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Prospective HIV Clinical Trial Comparison by Expected Kullback-Leibler Divergence

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Abstract

The sample frequency and volume of blood that can be drawn from a single patient is meticulously restricted under the human subject protection protocols established by an institutional review board (IRB). Consequently, the amount of samples that can be taken during a particular experiment is limited. In order to ensure an effective experiment design, considerations must be taken choosing when to take patient samples. A validated model of HIV-1 viral replication and 2-LTR production is exploited to find sub-optimal sampling schedules that maximize information content of the experiment outcome. This is done through a Forward Stepwise Regression (FSR) process with Kullback Liebler Divergence (KLD) as a selection criterion. Suboptimal schedules are found for an experiment taking four sample points over a possible span of 20 weeks. All schedules found with the FSR process contain significantly more information than both a uniform schedule and a schedule used in a previous experiment with 4 sample points. This work demonstrates the advantages of using KLD as a tool in the experiment design process to increase information content.

I. INTRODUCTION

Research into the Human Immunodeficiency Virus (HIV) has led to considerable advances in the treatment of the disease. Under the primary treatment, combined antiretroviral therapy (cART), patients' viral levels remain suppressed to very low levels. Unfortunately, as effective as the treatment is, it is not able to completely eradicate the virus [4], [5], [6], [7], [8]. One theory for this behavior is there may be low-level viral replication taking place, particularly in sanctuary sites where antiretroviral drug concentrations are suppressed [9], [10], [11].

One way to test for ongoing replication is to intensify treatment by administering an integrase inhibitor in addition to the cART cocktail. The integrase inhibitor will prevent the viral DNA from integrating into the host DNA. Once a failure to integrate occurs, host enzymes will form the viral DNA into circles with two copies of the long term repeat called 2-LTR circles [1], [3]. These 2-LTR artifacts are thus a marker of ongoing replication and provide a measure of the amount of low-level replication occurring [3]. A model of the viral and 2-LTR dynamics has been developed and validated against data from a previous study

[1], [2]. Previous investigations have attempted to quantify the amount of on-going replication by measuring 2-LTR have sampled at arbitrary time points [3]. Considering the dynamics of the system in addition to the measurement noise, the time points selected are not believed to be sufficient for accurate quantification of ongoing replication. We present a method to estimate more optimal sampling schedules by analyzing the expected information content in the schedules.

The model parameter values were estimated in previous work using a Bayesian Markov Chain Monte Carlo method (MCMC) [1], [2]. This set of parameters together constitutes a multivariate distribution of possible values for the parameters. For computational simplicity we perform an Unscented Transform (UT) of the distribution. This allows us to simplify our multivariate distribution to a set of $2N+1$ points, where N is the number of dimensions, with the same first and second moment characteristics as the original distribution [16]. These $2N+1$ points are then used as the simulated HIV-1 experimental patients in our analysis. We present the design of an algorithm that uses these patients in a forward stepwise regression analysis to find a sample schedule with the best weighted average information gain for the simulated patients.

II. METHODS

A. HIV-1 2-LTR Model

We use a two-state ordinary differential equation model of 2-LTR dynamics following intensification with an integrase inhibitor previously developed by Luo et al. [1], [2]. Their two states describe both the concentration of 2-LTR circles and the concentration of actively infected CD4+ T Cells in the blood. These equations have the form:

$$\begin{aligned}\dot{\mathbf{y}} &= -(1 - (1 - \eta_{II} \mathbf{u}_{II})R)a\mathbf{y} + \mathbf{y}_e \\ \dot{\mathbf{c}} &= \phi k_{II}(1 - \eta_{II} \mathbf{u}_{II})R)a\mathbf{y} + k_{II} \eta_{II} \mathbf{u}_{II} R a \mathbf{y} - \delta \mathbf{c}\end{aligned}\quad (1)$$

where $\mathbf{y}$ is the concentration of actively infected cells and $\mathbf{c}$ is the concentration of 2-LTR circles. The term $\mathbf{y}_e$ is the entry rate into the blood of actively infected cells from exogenous sources unaffected by the integrase inhibitor, such as activation of latently infected cells. Luo et al. assume that the viral dynamics have reached a steady state prior to intensification with the integrase inhibitor. From this assumption they conclude that the concentration of raltegravir can be simplified to:

$$\begin{aligned}\mathbf{c}(t) &= \mathbf{c}(\infty) + (\mathbf{c}(0) - \mathbf{c}(\infty))e^{-\delta t} \\ &+ \mathbf{c}(\infty) \frac{\delta \eta_{II} R (e^{-\delta t} - e^{-\alpha(1 - (1 - \eta_{II})R)t})}{(1 - R)(\alpha(1 - (\eta_{II})R) - \delta)}\end{aligned}\quad (2)$$

with a steady state initial value of

$$\mathbf{c}(0) = \frac{k_{II} \mathbf{y}_e \phi R}{\delta(1 - R)} \quad (3)$$

and the final value of

$$c(\infty) = \frac{k_{II} \mathbf{y}_e (\phi + \eta_{II} - \phi \eta_{II}) R}{\delta (1 - (1 - \eta_{II}) R)} \quad (4)$$

