Supplementary Materials for One-Step Targeted Minimum Loss-based Estimation Based on Universal Least Favorable One-Dimensional Submodels

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Supplementary Appendix

A Universal score-specific submodel generalizing the universal least favorable submodel

This section could be read after Section 6 of the main paper.

Consider the above setting \( O \sim P_0 \in \mathcal{M}, \Psi : \mathcal{M} \to \mathbb{R}, \Psi(P) = \Psi_1(Q(P)), \) \( Q(P) = \arg \min Q \mathcal{L}(Q), \) \( \Psi \) is pathwise differentiable at \( P \) with canonical gradient \( D^*(Q(P), G(P)) \) for some nuisance parameter \( G \) that is orthogonal to \( \Psi \) in the sense that the nuisance tangent space of \( G \) is orthogonal to the tangent space of \( Q \).

In Section 5 we constructed universal least favorable models \( \{Q_\epsilon : \epsilon\} \) for any loss-based parameter \( Q \) whose loss-based score \( \frac{d}{d\epsilon} \mathcal{L}(Q_\epsilon) \) at \( \epsilon \) equals the efficient influence curve \( D^*(Q_\epsilon, G) \). Using this universal least favorable submodel through an initial estimator of \( Q_0 \) results in a TMLE that takes only one step, and, as any TMLE, is asymptotically efficient under regularity conditions.

Let \( L_2(G) \) be a loss function for \( G \) so that \( G(P) = \arg \min_{G_1 \in G(M)} \mathcal{PL}_2(G_1) \). Let \( L(Q, G) = L(Q) + L_2(G) \) be the sum loss-function for \( (Q, G) \). Let \( D_2(Q, G) \) be a user supplied element of the tangent space \( T_G(P) \) of \( G \) in \( L_2^0(P) \). Let’s define a local score-specific (i.e., \( D_2() \)-specific) submodel \( \{G_\epsilon^{sm} : \epsilon\} \subset G(M) \) as a submodel
We refer to such a submodel of $Q\{\cdot\}$ through $G$ at $\epsilon = 0$ satisfying
\[
\frac{d}{d\epsilon} L_2(G_\epsilon^{sm})\bigg|_{\epsilon=0} = D_2(Q, G).
\]
Then, given a local least favorable submodel \{$(Q_\epsilon^{lfm}, G_\epsilon^{sm}) : \epsilon$\} through $Q$, we have that \{$(Q_\epsilon^{lfm}, G_\epsilon^{sm}) : \epsilon$\} in $(Q, G)(M)$ satisfies
\[
\frac{d}{d\epsilon} L(Q_\epsilon^{lfm}, G_\epsilon^{sm})\bigg|_{\epsilon=0} = D(Q, G) \equiv D^*(Q, G) + D_2(Q, G).
\]
We refer to such a submodel \{$(Q_\epsilon^{lfm}, G_\epsilon^{sm}) : \epsilon$\} as a local $D()$-specific submodel.

Typically, $Q$ can be decomposed as $Q = (Q_1, Q_2)$ in which $Q_2$, the true value of $Q_2$ under $P_0$, can always be consistently estimated, and one select $D_2(Q = (Q_1, Q_2), G)$ so that $D_2(Q_1, Q_2, G_0)$ equals minus the projection of $D^*(Q_1, Q_2, G_0)$ onto a subspace of the tangent space of $G$ in $L^2(P_0)$, where we would rely on the model for $G$ to be correct. Such a choice implies that 1) for any $Q_1 D^*(Q_1, Q_2, G_0) - D_2(Q_1, Q_2, G_0)$ is a desired influence curve with significantly smaller variance than $D^*(Q_1, Q_2, G_0)$ at misspecified $Q_1$ and 2) $D^*(Q_{10}, Q_2, G_0) + D_2(Q_{10}, Q_2, G_0)$ is $D^*(Q_{10}, Q_2, G_0)$. That is, $D_2$ yields a correction to a misspecified $D^*(Q_1, Q_2, G_0)$ that only kicks in when $Q_1$ is misspecified. In this way, the model is still a local least favorable submodel so that the TMLE is asymptotically efficient when both $Q_0, G_0$ are consistently estimated.

Specifically, one might be given a user supplied influence curve $D^0(Q_1, Q_2, G_0)$ at $P_0$ (for any given $Q_1$), which one can represent as
\[
D^0(Q_1, Q_2, G_0) = D^*(Q_1, Q_2, G_0) + D_2(Q_1, Q_2, G_0),
\]
for some $D_2(Q_1, Q_2, G_0) \in T_G(P_0)$. One can now define the desired score as:
\[
D(Q_1, Q_2, G_0) = D^*(Q_1, Q_2, G_0) - \frac{P_0 \{D^*(Q_1, Q_2, G_0)D_2(Q_1, Q_2, G_0)\}}{P_0 D^2_2(Q_1, Q_2, G_0)} D_2(Q_1, Q_2, G_0).
\]
This influence curve has variance smaller than or equal to $D^0(Q_1, Q_2, G_0)$, and if $Q = Q_0$ (i.e. $Q_1 = Q_{10}$), then $D(Q_1, Q_2, G_0) = D^*(Q_0, G_0)$ is the efficient influence curve. By using this as the desired score equation, one will obtain a one-step TMLE that will be more efficient than an estimator with the user supplied influence curve $D^0(Q_1, Q_2, G_0)$ at $P_0$.

