a planned moderator due to the different effects of parenting based on gender found in previous research.

Procedure

This study was part of a larger research study investigating the relationship between academic processes and family background. Each participant took a survey through Qualtrics, a survey platform, where they answered questions on demographic characteristics, academic outcomes, family relations, and psychological processes.

Measures

Friendship Quality: For our study, we used the peer portion of the Inventory of Parents and Peer Attachment-Revised (Cronbach's α = .66-.86) to assess friendship quality (Armsden & Greenberg). This measure assessed friendship quality along three subscales: peer communication, peer alienation, and peer trust. Students rated the truth of each friendship statement, such as "my friends accept me as I am" and "I wish I had different friends", on a scale from 1 (almost never or never true) to 5 (almost always or always true).

Parental Control: For assessing parental control, we used the Parental Monitoring scale (Cronbach's α = .71 for mothers)), a scale designed for youth reporting (Moore, et al., 1999). The Parental Monitoring scale was used to assess the extent of parental monitoring experienced by the youth with higher scores indicating higher levels of parental monitoring. For this Parental Monitoring scale, students rated how much their parents knew about their personal life from a scale of 0 (knows nothing) to 4 (knows everything).

Parental Warmth: For assessing parenting warmth, we used the Parent-Youth Relationship Scale (Cronbach's α = .75 for residential mothers), also designed for youth reporting (Moore, et al., 1999). The Parent-Youth Relationship Scale was used to assess the parent-child relationship with higher scores indicating more positive relationships. For the Parent-Youth Relationship Scale, students rated how much parental support they received from a scale of 0 (never) to 4 (always). They also rated how much they agreed to statements of their parent from a scale of 0 (strongly disagree) to 4 (strongly agree).

Although the parental monitoring and parental-youth relationship scales were created for residential mothers/fathers and non-residential biological mothers/fathers and only used she/he pronouns, we included the terms 'legal guardians' and the pronouns they/them for inclusivity.

Demographic Variables: We also collected our gender variable from a binary gender question as students indicated 0 for men and 1 for women.

Results

Data Analysis Plan

Data was analyzed in a multiple regression analysis. Three models were created, each testing one aspect of friendship quality in relation to parental-youth relationship and parental monitoring. We also ran moderation analyses on the models with significant relationships.

Peer Communication

The results of the first regression model, where we analyzed the relationship between peer communication (M=3.874, SD=0.723) vs. parental-youth relationship (M=3.484, SD=0.502) vs. parental monitoring (M=3.086, SD=0.898), indi-

cated that the two predictors explained 6.0% of the variance on peer communication (R^2=0.060, F(2, 118)= 4.309, p<0.05). Results showed that only parental monitoring was significantly associated with peer communication (β=0.213, p=0.011, 95% CI=[0.050, 0.377]), where greater parental monitoring predicts greater peer communication.

Peer Alienation

The second model, analyzing the relationship between peer alienation (M=2.479, SD=0.608) vs. parental-youth relationship and parental monitoring, indicated that the two predictors explained 6.9% of the variance on peer alienation (R^2=0.069, F(2, 118)= 5.472, p<0.01). Results showed that only parental monitoring was significantly associated with peer alienation (β = −0.146, p<0.05, 95% CI= [−0.282, −0.010]), where greater parental monitoring predicts less peer alienation.

Peer Trust

The results of the third model, analyzing the relationship between peer trust (M=4.146, SD=0.712) vs. parental-youth relationship and parental monitoring, indicated that the two predictors explained 4.6% of the variance on peer trust (R^2= 0.046, F(2, 118)= 3.905, p<0.05). Results showed that neither of the two predictors were significantly associated with peer trust ($p_{\text{parent-youth relationship}}$=0.128, $p_{\text{parental monitoring}}$=0.209).

Overall Analyses

These results show that parental monitoring negatively predicts peer alienation and positively predicts peer communication while parent-youth relationship is not associated with any friendship quality variables.

Moderation

After finding a significant association between parental monitoring and peer communication and peer alienation, we conducted moderation analyses to see if gender was a moderator. We did not conduct moderation analyses for model three as no relationships were significant. For model one, gender did account for 11.5% of the variance (R^2=0.115, F(2, 112)= 8.382, β=0.440, p<0.01). The interaction effect was then entered into the model and was also significant (R^2=0.175, F(3, 111)= 9.057, β =−0.596, p<0.001). Two regression models showed that for male participants, parental monitoring had a more significant relationship with peer communication (β=0.738, p<0.001) as compared with female participants (β=0.142, p=0.0672) with parental monitoring leading to better peer communication. For model two, gender did not account for a significant amount of the variance (R^2= 0.061, F(2, 112)= 4.727, β =−0.050, p=0.712). Gender is therefore only a significant moderator for the relationship between peer communication and parental monitoring with parental monitoring having a greater effect on peer communication for male participants.

Effect	Estimate	*SE*	95% CI		*p*
			LL	*UL*	
Intercept	3.257	0.450	[2.365, 4.149]		<0.0001***
Parental-Youth Relationship	-0.012	0.148	[-0.304, 0.280]		0.936
Parental Monitoring	0.213	0.082	[0.499, 0.377]		0.011*
R^2	0.068				
Moderator Gender	0.440	0.159	[0.125, 0.755]		0.007**
Interaction between gender and parental monitoring	-0.596	0.197	[-0.985, -0.206]		0.003**
R^2	0.197	Adj. R^2	0.175		

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 1. Moderator Analysis: Peer Communication and Parenting Style

Effect	Estimate	*SE*	95% CI		*p*
			LL	*UL*	
Intercept	3.417	0.375	[2.675, 4.160]		<0.0001***
Parental-Youth Relationship	-0.140	0.123	[-0.383, 0.104]		0.258
Parental Monitoring	-0.146	0.069	[-0.282, -0.010]		0.035*
R^2	0.075				
Moderator Gender	-0.050	0.136	[0.125, 0.755]		0.712
R^2	0.078	Adj. R^2	0.061		

Note: * $p < 0.05$, *** $p < 0.001$

Table 2. Moderator Analysis: Peer Alienation and Parenting Style

Exploratory Analysis

For my exploratory analysis, I chose to look at the relationship between college belongingness (M=5.049, SD=1.148) and parental-youth relationship and parental monitoring. I ran a multiple regression model with college belongingness as the outcome and parental-youth relationship and parental monitoring as the predictors. The model indicated that the two predictors accounted for 9.6% of the variance (R^2= 0.096, F(2, 118)= 7.359, p<0.01). Unlike the previous models, results showed that only parental-youth relationship was significantly positively associated with college belongingness (β = 0.661, p<0.01, 95% CI= [0.208, 1.113]). Therefore, greater parental-youth relationship predicts greater college belongingness. However, college belongingness was not significantly associated with parental monitoring.

Effect	Estimate	*SE*	95% CI	*p*
			LL *UL*	
Intercept	3.049	0.445	[2.168, 3.930]	<0.0001***
Parental-Youth Relationship	0.223	0.146	[-0.065, 0.512]	0.128
Parental Monitoring	0.103	0.081	[-0.058, 0.264]	0.209
R^2	0.062	Adj. R^2	0.046	

Note: *** $p < 0.001$

Table 3. Multiple Regression: Peer Trust and Parenting Style

Effect	Estimate	*SE*	95% CI	*p*
			LL *UL*	
Intercept	2.451	0.698	[1.069, 3.833]	0.001**
Parental-Youth Relationship	0.661	0.229	[0.208, 1.113]	0.005**
Parental Monitoring	0.096	0.128	[-1.57, 0.349]	0.454
R^2	0.111	Adj. R^2	0.096	

Note: ** $p < 0.01$

Table 4. Multiple Regression: College Belongingness and Parting Style

Discussion

The aim of this research study was to examine how different parenting behaviors affect friendship quality in college students. We hypothesized that college students who had more controlling parents would have lower friendship quality while college students who had better relationships with their parents would have higher friendship quality. In addition, we hypothesized that gender would be a moderator to these effects.

In our primary analysis, we conducted multiple regression and moderation models. Contrary to our hypothesis, we found that more parental monitoring actually led to better friendship quality on two aspects: improved peer communication and less peer alienation. In this study, parental monitoring included parents knowing about participants' friends and teachers in school. On the other hand, relationships between parents and college students did not have an effect on friendship quality, with parental-youth relationship defined in terms of respect for the parent and parental support. As for moderation, our analysis found that gender was only a moderator between peer communication and parental monitoring, with parental monitoring having a more significant and greater effect on peer communication for male students. Our hypotheses were not supported and in fact our results were in opposition to our main hypotheses. In our exploratory analysis, where we also ran a multiple regression analysis, we found that better parental youth relationships actually led to more college belongingness.

One main limitation in this study is that our sample was entirely composed of college students from psychology courses as we had uploaded our study to SONA (a study platform where psychology students could complete research studies for credit). While there are other studies who use college students, we specifically used college students taking psychology courses, limiting generalization. Conducting a cross-sectional study was another limitation in this study(Oudekerk, et al., 2015). Since college students are not directly affected by their parents, it would have been better to conduct a longitudinal study following students from a young age or a cross-sectional study asking students to reflect on their parents' behavior when they were younger.. In addition, our measure for parental monitoring may not map directly onto parental control. Previous studies split control into psychological and behavioral control (Baumgardner & Boyatzis, 2017; Kuppens & Ceulemans, 2019) while we measured parental monitoring specifically, which may be perceived more positively than parental control as other parental control measures included more

negative language (Barber 1996). This might have led to our unexpected result where greater parental monitoring was associated with greater friendship quality. Finally, although previous studies have also used youth self-report as a way to measure parenting behaviors, only using self-reports limits the data as using parental measures would have corroborated any youth measures and made for stronger conclusions. We also used a correlational study design, which limits causal conclusions.

As stated above, this study could have been improved with a longitudinal design with the inclusion of parental responses. A longitudinal design would have been more accurate as peoples' reflections of the past are not as accurate as their reflections of their current states. In addition, since the sample was college students, they are not as connected to their parents and therefore not as affected by their parents as they were when they were younger. Measuring students while they are directly affected by their parents' behaviors would more accurately measure the effects of said behaviors. In addition, a longitudinal design would allow us to investigate how parental behaviors have or have not changed and whether those behaviors still affect youth when they attend college. Parental responses would provide for less biased data as we could take into account both youth report and parental report about parenting behaviors and see whether or not they agree. Incorporating these two designs into our study would strengthen our conclusions and provide more information on how parenting behaviors affect friendship quality.

Future studies could be longitudinal studies that include samples that did not attend college after high school and see how the relationship between parental behavior and friendship quality differs between college educated samples and non-college educated samples. In addition, future studies could include a qualitative aspect where students are interviewed about their parents' behaviors and their friendships, which could give a deeper insight into that relationship. It would also be informative to expand the parental monitoring measure to include technological monitoring and see if there is still the same positive relationship between technological monitoring and aspects of friendship quality.

Overall, our study shows that parental monitoring is actually a positive aspect of parental behavior in affecting youths' friendship quality. Parental monitoring is often seen as negative but this study shows that for some populations, this may not be the case. In addition, our results suggest that gender is a moderator to peer communication and parental monitoring, implying that parents who decide to monitor their children should take into account the gender of their child.. Parents who have male children should especially utilize parental monitoring in terms of knowing about their friends and about school life. Our study provides more information for parents who might be considering whether or not to increase monitoring on their child, which may in fact have a positive effect on their child's friendships but only in this limited sense.

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About the Author

Doing my own research started with the poster I developed sophomore year on college students and mental health. After creating the poster, I wanted to gain a deeper understanding on research and statistical methods. That lead me to take Research Methods in Psychology where I developed this paper. I chose this topic because I have always been interested in the effects of parenting on adolescents. As for advice, I would say to not be afraid to reach out to professors or graduate students who are doing research you are interested in! It's the best way to get involved.

Essence of the Twin Primes Conjecture

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Abstract

The Twin Primes Conjecture (TPC) concerns the nature of the consecutive prime numbers and the gap lengths between them. For instance, consider the first ten prime numbers as shown below:

$p_1 = 2$ $p_2 = 3$ $p_3 = 5$ $p_4 = 7$ $p_5 = 11$ $p_6 = 13$ $p_7 = 17$ $p_8 = 19$ $p_9 = 23$ $p_{10} = 29$

To determine the gap lengths between them, let us start by subtracting $p_n - p_{n-1}$ where p_n is the *nth* prime number. From the above list, one can easily discern that the most frequent gap length is 2. In fact, this is the basis for the TPC because it claims that there are infinitely many pairs of primes that differ by a gap length of 2, and these primes are known as the twin primes (i.e. 3 & 5, 11 & 13, 17 & 19, etc.). Although many mathematicians have come close to proving the conjecture, to this day, there still has not been a complete infallible proof published. Throughout the course of this paper, there will be an elementary discussion on the origin of the conjecture, the close attempts at its proof, the early contributors of the twin primes theory and more importantly, an examination of the supplemental ideas and proofs that were published regarding the conjecture. We will dissect the specific formulations and tools that were used to study the small and large gaps between the primes, and explore different branches of mathematics to accomplish this task, such as probability and number theory. Particularly, we will analyze the results by Zhang Yitang, who proved that there are infinitely many prime gaps of size n for some value of $n < 70{,}000{,}000$ [1]. Then, we will delve into the results of James Maynard and the Polymath Project (headed by Terence Tao) who worked together to reduce $n < 246$ [2]. We will examine the particular techniques used by these contributors, such as the sieves and the Elliott and Halberstam conjecture, which could potentially reduce n to 12 or 6, if proven to be true [3].

