Discussion of ‘Estimating time-varying causal excursion effect in mobile health with binary outcomes’
by T. Qian, et al.

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This is an interesting paper on an important problem. As internet-enabled devices become increasingly ubiquitous, manufacturers and developers are employing randomized experiments to optimize the performance of their products. The methods presented have close relationships to others in the literature, in particular to a series of papers by Robins, Hernán and collaborators on analyzing observational studies as a series of randomized trials (Hernán et al., 2005, 2008; Hernán and Robins, 2017), also described as emulating a desired target randomized trial (Hernán and Robins, 2016). There is also a close relationship to the history-restricted marginal structural models (MSM) of Neugebauer et al. (2007) and the history-adjusted MSM of Joffe et al. (2001); van der Laan et al. (2005); Petersen et al. (2007). See Figures 1–3 for graphical depictions of these models. However, there are important differences between the context in which all of the above models were proposed and that considered by Qian et al.; these differences have methodological implications.

To the best of our understanding a causal contrast is an excursion effect according to Qian et al.’s conception if it is:

(I) a contrast between the distributions of the potential outcomes under two “time-varying treatments [regimes] occurring over an interval of time extending into the future,” that deviate from the treatment protocol;

(II) a contrast that is “marginal over prior treatment assignments”.

As we show in §I below, analyses of contrasts with both of these characteristics were also considered in the above papers by Hernán et al. In addition, as noted by the authors and further explored in §II below, a similar marginalization idea to (II) was proposed in the literature on history-adjusted and restricted marginal structural models.
1 Relation to ‘Observational Studies Analyzed as Randomized Trials’

Although widely applied in the epidemiologic and medical literature, the analytic methods in the above papers of Hernán and Robins are less known to the statistical literature than alternative methods for analyzing causal effects of time-varying treatments such as doubly robust estimation of structural nested models and inverse probability of treatment weighting and doubly-robust estimation of marginal structural models including the history restricted and adjusted versions. It is our hope that, by demonstrating the close correspondence between Qian’s methodology for the analysis of sequential randomized experiments and Hernán and Robins’s methodology for analyzing observational studies, this commentary will serve to enhance the understanding of their commonalities and stimulate further methodological research. To demonstrate this correspondence, we begin by reviewing the formal counterfactual framework for studying the causal effects of time-varying treatments (Robins, 1986). We will largely follow the development of Robins and Hernán (2009).

A sequentially randomized experiment (SRE) is a randomized experiment in which the treatment \( A_t \) at each successive times \( t \) is randomly assigned with known randomization probabilities \( p_t(H_t) \) that, by design, may depend on a subject’s past treatment and covariate history \( H_t = (A_{t-1}, X_t) \) up to time \( t \); such trials were referred to as alternative designed RCTs in (Robins, 1986). The micro-randomized trial of Qian et al. (2021) are thus SREs. Following Qian et al., in a slight departure from the ordinary meaning of the protocol of a trial, we refer to the set of treatment probabilities \( \{p_t(H_t); t = 1, \ldots, T\} \) as the protocol of the SRE.

The identifying assumptions 1–3 of Qian et al. (2021), namely consistency, positivity, and sequential ignorability, will quite generally hold in a SRE. A key insight in Robins (1986) was to recognize that the three identifying assumptions could hold in an observational study and when they did so, the observational study can be conceptualized as a sequentially randomized experiment (run by nature), except that the protocol probabilities \( p_t(H_t) \) are unknown and therefore must be estimated from the data. However, in an observational study the assumption of sequential ignorability is not guaranteed by design and is not subject to empirical verification. The best one can do is to use subject-matter knowledge in the hope of collecting data in \( X_t \) on sufficiently many potential time-dependent confounders to plausibly satisfy the identifying assumptions 1–3.