Parameter definitions and units are defined below in Table I.

B. Kullback Leibler Calculation

In order to quantify the cost of each candidate schedule we calculate the Kullback Leibler Divergence between the prior multivariate distribution of the model parameters and the posterior distribution of the model parameters. Posterior distributions are calculated using a MCMC Metropolis hastings technique with Gibbs sampling [3]. The multivariate distribution is constructed from a set of five system parameters $\Theta(A, \phi, \eta_{II}, \delta)$. Parameters R, ϕ, η_{II} , and δ are exactly established from equation (2). Parameter A was derived as a an observable parameter which reduces the covariance between other parameters.

$$A \equiv \frac{k_{II} \mathbf{y}_e R}{\delta} \quad (5)$$

Calculation of the Kullback Leibler Divergence is done using equation

$$KLD = \frac{1}{2} \left(\ln \left(\frac{\det \Sigma_2}{\det \Sigma_1} \right) - n - \text{tr}(\Sigma_2^{-1} \Sigma_1) + (\mu_2 - \mu_1)^T \Sigma_2^{-1} (\mu_2 - \mu_1) \right) \quad (6)$$

where (μ_1, Σ_1) and (μ_2, Σ_2) are the mean vector and co-variances matrices of the prior and posterior multivariate distributions respectively and n is the number of dimensions in the distribution [12]. Because the natural log is used in the calculation of the kullback leibler divergence, the result is measure in natural units of information (nats). Equation (6) is applicable when all of the parameters are normally distributed. $\log(A), \log(\phi)$, and $\log(\delta)$ are normally distributed. Parameters η_{II} and R are transformed using the normal distribution quantile function.

$$F^{-1}(p) = \sqrt{2} \sum_{k=0}^{\infty} \frac{c_k}{2^{k+1}} \left(\frac{\sqrt{\pi}}{2} (2p - 1) \right)^{2k+1} \\ c_k = \sum_{m=0}^{k-1} \frac{c_m c_{k-1-m}}{(m+1)(2m+1)} \quad (7)$$

Kullback Leibler Divergence between distributions is conserved through all transformations.

In order to reduce the computational burden, we apply an unscented transform to our prior distribution to obtain 11 simulated patients that approximately represent the distribution of possible patients.

$$\begin{aligned}
 X_i &= \begin{cases} \mu, & i=0 \\ \mu + \sqrt{N \Sigma_i}, & 1 \leq i \leq N \\ \mu - \sqrt{N \Sigma_i}, & N < i \leq 2N \end{cases} \\
 X_i &= (A_i, \phi_i, R_i, \eta_{II_i}, \delta_i)
 \end{aligned} \quad (8)$$

where each X_i is a separate set of parameters. The μ and Σ_i terms are the mean of the prior distribution and the i_{th} column of the covariance matrix of the prior distribution respectively. N is the total number of dimensions in our prior distribution, which in this case is a 5 dimensional distribution. Kullback Leibler Divergence is calculated for each patient X_i and then averaged to find the expected KLD for each schedule.

C. Markov Chain Monte Carlo Methodology

For each candidate schedule we constructed simulated data for each of the 11 simulated unscented transform patients based on our model and measurement noise. The posterior distributions for parameter set $\Theta_i(A_i, \phi_i, R_i, \eta_{II_i}, \delta_i)$ are constructed for each patient i using a Markov Chain Monte Carlo technique. We define $c(t_k, \Theta_i)$ as the true concentration of 2-LTR DNA circles in the blood measured at sample point k for patient i using parameter set Θ_i . We assume measurement noise consistent with a droplet digital polymerase chain reaction (ddPCR) quantification assay. This leads to measurements as

$$\begin{aligned}
 m_{ik}(t_k) &= Poiss(\lambda_i), \\
 \lambda_i &= N \left(1 - e^{-\frac{c(t_k, \Theta_i) \times v}{N}} \right)
 \end{aligned} \quad (9)$$

where N is the number of droplets, c is the concentration of 2-LTR circles in the blood, and v is the sample volume.