Such a TMLE is analyzed by using that $P_n D(Q_{1n}, Q_{2n}, G_n) = 0$
\[
P_0 D(Q_{1n}, Q_{2n}, G_n) = \Psi(Q_0) - \Psi(Q_n) + R_{2n},
\]
for a second order term in $(Q_{2n} - Q_0)$ and $G_n^* - G_0$, even when $Q_{1n}^*$ is inconsistent for $Q_{10}$, so that
\[
\Psi(Q_n^*) - \Psi(Q_0) = (P_n - P_0) D(Q_{1n}^*, Q_{2n}, G_n^*) + R_{2n}.
\]
If now \( R_{2n} = o_p(1/\sqrt{n}) \), \( D(Q_{1n}^*, Q_{2n}, G_n^*) \) falls in a \( P_0 \)-Donsker class, \( P_0 \{ D(Q_{1n}^*, Q_{2n}, G_n^*) - D(Q_1, Q_{20}, G_0) \}^2 \to 0 \) in probability for some limits \( Q_1 \) and \( Q_{20} \) of \( Q_{1n}^* \) and \( Q_{2n} \), then it follows that

\[
\Psi(Q_{1n}^*) - \Psi(Q_0) = (P_n - P_0) D(Q_1, Q_{20}, G_0) + o_p(1/\sqrt{n}).
\]

In particular, if \( Q_1 = Q_{10} \) it is asymptotically efficient, but even at misspecified \( Q_1 \) it has a desired influence curve \( D(Q_1, Q_{20}, G_0) \). Note that this analysis assumes consistency of \( G_n \).

In the current literature such TMLEs have always been iterative TMLE, using more fitting than needed for the desired asymptotic properties (Gruber and van der Laan, 2012; Lendle et al., 2013). This motivates us again to define a universal score-specific (i.e., \( D() \)-specific) submodel as a submodel \( \{(Q_\epsilon, G_\epsilon) : \epsilon \} \subset (Q, G)(M) \) so that for all \( \epsilon \)

\[
\frac{d}{d\epsilon} L(Q_\epsilon, G_\epsilon) = D^*(Q_\epsilon, G_\epsilon) + D_2(Q_\epsilon, G_\epsilon).
\]

Such a universal submodel is defined by the recursive differential equation definition:

\[
(Q_{\epsilon+h}, G_{\epsilon+h}) = (Q_{\epsilon+h}, G_{\epsilon+h}),
\]

where we need to keep in mind that the submodel \( Q_{\epsilon+h} \) uses \( G_{\epsilon} \) in its definition (if it depends on \( G \)), and, similarly, the submodel \( G_{\epsilon+h} \) uses \( Q_\epsilon \) in its definition. As in the previous sections, this can be used to generate an analytic integral representation. However, in most applications such integral representations follow immediately, so that we just present the above recursive differentiable equation relation. Since

\[
\frac{d}{d\delta} L_{Q_{\epsilon,\delta}, G_{\epsilon,\delta}} \bigg|_{\delta=0} = D^*(Q_\epsilon, G_\epsilon) + D_2(Q_\epsilon, G_\epsilon),
\]

it follows that this submodel is indeed a universal score-specific submodel.

As before a TMLE using this universal score-specific submodel for updating \((Q, G)\) will only require one step, and the TMLE \((Q_{\epsilon_n}, G_{\epsilon_n})\) will solve the desired score equation

\[
0 = P_n D(Q_{\epsilon_n}, G_{\epsilon_n}) = P_n \{ D^*(Q_{\epsilon_n}, G_{\epsilon_n}) + D_2(Q_{\epsilon_n}, G_{\epsilon_n}) \},
\]

so that it can be analyzed as above showing that, under regularity conditions, it is asymptotically linear with influence curve \( D(Q_1, Q_{20}, G_0) \), which equals the efficient influence curve if \( Q_1 \) happens to be the true value \( Q_{10} \).

A.1 Example: Targeting the treatment mechanism in TMLE for the additive treatment effect to obtain a more efficient estimator at misspecified \( Q \)

Let \( O = (W, A, Y) \sim P_0 \) and let \( M \) be a model that puts at most restrictions on the conditional probability distribution \( g_0(a \mid W) = P_0(A = a \mid W) \). Let \( \Psi : M \to \mathbb{R} \).
be defined by \( \Psi(P) = E_P\{E_P(Y \mid A = 1, W) - E_P(Y \mid A = 0, W)\} \). We have that 
\( \Psi(P) = \Psi_1(Q) = \Psi_1(Q_W, Q) \) is only a function of the distribution \( Q_W \) of \( W \) and the conditional mean \( \bar{Q} \) of \( Y \), given \( A, W \). Let \( D^*(Q, g) \) be the efficient influence 
curve at \( P \), and let \( D^*_0(Q, g) = H_1(g)(Y - \bar{Q}) \) be the corresponding efficient score 
for \( \bar{Q} \), while \( D^*_b(Q) = \bar{Q}(1, W) - \bar{Q}(0, W) - \Psi(Q) \) is the corresponding efficient score 
of \( Q_W \), so that \( D^*(Q, g) = D^*_0(Q, g) + D^*_b(Q) \). For a given \( Q \), let

\[
D_2(\bar{Q}, Q_{20}, g_0) = -\Pi(D^*_0(\bar{Q}, g_0) \mid T_2(g_0)),
\]

where \( T_2(g_0) \subset L^2_0(P_0) \) is a subspace of the nonparametric tangent space of \( g \) at \( P_0 \) 
consisting of all functions of \((A, W)\) with conditional mean zero, given \( W \), and \( \Pi \) 
denotes the projection operator onto \( T_2(g_0) \) in the Hilbert space \( L^2_0(P_0) \). Since a
function of \( W \) is orthogonal to a function of \( A, W \) that has mean zero, given \( W \), we 
also have that

\[
D_2(\bar{Q}, Q_{20}, g_0) = -\Pi(D^*_0(\bar{Q}, g_0) + D^*_b(Q_{W0}, \bar{Q}) \mid T_2(g_0)) \\
= -\Pi(D^*(Q_{W0}, \bar{Q}, g_0) \mid T_2(g_0)).
\]

