Multilevel Monte Carlo estimation of expected information gains

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Abstract

In this paper we develop an efficient Monte Carlo algorithm for estimating the expected information gain that measures how much the information entropy about uncertain quantity of interest $\theta$ is reduced on average by collecting relevant data $Y$. The expected information gain is expressed as a nested expectation, with an outer expectation with respect to $Y$ and an inner expectation with respect to $\theta$. The standard, nested Monte Carlo method requires a total computational cost of $O(\varepsilon^{-3})$ to achieve a root-mean-square accuracy of $\varepsilon$. In this paper we reduce this to optimal $O(\varepsilon^{-2})$ by applying a multilevel Monte Carlo (MLMC) method. More precisely, we introduce an antithetic MLMC estimator for the expected information gain and provide a sufficient condition on the data model under which the antithetic property of the MLMC estimator is well exploited such that optimal complexity of $O(\varepsilon^{-2})$ is achieved. Furthermore, we discuss how to incorporate importance sampling techniques within the MLMC estimator to avoid so-called arithmetic underflow. Numerical experiments show the considerable computational savings compared to the nested Monte Carlo method for a simple test case and a more realistic pharmacokinetic model.

1 Introduction

The motivation for this research comes from construction of optimal Bayesian experimental designs, for which the so-called expected information gain has been often employed as a quality criterion of experimental designs, see for instance [4, 18, 13, 14, 1]. Let $\theta$ be a (possibly multi-dimensional) random variable which represents the uncertain quantity of interest. By collecting relevant data $Y_\xi$ (which is again possibly multi-dimensional) through carrying out some experiments under an experimental setup $\xi$, one can expect that the uncertainty of $\theta$, measured by the information entropy, can be reduced. The aim of Bayesian

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experimental designs is to find an optimal experimental setup $\xi^*$ such that the expected amount of the information entropy reduction about $\theta$ is maximized.

In what follows, we give a formal definition of the expected information gain for a particular experimental setup $\xi$. The information entropy of $\theta$ before collecting data $Y_\xi$ is given by

$$-E_{\theta}[\log p(\theta)],$$

where $p(\theta)$ denotes the prior probability density function of $\theta$, and the expectation is taken with respect to the same $p(\theta)$. On the other hand, after collecting data $Y_\xi$, the conditional information entropy of $\theta$ is

$$-E_{\theta|Y_\xi}[\log p(\theta|Y_\xi)],$$

where $p(\theta|Y_\xi)$ denotes the posterior probability density function of $\theta$ given $Y_\xi$ and the expectation here is taken with respect to $p(\theta|Y_\xi)$ instead of $p(\theta)$. Thus the expected conditional information entropy of $\theta$ by collecting data $Y_\xi$ is

$$E_{Y_\xi}[-E_{\theta|Y_\xi}[\log p(\theta|Y_\xi)]] .$$

Now the expected information gain measures the average amount of the reduction of the information entropy about $\theta$ by collecting data $Y_\xi$, and is defined by the difference

$$U_\xi := -E_{\theta}[\log p(\theta)] - E_{Y_\xi}[-E_{\theta|Y_\xi}[\log p(\theta|Y_\xi)]]$$

$$= E_{Y_\xi}[-E_{\theta|Y_\xi}[\log p(\theta)]] + E_{\theta|Y_\xi}[E_{\theta}[\log p(\theta|Y_\xi)]]$$

$$= E_{Y_\xi}E_{\theta|Y_\xi}[\log \frac{p(\theta|Y_\xi)}{p(\theta)}].$$

(1)

Here the inner expectation appearing in the right-most side is nothing but the Kullback-Leibler divergence between $p(\theta)$ and $p(\theta|Y_\xi)$. In the context of Bayesian experimental designs, it is considered that the larger the value of $U_\xi$, the more informative the data $Y_\xi$ is about $\theta$ and thus the better the experimental design $\xi$ is. This is why the expected information gain is used as a quality criterion of experimental designs.

Let us consider the following data model:

$$Y_\xi = g_\xi(\theta) + \epsilon,$$

(2)

where the function $g_\xi$ represents the deterministic part of the model response which depends on $\theta$ and $\xi$, and $\epsilon$ denotes the stochastic part of the model response, i.e., the measurement error. It is often the case where $\epsilon$ is assumed to be zero-mean Gaussian with covariance matrix $\Sigma_\epsilon$. Throughout this paper we assume that the prior probability density function of $\theta$, the function $g_\xi$, and the probability distribution of $\epsilon$ are given. As considered in [13, 14, 1], this data model can be extended to allow the repetition of experiments as

$$Y^{(i)}_\xi = g_\xi(\theta) + \epsilon^{(i)} \text{ for } i = 1, \ldots, N_\epsilon,$$
where \( N_e \) is the number of repetitive experiments and \( \epsilon^{(i)} \) are independent and identically distributed (i.i.d.) measurement errors. This extended model, however, can be easily rewritten into the form of (2) by concatenating \( Y_\xi = (Y_\xi^{(1)} \top, \ldots, Y_\xi^{(N_e)} \top) \top \) with a suitable choice of \( g_\xi \) and \( \epsilon \). Thus we stick to the original model (2) in this paper. Moreover, since we shall consider a fixed experimental setup \( \xi \), we omit the subscript \( \xi \) and simply write \( g, Y, U \) etc. when distinguishing different \( \xi \)'s is not important.

The aim of this paper is to develop an efficient Monte Carlo algorithm for estimating the expected information gain \( U \). In the next section, we introduce the standard, nested Monte Carlo method as a classical algorithm to estimate \( U \), and give a brief review of the relevant literature. Then in Section 3, after introducing the concept of a multilevel Monte Carlo (MLMC) method, we construct an MLMC estimator for \( U \) as an alternative, more efficient algorithm. We prove under a sufficient condition on the data model that the MLMC estimator can estimate \( U \) with a root-mean-square accuracy \( \varepsilon \) by the optimal computational complexity \( O(\varepsilon^{-2}) \). (Here and in what follows, the difference between the noise \( \epsilon \) and the accuracy \( \varepsilon \) should not be confused.) Moreover we discuss how to incorporate importance sampling techniques within the MLMC estimator, which might be quite useful in practical applications. Numerical experiments in Section 4 confirm the considerable computational savings compared to the nested Monte Carlo method not only for a simple test case but also for a more realistic pharmacokinetic model adapted from [17].

2 Nested Monte Carlo

The nested Monte Carlo (NMC) method is the most standard approach to estimate the expected information gain [18, 13, 1, 16]. Given the data model (2), it is straightforward to generate i.i.d. random samples of \( Y \) given a particular value of \( \theta \) and also those of \( Y \) itself. Besides, since \( Y - g(\theta) \) follows the probability distribution of \( \epsilon \), it is easy to compute \( p(Y | \theta) \) for given \( \theta \) and \( Y \). On the other hand, it is usually hard to generate i.i.d. random samples of \( \theta \) given a particular value of \( Y \) and to compute \( p(\theta | Y) \) and \( p(Y) \) for given \( \theta \) and \( Y \).

