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A framework for smartphone-enabled, patient-generated health data analysis

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Background: Digital medicine and smartphone-enabled health technologies provide a novel source of human health and human biology data. However, in part due to its intricacies, few methods have been established to analyze and interpret data in this domain. We previously conducted a six-month interventional trial examining the efficacy of a comprehensive smartphone-based health monitoring program for individuals with chronic disease. This included 38 individuals with hypertension who recorded 6,290 blood pressure readings over the trial. **Methods:** In the present study we provide a hypothesis testing framework for unstructured time series data, typical of patient-generated mobile device data. We used a mixed model approach for unequally spaced repeated measures using autoregressive and generalized autoregressive models, and applied this to the blood pressure data generated in this trial. **Results:** We were able to detect, roughly, a 2 mmHg decrease in both systolic and diastolic blood pressure over the course of the trial despite considerable intra- and inter-individual variation. Furthermore, by supplementing this finding by using a sequential analysis approach, we observed this result over three months prior to the official study end – highlighting the effectiveness of leveraging the digital nature of this data source to form timely conclusions. **Conclusions:** Health data generated through the use of smartphones and other mobile devices allow individuals the opportunity to make informed health decisions, and provide researchers the opportunity to address innovative health and biology questions. The hypothesis testing framework we present can be applied in future studies utilizing digital medicine technology or implemented in the technology itself to support the quantified self. The study was registered at clinicaltrials.gov (NCT01975428).

1 **A framework for smartphone-enabled, patient-generated health data analysis**

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18 **ABSTRACT**

19 **Background:** Digital medicine and smartphone-enabled health technologies provide a novel
20 source of human health and human biology data. However, in part due to its intricacies, few
21 methods have been established to analyze and interpret data in this domain. We previously
22 conducted a six-month interventional trial examining the efficacy of a comprehensive
23 smartphone-based health monitoring program for individuals with chronic disease. This included
24 38 individuals with hypertension who recorded 6,290 blood pressure readings over the trial.

25 **Methods:** In the present study we provide a hypothesis testing framework for unstructured time
26 series data, typical of patient-generated mobile device data. We used a mixed model approach
27 for unequally spaced repeated measures using autoregressive and generalized autoregressive
28 models, and applied this to the blood pressure data generated in this trial.

29 **Results:** We were able to detect, roughly, a 2 mmHg decrease in both systolic and diastolic
30 blood pressure over the course of the trial despite considerable intra- and inter-individual
31 variation. Furthermore, by supplementing this finding by using a sequential analysis approach,
32 we observed this result over three months prior to the official study end – highlighting the
33 effectiveness of leveraging the digital nature of this data source to form timely conclusions.

34 **Conclusions:** Health data generated through the use of smartphones and other mobile devices
35 allow individuals the opportunity to make informed health decisions, and provide researchers
36 the opportunity to address innovative health and biology questions. The hypothesis testing
37 framework we present can be applied in future studies utilizing digital medicine technology or
38 implemented in the technology itself to support the quantified self. The study was registered at
39 clinicaltrials.gov (NCT01975428).

40

41 **KEYWORDS**

42 quantified self; digital medicine; mobile blood pressure monitoring; mixed models; unequally
43 spaced repeated measures; spatial power law

44 INTRODUCTION

45 Empowered patients and health care consumers (Topol, 2015) have aligned with health data
46 tracking technologies to create the quantified self movement (Swan, 2013). Quantified self
47 involves the use of tracking one's own health-related data to understand trends and potentially
48 alter behavior in order to achieve a health goal. The size and scope of health tracking has and
49 continues to expand with the advent of digital medicine and mobile health (mHealth)
50 technologies enabled by smartphones and connected device infrastructures (Steinhubl, Muse &
51 Topol, 2015). For example, in certain individuals traditional daily weight monitoring has been
52 supplemented by apps that track food intake and devices that monitor physical activity in order
53 to achieve this health goal – a part of the 58% of mobile phone users that have downloaded a
54 health-related mobile app (Krebs & Duncan, 2015). Researchers have shown that in some
55 cases interventions using this technology alone can improve health outcomes, though this result
56 is far from universal (see (Free et al., 2013) for review) with the disparity likely due to numerous
57 factors including poor adherence and fatigue (Shaw et al., 2016), and failure of the intervention
58 to change behavior (Patel, Asch & Volpp, 2015).