For example, \( T_2(g_0) \) could be the tangent space of a parametric model through \( g_0 \). 
In the latter case this projection depends on covariances under \( P_0 \) so that \( Q_{20} \) indicates 
this dependence on \( P_0 \) beyond \( g_0 \), and it is clear that \( Q_{20} \) can be consistently 
estimated. We assume that \( T_2(g_0) \) (i.e., \( \mathcal{G} \)) is small enough so that the projection 
operator (i.e. \( Q_{20} \)) can indeed be consistently estimated. Because the nonparametric 
tangent space of \( g \) equals \( \{h(W)(A - \bar{g}_0(W)) : h\} \), this projection can be represented 
as \( D_2(\bar{Q}, Q_{20}, g_0)(A, W) = H_2(\bar{Q}, Q_{20}, g_0)(W)(A - \bar{g}_0(W)) \) for some \( H_2 \). The TMLE 
will now be tailored to solve \( P_n\{D^*(Q_{W,n}, \bar{Q}_n, g^*_n) + D_2(\bar{Q}_n^*, Q_{2n}, g^*_n)\} = 0 \), where 
\( Q_{W,n} \) is the unbiased empirical distribution of \( Q_{W0} \), \( Q_{2n} \) is the unbiased estimator 
of the covariances coded by \( Q_{20} \), while \( \bar{Q}_n, g^*_n \) are the targeted estimators of \( \bar{Q}_0, g_0 \), 
using the TMLE.

Given \((\bar{Q}, g)\), the local least favorable submodel through \( \bar{Q} \) and local desired 
submodel through \( g \) are defined by

\[
\text{Logit}^{\text{lfm}}_{\bar{Q}_t} = \text{Logit}^{\text{lfm}}_{\bar{Q}} - \epsilon H_1(g) \\
\text{Logit}^{\text{sm}}_{\bar{g}_t} = \text{Logit}^{\text{sm}}_{\bar{g}} - \epsilon H_2(\bar{Q}, Q, g).
\]

Let \( L_2(g) = -\log g \), and \( L(\bar{Q})(O) = -\{Y \log \bar{Q} + (1 - Y) \log(1 - \bar{Q})\} \) be the quasi-
log-likelihood loss. Let \( \bar{L}(\bar{Q}, g) = L(\bar{Q}) + L_2(g) \) be the sum loss function for \((\bar{Q}, g)\). 
The corresponding universal score-specific submodel through \((\bar{Q}, g)\) is defined by 
the following differential recursive relation: for \( \epsilon > 0 \)

\[
\text{Logit}_{\bar{Q}_{t+\epsilon}} = \text{Logit}_{\bar{Q}_t} - \epsilon H_1(g_t) \\
\text{Logit}_{\bar{g}_{t+\epsilon}} = \text{Logit}_{\bar{g}_t} - \epsilon H_2(\bar{Q}_t, Q_2, g_t).
\]
Similarly, we can define this submodel for $\epsilon < 0$. Equivalently, their integral representation is given by: for $\epsilon > 0$

\[
\text{Logit} \bar{Q}_{\epsilon} = \text{Logit} \bar{Q} - \int_0^\epsilon H_1(g_x)dx
\]

\[
\text{Logit} \bar{g}_{\epsilon} = \text{Logit} \bar{g} - \int_0^\epsilon H_2(\bar{Q}_x, Q_2, g_x)dx,
\]

and, for $\epsilon < 0$,

\[
\text{Logit} \bar{Q}_{\epsilon} = \text{Logit} \bar{Q} + \int_\epsilon^0 H_1(g_x)dx
\]

\[
\text{Logit} \bar{g}_{\epsilon} = \text{Logit} \bar{g} + \int_\epsilon^0 H_2(\bar{Q}_x, Q_2, g_x)dx.
\]

The TMLE based on this universal score-specific submodel is now computed as follows. Let $Q_{W,n}, \bar{Q}_n, g_n, Q_{2n}$ be the initial estimators. Let $h > 0$ be a small number. Determine first in which direction the empirical risk increases: $P_n \bar{L}(\bar{Q}_{n,h,} g_{n,h}) < P_n \bar{L}(\bar{Q}_n, g_n)$ or $P_n \bar{L}(\bar{Q}_{n,h,} g_{n,-h}) < P_n \bar{L}(\bar{Q}_n, g_n)$. Suppose that $h > 0$ is the direction that decreases the empirical risk of the sum loss function. Now, one finds the first local minimum $\epsilon_n$ of $\epsilon \rightarrow P_n \bar{L}(\bar{Q}_{n,\epsilon}, g_n^*)$ for $\epsilon > 0$. The TMLE of $(Q_{W,0}, \bar{Q}_0, g_0, Q_{20})$ using this universal score-specific submodel is defined by $(Q_{W,n}, Q_n^*, \bar{Q}_n^*, g_n^*, Q_{2n}^*)$ and the corresponding TMLE of $\psi_0$ is given by $\Psi(Q_{W,n}, Q_n^*, g_n^*)$. The TMLE solves $P_n \{D^*(Q_{W,n}, Q_n^*, g_n^*) + D_2(\bar{Q}_n^*, Q_{2n}^*, g_n^*)\} = 0$. By definition of $D_2$, the correction $D_2$ improves the efficiency of the TMLE relative to the TMLE that does not use this correction, where once again, it assumed that $g_n$ is consistent for $g_0$.

A.2 Using a universal score-specific submodel to obtain asymptotic linearity under milder conditions

Consider again the setting that $O \sim P_0 \in \mathcal{M}$, $\Psi(P) = \Psi_1(Q(P))$, $D^*(P) = D^*(Q(P), G(P))$ for a nuisance parameter $G(P)$ orthogonal to $Q(P)$. In the previous subsection we showed that targeting an initial estimator $g_n$ can make the TMLE more efficient at misspecified $Q_n$ when $g_n$ is a well behaved MLE of $g_0$ under a correctly specified model $G$ for $g_0$.

