Integration of non-transitive relationships in biomedical research
Master's Project Proposal

Non-transitivity is a phenomenon usually defined through the classical example of a set of four Efron dice. Scores on these dice are distributed in such a way that in the long run die A beats die B, B beats C, C beats D and D paradoxically beats A. Non-transitivity has been observed in machine learning/data science, econometrics, sports (tennis and chess), and recently in medical applications such as biology and clinical trials. Non-transitive relationships between different treatments of a clinical trial, for example, mean that there is no winning treatment that outperforms the others. Despite the presence of non-transitivity across diverse fields, our understanding of its implications for analytical conclusions remains limited.

The field is divided over the acceptability of non-transitivity. Some proponents advocate for methods that are exclusively transitive, such as comparisons of means. Conversely, others believe that when the time to all-cause death in a randomized trial forms a non-transitive loop, it provides crucial information, signifying the ineffectiveness of the treatments being compared. This latter viewpoint contends that non-transitivity is part of a more extensive phenomenon, the strength of stochastic relationships. We suggest that statistics capable of detecting stochastic precedence are attuned to this information, whereas traditional mean comparisons in subgroups are not. Thus, statistics that can form non-transitive loops are responsive to this property (win ratio, log-rank tests, hazard ratios and Area Under the Receiver Operating Characteristics Curve among others) and can serve as a valuable adjunct to more conventional measures.

Project goals:
In this project we will study how to integrate strength of stochastic precedence in medical and biological applications.

Work Plan:
1. Review literature on stochastic precedence and non-transitivity.
2. Classify most important statistics in medical field into transitive and non-transitive. A good source would be survival analysis: hazard ratios, logrank tests, a versatile test (Uno et al. 2015), Pepe and Femming test.
3. Create a hierarchy of the strength of stochastic precedence and place AUCROC and win statistics into this structure, similar to other fields. For example, a hierarchy of different levels of stochastic precedents that guarantee for example:
    a. AUCROC=1,
    b. Non-transitivity,
    c. Specific relationships among means
4. Determine whether we can propose other stochastic order relationship(s) that are more relevant to medical research.
5. Apply what we learned in this project to the analysis of randomized controlled trials. Specifically, to ALLHAT trial of blood pressure treatments and other trials as available.
6. Write a draft of a scientific manuscript, which can form the basis of a Masters' thesis.

Prerequisites:
1. An interest to conduct original research in a fast-moving field
2. An interest in and knowledge of applied statistical methods

3. Strong background in proof-based mathematics
4. An interest in applying results to analysis of clinical trials and classification models
5. Interest in developing theoretical methods independently and in a team and applying them to the medical field
6. Experience in Python and/or R programming

Grading:

- To receive a 6 the student must: meet the general goals and timeline of the thesis; work independently, demonstrate curiosity in the thesis topic and contribute her/his own ideas; communicate intermediate results clearly; write detailed and clear intermediate and final reports; document project code well; give a clear final presentation; produce results that are at the level expected for acceptance at leading international conferences or peer-reviewed journals.
- To receive a 5 the student must: meet the general goals of the thesis; work independently; write a detailed and clear final report; and give a clear final presentation; document project code well.
- To receive a 4 the student must: partially meet the general goals of the thesis; work somewhat independently; write a satisfactory final report; and give an understandable final presentation; document project code well.

Advisors:	Dr. Olga Demler demlero@ethz.ch	ETH D-INFK/ BWH, Harvard Medical School
Supervisor:	Prof. Dr. Gunnar Rätsch	D-INFK

References:

Demler OV et al Non-transitivity of the Win Ratio and Area Under the Receiver Operating Characteristics Curve (AUC): a case for evaluating the strength of stochastic comparisons https://arxiv.org/abs/2309.01791,

Lumley, T. and Gillen, D.L., 2016. Characterising transitive two-sample tests. *Statistics & Probability Letters*, *109*, pp.118-123.

Poddiakov, A.N., 2023. Are mathematicians, physicists and biologists irrational? Mathematical and natural science studies vs. the transitivity axiom. *Mathematical and natural science studies vs. the transitivity axiom (February 16, 2023)*.

Liao, M.J., Miano, A., Nguyen, C.B., Chao, L. and Hasty, J., 2020. Survival of the weakest in non-transitive asymmetric interactions among strains of E. coli. *Nature communications*, *11*(1), p.6055.

Uno, H., Wittes, J., Fu, H., Solomon, S.D., Claggett, B., Tian, L., Cai, T., Pfeffer, M.A., Evans, S.R. and Wei, L.J., 2015. Alternatives to hazard ratios for comparing the efficacy or safety of therapies in noninferiority studies. *Annals of internal medicine*, *163*(2), pp.127-134.

Pepe, M.S. and Fleming, T.R., 1991. Weighted Kaplan-Meier statistics: Large sample and optimality considerations. *Journal of the Royal Statistical Society Series B: Statistical Methodology*, *53*(2), pp.341-352.

Pocock, S.J., Ariti, C.A., Collier, T.J. and Wang, D., 2012. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. European heart journal, 33(2), pp.176-182.