Cumming School of Medicine

Evolution of variable mutative organisms
Summary of Literature

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1 Project Outline

A project proposal may or may not appear here. It depends on how private the material should be.

2 References Discussion

This section is intended for me to write notes connecting the material in the references with observations and comments.

References

[1] ; on behalf of the ACMG Laboratory Quality Assurance Committee, S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W. W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, and H. L. Rehm, "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology," *Genetics in Medicine*, vol. 17, no. 5, pp. 405–423, may 2015. [Online]. Available: http://www.nature.com/articles/gim201530

This is the guidlines for assessing the pathogeneity of a genetic variant by the ACMG. These guidlines are fairly exustive but are currently a bit out of date in my opinion with regard to in silico methods. The go

through an exhaustive list of impacts. These impacts are ranked as supporting, moderate, strong, and very strong when evaluating pathogenetiy. and stand alone, strong, and supporting with regard to benign evidence. To list the impacts and evidence is not usful, but there are some select quotes highlighted in the lext about population genetics and the use of in silico solutions.

[2] S. Balsamo and A. Marin, "Separable solutions for Markov processes in random environments," *European Journal of Operational Research*, vol. 229, no. 2, pp. 391–403, sep 2013. [Online]. Available: https://linkinghub.elsevier.com/retrieve/pii/S0377221713002191

NOT CLEAR YET.

[3] A. J. de Koning and B. D. Sanctis, "The rate of molecular evolution when mutation may not be weak," *bioRxiv*, 2018.

This paper is quite dense. It it well written and covers a lagre number of topics. These mostly consern the topic of looking at how we define evolution, and how this definition is influced by the assupmutons from nutral theory. This paper does derive a new equations free of assumptions besides the ones used to derive inputs. it then demonstraights the descriptcies between the models.

[4] M. M. Desai, D. S. Fisher, and A. W. Murray, "The speed of evolution and maintenance of variation in asexual populations," *Current Biology*, vol. 17, no. 5, pp. 385–394, 2007. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0960982207009840

This paper reviews CI topics and provides a new model which allows for full CI. Meaning the new clones are allowed to apeare in the population and an arbirary number of them could be competing at a given time. The trade off for this generalizability is the assumptions that all mutants have the same fitness/ selective properties.

[5] E. Domingo and C. Perales, "Viral quasispecies," *PLOS Genetics*, vol. 15, no. 10, p. e1008271, oct 2019. [Online]. Available: https://dx.plos.org/10.1371/journal.pgen.1008271

A comprehensive review of support for Quasi-Species theory. This paper covers he hsitorical basis and gives a comprehensive coverage of evidence for viral QS. It also discusses the following topics, Error-prone replication and mutant spectra, phenotypic reservoir, adaptive parameters, intramutant spectrum quasispecies memory, sequence space, population bottle neck, biological constranits, connections with viral pathogenesis, and QS and long term evolution.

[6] J. Frazer, P. Notin, M. Dias, A. Gomez, J. K. Min, K. Brock, Y. Gal, and D. S. Marks, "Disease variant prediction with deep generative models of evolutionary

data," *Nature*, vol. 599, no. 7883, pp. 91–95, nov 2021. [Online]. Available: https://www.nature.com/articles/s41586-021-04043-8

This paper covers a neural net work that uses the amino acid sequence of differnt protiens to produce a evolutionary index. The evolutionary index is then used to produce a distribution of of differnt sequences and make a prediction of B̈enign, unknowen, and Pathogenic. The distribution allows for an estimate of the confidence of the prediction. They used unsupervised learning and were able to achive an avg AUC = 0.92

[7] P. Gerrish and R. Lenski, "The fate of competing beneficial mutations in an asexual population," *Genetica*, vol. 102-103, pp. 127–44, 03 1998.

This is a paper sumerizing the work done on Cloneal Interferance (CI), since the original paper. The paper provides a summary of the differnt extentions on the original CI paper including adding more then one clone at a time and using deterministic models to characterize the general behaviour.

