Measuring Effects of Medication Adherence on Time-Varying Health Outcomes using Bayesian Dynamic Linear Models

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Abstract

One of the most significant barriers to medication treatment is patients’ non-adherence to a prescribed medication regimen. The extent of the impact of poor adherence on resulting health measures is often unknown, and typical analyses ignore the time-varying nature of adherence. This paper develops a modeling framework for longitudinally recorded health measures modeled as a function of time-varying medication adherence or other time-varying covariates. Our framework, which relies on normal Bayesian dynamic linear models (DLMs), accounts for time-varying covariates such as adherence and non-dynamic covariates such as baseline health characteristics. Given the inefficiencies using standard inferential procedures for DLMs associated with infrequent and irregularly recorded response data, we develop an approach that relies on factoring the posterior density into a product of two terms; a marginal posterior density for the non-dynamic parameters, and a multivariate normal posterior density of the dynamic parameters conditional on the non-dynamic ones. This factorization leads to a two-stage process for inference in which the non-dynamic parameters can be inferred separately from the time-varying parameters. We demonstrate the application of this model to the time-varying effect of anti-hypertensive medication on blood pressure levels from a cohort of patients diagnosed with hypertension. Our model results are compared to ones in which adherence is incorporated through non-dynamic summaries.

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1 Introduction

Over 85 million American adults, or about one third of the population over 20 years old, suffer from hypertension (Benjamin et al., 2018). Approximately 16% of adults in the United States are unaware that they have hypertension (Benjamin et al., 2018). Left untreated, hypertension can lead to a range of serious and costly health concerns such as cardiovascular disease, stroke, and renal disease (Amery et al., 1985; Probstfield, 1991). Among the many factors associated with uncontrolled BP, poor adherence to prescribed anti-hypertensive medications is of increasing concern to clinicians, health care systems, and other stakeholders (Choo et al., 1999; Morisky et al., 1986; Osterberg and Blaschke, 2005). Little doubt exists that patients who adhere poorly to their prescribed medication are at risk for worse BP outcomes. Given the large variation in adherence, both across patients and temporally within patients, it is an open question how to accurately measure the impact of varying adherence patterns on BP levels. Furthermore, the variation in adherence patterns creates difficulties in accurately measuring the effects of socio-demographic and health risk factors on BP levels.

This paper develops a Bayesian dynamic linear model (Durbin and Koopman, 2001; West and Harrison, 1997; Petris et al., 2009) for health measures recorded over time as a function of time-varying adherence, with a particular application to the effects of anti-hypertensive medication on BP levels. Bayesian dynamic linear models (DLMs) have a long history as a statistical framework for forecasting and measuring trajectories in many domains, including real-time missile tracking and financial securities forecasting, but rarely in the health context. We apply DLMs to describe time-varying health measures (like blood pressure levels) as a function of detailed adherence (or other time-varying covariates) and individual demographics.
and comorbidities measured typically at study baseline. The application of DLMs to the time-varying adherence on health measures is novel, but fits naturally into the DLM framework because these measures can be “tracked” over time as adherence data accumulate. Because the DLM framework permits the inclusion of patient-level predictors, the model can be applied to measuring effects of socio-economic or racial disparities, or the effects of different comorbid conditions. In these settings, our model can control for differential medication adherence patterns, resulting in more accurate measurement of the effects of other covariates.

Data for studies in which the estimated effects of time-varying adherence on health measures are desired usually consist of three components. First, adherence data for each study participant are assumed to be collected through electronic monitoring devices. These devices electronically time-stamp each time the pill container is opened, and permit an accurate recording of when a patient took their medication. Second, health and socio-demographic are typically recorded at the start of medication adherence studies, and are often non-dynamic. Finally, health measures which might be impacted by differential medication adherence are recorded over time at intermittent intervals. Such measures are often recorded at clinic visits, the timing of which may be determined by the patient. Thus it is quite common for the number of health measures per study patient to be much fewer than the number of days in which medication adherence information is recorded.

The DLM framework is challenged by having much fewer days with health measures compared to the number of days of adherence measurements. In typical uses of DLMs, both time-varying covariates and responses are measured at every time point, and inference for the time-varying state parameters can be accomplished using standard Bayesian updating algorithms (West and Harrison [1997], Chapter 16). With adherence data, when the responses are measured at irregular and infrequent
intervals, the usual updating approaches can be demonstrably inefficient. Instead, we
develop an inferential approach in a Bayesian setting that takes advantage of factor-
ing the posterior density into a product of two terms. The first term involves the exact
marginal likelihood of the DLM, marginalizing out the dynamic state process. The
second is the conditional posterior density for the state process parameters. These
together allow us to determine the posterior distribution for the non-dynamic param-
eters using standard Markov chain Monte Carlo (MCMC) techniques as a first stage
and the state process parameters as a second stage without resorting to needlessly
complex computational tools. With a DLM that has normally distributed responses
and a stochastic process for the latent states the has normal innovations, the factor-
ization is the product of two multivariate normal densities. This factored posterior
density also easily permits inference for the non-dynamic parameters, which in the
setting of medication adherence is likely of interest because the researcher may want
to understand the effect of baseline health characteristics on the health measures
controlling for differential adherence.

The remainder of this paper is organized as follows. In Section 2 we introduce
a motivating example and details of the study cohort. We specify the DLM for our
framework in Section 3. The model, which assumes an autoregressive structure, ac-
counts for possibly multivariate health measures which may or may not be measured
simultaneously. We then develop our computational approach for inference in Sec-
tion 4. We apply our methods to modeling BP in Section 5 where we compare our
methods to typical models used to measure the effects of adherence. We conclude
in Section 6 with a discussion on the limitations and potential extensions of our
methods.
2 Data

The data we analyzed were obtained from the baseline pre-randomization period of a trial that studied the effects of a provider-patient communication skill-building intervention on adherence to anti-hypertensive medication and on BP control (clinicaltrials.gov ID: NCT00201149). Patients were recruited from seven outpatient primary care clinics at Boston Medical Center, an inner-city safety-net hospital affiliated with the Boston University School of Medicine. Patients enrolled into the study from August 2004 and June 2006, meeting several eligibility criteria. These included that the patients were of white or black race (African or Caribbean descent), were at least 21 years old, had an outpatient diagnosis of hypertension on at least three different occasions prior to study enrollment, and were currently on anti-hypertensive medication. The cohort size was 869 patients. The study involved measuring anti-hypertensive medication-taking using Medication Event Monitoring System (MEMS) caps, a particular type of electronic pill-top monitoring device. Patients were given their most frequently taken anti-hypertensive medications in a bottle with a MEMS cap, and were instructed to open the bottle each time they took a dose. Each MEMS cap contained a microprocessor that recorded the date and time whenever the bottle was opened, and the timing information was then downloaded through a wireless receiver after the patient returned the MEMS cap. Our study focused on medication-taking behavior during the entire pre-randomization baseline period of the study. A patient was considered adherent to the prescribed medication on a day if the MEMS cap was opened as many times as the daily medication dosing frequency, and not adherent otherwise. These measurements were recoded on a daily basis, but the duration over which adherence information was measured varied by patient. Blood pressure measurements were recorded less frequently as they were obtained as part of routine
The BP readings were assessed using manual or electronic devices, and were obtained by clinical staff including physicians, nurses and medical assistants. In cases where multiple readings were obtained on a single day (typically at the same clinic visit), the individual values were recorded. Diastolic and systolic blood pressure values (DBP and SBP respectively) were recorded separately.