Using this simulated data we then use an MCMC technique to find posterior distributions for each parameter set $\Theta_i(A_i, \phi_i, R_i, \eta_{II_i}, \delta_i)$. The posterior distributions from (citation) were the basis for the uninformative prior distributions $P(\Theta_i)$. The likelihood function for our MCMC calculation takes the form

$$L(\Theta_i | m_{ik}) = f_{LN}(m_{ik}(t_k), N(1 - e^{-\frac{c(t_k, \Theta_i) \times v}{N}})) \quad (10)$$

where f_{LN} denotes the probability mass function of the Poisson distribution function.

Applying Bayes theorem we arrive at the equation

$$P(\Theta_i | m_{ik}) = \frac{L(\Theta_i | m_{ik}) P(\Theta_i)}{\int_0^\infty P(m_{ik} | \Theta_i) P(\Theta) d\Theta} \quad (11)$$

However, $\int_0^\infty P(m_{ik}|\Theta_i)P(\Theta)d\Theta$ is a constant scaling factor of the posterior distribution. For computational simplicity we simplify and arrive at the equation

$$P(\Theta_i|m_{ik})\propto L(\Theta_i|m_{ik})P(\Theta_i) \quad (12)$$

which has the same form and conserves the Kullback Liebler Divergence.

D. Stepwise Regression

Without knowledge of the dynamics of the system standard procedure would be to select a uniform sampling schedule. Our intention is to find a schedule that will yield more information from the experiment than such a schedule. We arrive at a suboptimal schedule $S = \{S_{t1}, \dots, S_{tn}\}$ through a process of forward stepwise regression, with S_{t1} being the first sample selected and the process continued until n samples are chosen. We consider a possible time span of 20 weeks for the experiment. Setting a maximum sampling frequency of one sample per day we arrive at 141 possible sampling points including a sample at time zero. Four samples will be drawn leading to a total of approximately 1.6×10^7 possible schedules.

The first step is to simulate data for the 11 Unscented Transform patients for a single day and calculate the posterior distribution and subsequently the Kullback Leibler divergence. After this is done for all 141 days we choose the day that returned the highest information gain and set it as S_{t1} . This process is then repeated holding S_{t1} and cycling through the remaining 140 days to find the sample day that has the highest Kullback Leibler Divergence given the first sample. Ultimately, as expressed in Figure 1, this forward stepwise regression process is repeated over and over again holding the results from the previous iteration to find the day with highest Kullback Leibler Divergence until n samples are chosen. The final schedule S then comprises our suboptimal sampling schedule. Mathematically this takes the form

$$\begin{aligned} S &= \{S_{t1}, \dots, S_{tn}\} \\ &= \{S_{t1}, \dots, S_{tn-1}, \sup(KLD(S_{t1}:S_{tf}|S_{t1}, \dots, S_{tn-1}))\} \end{aligned} \quad (13)$$

where S_{tf} is the last possible sample day.

III. RESULTS

A. Stepwise Regression Results

The forward stepwise regression technique was performed to locate a suboptimal sampling schedule. Results of the analysis are shown in figure 2 for the first eight weeks post intensification. The plot shows the Kullback Leibler Divergence plotted against each individual sample day for every run through the stepwise regression in selecting the four points. From the plot of the selection of the first sample point, we can observe how the information content of each sample point changes throughout the sampling range. There is a small spike in KLD over the first three weeks post intensification with an apex at sample day

1. The algorithm then chose this sample point to hold constant during the next cycle through the stepwise regression.

Given the selection of the first sample point the plot of the second sample point selection demonstrates that with the first point held fixed all the rest of points yield more information. This is perhaps an intuitive result since we are now examining the information content of two sample points during this cycle through the stepwise regression contrary to one sample point as in the first cycle. There is again a slight peak at the beginning leading to the selection of day 6 as the second point.

Similar behavior is apparent in the next plot during selection of the third point. There is slightly more information across all of the sample points given the selection of the first two points when compared to information content in the selection of the second sample point. There is a slight peak again within the first two weeks; however, this time it is less pronounced. Even so, the third point is selected at day 2. Trending towards a uniform distribution, the plot of the selection of the fourth point exhibits only slightly more information for samples toward the beginning of the 20 weeks. The procedure selected day 5 as the final sample day.

