# Combining dynamic modelling, expectation-maximization and machine learning for predicting individual response to immunotherapy in patients with advanced melanoma

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Immune checkpoint inhibitors have significantly improved the treatment of cancers. Yet, the overall response rate to these drugs is low, and predictive tools for selecting responsive patients are needed. Previously, we have developed an algorithm for predicting the response of patients with advanced melanoma to pembrolizumab [1]. This algorithm was based on a mechanistic mathematical model for the interactions of the immune system and melanoma tumors. We used data of 54 patients from Israel and Germany to develop and initially validate this algorithm, with reasonable accuracy (Cohen's kappa=0.489 for predicting the time interval of progression). In the present work we aim at validating the algorithm by an independent patient population from the Victorian Melanoma Service at Monash University, Australia. The original algorithm failed to satisfactorily generalize to the new data. This can be attributed to batch effect (patients from a different origin, a different period, or treated in a different health system). To expand the applicability of our algorithm, we trained and validated it by the entire patient cohort from the three different sources, applying an improved statistical and modeling methodology. In this work we demonstrate how an intricate predictive algorithm, involving statistical and mechanistic dynamical models can be sequentially improved by fine-tuning and testing on additional clinical data. Our goal is to develop a flexible framework for providing reliable quantitative response predictions (e.g., the time to radiological progression) for newly admitted patients, which will become an informative tool aiding clinicians in their decision making.

## References

[1] Tsur N, Kogan Y, Avizov-Khodak E, Vaeth D, Vogler N, Utikal J, Lotem M, Agur Z, *Predicting response to pembrolizumab in metastatic melanoma by a new personalization algorithm*, J of Translational Medicine 2019;17(1):338. doi: 10.1186/s12967-019-2081-2

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