In addition to detailed time-varying adherence and BP readings, other patient-specific baseline information was collected. Race (white versus African American), gender, income, and age at the start of the study were recorded for each patient. From electronic medical records, the following comorbidities (as binary variables) were investigated in our study, given their potential impact on overall BP levels: Presence of cerebrovascular disease, congestive heart failure, chronic kidney disease, coronary artery disease, diabetes mellitus, hyperlipidemia, peripheral vascular disease, and obesity (defined as body mass index greater than 30\(kg/m^2\)).

To motivate our modeling framework, consider the data from one of the patients in the study cohort displayed in Figure 1. The figure shows the DBP and SBP measures on the three days the patient had their blood pressure measured, and daily indications of whether the patient was adherent. This patient was adherent for a total of 29 of 82 days. However, this simple summary masks the time-varying pattern of the patient’s adherence. The patient began the study by being fully adherent to their prescribed medication, during which time their blood pressure remained under control. After 20 days, the patient started becoming less adherent, and starting around day 38 the patient discontinued taking their medication altogether. Over this latter period, the patient’s BP increased, and by the end of the study period the patient has DBP and SBP values that were not under control. Besides suggesting a potential link between adherence and BP measures, this example motivates a dynamic linear model for...
Figure 1: Example BP and adherence data for a study patient. Red squares are diastolic BP, red dots are systolic BP, and the black dots near the horizontal axis indicate whether the patient was adherent on a particular day (filled dots indicate adherence, open dots indicate non-adherence).

health measures that accounts for time-varying adherence.
3 A dynamic model for multivariate health measures

We propose a statistical framework for multivariate time-varying health measures as a function of medication adherence that is a member of the class of Bayesian dynamic linear models. Let $y_{itk}$ be the value of the $k^{th}$ health measure, $k = 1, \ldots, K$, for patient $i$ at time $t$, $t = 1, \ldots, T_i$. We assume that time is discretized and equally spaced (e.g., days), and that health measures are observed only at times $t_1, t_2, \ldots, t_{m_i}$.

Let $y_{it}$, generally, indicate a vector collecting all outcomes across the dotted index into a column vector. In this example we collect the outcomes for patient $i$ at time $t$, i.e., $y_{it} = (y_{it1}, \ldots, y_{itK})^T$. Similarly, $y_{i,k}$ collects the $k^{th}$ outcome observed at times $(t_1, \ldots, t_{m_i})$ for patient $i$, i.e., $y_{i,k} = (y_{it1k}, \ldots, y_{itmk})^T$. Our framework assumes that $y_{it}$ is an observed measurement generated from a distribution with mean $\mu_{it}$ which follows a stochastic process. The framework recognizes that actual measurements on a given day could vary around a mean level due to various influences including emotional state, activity level, recent alcohol consumption, ambient temperature, and other unobserved factors that might affect the outcomes.

The mean process at time $t$ is modeled as the sum of the contributions of a non-dynamic term and a stochastic term. Specifically, we assume

$$y_{it} = \mu_{it} + \varepsilon_{it}$$

$$= \beta x_i + \alpha_{it} + \varepsilon_{it}$$

(1)

where $x_i$ is a vector of $p$ non-dynamic covariates typically measured at baseline and $\beta$ are the corresponding linear coefficients, and where $\alpha_{it}$ is a stochastic process that may depend on dynamic covariates, such as time-varying adherence. Here
\( y_{it}, \mu_{it}, \alpha_{it}, \) and \( \varepsilon_{it} \) are all vectors of length \( K \) corresponding to the observation, mean outcome process, latent state model and sampling error respectively. The non-dynamic covariate effects \( \beta \) are of dimension \( K \times p \). We use \( \beta_k \) to denote the \( k^{th} \) row of \( \beta \), i.e., the non-dynamic covariate effects on the \( k^{th} \) outcome. The error term for subject \( i \) at time \( t \), \( \varepsilon_{it} \), accounts for typical sampling variability, measurement error and possible correlation of the outcomes within patient and time. We further assume that \( \varepsilon_{it} \sim N(0, \Sigma_{\varepsilon}) \) with possibly non-diagonal covariance matrix \( \Sigma_{\varepsilon} \).

If patient \( i \)'s adherence is tracked for \( T_i \) consecutive days, we indicate this measurement set as \( \{1, \ldots, T_i\} \), and denote the collection of time-varying adherence measures as \( \{c_{it}\}_{t=1}^{T_i} \). We let \( c_{it} = 1 \) if patient \( i \) was adherent on day \( t \) and \( -1 \) otherwise. As we describe below, we extend the definition of \( c_{it} \) to include other time-varying covariates. We further let \( T_i = \{t_1, \ldots, t_{m_i}\} \subset \{1, 2, \ldots, T_i\} \) denote the set of \( m_i \) days on which the outcomes were measured for patient \( i \). The set of outcome measurements for patient \( i \) is denoted by \( y_i = \{y_{it}\}_{t \in T_i} \). Crucially, we assume that \( m_i << T_i \) for all \( i \).