Suppose now that $g_n$ is based on a machine learning algorithm such as the ensemble super-learner based on a user supplied library of machine learning algorithms. We want to guarantee that the TMLE remains asymptotically linear even when $Q_n$ is misspecified, but now without relying on $g_n$ to be an MLE of a relatively small correct model. Instead we will rely on $g_n$ to converge at a good enough (non-$\sqrt{n}$)-rate to $g_0$ (van der Laan, 2012). We will now show how this can be achieved with a universal score-specific submodel. Suppose that we use the TMLE $(Q_n^* = Q_{n,\epsilon_n}, G_n^* = G_{n,\epsilon_n})$.
based on a universal score-specific submodel \((Q_{n,e}, G_{n,e})\) so that

\[
P_n \{ D^*(Q_n^*, G_n^*) + D_2(Q_n^*, G_n^*) \} = 0. \tag{1}
\]

We will now go through a template for proving asymptotic linearity of \(\Psi(Q_n^*)\), which will then demonstrate how \(D_2\) needs to be chosen. Firstly, we use that

\[
-P_0 D^*(Q_n^*, G_n^*) = \Psi(Q_n^*) - \Psi(Q_0) + R_2(Q_n^*, Q_0, G_n^*, G_0), \tag{2}
\]

where \(R_2\) is a second order term in differences \(f_1(Q_n^*) - f_1(Q_0)\) and \(f_2(G_n^*) - f_2(G_0)\) for some \(f_1, f_2\). Since \(Q_n^*\) can be inconsistent, this second order term cannot be assumed to be negligible. This second order term is assumed to have the so called double robust structure so that \(R_2(Q_0, Q_0, G, G_0) = R_2(Q, Q_0, G_0, G_0) = 0\), i.e. it equals zero when either \(Q_0\) or \(G_0\) is correctly specified. Combining (1) and (2) yields:

\[
(P_n - P_0) \{ D^*(Q_n^*, G_n^*) + D_2(Q_n^*, G_n^*) \} = \Psi(Q_n^*) - \Psi(Q_0) + R_2(Q_n^*, Q_0, G_n^*, G_0) - P_0 D_2(Q_n^*, G_n^*).
\tag{3}
\]

Suppose now that by utilizing the special structure of \(R_2()\) we can construct a data adaptive real valued \(G \to \Phi_n(G)\) such that

\[
R_2(Q_n^*, Q_0, G_n^*, G_0) = \Phi_n(G_n^*) - \Phi_n(G_0) + R_{2n},
\tag{4}
\]

for some second order term in terms of differences \((G_n - G_0)\) and \(Q_n^* - Q_0^*\) for some much easier to estimate parameter \(Q_0^*\) of \((Q_0, G_0)\). We would now assume that \(R_{2n} = o_P(1/\sqrt{n})\).

For example, in the \(EY_1\) example, we have

\[
R_2(Q, Q_0, G, G_0) = P_0(\bar{Q} - \bar{Q}_0)(\bar{g} - \bar{g}_0)/\bar{g} = -E_0 \{ E_0(Y - \bar{Q}(W) \mid A = 1, \bar{g}_0, \bar{Q})((\bar{g} - \bar{g}_0)/\bar{g}) = -\Phi_{\bar{Q}, \bar{g}, \bar{g}_0}(\bar{g}) - \Phi_{\bar{Q}, \bar{g}, \bar{g}_0}(\bar{g}_0),
\]

where

\[
\Phi_{\bar{Q}, \bar{g}, \bar{g}_0}(\bar{g}_1) = P_0 E_0(Y - \bar{Q} \mid A = 1, \bar{g}_0, \bar{Q}) \bar{g}_1/\bar{g}.
\]

Define \(Q_{20} = E_0(Y - Q \mid A = 1, \bar{g}_0, \bar{Q})\) and let \(Q_{2n}\) be the corresponding estimator \(E_n(Y - Q_n \mid A = 1, \bar{g}_n, \bar{Q}_n)\), treating \(\bar{g}_n, \bar{Q}_n\) as fixed functions of \(W\). Then, we can also denote \(\Phi_{\bar{Q}, \bar{g}, \bar{g}_0} = \Phi_{Q_{20}, Q_{2n}}\), and we can define \(\Phi_n\) by \(\Phi_{Q_{2n}, Q_{W,n}}\). Thus, in this example, we can define

\[
\Phi_n(\bar{g}_1) = E P_n E_n(Y - \bar{Q}_n \mid A = 1, \bar{g}_n, \bar{Q}_n) \bar{g}_1/\bar{g}_n,
\]

and the second order term \(R_{2n}^a\) involves square differences \((\bar{g}_n - \bar{g}_0)^2\), \((\bar{Q}_{2n} - \bar{Q}_{20})(\bar{g}_n - \bar{g}_0)\), and square differences involving \((P_n - P_0)\) over \(W\), all reasonable second order terms.
So combining (6) with (4) yields:

\[
(P_n - P_0)\{D^*(Q_n^*, G_n^*) + D_2(Q_n^*, G_n^*)\} = \Psi(Q_n^*) - \Psi(Q_0) + \Phi_n(G_n^*) - \Phi_n(G_0) - P_0D_2(Q_n^*, G_n^*) + o_P(1/\sqrt{n}).
\]