An important characteristic about the forward stepwise regression process to note is that with each additional cycle and the addition of a new sample point the amount of information is increased. This behavior is asymptotic as the addition of more and more sample points will lead to a smaller and smaller increase in total information converging towards a limit of maximum information for the given sampling frequency. Further analysis of this tendency will be done in future work.

The degree of ongoing replication prior to intensification with the integrase inhibitor along with efficacy of the drug largely determine the dynamics of the 2-LTR post intensification. This variability among patients is captured in the prior distribution of our parameter set Θ and is approximated by our 11 sigma points. When there is substantial ongoing replication prior to intensification there will be marked increase in 2-LTR; however, there will also be a significant decrease in infection events. This will lead to a sudden decrease in 2-LTR following the initial the initial spur in concentration. Conversely, if there are low levels of replication prior to intensification, there will be an increase in 2-LTR concentration but this increase will not have a significant impact on infection events. This will lead to more sustained levels of 2-LTR (citation).

Figure 3 shows the dynamics of our 11 sigma point patients over the first eight weeks following intensification. The expected transient behavior is evident to varying degrees among the theoretical patients. For all of the patients the transient behavior is resolved by the fourth week and in most patients by the end of the the second week. This demonstrates that the majority of the information about the dynamics of the system occurs very early.

This property is also conveyed in figure 4 where 1000 random points are chosen and from the multivariate prior distribution to represent 1000 random patients. Simulated data is created for these patients and sampled on a weekly basis. A box and whisker plot of the

distribution of the resulting 2-LTR concentration is shown. Evident by the plot, the behavior across the patients is most dynamic in the first four to five weeks.

B. Schedule Comparison

In order to establish that the forward stepwise regression method is a valid tool for choosing a schedule that will maximize the amount of information we will gain in a given experiment, we compare two schedules output from the FSR method with two other experimental schedules presented in table 2.

All four schedules are composed of four samples assuming a maximum sampling frequency of one sample per day. The first schedule output from the FSR method takes samples at day 2,3,5 and 9. The second schedule output from the FSR method takes samples at day 2,3 7 and 8. The third schedule is an actual schedule used by Hatano et al. in an experiment to measure 2-LTR concentration following intensification with the integrase inhibitor raltegravir (citation). In their study, Hatano et al. took samples at Day 0,7,14 and 56. The final schedule is an example of a sample schedule, which a naïve investigator, with little or no knowledge of what dynamics to expect, might choose. This schedule is a Uniform sample schedule with samples taken every two weeks starting at day 0 (day 0, 14, 28 and 42). These schedules are laid out graphically against the dynamics of the sigma points in figure 5.

From the plots, we find that the forward stepwise regression method was fairly consistent in the selection of the four sample points. In both cases it preferred two points sampled at high frequency in the beginning as the 2-LTR concentration was rising and two points sample at high frequency as the 2-LTR concentration decayed. The four points chosen in both the Hatano schedule and the Uniform schedule are significantly more spaced out.

Figure 6 shows the variation in Kullback Leibler divergence values the four schedules. Due to the stochasticity in the measurements, there will be fluctuations in KLD for each schedule. Consequently, the KLD was calculated 50 times for each schedule so that a 95 percent confidence interval could be established. The results show that the 95 percent confidence intervals for the two FSR schedules do not intersect so these two schedules are found to be significantly different with respect to information content. The difference in KLD between the best FSR schedule and the Hatano schedule is very large and even larger between for the uniform schedule. The difference in KLD between the two FSR schedules and the Hatano schedule correspond to an average information gain of over 200 nats across the five dimensional parameter set.

The results of the schedule comparison are summarized in Table III, which displays the average KLD value across all schedules for both the total KLD and the individual parameters. Very little information was gained for parameters ϕ and δ for any of the schedules. A considerable amount of information was gained for parameter R with the largest gains corresponding to the FSR schedules. Only a moderate amount of information was gained for parameters A and η_{III} . The average information gained for parameter η_{III} was slightly higher for the FSR schedules. Interestingly, the average information gained for parameter A was slightly higher for the uniform schedule when compared to the two FSR schedules.

IV. DISCUSSION

This method contains inherent stochasticity due to the measurements. It also makes several assumptions in order to reduce the computational complexity, such as the usage of 11 unscented transform sigma points as an estimate of a 5 dimensional distribution and the exploitation of conditional dependencies to construct suboptimal sample schedules in the forward stepwise regression.

Nevertheless, the tools used in this method serve as a suitable technique in both the estimation of the information content in given schedule and the selection of suboptimal schedules in order to maximize information content in the experiment outcome.