Based on this fact, we use Bayes’ theorem

\[
p(\theta | Y) = \frac{p(\theta)p(Y | \theta)}{p(Y)} = \frac{p(\theta)p(Y | \theta)}{\mathbb{E}_\theta[p(Y | \theta)]}
\]

to rewrite the expected information gain \( U (1) \) into

\[
U = \mathbb{E}_Y \mathbb{E}_{\theta | Y} \left[ \log \frac{p(Y | \theta)}{\mathbb{E}_\theta[p(Y | \theta)]} \right]
= \mathbb{E}_Y \mathbb{E}_{\theta | Y} \left[ \log p(Y | \theta) \right] - \mathbb{E}_Y \left[ \log \mathbb{E}_\theta[p(Y | \theta)] \right]
= \mathbb{E}_\theta \mathbb{E}_{Y | \theta} \left[ \log p(Y | \theta) \right] - \mathbb{E}_Y \left[ \log \mathbb{E}_\theta[p(Y | \theta)] \right].
\]

With this form of \( U \), the NMC estimator for the expected information gain is
given by

\[
\frac{1}{N} \sum_{n=1}^{N} \left[ \log p(Y^{(n)} | \theta^{(n,0)}) - \log \left( \frac{1}{M} \sum_{m=1}^{M} p(Y^{(n)} | \theta^{(n,m)}) \right) \right]
\]

(4)

for \( M, N > 0 \), where \( \theta^{(n,0)}, \theta^{(n,1)}, \ldots, \theta^{(n,m)} \) denote i.i.d. random samples of \( \theta \), and \( Y^{(n)} \) denotes a random sample of \( Y \) generated conditionally on \( \theta^{(n,0)} \).

In [18], Ryan showed that the bias and the variance of the NMC estimator are of \( O(M^{-1}) \) and of \( O(N^{-1}) \), respectively. Since the mean square error of the NMC estimator is given by the sum of the variance and the squared bias, \( U \) can be estimated with a root-mean-square accuracy \( \varepsilon \) by using \( N = O(\varepsilon^{-1}) \) and \( M = O(\varepsilon^{-2}) \) samples. Assuming that each computation of \( g \), which is necessary for calculating \( p(Y | \theta) \), can be performed with unit cost, the total computational complexity is \( N(M + 1) = O(\varepsilon^{-3}) \).

Much more recently, in [1], Beck et al. provided a thorough error analysis of the NMC estimator and derive the optimal allocation of \( N \) and \( M \) for a given \( \varepsilon \). In fact, they consider the situation where \( g \) cannot be computed exactly and only its discretized approximation \( g_h \) with a mesh discretization parameter \( h \) is available. Here it is assumed that, as \( h \) gets smaller, \( g_h \) approaches to \( g \), but at the same time, the computational cost of \( g_h \) increases. Therefore, their optimization deals with not only the number of samples \( N \) and \( M \) but also the parameter \( h \). In this paper, we assume that \( g \) can be computed exactly, so that dealing with such situations is left open for future works, see Section 5.

More importantly, Beck et al. incorporated importance sampling based on the Laplace approximation from [14] within the NMC estimator. This approach is quite useful in reducing the number of inner samples \( M \) substantially and also in mitigating the risk of so-called arithmetic underflow: when \( p(Y | \theta) \) (as a function of \( \theta \) for a fixed \( Y \)) is highly concentrated around a certain value of \( \theta \), the Monte Carlo estimate of the inner expectation

\[
\frac{1}{M} \sum_{m=1}^{M} p(Y^{(n)} | \theta^{(n,m)})
\]

appearing in (4) can be numerically zero. Taking the logarithm of 0 of course returns error. This can happen in practice especially for small \( M \). Therefore, it is desirable to apply a change of measure such that most of the samples of \( \theta \) are concentrated properly depending on \( Y^{(n)} \), which is exactly what the Laplace-based importance sampling aims to do. We note, however, that using importance sampling does not improve the order of computational complexity, so that the necessary cost of \( O(\varepsilon^{-3}) \) remains unchanged.
3 Multilevel Monte Carlo

3.1 Basic theory of MLMC

In order to reduce the total computational complexity from $O(\varepsilon^{-3})$ to $O(\varepsilon^{-2})$, we consider applying a multilevel Monte Carlo (MLMC) method [5, 6]. The MLMC method has already been applied to estimate nested expectations of the form

$$E[f(E[g(X, Y) | Y])]$$

for independent random variables $X$ and $Y$, where an outer expectation is taken with respect to $Y$ and an inner one is taken with respect to $X$, see [3, 6, 7, 8]. In particular, the case where $f$ is smooth has been briefly discussed in [6, Section 9]. In this paper we make a rigorous argument when $f$ is a logarithmic function.

Before introducing an MLMC estimator for the expected information gain, we give an overview of the MLMC method. Let $P$ be a random output variable which cannot be sampled exactly, and let $P_0, P_1, \ldots$ be a sequence of random variables which approximate $P$ with increasing accuracy but also with increasing cost. The problem here is to estimate $E[P]$ efficiently.

For $L \in \mathbb{Z}_{> 0}$ we have the following telescoping sum

$$E[P_L] = E[P_0] + \sum_{\ell=1}^{L} E[P_\ell - P_{\ell-1}]. \quad (5)$$

The standard Monte Carlo method estimates the left-hand side directly by

$$Z_{MC} = \frac{1}{N} \sum_{i=1}^{N} P_{L}^{(i)}. \quad (6)$$

The mean square error of $Z_{MC}$ is given by the sum of variance and squared bias:

$$E[(Z_{MC} - E[P])^2] = \frac{V[P_L]}{N} + (E[P_L] - P)^2. \quad (7)$$

The MLMC method, on the other hand, independently estimates each term on the right-hand side of (5). In general, if we have a sequence of random variables $Z_0, Z_1, \ldots$ which satisfy $E[Z_0] = E[P_0]$ and $E[Z_\ell] = E[P_\ell - P_{\ell-1}]$ for $\ell \in \mathbb{Z}_{> 0}$, the MLMC estimator is given by

$$Z_{MLMC} = \sum_{\ell=0}^{L} \frac{1}{N_{\ell}} \sum_{i=1}^{N_{\ell}} Z_{\ell}^{(i)}. \quad (8)$$

The mean square error of $Z_{MLMC}$ is

$$E[(Z_{MLMC} - E[P])^2] = \sum_{\ell=0}^{L} \frac{V[Z_\ell]}{N_{\ell}} + (E[P_L] - P)^2. \quad (9)$$
For the same underlying stochastic sample, $P_\ell$ and $P_{\ell-1}$ can be well correlated and thus $\mathbb{V}[Z_\ell]$ is expected to get smaller as the level $\ell$ increases. This means that, in order to estimate $\mathbb{E}[Z_\ell]$ with a fixed root-mean-square accuracy, the necessary number of samples $N_\ell$ decreases as $\ell$ increases, and, as a consequence, most of the number of samples are allocated on smaller levels for estimating $\mathbb{E}[P_L]$. Since the cost for each computation of $Z_\ell$ is assumed to be cheaper for smaller $\ell$, the overall computational cost can be significantly reduced compared to the standard Monte Carlo method.