Let \(D_{2,n}(P_0)\) be efficient influence curve of \(\Phi_n\) at \(P_0\), viewing \(\Phi_n\) as a given real value parameter defined on \(M\). By augmenting the original definition of \(Q\) with whatever extra parameters are needed to evaluate this efficient influence curve, we can denote \(D_{2,0}(P_0)\) with \(D_2(Q_0, G_0, \gamma_0)\), where \(\gamma_0\) is estimated with \(\gamma_n\). By the general property of a canonical gradient of a target parameter mapping, one will have that

\[
-P_0D_2(Q_n^*, G_n^*, \gamma_n) = \Phi_n(G_0) - \Phi_n(G_n) + R_{2n}^b,
\]

where \(R_{2n}^b\) is a second order term. We will assume \(R_{2n}^b = o_P(1/\sqrt{n})\). Combining this with the previous equation yields:

\[
(P_n - P_0)\{D^*(Q_n^*, G_n^*) + D_2(Q_n^*, G_n^*, \gamma_n)\} = \Psi(Q_n^*) - \Psi(Q_0) + o_P(1/\sqrt{n}),
\]

where the \(o_P(1/\sqrt{n})\) now equals \(R_{2n}^a + R_{2n}^b\). That is, we have shown

\[
\Psi(Q_n^*) - \Psi(Q_0) = (P_n - P_0)\{D^*(Q_n^*, G_n^*) + D_2(Q_n^*, G_n^*, \gamma_n)\} + o_P(1/\sqrt{n}).
\]

We can now finalize the proof as usual by assuming that \(\bar{D}(Q_n^*, G_n^*) = D^*(Q_n^*, G_n^*) + D_2(Q_n^*, G_n^*, \gamma_n)\) falls in a \(P_0\)-Donsker class with probability tending to 1, and \(P_0\{\bar{D}(Q_n^*, G_n^*, \gamma_n) - D(Q, G_0, \gamma_0)\}^2\) converges to zero in probability for some possibly misspecified \(Q \neq Q_0\), so that

\[
\Psi(Q_n^*) - \Psi(Q_0) = (P_n - P_0)\bar{D}(Q, G_0, \gamma_0) + o_P(1/\sqrt{n}).
\]

When \(Q = Q_0\), it follows that \(D_2(Q_0, G_0, \gamma_0) = 0\), so that this TMLE \(\Psi(Q_n^*)\) is asymptotically efficient when both \(Q_n, G_n\) are consistent.

To conclude, we selected \(D_2(Q_0, G_0, \gamma_0)\) to be equal to the efficient influence curve of \(G \rightarrow \Phi_0(G)\), a parameter that is constructed by careful study of the second order term \(R_{2n}(Q, Q_0, G, G_0) \approx \Phi_0(G) - \Phi_0(G_0)\) where the dependence on \(P_0\) of \(\Phi_0\) requires a much easier to estimate function of \(Q_0, G_0\). Using the TMLE based on the corresponding universal score-specific submodel, we obtain a TMLE that preserves asymptotic linearity when \(Q_n\) is inconsistent, but still consistent for the easier to estimate pieces needed to make the second order terms, \(R_{2n}^a, R_{2n}^b, o_P(1/\sqrt{n})\), under regularity conditions.

The proof above proves the following formal theorem.

**Theorem 1** Define the second order term \(R_2()\) by

\[
-P_0D^*(Q, G) = \Psi(Q) - \Psi(Q_0) + R_2(Q, Q_0, G, G_0).
\]
For a given \((Q_1, G_1, \gamma)\), let \(\Phi_{Q_1,G_1,\gamma} : \mathcal{M} \to \Phi_{Q_1,G_1,\gamma}(\mathcal{M})\) be a parameter mapping, where \(\Phi_{Q_1,G_1,\gamma}(P) = \Phi_{1,Q_1,G_1,\gamma}(G(P))\) only depends on \(P\) through \(G(P)\), and it is indexed by an unknown parameter \(\Gamma : \mathcal{M} \to \Gamma(\mathcal{M})\) (which can be consistently estimated). We use this parameter to approximate the second order term \(R_2()\) as follows:

\[
R_2(Q, Q_0, G, G_0) = \Phi_{1,Q,G,\gamma_0}(G) - \Phi_{1,Q,G,\gamma_0}(G_0) + R^2_2(\gamma_0, Q^r, Q_0, G, G_0)
\]

for some second order term \(R^2_2\) in differences \(Q^r - Q_0\) and \(G - G_0\) for some relatively easy to estimate \(Q^r_0\) (relative to original \(Q_0\)). Let \(D_{Q,G,\gamma}(Q, G)\) be the efficient influence curve of \(\Phi_{Q,G,\gamma}\) at \(P_0\). Let the second order term \(R_{2,Q,G,\gamma}()\) be defined by:

\[
-P_0D_{Q,G,\gamma}(Q, G) = \Phi_{Q,G,\gamma}(G_0) - \Phi_{Q,G,\gamma}(G) + R_{2,Q,G,\gamma}(Q^r, Q_0, G, G_0),
\]

where again \(R_{2,Q,G,\gamma}()\) is second order in terms of an easier to estimate parameter \(Q^r_0\) instead of original \(Q_0\).

Let \(\gamma_n\) be a consistent estimator of \(\gamma_0\). Let \((Q_n^*, G_n^*)\) be an estimator of \((Q_0, G_0)\) that solves

\[
0 = P_nD(Q_n^*, G_n^*, \gamma_n) = P_n\{D^*(Q_n^*, G_n^*) + D_{Q_n^*,G_n^*,\gamma_n}(Q_n^r, G_n^r)\}.
\]

Assume \(R^2_{Q,G,\gamma}(\gamma_0, Q_n^r, Q^r_0, G_n^r, G_0) = o_P(1/\sqrt{n})\) and \(R_{2,Q_n^r,G_n^r,\gamma_n}(Q_n^r, Q^r_0, G_n^r, G_0) = o_P(1/\sqrt{n})\). Assume also that \(D(Q_n^*, G_n^*, \gamma_n)\) falls in a \(P_0\)-Donsker class with probability tending to 1, \(P_0\{D(Q_n^*, G_n^*, \gamma_n) - D(Q, G_0, \gamma_0)\}^2\) converges to zero in probability for some possibly misspecified \(Q \neq Q_0\). Then,

\[
\Psi(Q_n^*) - \Psi(Q_0) = (P_n - P_0)D(Q, G_0, \gamma_0) + o_P(1/\sqrt{n})\]

