Using interpolation to reduce computing time for analysis of large but simple data sets with application to design of epidemiological studies

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Abstract

One way to investigate the precision of estimates likely to result from planned experiments and planned epidemiological studies is to simulate a large number of possible outcomes and analyse the sets of possible results. This appears to be computationally expensive for some multi-stage designs, so choice of designs is instead based on theoretical derivation of expected information. This paper shows that for some types of studies the analysis of large numbers of simulated outcomes can be achieved more rapidly by making use of interpolation.

Keywords

Experimental design; interpolation; maximum likelihood; multi-stage epidemiological studies

Introduction

The general problem that motivated this work is the design of cost-effective large epidemiological studies. More specifically, consider investigating the health effects of environmental exposures when the cost of accurately measuring environmental exposure is large. Two-stage designs are often practical, with environmental exposure being measured to greater precision in the second stage than in the first stage.

We will consider in detail the first hypothetical two-stage trial presented in Table 1 of Morara et al (2007) which is intended for assessing the relationship between pesticide exposure and autism. The first stage of the study has 63350 people. Their autism status is assessed without error and their pesticide exposure is measured by a method which has correlation 0.3 on a logarithmic scale with the true pesticide exposure. In the second stage of the study, 219 individuals are chosen at random and their true pesticide exposures are measured accurately.

Our approach to studying the usefulness of this experimental design is to simulate a large number of sets of data, to estimate the parameters of the model using each set of data, and to summarize the performance of the experimental design by looking at the distribution over simulations of parameter estimates and their standard errors.

The logarithm of true pesticide exposure, $Z$, was taken to have a standard normal distribution. The logarithm of the approximate measure of pesticide exposure, $Z_A$, was computed as

$$Z_A = Z + \varepsilon$$
where $\varepsilon$ has a normal distribution with mean zero and variance $91/9$. This variance has been chosen so that the correlation of $Z_A$ and $Z$ is $\text{Cov}(Z_A, Z)/\sqrt{\text{Var}(Z_A)\text{Var}(Z)} = 1/\sqrt{100}/9 = 0.3$. The response variable, $Y$, is one if a person is autistic and zero otherwise. The logit of the probability of autism is $(Z - 4.733)/0.693$. This relationship was chosen so that a unit increase in the natural logarithm of pesticide exposure increases the odds of autism by a factor of 2 and the overall risk of autism is $3/1000$.

After each set of data is simulated, a model of the same form as the one used to generate the data is fitted by maximum likelihood. There are seven parameters: the mean and standard deviation of the true pesticide exposure, the mean and standard deviation of approximate pesticide exposure, the correlation between true and approximate pesticide exposure, and the location and scale parameters of the logistic relationship between true pesticide exposure and the probability of autism. These parameters are collectively denoted by $\theta$.

For the 219 people participating in the second stage of the study, their contribution to the log likelihood of $\theta$ is the logarithm of the density of $Y$ given $X$ which can be easily computed using the probability density of a logistic distribution. For the 63350 − 219 = 63131 people not participating in the second stage of the study, their contribution to the log likelihood of $\theta$ is the logarithm of the density of $Y$ given $Z_A$. This density can be computed by integrating the density of $Y$ given $Z$ over the distribution of $Z$ given $Z_A$. This integration can be done to sufficient accuracy by using 8-point Hermite integration.

If we compute each of the logistic densities separately, then there are $219 + 63131 \times 8 = 505267$ of them to be computed for each evaluation of the log likelihood. The log likelihood will be evaluated many times during the process of estimating $\theta$ by maximum likelihood. We expect to need to do this for many simulated data sets for each of many possible experimental designs. The total computer time required to do this would be inconveniently large.

The basic idea

The characteristic of this situation that we can exploit to speed up the computations is that, for given $\theta$, the contributions to the log likelihood for the people not participating in the second stage of the study are a function of only a single number, $Z_A$. For large data sets, the total of these contributions can generally be computed much more efficiently by using piecewise polynomial interpolation than by computing each of them directly.