Introduction

The foundation for the Twin Primes Conjecture arises from Euclid's Proof of the Infinitude of Primes (300 BC) [4]. Euclid had theorized that there were infinitely many primes, and we see an excerpt of his proof below...

Suppose that $p_1 = 2 < p_2 = 3 < \ldots < p_n$ are all primes and that p_n is the *nth* prime. Now, let $P = p_1p_2\ldots p_n + 1$ and assume p be a prime dividing P. Then, we observe that p cannot be any of p_1, p_2, $\ldots p_n$ or otherwise, p would divide the difference $P - p_1p_2\ldots p_n = 1$, which is impossible. So, p is yet another prime number, and $p_1, p_2,\ldots p_n$ would not be a finite number of primes (i.e. all of the primes).

From here, we can examine the numerical gaps between the consecutive prime numbers and pose two reasonable questions:

1. How small can $p_n - p_{n-1}$ be where p_n is the *nth* prime number?

2. How large can $p_n - p_{n-1}$ be where p_n is the *nth* prime number?

The first question is a rephrasing of the Twins Prime Conjecture which claims that $p_n - p_{n-1} = 2$ infinitely often. Essentially, this claims that although the gaps between the primes can get smaller or larger, they should eventually return to gap length two more often. Subsequently, it is appropriate to examine a similar conjecture posed by Alphonse De Polignac, which states: For any positive even number n, there are infinitely many prime gaps of size n [5]. In other words: there are infinitely many cases of two consecutive prime numbers with a difference of n.

However, although this conjecture has not yet been proved nor disproved for any value of n, it did engender a breakthrough by Yitang Zhang of the University of New Hampshire, which claims that there are infinitely many prime gaps of size n for some value of $n < 70{,}000{,}000$ [1].

$$p_n - p_{n-1} \leq 70{,}000{,}000$$

Zhang's result provided evidence that there are infinitely many primes with a fixed gap length, and we knew the upper bound for that length. Surprisingly, this allowed for numerous other mathematicians to start improving this upper bound by employing sieves and other useful techniques. For instance, the Polymath Project improved this upper bound to ≤ 4,680. When James Maynard was able to improve this bound to a shocking ≤ 600, the Polymath Project invited Maynard to collaborate,

and within months, they were able to reduce this lower bound to ≤ 246 [2]. More importantly, these results were proved with the emphasis on Sieve Theory, which is where the Elliot-Halberstam conjecture – a generalized Riemann Hypothesis for Sieve theorists – is utilized. If this conjecture is true, it would be possible to improve the upper bound to 12 or even 6.

Large Prime Gaps

Now, let us focus on the second question on how large the gaps can be [6]. For example, take a look at this list of consecutive numbers...

$$n! + 2,\ n! + 3,\ n! + 4,\ldots n! + n,$$

where $n \geq 2$.

What is interesting about this list is that all the numbers are composite, with a length of $n-1$. This implies that the primes not in this list must at least have a gap of $n-1$. Since n can be as large as we want, the prime gaps can also be as large as we want. This paper will examine the various methods to improve the prime gap length in the Twin Primes Conjecture.

Small Prime Gaps

First, we will examine the Prime Number Theorem of 1896 [7], which describes the asymptotic distribution of the prime numbers among the positive integers. It formalizes the intuitive idea that primes become less common as they become larger, by precisely quantifying the rate at which this occurs. Essentially, this tells us roughly how many given primes there are up to any given level (*#of primes ≤ x*).

$$Number\ of\ primes \leq x = (1 + O(1))\frac{x}{log(x)}$$

Therefore, from the Pigeonhole Principle [8], if n items are put into m containers, with $n > m$, then at least one container must contain more than one item. This tells us that among the primes up to x, there is at least one prime gap $p_n - p_{n-1} \geq log(x)$. In other words, we can say that $p_n - p_{n-1} \geq log(p_n)$ infinitely often.

Cramér's Model and Probabilistic Formulation

Now, let us delve into Cramér's Model, a more stochastic approach to determining the distribution of the primes. Cramér posited that the number of primes up to a bound x, (i.e. *primes* <= x), for which he did not know the cardinality of the set, was entirely random [9]. Thus, he modeled the number of primes less than x by a random subset of numbers <= x of cardinality $\sqrt{\frac{x}{\log(x)}}$, essentially giving up on the question of whether there is a pattern to the primes.

Cramér's model proposed that the primes behaved pseudo-randomly. So, if we take a random set of the number of primes, then we will find a lot of twins (i.e., primes that are just a gap length of two apart). Moreover, the distribution of this model looked like a Poisson random variable, where it has an exponential variable of $\mu = log(x)$. Cramér's conjecture is based on a probabilistic model in which the probability that a number of size x is prime

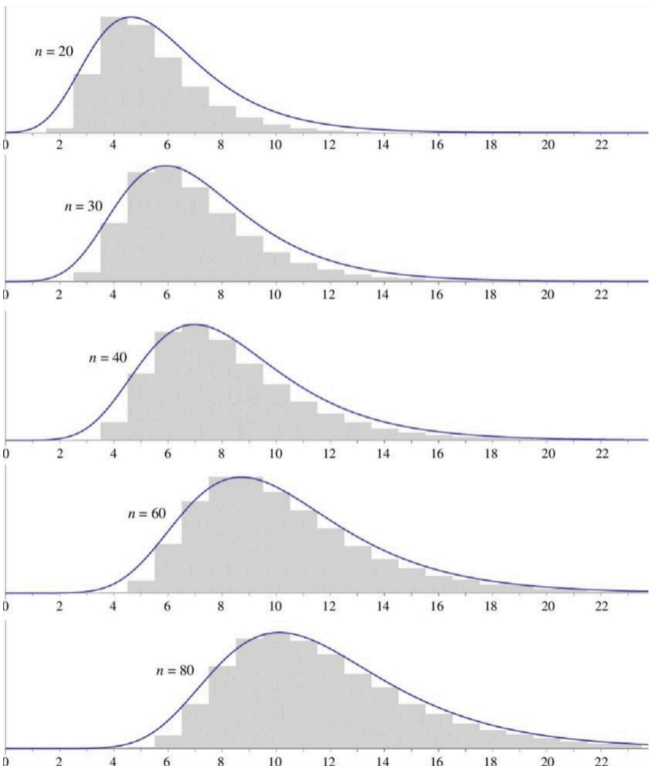

Figure 1. An image of Cramér's Model for varying $\sqrt{n}$

is $\sqrt{\frac{1}{\log(x)}}$. This is known as the Cramér random model or Cramér's Model of the Primes, and in Figure 1, one can observe the distribution of primes for various n.

$$p_n - p_{n-1} \geq c * log(p_n)^2$$

infinitely often for a sufficiently small constant c.

$$p_n - p_{n-1} \geq C * log(p_n)^2$$

finitely often for a large constant C.

Small Prime Gaps Revisited with Probabilistic Formulation

The same Pigeonhole Principle that gives us evidence for large prime gaps also gives us support for the small prime gaps.

Goldston, Pintz, and Yıldırım asserts that the number of primes between a bound x and $2x$ was represented by $\sqrt{\frac{x}{\log(x)}}$. Thus, by utilizing the Pigeonhole

Principle, we can infer that there exists a prime gap of length $<<log(x)$ in the interval $[x, 2x]$ [10]. Since we would like a bounded prime gap, we must rephrase our argument in probabilistic terms.

Let us try to find a prime randomly, where n is a uniform random number between [x,2x], and we can compute the probability that the number is prime as $\sqrt{\frac{1}{\log(x)}}$.

Similarly, if we look at the probability that $n+1$ is prime $p(n+1)$, then this probability is also $\sqrt{\frac{1}{\log(x)}}$.

So, we can shift our random number by some variable h, where $p(n+h)$ and the probability will still be $\sqrt{\frac{1}{\log(x)}}$.

Hence, if we choose h about the size of $log(x)$, then the total probability sum becomes $\sqrt{\sum P(n+h)_{prime} > 1}$. The Probabilistic Pigeonhole Principle tells us that if any set of events has a probability greater than 1, then somewhere in the event space two of those events must occur together, which means they cannot be disjoint. Therefore, somewhere for some n, there must be two shifts where $n + h$ are both prime and this is our prime gap of size less than $log(x)$.

Additionally, we can reduce the gap size further by taking targeted shifts in our h values as long as the total probability is more than 1. Then, we can create fairly small sized gaps between our primes. However, we cannot do better than the $log(x)$ regardless of how we choose our n values.

Moreover, once we rephrase this argument probabilistically, there is no reason that we need to pick our n uniformly. If we choose n non-uniformly, we will have a better chance of making the consecutive $n + h$'s prime, and we can increase the probability of each event. Therefore, we would need fewer events for the total probability to be more than 1.

Alternatively, we can phrase things in a non-probabilistic manner by choosing a different distribution for our primes. Hence, our new goal is to find a probability of distribution or a series of positive numbers between $[x, 2x]$. For instance, $v(n) \geq 0$ for $n \in [x,2x]$, and we can use these weights to create a probability distribution by normalizing by the total sum of the weights, as follows [11].

$$\sum_{i=1}^{k} \frac{\sum_{x\leq n\leq 2x} v(n)_{n+h \text{ is prime}}}{\sum_{x\leq n\leq 2x} v(n)}$$

Thus, if we sum up all these probabilities and it equates to more than 1, then for some n, at least two of the $n+h_i$'s are prime. Essentially, we need to find a clever choice for a weight $v(n)$, where the numerator is big and the denominator is small enough. This is what sets up our idea of a sieve for finding small and large prime gaps, even though the purpose of sieves is to capture primes. We discussed the uniform weights earlier, but that does not work very well since the bound is only $log(x)$.

Selberg Sieve

What criteria do we need to assess in order to pick optimal weights $v(n)$? Most importantly, we want the weights to be positive and simple enough that we can calculate the sums, and currently, the best choice of weights we have are from the Selberg Sieve [12].

The Selberg sieve was devised by Atle Selberg in the 1940s, and it is a technique for estimating the size of "sifted sets" of positive integers, which satisfy a set of conditions which are expressed by congruences.

So, we wish to create a sieve such that $n + h_1$, $n + h_2$, $n + h_3$ all have a high chance of being prime.

Therefore, we take all the numbers that we want to be prime, multiply them together $(n + h_1)(n + h_2)(n + h_3)$, and examine all the divisors of this product. Then, we take some sum λ_d and square the sum, but do not take all of the factors. Instead, we take factors up to a certain bound $d \leq R$, and square it to make sure $v(n)$ is always positive, even though the weights can be negative. Ultimately, our sum looks like

$$\sum_{x\leq n\leq 2x} v(n) = \Big(\sum_{d_1,d_2\leq R} \lambda_{d_1}\lambda_{d_2} \sum_{\substack{d_1,d_2 \\ (n+h_1)(n+h_2)(n+h_3)}} 1\Big)^2$$

As long as we pick $\sqrt{R < \sqrt{x}}$, then we get a quadratic form in the coefficients, and the second sum's purpose is counting how many primes there are in the arithmetic progression. To control this, we use axioms about the number of primes in arithmetic progressions. This leads us to Dirichlet's theorem [13], which states that: For any positive integers a and m such that $(a, m) = 1$, there exists infinitely many primes p such that $p \equiv a \bmod m$.

Hence, any arithmetic progression, unless it obviously contains finitely many primes (first term and common difference not co-prime), contains infinitely many primes [14].

For any positive integers a and m such that (a, m) = 1, we have

$$\sum_{\substack{p\leq x \\ p\equiv a \mod m}} \frac{1}{p} = \frac{1}{\phi(m)} log\ log(x) + O(1)$$

where the sum is over all primes p less than x that are congruent to a mod m, and $\phi(x)$ is the totient function.

This allows us to examine a failed proof of the Twin Prime Conjecture that is adopted from Dirichlet's

Theorem [15].

If one can show that the sum $\beta = \frac{1}{3}+\frac{1}{5}+\frac{1}{5}+\frac{1}{7}+\frac{1}{11}+\frac{1}{13}+\frac{1}{17}+\frac{1}{19}+\cdots+$

of the reciprocals of twin primes diverges, this would imply that there are infinitely many twin primes. Unfortunately, it has been shown that this sum converges to a constant *B*, known as Brun's constant. This could mean either that there are finitely many twin prime pairs, or that they are spaced "too far apart" for this series to diverge.