Changes in \( \alpha_{it} \) are assumed to be reflected by whether a patient takes the prescribed medication along with any other time-varying covariates. We assume an AR(1) model on the latent states \( \{\alpha_{it}\} \) and incorporate the \( c_{it} \) as time-varying covariates. Other forms of stochastic processes are possible, including autoregressive processes of higher order. More generally, if \( c_{it} \) is of dimension \( r \), then we assume a process on \( \alpha_{it} \) given by

\[
\alpha_{it} = \rho \alpha_{i,t-1} + \phi c_{it} + \nu_{it} \tag{2}
\]

where \( \rho \) is the \( K \)-dimensional diagonal matrix of first-order autoregressive parameters, that is, \( \rho = \text{diag}(\rho_1, \rho_2, \ldots, \rho_K) \). We assume \( |\rho_k| < 1 \) to ensure stationar-
ity. The time-varying outcome effects $\phi$ is a $K \times r$ matrix. We let $\phi_k$ denote the $k^{th}$ row of $\phi$, i.e., the time-varying covariate effects on the $k^{th}$ outcome. We further assume in (2) that the innovations $\nu_{it}$ have zero-mean MVN distributions with diagonal covariance matrix $\Sigma_{\nu} = \text{diag}(\sigma_{\nu 1}^2, \sigma_{\nu 1}^2, \ldots, \sigma_{\nu K}^2)$. Similarly we assume $\alpha_{i1} \sim N_K(0, \Sigma_0)$ with $\Sigma_0 = \text{diag}(\sigma_{01}^2, \sigma_{01}^2, \ldots, \sigma_{0K}^2)$. Let $\theta$ denote the non-dynamic parameters $\theta = (\beta, \Sigma_\varepsilon, \rho, \phi, \Sigma_\nu, \Sigma_0)$. Equations (1) and (2) define the distributions $p(y_{it} | \alpha_{it}, x_i, \theta)$ and $p(\alpha_{it} | \alpha_{i,t-1}, \ldots, \theta, c_{it})$ respectively.

Figure 2 contains a simulated example of a patient with a scalar outcome over a 30-day period corresponding to the model in (1) and (2). The bottom of the figure displays the adherence indicator simulated independently with a 90% probability of adherence. The adherence effect is simulated to be large and negative ($\phi = -0.5$). The contribution of the non-dynamic covariates is assumed to be $x_i^T \beta = 130$.

As evidenced in Figure 2, the mean process generally declines on days when a patient is adherent. This is not always the case, and an increase can occur when the corresponding innovation $\nu_t$ is large and positive offsetting the impact of the patient taking their medication. The observed health measure is normally distributed around the mean for the day on which the measure is recorded. On day 1, for example, the health measure is higher than the mean, and on day 15 the health measure is lower than the mean.

This model is attractive for relating health measures to time-varying adherence for several reasons. First, the model can account for non-dynamic baseline variables as well as time-varying adherence. This model feature permits disentangling the effects of detailed adherence from patient-specific socio-demographic and health covariates. Second, in settings where multiple outcome measures are observed at time $t$, inference for the sampling variability $\Sigma_\varepsilon$ can be made more precise, and help to separate from the innovation variability $\Sigma_\nu$. 

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The assumption of an AR(1) model component has a well-known asymptotic mean under full adherence and full non-adherence. Specifically, the overall effect of repeated days of adherence on the outcome measure converges for increasing values of $t$ as $\alpha_{it} \rightarrow (I - \rho)^{-1} \phi$. We can therefore predict that if patient $i$ were to continue to be fully adherent, their mean outcomes would tend to $\mu_{it} \rightarrow \beta x_i + (I - \rho)^{-1} \phi$. An analogous calculation can be performed when the patient is fully non-adherent. This property permits estimating the best-case or worst-case health measure means.
for perfect adherence or perfect non-adherence, even when patients’ adherence level
is somewhere in between.

4 Marginal Dynamic Linear Models

Inference for the model in Section 3 is challenging given the large number of param-
eters, both the non-dynamic parameters \( \theta \) as well as the time-varying parameters \( \alpha \). In particular, if the number of recorded adherence indicators per patient is large,
then the size of \( \alpha \) is similarly large. Standard Bayesian inferential methods through
posterior simulation approaches for such a highly parameterized model can result in
slow convergence and unreliable inferences.

Advances in Bayesian computation have made highly parameterized dynamic
models more tractable. With recent developments in sequential Monte-Carlo (SMC)
with software packages like Libbi (Murray, 2013), sampling the induced high-dimensional
latent states of the DLM has become computationally feasible and accessible. The
majority of these advances are in situations where the likelihoods can not be com-
puted directly and are instead approximated. Marginal sampling schemes, like the
particle marginal Metropolis-Hastings (PMMH) algorithm (Andrieu et al., 2010),
alternately sample the structural parameters and latent process parameters and ac-
cept or reject them with an adjusted Metropolis-Hastings step accounting for the
approximation of the likelihood needed in sampling the latent space. Recent work
(Bhattacharya and Wilson, 2018) approximates the posterior of the structural pa-
rameters on a grid of points, reducing the possible sampling values to a discrete
set. SMC has also been adapted to this situation in methods like SMC\(^2\) (Chopin
et al., 2012), or more aptly named Particle SMC, where one can exploit the known
sequential structure of otherwise intractable likelihoods.
Our approach takes advantage of factoring the joint posterior density of \( \theta \) and \( \alpha \) as follows

\[
p(\alpha, \theta | y) = p(\theta | y)p(\alpha | \theta, y).
\]  

(3)

where we omit the dependence on both \( \{c_{it}\} \) and \( x_i \). The first factor in (3) is discussed below, while the second factor, the conditional posterior density of the latent process parameters, can be derived exactly and is discussed in Section 4.2.

Marginal inference about \( \theta \) can be accomplished by integrating (3) with respect to \( \alpha \), yielding the first factor in the expression. This factor can be expanded using Bayes’ Theorem as

\[
p(\theta | y) = \frac{p(y | \theta)p(\theta)}{p(y)}.\]

(4)

The marginal likelihood, \( p(y | \theta) \), in the numerator is determined from

\[
p(y | \theta) = \int p(y, \alpha | \theta)d\alpha.
\]

(5)

As we derive in Section 4.1, the marginal distribution in (5) is multivariate normal (MVN) with a mean and variance that depend only on the fixed model parameters \( \theta \), the adherence measures \( \{c_{it}\} \) and individual covariates \( x_i \). This marginalization is made possible by normality of the latent state innovations \( \nu_{it} \) and sampling error \( \varepsilon_{it} \). Inference for \( \theta \) can therefore be obtained directly from this marginal distribution.
4.1 Marginal Likelihood of the DLM