A deterministic treatment regime is a set of functions (rules) \( g = \{g_1(x_1), \ldots, g_T(x_T, \overline{A}_{T-1})\} \) which specify treatment \( a_t \) at time \( t \) as a deterministic function \( g_t \) of the subject’s past data \( h_t = (x_t, a_{t-1}) \). A random regime replaces the functions \( g_t \) by conditional densities specifying the distribution of \( A_t \) given \( X_t, \overline{A}_{t-1} \) under the regime. We call a regime dynamic if either \( g_t \) or the corresponding conditional distribution depends on \( X_t \), and non-dynamic or static otherwise. Using this terminology an SRE is a dynamic random regime. We denote the potential outcomes under a regime \( g \) as \( O(g) \). We note that in a medical context the optimal treatment strategy must be a dynamic regime whenever a drug treatment, such as a chemo-therapeutic agent, has serious associated toxicities; whenever a patient develops a severe toxicity such as a low white cell count, it is essential to temporarily discontinue the drug.

It follows from the above that a contrast between the distributions of \( O(g) \) and \( O(g') \) under regimes \( g \) and \( g' \) thus trivially corresponds to (I) in our understanding of an excursion effect. We now turn our attention to the estimation of excursion effects marginalized over prior treat-
ment assignments (II). We first review methods that use observational data to emulate a series of hypothetical randomized target trials as introduced in the aforementioned papers of Hernán and Robins. A novel aspect of the emulation is that each subject in the observational data set is enrolled in all of the target trials for which she is eligible, instead of a single trial. It is this feature that underlies the correspondence between this methodology and that of Qian et al.

A target trial is a RCT one would like to conduct on HMO members but cannot due to ethical, financial and/or logistical reasons. As a specific example, we consider emulation of target trials designed to estimate the effect of post-menopausal hormone (PMH) therapy on the $\Delta$-year risk of breast cancer in post-menopausal women who are within 10 years of menopause at time of randomization, are members of a large HMO, such as Kaiser Permanente, and have not taken PMH for a year prior to enrollment. The time index $t$ will denote years since January 1, 2000. We have available the observational data $O = (X_0, A_0, \ldots, X_T, A_T, X_{T+1})$ on female HMO members contained in the HMO electronic medical records [EMR], where $X_0$ includes all EMR data prior to time 0. We will show that it is possible to specify a target trial design such that the causal estimand as well as the identifying formula for and an estimator of this effect are formally identical to those described by [Qian et al] (2021). In order to specify the target trial design and outcome we define the following \{0,1\} dichotomous variables:

$A_t$: $A_t = 1$ if taking hormones at $t$,

$D_t$: $D_t = 1$ if clinical breast cancer is diagnosed at or before $t$;

$I_t^*$: $I_t^* = 0$ indicates treatment ineligibility at $t$. In our case, since PMHs are sometimes considered to be medically contraindicated in premenopausal women or women with history of deep vein thrombosis (DVT) or breast cancer, we have $I_t^* = 0$ if DVT or breast cancer has occurred at or before $t$ or if the woman is pre-menopausal;

$I_t$: $I_t = 0$ indicates the subject is ineligible for a target trial with enrollment at $t$; in our case $I_t = 0$ if and only if at least one of the following is true: the patient is treatment ineligible ($I_t^* = 0$), the women is greater than 10 years from menopause, or the patient has been on PMH during the past year so that $A_{t-1} = 1$.

We begin by considering a single target trial in which trial eligible HMO members are enrolled and randomized on a specific calendar date $t$ years from 1 January 2000. For the sake of concreteness we take $t = 4$. Consider a woman who is trial eligible at $t$ so that $I_t = 1$. The trial outcome $Y_{t,\Delta}$ is development of clinical breast cancer within $\Delta$ years from randomization i.e. $Y_{t,\Delta} = D_{t+\Delta}$. She is randomized with probability 1/2 to the arm $G = g^*$ or $G = g'$, where $g^*$ and $g'$ are the treatment regimes being compared in the target trial. As an example, since women are often prescribed PMH for one year, two natural regimes to compare would be $g^* = (\overline{A}_{t-1}, 1, \overline{0}_{\Delta-1})$ corresponding to one year of PMH followed by $\Delta - 1$ years without, and $g' = (\overline{A}_{t-1}, 0, \overline{0}_{\Delta-1})$, corresponding to no PMH for the next $\Delta$ years.

