**Motivations**

The precise estimation of interaction is heavily dependent on the assumption of scales (i.e., interaction on multiplicative scales and interaction on additive scales). To be more specifically, the presence, sign, and magnitude of an interaction may all depend on the scale. In addition, the difference scale is useful for optimizing public health interventions (i.e., determining which subgroups would benefit most from treatment and assessing the public health significance of interaction. Previous literatures recommended to present both additive and multiplicative measures of interaction. However, measures of multiplicative interaction are most frequently reported, due to the convenience of logistics regression application, while additional work is required to obtain measures of additive interaction, leading to the less practical reporting of this measure. Here we reported measures of interactions on both scales using dataset generated with interaction on either scale and assessed the difference between true value and estimated value with respect to different conditions (Table 1).

Additionally, the true scales of interaction are usually unknown in epidemiology studies, and the decision will significantly rely on clinical and biological knowledge. Here we applied both traditional epidemiology models (i.e., generalized linear model, GLM) and machine learning techniques (i.e., IPTW) to figure to whether ML could outperform in measuring the interaction relationship without making assumption of the interaction scale.

**Methods**

we applied two types of data-generating mechanisms to construct data sets with interaction on different scales (i.e., multiplicative scale and additive scale). For both mechanisms, exposure *X*, effect modifier *M*, and outcome *Y* are assumed to be binary through the article (i.e., *X*∈{0;1}, *M*∈{0;1}, and *Y*∈{0;1}). The interaction between exposure and effect modifier can be assessed by including the product of *X* and *M* in the regression model as an additional covariate.

Per data-generating mechanism for multiplicative interaction, the effect of exposure *X*, effect modifier *M*, and their interaction on the probability of outcome is modelled as

and binary outcome Y is drawn from a binary distribution with B (n, p=P(Y=1)). In Eq.(1), odds ratio for exposure, odds ratios for effect modifier, and true multiplicative interaction. Generalized linear models (GLMs) with a logit link are fitted on the data generated for each scenario and the regression coefficients are used for the calculation of estimated interaction on both scale (Table 1, column 2). Both true and estimated additive interactions for data generated with multiplicative interaction were measured using relative excess risk due to interaction (RERI), assuming that the odds ratios approximate risk ratios.

Per data-generating mechanism for additive interaction, the effect of exposure *X*, effect modifier *M*, and their interaction on the probability of outcome is modelled as

and binary outcome Y is drawn from a binary distribution with B (n, p=P(Y=1)). In Eq.(2), risk difference for exposure, risk difference for effect modifier, and true additive interaction. Generalized linear models (GLMs) with an identity link are fitted on the data generated for each scenario and the regression coefficients are used for the calculation of estimated interaction on both scale (Table 1, column 3). Both true and estimated additive interactions for data generated with additive interaction were measured on the risk ratio scale, the effect of both exposures together exceeds the product of the effects of the two exposures considered separately.

Table 1. Equations for true and estimated interaction on both scale

|  |  |  |  |
| --- | --- | --- | --- |
|  | Interaction Scale | Multiplicative interaction | Additive interaction |
| True | Additive |  |  |
| Multiplicative |  |  |
| Estimated | GLM Model |  |  |
| Additive |  |  |
| Multiplicative |  |  |

Numerous different settings were considered to evaluate varying conditions (Table 1). For each simulation scenario, 100 Monte Carlo simulations, each with a sample size of 500 subjects, were generated. Performance was evaluated via relative biasand MSE () for the points estimates of additive interaction, as well as log transformed relative bias and corresponding MSE () for the points estimates of multiplicative interaction. Multiplicative interactions were log transformed to be comparable to additive interaction (i.e., the range of log transformed multiplicative interaction is the same as additive interaction, from - to ).

Table 2. Range of different settings when simulating data on different scales

|  |  |  |
| --- | --- | --- |
| Settings | Mechanism for multiplicative interaction | Mechanism for additive interaction |
|  |  |  |
|  | ) |  |
|  | ) |  |
|  | ) |  |
|  | 1 | 0.1 |

All aspects of the simulation study including data generation, estimating regression coefficients, and summarizing and visualizing the results were performed with the statistical software R.

Results

Figure 1. Summary of estimated interactions and true interactions, using data generated with interaction on additive scales.

Calendar

Description automatically generated with low confidenceChart

Description automatically generated

We first compared the estimated interaction and true interaction on both scales. The estimated interaction on additive scale was shown less sensitive to the change of effect of exposure on outcome (RD) and probability of the exposure (Pi), compared to the estimated interaction on multiplicative scale. The estimated interaction on multiplicative scale decreased with the increased of RD holding true additive interaction constant. In addition, 95% CIs of estimated interactions on additive scale remained tight to the change of parameters, while 95% CIs of estimated interactions on multiplicative scale became wider along with the increase of probability of the exposure.

Figure 2. Summary relative bias of estimated interaction, using data generated with interaction on additive scales.

Chart

Description automatically generated

Chart

Description automatically generated

We then compared the bias of estimated interactions on both scales. The bias of estimated additive interaction is more sensitive to the change of parameters (compare red to blue), when data was generated with sub-additive interaction. However, the bias of estimated additive interaction is less sensitive to the change of parameters, when data was generated with supper-additive interaction. The confidence interval of bias of estimated additive interaction is wider when the magnitude of true additive interaction is smaller. The confidence interval of bias of estimated multiplicative interaction becomes wider along with the increase of Pi.

Figure 3. Summary of estimated interactions and true interactions, using data generated with interaction on multiplicative scales.

Chart

Description automatically generated

Chart

Description automatically generated

We first compared the estimated interaction and true interaction on both scales. The estimated interaction on additive scale was shown more sensitive to the change of effect of exposure on outcome (OR) and probability of the exposure (Pi), compared to the estimated interaction on multiplicative scale. In addition, 95% CIs of estimated interactions on additive scale become wider along with the increase of magnitude of the true interaction on multiplicative scale, while 95% CIs of estimated interactions on multiplicative scale became wider along with the increase of probability of the exposure.

Figure 4. Summary relative bias of estimated interaction, using data generated with interaction on multiplicative scales (true multiplicative interaction > 1).

Chart

Description automatically generated

Calendar

Description automatically generated with medium confidence

The variance of relative bias for interaction on both scales decreased with increasing effect of exposure and increasing magnitude of true multiplicative interaction, respectively. Quadratic association was found between the probability of the exposure and the relative biased for interaction on multiplicative scale. On additive scale, interactions were more likely to be underestimated (relative bias < 0) when the exposure was protective to the outcome (OR < 1).