59

60 While new, better, more user-friendly technologies will continue to be developed, vying for the
61 appreciable forecasted growth of the industry (Statista, 2016), we and others believe the future
62 of the field is not simply in the devices and software themselves, but in the data they generate
63 (Gibbs, 2015). Such data can help guide individual health decisions – the crux of the quantified
64 self movement – but can also be used to address novel human health and biology questions
65 (Steinhubl et al., 2015). Yet there exists a sizable gap between the data that is generated and
66 the methods available to analyze and interpreted such data (Fawcett, 2015). Indeed, most such
67 devices and apps simply display the data, leaving any inference up to the user and anyone the
68 user wishes to share the data with (e.g., their physician). However, even the most data
69 experienced users and health care providers may find identifying subtle trends in such complex

70 data a daunting task. These challenges also extend to researchers who may wish to examine
71 data captured from these technologies as, in addition to inherent technical obstacles such as
72 data collection and data security, few analytic methods are established and general software
73 packages are not readily available.

74

75 These technologies present the opportunity to examine health data in nontraditional ways.
76 Rather than large intermittent gaps in health measures between doctor or study visits, data can
77 be collected in relatively high resolution. Such high resolution data allows users and researchers
78 to detect unique trends and relationships that were never before possible. For example, a
79 diabetic patient using a continuous glucose monitor can now assess their minute-to-minute
80 health rather than rely on single, low resolution measures such as hemoglobin A1c levels, which
81 does not accurately assess health variability (Virtue et al., 2004). Furthermore, access to such
82 high-resolution human health data in nontraditional settings (e.g., normal, at home environment)
83 allows us to evaluate “real world” health and not be relegated to artificial worlds created in
84 clinical trials that suffer from poor clinical practice adoption (Goss, Elmore & Lessler, 2003). Yet
85 in order to form scientific conclusions in this new frontier, novel methods and adaptations of
86 existing approaches must be developed to account for the intricacies of patient-generated data.

87

88 While numerous digital medicine biosensors, devices, and applications have been
89 manufactured to measure various aspects of human physiology and exposome, perhaps no
90 metric epitomizes both the contemporary challenge and opportunity of this field more than blood
91 pressure. Heart disease is the leading cause of death in the United States, with hypertension
92 being the leading contributor of disease (National Center for Health Statistics, 2012). With
93 proper management, hypertension can be controlled and the health consequences of
94 uncontrolled hypertension can largely be avoided. Nevertheless, in the United States only 48%
95 of individuals with hypertension have their condition under control (Farley et al., 2010). It is

96 unsurprising that hypertension has been a target for patient-centric, mHealth disease
97 management (Logan, 2013). Yet the technology to continuously monitor blood pressure in the
98 outpatient setting is still developing as manufacturers have not entirely solved the technical
99 aspects of truly passive monitoring. Thus, the current state of the field largely includes mobile
100 blood pressure cuffs in which readings are initiated by the user. As users may take a reading at
101 any time, evaluating temporal trends in this data requires added consideration.

102

103 In this study we present a hypothesis testing framework in which we examined blood pressure
104 readings taken at variable, uncontrolled time points in individuals enrolled in a smartphone-
105 based health monitoring intervention trial – though the approach we present can be adapted to
106 other similarly structured data. In total, 38 study participants recorded and provided us with
107 blood pressure data on 6,290 occasions. We find that by leveraging all data across individuals
108 we were able to detect an approximately 2 mmHg decrease in blood pressure over a 6 month
109 trial, despite considerable intra- and inter-individual variation. We then discuss how this and
110 other techniques can be implemented in data analyses of the quantified self and in future study
111 designs.

112

113 **METHODS**

114 **Study participants**

115 The present investigation is a sub-analysis of a study conducted by the Scripps Translational
116 Science Institute named the Wired for Health (WFH) study (Bloss et al., 2016). In brief, the WFH
117 study was a 6 month, randomized-controlled trial investigating the practice of a smartphone-
118 based health monitoring program in individuals with chronic disease, and was accompanied by
119 an online and mobile tracking infrastructure. Eligible participants were over the age of 18 who
120 were insured by Scripps Health and had submitted at least one health insurance claim for
121 hypertension, diabetes, or cardiac arrhythmia in 2012. Participants were equally randomized to

122 the control or monitoring arms (details below). In total, 160 participants enrolled in the WFH
123 study, with the majority (51.3%) being in the top quartile of health insurance claims in 2012.
124 Only individuals with hypertension (n=135) were considered in the present study. Among those,
125 112 completed the study, including 53 in the control and 59 in the monitoring group. After
126 screening device readings data for technical limitations (n=19) and study noncompliance (n=2),
127 38 hypertensive individuals from the monitor group had complete readings data. This study
128 focuses on these 38 individuals. This study was approved by the Scripps Institutional Review
129 Board, and all study participants provided informed consent.

