Abstract: - In this paper, the Markov Chain Monte Carlo (MCMC) method and Generalized Least Square (GLS) method are used to estimate the parameters in a glucose/insulin nonlinear differential model with GLP1-DPP4 interaction, describing the glucose-insulin metabolism. The model is used to generate the data that consists of the time-concentration measurements of plasma glucose and of insulin, which are important in Diabetes Mellitus (DM) treatment. Details on our application of MCMC and GLS to estimate parameters in the model are given in this paper. Our results suggest that MCMC is better able to estimate the parameters based on smaller bias and standard deviation. Although MCMC requires more calculation time than GLS, it offers a more appropriate method, in our opinion, for nonlinear model parameter estimations with no knowledge of the distribution of the data and when heterogeneity of variance is evident.

Key-Words: - DPP-4, GLP-1, glucose/insulin metabolism, MCMC, GLS, nonlinear differential equations model.

1 Introduction
The study of glucose and insulin metabolism is fundamental to the understanding of the mechanisms and the diagnosis of diabetes mellitus (DM), a widely spread disease affecting a growing number of people, especially in the developed countries. There are three major forms of diabetes: type 1 diabetes mellitus (T1DM, also known as insulin-dependent or juvenile-onset diabetes), type 2 diabetes mellitus (T2DM, also known as non-insulin-dependent or maturity-onset diabetes), and gestational diabetes.

Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells). Therefore, lack of insulin or the insensitivity of its receptors plays a central role in all forms of DM. Gestational diabetes develops in a small percentage of pregnant women and usually resolves after parturition. T1DM affects less than 10% of diabetic people and is an autoimmune disease in which the destruction of pancreatic beta-cells causes insulin deficiency. T2DM is, instead, a progressive disease, typically associated with obesity. There are several mechanisms that can be involved in T2DM, such as defects in insulin receptors which lead to a compromised insulin sensitivity in peripheral tissues (peripheral insulin resistance) or in the liver (central insulin resistance). In peripheral insulin resistance, tissues do not absorb glucose correctly, while in central insulin resistance, hepatic glucose output is not correctly inhibited leading to unnecessary glucose production. T2DM can also exhibit insulin secretion insufficiency when the pancreatic beta-cells are compromised. All these scenarios lead to an excess of glucose in the blood, a condition called hyperglycemia, that can lead to a number of dangerous consequences. Polyuria (frequent urination) causes loss of electrolytes, dehydration and polydipsia (excess of thirst). Loss of calories leads to polyphagia (excess of hunger), negative nitrogen balance, acidosis and hyperpnea (increased depth of breathing). These and other hyperglycemia related problems can eventually cause coma and death [1].

In order to study insulin and glucose metabolism, several mathematical models [2-4, 5, 6, 7] have been proposed, describing the effect of DM in the attempt to answer questions related to physiological complications.

In the present study, we concentrate on the roles of Glucagon-like peptide-1 (GLP-1) and dipeptidyl-peptidase-4 (DPP-4) on the glucose/insulin metabolism. GLP-1 is secreted from the L-cells of the intestinal mucosa (mostly of the ileum) after
meal ingestion and reduces post-prandial glycaemia, enhancing insulin secretion and delaying gastric emptying [8]. The enzyme DPP-4 is a peptidase that inactivates GLP-1 and rapidly reduces its circulating levels [9].

Here, we perform and compare two statistical methodologies for parameter estimation. The Markov Chain Monte Carlo method (MCMC), which is used in a Bayesian setting, implemented in the repeated measurement data framework, and the Generalized Least Square method (GLS), which is used in the classical statistical formulation, are used to estimate some parameters in a glucose/insulin model with GLP1-DPP4 interaction.

In this study, data on a fixed number of subjects are generated with errors from the glucose/insulin model with GLP1-DPP4 interaction, when the model and its numerical integration are implemented in MATLAB. We focus on the comparison between the two procedures performed in terms of the point and interval parameter estimators. We apply the Bayesian models for the hierarchical nonlinear framework, which is regarded as an extension of the nonlinear regression models to handle data from several individuals, to provide the intra- and inter-individual variation. Finally, the results are compared and analyzed.