The ratio we examined earlier with the Selberg Sieve becomes a ratio of two quadratic forms with coefficients that we can choose. The goal would be to make the ratio as close to 1 as possible but very difficult to make it equal to 1.

Zhang, Maynard and The Polymath Project's Contributions

Now, we have set the stage for the breakthrough work of the aforementioned mathematicians. In fact, the first step taken by Yitang Zhang was the most useful as he found a new fact for primes in arithmetic progressions. For instance, Zhang utilized the Bombieri-Vinogradov theorem, which states [16]:

Let x and Q be any two positive real numbers with $x^{1/2}\log^{-A}x \le Q \le x^{1/2}$.

Then, $\sum_{q\le Q} max_{y\le x} max_{\substack{1\le a\le q \\ (a,q)=1}} \left|\psi(y;q,a)-\frac{y}{\varphi(q)}\right| = O(x^{\frac{1}{2}}Q(\log x)^5)$. Here $\varphi(q)$ is the Euler totient function, which is the number of summands for the modulus q, and $\psi(x;q,a) = \sum_{\substack{n\le x \\ n\equiv a \bmod q}} \Lambda(n)$, where Λ denotes the von Mangoldt function.

A simple description of this result is that it addresses the error term in the prime number theorem for arithmetic progressions, averaged over the moduli q up to Q. For a certain range of Q, which are around $\sqrt{x}$, if we neglect logarithmic factors, the error averaged is nearly as small as $\sqrt{x}$. This is not obvious, and without the averaging, it is close to the strength of the Generalized Riemann Hypothesis (GRH) [13].

Basically, if we want to count the number of primes up to x in an arithmetic progression for some *a mod*(*q*), this is fairly easy when q is small. But as q gets bigger and bigger, the progression gets sparser and sparser, and it becomes more difficult to count the primes. The basis of sieve theory allows you to count the primes in an arithmetic progression if the spacing q is not too big. Here, $q < \sqrt{x}$ and what Yitang did was to stretch the limit a little by spacing the primes slightly bigger than $q < x+\epsilon$. He arrived at his 70,000,000 bound with the ratio mentioned earlier to be slightly bigger than 1 for some k = 3,000,000, resulting in the value of ϵ = 1/568 [11].

Next, we go on to the work of James Maynard who realized that he could pick a more general sieve. Instead of looking at the factors of a single product, he proposed that we can look at the sum of the separate factors [2]. This allows for another quadratic optimization problem, but now in many dimensions rather than just 1 from the Selberg sieve. Below is a rendition of Maynard's Sieve:

$$v(n) = \left(\sum_{d_1,d_2,\ldots d_R \mid ln+h_k} \lambda_{d_1,\ldots,\lambda_{d_k}}\right)^2$$

From this point on, the Polymath Project got experts in quadratic optimization problems and were able to reduce the bound even further to 246 without the assumptions of the Elliott-Halberstam conjecture [3].

Conjecture on a Conjecture: How the Elliott Halberstam conjecture can reduce n to 12 or 6

The Elliott-Halberstam conjecture is a generalized version of the Bombieri-Vinogradov theorem, and this conjecture states the following: [3]

If q is a positive integer and a is coprime to q, we let $\pi(x; q, a)$ denote the number of primes less than or equal to x which are equal to a modulo q. Dirichlet's theorem on primes in arithmetic progressions then tells us that $\pi(x;q,a) \approx \frac{\pi(x)}{\varphi(q)}$ where φ is Euler's totient function. If we then define the error function $E(x;q) = max_{\gcd(a,q)=1}\left|\pi(x;q,a)-\frac{\pi(x)}{\varphi(q)}\right.$ where the max is taken over all a coprime to q, then the Elliott-Halberstam conjecture is the assertion that for every $\theta < 1$ and $A > 0$, there exists a constant $C > 0$ such that $\sum_{1\le q<x^\theta} E(x;q) \le \frac{C_x}{log^{A_x}}$ for all $x > 2$ [17].

A direct consequence of this conjecture occurred in November 2013, when James Maynard showed that subject to the Elliott-Halberstam conjecture, one can show the existence of infinitely many pairs of consecutive primes that differ by at most 12 Furthermore, in August 2014, the Polymath group showed that subject to the generalized Elliott-Halberstam conjecture, one can show the existence of infinitely many pairs of consecutive primes that differ by at most 6 [17]. But if we do not assume the Elliott-Halberstam conjecture, the lowest proven bound is only 246 [3].

Conclusion

In our discussion of the Twin Primes Conjecture (TPC), we explored that even without the Elliott-Halberstam conjecture, we can utilize various tools and methods in number theory and probability to be able to prove the prime gap length to be ≤ 246. Moreover, we supposed that primes are distributed randomly, but when we were able to control that randomness through sieves, we found that the

gaps between primes can be formulated. However, the strength of the sieves is largely dependent on how we define our aforementioned weights, and for the time being, we cannot improve what we already have. Hopefully, in the coming years, if and when the Riemann Hypothesis is proven to be true, we can expect everything that it influences, such as the Elliott–Halberstam conjecture, to follow suit. At that instant, we will finally be able to prove the TPC. I wish to end with a quote from Euler, which I believe captures the peculiar beauty of this conjecture: "mathematicians have tried in vain to this day to discover some order in the sequence of prime numbers, and we have reason to believe that it is a mystery into which the human mind will never penetrate."[18]

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About the Author

Sid Seenivasa is a senior at the University of Rochester that is involved in active computational biology research but spends his free time exploring number theory, primarily the primes. Inspired by the Riemann Hypothesis, he has sought after a formula or method for generating prime numbers; though he would have much better luck betting on the Dallas Mavericks to win a championship! Nonetheless, Sid believes that there is a natural beauty to the order of mathematics, and that any person that is fascinated by patterns or puzzles in math should give math research a chance. In fact, Sid didn't officially get involved in math research until his senior year, where a course in Real Analysis gave him that push.

Asherah's Decline: The Burning of Sacred Poles

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Abstract

A recurring theme within the Hebrew Bible is the repeated denigration of ancient Near Eastern deities apart from the god of the ancient Israelites, Yahweh, as well as the proscription of all ritual and worship activities directed towards non-Israelite deities. The dominant theological discourse in the biblical narratives is one which supports the exclusive worship of Yahweh. Biblical scholars have spent years analyzing these divine figures and their role and importance to ancient Israelites.

Paired with the Hebrew Bible, religious scholars have found extra-biblical sources to support evidence of these figures more broadly throughout the ancient Near East. More specifically, with the discovery of the Keilalphabetische Texte aus Ugarit, or the KTU, the rediscovery of an ancient Near Eastern goddess, Asherah, illuminates a long tradition of misogyny, misrepresentation, and occlusion on the part of both foundational biblical scholars and the work of biblical writers such as the Deuteronomistic Historian. Biblical sources compiled by the Deuteronomistic Historian encouraged a polemic against the goddess Asherah, whose worship took place within the Northern Kingdom of Judea during the Divided Monarchy. The Deuteronomistic Historian's polemic provided insight into the popular interest and widespread practice of the worship of Asherah within the ancient Near East. Still, the KTU illuminated the true ubiquity of Asherah worship. Nevertheless, inherent biases of biblical scholars uphold the beliefs of the Deuteronomistic Historian, skewing scholarship of the goddess Asherah and her worship within the ancient Near East.

Drawing on the foundational work of Frank Moore Cross, Mark S. Smith, and W. F. Albright, as well as the more recent scholarship by scholars such as Peggy Day and Tilde Binger, I propose a diachronic analysis of the place of Asherah in ancient Near Eastern mythology with specific attention to her evolving role in ancient Israelite religious practice. In particular, I want to examine the ways in which the worship of Asherah was proscribed and censured by certain groups of ancient Israelites who encouraged the sole worship of Yahweh. To achieve this study, I will analyze the history of scholarship, focusing on the discovery of the KTU in 1929, and I will explain the types of texts found in the KTU corpus and their importance as an example of opposition to the work of the Deuteronomistic Historian. Then, I will deconstruct the early analysis of the KTU by focusing on the inherent biases of foundational authors and their inclination to support the arguments made by the Deuteronomistic Historian in regard to the worship of Asherah. From there, the arguments of the Deuteronomistic Historian will be analyzed through language, rhetorical devices, and a discussion of a newly developed theological framework that suppresses the worship of Asherah. After establishing the Deuteronomistic Historians' motives, I will examine the archeological evidence throughout the ancient Near East that suggests the worship of Asherah, both as a single deity and with her male consorts. Finally, it is important to restore Asherah to the narrative provided within the KTU, which is diametrically opposed to the narrative provided by the Deuteronomistic Historian.

History of Scholarship

Little was known about the Ancient Near Eastern kingdom of Ugarit prior to 1929. Although several texts in the archives of Amarna in Egypt mentioned Ugarit, they revealed no precise information about its location. In 1929, however, a group of archeologists excavated a corpus of cuneiform tablets at Ras Shamra which has come to be known as the Keilalphabetische Texte aus Ugarit, or the KTU. The KTU corpus, which contains 4,080 texts that date primarily to the twelfth century BCE, provided crucial information needed to locate the capital of Ugarit, but more significantly, provided historians and archaeologists with a wealth of information about social, cultural, economic, and political life in Ugarit.

Texts in the corpus span a wide range of genres and supply information about imperial powers, political treaties, dynastic succession, religious ritual, and mythic literature. More specifically, the corpus includes famous epic poems and mythic narratives such as the Baal Epic, the Legend of Keret, The Loves of Baal and Anat, and the Legend of Aqhat which enriches our understanding of not only Ugaritic mythology, but also of the shared themes and motifs of other ancient Near Eastern mythological traditions, such as those in Canaanite and biblical texts. Additionally, the corpus includes texts that pertain to religious life in Ugarit, such as ritual incantations, festival preparations, and instructions for sacrificial practices.

The discovery of the KTU corpus inaugurated a new stage of scholarly interest in ancient Near Eastern religion, myth, and society. Important foundational work on the KTU was done by

scholars such as W.F. Albright and Frank Moore Cross. Much of this early work interpreting and analyzing the Ugartic corpus focused on establishing areas of discontinuity and difference between the mythology, theology, and practices typical of the Kingdom of Ugarit and those described and elaborated in ancient Israelite texts such as biblical texts. For example, W. F. Albright argues that Ugaritic and Canaanite mythology and practice showed remarkable similarities to each other, and further claims that they were both distinct from those found in ancient Israelite sources, such as the biblical texts that comprise the Deuteronomistic History. More specifically, Albright consistently distinguishes biblical theology, mythology, and practice from a range of ancient Near Eastern cultures and societies that he tends to conflate with one another. Albright uncritically accepts the historical veracity of the Deuteronomistic History. He recapitulates the anti-Canaanite and anti-Ugaritic polemic of biblical texts, discussing the extent to which ancient Israelites had fully embraced the monotheism that later characterized ancient Israelite religion and early Judaism.

Albright's interpretive bias leads him not only to insist upon the ubiquity of monotheism among the ancient Israelites but also to characterize biblical religion and theology as morally superior to that of what he defines as Canaanite religion. For example, when discussing the story of Queen Jezebel and King Ahab in which they establish the state worship of Asherah and Baal within northern Israel in I Kings 18:19, he asserts,

With the epidemic ecstaticism, its colorful ritual of fertility, and probably its picturesque initiations, it stood in sharp contrast to the sober hues and stern morality of Yahwism, even when the latter was made more palatable to the common man by sacrificial ritual and solemn chants.

Albright's viewpoint contributes to biases within the field that suggest the Canaanite religion is somehow inferior to the Israelite religion; Albright himself went even further in his evaluative judgments by claiming that Christianity is far superior to both. As such, Albright endorses the position of the Deuteronomistic Historian who privileges the theology and politics of the Yahweh Alone Party.

With the discovery of the KTU, however, scholars had new resources for developing a deeper understanding of Canaanite deities, myths, rites, and practices. Several divine figures appear throughout the KTU such as El, Baal, Asherah, Anat, and Yam. These gods and goddesses engage in a range of interactions throughout the various mythic and literary texts within the corpus. They have feasts, war with one another, murder each other, and have children together. Spurred by the wealth of new information about ancient Near Eastern religion and culture, a new generation of scholars turned their analytical attention to the ways in which the KTU corpus complicates and adds to our understanding of the complex religious landscape of the ancient Near Eastern world, including ancient Israel. It soon became clear that Albright's assertions about the ubiquity and popularity of monotheism among ancient Israelites are questionable as are his evaluative claims about the ostensible "superiority" of ancient Israelite culture and society over that of the Canaanites. The mythic narratives suggest a far more complex set of relationships and connections between the God of Israel and those of surrounding Near Eastern societies as well as the possibility of a range of ritual practices performed throughout ancient Israel among those who worshiped not only the God of Israel but also the other gods and goddesses that comprise the shared pantheon of the ancient Near East.