We take as our contrast the $t$-specific counterfactual blip function between the above regimes $g^*$ and $g'$ on the multiplicative scale:

$$\beta_{t,\Delta}(S_t) = \log \frac{E\{Y_{t,\Delta}(\overline{A}_{t-1}, 1, \overline{0}_{\Delta-1}) | S_t(\overline{A}_{t-1}), I_t(\overline{A}_{t-1}) = 1\}}{E\{Y_{t,\Delta}(\overline{A}_{t-1}, 0, \overline{0}_{\Delta-1}) | S_t(\overline{A}_{t-1}), I_t(\overline{A}_{t-1}) = 1\}}.$$ (1)
Figure 1: A marginal structural model (a) specifies the expected counterfactual outcome for \( Y = Y_T \) under every static regime \((a_1, \ldots, a_T)\) given baseline covariates indicated by the grey rectangle; A structural nested mean model (b) specifies contrasts for all times \( t \) giving the difference in expected counterfactual outcome from receiving a final blip of treatment at time \( t \), given all treatment and covariates prior to \( t \).

Here \( S_t(A_{t-1}) = S_t \subset H_t \) is a vector of covariates chosen by an investigator wishing to determine whether these covariates modify the effect of treatment on this scale. Note that the RHS of (1) was written as \( \beta_M \{ t, S_t(A_{t-1}) \} \) by Qian et al. (2021); we write \( t \) and \( \Delta \) as subscripts because, to this point, we are considering \( t \) and \( \Delta \) fixed; see Figure 2(a).

Contrast (1) is an excursion effect in both sense (I) and (II) since it does not condition on all of \( H_t \). Had we actually conducted this target trial, the contrast (1) would then be identified from the target trial data \((O, G)\) by

\[
\log \frac{E\{Y_{t,\Delta} | S_t, I_t = 1, G = g^*\}}{E\{Y_{t,\Delta} | S_t, I_t = 1, G = g'\}}.
\]

However, by definition, the variable \( G \) does not exist in the observational data \( O \) since there was no randomization at \( t = 4 \), or indeed, at any other time! Hence there is no particular reason to privilege \( t = 4 \) rather than any other value of \( t \). That is, for the particular choice of regimes \( g \) and \( g' \) above, the observational data can be used to emulate a series of \( T-\Delta+2 \) target trials with enrollment at \( t = 0, \ldots, T-\Delta+1 \) and estimand \( \beta_{\Delta}(t, S_t) \), where \( \Delta \) remains fixed. Each woman in the observational data is enrolled in each of \( T-\Delta+2 \) target trials for which she satisfies the eligibility criteria \( I_t = 1 \).

Under the identifying assumptions 1–3 of Qian et al. (2021), the parameters \( \beta_{\Delta}(t, S_t) \) are identified from the observational data \( O \). The identifying formula is formally the same as that given in Eq. (4) of Qian et al. It follows that if we imposed the parametric model of Qian et al. for \( \beta_{\Delta}(t, S_t) \) given by their Eq. (9) indexed by \( \beta \) and also their nuisance model indexed by \( \alpha \) then we could use the estimating function given by their Eq. (10), except, because we are in an observational study, we must estimate the unknown treatment probabilities \( p_j(h_t) \) from the data. If our estimates of \( p_t(h_t) \), \( t = 0, \ldots, T \), are consistent then the estimator of \((\beta, \alpha)\) given by Qian et al. Eq. (10) will be consistent.

However, because consistency of our estimators of \( p_t(h_t) \) cannot be assured, we would like to use a doubly robust estimator of \( \beta_{\Delta}(t, S_t) \). The estimator of Qian et al. Eq. (10) is not doubly robust. This is due to the fact that in the final product of the expression in Eq. (11) for the
Figure 2: (a) The Qian et al. excursion model consisting of contrasts for a final blip of treatment with a fixed time $\Delta$ to outcome $Y = Y_{t, \Delta}$; (b) The analysis of Hernández et al. (2005, 2008) estimates the full survival curve and hence models all possible trial durations $\Delta$ to the outcome $Y = Y_k$; see Eq. (5); chosen estimands were contrasts between always receiving treatment versus never receiving treatment. Both models are conditioned on a history of a fixed length.