2 Procedure

2.1 Glucose/insulin model with GLP1-DPP4 interaction

We here introduce a model representing glucose and insulin homeostasis and accounting for the effects of GLP-1 and DPP-4 peptides. The model is used to generate data of individual glucose and insulin concentrations in time.

Glucose dynamics is described by three state variables, each one representing glucose in a different stage during its metabolism, from entering the body within the meal, to its final absorption into the blood stream. Glucose first appears in the stomach within the meal, it is then transferred to the duodenum. Glucose passes through it. GLP-1, which is released from the gut when glucose passes through it. GLP-1 is rapidly degraded from DPP-4, which is an ubiquitous enzyme, present in several forms and carrying out different actions in the body, depending on its location and specificity. The degradation of GLP-1 from DPP-4 is a safety mechanism which guarantees that, when glucose is not in the gut and its plasma concentration is not going to increase, incretins stop stimulating insulin secretion. Figure 1 gives a schematic description of the glucose/insulin interaction with GLP1-DPP4 interaction. The referenced mathematical model of this process is as follows.

\[
\frac{dS(t)}{dt} = -K_{sg}S(t) + K_{sd}D(t) + T_{p}, S(t_0) = S_0
\]  

(1)

\[
\frac{dD(t)}{dt} = K_{sd}S(t) - K_{gd}D(t) + T_{p}, D(t_0) = 0
\]  

(2)

\[
\frac{dG(t)}{dt} = -K_{sg}G(t) + \frac{K_{sd}D(t)}{V_g} + T_{p}, G(t_0) = G_0
\]  

(3)

\[
\frac{dI(t)}{dt} = -K_{si}I(t) + T_{ig}G(t) + T_{igc}N(t)G(t), I(t_0) = I_0
\]  

(4)

\[
\frac{dN(t)}{dt} = T_{sd}D(t) - K_{sd}P(t)N(t) - K_{sg}N(t) + T_{pc}N(t_0) = N_0
\]  

(5)

\[
\frac{dP(t)}{dt} = -K_{sp}P(t) + T_p, P(t_0) = P_0
\]  

(6)

where \( S, D, G, I, N \) and \( P \) are, respectively: the amount of ingested glucose appearing in the stomach; glucose concentration in the duodenum; plasma glucose concentration; plasma insulin concentration; plasma GLP-1 concentration; plasma DPP4 concentration. In equation (1), the initial condition, \( S_0 \), represents the amount of ingested glucose, and the only term on the right hand-side represents glucose elimination from the stomach, where \( K_{sg} \) is the transfer rate from the stomach to the duodenum. Equation (2) describes the dynamics of glucose concentration in the duodenum. The first term represents the entry from the stomach, while the elimination term is plasma absorption, \( K_{gd} \), being the transfer rate constant from the duodenum to the blood. Equation (3) represents plasma glucose concentration dynamics. This is described by: insulin-independent glucose tissue uptake, where \( K_{ig} \) is the glucose-dependent elimination rate constant; insulin-dependent glucose tissue uptake, where \( K_{igc} \) is the second order elimination rate constant, insulin and glucose-dependent; entry from the duodenum, where \( V_g \) in the denominator is the distribution volume for glucose; and the constant
entry depending on liver release, where $T_{gi}$ is the constant rate of hepatic glucose production. Insulin dynamics is described by equation (4), the first term represents physiological insulin elimination, where $K_{si}$ is the disappearance rate constant. The two entries depend, respectively: on glucose concentration, $T_{gi}$, being the production rate constant of pancreatic release of insulin due to glucose, and on GLP-1 stimulatory effect, where $T_{igN}$ is the rate of pancreatic release of insulin due to incretin action. Equation (5) represents GLP-1 dynamics, where the first term corresponds to the release due to glucose concentration in the duodenum, $T_{g}$, being the $D$ dependent constant production rate. GLP-1 elimination due to DPP-4 cleavage is represented by the second right term, where $K_{xg}$ is the disappearance rate constant, GLP-1 and DPP-4 dependent. The physiological GLP-1 elimination is described by the third term where $K_{ag}$ is the disappearance rate constant. A constant entry is also assumed, represented by the last term, where $T_{a}$ is the constant production rate. The last equation (6) describes DPP-4 dynamics, where $K_{ag}$ in the elimination term is the disappearance rate constant, DPP-4 dependent, and the last term corresponds to DPP-4 production, where $T_{p}$ is the appearance rate constant.