Early Analysis of the KTU

One of the more controversial figures to appear in the KTU was the goddess Asherah. The goddess Asherah was actively worshiped as early as the thirteenth century BCE in the city of Ugarit; rituals associated with Ashereh continued throughout the ancient Near East until at least 800 BCE in Samaria. As portrayed in a range of ancient Near Eastern texts, Asherah's function stays relatively the same; she is portrayed as the consort goddess of the primary male deity and as the creator of the gods. Although W. F Albright makes note of Asherah's prominence within the KTU, he does not analyze her role except to note her position as the consort to the primary male deities and to suggest that her primary functions are related to the themes of marriage and childbearing. His discussion of Asherah does not go beyond analyzing her connection to the male deity, El.

El's consort was the goddess Ashirat, the Asherah of the Bible, often called "Ashirat of the Sea," meaning originally perhaps "She who Treads the Sea." This goddess was also worshiped by South Arabians and Amorites; a votive inscription in Sumerian which was erected to her by an Amorite of the 18th century BC calls her "the bride of heaven."

Nevertheless, Asherah's role within the ancient Near East spans beyond Albright's interpretation. Albright's lack of hermeneutical interest in Asherah stems from his uncritical acceptance of the representation of the goddess in the Hebrew Bible in general and in the Deuteronomistic History in particular.=

The Deuteronomistic History (Deuteronomy–2 Kings)

Albright's interpretation of the KTU corpus and the role of Asherah in ancient Near Eastern mythology is deeply influenced by his uncritical acceptance of the ideological perspective of ancient Israelite texts in the Hebrew Bible. More specifically, Albright recapitulates the anti-Canaanite discourse reflected in the Deuteronomistic History. The Deuteronomistic History, composed primarily during the late seventh century BCE during the reign of King Josiah, spans from Joshua to 2 Kings with Deuteronomy acting as its theological preface. Written against the backdrop of the pressure of

the Babylonian incursion into the Kingdoms of Israel and Judah, the Deuteronomistic Historian presents a didactic history in which he argues that the rise and fall of the nation of Israel are explicitly linked to the sole and correct worship of Yahweh. The Deuteronomistic Historian's condemnation of all worship except that of the sole worship of Yahweh is evident not only in his censure of other ancient Near Eastern deities but also in his polemic against the Northern Kingdom of Israel. The fall of the Northern Kingdom to the Assyrians is presented as a punishment for the tolerance of ostensibly idolatrous and improper worship established at northern religious sites such as Bethel and Dan. Understanding the realm of geopolitics to be under the control of the God of Israel, the Deuteronomistic Historian weaves his theology of retributive justice throughout his account of the rise and fall of the nation of Israel and his denunciation of "false worship" serves as the primary explanatory model for understanding the loss of Israelite sovereignty over their land.

The Deuteronomistic Historian sought to promote the religious reforms implemented by King Josiah in the late seventh century BCE as a strategy to avoid the impending conquest of Judah by the Babylonians. The eventual conquest is then interpreted by the Deuteronomistic Historian in theological terms as the result of the failure of the Judahites to embrace the religious reforms that would have restored the correct worship of Yahweh. The book of Jeremiah , compiled alongside the Deuteronomistic History, displayed the same theological interpretations and stressed the strict and proper worship of Yahweh.

In addition to the condemnation of the idolatrous worship in the Northern Kingdom of Israel, the Deuteronomistic Historian also denounces the worship of other deities such as Baal and Asherah, marking any ritual or worship not approved by the priestly caste idolatry. The polemic against Asherah is echoed by the contemporaneous prophet Jeremiah. For example, Jeremiah focuses on representing the worship of Asherah as actions of the past. In Jeremiah 17, the prophet outlines the sins of Judah which directly led to their fall: "while their children remember their altars and their sacred poles, beside every green tree, and on the high hills, on the mountains in the open country. Your wealth and all your treasures I will give for spoil as the price of your sin throughout all your territory." Clearly what we see within the Deuteronomistic History and Jeremiah are the theological and ideological perspectives of a strata of ancient Judean society who are against the worship of other deities and who chose to interpret the Babylonian Conquest as a punishment from Yahweh for incorrect worship. The ideology of strict monotheism and the polemic against the worship of other deities reflects the theology of the "Yahweh Alone Party."

The Yahweh Alone Party

The Deuteronomistic Historian reflects the ideology of a strata of ancient Israelite society which, by the late seventh century BCE, had increasingly been promulgating strict theological monotheism and the sole worship of Yahweh. As Herbert Niehr argues,

According to the narrative tradition of the [Hebrew Bible] as especially found in Deuteronomy and in the work of the deuteronomistic historians (Joshua–2 Kings), the history of Israel is marked throughout by a fundamental opposition between Israel and Canaan. Israel entered the promised land from the desert, bringing with it the uncorrupted cult of YHWH as its only god.

For the Deuteronomistic Historian, the appellation "Canaanite" is deployed as a highly polemical category central to the depiction of a distinctive cultural group that is presented in opposition to the "one central, Jerusalemite cult and the adherence to only one God." Despite the censure of those Israelites who insisted upon the worship of Yahweh alone—the Yahweh Alone Party or the proponents of strict Yahwism—it seems clear that many ancient Israelites and Judahites had no difficulties worshiping other deities alongside Yahweh. The attempts of the Deuteronomistic Historian to proscribe the worship of others alongside Yahweh reflect the attempt to impose strict Yahwism on the populace. The Yahweh Alone Party existed alongside other ancient Judahites who enjoyed and accepted the widespread worship of other ancient Near Eastern deities alongside Yahweh over and against the attempts of the Deuteronomistic Historian to promulgate strict theological monotheism. The Deuteronomistic Historian and other members of the Yahweh Alone Party attempted to create a new orthodoxy.

Deities, like Baal and Asherah, are thus labeled by the Deuteronomistic Historian as a threat to the "true" worship of Yahweh.The Deuteronomistic Historian's insistence on strict Yahwism is an attempt to reify a new orthodoxy of strict monotheism and to cast aspersions on the heterodox worship practices of polytheistic Judahites. In her discussion of the Deuteronomistic Historian's polemic, Tilde Binger notes that "this heterodoxy is portrayed by means of presenting those, wished to be denigrated by the author, as being worshippers of a pantheon rather than being loyal devotees of the one 'true' God." It stands to reason that if the Deuteronomistic Historian prohibits the worship of other deities, then these deities were worshiped across the ancient Near East, especially in the Kingdom of Judea.

However foundational Albright's analysis of the KTU was, his work has left the field with more questions than answers. Subsequent generations of scholars have had to redress the imbalances in Albright's work, especially relating to his evaluative comparisons of Israelite and biblical traditions with the religion, culture, and practices of other ancient Near Eastern societies. Rejecting Albright's stark contrast between Canaanite, Ugaritic, and Israelite theology, scholars seek to expand the understanding of the complexity of the relationship between mythic and cultic practices of various cultures in the ancient Near East. For example, Mark S. Smith argues that

Yahweh replaced El as the head of the pantheon through epithetic substitution, where over time, one deity begins to take over traits and correspondences that belonged to another deity, ideally collapsing the tiers of divinity that were present within the Ugaritic and early Israelite pantheon. Frank Moore Cross shares this perspective, and argues that worship of El was inactive and distant within the pantheon throughout the ancient Near East, which gave him the ability to amalgamate within a new divine figure. Through divine substitution Asherah, then, was appointed as Yahweh's consort instead of El's by the eighth century BCE, which led to the polemic installed by the Deuteronomistic Historian. However, this is a controversial theory within the field at the moment.

Susan Ackerman reminds us that the cultural influence of these parties on one another is not entirely understandable, and scholars like Lowell K. Handy agree. The data suggests that there was a group of Yahwists who disagreed with the Deuteronomistic Historian within Judea and continued to worship both Yahweh and Asherah, despite the prohibitions of the Yahweh Alone Party. Epithetic substitution ignores the fact that there were parties who disagreed with the proponents of strict Yahwism and the Deuteronomistic Historian to begin with, even insinuating that there is an evolutionary trajectory between Ugaritic mythology and ancient monotheistic Israelite practice. Rather, viewing this phenomenon through the lens of syncretism allows for the flexibility needed in analyzing this countermovement. Through religious syncretism, the parties of the Deuteronomistic Historian and the broader ancient Near East demonstrate flexible categories with an interesting dynamic. Therefore, if Asherah was conceptualized in the broader Ancient Near East as the consort goddess to Yahweh, who was now the high god of their pantheon, before or during the time of the Deuteronomistic Historians' writings, it would mean that her worship spanned both local and temple religious practice. This rise in local and national worship arguably led to a deep-rooted polemic against her worship within the Hebrew Bible.

Asherah–Goddess, Grove, or Sacred Pole: The Problem of Translation

Interpretations of the theology and rituals associated with the goddess Asherah always begin with the range of issues related to the translation and meaning of her name. There is significant scholarship on the etymology of the name Asherah and on the range of ways her name has been translated, both in ancient texts and in contemporary translations. To state the problem plainly, the divine name Asherah can be and also has been translated to mean, variously, "grove," "tree," and "sacred pole." Translation is itself an act of interpretation and the fact that the same term can be and has been interpreted as either the name of the goddess herself or as ritual cult objects has hampered our understanding of Asherah and the cult practices associated with her.

Before the discovery of the KTU, the only source of assessment scholars had was the Hebrew Bible which provided a wealth of information regarding social and religious life within the ancient Near East, with particular attention to the lives of Israelites. The Deuteronomistic Historian provides scholars with a history on the religious reforms implemented by King Josiah. Biblical scholars had to make assumptions about other ancient Near Eastern religious practices based on thebiases promulgated by the authors of the Hebrew Bible. With the discovery of the KTU, however, there is now a corpus of evidence that enables a new perspective in understanding the religious plurality of the ancient Near East. The perspective within the KTU acknowledges Asherah as her own divine entity, a goddess that people made sacrifices to and worshiped alongside a male consort, rather than simply a sacred pole–a perspective in contrast to the views of the Deuteronomistic Historian.

Within the biblical narrative as set forth by the Deuteronomistic Historian, Asherah is consistently translated as a "sacred pole" rather than a proper name. When the Deuteronomistic Historian refers to Asherah in his texts, he refers to her as הרשא or in the plural asסירשא. According to Susan Ackerman, this word means "either the cult object Asherah, the stylized tree sacred to the goddess Asherah (as it does over thirty times in the Hebrew Bible), or it means the goddess herself." This conflation is a purposeful attempt to linguistically associate Asherah the goddess with a cult object that represents her. The amalgamation of the goddess herself with the cult object effectively functions to elide her presence as an independent deity in the Deuteronomistic History. At other points in the Deuteronomistic History, the Historian refers to Asherah in a way that requires translation to a proper name, suggesting that the Historian understands both definitions of הרשא. For example, in I Kings 15:13, "He also removed his mother Maacah from the queen mother, because she made an abominable image for Asherah…" In this verse, the Hebrew phrase הרשאל typically represents a possessive relationship "to Asherah." As Tilde Binger notes, if הרשא in this context referred to a cult object that possessed itself, the passage would be nonsensical.

What is significant about the Deuteronomistic Historian superimposing Asherah's cult object, an asherah, over her proper name is that it indicates a direct suppression of divine status. By conflating an asherah with the goddess Asherah, the Deuteronomistic Historian develops a new theological interpretation that renders the worship of Asherah in Judah as the worship of a simple object rather than a divine being. Within the Hebrew Bible, the word הרשא is mentioned forty times. Out of these forty times, there are six times in which the word הרשא is referencing the goddess Asherah, while the other thirty-four are referencing a cult object. The six times in which the Deuteronomistic Historian refers to הרשא as a proper noun represent an understanding on the

part of the authors that Asherah was the name for a goddess rather than simply a cult object.

The Deuteronomistic Historian's conflation of the goddess with her cult object as part of a strategy to occlude possible evidence of the widespread worship of Asherah seems to have worked. By the time the Septuagint translation of the Hebrew Bible is produced in the third century BCE, there seems to be no recollection of the goddess Asherah as a deity in her own right. Rather, we see that Asherah is rendered into the Greek ἄλσος, which simply means "grove." Tilde Binger argues that the meaning of the Septuagint references to Asherah are radically different from the original Hebrew. For example, I Kings 15:13 reads, "And he removed Ana, his mother, from power just as he did with the assemblies in her groves. And Asa cut down her 'images' and burned [them] with fire in the brook of Kidron." Binger cites that "it seems as if the Greek version is translated (or written) from a completely different Vorlage." The fact that the Jewish translators, who translated the Hebrew Bible's texts into the Septuagint, lack awareness of the goddess Asherah demonstrates the effectiveness of the Deuteronomistic Historian's strategy of suppressing evidence of Asherah and worship practices associated with her. The translators had no real concept of Asherah and therefore could only translate her name as "grove" and understood her name to be a linguistic representation. This issue is compounded by the work of the Deuteronomistic Historian who often conflates Asherah with her cultic object, at times purposefully, to discredit her worship. John Day argues that

The view that we find in the Septuagint and the Mishnah is that the Asherim were living trees. Thus, the Septuagint generally translated "Asherah" as "grove," and this was followed by the Vulgate, and hence the well-known rendering of the Authorized Version, "grove." For the Mishnah the Asherim were likewise living trees which were worshiped, for example, grapevines, pomegranates, walnuts, myrtle, and willows.