[8] J. Haigh, "The accumulation of deleterious genes in a population muller's ratchet," *Theoretical Population Biology*, vol. 14, no. 2, pp. 251–267, 1978. [Online]. Available: https://www.sciencedirect.com/science/article/pii/0040580978900278

This is a classic paper. Beautiful old math paper with wonky old math notation. Several closed equations are derived to show that positive mutations must appeare in the populations since the pop would go to exinction with out it. The models produced in this paper prodminently show MUller's Ratchet in full effect, and produce sumary satistics since computing resorces were scarese at the time.

[9] P. G. Harrison, "Reversed processes, product forms and a non-product form," *Linear Algebra and its Applications*, vol. 386, pp. 359–381, jul 2004. [Online]. Available: https://linkinghub.elsevier.com/retrieve/pii/S0024379504001089

NOT CLEAR YET.

[10] E. C. Holmes and A. Moya, "Is the Quasispecies Concept Relevant to RNA Viruses?" *Journal of Virology*, vol. 76, no. 1, pp. 460–462, jan 2002. [Online]. Available: https://journals.asm.org/doi/10.1128/JVI.76.1.460-462.2002

This is a letter to the editor, discussing the issues of applying quasi-species to viral RNA. It starts by critisizing the lack of formal definitions of QS. This letter ardresses, critisims (lack of def, lack of drift), and evidence (strong theoretic basis?) it makes arguments but many seem flimsy now.

[11] M. A. Huynen, P. F. Stadler, and W. Fontana, "Smoothness within ruggedness: the role of neutrality in adaptation," *Proceedings of the National Academy of Sciences*, vol. 93, no. 1, pp. 397–401, 1996. [Online]. Available: https://www.pnas.org/content/93/1/397

This paper is fascianting. It used a simulation to show the importance of nutral mutation on secondary structure evolution. This was achived by simulationg mtation using a diffution model with imperically derived hyper params. This paper then shows that nutral mutation allows for nutral movement to new wells of fitness, that are otherwise unreachable f selective forces are too strong. Worth Re-reading. :)

[12] M. Kimura, "Evolutionary Rate at the Molecular Level," *Nature*, vol. 217, no. 5129, pp. 624–626, feb 1968. [Online]. Available: https://www.nature.com/articles/217624a0

A paper on the early scuttle butt of how to compute mutation rates. It draws its own conclusion, which has been since refuted but has realted neutral theory with molecular evolution which is molecular clock theory.

[13] I. Krukov and A. J. de Koning, "Haldane's probability of mutant survival is not the probability of allele establishment," *bioRxiv*, 2019. [Online]. Available: https://www.biorxiv.org/content/early/2019/07/16/704577

This paper reinterprates the idea of establishment from the inital notes of Haldane. The idea that establishment is the point at which a population is no longer suseptabl to drift was the orginigal and provailing theory for establishment. This paper recontextualizes it as a population frequency where the odds ratio between going to fixation and exinction are K. They derive many nice formaula and show examples.

[14] S. Matuszewski, L. Ormond, C. Bank, and J. D. Jensen, "Two sides of the same coin: A population genetics perspective on lethal mutagenesis and mutational meltdown ," *Virus Evolution*, vol. 3, no. 1, 03 2017. [Online]. Available: https://doi.org/10.1093/ve/vex004

An exellent review paper. It goes through and cites many of the ideas and evidence for and against many of them. This paper also makes some unfair assumptions in my opinion. Mainly that if mean fitness is less than 1, the population will go extinct, this seems like a gross over assumption. The population will certainly decrease, but depending of the facorts which drive the change in fitness must be considered when making such a statement.

[15] A. Moya, E. C. Holmes, and G.-C. Fernando, "The population genetics and evolutionary epidemiology of RNA viruses," *Nature Reviews Microbiology*, vol. 2, no. 4, pp. 279–288, apr 2004. [Online]. Available: http://www.nature.com/articles/nrmicro863

This paper reviews viral RNA mechanisms and some quantifications around the variables of mutation. Then it discusses how studies are structred for wet lab research of mutation and evolution studies. Helps to give a large overview of the topic of viral RNA without discussing Quasi-Species.