2.2 Materials and Methods

The objective of this work is to estimate the unknown parameters $K_{gj}$, $K_{xg}$, $K_{ag}$, $K_{si}$ and $V_{g}$ in (3) and (4), describing the differences over time of concentration measurements of plasma glucose $G(t)$, and of insulin $I(t)$, by using MCMC and GLS methods. By using MATLAB, data and errors for 30 subjects were generated from the glucose/insulin nonlinear differential equations model with GLP1-DPP4 interaction. The data consist of the time concentration measurements of plasma glucose $G(t)$, and of insulin $I(t)$, every 10 minutes, ranging from 0 to 300 minutes, during which $G_{i}(t)$ and $I_{i}(t)$ of the subject $k$ were found. Table 1 reports the definition of all the quantities in (3) and (4).

Let us consider $y_{ij} = f_{xij}(\beta_{j}, t_{ij}) + e_{ij}$, where $y_{ij}$ denotes the variable concentration of the subject $k$; $k = 1, 2, 3, ..., 30$, at time $j$; $j = 1, 2, 3, ..., 30$, while $\chi$ is equal to $G$ for glucose or $I$ for insulin. Then, $f_{xij}(\beta_{j}, t_{ij})$ represents the prediction functions at time $j$ for the $k$-th subject, which is derived from the numeric solution $\hat{f}(\beta_{j}, t, \chi)$ of the following differential equation model:

$$\frac{d\tilde{G}(t)}{dt} = -K_{xg}G(t) - K_{ag}I(t)G(t) + \frac{K_{yG}D(t)}{V_{g}} + T_{g}G(t_{0}) - G_{b}$$ (7)

$$\frac{dI(t)}{dt} = -K_{si}I(t) + T_{IG}G(t) + T_{igN}N(t)G(t_{0}) - I_{b}$$ (8)

Hierarchical nonlinear models are typically applied to biostatistical problems. These models arise frequently in situations where several measurements are made on a number of subjects. Repeated measurements on a subject may be taken over time, at different analyte concentrations. The existence of repeated measurements requires particular care in characterizing the random variation in the data. In particular, it is important to recognize explicitly two levels of variability: random variation among measurements within a given subject (intra-individual variation) and random variation among subjects (inter-individual variation). Normally, specification of a distribution to characterize inter-individual variation is too

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Units</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t$</td>
<td>min</td>
<td>Time</td>
</tr>
<tr>
<td>$G(t)$</td>
<td>mmol</td>
<td>Amount of ingested glucose in the duodenum</td>
</tr>
<tr>
<td>$I(t)$</td>
<td>pM</td>
<td>Plasma insulin concentration</td>
</tr>
<tr>
<td>$N(t)$</td>
<td>pM</td>
<td>Plasma GLP-1 concentration</td>
</tr>
<tr>
<td>$D(t)$</td>
<td>mmol</td>
<td>Amount of ingested glucose appearing in the duodenum</td>
</tr>
<tr>
<td>$K_{xg}$</td>
<td>min$^{-1}$</td>
<td>The insulin-independent rate constant of tissue glucose uptake</td>
</tr>
<tr>
<td>$K_{ag}$</td>
<td>min$^{-1}$/pM</td>
<td>The insulin-dependent rate constant of tissue glucose uptake</td>
</tr>
<tr>
<td>$K_{gj}$</td>
<td>min$^{-1}$</td>
<td>The rate constant of glucose absorbed from the duodenum into the blood</td>
</tr>
<tr>
<td>$K_{si}$</td>
<td>min$^{-1}$</td>
<td>The disappearance rate constant for insulin</td>
</tr>
<tr>
<td>$V_{g}$</td>
<td>L</td>
<td>The distribution volume for glucose</td>
</tr>
<tr>
<td>$T_{gj}$</td>
<td>pM/min</td>
<td>The increase in plasma glucose concentration due to hepatic glucose release</td>
</tr>
<tr>
<td>$G_{b}$</td>
<td>mM</td>
<td>Glycemia at $t_{0}$</td>
</tr>
<tr>
<td>$I_{b}$</td>
<td>pM</td>
<td>Insulinemia at $t_{0}$</td>
</tr>
<tr>
<td>$T_{IG}$</td>
<td>pM/min/mM</td>
<td>The rate of pancreatic release of insulin due to glucose</td>
</tr>
<tr>
<td>$T_{igN}$</td>
<td>pM/min/pM/mM</td>
<td>The rate of pancreatic release of insulin due to GLP-1</td>
</tr>
</tbody>
</table>