In his seminal work [5], Giles made this observation explicit as follows, see also a recent review [6]:

**Theorem 1.** Let $P$ be a random variable and let $P_\ell$ denote the corresponding level $\ell$ approximation of $P$. If there exist independent random variables $Z_\ell$ with expected cost $C_\ell$ and variance $V_\ell$, and positive constants $\alpha, \beta, \gamma, c_1, c_2, c_3$ such that

1. $|\mathbb{E}[P_\ell - P]| \leq c_1 2^{-\alpha\ell}$,
2. $\mathbb{E}[Z_\ell] = \begin{cases} \mathbb{E}[P_0] & \ell = 0, \\ \mathbb{E}[P_\ell - P_{\ell-1}] & \ell > 0, \end{cases}$
3. $V_\ell \leq c_2 2^{-\beta\ell}$,
4. $C_\ell \leq c_3 2^{\gamma\ell}$,

then there exists a positive constant $c_4$ such that for any $\varepsilon < e^{-1}$ there are $L$ and $N_\ell$ for which the MLMC estimator (8) has a mean square error less than $\varepsilon^2$ with a computational complexity $C$ with bound

$$\mathbb{E}[C] \leq \begin{cases} c_4 \varepsilon^{-2} & \beta > \gamma, \\ c_4 \varepsilon^{-2} (\log \varepsilon)^2 & \beta = \gamma, \\ c_4 \varepsilon^{-2 - (\gamma - \beta)/\alpha} & \beta < \gamma. \end{cases}$$

**Remark 1.** As discussed for instance in [7, Section 2.1], a computational complexity for the standard Monte Carlo estimator to have a mean square error less than $\varepsilon^2$ is of $O(\varepsilon^{-2 - \gamma/\alpha})$. Thus regardless of the values of $\beta$ and $\gamma$, the MLMC estimator has an asymptotically better complexity bound than the standard Monte Carlo estimator.

### 3.2 MLMC estimator for expected information gains

Here we introduce an MLMC estimator for the expected information gain. First let us define a random output variable

$$P := \log p(Y | \theta) - \log \mathbb{E}_\theta[p(Y | \theta)].$$

where $Y$ is distributed conditionally on the random variable $\theta$ of the first term. It is obvious that $P$ cannot be computed exactly because of the expectation
\(E_\theta[p(Y \mid \theta)]\) appearing in the second term. We can introduce a sequence of approximations \(P_0, P_1, \ldots\) of \(P\) with increasing accuracy but also with increasing cost as follows:

\[
P_\ell = \log p(Y \mid \theta) - \log \left( \frac{1}{M_\ell} \sum_{m=1}^{M_\ell} p(Y \mid \theta^{(m)}) \right)
= : \log p(Y \mid \theta) - \log (1)_{M_\ell}^{M_\ell}
\]

for an increasing sequence \(M_0 < M_1 < \ldots\) such that \(M_\ell \to \infty\) as \(\ell \to \infty\). That is, \(P_\ell\) is the standard Monte Carlo estimator of \(P\) using \(M_\ell\) random samples of \(\theta\). Thus we have \(\lim_{\ell \to \infty} E[P_\ell] = E[P] = U\). Note that the standard, nested Monte Carlo estimator (4) is essentially the same as (6) with \(P_L\) given as above for a fixed \(L\).

In what follows, let \(M_\ell := M_0 2^\ell\) for some \(M_0 \in \mathbb{Z}_{>0}\) for all \(\ell \geq 0\), i.e., we consider a geometric sequence for \(M_\ell\). Then a sequence of corrections \(Z_0, Z_1, \ldots\) is defined as follows: \(Z_0\) is the same as \(P_0\), given by

\[
Z_0 = \log p(Y \mid \theta) - \log (Y \mid \cdot)_{M_0}^{M_0}.
\]

For \(\ell > 0\), the simplest one is

\[
Z_\ell = P_\ell - P_{\ell-1} = \log (Y \mid \cdot)_{M_{\ell-1}}^{M_{\ell-1}} - \log (Y \mid \cdot)_{M_{\ell}}^{M_{\ell}},
\]

where the first \(M_{\ell-1}\) random samples of \(\theta\) used in the second term is also used in the first term. However, according to [9, 3, 6, 7], we can consider a better “tight coupling” of \(P_\ell\) and \(P_{\ell-1}\). Namely, the set of \(M_0 2^\ell\) random samples of \(\theta\) used to compute \(P_\ell\) is divided into two disjoint sets of \(M_0 2^{\ell-1}\) samples to compute two realizations of \(P_{\ell-1}\), denoted by \(P_{\ell-1}^{(a)}\) and \(P_{\ell-1}^{(b)}\), respectively. In this way \(Z_\ell\) is given by

\[
Z_\ell = P_\ell - \frac{1}{2} \left[ P_{\ell-1}^{(a)} + P_{\ell-1}^{(b)} \right]
= \log p(Y \mid \theta) - \log (Y \mid \cdot)_{M_0 2^\ell}^{M_0 2^\ell}
- \frac{1}{2} \left[ \log p(Y \mid \theta) - \log p(Y \mid \cdot)^{(a)} + \log p(Y \mid \theta) - \log p(Y \mid \cdot)^{(b)} \right]
= \frac{1}{2} \left[ \log (Y \mid \cdot)^{(a)} + \log (Y \mid \cdot)^{(b)} \right] - \log p(Y \mid \cdot),
\]

where

- \(p(Y \mid \cdot)\) denotes an average of \(p(Y \mid \theta)\) over \(M_0 2^\ell\) random samples of \(\theta\) (note that we omit the superscript \(M_0 2^\ell\) since it is clear from the level of \(Z_\ell\));

- \(p(Y \mid \cdot)^{(a)}\) denotes an average of \(p(Y \mid \theta)\) over the first \(M_0 2^{\ell-1}\) random samples of \(\theta\) used in \(p(Y \mid \cdot)\);
• $p(Y \mid \cdot)^{(b)}$ denotes an average of $p(Y \mid \theta)$ over the second $M_0 2^{\ell-1}$ random samples of $\theta$ used in $p(Y \mid \cdot)$,

for a randomly generated $Y$. Because of the independence of $P^{(a)}$ and $P^{(b)}$, we see that $\mathbb{E}[Z_\ell] = \mathbb{E}[P_\ell - P_{\ell-1}]$. Moreover, it is important that the following "antithetic" property of $Z_\ell$ holds:

$$
\frac{1}{2} \left[ p(Y \mid \cdot)^{(a)} + p(Y \mid \cdot)^{(b)} \right] = p(Y \mid \cdot). \quad (11)
$$

Due to the concavity of log, this $Z_\ell$ is always non-positive when $\ell \geq 1$.