The goal if this work is to demonstrate the advantages of using the Kullback Leibler divergence in the design of clinical experiments. In forthcoming work we intend to extend the concepts developed in this paper to a more rigorous method which will use fewer assumptions and eliminate the conditional dependencies present in the FSR method.

V. FUTURE WORK

A. Genetic Algorithm

The forward stepwise regression method is a quick and valuable method of choosing a suboptimal information schedule. However, the inherent conditional dependencies programmed into the method present limitations toward selecting an optimal schedule. For this reason a more exhaustive search method that does not impose any conditional dependencies is preferred. Although it would incur a much higher computational burden, a more appropriate optimization method for this application would be to use a Genetic Algorithm.

Due to the inherent binary nature of sampling schedules, 0 being a day when no sample is taken and 1 being a day when a sample is taken, the search for optimal sampling schedules lends itself well to the use of a genetic algorithm. After we find a schedule using the stepwise regression method, we could then seed a genetic algorithm with the schedule in order to hone in on a more optimal schedule.

Genetic algorithms are a method of evolutionary computation that would work by separating the sampling space into genes [13], [14], [15]. These genes would then be base pairs, similar to genetics in the biological sense. Instead of AC and TG in or genes we would use 1 and 0 to represent a day when sample is taken or not taken respectively. A set of these genes together would constitute one chromosome and would represent one sampling schedule in our case. This chromosome would then be assessed for fitness in the form of kullback leibler divergence. Chromosomes with greater fitness would be allowed to reproduce with other fit chromosomes in order to create new children, or sampling schedules, to be evaluated.

Children are created though a series of crossovers between the genes of the chromosomes as well as random mutations between base pairs. An example is shown in figure 7. The best performing children would produce the children for the next generation and the process would continue towards an optimal solution. Performing the search this way would relieve

the dependency issues that were presented in the forward stepwise regression method at a cost of computational complexity [13], [14], [15].

B. Additional Future Work

This work indicated the usefulness of kullback leilber divergence as a measure of cost for optimization. Using the forward stepwise regression method we optimized our sampling schedule to yield the schedule we the greatest average information gain across all parameters. The method can also be extended to optimize sampling schedules for any of the individual parameters in which the investigator might be interested. In this study we restricted ourselves to a four point sampling schedule with a maximum sampling frequency of one sample per day. In future work we will perform the analysis with higher sampling frequencies and more sample points for comparison.

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Fig. 1.

A diagram summarizing the procedure for the forward stepwise regression process.

Fig. 2.
Results of the Stepwise Regression Analysis.

Fig. 3.

Plot of the dynamics of the of the Sigma Points Patients for the first 8 weeks.

Fig. 4.
Plot of the distribution of 2-LTR concentration of 1000 random patients over the 20 Week schedule.

Fig. 5.
Plot of the sigma point patient trajectories with the sampling schedules.

Fig. 6.
Kullback Leibler Divergence comparison for four different schedules.

TABLE I

Model Parameter Definitions

Parameter	Definition	Units
y	concentration of infected cells	cells/ 10^6 PBMC
c	concentration of 2-LTR circles	2LTR/ 10^6 PBMC
R	probability infected cell infects a target cell in a generation	unitless
a	death rate of actively infected cells	day^{-1}
y_e	rate of exogenous production of infected	infected cells/ 10^6 PBMCxDay
η_{II}	Ratio-reduction in R following integrase inhibitor intensification	unitless
u_{II}	Ratio-reduction in R following integrase inhibitor intensification	unitless
ϕ	Ratio of probability of 2-LTR formation with integrase inhibitor vs without	unitless
k_{II}	The probability of 2-LTR circle formation when integrase inhibitor is present	2LTR/ infected cells
δ	decay rate of 2-LTR circles	day^{-1}

TABLE II

Sample Schedules

	Sample 1	Sample 2	Sample 3	Sample 4
FSR 1	Day 1	Day 2	Day 5	Day 6
FSR 2	Day 2	Day 3	Day 7	Day 8
Hatano	Day 0	Day 7	Day 14	Day 56
Uniform	Day 0	Day 14	Day 28	Day 42

TABLE III

Average KLD values for each schedule

	FSR 1	FSR 2	Hatano	Uniform
Total	306.0937	264.8131	58.3099	28.8322
A	3.3166	4.1616	4.0838	4.2850
ϕ	0.0048	0.0045	0.0087	0.0093
R	42.3302	42.0114	30.5067	20.4679
η_{II}	1.0419	0.7335	0.1713	0.1306
δ	0.0095	0.0089	0.0061	0.0052