We explain our marginalization approach in the case of a DLM with a single outcome variable \(k = 1\) and for one individual, and assume a single baseline covariate \(p = 1\) and single time-varying covariate \(r = 1\) which is assumed to be an adherence indicator. The parameters in \(\theta\) are therefore \((\beta, \sigma^2_\varepsilon, \rho, \sigma^2_\nu, \sigma^2_0)\). We assume that both adherence indicators and time-varying outcomes are measured over \(T\) consecutive days; the outcomes are \((y_1, y_2, ..., y_T)\) and the adherence indicators are \(c = (c_1, c_2, ..., c_T)\). We can write the vector of outcomes as the sum of a shared non-time-varying component, a time-varying component and an error term as

\[
\begin{pmatrix}
y_1 \\
y_2 \\
\vdots \\
y_T \\
\end{pmatrix} = 
\begin{pmatrix}
\beta x \\
\beta x \\
\vdots \\
\beta x \\
\end{pmatrix} + 
\begin{pmatrix}
\alpha_1 \\
\alpha_2 \\
\vdots \\
\alpha_T \\
\end{pmatrix} + 
\begin{pmatrix}
\varepsilon_1 \\
\varepsilon_2 \\
\vdots \\
\varepsilon_T \\
\end{pmatrix} = \beta x 1_T + \alpha + \varepsilon. 
\tag{6}
\]

where we use the \(1_T\) notation to indicate a column vector of length \(T\) consisting of all ones. The following development is conditional on \(\theta\) and covariates \((x, c)\) unless noted otherwise. Thus the first term on the right hand side of Equation (6), \(\beta x 1_T\), is treated as a constant vector. The third term is distributed as

\[\varepsilon \sim N_T(\mathbf{0}, \sigma^2_\varepsilon I),\]

where \(\mathbf{0}\) is a column vector of zeros, and \(I\) is a \(T\)-dimensional identity matrix.

Because the initial latent variable \(\alpha_1\) is normally distributed, and each \(\alpha_t\) conditional on the previous latent variables is a linear combination of normal random variables, then \((\alpha_1, ..., \alpha_T)\) is MVN.
The AR(1) structure of the latent states admit a recursive mean and variance calculation

\[ E[\alpha_t] = \rho E[\alpha_{t-1}] + \phi c_t, \]
\[ \text{Var}[\alpha_t] = \rho^2 \text{Var}[\alpha_{t-1}] + \sigma_\nu^2. \]

This recursion and the initial conditions imply a general formula for the mean and variance of \( \alpha_t \)

\[ E_t = E[\alpha_t] = \phi \sum_{k=2}^{t} \rho^{t-k} c_k \]
\[ V_t = \text{Var}[\alpha_t] = \sigma_\nu^2 \sum_{k=2}^{t} \rho^{2(t-k)} + \rho^2 \sigma_0^2 \]

for \( t \in \{2, \ldots, T\} \) with initial mean \( E_1 = E[\alpha_1] = 0 \) and initial variance \( V_1 = \text{Var}[\alpha_1] = \sigma_0^2 \). We collect the mean terms into a vector

\[ \mathbf{E} = (E_1, \ldots, E_T). \]

The covariance follows a similar recursion,

\[ \text{Cov}(\alpha_t, \alpha_{t-1}) = \text{Cov}(\rho \alpha_{t-1} + \phi c_t + \nu_t, \alpha_{t-1}) = \rho \text{Var}[\alpha_{t-1}]. \]

We apply the recursion to obtain a general form of the covariance for \( t \in \{2, \ldots, T\} \) and \( k \in \{0, \ldots, t - 1\} \)

\[ \text{Cov}(\alpha_t, \alpha_{t-k}) = \rho^k \text{Var}[\alpha_{t-k}] = \rho^k V_{t-k}. \]
More compactly, the covariance matrix is

\[
\Sigma = \begin{pmatrix}
V_1 & \rho V_1 & \rho^2 V_1 & \ldots & \rho^{T-1} V_1 \\
\rho V_1 & V_2 & \rho V_2 & \ldots & \rho^{T-2} V_2 \\
\rho^2 V_1 & \rho V_2 & V_3 & \ldots & \rho^{T-3} V_3 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
\rho^{T-1} V_1 & \rho^{T-2} V_2 & \rho^{T-3} V_3 & \ldots & V_T
\end{pmatrix}.
\] (9)

The distribution of the terms in Equation (6) can be written explicitly as

\[(y_1, y_2, \ldots, y_T)^T \sim N_T(\beta x 1_T + E_T, \Sigma + \sigma^2 I).\] (10)

The distribution in (10) is proportional to the marginal likelihood for \(T\) sequentially-observed outcomes, marginalizing out the latent parameters.

Let \(T = \{t_1, t_2, \ldots, t_m\}\) be the actual observation times, and let

\[E_T = (E_{t_1}, E_{t_2}, \ldots, E_{t_m})^T.\]

By properties of the MVN distribution, the outcome vector \(y_\cdot = (y_{t_1}, y_{t_2}, \ldots, y_{t_m})^T\) is also MVN with mean and covariance respectively

\[
\mathbb{E}[y_\cdot] = \beta x 1_{|T|} + E_T
\]
\[
\text{Var}[y_\cdot] = \Sigma_{T \times T} + \sigma^2 I_{|T|}.
\] (11)

The notation \(\Sigma_{T \times T}\) indicates subsetting the covariance matrix \(\Sigma\) to the corresponding rows and columns designated by \(T\). If, for example, \(T = \{1, 7, 9\}\) the first, seventh and ninth rows and columns are taken from \(\Sigma\) making \(\Sigma_{T \times T}\) a \(3 \times 3\) matrix. One
consequence of the marginalization is that if we observe multiple measurements of
the same outcome on a single day, they will only vary according to $\sigma^2_z$.

It is worth noting that even though this marginal distribution does not depend on
the time-varying parameters, the autoregressive structure remains in both the mean
and covariance. For example, the centered marginal mean of $y_t$ can be shown with
simple algebraic manipulation to be

$$(\mathbb{E}[y_t] - \beta x) = \rho (\mathbb{E}[y_{t-1}] - \beta x) + \phi c_t.$$ 

This is the same recursive relationship of the dynamic component of our DLM in (2).
Even though we marginalize out the time-varying parameters, their sequential struc-
ture is retained.

The calculations above were derived for one study participant and a single out-
come variable. These calculations can also be extended to multivariate outcome mea-
urements. The marginal mean and covariance are both individual- and outcome-
dependent, as both $\phi_k$ and $\alpha_{ikt}$ vary by outcome and individual. When referring to
multiple study participants and multiple outcome variables, we can make the depen-
dence explicit by denoting the quantities in (8) and (9) for outcome $k$ of individual
$i$ as $\mathbf{E}_{ik}$ and $\Sigma_{ik}$ respectively.