In this paper, we always consider the latter definition of $Z_\ell$ for $\ell > 0$. Our MLMC estimator for the expected information gain is given by (8) for $L \in \mathbb{Z}^\ell > 0$ and $N_0, \ldots, N_L \in \mathbb{Z}^\ell > 0$ into which the above $Z_\ell$ is substituted. It is already clear from the construction of $Z_\ell$ that the parameter $\gamma$ in Theorem 1 should be 1.

### 3.3 MLMC variance analysis

In this subsection we prove $\beta > \gamma$ for $Z_\ell$ defined in (10), meaning that our MLMC estimator is in the first regime of Theorem 1, so that the total computational complexity is $O(\varepsilon^{-2})$.

In order to prove the main theorem below, we need the following results.

**Lemma 1.** Let $X$ be a random variable with zero mean, and let $X_N$ be an average of $N$ i.i.d. samples of $X$. If $\mathbb{E}[|X|^p]$ is finite for $p \geq 2$, there exists a constant $C_p$ depending only on $p$ such that

$$
\mathbb{E}[|X_N|^p] \leq C_p \frac{\mathbb{E}[|X|^p]}{N^{p/2}} \quad \text{and} \quad \mathbb{P}[|X_N| > c] \leq C_p e^{c^p N^{p/2}}.
$$

**Proof.** See [7, Lemma 1].

**Lemma 2.** Let $X > 0$ be a positive random variable with mean $\mu$ such that $\mathbb{E}[X^2] < \infty$, and let $X_N$ be an average of $N$ i.i.d. samples of $X$. Let $\rho$ be a probability density function of $X$ and assume that there exist a non-increasing function $g > 0$ and a constant $0 < \xi_0 < 1/3$ such that

$$
G := \int_0^{\xi_0 \mu} g(x) \rho(x) \, dx < \infty
$$

holds. Then, the probability density function of $X_N$, denoted by $\rho_N$, satisfies

$$
G_N := \int_0^{\xi_0 \mu} g(x) \rho_N(x) \, dx \leq G N \exp \left\{ -\frac{(1 - 3\xi_0)^2 \mu^2}{2\mathbb{E}[X^2]} (N - 1) \right\}.
$$

**Proof.** We prove the lemma by induction on $N$. Since the result is trivial when $N = 1$, let us assume $N \geq 2$. Consider the decomposition $N = N_1 + N_2$ such that $N_1, N_2 \in \mathbb{Z}_{>0}$ and $1/2 < N_1/N_2 < 2$. Note that such a decomposition is always possible for any $N \geq 2$. Using the identity $N X_N = N_1 X_{N_1} + N_2 X_{N_2}$
for independent $\overline{X}_{N_1}$ and $\overline{X}_{N_2}$, the convolution of probability density functions gives

$$G_N = \int_0^{\xi_0 \mu} g(x) \left[ N \int_0^{N_x} 1 \frac{N_x}{N_1} \rho_{N_1} \left( \frac{y}{N_1} \right) \cdot \frac{1}{N_2} \rho_{N_2} \left( \frac{N_y - y}{N_2} \right) \right] \, dx$$

$$= \int_0^{\xi_0 \mu} g(x) \left[ N \int_0^{N_x} 1 \frac{N_x}{N_1} \rho_{N_1} \left( \frac{y}{N_1} \right) \cdot \frac{1}{N_2} \rho_{N_2} \left( \frac{N_y - y}{N_2} \right) \right] \, dx$$

$$+ \int_0^{\xi_0 \mu} g(x) \left[ N \int_0^{N_x} 1 \frac{N_x}{N_1} \rho_{N_1} \left( \frac{N_y - y}{N_1} \right) \cdot \frac{1}{N_2} \rho_{N_2} \left( \frac{y}{N_2} \right) \right] \, dx$$

$$= \int_0^{\xi_0 \mu} g(x) \left[ \frac{N}{N_2} \int_0^x \rho_{N_1}(y) \rho_{N_2} \left( \frac{N_y - y}{N_2} \right) \right] \, dx$$

$$+ \int_0^{\xi_0 \mu} g(x) \left[ \frac{N}{N_1} \int_0^x \rho_{N_1} \left( \frac{N_y - y}{N_1} \right) \rho_{N_2}(y) \right] \, dx$$

$$\leq \frac{N}{N_2} \int_0^{\xi_0 \mu} g(y) \rho_{N_1}(y) \int_y^{\xi_0 \mu} \rho_{N_2} \left( \frac{N_y - y}{N_2} \right) \, dx \, dy$$

$$+ \frac{N}{N_1} \int_0^{\xi_0 \mu} g(y) \rho_{N_2}(y) \int_y^{\xi_0 \mu} \rho_{N_1} \left( \frac{N_y - y}{N_1} \right) \, dx \, dy$$

$$= \int_0^{\xi_0 \mu} g(y) \rho_{N_1}(y) \int_y^{\xi_0 \mu} \rho_{N_2} \left( \frac{N_y - y}{N_2} \right) \, dx \, dy$$

$$+ \int_0^{\xi_0 \mu} g(y) \rho_{N_2}(y) \int_y^{\xi_0 \mu} \rho_{N_1} \left( \frac{N_y - y}{N_1} \right) \, dx \, dy$$

$$= \int_0^{\xi_0 \mu} g(y) \rho_{N_1}(y) \left[ \mu - \frac{N \xi_0 \mu - N_1 y}{N_2} \right] \, dy$$

$$+ \int_0^{\xi_0 \mu} g(y) \rho_{N_2}(y) \left[ \mu - \frac{N \xi_0 \mu - N_2 y}{N_1} \right] \, dy.$$ 

Since it is assumed that $1/2 < N_1/N_2 < 2$, for any $0 < y < \xi_0 \mu$, we have

$$\left( y, \frac{N \xi_0 \mu - N_1 y}{N_2} \right), \left( y, \frac{N \xi_0 \mu - N_2 y}{N_1} \right) \subseteq (0, 3 \xi_0 \mu).$$

It follows from this fact, the concentration inequality given in [15, Theorem 2.1] (see also [2, Chapter 2.5.2]) and the induction assumption that

$$G_N \leq \int_0^{\xi_0 \mu} g(y) \rho_{N_1}(y) \, dy \cdot \mathbb{P} \left[ \overline{X}_{N_1} \leq \mu - (1 - \xi_0 \mu) \right]$$

$$+ \int_0^{\xi_0 \mu} g(y) \rho_{N_2}(y) \, dy \cdot \mathbb{P} \left[ \overline{X}_{N_2} \leq \mu - (1 - \xi_0 \mu) \right]$$

$$\leq G_{N_1} \exp \left\{ -\frac{(1 - \xi_0 \mu)^2 \mu^2}{2E[X^2]} N_2 \right\} + G_{N_2} \exp \left\{ -\frac{(1 - \xi_0 \mu)^2 \mu^2}{2E[X^2]} N_1 \right\}$$
\[\leq GN \exp \left\{ \frac{(1 - 3\xi_0)^2 \mu^2}{2\mathbb{E}[X^2]} (N - 1) \right\},\]

which completes the proof of the lemma. \(\square\)