As absolute monotheism developed in Israel and became more widely accepted, Asherah and any knowledge of her disappeared, first by means of conflation with her cult objects and secondly, by the loss in meaning of her name as related to trees or a "grove" of trees.

Early biblical scholars such as Albright reinscribe the biases of their sources when they recapitulate the views reflected in the biblical texts. In other words, the occlusion of Asherah on the part of the Deuteronomistic Historian and subsequently the translators of the Septuagint was further reified by contemporary biblical scholars. Until the discovery of the KTU in 1929, Asherah continued to be translated as sacred pole and grove and interest in the figure of the goddess Asherah was minimal. Indeed, ἄλσος means "grove," however, there was context lost to scholars until the discovery of the KTU and the information that an asherah was both a cultic object, deemed by the Deuteronomistic Historian, and the proper name for the goddess Asherah. Therefore, it is important to understand the argument of the Deuteronomistic Historian to properly restore Asherah in a narrative of the Ancient Near East.

Asherah's Demotion from Goddess to Sacred Pole

The Deuteronomistic Historian consistently conflates Asherah with her cultic object as an attempt to occlude worship of her from the didactic history of Israel that he presents. For example, the Deuteronomistic Historian writes, "You shall not plant any tree as a sacred pole beside the altar that you make for the Lord your God; nor shall you set up a stone pillar – things that the Lord your God hates." William Dever reiterates an important point, that "tree-like representations of Asherah were not, in fact, 'idols' that people personified and worshiped in place of Yahweh (although the Deuteronomists would have viewed them that way)." Within this quotation from Deuteronomy, the author prohibits the erection of any sacred poles or stone pillars next to an altar dedicated to Yahweh. These sacred poles and stone pillars, then, are representations of the idolatrous worship of Yahweh according to the Deuteronomistic Historian, and not idols dedicated to other gods. At times, a sacred pole is simply erected without any explanation as to why or for whom. This type of worship, planting sacred poles or setting up stone pillars illustrates a broader ritual practice within the ancient Near East, specifically the worship of Asherah and Baal respectively. William Dever asserts,

Asherah, her tree symbolism, and high places with altars in groves of trees were all held to be typical of Canaanite "fertility" cults and were thus anathema to the biblical writers. But why would later reforming priests and prophets condemn these things so vociferously unless they remained popular in Israelite religion?

It is through these verses in Deuteronomy that we begin to understand the bias and prohibition of worship on the part of the Deuteronomistic Historian and the Yahweh Alone Party.

What these verses in Deuteronomy indicate is that there is evidence to suggest that there was widespread worship of Yahweh and Asherah within the same ritual space. There is no reason to prohibit a practice that no one is actively practicing. Proscription of specific ritual activities is only necessary if such rites are being actively performed. Tilde Binger agrees, arguing

This verse, then, can only be used to indicate that Asherah could be placed beside the altar of Yahweh, and that the group trying to get rid of this Asherah are very particular about forbidding her co-existence, with Yahweh.

According to the texts of the Deuteronomistic Historian, worship of Asherah is prohibited, as Yahweh forbids this type of worship constantly throughout the prophetic texts of the Hebrew Bible. These sacred poles, then, were deemed examples of idolatrous worship and therefore against the one true God: Yahweh. Susan

Ackerman states, "The Deuteronomistic history reports Israelite asherim during the period of the League and in the period of the Divided Monarchy, both in the North and South. Of the Judean asherim, almost all are located in Jerusalem."

Therefore, I argue that Asherah was strategically demoted from her divine status and rendered as a "sacred pole" as an attempt to illustrate a new theological invention by the Deuteronomistic Historian that worked to suppress the worship of Asherah within the Ancient Near East by targeting the practices within the Northern Kingdom. By the time the Septuagint was translated in the third century BCE, the Deuteronomistic Historian had already contributed to the cultural erasure of Asherah by conflating her with her cultic object.

Asherah and Her Consorts: Baal, El, and Yahweh

In addition to the linguistic shift in which the Deuteronomistic Historian suggests that הרשא is merely a cult object, a "sacred pole," rather than a reference to the goddess herself, the Deuteronomistic Historian also implies that asherim, סירשא (or sacred poles), were being used improperly as part of the cult of Yahweh. In this case, סירשא is referring to a plural noun, subjecting the goddess to asherahs rather than the possessive: Asherah's cult object. When the Deuteronomistic Historian does this, he does so in a way that distances Asherah from Yahweh, consistently linking Asherah with Yahweh's biggest competitor Baal. This feud between Yahweh and Baal is perfectly illustrated in I Kings 18, where the prophet Elijah faces off against Ahab and the prophets of Baal and Asherah to determine whose gods are stronger, and states, "Now therefore have all Israel assemble for me at Mount Carmel, with the four hundred fifty prophets of Baal and the four hundred prophets of Asherah, who eat at Jezebel's table." The Deuteronomistic Historian routinely links Asherah with Baal like in I Kings 19:19, thereby insinuating some sort of consortship between the two deities. This pairing is usually indicated linguistically by the words סירשא and סילעב. As I will review later, there is no relationship between Baal and Asherah that would insinuate a consortship. In fact, Baal's lover, Anat, was his sister and wife within Ugaritic Mythology. This then shows that the Deuteronomistic Historian uses Baal and the term סילעב to connect Asherah with this opposing cult of Yahweh, thus suppressing her worship from the Judahite pantheon. By pairing Asherah with Baal linguistically, the Deuteronomistic Historian separates Asherah from Yahweh and uses an implied consortship with Baal as a reason to occlude her from worship in the centralized Judahite cult of Yahweh.

Throughout the works of the Deuteronomistic Historian, Asherah's demotion from deity to cultic object happens several times through the pairing of her with the god Baal, rather than with Yahweh. Baal's cult, according to the biblical narrative, is in opposition to that of Yahweh. John Day asserts,

When reading the Old Testament it becomes clear that it was the Baal cult that provided the greatest and most enduring threat to the development of exclusive Yahweh worship within ancient Israel. The fact that the Israelites were settled among the Canaanites, for whom the worship of Baal was so important, and that Palestine is a land utterly dependent for its fertility upon the rain, which was held to be Baal's special realm of influence, accounts for the tempting nature of this cult as well as the strength of the Old Testament polemic against it.

Like Asherah, Baal also faced direct censure on the part of the Deuteronomistic Historian and the Yahweh Alone Party. In Judges 3:7, the Deuteronomist writes, "The Israelites did what was evil in the sight of the Lord, forgetting the Lord their god, and worshiping the Baals and the Asherahs." Interestingly, the text refers to Asherah and Baal in the plural, suggesting that there are a multitude of places to worship these deities. The author refers to these altars as "Asherahs" and "Baals" as a category. The acknowledgment of multiple altars on the part of the Deuteronomistic Historian supports the idea that throughout the ancient Near East the proponents of strict Yahwism were actively campaigning against the worship of other deities by writing about Yahweh's dissatisfaction with the ongoing worship of multiple deities among the Israelites.

Throughout the narrative of I and II Kings, the Deuteronomistic Historian recounts the history of Israel from the death of David until the succession of Solomon. The Deuteronomistic Historian is concerned with the sole worship of Yahweh and supports the suppression of the worship of other deities by requiring covenant laws to be obeyed and the worship of Yahweh to only occur within proscribed places, and uses the Northern Kingdom of Judea as an example of idolatry. Within this narrative arc, the polemic against Asherah is focused against the northern kings, whose worship of "Canaanite" deities strictly opposes that of the Deuteronomistic Historian, and the Southern Kingdom of Israel after the events leading to the dividing of the United Monarchy. Beginning in chapter fourteen, the Kingdom of Judah is the object of Yahweh's wrath because "they also built for themselves high places, pillars, and sacred poles on every high hill and under every green tree; there were also male temple prostitutes in the land." Yahweh's wrath continues against the Kingdom of Judah until the reign of King Asa. At this point in the story, there is a narrative scene in which Asa denounces his mother for worshiping Asherah.

Asa did what was right in the sight of the Lord, as his father David had done. He put away the male temple prostitutes out of the land, and removed all the idols that his ancestors had made. He also removed his mother Maacah from being queen mother, because she had made an abominable image for Asherah; Asa cut down her image and burned it at the Wadi Kidron.

By cutting down and burning the "abominable image for Asherah," Asa is given favor in the eyes

of the Lord, Yahweh. This rhetoric continued through the reign of Ahab. For example, in I Kings 16, Ahab, the son of Omri, begins to rule over Israel. Within the narrative, he marries Jezebel, who is the daughter of King Ethbaal of the Sidonians, known for worshiping the god Baal, the direct divine opponent to Yahweh. Ahab and Jezebel erect an altar for Baal and next to the altar for Baal, "Ahab also made a sacred pole." What we see within this narrative arc, according to the Deuteronomistic Historian, is extreme religious reform on the part of the Yahweh Alone Party, who conflate and demote other deities in favor of the sole worship of Yahweh.

Throughout II Kings, rhetoric against the worship of Asherah continued in the form of more religious reforms on the behalf of Josiah, who begins his reign of Israel similar to that of King Asa within I Kings 15. King Josiah, commanded the high priest Hilkiah, the priests of the second order, and the guardians of the threshold, to bring out of the temple of the Lord all the vessels made for Baal, for Asherah, and for all the host of heaven; he burned them outside Jerusalem in the fields of the Kidron, and carried their ashes to Bethel. He deposed of the idolatrous pries whom the kings of Judah had ordained to make offerings in the high places at the cities of Judah and around Jerusalem; those also who made offerings to Baal, to the sun, the moon, the constellations, and all the host of the heavens. He brought out the image of Asherah, from the house of the Lord, outside Jerusalem, to the Wadi Kidron, burned it at the Wadi Kidron, beat it to dust and threw the dust of it upon the graves of the common people. He broke down the houses of the male temple prostitutes that were in the house of the Lord, where the women did weaving for Asherah.

In these verses, Asherah is conflated with her cult objects (sacred poles) and is associated with Baal–as an attempt to separate her from Yahweh–and the destruction of her cultic object at the hands of King Josiah. The destruction is described nearly identically to that of King Asa, presumably as an attempt to revere the kings and their dedication to Yahweh. William Dever asserts that during the time of Josianic reform, Judean pillar-base figurines, or Asherah figurines were, "flourishing precisely during the attempted reforms of Hezekiah and Josiah, one of whose principal objectives was eliminating the cult of Asherah." Therefore, it is important to discuss the physical evidence scholars have of the worship of Asherah and compare it to the polemic put forth by the Deuteronomistic Historian in order to create a well-rounded narrative of ancient Near Eastern religious practice.

Archeological Evidence for the Worship of Asherah

William Dever's book Did God Have a Wife? details at length the archaeological evidence that has been found throughout the ancient Near East that testifies to local folk worship. This observation is key, as it challenges the narrative proposed by the Deuteronomistic Historian. Throughout his analysis of the archeological evidence, Dever discusses the archeology of ten different sites dating from the twelfth to tenth centuries BCE. Within these ten different sites, cult objects have been found that can be linked to the worship of Asherah within these local, family shrines. For example, terra-cotta "cult stands" have been found throughout excavations dating back from the twelfth to sixth centuries BCE. Dever describes some of these stands, remarking, "Other stands, later in the Iron Age and now more specifically 'Israelite,' have a high slender column and drooping 'fronds' around the top that are reminiscent of palm trees, often associated with the goddess Asherah." The notable observation given by Dever relies on the fact that within the biblical narrative, there is no mention of these terra-cotta stands. This suggests that the worship involved with these offering stands were not part of formal temple worship, but rather were used in domestic ritual practice. As established within the previous section, worship of Asherah was suppressed by the Deuteronomistic Historian after religious reforms called for the centralization of worship to Jerusalem itself. Therefore, these stands, associated with the goddess are reminiscent of a decentralized folk religious practice performed widely at the detest of the Deuteronomistic Historian and the Yahweh Alone Party.

Besides the terra-cotta stands, excavations have revealed pillar-base figurines from seventh century BCE Jerusalem. Karel Vriezen contemplates the iconography of these figurines, arguing that they represent the goddess Asherah. Notable features of these pillar-base figurines include the upper part of the body, naked and supporting their breasts. This iconography goes beyond figurines, including pendants that are often focused on the figure, "portrayed as the life-giving goddess: plants go forth from her, animals feed from her, and she offers her breasts for nursing." Iconographies such as these are consistent with Ugaritic descriptions of Asherah, as she is often referred to by her epithet as the "Creatress of the Gods," and has an entire narrative episode where she nurses newly born deities with her breasts. Between the prevalence and quantity of terra-cotta altars, figurines, and pendants throughout the ancient Near East, it is undeniable the worship of Asherah was a widespread, popular religious practice. However, the question remains: Was Asherah worshiped on a broader state level next to Yahweh?