For Lagrange interpolation, Abramowitz and Stegun (1965, formula 25.2.2) tells us that for the $i$th given nodes $x_0, x_1, \ldots, x_n$ and corresponding function values $f_0, f_1, \ldots, f_n$, the interpolated value at $x$ is $\sum_{i=0}^{n} l_i(x)f_i$ where

$$l_i(x) = \frac{(x - x_0) \cdots (x - x_{i-1})(x - x_{i+1}) \cdots (x - x_n)}{(x_i - x_0) \cdots (x_i - x_{i-1})(x_i - x_{i+1}) \cdots (x_i - x_n)}.$$  

For instance, if the nodes are taken to be $x_i = i$ for $i = 0, 1, \ldots, 19$ then for $x = 4.5$ the weights, $l_i(4.5)$, are 0.00001019143, -0.0000289622, 0.003136923, -0.0296265, 0.355518, 1.066554, -0.8295419, 0.9243467, -0.9903715, 0.9414643, -0.770289, 0.533277, -0.3081156, 0.1463898, -0.05613442, 0.01692943, -0.003864326, 0.0006273847, -0.00061454575 and 0.000003162859, respectively. This method of interpolation is equivalent to putting a polynomial of order $n$ through the interpolation nodes and evaluating this polynomial at $x$.

We have generally used equally-spaced interpolation nodes. Two well-known reasons for being wary of polynomial interpolation do not stop this procedure from being useful.

1. When high-order polynomials are fitted to data, the coefficients of the fitted polynomials are very sensitive to the function values. This is not a problem because we only make use of
the fitted values; and these are usually not particularly sensitive to the function values, as can be seen by looking at Lagrange weights like the ones above. For instance, if the value $f_{19}$ was increased by 1 then the interpolated value at $x = 4.5$ would be increased by only 0.000003162859, though the coefficients of the fitted polynomial would be dramatically changed.

2. Increasing the number of equally-spaced nodes does not guarantee that interpolation becomes more accurate, as is well known for Runge’s function $f(x) = 1/(1 + 25x^2)$ over the range from $-1$ to $+1$. This potential problem is overcome by using piecewise polynomial interpolation (rather than using a single interpolation formula over the entire range of interest), and by allowing the interpolation nodes to have a range greater than the range over which interpolation is required. For instance, to interpolate Runge’s function we might use the twenty nodes $-1.06, -1.04, -1.02, -1.00, \ldots, -0.68$ for computing interpolated values for $x$ in the range from $-1.00$ to $-0.74$; and use seven other regions of interpolation transposed to the right by multiples of 0.26 from this range. This set of eight polynomials fitted to overlapping sets of 20 nodes gives a maximum interpolation error less than $10^{-8}$. The maximum interpolation could be further reduced by reducing the spacing of interpolation nodes while keeping the order of interpolation constant.

Suppose that we wish to optimize a function of the form $S(\theta) = \sum_{i=1}^{N} g(x_i|\theta)$ over some possibly multi-dimensional parameter $\theta$. In the applications of interest, $g$ is usually log likelihood or something similar. Rather than computing $g(x_i|\theta)$ separately for each $x_i$, first compute $g(R_j|\theta)$ for a set of $M$ interpolation nodes, denoted $R_j$. Provided that the interpolation nodes are appropriately chosen, the values $g(x_i|\theta)$ can all be closely approximated by interpolation, so we can compute weights, $w_{ij}$, such that $g(x_i|\theta) \approx \sum_{j=1}^{M} w_{ij} g(R_j|\theta)$. Now

$$S(\theta) \approx \sum_{i=1}^{N} \sum_{j=1}^{M} w_{ij} g(R_j|\theta) = \sum_{j=1}^{M} \sum_{i=1}^{N} w_{ij} g(R_j|\theta) = \sum_{j=1}^{M} W_j g(R_j|\theta)$$

where the total weights associated with the interpolation nodes are $W_j = \sum_{i=1}^{N} w_{ij}$. The $W_j$ do not depend on $\theta$, so computing the approximation $\sum_{j=1}^{M} W_j g(R_j|\theta)$ requires only $M$ computations of the function $g$, whereas the direct computation of $S(\theta)$ requires $N$ computations of the function $g$. This is a substantial saving, since $M < < N$. Furthermore, when analysing simulated data as part of the design of a proposed large experimental study the number of interpolation nodes, $M$, does not need to be made larger as the size of the study, $N$, is increased.