### A.3 Universal score-specific submodels for one-step higher-order TMLE

Of course, the above formulation can be further generalized as follows. Given a local desired submodel for which \(\frac{d}{d\epsilon} L(Q_{\epsilon}^{lim})\) \(|\epsilon = 0 = D(Q, G)\) for some specified \(D(Q, G)\), the corresponding universal score-specific submodel is defined by the recursive differential equation definition:

\[
Q_{\epsilon + d\epsilon} = Q_{\epsilon, d\epsilon}^{lim}.
\]

Under weak regularity condition, this now satisfies that \(\frac{d}{d\epsilon} L(Q_{\epsilon}) = D(Q_{\epsilon}, G)\), and the one-step TMLE defined by \(Q_{\epsilon_n}\) with \(\epsilon_n = \arg\min_{\epsilon} P_n L(Q_{\epsilon})\) solves \(P_n D(Q_{\epsilon_n}, G) = 0\). Therefore, this universal score-specific submodel can also be used to define one-step second-order TMLE of second order pathwise differentiable parameters (Carone et al., 2014; Diaz et al., 2015). In this case \(D(Q, G)\) plays the role of \(D(Q, G) = D^1(Q, G) + P_n D^2(Q, G)\), where \(D^j(Q, G)\) is the \(j\)-th order efficient influence function, \(j = 1, 2\) (Robins et al., 2008). Given an initial estimator \((Q_n, G_n)\), the TMLE \(Q_{n,\epsilon_n}\) solves \(P_n D^1(Q_{n,\epsilon_n}, G_n) + P_n D^2(Q_{n,\epsilon_n}, G_n) = 0\), providing the basis for asymptotic efficiency of the second order TMLE under a condition that a third-order difference between \((Q_{\epsilon_n}, G_n)\) and \((Q_0, G_0)\) is \(o_P(1/\sqrt{n})\), while a first order TMLE relies on a second order difference being \(o_P(1/\sqrt{n})\).
B Generalization to universal least favorable submodels with loss-functions that depend on nuisance parameters

This section could be read after Section 5. Let \( O \sim P_0 \in \mathcal{M}, \Psi : \mathcal{M} \rightarrow \mathbb{R}, D^*(P) = D^*(Q(P), G(P)) \), and let the tangent space of \( G(P) \) be orthogonal to the tangent space of \( Q(P) \). Consider a loss function \( \mathcal{L}_{\Gamma}(Q) \) so that \( Q(P) = \arg\min_Q \mathcal{L}_{\Gamma}(Q) \), where \( \Gamma : \mathcal{M} \rightarrow \mathcal{G}(\mathcal{M}) \) is some nuisance parameter. For example, \( \Gamma(P) \) might depend on \( P \) through \( Q(P), G(P) \), or both \( (Q(P), G(P)) \). Let \( \{Q_{\epsilon}^{\text{lim}} : \epsilon\} \) be a local least favorable submodel through \( Q = Q(P) \) at \( \epsilon = 0 \) w.r.t. this loss function \( \mathcal{L}_{\epsilon} \):

\[
\frac{d}{d\epsilon} \mathcal{L}_{\Gamma(P)}(Q_{\epsilon}^{\text{lim}}) \bigg|_{\epsilon = 0} = D^*(Q(P), G(P)).
\]

A TMLE based on this local least favorable submodel could now proceed in the following two manners. Simultaneously, the resulting universal least favorable submodel and corresponding one-step TMLE will follow naturally and be described as well.

**Case I: Fixing the nuisance parameter in the loss-function.** Given an initial \( \{Q, G\} \), and corresponding \( \gamma = \Gamma(Q, G) \) or external estimate \( \gamma \), one defines

\[
\epsilon^0_n = \arg\min_{\epsilon} P_n \mathcal{L}_{\gamma(Q_{\epsilon}^{\text{lim}})},
\]

one defines the update \( Q^1 = Q_{\epsilon^0_n}^{\text{lim}} \), and one iterates this updating process with

\[
\epsilon^k_n = \arg\min_{\epsilon} P_n \mathcal{L}_{\gamma(Q_{\epsilon}^{\text{lim}})},
\]

\( k = 1, 2, \ldots \) till \( \epsilon^K_n \approx 0 \), thus fixing \( \gamma \) throughout. The TMLE of \( Q_0 \) based on this local least favorable submodel is now \( Q^* = Q^K \), and solves

\[
P_n D^*(\gamma, Q^*, G) \approx 0,
\]

where

\[
D^*(\gamma, Q, G) = \frac{d}{d\epsilon} \mathcal{L}_{\gamma(Q_{\epsilon}^{\text{lim}})} \bigg|_{\epsilon = 0}.
\]

Under reasonable conditions on the estimator of \( \gamma_0 = \Gamma(P_0) \), one will still have

\[
-P_0 D^*(\gamma, Q, G) = \Psi(Q) - \Psi(Q_0) + R_2(\gamma, \gamma_0, Q, Q_0, G, G_0),
\]

for a second order term involving square differences of \( (Q - Q_0), (G - G_0) \), and \( \gamma - \gamma_0 \). Therefore, one can still establish asymptotic efficiency of such a TMLE under the condition that the second order term is \( o_P(1/\sqrt{n}) \), and some regularity conditions.

The price we paid by fixing the nuisance parameter in the loss function is that the
TMLE now solves an incompatible efficient influence curve equation in the sense that the estimator \( \gamma \) will not be compatible with the TMLE \((Q^*_n, G_n)\). Generally, speaking this seems of little consequence, as long as \( D^*(\gamma, Q, G) \) still has the desired second order expansion (7).