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difficult. There are many models to take into account this variation. In the present work, we used a Bayesian model specification to represent the inter-individual variation. A Bayesian nonlinear model involves 3 stages, according to Davidian and Giltinan [10], as in the following.

**Stage I** Intra-individual variation

In this stage, we specify the mean response and variance-covariance structure for a given subject.

\[
y_k = f_{y_k}(\beta_k, t_{ik}) + \epsilon_k, \quad \epsilon_k \sim N(0, \sigma^2)
\]

where \( \sigma^2 \) is the variance-covariance vector parameter, and \( f_y \) and \( f_e \) are the mean responses for the glucose and insulin, respectively.

**Stage II** Inter-individual variation

The second stage involves a model for variation in characteristics, such as gender, age or simply to biological variability among different individuals. In this work, we consider the simplest case of linear model:

\[
\theta_i = \beta_0 + b_i, \quad b_i \sim N(0,\Sigma)
\]

where \( \beta_0 = \log(\beta_0) = \log(K_{\sigma}, K_{\nu}, V) \) for the joint covariance matrix for all random effects; and \( \beta_0 \) is the individual estimate for Subject \( k \).

**Stage III** Hyperprior distribution

The model specification is completed by an assumption of a distribution for all parameters in Stages 1 and 2: \( \beta, \xi \) and \( D \):

\[
\theta_i \sim N(\theta^*, \Sigma^*), \quad D^{-1} \sim \text{Wishart}(\rho, [\rho D^*]^{-1}), \quad (\sigma^2) \sim \text{Gamma}(1/2, 1/2)
\]

where \( \text{Wishart} \) and \( \text{Gamma} \) represent Wishart and Gamma distributions, respectively.

### 2.3 MCMC Implementation

By following the studies of Davidian and Giltinan [10], Gelfand et al. [11] and Wakefield et al. [12], it can be shown from stages 1, 2 and 3 that the full conditional distribution—the distribution of the parameters given the remaining parameters and the data, and for the parameters \( \theta, D \) and \( \sigma^2 \), may be written explicitly as

\[
\pi(\theta,y_1,...,y_n,\sigma^2,\Sigma) = N(V(mD^{-1}+\Sigma^{-1})\theta,\Sigma)
\]

\[
\pi(D^{-1}|y,\theta_1,...,\theta_m,\sigma^2,\Sigma) = \text{Wishart}(\Sigma^{-1}+m\Sigma, \rho)
\]

\[
\pi(\sigma^2|y,\theta_1,...,\theta_m,\Sigma) = \text{Gamma}(1/2, 1/2)
\]

\[
\pi(\theta_i|y_j,\theta_{ij},...,\theta_{ik},\Sigma) = \text{Normal}(\hat{\theta}_{ik}, (\Sigma^{-1}+\rho D^{-1})^{-1})
\]

The proceeding for MCMC method by using the Metropolis – Hastings algorithm inside the Gibbs sampling to draw the samples of the parameters from Bayesian posterior distribution is given as follows.