Because the majority of the structure is contained within outcome (recall $\rho$
is a diagonal matrix), we organize the multivariate outcomes as follows. We col-
clect the outcome $k$ observed through time $t = 1, ..., T_i$ into a $T_i \times 1$ vector $\mathbf{y}_{i,k} =
(y_{1ik}, y_{2ik}, ..., y_{Ti,k})^T$. The marginal likelihood of a vector of complete outcome mea-

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surements can be written as

\[
\begin{pmatrix}
  y_{i1} \\
  y_{i2} \\
  \vdots \\
  y_{ik}
\end{pmatrix} \mid \theta \sim N_{kT} \left( E_i + \beta x_i \otimes 1_{T_i}, \Sigma_i + \Sigma_\epsilon \otimes I_{T_i} \right)
\] (12)

where $\otimes$ is the Kronecker product, and where

\[
E_i = \begin{pmatrix}
  E_{i1} \\
  E_{i2} \\
  \vdots \\
  E_{ik}
\end{pmatrix} \quad \text{and} \quad \Sigma_i = \begin{pmatrix}
  \Sigma_{i1} & 0 & \cdots & 0 \\
  0 & \Sigma_{i2} & \cdots & 0 \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & 0 & \cdots & \Sigma_{ik}
\end{pmatrix}.
\] (13)

As in (11), we can derive the marginal distribution of the outcome measures $y_i .. | \theta$ by subsetting the appropriate rows and columns of the quantities in (13).

If we assume that outcomes between study participants are independent conditional on $\theta$, the marginal distribution of outcomes unconditional on the time-varying parameters is given by

\[
p (y_1 .., y_n .. | \theta, x, c) = \prod_{i=1}^n p (y_i .. | \theta, x_i, c_i ..).
\] (14)

This simple marginalization drastically reduces the number of parameters in the model and simplifies computation. We can conduct inference on our non-dynamic parameters in a Bayesian setting by introducing a prior distribution for $\theta$ and using the marginal likelihood of $\theta$ which is proportional to (14). The posterior density for
the non-dynamic parameters is given by

\[
p(\theta \mid \{y_i\}_{i=1}^n, x, c) \propto p(\theta) \prod_{i=1}^n p(y_i \mid \theta, x_i, c_i).
\] (15)

Inference can be performed in a straightforward and efficient way via MCMC, or using Hamiltonian Monte Carlo (Homan and Gelman, 2014) sampling to obtain draws from the posterior distribution, as implemented in STAN (Carpenter et al., 2017). Alternatively, posterior sampling could be obtained using Sequential Monte-carlo (SMC) in software packages like Libbi (Murray, 2013). SMC works with the sequential likelihoods \( p(y_{it_j} \mid y_{it_1}, \ldots, y_{it_{j-1}}, \theta) \), which are easily available in our framework because they are conditional distributions of the Multivariate Normal distribution in (12).

### 4.2 Inference for the Latent Process

Posterior inference for \( \alpha \) can be determined once \( p(\theta \mid y) \) has been obtained by exploiting the factorization of the posterior density in (3). To do so, we note that the joint distribution of \( \alpha \) and \( y \) conditional on \( \theta \) is MVN. For our development, we consider the case in which outcomes are observed for \( T \) consecutive days. With a \( k \)-dimensional outcome variable, \( \alpha \) contains \( kT \) elements and \( y \) contains \( kT \) (scalar) outcomes. Using the notation in (13), the joint distribution of outcomes and time-
varying parameters is

\[
\begin{pmatrix}
\alpha_{i,1} \\
\vdots \\
\alpha_{i,k} \\
y_{i,1} \\
\vdots \\
y_{i,k}
\end{pmatrix}
\sim N_{2kT}
\begin{pmatrix}
\begin{pmatrix}
E_i \\
\Sigma_i \\
\Sigma_{i,1} + \Sigma_{\epsilon,1} \otimes I_{T_i}
\end{pmatrix}
\end{pmatrix}
\begin{pmatrix}
\begin{pmatrix}
E_i \\
\Sigma_i \\
\Sigma_{i,1} + \Sigma_{\epsilon,1} \otimes I_{T_i}
\end{pmatrix}
\end{pmatrix}.
\quad (16)
\]

The quantities on the diagonal of the covariance matrix in (16) were determined in Section 4.1. The covariance of \( y_{i,k} \) and \( \alpha_{i,\ell} \) (for \( k \neq \ell \)), conditional on \( \theta \), can be shown to be \( 0 \) as follows (with conditioning on \( \theta \) suppressed).

\[
\text{Cov}(\alpha_{i,l}, y_{i,k}) = \mathbb{E}[\text{Cov}(\alpha_{i,l}, y_{i,k}|\alpha_{i,k})] + \text{Cov}(\mathbb{E}[\alpha_{i,l}|\alpha_{i,k}], \mathbb{E}[y_{i,k}|\alpha_{i,k}])
\]
\[
= \mathbb{E}[\text{Cov}(\alpha_{i,l}, \beta x_i + \alpha_{i,k} + \epsilon_{i,k}|\alpha_{i,k})] + \text{Cov}(\alpha_{i,l}, \beta x_i + \alpha_{i,k})
\]
\[
= \mathbb{E}[\text{Cov}(\alpha_{i,l}, \epsilon_{i,k})] + \text{Cov}(\alpha_{i,l}, \alpha_{i,k})
\]
\[
= 0.
\]

We can subset the mean vector and covariance matrix of (16) as in (11) to account for the sporadically observed outcomes, but we continue to assume that the response values are observed at each time period. The conditional posterior distribution of the latent parameters is determined from the joint distribution in (16) by conditioning...
on $\mathbf{y}$ as

$$
\begin{pmatrix}
\alpha_{i,1} \\
\vdots \\
\alpha_{i,k}
\end{pmatrix}
\begin{pmatrix}
y_{i,1}, ..., y_{i,K} \\
\theta \sim N_{kT} \left( \bar{\alpha}_i, \bar{\Sigma}_i \right)
\end{pmatrix}
$$

where

$$
\bar{\alpha}_i = (\mathbf{E}_i) + \Sigma_i (\Sigma_i + \Sigma_\varepsilon \otimes I_{T_i})^{-1} \mathbf{y}_{i,1} - (\mathbf{E}_i + \beta \mathbf{x}_i \otimes 1_{T_i})
$$

and

$$
\bar{\Sigma}_i = \Sigma_i - \Sigma_i (\Sigma_i + \Sigma_\varepsilon \otimes I_{T_i})^{-1} \Sigma_i.
$$

We can use the joint distribution specified in (17) along with the posterior distribution on the structural parameters shown in (15) to sample from the latent process parameters by first simulating $\theta^* \sim p(\theta | \mathbf{y}_{1,\ldots,n}, \mathbf{x}, \mathbf{c})$ and then sampling from $p(\alpha_{i,1}, ..., \alpha_{i,k} | \mathbf{y}_{1,\ldots,n}, \theta^*)$.

5 Application to BP Study

We return to an application of our framework to modeling time-varying BP as a function of time-varying adherence to anti-hypertensive medication and baseline co-morbidities and demographics described in Section 2. We begin with a discussion of models often used in this task that incorporate adherence as non-dynamic information. We also address missing adherence measures for a fraction of patients.
5.1 Non-dynamic models incorporating adherence

Adherence to medication is typically incorporated into outcome models in one of two ways. The average adherence for the study period is either used directly or is dichotomized into two groups, those below a certain threshold and those above, indicating “poor” versus “good” adherence (Rose et al., 2011; Lee et al., 2006; Schroeder et al., 2004). Either of these approaches includes adherence as a non-dynamic covariate in the model. Repeated outcome measures are accompanied by patient-specific random effects.