Figure 3: (a) A history-restricted marginal structural model consists of multiple marginal structural models for different endpoints, conditioned on a history of a fixed length. (b) A history-adjusted marginal structural model consists of multiple marginal structural models at different times for the same endpoint. History-adjusted models are over-parameterized and thus potentially may imply multiple contradictory estimates for the same counterfactual mean.
weight $J_t$, the projection of the terms $1(A_j = 0)/\{1 - p_j(H_j)\}$ from $t + 1$ to $t + \Delta - 1$ onto the scores, subtracting off this projection would generally increase efficiency; see, for example, Robins and Rotnitzky (1992); Murphy et al. (2001).

Qian et al. only considered the blip to zero contrasts (1) between the counterfactual outcome $Y_{t,\Delta}(A_{t-1}, 1, \overline{0}_{\Delta-1})$ under the static regime $g^* = (A_{t-1}, 1, \overline{0}_{\Delta-1})$ and the outcome $Y_{t,\Delta}(A_{t-1}, 0, \overline{0}_{\Delta-1})$ under the static regime $g' = (A_{t-1}, 0, \overline{0}_{\Delta-1})$, although they also note that their results can be extended to contrasts between other (identified) excursions.

To the best of our understanding, for Qian et al. the variables $I_t$ and $I_t^*$ are identical and therefore treatment is withheld when $I_t = 0$. In that case, as implicitly recognized by Qian et al., the two regimes occurring in (1) are the only static regimes that are identified without further assumptions. This is because any other static regime $g$ will have $a_m = 1$ for some $m > t$. However, if $I_m^* = I_m = 0$ with positive probability under $g$ then the counterfactual outcome will not be identified since $I_m = 0$ deterministically implies $A_m = 0$ and thus positivity fails. Note that the blip excursion (1) is only identifiable without further assumptions because there is “one-sided compliance”, so that if $I_m^* = 0$ for $m > t$, then they receive treatment $A_m = 0$. For further discussion of this point in a medical setting, see Hernán and Robins (2017).

2 Relation to Varieties of Marginal Structural Models

2.1 History-Restricted Marginal Structural Models

As noted by Qian et al. the problem context is similar to that for which the history restricted marginal structural models (HR-MSMs) (Neugebauer et al., 2007) were developed. Here we show that, as Qian et al. suggest, these models can be viewed as identifying a large number of excursion effects. To avoid complexity (notational and otherwise) that obscures the central point we wish to make in this section, we shall assume that $I_m^* = I_m = 1$ with probability 1 so that we can restrict the discussion to static regimes. A HR-MSM is a model for $E\{Y_{t,\Delta}(A_{t-1}, a_t, \ldots, a_{t+\Delta}) \mid S_t(A_{t-1}, I_t(A_{t-1}) = 1)\}$ all $t \in \{1, \ldots, T - \Delta + 1\}$, all $(a_0, \ldots, a_T) \in \{0, 1\}^{T+1}$ and a single pre-specified $\Delta$; see Figure 3(a).

To see the connection with the model of Qian et al. consider a simple HR-MSM that is linear in cumulative exposure on a log scale with parameters $(\alpha_t, \beta_t)$:

$$\log E\{Y_{t,\Delta}(A_{t-1}, a_t, \ldots, a_{t+\Delta}) \mid S_t, I_t = 1\} = b_{t,\Delta}(S_t; \alpha_t) + \beta_t \sum_{j=t}^{t+\Delta} a_j. \quad (2)$$

The model (2) satisfies

$$\beta_{t,\Delta}(S_t) = \log \frac{E\{Y_{t,\Delta}(A_{t-1}, a_t, \ldots, a_{t+\Delta}) \mid S_t(A_{t-1}), I_t(A_{t-1}) = 1\}}{E\{Y_{t,\Delta}(A_{t-1}, 0, \overline{0}_{\Delta-1}) \mid S_t(A_{t-1}), I_t(A_{t-1}) = 1\}} = \beta_t \sum_{j=t}^{t+\Delta} a_j. \quad (3)$$