The construction of an \( L_\gamma \)-specific universal least favorable submodel can now proceed analogue to the case that the loss-function was known by replacing \( L(Q) \) by \( L_\gamma(Q) \), and \( D^*(\gamma, Q, G) \) by \( D^*(\gamma, Q, G) \) fixing \( \gamma \). In other words, we define the \( L_\gamma \)-specific universal least favorable submodel by the differential equation: for \( \epsilon > 0 \) and \( d\epsilon > 0 \),

\[
Q_{\epsilon + d\epsilon} = Q_{\epsilon, d\epsilon}^{\text{lim}},
\]

and, similarly for \( \epsilon < 0 \) and \( d\epsilon < 0 \), we define \( Q_{\epsilon - d\epsilon} = Q_{\epsilon, d\epsilon}^{\text{lim}} \). By our previous results, we now have that for all \( \epsilon > 0 \),

\[
\frac{d}{d\epsilon} L_\gamma(Q_\epsilon) = D^*(\gamma, Q_\epsilon, G),
\]

and similarly for \( \epsilon < 0 \). The TMLE using this \( L_\gamma \)-specific universal least favorable submodel takes only one step so that the TMLE of \( Q_0 \) is given by \( Q^* = Q_{\epsilon_0} \), solving \( P_n D^*(\gamma, Q^*, G) = 0 \).

**Case II: Updating the nuisance parameter.** Given an initial \((Q, G)\), and corresponding \( \gamma = \Gamma(Q, G) \), one defines

\[
\epsilon_0^n = \arg \min_{\epsilon} P_n L_\gamma(Q_\epsilon^{\text{lim}}).
\]

One defines the update \( Q^1 = Q_{\epsilon_0}^{\text{lim}} \), and \( \gamma^1 = \Gamma(Q^1, G) \), and one iterates this updating process with

\[
\epsilon_k^n = \arg \min_{\epsilon} P_n L_\gamma(Q_\epsilon^{k,\text{lim}}),
\]

\( k = 1, 2, \ldots \) till \( \epsilon_k^n \approx 0 \), thus updating \( \gamma^k \) throughout. The TMLE of \( Q_0 \) based on this local least favorable submodel is now \( Q^* = Q^K \), and solves

\[
P_n D^*(Q^*, G) \approx 0.
\]

The asymptotic efficiency of the TMLE under the usual conditions follows accordingly.

We define the universal least favorable submodel by the same differential equation as above for the fixed loss-function case: for \( \epsilon > 0 \) and \( d\epsilon > 0 \),

\[
Q_{\epsilon + d\epsilon} = Q_{\epsilon, d\epsilon}^{\text{lim}},
\]

and, similarly for \( \epsilon < 0 \) and \( d\epsilon < 0 \), we define \( Q_{\epsilon - d\epsilon} = Q_{\epsilon, d\epsilon}^{\text{lim}} \). As a consequence, for all \( \epsilon > 0 \),

\[
\frac{d}{dh} L_\Gamma(Q_\epsilon, G)(Q_{\epsilon + h}) \bigg|_{h=0} = D^*(Q_\epsilon, G).
\]
Thus, for all $\epsilon > 0$,

$$\frac{d}{d\epsilon} L_\gamma(Q_\epsilon) = D^*(Q_\epsilon, G).$$

The MLE-step for the one-step TMLE is now defined as follows. First determine the sign of $h$ for which $P_n\gamma L_\gamma(Q,G)(Q_{\epsilon + h}^\text{lim}) < P_n\gamma L_\gamma(Q,G)(Q_\epsilon)$. Suppose the empirical risk decreases in the direction $h > 0$. Now, we determine the first $\epsilon_0 > 0$ for which

$$\frac{d}{dh} P_n\gamma L_\gamma(Q,G)(Q_{\epsilon + h})\bigg|_{h=0} = 0,$$

or equivalently, at which $P_nD^*(Q_\epsilon, G) = 0$.

Notice that this corresponds with the first $\epsilon_0$ at which $P_n\gamma L_\gamma(Q_\epsilon, G)(Q_{\epsilon + h})$ is not increasing in $h > 0$ anymore.

The TMLE using this universal least favorable submodel w.r.t loss $L_\gamma(Q)$ takes only one step so that the TMLE of $Q_0$ is given by $Q_\star = Q_{\epsilon_0}$, solving $P_nD^*(Q_\star, G) = 0$.

B.1 Example: Sequential regression TMLE of counterfactual mean for multiple time point intervention using universal least favorable model

Here we develop a TMLE based on the universal one-dimensional least favorable submodel, while in our previous work (Gruber and van der Laan, 2012; Bang and Robins, 2005) we use a local least favorable submodel with a parameter for each time point. Let $O = (L(0), A(0), L(1), A(1), Y) \sim P_0$, and let the statistical model $\mathcal{M}$ only put restrictions on the conditional probability distributions $g_{A(0)}$ and $g_{A(1)}$ of $A(0)$, given $L(0)$, and $A(1)$, given $L(1)$, $A(0)$, respectively. Let $L(0) \rightarrow d_0(L(0))$ and $L(1) \rightarrow d_1(\bar{L}(1))$ be two functions that can be used to deterministically assign treatment $A(0) = d_0(L(0))$ and $A(1) = d_1(\bar{L}(1))$, respectively. Let $\bar{d} = (d_0, d_1)$.

Given this dynamic treatment regimen $(d_0, d_1)$ we define the target parameter $\Psi : \mathcal{M} \rightarrow \mathbb{R}$ by

$$\Psi(P) = E_P\{E_P(Y \mid \bar{A}(1) = \bar{d}(\bar{L}(1)), \bar{L}(1)) \mid A(0) = d_0(L(0)), L(0))\}.$$

Let $\bar{Q}^2 = E_P(Y \mid \bar{A}(1) = \bar{d}(\bar{L}(1)), \bar{L}(1)), \bar{Q}^1 = E_P(\bar{Q}^2 \mid A(0) = d_0(L(0)), L(0))$, and $\bar{Q}^0 = E_P(\bar{Q}^1)$. Let $\bar{Q} = (\bar{Q}^2, \bar{Q}^1)$, and $Q = (Q, Q^0)$ and note that $\Psi(P) = \Psi_1(Q) = Q^0$.