Now we prove:

**Theorem 2.** Denote by \(\rho_Y\) the probability density function of a positive random variable \(p(Y|\theta)/p(Y)\) for a particular value of \(Y\). Assume that there exists a constant \(0 < \xi_0 < 1/3\) such that

\[\sup_Y \int_0^{\xi_0} (\log x - x + 1)^2 \rho_Y(x) \, dx < \infty, \tag{12}\]

and that there exists \(p^* \geq 0\) such that

\[\mathbb{E}_Y \left[ \mathbb{E}_{\theta} \left[ \frac{p(Y|\theta)}{p(Y)} \right]^{4|Y|^{1+p}} \right] < \infty. \tag{13}\]

for all \(0 \leq p \leq p^*\). Then we have

\[\mathbb{E}[|Z_\ell|] = O(2^{-\ell}) \quad \text{and} \quad \mathbb{V}[Z_\ell] = O(2^{-(1+\min(1,2p^*))\ell}).\]

**Proof.** Using the antithetic property (11), we have

\[Z_\ell = \frac{1}{2} \left[ \log \frac{p(Y|\cdot)^{(a)}}{p(Y)} + \log \frac{p(Y|\cdot)^{(b)}}{p(Y)} \right] - \log \frac{p(Y|\cdot)}{p(Y)} \]

\[- \frac{1}{2} \left[ \frac{p(Y|\cdot)^{(a)}}{p(Y)} + \frac{p(Y|\cdot)^{(b)}}{p(Y)} \right] + \frac{p(Y|\cdot)}{p(Y)}\]

\[= \frac{1}{2} \left[ \log \frac{p(Y|\cdot)^{(a)}}{p(Y)} - \frac{p(Y|\cdot)^{(a)}}{p(Y)} + 1 \right] \]

\[+ \frac{1}{2} \left[ \log \frac{p(Y|\cdot)^{(b)}}{p(Y)} - \frac{p(Y|\cdot)^{(b)}}{p(Y)} + 1 \right] - \left[ \log \frac{p(Y|\cdot)}{p(Y)} - \frac{p(Y|\cdot)}{p(Y)} + 1 \right].\]

Applying Jensen’s inequality gives

\[|Z_\ell|^2 \leq \left[ \log \frac{p(Y|\cdot)^{(a)}}{p(Y)} - \frac{p(Y|\cdot)^{(a)}}{p(Y)} + 1 \right]^2 \]

\[+ \left[ \log \frac{p(Y|\cdot)^{(b)}}{p(Y)} - \frac{p(Y|\cdot)^{(b)}}{p(Y)} + 1 \right]^2 + 2 \left[ \log \frac{p(Y|\cdot)}{p(Y)} - \frac{p(Y|\cdot)}{p(Y)} + 1 \right]^2. \tag{14}\]

In what follows, we show a bound on the expectation of the last term of (14).
For a particular value of $Y$, we denote the probability density function of $p(Y | \cdot)/p(Y)$ by $\overline{p}_Y$. Then we have

$$E \left[ \left( \log \frac{p(Y | \cdot)}{p(Y)} - \frac{p(Y | \cdot)}{p(Y)} + 1 \right)^2 \mid Y \right] = \int_0^\infty (\log x - x + 1)^2 \overline{p}_Y(x) \, dx$$

$$= \int_0^{\xi_0} (\log x - x + 1)^2 \overline{p}_Y(x) \, dx + \int_0^\infty (\log x - x + 1)^2 \overline{p}_Y(x) \, dx. \quad (15)$$

As the mean of the random variable $p(Y | \cdot)/p(Y)$ (for a fixed $Y$) equals to 1, the assumption (12) and Lemma 2 ensure the existence of a positive constant $I_0$ such that, for any $Y$, the first term of (15) is bounded as

$$\int_0^{\xi_0} (\log x - x + 1)^2 \overline{p}_Y(x) \, dx \leq I_0 M_0 2^\ell \exp \left\{ -\frac{(1 - 3\xi_0)^2}{2E_0[p(Y | \theta)/p(Y)]^2} (M_0 2^\ell - 1) \right\}.$$

Since $e^x \geq x^{2+2p^*}/\Gamma(3 + 2p^*)$ holds for $p^* \geq 0$ and any $x \geq 0$, where $\Gamma$ denote the gamma function, we further have

$$\int_0^{\xi_0} (\log x - x + 1)^2 \overline{p}_Y(x) \, dx \leq \frac{I_0 \Gamma(3 + 2p^*)^{2+2p^*}}{(1 - 3\xi_0)^{4+4p^*}} \left( E_0 \left[ \left( \frac{p(Y | \theta)}{p(Y)} \right)^2 \mid Y \right] \right)^{2+2p^*} \frac{M_0 2^\ell}{(M_0 2^\ell - 1)^{2+2p^*}}$$

$$\leq \frac{I_0 \Gamma(3 + 2p^*)^{2+2p^*}}{(1 - 3\xi_0)^{4+4p^*}} \left( E_0 \left[ \left( \frac{p(Y | \theta)}{p(Y)} \right)^4 \mid Y \right] \right)^{1+p^*} \frac{M_0 2^\ell}{(M_0 2^\ell - 1)^{2+2p^*}},$$

when $M_0 2^\ell > 1$, where we used Hölder’s inequality in the second inequality.

For any $x \geq \xi_0$ with $0 < \xi_0 < 1/3$, we have

$$| \log x - x + 1 | \leq \frac{1}{2\xi_0} (x - 1)^2,$$

from which the second term of of (15) is bounded as

$$\int_0^{\xi_0} (\log x - x + 1)^2 \overline{p}_Y(x) \, dx \leq \frac{1}{4\xi_0} \int_0^{\xi_0} (x - 1)^4 \overline{p}_Y(x) \, dx \leq \frac{1}{4\xi_0} \int_0^{\xi_0} (x - 1)^4 \overline{p}_Y(x) \, dx$$

$$= \frac{1}{4\xi_0} E \left[ \left( \frac{p(Y | \cdot)}{p(Y)} - 1 \right)^4 \mid Y \right] \leq \frac{C_4}{4\xi_0^2 (M_0 2^\ell)^2} E_0 \left[ \left( \frac{p(Y | \theta)}{p(Y)} - 1 \right)^4 \mid Y \right],$$