The model (2) satisfies (II) because the contrasts (3) are marginal over prior treatment assignments. It also satisfies (I) in that it specifies, for every $t$ and every value of $S_t$ a contrast between each of the $2^\Delta - 1$ regimes $(a_t, \ldots, a_{t+\Delta})$ and $\overline{0}_{\Delta}$. As a consequence a parametric model such as (2) is highly unlikely to be correctly specified except under the null.
An HR-MSM, such as (2), that does not link the parameters for different times is simply a collection of ordinary marginal structural models that therefore can be fitted separately (Robins et al., 2007). Of course, they become related if one chooses to impose stationarity assumptions, such as $\beta_t = \beta$ for all $t$.

### 2.2 History-Adjusted Marginal Structural Models

A History-Adjusted Marginal Structural Model (Joffe et al., 2001; van der Laan et al., 2005; Petersen et al., 2007) differs from a HR-MSM only in that, in the model definition the phrase a “single prespecified $\Delta$” is replaced by “all $\Delta \in \{1, \ldots, T-t+1\}$,” see Figure 3(b).

In contrast to history-restricted models, Robins et al. (2007) show in their appendix that in the case where the set $S_t$ is the entire history $H_t$, then the models may be over-parametrized and hence may be incoherent in the following sense: a given counterfactual mean may be expressed both as a function of one subset of the model parameters and as a different function of a second non-overlapping subset of parameters. As shown by Robins et al, this implies that one could fit a mis-specified history-adjusted model and produce two separate estimates of the mean of a particular counterfactual regime which differ in sign, with the difference between the estimates many standard errors from zero, hence rendering the analysis useless for decision-making.

In fact the same phenomena may arise when we only condition on $S_t$. Specifically, consider a distribution satisfying $\beta_{m,\Delta}(H_m) = \beta_{m,\Delta}(S_t)$ for some $t$ and all $(m, \Delta)$ such that $m \geq t$ and $m + \Delta = k$ for some fixed $k$. Then the argument given in the appendix of Robins et al. (2007) goes through unchanged. Such a distribution will always exist because the parameters $\beta_{m,\Delta}(H_m)$ are variation independent; see §3 below.

Prior to Robins et al. (2007), the consequential distinction between HA-MSM and HR-MSM was not recognized; both models were referred to as HA-MSM in the literature. Robins et al. argued that the two models should be differentiated and proposed the definitions given above, although the moniker HR-MSM was coined by Neugebauer et al. (2007). Readers should be aware that not all authors have adopted the model definitions given here.

### 3 Target Trials with Multiple Endpoints

In their published data analyses, Hernán et al. (2005, 2008) took as the target trial a randomized controlled trial that compared the regime $g^{con} = (A_{t-1}, T_\Delta)$ corresponding to continuous treatment for the next $\Delta$ years to the regime $g' = (A_{t-1}, 0)$, corresponding to no treatment for the next $\Delta$ years. The corresponding contrast on the log risk ratio between these regimes scale is thus

$$
\beta_{t,\Delta}(S_t) = \log \frac{E\{Y_{t,\Delta}(A_{t-1}, 1, T_{\Delta-1}) \mid S_t(A_{t-1}), I_t(A_{t-1}) = 1\}}{E\{Y_{t,\Delta}(A_{t-1}, 0, T_{\Delta-1}) \mid S_t(A_{t-1}), I_t(A_{t-1}) = 1\}}.
$$