We present these alternative models in the context of BP outcomes, a bivariate measure. We label the outcomes 1 for Systolic BP and 2 for Diastolic BP. These models take the form

$$\begin{pmatrix} y_{it1} \\ y_{it2} \end{pmatrix} = \begin{pmatrix} x_i \beta_1 \\ x_i \beta_2 \end{pmatrix} + \begin{pmatrix} \delta_{i1} \\ \delta_{i2} \end{pmatrix} + \begin{pmatrix} c_i \gamma_1 \\ c_i \gamma_2 \end{pmatrix} + \begin{pmatrix} \varepsilon_{it1} \\ \varepsilon_{it2} \end{pmatrix}$$

(18)

with two different adherence measures, $\bar{c}_i$. We first consider average adherence, $\bar{c}_i = T^{-1}_i \sum_{t=1}^{T_i} c_{it}$ over $T_i$ days for patient $i$. In this case we would interpret the adherence effect parameters $(\gamma_1, \gamma_2)$ as the differences in BP of being fully adherent relative to being fully non-adherent, controlling for the baseline covariates. We also consider a dichotomized summary $\bar{c}_i = 1 \left\{ \left( T^{-1}_i \sum_{t=1}^{T_i} c_{it} \right) > 2p - 1 \right\}$, an indicator of overall adherence. In this case $(\gamma_1, \gamma_2)$ would be interpreted as the differences in BP for those with “good” ($\bar{c}_i = 1$) versus “poor” ($\bar{c}_i = 0$) adherence. Several values of $p$ were considered to assess the sensitivity to this choice, but we present results for $p = 0.8$ which is a conventional choice (Schroeder et al., 2004). The model in Equation (18) includes patient-specific random effects $\delta_{i1} \sim N(0, \sigma_{\delta_1}^2)$ and $\delta_{i2} \sim N(0, \sigma_{\delta_2}^2)$. 

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We compare the fit of the above two non-dynamic models to our dynamic model framework. The non-dynamic approach has a potential advantage of being more robust to detailed model misspecification relative to our dynamic model, particularly with the choice of the specific model for the evolution of the health measures as a function of daily adherence. However, incorporating average adherence may mask important time-varying effects of detailed adherence. We explore this tradeoff in Section 5.3.

5.2 Missing adherence indicators

Not all of the patients in our cohort have completely observed adherence indicators. Among the 503 patients in our analyses, 70 have at least one day of missing adherence. Adherence could be missing due to MEMS cap malfunctions, hospital inpatient stays in which the MEMS containers were not used, or other causes. The majority (50) of the 70 patients had only one or two missing adherence values. In the most extreme case one patient was missing 48 out of 102 adherence measures.

For patient $i$, let $c_{i}^{obs} = \{c_{it}\}_{t \in T_{obs}}$ be the set of observed adherence values and $c_{i}^{mis} = \{c_{it}\}_{t \in T_{mis}}$ be the set of missing adherence values. Letting $\eta_{i}$ represent the parameters describing a potential adherence model for patient $i$, the posterior density in (15) conditional on the observed adherence data only is

$$p(\theta | y_{i\ldots}, x_{i}, c_{i}^{obs}) = \int p(\theta, c_{i}^{mis}, \eta_{i} | y_{i\ldots}, x_{i}, c_{i}^{obs}) \ d c_{i}^{mis} \ d \eta_{i}$$

$$= \int p(\theta | y_{i\ldots}, x_{i}, c_{i}^{obs}, c_{i}^{mis}, \eta_{i}) p(c_{i}^{mis} | y_{i\ldots}, x_{i}, c_{i}^{obs}, \eta_{i}) p(\eta_{i} | y_{i\ldots}, x_{i}, c_{i}^{obs}) \ d c_{i}^{mis} \ d \eta_{i}$$

$$= (a) \int p(\theta | y_{i\ldots}, x_{i}, c_{i}^{obs}, c_{i}^{mis}, \eta_{i}) p(c_{i}^{mis} | \eta_{i}) p(\eta_{i} | c_{i}^{obs}) \ d c_{i}^{mis} \ d \eta_{i}. \quad (19)$$

The last line in (19) labeled $(a)$ involves a set of modeling choices. First, we as-
sume that the adherence model parameters do not depend on other covariates or
the outcomes, and this is reflected by assuming \( p(\eta_i|y_i, x_i, c_i^{\text{obs}}) = p(\eta_i|c_i^{\text{obs}}) \). Other
approaches, such as those described by Naranjo et al. (2013), provide a framework
for modeling missing time-varying covariates in DLMs with complex models. How-
ever, our assumption is conservative but likely more robust to model misspecification.
Second, \( p(c_i^{\text{mis}}|y_i, x_i, c_i^{\text{obs}}, \eta_i) = p(c_i^{\text{mis}}|\eta_i) \), implies that the missing adherence val-
ues can be simulated directly from our adherence model, represented by \( \eta_i \), without
regard to individual-level characteristics. Again, this is a conservative choice be-
cause adding information to the imputation model could help improve predictions if
properly modeled.

We simulate the missing adherence measures from Beta-Bernoulli distributions
that depend only on adherence measures for each patient separately. Letting \( \eta_i \)
represent patient \( i \)'s overall adherence, the unobserved adherence values are drawn
from a Bernoulli distribution

\[
\{c_{it}\}_{t \in T}|\eta_i \sim \text{Bernoulli}(\eta_i)
\]

where the \( c_{it} = 2c_{it}^* - 1 \) take on values \( \{-1, 1\} \). Under a uniform prior distribution
on patient \( i \)'s adherence rate, the posterior distribution for \( \eta_i \) is given by

\[
\eta_i|\{c_{it}\}_{t \in T_{\text{obs}}} \sim \text{Beta}(n_{i,1} + 1, n_{i,-1} + 1)
\]

when they were observed to be adherent \( n_{i,1} \) days and non-adherent \( n_{i,-1} \) days.

We repeated the simulation process 20 times and combined the posterior samples
for a proper Bayesian multiple-imputation analysis (Little and Rubin, 2002) for our
non-dynamic models. For our fully Bayesian model, the simulated adherence values
were incorporated into our posterior simulation analyses. We found that in both cases inference of our non-dynamic parameters $\theta$ was not sensitive to the missing adherence values.