[16] on behalf of the ClinGen Sequence Variant Interpretation Working Group (ClinGen SVI), S. V. Tavtigian, M. S. Greenblatt, S. M. Harrison, R. L. Nussbaum,

S. A. Prabhu, K. M. Boucher, and L. G. Biesecker, "Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework," *Genetics in Medicine*, vol. 20, no. 9, pp. 1054–1060, sep 2018. [Online]. Available: http://www.nature.com/articles/gim2017210

This paper uses naive bayes method to develop a classifier for pathogeneity of a genetic varient. This method is okay, it is not very strong, but is laying the ground work for future studies. It does a good job of relating the ACMG guidelines to a mathematical framework.

[17] H. A. Orr, "The Rate of Adaptation in Asexuals," *Genetics*, vol. 155, no. 2, pp. 961–968, 06 2000. [Online]. Available: https://doi.org/10.1093/genetics/155.2.961

A fantatstic paper, very similar to the results to the de Koning 2018 bio Arxiv paper. They looked at the effect of mutation rate on asexual populations and tried to find optimal adaptation rates. Through the assumptions made they were able to show that optimal mutation rate for adaptation is actually at the deleterious mutation frequency. Quite strange but they showed it under several sets of assumptions. FANTASTIC!

[18] J. M. Smith, "What determines the rate of evolution?" *The American Naturalist*, vol. 110, no. 973, pp. 331–338, 1976. [Online]. Available: http://www.jstor.org/stable/2459757

This paper discusses the pro's and con's of using differnt measures for understanding the evolution rates. The main idea is to use the fitness and its related measures as a stand in for the rate of adaptation.

[19] P. D. Sniegowski and P. J. Gerrish, "Beneficial mutations and the dynamics of adaptation in asexual populations," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 365, no. 1544, pp. 1255–1263, 2010. [Online]. Available: https://royalsocietypublishing.org/doi/abs/10.1098/rstb.2009.0290

The paper provides a review of models and developments for clonal interferance modles. This sub area of asexual populations has grown significantly since the 1990's when the first CI model was proposed. This paper breacks the models in the 3 catagories, Strong Seceltion Weak Mutation (SSWM), (SSSM), and (WSSM). The historical analysis and motivation for SSSM was discussed at legnth.

[20] A. Wagner, "Information theory, evolutionary innovations and evolvability," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 372, no. 1735, p. 20160416, Oct 2017. [Online]. Available: https://doi.org/10.1098/rstb.2016.0416

This paper looked at the idea of applying information theory to the mapping between Phenotype space and genotype space. The model selected had significant restrictions for simplicity, but did allow for the establishing of some interesting results, like the fact that "The complexity increase is generally lower if the old site had high information content, which shows

that phenotypic information change can depend on ancestral phenotypes and are thus contingent on evolution theory." These results are based on the understanding of the amount of information stuck in a given moleclar structure.

[21] C. O. Wilke, "Molecular clock in neutral protein evolution," *BMC Genetics*, vol. 5, no. 1, p. 25, 2004. [Online]. Available: http://bmcgenet.biomedcentral.com/articles/10.1186/1471-2156-5-25

An interesting paper discussing the impact of population size and mutation rate on the interpitation of molecular clock theory. This was an attempt to show that neutral theory could be used to help awnser the disconect of emperical results and molecular clock theory, called "overdispersed molecular clock". They were able to help account for overdisperstion when mutation is low and population is resnably low.

[22] ——, "The Speed of Adaptation in Large Asexual Populations," *Genetics*, vol. 167, no. 4, pp. 2045–2053, 08 2004. [Online]. Available: https://doi.org/10.1534/genetics.104.027136

Cool paper, Wilke does derive nice closed form equations, classic Wilke. Shows that as mutation increases rate of evolution decreases, this is because his def of adaptation is related to fixation. Interesting results all the same.

[23] ——, "Quasispecies theory in the context of population genetics," *BMC Evolutionary Biology*, vol. 5, no. 1, p. 44, dec 2005. [Online]. Available: https://bmcevolbiol.biomedcentral.com/articles/10.1186/1471-2148-5-44

This paper is wonderful, it describes and relates the equations from quasispecies and the conscepts from evolutionary theory. It shows how the QS equations can be derived from the principals mutation-selection equations.