To answer this question, we need to consider the evidence for the pillars erected near Yahweh's altars that the Deuteronomistic Historian prohibited and called for the removal of. Karel Vriezen describes the scene in the excavation on Tel Lachish,

In the excavations on Tel Lachish outside the cult room 49 (stratum V, tenth century BCE), the remains have been found of a raised platform with a pillar (1.20 m high) next to it, directly in front of which there is a rounded heap of black ashes (0.50 m diameter) of olive wood. This pillar may be interpreted as a sacred pillar (Hebr. masseba)

and the ashes as the remains of a sacred pole (Hebr. 'asera). Near to this pillar, both in stratum IV and in stratum III, a pit was dug. Both pits were used as depositories for discarded cult objects (favissa), as they contained the remains of four sacred pillars (0.60–0.70 m high) and of figurines.

Though Vriezen only suspects that these ashes could be interpreted as the remnants of a "sacred pillar," I believe the detailed observations coincide with the worship of Asherah and Yahweh. The dating of the cult room to the tenth century BCE would make this site active after the height of the worship of Asherah in a different geographical area than the city of Ugarit. Yet, we have evidence of worship consistent with that of the Deuteronomistic Historians' description in I and II Kings. The archaeological evidence suggests that besides the altar dedicated to Yahweh were the remains of not only one, but four wooden pillars. If these pillars were sacred poles, then Asherah's cult object would have been present near the cult object of Yahweh, indicating that this site of worship was dedicated to the pluralistic worship of both Asherah and Yahweh together.

Archeological evidence of Asherah worship seems central to domestic worship between terra-cotta offering stands, figurines, and remnants of pillars. However, there is also evidence for her worship spanning to a broader regional, state-led worship. From 1975 to 1976, an eighth-century BCE site at Kuntillet 'Ajrud was excavated by archeologist Ze'ev Meshel. Within this site, Meshel found fragmentary Hebrew inscriptions and painted scenes that suggest both Asherah and Yahweh were worshiped together within a ritualistic context. For example, William Dever notes that in one of the bench rooms, an inscription reads, "To Yahweh of Teiman and to his Asherah." On a large store jar, labeled as Pithos A, a longer inscription ends with the invocation, "I blessed you by (or to) Yahweh of Samaria and by his Asherah." Pithos A includes a depiction of three figures within a cultic scene. Scholars debate whether one of the figures, seated and holding some kind of object, is in fact the goddess Asherah. John Day asserts that the figures depicted are not Yahweh and Asherah. He says, "Granted that the deities Yahweh and Asherah are not depicted on Pithos A from Kuntillet 'Ajrud, several scholars have still supposed that 'Yahweh and his Asherah' refers to Yahweh and the goddess Asherah." However, Dever disagrees with Day and presents the postulation that if this figure is in fact a deity, "she can only be Asherah." He cites his own analysis of inscriptions of the throne depicted within Pithos A, represented by different archeological sites and pieces such as an electrum pendant he says is from Ugarit dating to 1300 BCE. If Asherah and Yahweh were paired together in the inscription and in pictorial arrangements, it suggests that they were worshiped within the same space together.

Asherah's presence within the ancient Near East so far relies on history recounted by the Deuteronomistic Historian and the archeological evidence of her widespread worship.

Consequently, we have only come to two basic conclusions. The first is that the worship of Asherah was actively dismissed as idolatry by the Yahweh Alone Party and is represented by the narrative employment of the Deuteronomistic Historian. This polemic against the worship of Asherah within the Deuteronomistic History was key evidence that contributed to her cultural erasure until the KTU was discovered in 1929. The second conclusion is that archeological evidence such as terra-cotta pots, figurines, ritual inscriptions, and home altars suggest that worship of Asherah was widespread throughout the ancient Near East from its height in Ugarit during the thirteenth to twelfth centuries BCE to at least 800 BCE. This widespread worship must have led to the polemic against the worship of Asherah on the part of the Deuteronomistic Historian. I am inclined to agree with Dever in saying that there is no reason to prohibit worship that is not occurring within your community. However, throughout all this discussion, Asherah's identity has yet to be restored into her own narrative and therefore deserves meditation and analysis in its own right, countering the efforts made by proponents of strict Yahwism and the Deuteronomistic Historian.

Restoring Asherah in the Narrative

Throughout the Hebrew Bible, the worship ofAsherah faces a polemic from the Deuteronomistic Historian. John Day notes that "the name Athirat occurs as Asherah in the Old Testament, but understandably the Yahweh Alone Party which compiled the Old Testament rejected the notion that Yahweh had a wife Asherah." The proponents of strict Yahwism acted in direct opposition to what they believed as idolatrous worship, fueling polemics against various deities found throughout the Hebrew Bible. Idolatrous worship included popular worship of ancient Near Eastern deities, such as Yam, Baal, and Asherah. The polemic against the worship of Asherah illustrates a group of elite, pre-exilic Israelites who insisted on the sole worship of Yahweh as the primary deity. Peggy Day states,

According to the most widely accepted theory, the Deuteronomistic History was compiled, in two editions, in the late 7th/early 6th c. BCE and spans the books of Deuteronomy through 2 Kings. The compilers of the DH championed the kings of the family of David as the only legitimate rules of ancient Israel, insisted upon the exclusive worship of Yahweh, and considered the Jerusalem temple to be the only licit site of Yahweh's cult.

While the Deuteronomistic Historian amplifies this polemic against so-called idolatry, it is clear from the Deuteronomistic History and the prophetic texts that ancient Israelites were engaged in the cultic worship of several gods and goddesses that were worshiped throughout the ancient Near East. While scholars such as Albright seem content to reinscribe the censure of the worship of other deities as idolatry, later scholars sharply questioned such interpretations as masking the complexity and variety of ancient Israelite worship.

The cultural shift from polytheism to monotheism also accounts for the polemic against Asherah's worship, as the Yahweh Alone Party's power and rhetoric grew in popularity, so did the polemic. There is evidence to oppose the Deuteronomistic Historians' assertion of a widespread polytheistic worship throughout the ancient Near East. Archeological evidence such as caches of amulets and altars suggests that worship of Asherah was domestic and state-led . In addition, the KTU establishes Asherah as a goddess who received sacrifices within the mythic and ritual literature. Worship of Asherah spanned across the ancient Near East, requiring the Deuteronomistic Historian to prohibit the Yahweh Alone Party from participating in social ritual practices.

The widespread worship of Asherah illustrates that the ancient Near East was a place with diverse religious life. On the one hand, there were the popular widespread, folk, practices which include the recognition and worship of various deities throughout the geographical area, which often promoted ritual within the home. On the other hand, there were the practices of the Deuteronomistic Historian which promoted a Yahweh-centered theology on a state-wide level. These two perspectives are in opposition with one another. Therefore, I argue that an analysis of Asherah within Canaanite myth, Ugaritic religion, biblical literature, and Israelite archeology illustrates the biases of the Deuteronomistic Historian and illuminates a more accurate perspective on ancient Near East religious practice.

An analysis of Asherah's place within the ancient Near East and the Ugaritic pantheon relies on clearly defining who the goddess was. Asherah's proper name within the KTU is commonly referred to as 'atrt, vocalized as Athirat. Her range of epithets includes the "Lion Lady," "the Procreatress of the Gods," "Qudsu," and "Lady of the Sea." There is also much debate on the antique spelling of her name. It has been translated to Asirta, Athirat, 'atrt, Ashtoreth/ Ashtaroth, Athiratu, and finally the most prevalent example within the biblical narrative: grove or sacred pole. The difference between Asherah and Athiratu could originate from the dispute in translation between the KTU and the biblical narrative in which the word Asherah can be found forty different times. John Day has argued that the word Asherah originated from Septuagint and the Mishnah because Asherim was translated as "living trees," which led to biblical translations such as the New Revised Standard Version, in which Asherah is translated as "sacred pole" or "grove." Like John Day, Peggy Day argues with this translation, saying, "The New Revised Standard Version most often translates the Hebrew word for this cult symbol (ie. Asera, or Asherah) as 'sacred pole,' thus obscuring the linguistic relationship between the symbol and the goddess it represents." The field has long argued the issues of language, etymology, and translation in regard to Asherah's role within the Canaanite and Ugaritic pantheon, and the biblical narrative, as well as her relation to the cultic objects which symbolized her worship. This argument has yet to be resolved; however, current scholarship agrees on the aforementioned epithets and translations.

Throughout the KTU, Asherah is a high-ranking deity. She is the consort to the main Ugaritic god, El, and is often given essential roles of mediation between gods, like in the Baal Epic where she is called upon by Baal to help him gain El's favor so that he may have a "house like the gods." Her relationship with El is expanded upon greatly in KTU 1.4, which states, "At the feet of Ilu she bowed and fell down, prostrated herself, and honored him." She shows him reverence by prostrating herself to which he then, addressing her by two significant epithets, asks, "Why have you arrived, Lady Athiratu of the Sea? Why have you come, Creatress of the gods?" Within the mythic narrative, El, the highest god, addresses the goddess as two epithets that exist outside of her connection with him. The next few lines, "If only the love of Ilu, the King, could stimulate you, the affection of the Bull could arouse you!" insinuate a sexual relationship between the two of them. The consortship between Asherah and El allows her to speak on behalf of Baal and advocate for the building of his temple, demonstrating that the goddess had some power over lesser gods. I agree with Tilde Binger who argues,

One possibility is that my original proposal of her being positioned as "the perfect woman" is wrong, another that the combination gave rise to no comment in ancient Ugarit. A woman was a woman was a woman. Regardless of her status, a woman still bowed before the male of the species, and a goddess was – irrespective of the actual power she wielded – seen as subordinate to the ruling male god. The actual distribution of power was one thing, proper behavior was another. As such she had to observe the rules pertaining to women in general. Even the queen or queen-dowager bows to the king.

Asherah needed to adhere to the proper status of traditional womanhood regardless of her power according to Ugaritic myth. Though she is depicted as a powerful goddess, earning her the title "Creatress of the gods," she is presented as a woman in ancient Near Eastern society.

Asherah is described many times through her connection to her sons. This is most often translated as "the sons of Athiratu" throughout the KTU. As the story of KTU 1.4 progresses, Baal "invited his brothers to his mansion, his kin inside his palace, he called the seventy sons of Athiratu." One significant son, Yam, a god of the sea, is vanquished by Baal for wanting dominion over the world. Asherah's association with her sons gives her additional powers within the divine court. For example, when Baal is defeated by Mot within the Baal Cycle, it is Asherah who is given the power to appoint the next king out of her sons by El, "Ilu cried aloud to Lady Athiratu of the Sea: 'Listen, O Lady Athiratu of the Sea! Give one of your sons, that I make you king!'" Mark S. Smith meditates on this mythical scene by saying,

She [Asherah] may even participate in the

decision-making process, perhaps in the selection of a successor to Baal in 1.4 I. It has often been suggested that Athirat in these instances reflects the role of the royal wife (though not the royal mother), who intercedes with her husband in political matters that affect the well-being of her sons.

Other scholars, such as Handy, have argued similarly about Asherah's power according to her connections with El and her sons. Handy states, "Asherah, as mother of the gods, Queen Mother in the universal organization, and owner of the gods, selected the candidates for the respective positions of authority." This ability to appoint the future king is elaborated by Binger, who makes note that Asherah's word is the final one, regardless of the interjections from El. In an excerpt from An Anthology of Religious Texts from Ugarit, "Lady Athiratu of the Sea answered: 'Shouldn't we make king Athtaru the Rich? Let Athtaru the Rich be made king!' Then Athtaru the Rich went up into the highlands of Sapanu." It is Asherah who gives the final word on the appointment of Athtaru as king, not the highest god.

From the earliest texts within the KTU, we observe lists of sacrifices ordered for the divine agents including Asherah. Johannes C. de Moor notes that according to KTU 1.41, during the month of the "First-of-the-Wine," Athiratu receives "a ram" as a religious sacrifice on both the fourth and fifteenth day of the grand festival. He argues that on the fifth day of this festival, Asherah receives an untranslatable sacrifice connected to "One full shekel of silver for the House of Ilu." In addition to the festival sacrifices, Asherah was called upon to help with exorcisms, "When the fury of the shade begins, look! In the soul of Lady Athiratu in the heart of your potter, may you be moulded!" This invocation could represent a connection between Asherah's incorporation into both the cultic life of Ugarit and the mythological traditions thereof.