5.3 Analysis of BP measures

Table 1 displays the number of BP measurements among our 503 patients during the study period. While a majority (69.8%) had either one or two BP readings, a substantial number of patients had 3 or more. The number of BP readings totalled 1152, averaging 2.29 readings per patient.

| Number of BP Readings | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8+  |
|-----------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Number of Patients    | 226 | 125 | 72  | 28  | 16  | 12  | 15  | 9   |
| Percent of Patients   | 44.90 | 24.90 | 14.30 | 5.60 | 3.20 | 2.40 | 3.00 | 1.79 |

Table 1: Number of BP readings during the study period.

For the period of the study, the proportion of days that patients took their medication varied widely. The proportions ranged from 8.9% to 100%, with a median of 95.1% and a mean of 88.9%. These adherence rates on average were high, with many patients being fully adherent throughout the study period. Only 19.1% of patients had below 80% adherence. The high degree of adherence is consistent with recruiting patients for the study who were continual users of anti-hypertensive medication. On average, adherence was recorded over 98 days per patient (minimum and maximum of 21 and 395 days, respectively, with an inter-quartile range of 14), with 75% of patients followed between 84 and 112 days.

Baseline summaries of the non-dynamic covariates appear in Table 2. A majority of the cohort consisted of women, more patients of black race (African or Caribbean descent) than white, and a large fraction of low-income patients. The cohort also
|                                | Mean (Std Dev) | Percent |
|--------------------------------|----------------|---------|
| Age (y)                        | 60.3(11.1)     |         |
| DBP at Enrollment              | 79.7(11.5)     |         |
| SBP at Enrollment              | 133.5(19.6)    |         |
| Female                         | 67.5           |         |
| African-American               | 54.9           |         |
| Income below $20,000           | 44.3           |         |
| Obese                          | 60.6           |         |
| Cerebral Vascular Disease      | 5.6            |         |
| Congestive Heart Failure       | 3.8            |         |
| Renal Insufficiency            | 6.8            |         |
| Coronary Artery Disease        | 14.9           |         |
| Diabetes                       | 36.2           |         |
| Hyperlipidemia                 | 57.1           |         |
| Peripheral Vascular Disease    | 6.2            |         |

Table 2: Baseline socio-demographic and health characteristics of the patients in the study cohort.

consisted of mostly obese patients, and had a moderately high comorbidity burden. Based on 503 patients with BP readings within 14 days of enrollment, the cohort on average had relatively well-controlled hypertension at baseline, as all patients were prescribed anti-hypertensive medication (though adherent to varying extents). The cohort consisted of 26.2% having DBP>80 mm Hg and SBP>130 mm Hg), and 7.8% having DBP>90 mm Hg and SBP>140 mm Hg).

A prior distribution was assumed for the alternative models specified in (18). For k = 1, 2, indicating systolic and diastolic BP measures separately, we assumed the
following.

\[
\begin{align*}
\rho_k & \sim U(-1, 1) \\
\phi_k & \sim N(0, 25) \\
\gamma_k & \sim N(0, 25) \\
\sigma_{\varepsilon_k} & \sim U(0, 30), \rho_\varepsilon \sim U(-1, 1) \\
\sigma_{\nu_k} & \sim U(0, 10), \sigma_{\theta_k} \sim U(0, 30) \\
\beta_{11} & \sim N(120, 400), \beta_{12} \sim N(80, 400) \\
\beta_{jk} & \sim N(0, 400), j = 2, \ldots, p \\
\sigma_{U_k} & \sim U(0, 30)
\end{align*}
\]

The prior components were selected to be vague but proper. The intercepts \(\beta_{1k}\) had distributions centered near the typical systolic and diastolic BPs, but had variances that were sufficiently large to acknowledge the uncertainty in the effects. We assumed uniform prior components with compact support for the standard deviation parameters, as recommended by Gelman et al. (2006). The correlation and autocorrelation parameters were assumed to have uniform prior components as in the dynamic model parametrization. Convergence of the MCMC simulated values was inspected with trace plots of multiple chains, and using the Gelman-Rubin convergence statistic (Gelman and Rubin, 1992).

Table 3 presents posterior means and 90% central posterior intervals for the non-dynamic covariate effects using the DLM. The point estimates and intervals are reported for the DLM only; the effects in the alternative models that were significant at the 0.1 level are indicated with a † (for the average adherence model) or a ‡ (for the dichotomized adherence model). Effects with 90% central posterior intervals not
containing 0 marked with an asterisk (⋆). Based on the model fits, the estimated covariate effects tend to be similar across all models with the point estimates tending to agree in magnitude and sign. Even though the DLM covariate effects tended to have narrower intervals on average (3% reduction), the significance of the findings tended to agree as well. In particular, the effect of race (white versus non-white) was significantly negative, indicating that whites tended to have lower blood pressure controlling for all other variables and time-varying adherence. Patients who were obese at the beginning of the study tended to have significantly higher DBP and SBP. These findings are consistent with the results of previous studies [Kressin et al., 2010; Rose et al., 2011] in their significance and direction of the effects. Both of these,
except for the effect of being white on mean diastolic BP, agreed with the alternative models in terms of significance and directionality of the effect.

Table 4 reports inferences for the standard error and correlations of \((\varepsilon_{it})\) for all three models. Comparing the sampling standard deviation estimates across models

| Dynamic linear model | Variable | Systolic (90% CI) | Diastolic (90% CI) |
|---------------------|----------|-------------------|-------------------|
| Standard Errors:    | 13.37    | (12.46, 14.25)    | 8.11              | (7.68, 8.54) |
| Correlation:        | 0.62     | (0.57, 0.67)      |                   |               |

| Average Adherence Model | Variable | Systolic (90% CI) | Diastolic (90% CI) |
|-------------------------|----------|-------------------|-------------------|
| Standard Errors:        | 14.53    | (13.87, 15.21)    | 8.34              | (7.97, 8.72) |
| Correlation:            | 0.58     | (0.54, 0.62)      |                   |               |

| Dichotomized Adherence Model | Variable | Systolic (90% CI) | Diastolic (90% CI) |
|-----------------------------|----------|-------------------|-------------------|
| Standard Errors:            | 14.5     | (13.86, 15.18)    | 8.34              | (7.96, 8.72) |
| Correlation:                | 0.58     | (0.54, 0.62)      |                   |               |

Table 4: Measurement error estimates for three models.

provides an indication of the gains in modeling the adherence effects as time-varying. The standard error estimates for the alternative adherence models tend to be slightly larger than those given by the DLM, which is consistent with previous work (Rose et al., 2011). The time-varying adherence explicitly captured in the DLM may account for the extra variation in the outcomes of the alternative adherence models through a reduction in the estimated measurement error variance.