**Computing practicalities**

These computations can make use of a module which is a function that takes as inputs the spacing and range of a set of interpolation nodes and a set of nodes, $\{x_j\}$, at which the unspecified function $g$ is to be evaluated, and returns the set of interpolation nodes, $\{R_j\}$, and the sums of interpolation weights associated with these interpolation nodes, $W_j = \sum_{i=1}^{N} w_{ij}$. With many interpreted systems, code for this key initial computation might be written in a compiled language such as C or Fortran and made available as a dynamically linked module.

In practice, one of the most difficult tasks is choosing the spacing between interpolation nodes. A relevant theoretical result is that for Lagrangian interpolation the interpolation error at $x$ between $x_1$ and $x_M$ based on function values $f(x_1), f(x_2), \ldots, f(x_M)$, can be expressed in the form

$$(x - x_1)(x - x_2)\ldots(x - x_M)\frac{f^{M}(\xi)}{M!}$$
for some point $\xi$ such that $x_1 < \xi < x_M$. See, for instance, Abramowitz and Stegun (1965, formula 25.2.3) or Dahlquist and Björk (2008, theorem 4.2.3). The practical importance of this formula is that the absolute interpolation error often behaves roughly like the $M$th power of the spacing between interpolation nodes. For interpolation making use of $M$ interpolation nodes, if the absolute interpolation error for node spacing $h$ is $\varepsilon_1$ and it is desired to achieve absolute interpolation error $\varepsilon_2$ then $h$ should be changed to be $h(\varepsilon_2/\varepsilon_1)^{1/M}$ or smaller.

When applying this procedure, it is important to obtain several estimates of the interpolation error being achieved for many different $x$ values, in order to reduce the risk that the apparent absolute estimated interpolation error is much smaller than is typical for similar $x$ values.

In order to reduce rounding errors, it is desirable that the absolute values of the weights, $w_{ij}$, not be too large. When using equally-spaced interpolation nodes, this can be achieved by not using interpolation formulae for points near the extreme nodes. A simple rule when using 20 equally-spaced interpolation nodes is to ensure that there are three interpolation nodes smaller than all of the $x_i$ and three interpolation nodes larger than all of the $x_i$. This rule ensures that the sum of absolute interpolation weights does not exceed 72.8.

Our preference for equally-spaced interpolation nodes rather than Chebyshev nodes was based on comparing the interpolation accuracy achieved when the two methods were used for piecewise polynomial interpolation with the same number of nodes per unit length. For a set of 20 standard Chebyshev nodes, namely $\cos(\pi/40)$, $\cos(3\pi/40)$, $\ldots$, $\cos(39\pi/40)$ over the range from $-1$ to $+1$, there are 10 nodes per unit length. The nodes for the interpolation over one region are completely distinct from the nodes used over the adjacent regions.

For equally-spaced interpolation nodes with 10 nodes per unit length, the nodes might be at integer multiples of 0.1. We might use sets of 20 nodes such as those at $-1.0$, $-0.9$, $\ldots$, 0.9 for interpolation over ranges of length 1.3, such as the range from 0.7 to 0.6 in this case, if we use the rule suggested above. More accurate interpolation was achieved using the equally-spaced interpolation nodes. The greater accuracy is achieved essentially because (when the number of nodes per unit length is the same) the regions used for piecewise polynomial interpolation with equally-spaced interpolation nodes are smaller than the regions used with Chebyshev nodes.

An alternative comparison was based on using piecewise polynomial interpolation regions for equally-spaced nodes of the same size as the regions used for Chebyshev interpolation. Interpolation over the range from $-1$ to $+1$ making use of the 27 equally spaced nodes between $-1.3$ and $+1.3$ was even more accurate. Essentially, equally-spaced interpolation nodes give better interpolation accuracy for a given number of nodes per unit length because the interpolation in each region of the piecewise polynomial interpolation is able to make use of the nodes from adjacent regions.