In addition, Theodore J. Lewis has translated a text entitled, "The Birth of the Gracious Gods." He mentions that within the texts, scholars argue about the nature of Asherah because throughout the text she is consistently paired with the name Rahmayyu. For example, "Fertile fields, fields divine, The fields of Athiratu and Rahmauyyu." The narrative of the story depicts a promiscuous scene of passionate love between these figures and El. This scene ends with the birth of two gods, translated by Lewis as "The two travail and give birth to the gods Dawn and Dusk." We learn that the gods, Dawn and Dusk, gain their nourishment from nursing on the goddess Asherah. An excerpt from the Ugaritic Narrative Poetry reads, "Let me invoke the gracious gods, [paired devourers of the day that] bore them. Who suck the teats of Athiratu's breasts." Lewis speculates that this text illustrates a ritual of "sacred play (a seven fold rite involving fire, song, and offerings)" and

In the second half of the text, ritual gives way to myth as the author chooses to place front and center the sexual activity of El; the role of a pair of maidens who become his wives' and the offspring, who are marked by a ravenous appetite. Many scholars have concluded that this text is the best example of how mythical narratives and rituals were wedded at ancient Ugarit.

Throughout the text, Asherah seems to invoke her most important roles within Ugaritic mythology as the creatress, mother of all gods, and the queen consort to El, though apparently she is not the only consort to the high god.

Asherah according to the Ugaritic narrative is a high-ranking, powerful deity. Some of her responsibilities include appointing kings, addressing El on behalf of lesser gods, creating gods, and sexually satisfying El. In her analysis of Asherah, Tilde Binger meditates on the ways that Asherah is presented within her narratives, specifically how she is a representation of ancient womanhood.

Asherah is presented as the ideal wife and mother, her answer is the perfect one. A good woman knows her place, and does not propose to tell any man in the family, be he brother, father, husband, uncle or grown son, what to do. Naturally a mere woman should not meddle in the important affairs of men.

At the same time, Asherah is not only an embodiment of "perfect womanhood," but she maintained power by influencing El and being recognized as the creatress of the gods.

The Ugaritic Asherah is given full recognition as the progenitress or creatress of the gods; she can if not rule, then at least influence El; and she is very powerful, both in her own right and through her sons, the gods. She is not a passive or dethroned creator-goddess like those known to us from both Greek and Babylonian mythology.

Throughout the Deuteronomistic History, we see these aspects of womanhood, such as fertility, highlighted, perhaps as a way to emphasize an impurity about her worship that should stand in stark contrast to "sober hues and stern morality of Yahwism." Nevertheless, Asherah is not solely a sacred pole as the Deuteronomistic Historian would have readers believe. Instead, she is a powerful goddess, whose worship spread throughout the ancient Near East. As such, the Deuteronomistic Historian disregarded the myths of Ugarit, turning the figure of Asherah from the goddess outlined within the KTU to a sacred pole.

Final Remarks

The discovery of the KTU in 1929 enacted an invigorating motivation within the field of biblical studies. Scholars had a new wealth of knowledge that represented the true religious plurality of the ancient Near East, especially regarding biblical authors, their motivations, and biases. Within the KTU, the goddess Asherah was a controversial figure whose occlusion from the cult of Yahweh began with the conflation between her cult object and her proper name. Her occlusion was further suppressed by the inaccuracy of the Jewish translators of the Septuingint. Finally, the biases of early biblical scholars allowed for the elevation

of the Deuteronomistic Historian's narrative over the narrative of KTU. Truly, the discovery of the KTU illuminated a long tradition of misunderstanding and suppression regarding the figure of Asherah. As such, it is important to deconstruct the arguments that allowed for the obstruction of Asherah and restore her to the narrative provided by Ugaritic mythology.

Studies of ancient Near Eastern goddesses suffer from past mistranslation, ulterior motives, and misogyny, as well as the elevation of presumed righteous men. This combination of factors means that to study the figure Asherah, one must be able to enter an intense conversation between scholars that continues to be marked by division and controversy. Proper interpretation also requires a full deconstruction of the past that relies on understanding the intricacies of gender and even ascribing those intricacies to divine figures in order to recognize where past arguments have faltered. Going forward, scholars who have learned from the biases of superiority from the past can better understand the complexity of religious society within the ancient Near East. The study of Asherah represents a conversation between scholars, both past and present because it relies on reconstructing a better image of the past.

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About the Author

Casey A'Hearn is currently an MA student at the University of Alabama. During their undergraduate work at the University of Rochester, Casey wanted to explore the ways in which the goddess Asherah had been limited by the Deuteronomistic Historian and early biblical scholars. With feminist theory in mind, Casey argued for the restoration of the goddess to the narrative. When asked to give advice to any other undergraduate students interested in research, Casey responded, "Follow the research rabbit holes. Take yourself on your own wonderland journey. Research what you are passionate about because no one else will care more than you do."

Innovative Method to Assess the Viability of Fusion in a Plasma Using a Wollaston Prism

Joanna Rosenbluth '24, *Optical Engineering*
Advised by Steven Ivancic, Laboratory for Laser Energetics

Abstract

Thomson scattering is a powerful technique used to quantitatively measure the temperature and density of plasma (Swadling et al., 2022). However, background noise from plasma self-emission often limits our ability to make precise measurements. Scientists at the Laboratory for Laser Energetics in Rochester, NY working in collaboration with Dr. George Swadling from Lawrence Livermore National Labs have designed a diagnostic to partially separate the plasma self-emission from the Thomson Scattering signal using an α-BBO Wollaston Prism. OSLO optical modeling predicts that our system would image with greater spatial resolution than the existing camera diagnostics can resolve. Therefore, the optical design will not be the performance limiting factor in this measurement. Learning more about the temperature and density of plasma will assist scientists when designing experiments to achieve fusion.

This paper focuses on the optical design and the theory behind the separation of the Thomson scattering signal from the plasma self-emission background radiation. A paper will be published by scientists from LLE and LLNL at a later date detailing the final results of the plasma properties measured.

1. Introduction

Fusion occurs when two nuclei have sufficient kinetic energy to overcome the coulomb repulsion pushing them apart. At LLE, Deuterium and Tritium (Hydrogen isotopes) are the nuclei that are fused together. Deuterium has 1 proton and 1 neutron, while Tritium has 1 proton and 2 neutrons. The fusing of these two nuclei results in the formation of a Helium-4 nucleus (2 protons and 2 neutrons) and a free neutron. The combined mass of the Deuterium and Tritium nuclei is greater than the combined mass of the Helium nucleus and the neutron. This loss in mass is equivalent to 17.6 MeV of Energy due to Einstein's equation $E = mc^2$, where m is the loss of mass, E is the energy of the emitted radiation, and c is the speed of light (Nave, 2023).

A Deuterium and Tritium plasma needs sufficient kinetic energy for the nuclei to get close enough together to fuse. In order to make this reaction self-sustaining, the plasma must have a high enough density so collisions will continue to occur.

These plasma properties can be measured using a phenomenon known as Thomson scattering. To initiate Thomson scattering, a polarized pulsed laser is directed at the plasma. This causes the nuclei to vibrate as dipoles in the orientation that is polarized by the laser. As a result photons are emitted with the same polarization as the incoming laser. The random movement of the nuclei due to the plasma's high temperature means that some nuclei will have velocity components moving toward the detector and some will have velocity components moving away from the detector during laser pulse interaction. This causes the emitted photon's wavelength to either increase or decrease from the laser wavelength due to the Doppler effect. This results in the Thomson scattering signal having a spectrum of wavelengths. This spectrum can be analyzed to determine the velocity of the nuclei in the plasma, which measures temperature.

The high-temperature plasma emits Bremsstrahlung radiation and limits the measurement of the Thomson scattering signal because part of the radiation spectrum overlaps with the spectrum of Thomson scattering; this is known as plasma self-emission. We must account for this in order to get accurate measurements using the Thomson scattering signal.

The purpose of this optical design is to utilize the polarization of the Thomson scattering signal in order to separate it from the randomly polarized plasma self-emission. This is achieved by using a Wollaston prism to separate the Thomson scattering signal as well as 50% of the backgrounds from each other. Once these two channels are imaged onto a detector, the channel with 50% of the background can be subtracted from the channel with the Thomson scattering signal and 50% of the background to remove the background pedestal from the Thomson scattered signal.

2. Background Subtraction Method: Wollaston Prism

Wollaston prisms are commonly used to angularly separate orthogonal polarizations. A Wollaston prism consists of two birefringent prisms of the same material cemented together so that their crystal optic axes are orthogonal to each other. The unique atomic properties of birefringent materials cause its index of refraction to vary between no and ne depending on an incident beam's polarization vector orientation with respect to the material's crystal optic axis. These different indices cause the beams to angularly deviate. The deviation angle between the two beams can be calculated using Snell's Law (Swadling & Katz, 2022). γ and ψ are the deviation angles at the interface between the two prisms and the interface between the second prism and air, respectively. All angles are with respect to the Wollaston prism optical axis and α represents the Wollaston Prism Angle.

$$\gamma_{p/s} = \left(\frac{n_{o/e}}{n_{e/o}} sin(\alpha)\right) - \alpha \quad (2\text{-}1)$$

$$\psi_{p/s} = \left(n_{o/e} sin\left(\gamma_{p/s}\right)\right) \quad (2\text{-}2)$$

This angular deviation will cause the two beams (labeled s and p) to be separated angularly after exiting the Wollaston prism. A randomly polarized beam incident on a Wollaston prism will be split equally into the s and p channels.

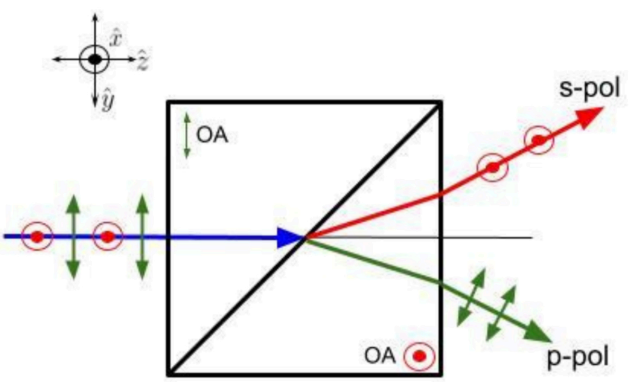

Figure 2-1. Wollaston prism separating the linear polarizations of a beam in both x and y directions.

Another important property of birefringent materials is their spectral dispersion. Since n_o and n_e both depend on wavelength, the deviation angles γ and ψ will also vary with wavelength. Spectral dispersion makes the Wollaston prism a much better choice than other types of prisms for this experiment because the Wollaston prism provides a spectrum for both polarizations. We chose α-BBO as the birefringent material of our Wollaston prism because it has both high dispersion and high transmission in this experiment's wavelength range (190 nm–230 nm). Below are the Sellmeier equations for α-BBO, which are plotted in Figure 2-2. The relationship between n_o and n_e is non-linear, causing dispersion to decrease as wavelength increases.

$$n_o^2 = 2.747 + \frac{.01878}{\lambda^2 - .01822} - .01354\lambda^2 \quad (2\text{-}3)$$

$$n_e^2 = 2.3174 + \frac{.01224}{\lambda^2 - .01667} - .01516\lambda^2 \quad (2\text{-}4)$$

These equations were used along with equations 2-1 and 2-2 to calculate the deviation angle and spectral dispersion curves shown in figures 2-3 and 2-4. The Wollaston prism angle () was chosen to be 22° in order for the spectral range of interest to appropriately fill the detector. Figure 2-5 shows the Wollaston prism performance in FRED optical modeling software.

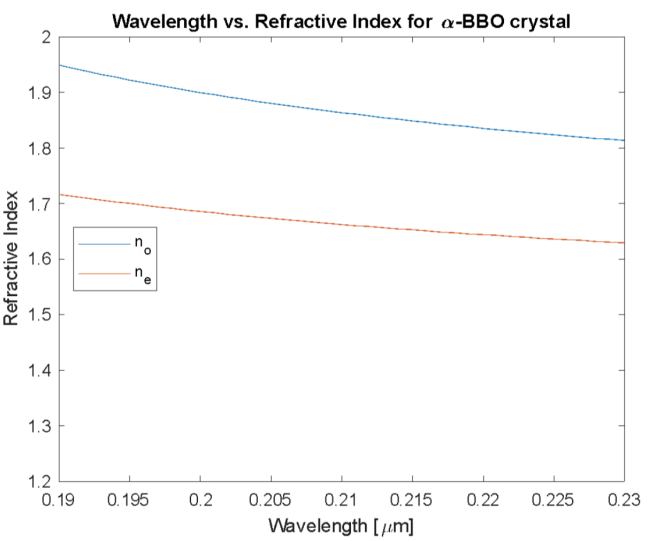

Figure 2-2. Ordinary and extraordinary refractive indices of α-BBO (MT optics, 2023).