Table 5 contains the adherence effects for our models. The adherence effects across the three models are not directly comparable, given the different approaches to incorporate adherence. The average adherence model indicates that the difference between those who were fully adherent and those who were fully non-adherent, controlling for other covariates, is about \(-9.2\) and \(-9.5\) for systolic and diastolic,
|                | Systolic (90% CI) | Diastolic (90% CI) |
|----------------|------------------|-------------------|
| Adherence effect: | -0.48 (-0.84, -0.2)* | -0.24 (-0.43, -0.09)* |
| Asymptotic Adherence effect: | -3.87 (-5.98, -1.83)* | -3.15 (-4.38, -1.94)* |

|                | Systolic (90% CI) | Diastolic (90% CI) |
|----------------|------------------|-------------------|
| Adherence effect: | -9.24 (-16.03, -2.22)* | -9.46 (-13.55, -5.52)* |

|                | Systolic (90% CI) | Diastolic (90% CI) |
|----------------|------------------|-------------------|
| Adherence effect: | -5.49 (-8.26, -2.75)* | -3.78 (-5.27, -2.2)* |

Table 5: Adherence effects for the models considered

respectively. This implies, for example, that a 10% additive increase in adherence corresponds to a 0.92 and 0.95 reduction in systolic and diastolic blood pressure, respectively. However, this effect size assumes that the relationship between average adherence and blood pressure is linear and holds throughout the entire range of adherence. Given the limited range of average adherence observed in the data (90% of patients have average adherence above 70.5%), interpreting this effect beyond this range is not recommended because it involves extrapolating beyond the data. The dichotomized adherence model shows similar results. In particular this approach involves comparing those with relatively good overall adherence (above 80% adherent) to everyone else. Based on the dichotomized adherence model, the benefit of being in the former group is indicated by a lower blood pressure of $-5.49$ and $-3.78$ on average for systolic and diastolic blood pressure.

The DLM gives similar results. The effect of taking medication can be inferred on a daily basis. The results of the model fit suggest a small but significant reduction of blood-pressure from taking the medication on a daily basis, $-0.24$ mm Hg and $-0.12$ mm Hg on average for systolic and diastolic BP, respectively. These estimates imply that, accounting for the correlation estimate, a patient who is adherent over
consecutive days would experience a long-term reduction in systolic BP by $-3.9$ mm Hg, and a long-term reduction in diastolic BP by $-3.15$ mm Hg. The magnitudes of an increase in long-term BP for continued non-adherence is the same but in the opposite direction. Overall, the adherence effects tend to agree in terms of the significance and direction for the different models. However, the DLM provides a clearer interpretation of these parameters that is consistent with the time-varying nature of the data.

Another benefit of the DLM is our ability to infer the latent BP for unobserved days using the procedure discussed in Section 4.2. Figure 3 contains an example of posterior draws of the mean process $\mu_{it} = \beta x_i + \alpha_{it}$, for the patient presented in Figure 1. The solid line indicates the posterior mean of the latent process while the dashed lines indicate a 90% credible envelope across time. That is, for each time $t$, a 90% credible interval of $\alpha_{it1}, \alpha_{it2} | \{y_{it}\}_{i=1}^n$ is shown. The estimated mean DBP and SBP processes vary gradually over time, with shifts in direction indicated by medication adherence variation.

6 Discussion

In this article we propose a multivariate DLM that can be used for modeling time-varying outcome measures as a function of detailed medication adherence or other time-varying covariates. While DLMs are of common use, our particular setting benefits from a two-stage computational approach made possible by factorizing the posterior density into the dynamic and non-dynamic parameters. Typical analyses in this setting ignore the time-varying structure of medication adherence and instead examine this relationship between adherence and outcomes via correlations with non-dynamic adherence measures (e.g., time-averaged adherence). Our framework
Figure 3: 90% central posterior intervals for the mean blood pressure $\{\mu_{it}\}$ for one study subject. The solid lines are the estimated mean DBP and SBP, and the dashed lines are the point-wise posterior intervals. Horizontal dotted lines are drawn at the baseline-estimated mean DBP and SBP.
explicitly provides a measure of daily impact of medication-taking and meaningful bounds for mean BP while controlling for baseline covariates.

Our modeling approach is sufficiently flexible to permit a wide range of assumptions distinct from those we included in our hypertension application. For example, we assumed an AR(1) modeling structure for the mean outcome process, and this assumption can be justified based on the pharmacokinetic properties of the medications. In other settings, alternative mean processes can be considered, including higher order AR processes, growth curves, and so on. Our baseline covariates were modeled linearly, but our framework permits non-linear inclusion of covariate information for both baseline non-dynamic covariates, as well as the dynamic predictors in the mean process component of our model. A crucial assumption of our framework is that the outcome distribution is multivariate normal, as this assumption allows for the marginalization strategy that leads to an efficient computational procedure. However, with some non-normal outcome distributions, various strategies can be employed that can potentially take advantage of the marginalization idea. For example, non-normal outcome densities can be approximated by normal distributions after which the marginalization can be performed; then a Metropolis-Hastings algorithm would be incorporated into the posterior sampling procedure that would account for the non-normality of the original sampling distribution. Such a procedure is likely to be far more efficient than sampling the dynamic parameters directly as part of model fitting.

The proposed modeling framework also permits extensions that are straightforward to incorporate. For example, multivariate outcomes that are recorded at staggered intervals can be accommodated by marginalizing the distribution in (12) appropriately. We may also believe that the effect of adherence to medication varies from person to person. We can then include patient-specific adherence effects with a
hierarchical prior on these parameters to share information across individuals. Our analyses did not acknowledge differences among anti-hypertensive medications, but our framework permits distinguishing differential medication effects in a natural manner. The effects of different medications, perhaps grouped by relevant characteristics such as whether the medication is short-acting or long-lasting, or by medication type (e.g., for hypertension, diuretics, ACE inhibitors, etc.), can be included as separate time-varying effects in the dynamic component of our model. Dosages and dosing frequencies can serve as covariates for the effects of particular medications.

The framework we developed can help establish answers to questions of interest to clinicians and medical researchers that have been difficult to assess through simpler models. In particular, our model can establish the effects of different socio-demographic or health factors on health outcomes that control for detailed time-varying adherence to medication by recognizing that medication-taking behaviors can change over time. From our framework, we can also estimate the daily improvement in being adherent to one’s medication, controlling for socio-demographic and health characteristics, but also the likely long-range achievable mean outcomes. We can also use the model to forecast health outcomes as a function of specified patterns of adherence, potentially serving as a tool for medical decision-making by clinicians. Our approach provides a robust framework for understanding the impacts of poor medication adherence as clinicians and patients work together to improve their medication treatment.
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