INF 501: Tollis Response

When I envision the field of informatics, genomic studies is one of the first fields I picture because of its large datasets and high impact in healthcare. This week Dr. Marc Tollis provided two papers that introduced the class to comparative genomics and followed by a comprehensive talk that engagingly walked through issues in comparative genomics through the lens of cancer evolution. Our discussion then helped to clarify complex topics in genomics such as DNA replication, gene alignment, and how identification of homologous genes in DNA sequencing works. In this paper I will focus on first summarizing Dr. Tollis' work and contextualizing each major topic within a larger scope of both informatics and science. I will then draw similarities and differences between Dr. Tollis' research and my own research interests, both past and present.

1 Dr. Tollis' Research

This week's topic focused two papers from Dr. Tollis, one a synthesis of mammalian cancer suppression and another on the diversification of *Anolis* lizard lineages, to set the stage for a broad talk that guided us into the world of comparative genomics. The mammalian cancer suppression synthesis laid a solid foundation of the issues in comparative genomics and insights gained to ultimately better understand human cancer prevention and treatment. The second paper on anoles lizard evolution showed how rapid background evolution in anoles and snakes was juxtaposed by highly preserved protein coding sequences resulting in unique morphometric diversity. Dr. Tollis then began his talk introducing Peto's Paradox (discussed further below) which was used to motivate other questions in evolutionary genomics and cancer studies. The talk concluded with 'frontiers in comparative oncology' and Dr. Tollis' personal research goals.

1.1 Mammalian Cancer Suppression Evolution

Cancer suppression genetic studies are an ever-growing topic due to the perceived hope to inform human cancer prevention. Dr. Tollis' paper (Tollis et al., 2017) highlights cancer suppression mechanisms across multiple mammalian species in a synthesis that allowed the reader to understand how these studies can possibly impact human cancer prevention. The paper opens with the 'unique' African naked mole rat; unique because of its seven-fold longer lifespan than the mouse even though both species are of similar body size. Genomics studies sought to

explore why there is such a disparity in life spans discovering the divergence of telomerase activity from other mammal telomerase activity in the naked mole rat, but more work is required to solidify this idea. Alternative forms of cancer suppression, including mutations in the TP53 tumor suppressor gene and positive selection on both DNA damage repair genes and response pathway genes, were contextualized in moles, bats, bowhead whales, and elephants, to name a few. The range in size of species that developed cancer suppression activity was then described using Peto's Paradox which states that an animal's body size should be proportional to its likelihood of cancer occurrence. However, an important caveat to the paradox is that it holds true at the organismal level, but not at the species level possibly due to fewer cells and lower levels of growth hormone for smaller individuals. These examples highlight how diverse cancer suppression can be for different species with different life histories and how findings may one day be applied to aid human patients. Diversity in cancer suppression is an exciting field of study because it allows for scientists to develop and test multiple methods in human cancer prevention. Additionally, by studying multiple species' cancer suppression tactics, we better understand the mechanics of the genome and document more regions of the genome.

1.2 *Anolis* Comparative Genomics

The mammalian comparative genomics synthesis laid out a useful background to read the anoles lizard paper (Tollis et al., 2018). The study focused on three species that occupy different neotropical microhabitats. This selection in species allowed for the study of both ecological and phylogenetic diversification histories. The methods for the paper at first were difficult to follow for but after Dr. Tollis' presentation and our discussion the methods were more intuitive. The study proceeded by sequencing each species' genome and identifying regions that shared similarities in protein coding which then allowed for genome alignment. Following alignment, each genome was compared by summing base pair substitutions per million years which revealed more rapid evolution of the 400 anole lizard species than other vertebrate evolution rates. The hypotheses for this rapid evolution were attributed to either punctuated equilibria models or ecological opportunity. Even though the anoles species experience accelerated evolution, the acceleration was observed in non-functional regions of the genome while protein coding regions were highly conserved. There were exceptions, however, where observed differences occurred for behavior, sensory perception, reproduction, and limb development genes. The take-aways from this study focus on improving the understanding of vertebrate evolution and advancing

reptile genomics which has received relatively little attention compared to mammalian studies. Instead of applicability to healthcare, this paper can contribute to understanding how diversity in taxonomic evolution emerged and may be helpful informing conservation efforts. This will require deeper research in to more diverse species as gene sequencing only recently became affordable and has primarily focused on a narrow range of mammalian genomes.

1.3 Presentation

Dr. Tollis was able to take concepts from his papers, primarily Peto's Paradox, and introduce motivations why comparative genomics is an important field to be aware of. These motivations included how genomics contribute to conservation work, the need to better understand the tree of life, and cancer research. In conservation, it is important to understand whether endangered or threatened species are pressured by human actions, such as the development of solar arrays and their impact on desert tortoises. If human development impacts sensitive species that represent unique genomes, the impact may be detrimental to the animal population and in turn the development may have to be altered. Genomics can also bolster phylogenetic studies that until the past few decades focused on classifying species relations solely on phenotypic similarities and dissimilarities. This becomes important in also better understanding evolutionary pathways, such as why the Tuatara lineage has remained relatively unchanged since the Triassic. The final motivation was how genomics works to understand cancer suppression in various species. Peto's Paradox framed how long lived and large bodied species have paradoxically developed cancer suppression methods when they should instead be more susceptible to high cancer rates. However, birds not only have low cancer rates and small bodies but also violate Cope's Rule that states species lineages develop larger body size over time. Interestingly, aves has reduced in body size over time, hypothesized to be due to the evolution of flight allowing for avoidance of predation but retaining larger ancestral cancer suppression methods. Understanding how drastically different species' life histories can independently develop cancer suppression is a method to potentially apply these findings to human evolutionary medicine treatment. Dr. Tollis easily transitioned between these topics and concluded by emphasizing his desire to continue science communication engagement, specifically here on the Colorado Plateau. His future work aims at furthering cancer suppression pathway evolution and taxonomic diversification.

