ESTIMATING CAUSAL EFFECTS OF MULTI-DIMENSIONAL BIOMARKERS FROM REPEATED MEASURES UNDER TREATMENT: METHODS AND APPLICATION TO IMMUNOTHERAPY IN METASTATIC MELANOMA

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When assessing the effects of multidimensional biomarkers collected at treatment initiation and under treatment, setting the level of the expression of a given biomarker is unfeasible. Identifying the causal effect of a marker in observational context is challenging because the expression values of other biomarkers induce confounding.

In a multidimensional context, relationships between variables cannot be ordered within a directed acyclic graph (DAG); in fact conditional dependencies determine only the skeleton and the so-called v-structures of the graph. A same set of conditional dependencies can be described by several DAGs constituting an equivalent class named completed partially directed acyclic graph (CPDAG).
Causal inference methods such as IDA [1] (Intervention calculus when DAG is absent) have been introduced to identify DAGs and causal effects when the DAG in unknown by estimating the CPDAG using the PC-algorithm [2] and the intervention calculus [3].

When considering any set $S \subseteq \{X_1, \ldots, X_p, Y\} \backslash \{X_i\}$, the causal effect of biomarker X_i on outcome Y is given by the regression coefficient β_i of X_i on Y and S.

$$Y \sim \beta_i X_i + S, with\ Y \notin S.$$

Integrating repeated measures implies that a given X_i measured at time t' could only be caused by its parents. Potential parents are biomarkers which are measured earlier at time t with $t < t'$. In the DAG, arrow could only be directed from ancestor to descendant (Figure 1).
Including a priori expert knowledge on causal pathways improve the identification of the true causal DAG and enhance the performance of the methods by reducing the size of the equivalent classes (figure 2).

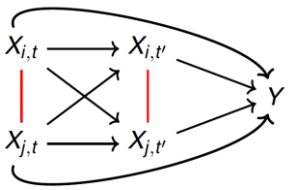

Figure 2

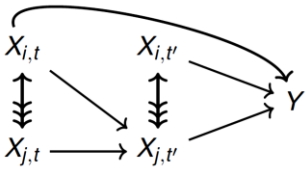

Figure 1

We aimed to extend the IDA through two different ways such as the integration of repeated measures of biomarkers (fig.1) and the knowledge of experts (fig.2).
Application: We will apply our methods to identify among 150 immunologic markers measured at treatment initiation or under treatment (from baseline to up to 5 infusions) in 39 patients with metastatic melanoma treated with ipilimumab those associated with three binary endpoints: occurrence of toxicity, of progression and of death.

References:
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3.Pearl J. Causality. Cambridge university press; 2009 Sep 14.