11
where we used Lemma 1 in the last inequality. Taking an outer expectation with respect to $Y$, based on the assumption (16), we obtain a bound on the expectation of the last term of (14):

$$
E \left[ \left( \log \frac{p(Y \mid \theta)}{p(Y)} - \frac{p(Y \mid \theta)}{p(Y)} + 1 \right)^2 \right]
$$

$$
= E_Y \left[ E \left[ \left( \log \frac{p(Y \mid \theta)}{p(Y)} - \frac{p(Y \mid \theta)}{p(Y)} + 1 \right)^2 \mid Y \right] \right]
$$

$$
\leq \frac{I_0 \Gamma(3 + 2p^\star)2^{2+2p^\star}}{(1 - 3ξ_0)^{4+4p^\star}} E_Y \left[ \left( E_{\theta} \left[ \frac{p(Y | \theta)}{p(Y)} \right] \mid Y \right)^{1+p^\star} \right] \frac{M_0^{2\ell}}{(M_0^{2\ell} - 1)^{2+2p^\star}} + \frac{C_4}{4ξ_0^2(M_0^{2\ell})^2} E_Y \left[ E_{\theta} \left[ \left| \frac{p(Y | \theta)}{p(Y)} - 1 \right| \right] \mid Y \right]
$$

Since similar bounds exist for the expectations of the first two terms of (14), we obtain a bound on the variance of $Z_\ell$:

$$
\text{Var}[Z_\ell] \leq E[Z_\ell^2] = O(2^{-(1+\min(1,2p^\star))\ell}).
$$

A bound on the expectation of $Z_\ell$ can be shown in a similar manner. □

**Remark 2.** As is clear from the proof, the “left-tail part”, i.e., the first term of (15), decays sufficiently fast and is negligible as compared to the remaining part when $p^\star > 1/2$, whereas the situation becomes opposite when $p^\star < 1/2$.

**Remark 3.** This theorem proves the parameters $\alpha$ and $\beta$ appearing in Theorem 1 should be $\alpha = 1$ and $\beta = 1+\min(1,2p^\star)$, respectively. Since we have $\gamma = 1$, our MLMC estimator is in the regime $\beta > \gamma$ whenever $p^\star > 0$, implying that the optimal computational complexity of $O(\varepsilon^{-2})$ can be achieved for estimating the expected information gain $U$. As mentioned in Remark 1, the standard (nested, in this case) Monte Carlo method only achieves the complexity of $O(\varepsilon^{-2-\gamma/\alpha})$. Since $\alpha = \gamma = 1$, we recover the results of [18, 1].

### 3.4 Incorporating importance sampling

In practice, it might be the case where $p(Y \mid \theta)$, as a function of $\theta$ for a fixed $Y$, is highly concentrated around a certain value of $\theta$. If i.i.d. random samples of $\theta$ are distributed outside the concentrated region, the Monte Carlo estimates $\bar{p}(Y \mid \cdot)^{(a)}, \bar{p}(Y \mid \cdot)^{(b)}$ and $\bar{p}(Y \mid \cdot)$ can be numerically zero in computers. This issue is called arithmetic underflow [1]. If this happens, computers return error because we take the logarithm of 0 for computing $Z_\ell$. To avoid this issue, we incorporate importance sampling into the MLMC estimator.
Let \( q(\theta | Y) \) be an importance distribution of \( \theta \) which satisfies \( q(\theta | Y) > 0 \) whenever \( p(\theta) > 0 \). For a given \( Y \), we have the following identity

\[
p(Y) = \mathbb{E}_\theta [p(Y | \theta)] = \mathbb{E}_{\theta \sim q(\cdot | Y)} \left[ \frac{p(Y | \theta)p(\theta)}{q(\theta | Y)} \right],
\]

so that the expected information gain \( U \) becomes

\[
U = \mathbb{E}_\theta \left[ \mathbb{E}_{Y | \theta} [\log p(Y | \theta)] \right] - \mathbb{E}_Y \left[ \log \mathbb{E}_{\theta \sim q(\cdot | Y)} \left[ \frac{p(Y | \theta)p(\theta)}{q(\theta | Y)} \right] \right].
\]

The corresponding random variables \( P_\ell \) and \( Z_\ell \) used in the MLMC estimator are replaced by

\[
\hat{P}_\ell = \log p(Y | \theta) - \log \left( \frac{p(Y | \cdot)p(\cdot)}{q(\cdot | Y)} \right)^{M_\ell}
\]

\[
\hat{Z}_0 = \log p(Y | \theta) - \log \left( \frac{p(Y | \cdot)p(\cdot)}{q(\cdot | Y)} \right)^{M_0}
\]

\[
\hat{Z}_\ell = \frac{1}{2} \left[ \log \left( \frac{p(Y | \cdot)p(\cdot)}{q(\cdot | Y)} \right)^{(a)} + \log \left( \frac{p(Y | \cdot)p(\cdot)}{q(\cdot | Y)} \right)^{(b)} \right] - \log \left( \frac{p(Y | \cdot)p(\cdot)}{q(\cdot | Y)} \right),
\]

respectively, where the averages are taken with respect to i.i.d. random samples of \( \theta \sim q(\cdot | Y) \) for a randomly chosen \( Y \).

**Remark 4.** Denote by \( \hat{\rho}_Y \) the probability density function of a positive random variable \( p(Y | \theta)p(\theta)/(q(\theta | Y)p(Y)) \) for a particular value of \( Y \). Assume that there exists a constant \( 0 < \xi_0 < 1/3 \) such that

\[
\sup_Y \int_0^{\xi_0} (\log x - x + 1)^2 \hat{\rho}_Y(x) \, dx < \infty,
\]

and that there exists \( p^* \geq 0 \) such that

\[
\mathbb{E}_Y \left[ \mathbb{E}_{\theta \sim q(\cdot | Y)} \left[ \frac{p(Y | \theta)p(\theta)}{q(\theta | Y)p(Y)^4} | Y \right]^{1+p} \right] < \infty.
\]

for all \( 0 \leq p \leq p^* \). Then a similar proof to that used in Theorem 2 goes through and we obtain

\[
\mathbb{E}[|\hat{Z}_\ell|] = O(2^{-\ell}) \quad \text{and} \quad \text{Var}[\hat{Z}_\ell] = O(2^{-(1+\min(1,2p^*)\ell)}).
\]

Hence the MLMC estimator with importance sampling still achieves the computational complexity of \( O(\varepsilon^{-2}) \) whenever \( p^* > 0 \).

The question is how to construct an importance distribution \( q(\theta | Y) \) depending on each particular problem. The common guideline is to find a good
approximation of the posterior distribution \( p(\theta | Y) \). The Laplace approximation method, which has been recently studied in \([14, 1]\) for estimating the expected information gain, is a method to approximate \( p(\theta | Y) \) by a (multivariate) Gaussian distribution: when the data \( Y \) is generated conditionally on the known value of \( \theta = \theta^* \), the Laplace method approximates \( p(\theta | Y) \) by a Gaussian distribution \( N(\hat{\theta}, \hat{\Sigma}) \), for instance, with

\[
\hat{\theta} = \theta^* - (J^\top(\theta^*)\Sigma e^{-1}J(\theta^*) + H^\top(\theta^*)\Sigma e^{-1}E_e - \nabla_\theta \nabla_\theta \log(p(\theta^*)))^{-1}J(\theta^*)\Sigma eE_e,
\]

\[
\hat{\Sigma} = \left( J^\top(\hat{\theta})\Sigma e^{-1}J(\hat{\theta}) - \nabla_\theta \nabla_\theta \log(p(\hat{\theta})) \right)^{-1}.
\]

Here we defined \( J(\theta) := -\nabla_\theta g(\theta) \), \( H(\theta) := -\nabla_\theta \nabla_\theta g(\theta) \), and \( E_e := Y - g(\theta^*) \). We refer to \([14, 1]\) for details. It is clear that we need to compute the first-order and second-order derivatives of \( g \) with respect to \( \theta \). When their analytical computations are not available, one may approximate them by finite differences.