130

131 **Monitoring intervention arm**

132 Hypertensive study participants in the monitoring group were provided with comprehensive
133 mobile blood pressure monitoring system: a Withings Blood Pressure Monitor, an iPhone 4 or
134 4s with linked applications, iPhone applications, and an online and mobile HealthyCircles
135 account. HealthyCircles is a Qualcomm Life health care coordination and management platform
136 with an integrated suite of management and consumer portals that can deliver chronic disease
137 education and connect users to their families, caregivers, and health care professionals.
138 Individuals were instructed to measure their blood pressure using this system twice a day, three
139 days a week, with the first measurement in the morning. If participant measurements dropped
140 below a desired level of compliance (less than three measurements a week for two consecutive
141 weeks) the participant was sent an email through their HealthyCircles account reiterating the
142 measurement schedule. Participants were also encouraged to take extra measurements if
143 deemed appropriate. Device readings data was collected using Qualcomm Life's cloud-to-cloud
144 data integration capability.

145

146 **Variables of interest**

147 The primary outcome of the present study was device-collected blood pressure measurements
148 in the 38 individuals with complete readings data in the monitoring group. The primary
149 independent variable is time since the beginning of enrollment in the study. The hour during the
150 day the measurement was taken was considered as a covariate.

151

152 **Statistical Analyses**

153 Device readings data was analyzed using two approaches: 1) a multiple N-of-1 approach in
154 which the data from each study participant was analyzed individually; and 2) a mixed model
155 approach combining all individuals for analysis.

156

157 In the multiple N-of-1 approach, blood pressure measures were regressed on time enrolled in
158 the study using linear regression, accounting for the time of day at which the measurements
159 were taken. Alternative covariance structures were modeled, but results were consistent with
160 those obtained from simple linear regression. In all cases, the effect of blood pressure over time
161 (i.e. slope) was recorded. Slope averages, inverse variance weighted averages, and
162 bootstrapped confidence intervals were calculated.

163

164 Alternatively, repeated measures mixed models were constructed to assess blood pressure
165 over time across all individuals. The general structure of the model is:

166

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}$$

167 where \mathbf{Y} is the vector of blood pressure measures, \mathbf{X} is a matrix of independent variables (i.e.
168 intercept, time, and covariates) with fixed effects $\boldsymbol{\beta}$, \mathbf{Z} is a matrix indicating the structure of the
169 between subject random effects \mathbf{u} with covariance matrix \mathbf{G} , and \mathbf{e} is the random error with
170 covariance matrix \mathbf{R} . It follows that $\text{Var}(\mathbf{Y}|\mathbf{u}) = \mathbf{R}$ and $\text{Var}(\mathbf{Y}) = \mathbf{V} = \mathbf{Z}\mathbf{G}\mathbf{Z}^T + \mathbf{R}$.

171

172 In the present study, \mathbf{R} represents the potential time-dependency of measures within subjects.
173 It follows that \mathbf{R} and subsequently \mathbf{V} are block diagonal. Below we refer to the block diagonal
174 elements of \mathbf{V} as Σ , and the elements of \mathbf{R} as $\Sigma_{\mathbf{R}}$. The primary hypothesis tested was
175 $H_0 : \beta_{\text{time}} = 0$. That is, was there a linear change in blood pressure measures in the study
176 population after accounting for individual variation and potential time-dependency between
177 measures? Time of day (in hours) was modeled as a fixed effect covariate with 24 levels. No
178 other covariates were modeled.

179

180 Three distinct covariance structures were modeled that were appropriate for the source of the
181 data and minimally complex on account of the large dimensions of \mathbf{V} : 1) compound symmetric
182 structure Σ (i.e. random effects only); 2) a first-order autoregressive structure with random
183 effects; and 3) a spatial power law/generalized autoregressive structure with random effects.
184 Model fit was assessed using AIC and BIC.

185

186 Finally, a sequential analysis approach was implemented using the mixed model approach
187 described above. Study device readings data was collected over a roughly ten and one-half
188 month period from the middle of August 2013 to July 2014. Data was partitioned into eleven
189 cumulative monthly periods. For example, one data partition included all device readings data
190 from the first month of the study, another included device readings data from the first two
191 months of the study, and so on. A mixed model with spatial power law covariance structure with
192 random effects was applied to each of the data partitions. Additionally, a sequential analysis
193 approach was implemented in an N-of-1 framework where readings from each individual alone
194 were partitioned into monthly blocks similar to that described above. Among individuals who did
195 demonstrate a significant increase or decrease in blood pressure at six months, the goal was
196 determine if changes in blood pressure could be observed prior to the conclusion of the

197 individual's study participation (e.g., if an individuals demonstrated a decrease in blood pressure
198 over 6 months, would we have observed that result after 5 months). Likewise, a spatial power
199 law covariance structure was assumed.

200

201 **RESULTS**

202 Demographic information on study participants is presented in Supplemental Table 1. Among
203 the 59 original study participants assigned to the monitoring intervention arm that completed the
204 study, 38 had complete device readings data. This cohort was predominantly Caucasian (87%)
205 and largely female (74%) with an average age of 57. A number of participants did not own a
206 smartphone prior to enrollment in the study (21%) with half owning an iPhone. Responses to
207 health-related survey questions are presented in Supplemental Table 2. We saw a general
208 increase in overall health by the end of the study. There was notable decrease in smoking
209 frequency and increase in exercise frequency. However, we note that these health
210 improvements were also observed in the control arm of the original study (data not presented),
211 suggesting that the monitoring intervention itself had no discernible impact on these traits.