1. Start with the initial values \( \theta^{(0)} = (\sigma^{(0)}, \theta^{(0)}, D^{(0)}, \gamma^{(0)}) \) where \( \gamma = \{\theta_i, i=1,2,...,30\} \) and choose \( \theta^{(0)} = \theta_0 \).
2. Obtain a new value \( \theta^{(i)} = (\sigma^{(i)}, \theta^{(i)}, D^{(i)}, \gamma^{(i)}) \) from \( \gamma^{(i-1)} \) throughout the proposal distribution:

\[
\begin{align*}
\theta^{(i)} &\sim \pi(\theta|x, y^{(i)}, D^{(i-1)}, \theta^{(i-1)}) \\
\sigma^{(i)} &\sim \pi(\sigma|x, y^{(i)}, D^{(i-1)}, \theta^{(i-1)}) \\
D^{(i)} &\sim \pi(D|x, y^{(i)}, \sigma^{(i)}, \theta^{(i)}) \\
\gamma^{(i)} &\sim \pi(\gamma|x, y^{(i)}, D^{(i)}, \theta^{(i-1)})
\end{align*}
\]

3. For \( \theta^{(i)} \), move a chain to a new value \( \phi \), which is generated from the proposal \( \phi(\theta^{(i-1)}) \), from \( \theta^{(i-1)} \). Evaluate

\[
\alpha(\phi/\theta^{(i-1)}) = \min\left\{ 1, \frac{\pi(\phi|x, y^{(i-1)}, \theta, D^{(i-1)}, \phi^{(i-1)})}{\pi(\theta^{(i-1)}|x, y^{(i)}, D^{(i)}, \phi^{(i-1)})} \right\}
\]

4. Sample a uniform \((0,1)\) random variable \( U \). If \( U \leq \alpha(\phi/\theta^{(i-1)}) \), then set \( \theta^{(i)} = \phi \), otherwise set \( \theta^{(i)} = \theta^{(i-1)} \) and the chain does not move.
5. Increase \( i \), and return to (2) until convergence is reached.

### 2.4 GLS Procedure

We applied GLS, which is a two-stage method, by following the studies of Panunzi, Palumbo, and De Gaetano [13]. We used the first run of MCMC to be
an initial value for this method. The proceeding is given as follows.

Stage I

1. In $K$ separate estimation procedures (where $K$ is the total number of subjects), obtain preliminary estimates $\hat{\beta}_k^{(p)}$ for each subject $k$, $k = 1, 2, \ldots, K$, by using Ordinary Least Squares (OLS) estimator.

2. Calculate residuals from (1) and estimate $\xi = (\sigma^2, \sigma^2)$ minimizing the following function:

$$PL = \sum_{k=1}^{K} \left[ \log \left( R_k^{(1)} \left( \beta_k^{(p)}, \xi \right) \right) + \left[ y_k - f_k(\beta_k^{(p)}) \right]^T R_k^{(1)} \left( \beta_k^{(p)}, \xi \right) \left[ y_k - f_k(\beta_k^{(p)}) \right] \right]$$

3. Construct estimated weight matrices which depend on the estimated parameters $\hat{\beta}^{(p)}$ and $\beta_k^{(p)}$:

$$\hat{R}_k(\beta_k^{(p)}, \hat{\xi})$$

4. Use the estimated weight matrices from (3), reestimate the $\beta_k$ for each subject $k$, $k = 1, 2, \ldots, 30$ by minimizing $\left[ y_k - f_k(\beta_k) \right]^T R_k^{(-1)} \left( \beta_k^{(p)}, \xi \right) \left[ y_k - f_k(\beta_k) \right]$

The resulting estimates can be treated as preliminary estimates and it is possible to return to (2). The algorithm should be iterated at least once and for each Subject $k$. $\beta_{GLS}$ denotes the final estimates.

Stage II

We obtain $\beta_{GLS}$ from Stage I, then the population estimators of the vector $\beta$ and the variance-covariance matrix $D$ are obtained by $\hat{\beta} = \frac{1}{20} \sum_{k=1}^{30} \beta_{GLS}$ and $\hat{D} = \frac{1}{(m-1)} \sum_{k=1}^{30} (\hat{\beta}_{GLS} - \hat{\beta})^T (\hat{\beta}_{GLS} - \hat{\beta})$.

3 Results

The results of MCMC application are obtained in about ten days. The entire run involves 20,000 iterations and the first 5,000 iterations are considered as burn-in period, while the GLS application converges in 21 iterations.

