Suppose we have an experiment to fit the Michaelis-Menten relationship

\[ y_i = \frac{\beta_1 x_i}{\beta_2 + x_i} + \epsilon_i, \quad i = 1, 2, \ldots, n, \]

where \( \epsilon_i \sim N(0, \sigma^2) \) (independent for each \( i \)). Suppose the ordinary least squares estimates are \( \hat{\beta}_1, \hat{\beta}_2 \), that \( \hat{s}^2 \) is the estimate of \( \sigma^2 \), and assume \( \text{Cov} \left( \begin{array}{c} \hat{\beta}_1 \\ \hat{\beta}_2 \end{array} \right) \approx \begin{pmatrix} a_{11} & a_{12} \\ a_{12} & a_{22} \end{pmatrix} \sigma^2 \).

(a) (30 points) Show that, as an approximation, we may take

\[ a_{11} = \frac{\sum x_i^2}{(\hat{\beta}_2 + x_i)^4} \left\{ \frac{\sum x_i^3}{(\hat{\beta}_2 + x_i)^2} \frac{\sum x_i^2}{(\hat{\beta}_2 + x_i)^4} - \left\{ \sum \frac{x_i^2}{(\hat{\beta}_2 + x_i)^3} \right\} \right\} \]

and give corresponding expressions for \( a_{12}, a_{22} \).

For the remainder of the question, assume that the traditional linear model distribution theory for \( (\hat{\beta}_1, \hat{\beta}_2, s^2) \) is also valid in this case — in particular, if \( k_1 \) and \( k_2 \) are constants and \( \text{Var}(k_1 \hat{\beta}_1 + k_2 \hat{\beta}_2) = k_3^2 \sigma^2 \) for some constant \( k_3 \), then \( (k_1 \hat{\beta}_1 + k_2 \hat{\beta}_2)/k_3^2 \) has a \( t_{n-2} \) distribution. Suppose we are interested in determining the value \( x = x^* \) for which the reaction rate \( \beta_1 x^*/(\beta_2 + x^*) \) is some predetermined value \( c \).

(b) (30 points) Suggest an estimator \( \hat{x}^* \), and calculate its approximate standard error by the delta method.

(c) (40 points) Show how it is possible to construct a \( 100(1 - \alpha)\% \) confidence set for \( x^* \) by means of a sequence of tests of the hypothesis \( H_0 : x^* = x_0 \) (for given \( x_0 \)) at significance level \( \alpha \). Assume \( t^* \) is the \( (1-\alpha/2) \)-quantile of the \( t_{n-2} \) distribution. Derive a condition (in terms of \( \hat{\beta}_1, \hat{\beta}_2, c \), etc.) for this confidence set to be a confidence interval, and show that in that case, the length of the interval is

\[
2c \sqrt{\left\{ \frac{(\hat{\beta}_2 (\hat{\beta}_1 - c) - s^2 t^* a_{12})^2}{(\hat{\beta}_1 - c)^2 - s^2 t^* a_{11}} - \left\{ (\hat{\beta}_1 - c)^2 - s^2 t^* a_{11} \right\} (\hat{\beta}_2 - s^2 t^* a_{22}) \right\} (\hat{\beta}_1 - c)^2 - s^2 t^* a_{11}}
\]

What happens in the cases where the confidence set is not an interval?