212

213 The implied goal of individuals participating in the study is better management of their condition.
214 In this regard, we considered observed blood pressure device readings collected over the
215 course of the study as outcomes of interest. Single blood pressure readings taken at, for
216 example, the enrollment and end of study visit can provide some level of inference on blood
217 pressure changes. However, this approach ignores all data that could be generated between
218 these time points and is vulnerable to biases and natural variation. Rather, we feel approaches
219 which leverage the entirety of the data are preferential. By utilizing Qualcomm's cloud-to-cloud
220 data integration capability, we were able to capture the measure and time recorded of each
221 blood pressure reading on 38 individuals in the monitoring group. While our inference is based
222 on these 38 individuals and is limited, we present our mathematical framework and modeling

223 below in attempt to answer the seemingly simple question: was blood pressure changing over
224 the course of the study?

225

226 In total, we collected 6,290 systolic and 6,265 diastolic blood pressure readings from these
227 individuals (Supplemental Data 1, Supplemental Data 2). Device readings were recorded
228 roughly uniform over the course of the study (Supplemental Figure 1). The number of readings
229 taken varied between individuals, with an average of 165 readings per person (sd=70, min=61,
230 max=416). The time of day that readings were taken was also variable, with a large proportion
231 of measurements taken in the early morning and afternoon. Few readings were taken in the late
232 morning and at night, though this was not necessarily surprising given we asked participants to
233 use the device in the morning, presumably before day time activities (Supplemental Figure 2).

234

235 *Multiple N-of-1 approach*

236 We first assessed the effect of time on blood pressure on each study participant individually
237 (Figure 1, Supplemental Figure 3). Among the 38 participants, 18 had nominally statistically
238 significant ($p < 0.05$) changes in systolic blood pressure and 21 had significant changes in
239 diastolic blood pressure. However, the number of participants with a significant decrease in
240 systolic blood pressure ($n=9$) was equal to the number with an increase ($n=9$), and was similarly
241 true for diastolic blood pressure (decrease: $n=12$, increase: $n=7$; $p=0.36$). This result also held
242 when we examined the estimated effects from all participants, regardless of p-value. There were
243 20 individuals with a decrease (i.e. negative slope) in systolic blood pressure against 18 with an
244 increase ($p=0.87$), and 21 with a decrease and 17 with an increase in diastolic blood pressure
245 ($p=0.62$). In efforts to summarize these results across individuals, we calculated the mean slope
246 and mean slope weighted by the square root of the number of readings each participant
247 recorded. We found limited evidence towards an overall decrease in systolic or diastolic blood
248 pressure. The weighted mean change in systolic blood pressure was -1.7 mmHg (95% CI: -4.7 ,

249 1.4) and diastolic blood pressure was -1.9 (95% CI: -4.0, 0.1). Results from the unweighted
 250 calculations were similar.

251

252 *Mixed model approach*

253 We then pooled device readings data from all study participants, and assessed the effect of time
 254 on blood pressure using the mixed model framework described previously with three possible
 255 covariance structures of \mathbf{R} , where $\Sigma_{\mathbf{R}}$ was 1) compound symmetric; 2) first-order
 256 autoregressive; or 3) generalized autoregressive for unequally spaced data (i.e. spatial power
 257 law).

258

259 We encountered one issue when applying the spatial power law structure mixed model. As
 260 opposed to the first-order autoregressive model in which

261
$$\Sigma_{\mathbf{R}} = \sigma^2 \begin{pmatrix} 1 & \rho & \rho^2 & & \\ \rho & 1 & \rho & \mathbf{L} & \\ \rho^2 & \rho & 1 & & \\ & & & \mathbf{M} & \\ & & & & \mathbf{O} \end{pmatrix}$$

262 where ρ is the correlation between two successive measures on the same subject, the spatial
 263 power law structure is a generalized form of the first-order autoregressive model in which

264
$$\Sigma_{\mathbf{R}} = \sigma^2 \begin{pmatrix} 1 & \rho^{t_2-t_1} & \rho^{t_3-t_1} & & \\ \rho^{t_2-t_1} & 1 & \rho^{t_3-t_2} & \mathbf{L} & \\ \rho^{t_3-t_1} & \rho^{t_3-t_2} & 1 & & \\ & & & \mathbf{M} & \\ & & & & \mathbf{O} \end{pmatrix}$$

265 where t_k is the time of the k^{th} measurement, and the difference $t_i - t_j$ is the lag between the
 266 i^{th} and j^{th} measure. When measurements are equally spaced, the spatial power law models
 267 simplifies to a first-order autoregressive model as the lag between measures is constant.
 268 Though we instructed study participants to measure their blood pressure at certain intervals, the