### 4 Numerical experiments

Two examples are presented here to demonstrate the efficiency of our MLMC estimator by comparing the numerical performance with that of the NMC estimator. In order to avoid arithmetic underflow, we always use the Laplace-based importance sampling within both the MLMC and the NMC estimators. The first example is a simple test case where the analytical value of \( U \) is available, while the second one is based on a more realistic pharmacokinetic (PK) model adapted from \([17]\). Throughout all the experiments, we set \( M_0 \) (the number of inner samples at level 0) to be 1.

#### 4.1 Simple test case

Let \( \theta \) be a vector in \( \mathbb{R}^p \) and consider the following linear data model:

\[
Y = A\theta + \epsilon,
\]

where \( A \in \mathbb{R}^{q \times p} \) and \( Y, \epsilon \in \mathbb{R}^q \). We assume that the prior distribution of \( \theta \) is given by the multivariate Gaussian distribution \( N(\mu_{\theta}, \Sigma_{\theta}) \) and the noise \( \epsilon \) follows \( N(0, \Sigma_e) \). Allowing to repeat experiments \( N_e \) times, the expected information gain for this model can be evaluated analytically as

\[
U = \frac{1}{2} \log |N_e \Sigma_e^{-1} A \Sigma_{\theta} A^\top + I|,
\]

where \( I \) denotes the identity matrix of size \( q \times q \).

In what follows, we set \( p = 2, q = 3, \mu_{\theta} = (1, 0)^\top \),

\[
\Sigma_{\theta} = \begin{bmatrix} 2 & -1 \\ -1 & 2 \end{bmatrix}, \quad A = \begin{bmatrix} 1 & 2 \\ 2 & 3 \\ 3 & 4 \end{bmatrix}, \quad \text{and} \quad \Sigma_e = \begin{bmatrix} 0.1 & -0.05 & 0 \\ -0.05 & 0.1 & -0.05 \\ 0 & -0.05 & 0.1 \end{bmatrix}.
\]
For this parameter setting, the analytical values of $U$ for the cases $N_e = 1$ and $N_e = 10$ are 4.4574 and 6.6642, respectively.

The numerical results for the case $N_e = 1$ are shown in Fig. 1. The left top plot shows the behaviors of the mean values of both $P_\ell$ and $Z_\ell$, where the means are estimated empirically by using $2 \times 10^4$ random samples for each level. Note that the logarithm of the absolute mean value in base 2 is plotted as a function of level. While the mean value of $P_\ell$ is almost constant, the absolute mean value of $Z_\ell$ decays geometrically fast as the level increases. The slope of the line for $Z_\ell$ is $-0.93$, which means $\alpha = 0.93$ and is in good agreement with Theorem 2.

The right top plot shows the behaviors of the empirical variances of both $P_\ell$ and $Z_\ell$. Here we again plot the logarithm of the variance in base 2 as a function of level. While the variance of $P_\ell$ is almost constant, the variance of $Z_\ell$ decays geometrically fast as the level increases. The slope of the line for $Z_\ell$ is $-1.64$, which means $\beta = 1.64$ and agrees well with Theorem 2. These two convergence results in conjunction with the fact $\gamma = 1$ indicate that the MLMC estimator can achieve the computational complexity of $O(\varepsilon^{-2})$ for estimating $U$.

In order to confirm that this is indeed the case in practice, we run the following algorithm which is a slight modification from one described in [6, Section 3.1].

**Algorithm 1.** Let $\omega \in (0, 1)$ be a user-specified parameter. For a target root-mean-square accuracy $\varepsilon$, start with $L = L_0$ and give an initial number of samples $N_\ell$ for all the levels $\ell = 0, \ldots, L$. Until extra samples need to be evaluated, repeat the following:

1. evaluate extra samples on each level.
2. compute (or update) the empirical variances $\hat{V}_\ell$ for $\ell = 0, \ldots, L$.
3. define optimal $N_\ell$ for $\ell = 0, \ldots, L$ according to
   
   $$N_\ell = \left( 1 - \omega \right)^{-1} \varepsilon^{-2} \sqrt{\frac{\bar{V}_\ell}{C_\ell} \sum_{\ell=0}^{L} \hat{V}_\ell C_\ell}.$$

4. test for the weak error convergence $|E[Z_L]|/(2^\alpha - 1) \leq \sqrt{\omega} \varepsilon$, where we use the empirical estimates for $E[Z_\ell]$ and $\alpha$.
5. if the weak error is not converged, let $L = L + 1$ and give an initial number of samples $N_{L}$. 

In this algorithm, the optimal allocation of $N_\ell$ given in Item 3 is derived by minimizing the total cost $\sum_{\ell=0}^{L} N_\ell C_\ell$ for a fixed variance $\sum_{\ell=0}^{L} V_\ell / N_\ell = (1 - \omega) \varepsilon^2$. The weak error convergence test in Item 4 comes from the assumption $E[Z_\ell] \propto 2^{-\alpha \ell}$, which leads to

$$E[P - P_L] = \sum_{\ell=L+1}^{\infty} E[Z_\ell] = \frac{E[Z_L]}{2^\alpha - 1}.$$
In this way, Algorithm 1 heuristically ensures that the mean square error (9) of the MLMC estimator is bounded above by

\[ E[(Z_{\text{MLMC}} - E[P])^2] = \sum_{\ell=0}^{L} \frac{V\ell}{N\ell} + (E[P_L - P])^2 \leq (1 - \omega)\varepsilon^2 + \omega\varepsilon^2 = \varepsilon^2. \]

In our experiments, we always put \( \omega = 0.25, L_0 = 2 \) and \( N_* = 10^3 \).

The left bottom plot of Fig. 1 shows the resulting allocation of \( N\ell \) from \( \ell = 0 \) to the maximum level \( \ell = L \) for different values of \( \varepsilon \). We see that, as \( \varepsilon \) decreases, the maximum level \( L \) increases so as to satisfy the weak error convergence. As expected, for any \( \varepsilon \), \( N\ell \) decreases geometrically as the level increases, i.e., most of the samples are allocated on the coarser levels. The right bottom plot compares the total cost required for the MLMC estimator to have the root-mean-square accuracy less than \( \varepsilon \) with that for the NMC estimator. Here the total cost for the NMC estimator is computed by

\[ C_L \times \frac{\hat{V}[P_L]}{(1 - \omega)\varepsilon^2} \]

for the same maximum level \( L \) with the MLMC estimator, so that the mean square error (7) of the NMC estimator is bounded above by \( \varepsilon^2 \). As the theoretical result predicted, we see that the total cost of the MLMC estimator is of \( O(\varepsilon^{-2}) \), whereas that of the NMC estimator is of \( O(\varepsilon^{-3}) \). For \( \varepsilon = 5 \times 10^{-4} \), the MLMC estimator is more than 380 times more efficient. The estimated \( U \) is 4.458, which agrees quite well with the analytical value.