2 Relationship to Personal Research

I found it surprising how easily I could relate to Dr. Tollis' work, particularly his research on anoles lizard evolutionary diversity. In addition, one of Dr. Tollis' leverages for genomics hinged on conservation of species and this aligns well with work that I am pursuing in identifying species that share both evolutionary diversity and globally endangered classification (EDGE). But, I also related to the work because prior to my time at NAU I focused on studying evolutionary ecology, a field that shares many theoretical and applied principles with comparative genomics. Even though I have no direct relationship to comparative genomics, the underlying motivations are shockingly similar to my own research interests.

The anoles work most closely resembles the work I am currently involved in at NAU. Dr. Tollis' study selected a suite of species that occupied unique spatial niches and the species also happened to correlate with unique evolutionary pathways. For example, differences in limb morphometry was found to evolve rapidly since roughly the Cenozoic allowing for lizard species to occupy unique microhabitats. Therefore, the occupation of different habitats was in part due to differences in genomic evolution for tropical anoles, of which over 400 species exist due to rapid evolutionary diversity. This relates closely with my current work which focuses on classifying species in niche distribution models, or simply mapping potential ecological spaces where species may occur in the past, present, and future. Modelling species distribution in the past ties in with understanding how anoles limb evolution allowed for species to occupy unique spatial habitats. We do not incorporate evolutionary factors very often, as they are highly complex and difficult to spatially contextualize. Instead, we opt to use historical, modern, and projected climate along with topographic data to map species extent. Unfortunately, anoles microhabitats are at too fine a scale to use the species distribution models effectively.

At the end of Dr. Tollis' presentation he mentioned future motivations for himself, one of which was loosely focused on going into museum records to find unique species of the Colorado Plateau that may be difficult to otherwise sequence DNA in the wild. This research aims to supplement the community with information on biodiversity, particularly for species that are vulnerable or endangered. My work with species distribution modelling also includes the mapping of Redlist species, or species that are listed with various levels of conservation concern (i.e. endangered or vulnerable). Specifically it is a goal to refine this list of species using a metric that further classifies species by their evolutionary 'uniqueness' (EDGE species) or how much

information would be lost in their taxa if they became extinct (Gumbs et al., 2018). My research and Dr. Tollis' research aim to better understand biodiversity; however, we seek to do so from highly different scales.

Finally, and along a more tangential relationship, in my undergraduate career I studied evolutionary ecology which focused on ecological concepts but included work with genomics and molecular biology. It has been quite some time since I was involved with evolutionary ecology, but there are many similarities between work with miRNA I was involved in and Dr. Tollis' DNA sequencing. I found comparative biology extremely interesting, studying how species uniquely develop specific phenotypes and behaviors and how these are based in evolutionary development. In summary, even though I cannot currently relate to comparative genomics, the underlying scientific principles like habitat suitability based on evolutionary pressures and a desire to understand biodiversity metrics link my work with Dr. Tollis' quite well.

3 Conclusions

This week, Dr. Marc Tollis exposed the class to the diverse and powerful field of comparative genomics where studies range from uncovering various pathways of cancer suppression to understanding how extremely diverse taxa, like *Anolis*, have rapidly evolved over what is perceived as an otherwise short time span. His presentation contextualized the readings within Peto's Paradox, a paradox that lays out the complex relationship of higher expected cancer rates correlating with body size and motivated future studies in genomics to help the public better understand the history of cancer. The work was inclusive of my own research interests understanding how biodiversity plays a role in nature, be it at the genomic or continental scale. Dr. Tollis was able to communicate many complex topics allowing for the discussion to expand into how his work fits within informatics.

References

Gumbs, R., Gray, C.L., Wearn, O.R., and Owen, N.R., 2018, Tetrapods on the EDGE: Overcoming data limitations to identify phylogenetic conservation priorities: PLoS ONE, v. 13, p. 1–19, doi: 10.1371/journal.pone.0194680.

Tollis, M., Hutchins, E.D., Stapley, J., Rupp, S.M., Eckalbar, W.L., Maayan, I., Lasku, E., Infante, C.R., Dennis, S.R., Robertson, J.A., May, C.M., Crusoe, M.R., Bermingham, E., Denardo, D.F., et al., 2018, Comparative Genomics Reveals Accelerated Evolution in Conserved Pathways during the Diversification of Anole Lizards: Genome Biology and Evolution, v. 10, p. 489–506, doi: 10.1093/gbe/evy013.

Tollis, M., Schiffman, J.D., and Boddy, A.M., 2017, Evolution of cancer suppression as revealed by mammalian comparative genomics: Current Opinion in Genetics and Development, v. 42, p. 40–47, doi: 10.1016/j.gde.2016.12.004.