269 time individuals chose to take these readings, and thus the lag between measures, varied
 270 considerably. In this context, we expected the spatial power law structure to be appropriate for
 271 the data collected. However, while the majority of consecutive measures had lags of six hours
 272 or more (Figure 2), we discovered a small number of consecutive measures with short lag that
 273 led to issue we alluded to above. To demonstrate this issue between consecutive
 274 measurements with short lag, consider the following example: three measurements are
 275 recorded at times labeled t_1 , t_2 , and t_3 . In this case,

$$276 \quad \Sigma_R = \sigma^2 \begin{pmatrix} 1 & \rho^{t_2-t_1} & \rho^{t_3-t_1} \\ \rho^{t_2-t_1} & 1 & \rho^{t_3-t_2} \\ \rho^{t_3-t_1} & \rho^{t_3-t_2} & 1 \end{pmatrix}.$$

277 However, when two measurements are taken relatively close together, say at t_1 and t_2
 278 compared to t_3 , then $t_2 - t_1$ is relatively close to zero and $t_3 - t_1 \approx t_3 - t_2$. The result on Σ_R is:

$$279 \quad \Sigma_R \approx \sigma^2 \begin{pmatrix} 1 & 1 & \rho^{t_3-t_1} \\ 1 & 1 & \rho^{t_3-t_1} \\ \rho^{t_3-t_1} & \rho^{t_3-t_1} & 1 \end{pmatrix}.$$

280 As can be seen, the first and second columns and rows are roughly equivalent, leading to
 281 singularity in this matrix, non-convergence, and inestimable effects. It should be noted that this
 282 issue does not manifest in the compound symmetric and first-order autoregressive models.

283

284 In order to solve this issue, we merged data readings taken within short periods of each other by
 285 taking the average over that time. We found that merging readings within a one hour period of
 286 each other eliminated the singularity of Σ_R while minimizing the number of readings
 287 manipulated. We still ran into singularity issues when using shorter time intervals (e.g. 15
 288 minute and 30 minute minimums). In total, we merged 826 systolic and 801 diastolic blood
 289 pressure readings within an hour of each other, with most merging (61%) being two readings

290 recorded within an hour. The subsequent dataset resulted in 5,464 systolic and diastolic
291 readings.

292

293 Mixed model results from the one-hour merged dataset are presented in Table 1. For each
294 model assessed, there was an approximately 2 mmHg decrease in systolic and diastolic blood
295 pressure across the sample over the study period ($p < 0.001$ in all cases). While both the first-
296 order autoregressive and spatial power law models with random effects had better model fit
297 than the random effects model alone, the first-order autoregressive model had slightly better
298 model fit. It should be noted that when we tested various merging strategies to eliminate the
299 singularity in the spatial power law Σ matrix (e.g. averaging blood pressure across the entire
300 day) sometimes the spatial power law model had the better fit. This suggests that while
301 accounting for time dependencies was important, the precise structure appeared to be less so.
302 This was true even though the spatial power law model appeared to be more appropriate, given
303 the readings were generally unequally spaced.

304

305 *Sequential analysis approach*

306 We next implemented a sequential analysis approach in which we modeled a spatial power law
307 structure with random effects on sequential subsets of the one-hour merged datasets. The goal
308 of this approach was to determine if and when we could have arrived at our primary conclusion
309 (i.e. systolic and diastolic blood pressure decrease 2 mmHg over the study) prior to the end of
310 the study. While the device readings data across all study participants was collected over ten
311 and a half months, after the first seven months of the study we would have arrived at a similar
312 conclusion (Figure 3, Supplemental Figure 4). Though all 38 participants had completed the
313 study or were enrolled by that time, and 4,686 blood pressure measures (86%) had taken place
314 by then, the prospect of arriving at a conclusion prior to the designed end of the study has some
315 benefit – particularly so when data is collected using digital medicine devices as we discuss

316 below. Furthermore, when applying a sequential analysis approach in an N-of-1 framework, we
317 were able to determine that 13 of the 15 individuals with nominally significant systolic blood
318 pressure changes, and 14 of the 18 individuals with diastolic blood pressure changes over 6
319 months demonstrated this trend ($p < 0.05$) by the fifth month of their study enrollment.

320

321 **DISCUSSION**

322 As digital, smartphone-enabled, and other patient-centric medical and health technologies have
323 the potential to improve individual health and the overall health care system, the quest to
324 develop the “best” technologies will remain ongoing. However, we and others feel the future of
325 this field is not simply in the devices, sensors, software, and wearables *per se* (Gibbs, 2015),
326 but in what the data generated from these tools can tell us about human health and biology.
327 Above we present a framework for hypothesis testing on unequally spaced time series data – a
328 common feature of data generated from these technologies. Applied to a subset of hypertensive
329 individuals enrolled in an interventional trial, we discovered that individuals participating had, on
330 the whole, a roughly 2 mmHg decrease of systolic and diastolic blood pressure over a 6 month
331 period. Using the methods presented we were able to observe this distinction despite
332 considerable intra and inter-individual variation in blood pressure measures, and without a
333 rigorously structured readings schedule.