As shown in Fig. 2, even for the case \( N_e = 10 \), similar convergence behaviors of the mean value \( E[Z\ell] \) and the variance \( V[Z\ell] \) are observed. In this case, the estimated values of \( \alpha \) and \( \beta \) are 0.99 and 1.97, respectively. For \( \varepsilon = 5 \times 10^{-4} \), the MLMC estimator achieves the computational saving of a factor more than 50. The estimated \( U \) is 6.664, which agrees well with the analytical value.

### 4.2 Pharmacokinetic model

Let us consider a more realistic example which is adapted from the PK model used in [17, Example 3]. Suppose that a drug is administrated to subjects. In order to reduce the uncertainty about a set of PK parameters, which affect the absorption, distribution and elimination of the drug in the subjects’ body, it would be helpful to take blood samples of the subjects at several different times and to measure the concentration of drug in the samples.

In the data model (2) considered in this paper, \( \theta \) is a set of PK parameters, \( \xi \) is a set of blood sampling times after the administration of the drug, denoted by \( \xi = (t_1, \ldots, t_J) \), and \( Y = (Y_1, \ldots, Y_J) \) is a vector of the measured drug concentration at times \( t = t_1, \ldots, t_J \). Following [17], let \( \theta = (k_a, k_e, V) \in \mathbb{R}_{>0}^3 \) with \( k_a \) being the first-order absorption constant, \( k_e \) the first-order elimination constant, \( V \) the volume of distribution. The drug concentration at time \( t_j \),
where hour is used as a unit, is modeled as

\[ Y_j = g_t(j, k_a, k_e, V) + \epsilon := \frac{D}{V} \left( e^{-k_et_j} - e^{-k_at_j} \right) + \epsilon \]

with the white noise \( \epsilon \sim N(0, 0.01) \). The difference from the original model in [17] is that we remove one noise term whose variance depends on the value of \( g_t \) for simplicity. The prior probability distributions of \( k_a, k_e \) and \( V \) are assumed independent and given by log \( k_a \sim N(0, 0.05) \), log \( k_e \sim N(\log 0.1, 0.05) \) and log \( V \sim N(\log 20, 0.05) \), respectively. Regarding the experimental setup \( \xi \), we follow [17] and consider three different blood sampling schemes with all \( J = 15 \):

1. (beta) \( \xi_1 \): Percentiles of the Beta \((0.7, 1.2)\) distribution, scaled to \([0, 24]\),
2. (even-spacing) \( \xi_2 \): \( t_j = 0.3 + 1.6 \times (j - 1) \),
3. (geometric) \( \xi_3 \): \( t_j = 0.94 \times 1.25^{j-1} \).

Figs. 3–5 show the MLMC numerical results for three respective experimental setups. For any setup, we can see the geometric decay of both \( |E[Z_\ell]| \) and \( \mathbb{V}[Z_\ell] \), which confirms the tight coupling of the corrections \( Z_\ell \). Similarly to the simple test case, the total cost for the MLMC estimator is of \( O(\varepsilon^{-2}) \), whereas that for the NMC estimator is of \( O(\varepsilon^{-3}) \). In Table 1, we summarize these results. In our problem setting, the expected information gain for the geometric-scheme sampling \( \xi_3 \) is slightly larger than that for the beta-scheme sampling \( \xi_1 \), which itself is larger than that for the even-spacing-scheme sampling \( \xi_2 \). Thus \( \xi_3 \) is the best experimental setup among these three. There may exist a better experimental setup yielding a larger \( U \), although such an investigation is beyond the scope of this paper.

Table 1: Summary of numerical results for the PK model

| Sampling scheme | \( \alpha \) | \( \beta \) | MLMC cost | NMC cost | saving | \( U \) |
|----------------|-----------|-----------|-----------|---------|--------|-------|
| beta           | 0.989     | 1.974     | \( 2.2 \times 10^7 \) | \( 1.3 \times 10^8 \) | 60     | 9.941 |
| even-spacing   | 0.983     | 1.981     | \( 2.4 \times 10^7 \) | \( 1.3 \times 10^8 \) | 57     | 9.513 |
| geometric      | 0.981     | 1.831     | \( 2.2 \times 10^7 \) | \( 1.3 \times 10^8 \) | 60     | 10.004|

The MLMC cost, the NMC cost and the saving are the results for \( \varepsilon = 5 \times 10^{-4} \).

5 Conclusion

In this paper we have developed an MLMC estimator for the expected information gain, which is one of the most important quality criteria of Bayesian experimental designs. Under a sufficient condition on the data model, we prove that our MLMC estimator achieves the computational complexity of \( O(\varepsilon^{-2}) \), which compares favorably with that of the nested Monte Carlo estimator, which is \( O(\varepsilon^{-3}) \). Combining importance sampling techniques with the MLMC estimator is straightforward and is quite helpful not only in reducing the variance of
the corrections $Z_\ell$ but also, as shown in [1], in mitigating the risk of arithmetic underflow. Numerical experiments support our theoretical result. We leave the following issues open for future research:

- an extension to the situation where the function $g$ can only be evaluated approximately. As studied in [1], in engineering applications, it is often the case that $g$ is a functional of the solution of partial differential equations and only approximate values of $g$ from finite difference or finite element approximations are available. As a natural extension of this paper, a multi-index Monte Carlo method [12] is expected to work well in such situations.

- the use of quasi-Monte Carlo (QMC) sampling instead of i.i.d. random sampling. The idea behind QMC sampling is that by distributing samples more uniformly or evenly over the domain, i.e., by generating “low-discrepancy” points or sequences, the rate of convergence for estimating expectations is to be improved. There are some works which combine QMC sampling with MLMC, see for instance [10, 11]. It is expected to achieve additional computational savings also in the current application.

- a combination with an optimization algorithm to find optimal Bayesian experimental designs. The ultimate goal in this direction of research would be to efficiently construct optimal Bayesian experimental designs. In this paper, we only dealt with an estimation of the expected information gain for a given experimental setup. Combining the MLMC estimator with an optimization algorithm would be a promising approach to attain this goal.

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Figure 1: Numerical results for the test case with $N_e = 1$
Figure 2: Numerical results for the test case with $N_e = 10$
Figure 3: Numerical results for the PK model with the beta-scheme sampling times
Figure 4: Numerical results for the PK model with the even-spacing-scheme sampling times
Figure 5: Numerical results for the PK model with the geometric-scheme sampling times