They further assumed that $I^*_m = 1$ w.p.1 at all times $m$, so that patients are always eligible to receive either treatment or control. Thus $\beta_{t,\Delta}(S_t)$ is identifiable under sequential randomization. Substantively, $Y_{t,\Delta}$ was the indicator of survival at $t + \Delta$ and the authors wished to compare regime-specific survival curves. Thus, as in a HA-MSM, they were interested in estimating $\beta_{t,\Delta}(t, S_t) = \beta_{t,\Delta}(S_t)$ for all $t \in \{1, \ldots, T-\Delta+1\}$ and $\Delta \in \{1, \ldots, T-t+1\}$; see Figure 2(b).
This raises the question of whether problems with overparametrization and incoherence might occur as with a HA-MSM. In fact, we can also ask this question for the contrast \( \beta(t, \Delta, S_t) \equiv \beta_{t, \Delta}(S_t) \) comparing \( (A_{t-1}, 1, \mathbb{U}_{\Delta-1}) \) with \( (A_{t-1}, 0, \mathbb{U}_{\Delta-1}) \) as earlier. We show that for both these contrasts incoherence does not occur. To see this, following (Robins, 2004), we first consider the case where \( H_t = S_t \). Then for any regime \( g \), dynamic or static, we define the regime specific blip functions:

\[
\gamma_{t,k}^g(H_t) = \log \frac{E\{Y_k(A_{t-1}, a_t = 1, g_{t+1}) \mid H_t\}}{E\{Y_k(A_{t-1}, a_t = 0, g_{t+1}) \mid H_t\}}, \quad \text{for } t = 1, \ldots, k;
\]

where we have reparametrized \( \{t, \Delta\} \) as \( (t, k) \) with \( k = t + \Delta, k \in \{2, \ldots, T\} \); the potential outcome \( Y_k(\cdot, \cdot, g_{t+1}) \) indicates that regime \( g \) is followed from \( t + 1 \) onwards. Further, if \( \gamma_{t,k}^g(H_t) = 0 \) with probability 1 for all \( t = 1, \ldots, k \), then under sequential randomization \( E\{Y_k(\overline{A}_{t-1}, \tilde{g}) \mid H_t\} = E\{Y_k \mid H_t\} \) with probability 1 for all \( t \) and identified regimes \( \tilde{g} \) (Robins, 2004), hence there is no causal effect of any regime, dynamic or static.

Consider the following two special cases:

1. The dynamic regime \( g_t(H_t, \overline{A}_{t-1}) \equiv A_{t-1} \) for \( t > 1 \). In this case \( Y_k(\overline{A}_{t-1}, a_t = 1, g_{t+1}) = Y_k(\overline{A}_{t-1}, 1) \), while \( Y_k(\overline{A}_{t-1}, a_t = 0, g_{t+1}) = Y_k(\overline{A}_{t-1}, 0) \). Thus \( \gamma_{t,k}^g(H_t) \) corresponds to (4).

2. The regime \( g_t(H_t, \overline{A}_{t-1}) = 0 \). Now \( Y_k(\overline{A}_{t-1}, a_t = 1, g_{t+1}) = Y_k(\overline{A}_{t-1}, a_t = 1, 0_{t+1}) \) and \( Y_k(\overline{A}_{t-1}, a_t = 0, g_{t+1}) = Y_k(\overline{A}_{t-1}, a_t = 0, 0_{t+1}) \). In this case \( \gamma_{t,k}^g(H_t) \) corresponds to (1) considered by Qian et al. with \( H_t = S_t \).

Robins (2004) and Robins et al. (2000, Theorem 8.5) proved that for any regime \( g \) with \( H_t = S_t \), the set of multiplicative blip functions \( \{\gamma_{t,k}^g, \text{ for all } t, k\} \) are variation independent provided each \( Y_k \) has support on \( [0, \infty) \). The discussion of Wang et al. (2017) generalizes this to the case where \( Y_k \) has support on \( \{0, 1\} \). Thus, when \( H_t = S_t \) neither \( \beta(t, \Delta, S_t) \) nor \( \beta^\text{con}_{t,k}(S_t) \) can be overparametrized or incoherent. We now argue the same is true in the general case with \( S_t \subset H_t \). Consider the following equalities:

