Evaluation of Approaches for Identifying High-Dimensional Individual-Level Surrogate Markers Applied to Vaccinology

M2 Internship

Background

Direct measurement of the primary outcome in a clinical trial is often time-consuming, expensive, or infeasible. For instance, when the outcome is rare, it may take many years to observe enough events to observe a statistically significant difference between groups, even if the treatment is effective. Consequently, there is considerable interest in identifying *surrogate markers*-variables that can be observed more quickly, at lower cost, or with greater ease, and that can serve as reliable substitutes for the primary outcome to accurately infer treatment effects [1].

Surrogate markers may be classed into two general categories. *Trial-level surrogates* (TLS) are predictive of the average treatment effect in a given population, whereas *individual-level surrogates* (ILS) allow for the prediction of individual treatment effects. Surrogates from these two classes are conceptually distinct and differ in clinical utility [2]: while TLS can be used to improve the efficiency of clinical trials, ILS can be used for patient-level decision making, known as precision medicine. The latter is particularly important in the context of vaccinology, where marked differences in vaccine responses are seen between individuals, a phenomenon which is poorly understood. The discovery of novel ILS for the vaccine response would therefore allow for the prediction of low-responder individuals whose treatment could be tailored to improve their chances of adequate disease protection.

High-throughput technologies, such as transcriptomics data, hold great promise for understanding the molecular factors associated with effective vaccine responses. Transcriptomic data describe gene expression-the process by which information encoded in DNA is transformed into proteins that shape phenotypes. Changes in gene expression occur in the first hours and days after vaccination and are likely to reflect early biological perturbations leading to protective immunity. Although previous works in the literature have explored the potential of transcriptomic data in the prediction of individual vaccine responses [3] and trial-level surrogacy [4], the concept of individual-level surrogacy has not been investigated. Due to the high-dimensional nature of the data, the evaluation of ILS in this context requires specialist methodology. The objectives of this internship project will be to identify, apply and compare different methodological approaches for evaluating ILS in the context of transcriptomic experiments in vaccine trials.

Objectives

1. Benchmark various univariate and multivariate approaches for the identification of individual-level surrogate markers in the high-dimensional context (e.g. with simulated data)
2. Apply the selected approaches to a public molecular vaccinology dataset [5]
3. Evaluate the robustness of any derived signatures across multiple studies & populations

Required Skills

- Master 2/Bachelor/Engineering school with a major in biostatistics or similar
- Programming proficiency with R
- Interest in biomedical research and scientific curiosity
- Written and spoken English proficiency

Hosting laboratory
SISTM Team
INSERM U1219 and INRIA Sud-Ouest

Location
Bordeaux Population Health Research Center
Université de Bordeaux – ISPED
146, Rue Léo Saignat
33076 Bordeaux

Duration:
Internship of 4 to 6 month available starting from January 2025.

Compensation:
Intern gratification according to government recommendations (15% of social security ceiling, i.e. around 660€/month).

Contact:
Send a detailed CV and a motivation letter to Boris Hejblum (boris.hejblum@u-bordeaux.fr) and Arthur Hughes (arthur.hughes@u-bordeaux.fr).

References

[1] Christensen, R., Ciani, O., Manyara, A. M., and Taylor, R. S. (March, 2024) Surrogate endpoints: a key concept in clinical epidemiology. *Journal of Clinical Epidemiology,* **167**, 111242.

[2] Buyse, M., Saad, E. D., Burzykowski, T., Regan, M. M., and Sweeney, C. S. (March, 2022) Surrogacy Beyond Prognosis: The Importance of "Trial-Level" Surrogacy. *The Oncologist,* **27**(4), 266–271.

[3] Querec, T. D., Akondy, R. S., Lee, E. K., Cao, W., Nakaya, H. I., Teuwen, D., Pirani, A., Gernert, K., Deng, J., Marzolf, B., Kennedy, K., Wu, H., Bennouna, S., Oluoch, H., Miller, J., Vencio, R. Z., Mulligan, M., Aderem, A., Ahmed, R., and Pulendran, B. (November, 2008) Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. *Nature Immunology,* **10**(1), 116–125.

[4] Hughes, A., Parast, L., Thiébaut, R., and Hejblum, B. P. (September, 2025) RISE: Two-Stage Rank-Based Identification of High-Dimensional Surrogate Markers Applied to Vaccinology. *Statistics in Medicine,* **44**(20–22).

[5] Hagan, T., Gerritsen, B., Tomalin, L. E., Fourati, S., Mulè, M. P., Chawla, D. G., Rychkov, D., Henrich, E., Miller, H. E. R., Diray-Arce, J., Dunn, P., Lee, A., Deckhut-Augustine, A., Gottardo, R., Haddad, E. K., Hafler, D. A., Harris, E., Farber, D., Kleinstein, S. H., Levy, O., McElrath, J., Montgomery, R. R., Peters, B., Pulendran, B., Rahman, A., Reed, E. F., Rouphael, N., Sarwal, M. M., Sékaly, R. P., Fernandez-Sesma, A., Sette, A., Stuart, K., Togias, A., Tsang, J. S., Levy, O., Gottardo, R., Sarwal, M. M., Tsang, J. S., Suárez-Fariñas, M., Sékaly, R.-P., Kleinstein, S. H., and Pulendran, B. (October, 2022) Transcriptional atlas of the human immune response to 13 vaccines reveals a common predictor of vaccine-induced antibody responses. *Nature Immunology,* **23**(12), 1788–1798.