Continuation of hypothetical epidemiological study on the link between pesticide exposure and autism

For the hypothetical two-stage trial assessing the relationship between pesticide exposure and autism which was discussed in the Introduction, we simulated 1000 different data sets in order to study the average performance of a trial with 63350 people in the first stage and 219 in the second stage. This option was specifically listed in Table 1 of Morara et al (2007), with the claim based on the expected information matrix that this design has “80% power, assuming a two-sided test at significance level 0.05”.

Our search for the maximum likelihood estimates for the seven parameters was done using a logarithmic scale for the standard deviations and a $\tanh(\rho)$ scale for the correlation, $\rho$, between $Z$ and $Z_A$ so that the search space did not need to be constrained. Standard errors of the
estimates were computed using the square roots of diagonal elements of the inverses of the hessian matrices found at the maximum likelihood estimates.

Out of the 1000 simulated data sets, there were two cases where the hessian matrix at the maximum likelihood estimate was not positive definite. Other evaluation of the usefulness of the experimental design concentrated on the scale parameter of the logistic relationship between true pesticide exposure and the probability of autism. There were only 15 cases where this parameter was not larger than 1.96 times its estimated standard error. Therefore the power of the test is estimated by the simulations to be 98.3%.

This is much larger than the 80% power claimed by Morara et al (2007). The difference in power appears to be largely due to the fact that we have estimated the standard error using the observed hessian matrix at the maximum likelihood estimate, whereas Morara et al (2007) used the expected hessian matrix at the true parameter values.

This is using R except for the computation of the sums of interpolation weights being in C, the 1000 simulations took 453 seconds in total on a one-year-old PC running at 3GHz when the interpolation-based methodology was used. For comparison, a single simulation without using interpolation took 93 seconds. The interpolation-based methodology is approximately 200 times faster.

Normal mixture models

As another illustration of the use of interpolation, consider the problem of estimating the five parameters to describe a two-component mixture of normal distributions. Simulated data was a million simulated numbers drawn from a mixture of a standard normal distribution with weight 30% and 70% weight for a normal distribution with mean 0.4 and standard deviation 1.3.

The computer time to fit the five parameters (two means, two standard deviations and a proportion) by maximum likelihood in the language R using a directly computed likelihood was 258 seconds. Using 20-node interpolation with spacing $h = 0.15$ between equally-spaced nodes, the time to compute the sums of interpolation weights using a function written in C and called from R was 0.23 seconds and the time to fit the model was 0.08 seconds. The answers obtained by the two methods agreed to about 8 significant figures, which is much more precision than necessary given that the standard errors in the estimates of the parameters are of the order of 1%. Using $h = 0.2$ and using $h = 0.1$ took similar amounts of computer time and gave virtually the same solution.

Discussion

The change in order of summation in Equation (1) is the key to the computational efficiency of the new methodology. It allows the total of a large number of terms to be computed without computing any of the individual terms.

For design of large experimental trials, the methodology proposed is more useful than calculation of the expected information matrix because it allows many aspects of variation over the range of possible experimental outcomes to be investigated. It allows estimation of the probability that there will be insufficient information to estimate all of the required parameters and estimation of the distribution over the range of possible experimental outcomes of standard errors of parameter estimates. We believe that it is a useful tool for the testing of possible designs for epidemiological trials.

However, this methodology is only useful when there is a single continuous response variable and at most a small number of categorical predictor variables. It is unlikely to be useful for analysis of epidemiological trials after the data are obtained, because the models fitted at that
time will generally be more complicated. There will often be additional continuous predictor variables such as age, weight, height and blood pressure. Also, there will often be a large number of categorical predictor variables.

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**References**

Abramowitz, M. and Stegun, I.A. (1965). Handbook of Mathematical Function with Formulas, Graphs, and Mathematical Tables. Dover.

Dahlquist, G and Björk, Å. (2008). Numerical Methods in Scientific Computing. Society for Industrial and Applied Mathematics.

Morara, M., Ryan, L, Houseman, A. and Strauss, W. (2007). Optimal design for epidemiological studies subject to designed missingness. Lifetime Data Analysis 13, 583–605.