334

335 Importantly, while we focused on time enrolled in the study as the independent variable of
336 interest, the framework we present can also be adapted to examine other temporal relationships
337 in similarly generated data. For example, this framework can be used to compare data captured
338 between discrete conditions such as intervention versus control, or to differentiate based on
339 other quantitative measures. In these cases, the X matrix presented above can be remodeled
340 to reflect the desired design matrix. Additionally, while our mixed model approach modeled data
341 across all 38 study participants collectively, this framework can be also adapted to examine

342 temporal trends on a single individual, such as that of an N-of-1 crossover design or how we
343 examined individual trends in the N-of-1 sequential analysis approach above. In this case, the
344 **Z** matrix can be omitted on account of no between subject effects, while **R** would remain.

345

346 One of the more intriguing aspects of this technology as a tool to enhance individual health is
347 that data is collected, stored, and presented digitally without the need for direct interaction
348 between the user and (as traditional) health professional. Likewise, we feel the processes of
349 data inference can also be built into the technology to bypass the need for data interpretation by
350 a professional data analyst. Certainly many technologies have such tools. Yet as new methods
351 and extension of existing approaches, such as the framework we presented, are developed,
352 these will need to be implemented into the technology in order to provide users with the best
353 opportunity to make informed health decisions based on this data. The most immediate way this
354 can be accomplished is by coding these methods directly on the device or software, or
355 accessible to a cloud server where computations can be performed. However, other options
356 include crowd-sourced initiatives such as an app store, where the public can design specialized
357 software which provides automated analyses and interpretation of data back to the user.

358

359 Alternatively, the digital nature of data obtained from this technology opens up a number of
360 interesting possibilities for researchers. Again, because data can be continuously collected
361 without the need for personnel (e.g., study coordinators) to interact with users/study
362 participants, approaches which benefit from data analyses over the course of the study may
363 prove beneficial. We attempted to show this in the sequential analysis approaches above in
364 which we were able to arrive at the primary study result over three months prior to the end of the
365 study. Methods like this can be implemented directly into the study design, such as those in
366 adaptive clinical trials. Moreover, because data on individuals can be recorded, collected,
367 analyzed, and interpreted in real time, concepts such as early stoppage due to success or futility

368 can apply not only to the study itself, but study participants as well – thereby minimizing risks,
369 reducing costs, and forming conclusions earlier.

370

371 Data collected from digital medicine and smartphone-enabled health technologies offers
372 tremendous potential to learn more about human health and biology. We applaud
373 manufacturers for striving towards more comprehensive monitoring technologies, and when
374 applicable encourage researchers to use this data source to help address research questions of
375 interest.

376

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380

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423 **FIGURE LEGENDS**

424 **Figure 1.** Normalized diastolic blood pressure readings. Each box is one study individual. Points
425 are arranged along the x-axis which represents the time in days from the beginning of the study,
426 and along the y-axis which represents the normalized diastolic blood pressure reading recorded
427 at that time. The red line is the least squares regression line. Individuals are ordered left to right,
428 top to bottom according to the number of readings recorded.

429

430 **Figure 2.** Histogram of the lag between consecutive measures. Measures recorded near each
431 other relative to others can lead to singularity in Σ_R .

432

433 **Figure 3.** Parameter estimate and corresponding 95% confidence interval assessing change in
434 diastolic blood pressure over the course of the study. By March 2014, three months prior to the
435 conclusion of the study, the primary study outcome (roughly 2 mmHg decrease) was
436 observable.

437

438 **TABLES**439 **Table 1.** Mixed model results. RE=random effects only (compound symmetric Σ_R),

440 RE+AR(1)=first-order autoregressive model with random effects, RE+SP=spatial power law with

441 random effects.

442

	Σ	AIC	BIC	Estimate (CI)	p
Systolic	RE	41604	41608	-2.11 (-3.13, -1.09)	5.19×10^{-5}
	RE+AR(1)	41495	41500	-2.11 (-3.29, -0.93)	4.45×10^{-4}
	RE+SP	41546	41550	-2.04 (-3.11, -0.98)	1.80×10^{-4}
Diastolic	RE	36725	36729	-2.04 (-2.69, -1.39)	9.41×10^{-10}
	RE+AR(1)	36620	36624	-2.06 (-2.81, -1.31)	8.17×10^{-8}
	RE+SP	36705	36710	-2.05 (-2.72, -1.37)	2.83×10^{-9}

443

444 **SUPPLEMENTAL LEGENDS**

445 **Supplemental Figure 1.** Histogram of the number of blood pressure readings recorded relative
446 to the time since study enrollment.