\[
\exp\{\gamma_{t,k}^g(S_t)\} = \frac{E\{Y_k(\overline{A}_{t-1}, a_t = 1, g_{t+1}) \mid S_t\}}{E\{Y_k(\overline{A}_{t-1}, a_t = 0, g_{t+1}) \mid S_t\}} = \frac{\int E\{Y_k(\overline{A}_{t-1}, a_t = 1, g_{t+1}) \mid H_t\} df(H_t|S_t)}{\int E\{Y_k(\overline{A}_{t-1}, a_t = 0, g_{t+1}) \mid H_t\} df(H_t|S_t)} = \frac{\int \exp\{\gamma_{t,k}^g(H_t)\} E\{Y_k(\overline{A}_{t-1}, a_t = 0, g_{t+1}) \mid H_t\} df(H_t|S_t)}{\int E\{Y_k(\overline{A}_{t-1}, a_t = 0, g_{t+1}) \mid H_t\} df(H_t|S_t)}.
\]

Hence \( \exp\{\gamma_{t,k}^g(S_t)\} \) is a weighted average of \( \exp\{\gamma_{t,k}^g(H_t)\} \). Consequently because \( \exp\{\gamma_{t,k}^g(H_t)\} \) are variation independent it follows that \( \exp\{\gamma_{t,k}^g(S_t)\} \) are also variation independent and thus coherent.
Figure 4: (a) A causal DAG with three treatments, two outcomes and no confounding; (b) An elaboration of the induced DAG induced by (a) on \{A_1, A_2, Y_2\}, \(U\) is unobserved.

4 Issues arising from the excursion effect depending on the design

The authors indicate that excursion effects should be interpreted in the context of the existing protocol. Here we illustrate via simple examples that changes in treatment assignment probabilities in the protocol can have a qualitative effect on both primary and secondary analyses.

Throughout these examples we suppose the availability indicators \(I_t\) are all one. Consider the data-generating process, corresponding to the first three nodes in the causal graph in Figure 4(a).

Note that there is no confounding between the treatments \(A_1, A_2, A_3\) and the outcomes \(Y_2, Y_3\). We made this choice to emphasize that the above phenomena is a consequence of the interaction between the causal effects of the treatments \(A_{i-1}\) and \(A_i\) on \(Y_i\), for \(i = 2, 3\).

To see this consider the following data-generating process:

\[
Y_2(a_1, a_2) \sim \text{Bernoulli}\{\exp(-a_2 + 2a_1 \cdot a_2)/4\}. \tag{6}
\]

Suppose treatment is assigned independently at \(t = 1, 2\), with \(\text{pr}(A_1 = 1) = \text{pr}(A_2 = 1) = \theta\). Consider the marginal excursion effect at \(t = 2\), with \(\Delta = 1\) and \(S = \emptyset\), \(\beta_{t,\Delta} = \log \left[ \frac{\text{E}\{Y_2(a_2 = 1)\}}{\text{E}\{Y_2(a_2 = 0)\}} \right] \).

By a simple calculation:

\[
\text{E}\{Y_2(a_2 = 1)\} = \sum_{a_1 \in \{0, 1\}} \text{E}\{Y_2(a_1, a_2 = 1) \mid A_1 = a_1\} \text{pr}(A_1 = a_1) = \sum_{a_1 \in \{0, 1\}} \text{E}(Y_2 \mid A_1 = a_1, A_2 = 1) \text{pr}(A_1 = a_1) = \{(1 - \theta)/e + \theta e\}/4;
\]

similarly \(\text{E}\{Y_2(a_2 = 0)\} = 1/4\). Hence:

\[
\beta_{t,\Delta} = \log \left[ \frac{\text{E}\{Y_2(a_2 = 1)\}}{\text{E}\{Y_2(a_2 = 0)\}} \right] = \log \{(1 - \theta)/e + \theta e\}.
\]

Hence \(\beta_{t,\Delta}\) is negative if \(\theta < 1/(1 + e)\), zero if \(\theta = 1/(1 + e)\) and positive if \(\theta > 1/(1 + e)\).