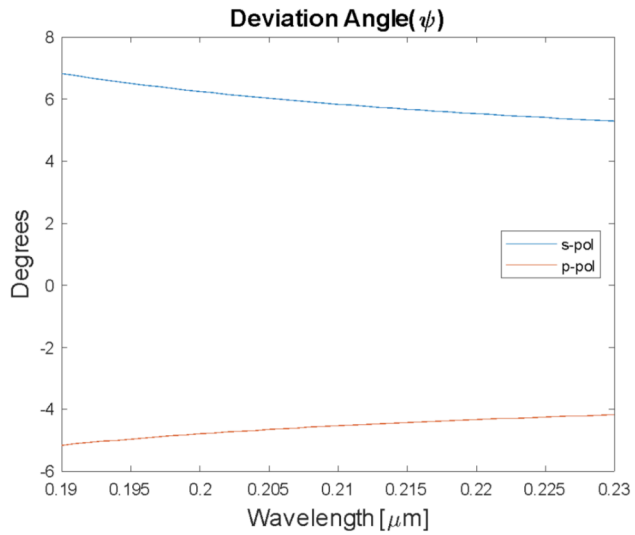

Figure 2-3. Deviation angle for a 22° Wollaston prism with respect to the Wollaston prism's optical axis.

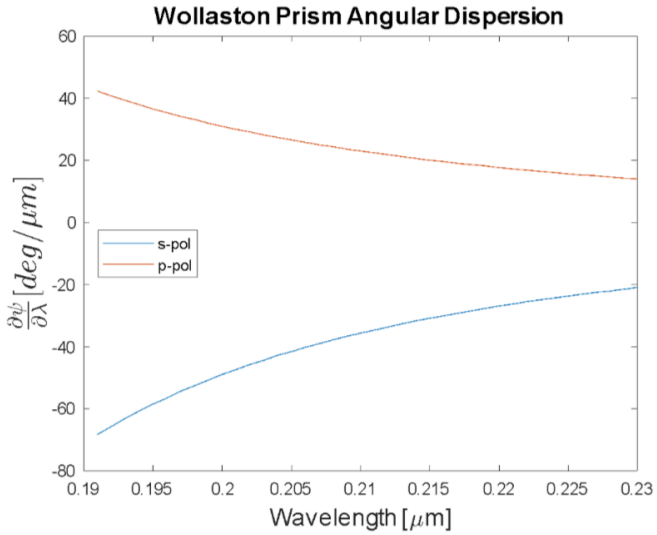

Figure 2-4. The non-linear relationship between wavelength and deviation angle displaying the relationship between angular dispersion and wavelength.

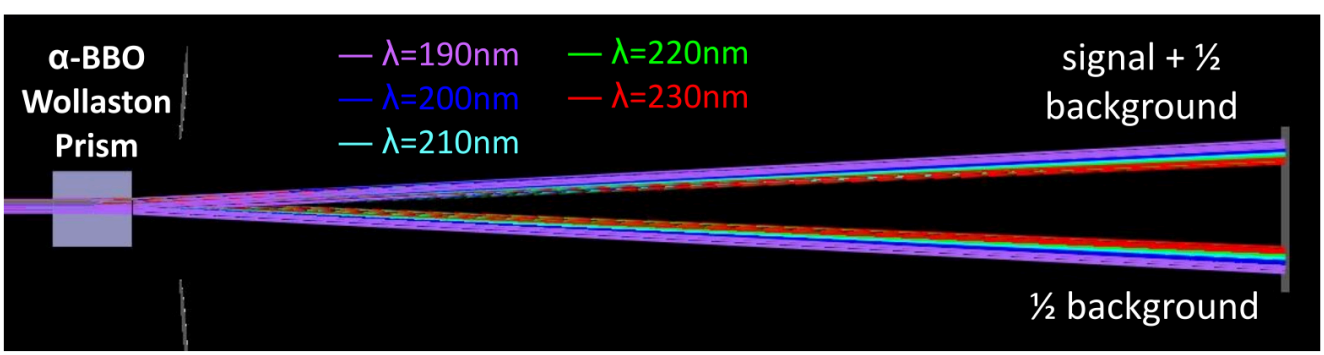

Figure 2-5. FRED optical modeling agrees with the deviation angle vs wavelength trend shown in figure 2-3.

3. Computer Modeling Results

This system was first modeled and optimized using OSLO. FRED was used for analysis due to its capability of ray tracing multiple polarizations simultaneously. The ROSS Streak Camera has a spatial resolution of 50μm (SYDOR Technologies), meaning that the s and p channels must be separated by more than 50μm on the Streak Camera's photocathode detector to prevent crosstalk. As shown in figure 3-1, the polarizations are separated by 2mm on the detector, which means no crosstalk will occur between the two channels.

Relay mirrors between the Wollaston prism and streak camera flip the wavelength order so that the shortest wavelength falls on the middle of the detector and the longest wavelengths fall on the edges of the detector. Any wavelengths below 190 nm will most likely be absorbed by air, placing the shortest wavelengths at the center of the detector, limiting the possibility of crosstalk between the two channels.

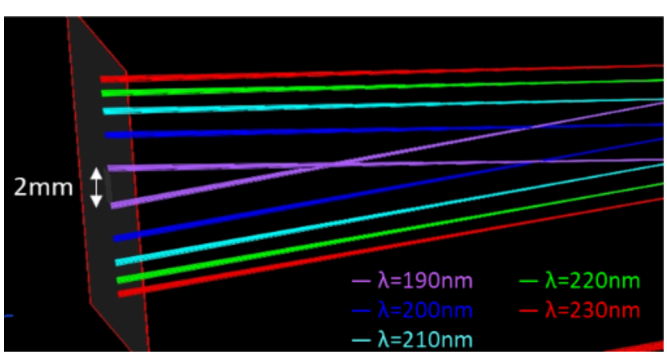

Figure 3-1. ROSS Streak camera photocathode detector with two channels separated by 2mm.

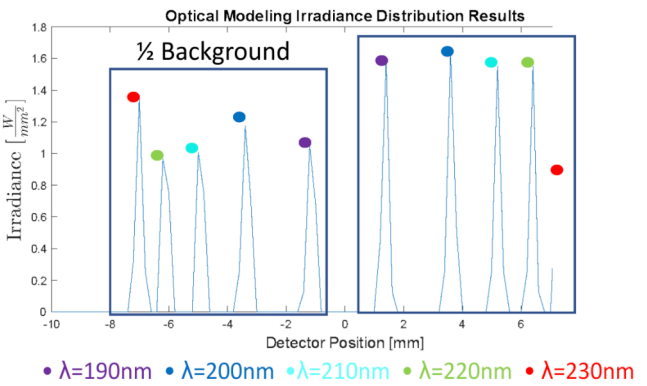

Figure 3-2. Streak camera photocathode irradiance distribution.

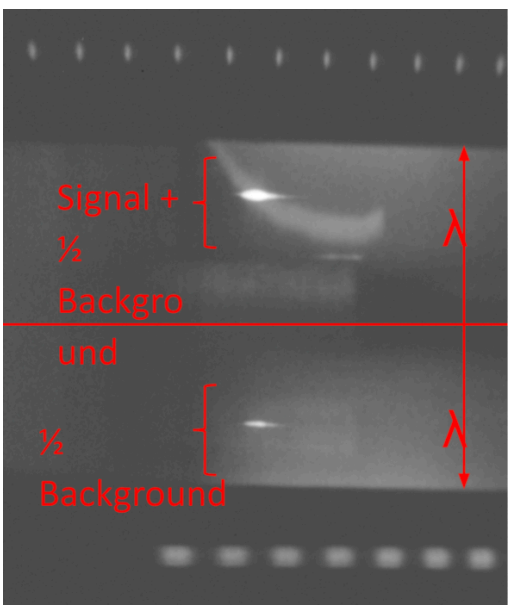

Figure 4-1. Time-resolved Thomson scattering spectrum and self-emission background.

4. Conclusion

This experiment took place on January 31st, 2023 at the Laboratory for Laser Energetics in Rochester, NY. Figure 4-1 shows data from one of the shots taken using a Beryllium target. The s and p channels are fully separated on the detector for accurate determination of the temperature and density of the plasma. The detailed results will be published in the future.. Temperature and density measurements can be repeated under different plasma conditions to evaluate the viability of fusion. Achieving a self-sustaining fusion reaction has the potential to provide unlimited sustainable energy with minimal carbon footprint or nuclear waste.

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About the Author

Joanna Rosenbluth graduated from the University of Rochester in 2023. During her time at the University, she found herself in an environment rich in opportunities to delve deeper into her growing areas of interest and pursued an opportunity at the University of Rochester Laboratory for Laser Energetics. Working under Dr. Steve Ivancic and Dr. Bob Boni, her work heavily focused on instrument development in support of experimental high-energy-density physics.

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Featured in This Issue

Effects of Ocean Acidification on Fish and Possibilities for Adaptation *Elizabeth Croyle '24 (p.14)*
Ocean acidification is the increase in oceanic CO2, which causes an increase in H+ and a decrease in available carbonate. Fish undergo behavioral and physiological changes due to elevated CO2 concentrations and temperature, with severe disruption of lateralization, olfactory sensitivity, and mineralization – and these effects are more severe with early exposure. Ocean acidification as a selective pressure will drive the contemporary evolution of many genes, but it is uncertain how intra and interspecific variation could affect developmental and transgenerational acclimation.

Investigating the Relationship Between Select Emergency Department Patient Characteristics and the Disposition of Emergency Department Patients Among Two South Korean Emergency Departments *Alan Ardelean '23 (p.24)*
Worldwide, the utilization of emergency departments is increasing. Despite differences in the standard and quality of emergency care by country, higher demands place unprecedented pressure on clinicians who face the mounting responsibility of timely intervention and appropriate care. This investigation included select ED patient characteristics in a multivariate model to determine which characteristics are correlated with a patient's disposition and to suggest which should be considered at the beginning of the care timeline. Results from this study carry practical implications for ED providers; they show that a patient's sex, injury status, and systolic blood pressure are significantly associated with their disposition.

Knowledge: A Fringe Definition and its Implications for the Unity of Science *Fletcher Seymour '24 (p.34)*
This paper explores how philosophers and scientists conceptualize Knowledge. It introduces a "fringe" definition of Knowledge, inspired by physicist-philosopher David Deutsch, and uses it to identify a common pattern that underlies evolution, behavior, cognition and the scientific endeavor. Included also is a discussion of the philosophical concept of "kinds" and the prevalence of "kinds" in cognitive and scientific models.

Investigating the Effect of Early Reperfusion Conditions in Reactive Oxygen Species Generation by Reverse Electron Transfer in Mitochondrial Complex I, Using a Mitochondrial Model *Caio Fukushima '23 (p.42)*
One of the main sources of damage during ischemia-reperfusion (a.k.a. heart attack) is reactive oxygen species (ROS) generation. It has been proposed that reverse electron transfer (RET) in Complex I of the electron transport chain of mitochondria is the main source of ROS generation upon reperfusion; however, this is based on mitochondrial models where many conditions of reperfusion were not considered. In this paper, I evaluated how conditions predicted to be present in reperfusion affect the contribution of RET to total ROS using mouse heart mitochondria.

Parental Behavior and Friendship Quality in College Students Emily Han *'24 (p.50)*
This study investigated the relationship between parental behavior and friendship quality in college students using an online survey. Contrary to the hypotheses, multiple regression analyses showed that parental monitoring led to greater peer communication and fewer peer alienation. In addition, moderation results indicated that parental monitoring had a greater effect on peer communication for male participants. Therefore, this study shows that parental monitoring may actually be useful for college students in developing better peer communication, especially for male college students.

Essence of the Twin Primes Conjecture *Siddarth Seenivasa '23 (p.57)*
This article delves into different branches of mathematics, namely probability theory and numerical analysis to craft tools, which can be used to prove that there exists an infinitude of primes that are at most 2 numbers apart. For instance, consider the primes 3 and 5, 5 and 7, 11 and 13, and so on. We would like to prove this phenomenon occurs infinitely often, and we will be exploring it through past results and abstract techniques to reach a consensus.

Asherah's Decline: The Burning of Sacred Poles *Casey Logan A'Hearn '22 (p.62)*
This article seeks to explore the figure of the goddess Asherah in the Hebrew Bible and the Keilalphabetische Texte aus Ugarit (KTU) to deconstruct the ways in which the Deuteronomistic Historian censured her worship in favor of the worship of Yahweh alone. Additionally, this article questions the motives of early biblical scholars, who elevated the theological opinions of the Deuteronomist Historian, making it difficult to study the goddess. Finally, the paper restores Asherah to the narrative provided within the KTU.

Innovative Method to Assess the Viability of Fusion in a Plasma Using a Wollaston Prism *Joanna Rosenbluth '24 (p.74)*
This article focuses on the optical design and the theory behind the separation of the Thomson scattering signal from the plasma self-emission background radiation. In order to address the limitations of the existing technique, scientists at the Laboratory for Laser Energetics and Lawrnece Livermore National Labs collaborated to design a diagnostic to partially separate the plasma self-emission which limits the original technique through background noise.

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