447

448 **Supplemental Figure 2.** Histogram of the number of blood pressure readings recorded relative
449 to the time of day (PST).

450

451 **Supplemental Figure 3.** Normalized systolic blood pressure readings. Each box is one study
452 individual. Points are arranged along the x-axis which represents the time in days from the
453 beginning of the study, and along the y-axis which represents the normalized diastolic blood
454 pressure reading recorded at that time. The red line is the least squares regression line.
455 Individuals are ordered left to right, top to bottom according to the number of readings recorded.

456

457 **Supplemental Figure 4.** Parameter estimate and corresponding 95% confidence interval
458 assessing change in systolic blood pressure over the course of the study.

459

460 **Supplemental Table 1. Study participant demographics at enrollment visit (n=38).** Values
461 are in counts (%) unless otherwise noted.

462

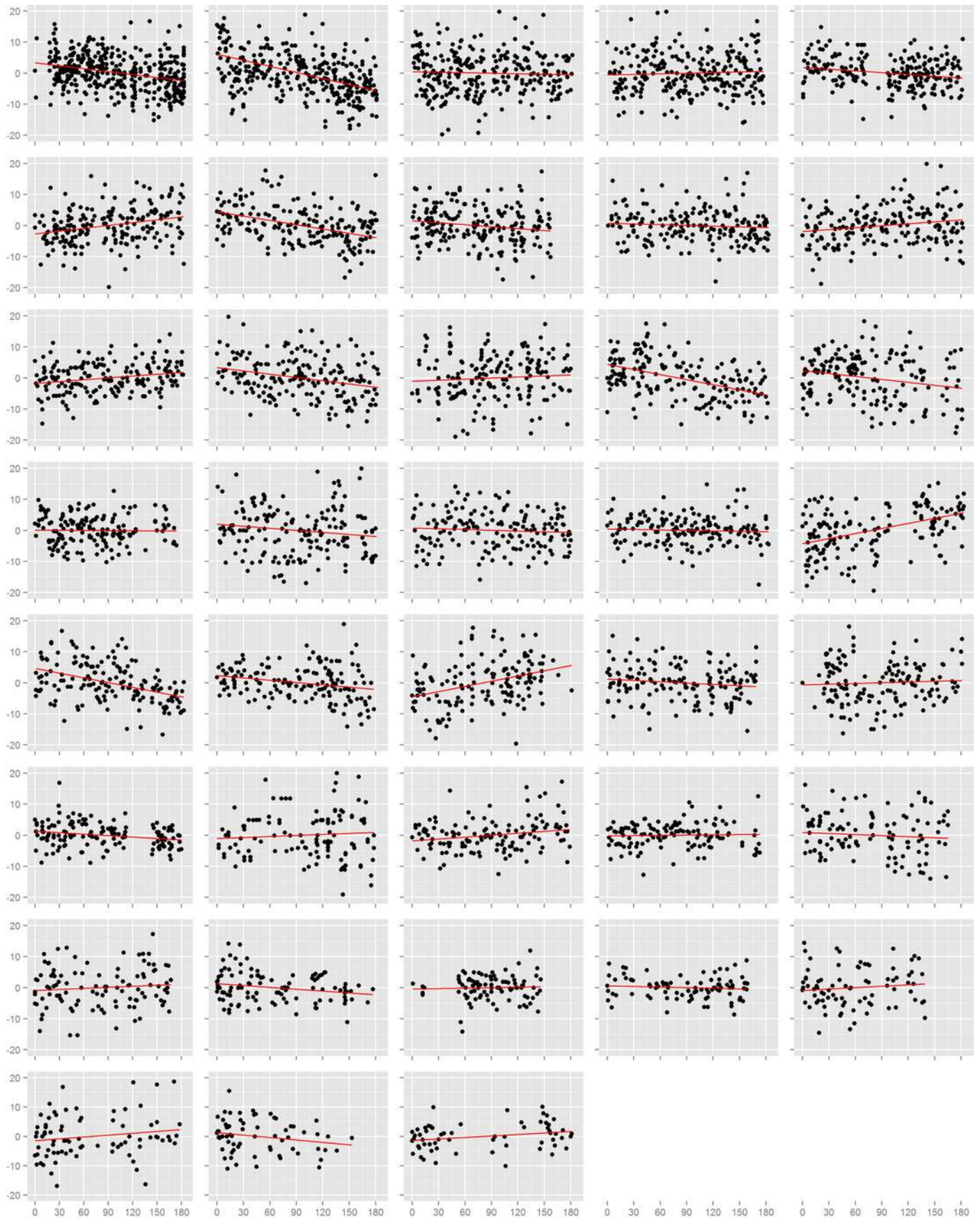
463 **Supplemental Table 2. Study participant self-assessment of health (n=38).** Values are in
464 counts (%) unless otherwise noted. * = values in mean (standard deviation).