Table 2 The true values (TV), posterior means (PM), standard deviation (SD) and 95% credible intervals (CI) of population parameters based on MCMC.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TV</th>
<th>PM</th>
<th>SD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{gd}$</td>
<td>0.04</td>
<td>0.04765</td>
<td>0.0236</td>
<td>(0.0392, 0.0561)</td>
</tr>
<tr>
<td>$K_{xg}$</td>
<td>0.001</td>
<td>0.00125</td>
<td>0.00039</td>
<td>(0.000112, 0.0014)</td>
</tr>
<tr>
<td>$K_{xgI}$</td>
<td>0.0001</td>
<td>0.000094</td>
<td>0.00007</td>
<td>(0.000069, 0.00119)</td>
</tr>
<tr>
<td>$K_{xi}$</td>
<td>0.03</td>
<td>0.0308</td>
<td>0.0146</td>
<td>(0.0256, 0.0361)</td>
</tr>
<tr>
<td>$V_g$</td>
<td>14</td>
<td>16.23</td>
<td>13.07</td>
<td>(11.55, 20.91)</td>
</tr>
</tbody>
</table>

Table 3 The true values (TV), point estimates (PM), standard deviation (SD) and 95% credible intervals (CI) of population parameters based on GLS.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TV</th>
<th>PM</th>
<th>SD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{gd}$</td>
<td>0.04</td>
<td>0.05463</td>
<td>0.0242</td>
<td>(0.0460, 0.0632)</td>
</tr>
<tr>
<td>$K_{xg}$</td>
<td>0.001</td>
<td>0.00232</td>
<td>0.0012</td>
<td>(0.0018, 0.0027)</td>
</tr>
<tr>
<td>$K_{xgI}$</td>
<td>0.0001</td>
<td>0.000109</td>
<td>0.00008</td>
<td>(0.000082, 0.00013)</td>
</tr>
<tr>
<td>$K_{xi}$</td>
<td>0.03</td>
<td>0.0312</td>
<td>0.0159</td>
<td>(0.0256, 0.0370)</td>
</tr>
<tr>
<td>$V_g$</td>
<td>14</td>
<td>19.29</td>
<td>14.62</td>
<td>(13.13, 21.45)</td>
</tr>
</tbody>
</table>

Fig. 1 Plot for Subject 1. Glucose and insulin (circles) concentrations versus time together with the predicted time-curves from the glucose/insulin model with GLP1-DPP4 interaction for Subject 1. The solid and dashed lines represent estimated subject curves based on MCMC and GLS, respectively. The generated values for Subject 1 are indicated by the open circles.

Fig. 2 Plot for Subject 29. Glucose and insulin (circles) concentrations versus time together with the predicted time-curves from the glucose/insulin model with GLP1-DPP4 interaction for Subject 29. The solid and dashed lines represent estimated subject curves based on MCMC and GLS, respectively. The generated values for Subject 29 are indicated by the open circles.
The initial values for MCMC and GLS methods for the subject parameters $\theta^0_i$ and population parameters $\theta^0$ were set to $\theta^0 = \log[0.05, 0.05, 0.00025, 0.025, 32.5]$. Table 2 and Table 3 report on a summary of the results of estimated population parameters based on MCMC and GLS, respectively. In Table 4, we present the estimates of subject-specific individual parameters. For comparison, the true parameter values and estimation bias are also presented for each parameter. Fig. 1 and 2 show the curves of estimated value for Subject 1 and Subject 29, respectively.

4 Conclusion
The main aim of this study is to investigate the application of MCMC and GLS methods to estimate parameters in the glucose/insulin nonlinear differential model with GLP1-DPP4 interaction. From our comparison between MCMC and GLS results, we observe that, in the estimations of $\gamma_dK_g$, $\gamma_gK_x$, $\gamma_gIK_x$, $\gamma_iK_g$ and $\gamma_v$, the bias and standard deviation for any parameters with the use of MCMC are smaller than with GLS. Thus, this indicates that MCMC performs better than GLS in estimating every parameter in the glucose/insulin nonlinear differential model with GLP1-DPP4 interaction. Based on the generated data, we suggest the use of MCMC instead of GLS for point estimation on the glucose/insulin nonlinear differential model with GLP1-DPP4 interaction because without any knowledge of the distribution of the data we can easily obtain more accurate posterior means through MCMC method than GLS method. Although, MCMC takes more time than GLS, MCMC would never give rise to such error as that arising from GLS.

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