Consequently, the meaning of the excursion effect is entirely dependent on the prior protocol, here the randomization probability for \(A_1\), that was in place before the contrasted excursions commenced at \(t = 2\). We take it that this is the sense in which, as the authors say, excursion
effects ‘can be interpreted as contrasts between excursions from the treatment protocol’ (emphasis added). In fact, this example suggests that in certain cases, including ‘primary’ analyses with $S_t = \emptyset$, it is only possible to interpret these effects in the context of the prior design.

Note that if instead we condition on the whole past, here $A_1$, as in a structural nested model, we obtain the following contrast:

$$\beta_{t, \Delta}(a_1) = \log \frac{E\{Y_2(a_1, a_2 = 1)\}}{E\{Y_2(a_1, a_2 = 0)\}} = -1 + 2a_1,$$

which is not a function of the randomization probabilities.

The dependence on the design also applies to secondary analyses of effect modifiers, including those that are independent of treatment. To see this, consider the causal graph shown in Figure 4(b), which can be seen as an elaboration, including an additional covariate $X_2$, of the induced sub-graph of the DAG in Figure 4(b) over $\{A_1, A_2, Y_2\}$. Further, suppose the variables are generated by the following mechanism

$$Y_2(0, 0), Y_2(1, 0) \sim_{iid} \text{Bernoulli}\{1/4\},$$
$$Y_2(0, 1) \mid X_2 \sim \text{Bernoulli}\{1/(1 + \exp(\alpha_0 - X_2))\},$$
$$Y_2(1, 1) \mid X_2 \sim \text{Bernoulli}\{1/(1 + \exp(\alpha_1 + X_2))\},$$

where $\alpha_0 = 2.666$, $\alpha_1 = -0.905$ and that $X_2 \sim N(0, 1)$. This specification is such that $E\{Y_2(a_1, a_2)\}$ is still given by (6). For $a_1 \in \{0, 1\}$ it holds that

$$E\{Y_2(a_1, 1) \mid X_2\} = \frac{a_1}{1 + \exp(\alpha_1 + X_2)} + \frac{1 - a_1}{1 + \exp(\alpha_0 - X_2)}.$$

Now consider the excursion effect with $S_t = X_2$ as the summary of $H_t$:

$$\beta_{t, \Delta}(X_2) = \log \frac{E\{Y(A_1, 1) \mid X_2\}}{E\{Y(A_1, 0) \mid X_2\}}$$
$$= \log \left\{ \theta/(1 + e^{\alpha_1 + X_2}) + (1 - \theta)/(1 + e^{\alpha_0 - X_2}) \right\} + \log 4. \quad (7)$$

We see from (7) that $\beta_{t, \Delta}(X_2)$ is an increasing function of $X_2$ for $\theta$ close to 0, while for $\theta$ close to 1 it is decreasing. Consequently, in this example, the qualitative conclusions from the secondary analysis will also depend on the randomization probability $\theta$.

4.1 Can excursion effects be used to modify the protocol?

The authors say that owing to the dependence of the excursion effect on the design this measure “informs how the current treatment protocol might be improved via moderation analysis on how these causal effects differ by individual contexts.” However, it is unclear how this would work in practice.

Consider, for example, the marginal parameter $\beta_M$ giving the causal effect of $A_2$ on $Y_2$ in the data generating process given by treatment (6). Suppose that the intention of treatment in this setting is to reduce the occurrence of $Y = 1$, so that negative values of $\beta_M$ indicate that
the treatment is working as intended. Further suppose that at first, while piloting the treatment, the experimenters use a small value of $\theta$, so $\theta < 1/(1 + e)$. As shown above, this will lead to a negative value of $\beta_M$. Buoyed by this news, the experimenters will likely then increase the assignment probability so that $\theta > 1/(1 + e)$. However, if they continue to monitor $\beta_M$ they will then find that $\beta_M$ is positive, indicating that the treatment is not working . . .

It is also true that the excursion effects obtained from analyses of observational studies as a series of randomized trials by Hernán and Robins will also depend on the ‘protocol’, but in their setting the ‘randomization probabilities’ are chosen by nature and are not subject to control by the experimenters, so the above is not an issue as there is only one design.

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