465

1

Normalized diastolic blood pressure readings.

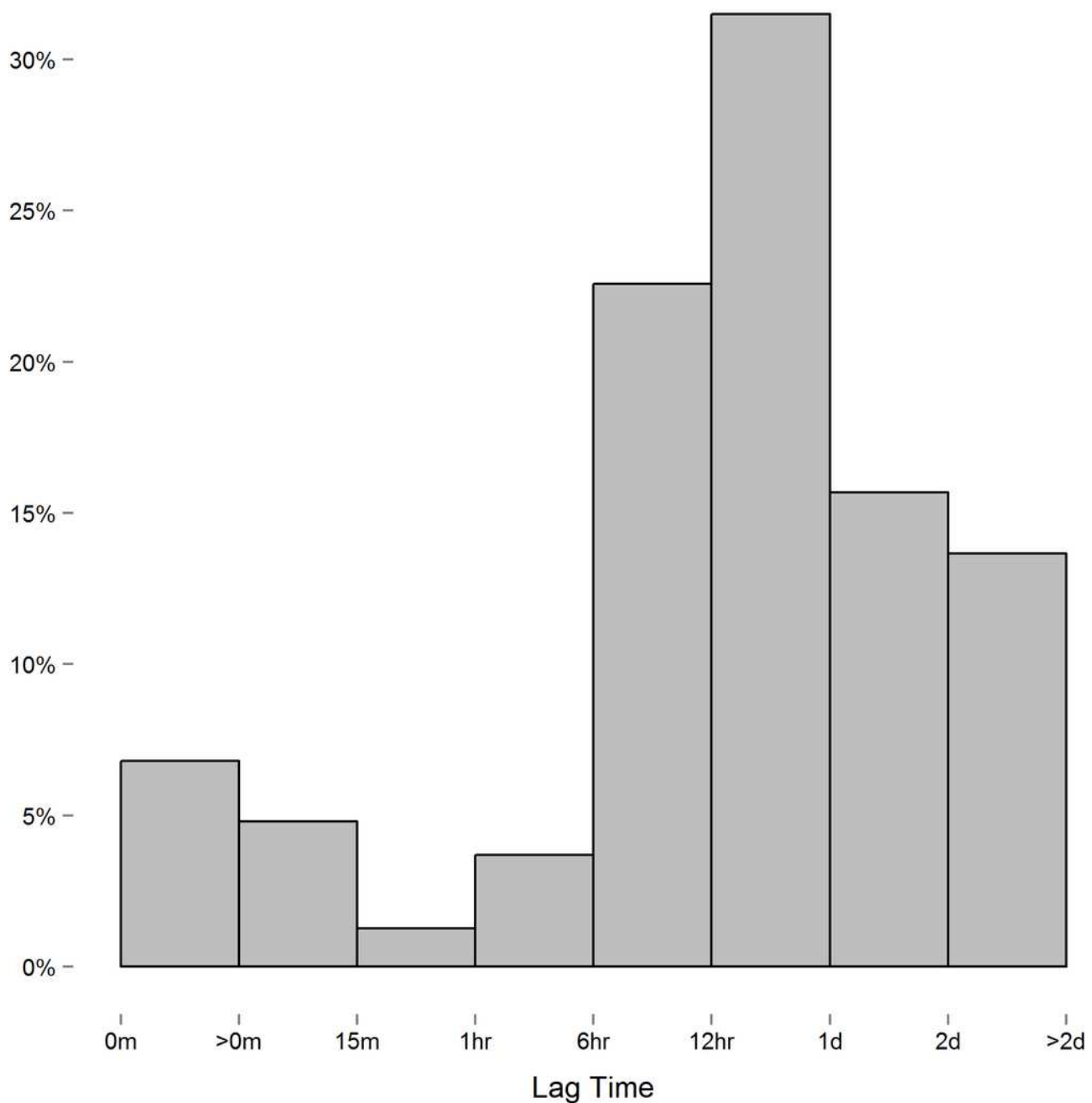
Each box is one study individual. Points are arranged along the x-axis which represents the time in days from the beginning of the study, and along the y-axis which represents the normalized diastolic blood pressure reading recorded at that time. The red line is the least squares regression line. Individuals are ordered left to right, top to bottom according to the number of readings recorded.



2

Histogram of the lag between consecutive measures.

Measures recorded near each other relative to others can lead to singularity in Σ_R .



3

Parameter estimate and corresponding 95% confidence interval assessing change in diastolic blood pressure over the course of the study.

By March 2014, three months prior to the conclusion of the study, the primary study outcome (roughly 2 mmHg decrease) was observable.