The efficient influence curve of $\Psi$ at $P$ is given by:

$$D^*(P) = \{\bar{Q}^1 - \bar{Q}^0\} + \frac{I(A(0) = d_0(L(0)))}{g_{A(0)}(O)}(\bar{Q}^2 - \bar{Q}^1) + \frac{I(A(1) = \bar{d}(L(1)))}{g_{A(0)}g_{A(1)}(O)}(Y - \bar{Q}^2) \equiv D_0^*(P) + D_1^*(P) + D_2^*(P).$$
We will also denote $D^*(P)$ with $D^*(Q, g)$, $g = (g_{A(0)}, g_{A(1)})$, $D^*_2(P) = D^*_2(Q, g)$ and $D^*_1(P) = D^*_1(Q, g)$.

Consider the following loss functions for the components of $\tilde{Q}$:

$$L_2(\tilde{Q}^2) = -I(\tilde{A}(1) = \tilde{d}(\tilde{L}(1))\{Y \log \tilde{Q}^2 + (1 - Y) \log(1 - \tilde{Q}^2)\}$$
$$L_{1,2}(\tilde{Q}^1) = -I(\tilde{A}(0) = d_0(L(0)))\{(\tilde{Q}^2 \log \tilde{Q}^1 + (1 - \tilde{Q}^2) \log(1 - \tilde{Q}^1)\}.\]

Given $\tilde{Q}_n$, we will estimate $\tilde{Q}_0$ with $\tilde{Q}_0 = P_n \tilde{Q}_n$, an empirical mean. As a consequence, we only need a TMLE of $\tilde{Q}_2$ and $\tilde{Q}_1$, and the TMLE of $\tilde{Q}_0$ follows by taking the empirical mean over $L(0)$ of the TMLE of $\tilde{Q}_0$.

We can now define the sum loss function for $\tilde{Q}$:

$$L_{Q^2}(\tilde{Q}) \equiv L_2(\tilde{Q}^2) + L_{1,2}(\tilde{Q}^1),$$

which is indexed by nuisance parameter $\tilde{Q}^2$ itself. For notational convenience, let’s denote this nuisance parameter with $\Gamma(\tilde{Q}) = \tilde{Q}^2$. Then, this loss-function can also be represented as:

$$L_\gamma(\tilde{Q}^2, \tilde{Q}^1) = L_2(\tilde{Q}^2) + L_{1,\gamma}(\tilde{Q}^1).$$

Indeed, we have $L_{\gamma_0}(\tilde{Q})$ is a valid loss function for $\tilde{Q}_0 = \arg\min_QL_0P_0L_{\gamma_0}(\tilde{Q})$. Consider the following local least favorable submodel through $\tilde{Q}$:

$$\text{Logit} \tilde{Q}^{2,\text{lfm}} = \text{Logit} \tilde{Q}^2 - \epsilon H_2(g)$$
$$\text{Logit} \tilde{Q}^{1,\text{lfm}} = \text{Logit} \tilde{Q}^1 - \epsilon H_1(g)$$

where $H_2(g) = I(\tilde{A}(1) = \tilde{d}(\tilde{L}(1)))/(g_{A(0)}g_{A(1)}(O))$ and $H_1(g) = I(\tilde{A}(0) = d_0(L(0)))/g_{A(0)}(O)$. Indeed, we have

$$\left.\left.\frac{d}{de}L_{Q^2}(\tilde{Q}^{\text{lfm}})\right|_{e=0}\right) = D^*_2(\tilde{Q}, g) + D^*_1(\tilde{Q}, g).$$

**Case I: Fixed loss function** $L_\gamma$. The corresponding $L_\gamma$-specific universal least favorable submodels are defined by the differential equation $\tilde{Q}^{2}_{\epsilon+de} = Q^{2,\text{lfm}}_{\epsilon,de}$ and $\tilde{Q}^{1}_{\epsilon+de} = Q^{1,\text{lfm}}_{\epsilon,de}$, which implies the integral representation given by

$$\text{Logit} \tilde{Q}^{2}_\epsilon = \text{Logit} \tilde{Q}^2 - \epsilon H_2(g)$$
$$\text{Logit} \tilde{Q}^{1}_\epsilon = \text{Logit} \tilde{Q}^1 - \epsilon H_1(g).$$

Thus, the $L_\gamma$-specific universal least favorable submodel through $\tilde{Q} = (\tilde{Q}^2, \tilde{Q}^1)$ equals the local least favorable submodel: $\tilde{Q}^{\text{lfm}} = \tilde{Q}_\epsilon$. Indeed,

$$\left.\left.\frac{d}{de}L_{Q^2}(\tilde{Q}_\epsilon)\right|_{e=0}\right) = H_2(g)(Y - \tilde{Q}^2_\epsilon) + H_1(g)(\tilde{Q}^2_\epsilon - \tilde{Q}^1_\epsilon)$$
$$\equiv D^*_2(\tilde{Q}^2_\epsilon, g) + D^*_1(\tilde{Q}^2_\epsilon, \tilde{Q}^1_\epsilon, g).$$
The one-step TMLE based on this $L_\gamma$-specific universal least favorable submodel is defined by

$$
\epsilon_n = \arg\min_{\epsilon} P_n L_{Q_n^2}(\bar{Q}_{n,\epsilon}),
$$

and the TMLE of $\bar{Q}_0$ is given by $\bar{Q}_{n,\epsilon_n}$. The resulting TMLE of $\psi_0$ is simply $\Psi(Q_{n,\epsilon_n}) = P_n \bar{Q}_{n,\epsilon_n}^1$. This TMLE will now solve the incompatible efficient influence curve equation $0 = P_n D^*(\bar{Q}_n^2, Q_n^*, g_n)$ defined by

$$
D^*(\bar{Q}_n^2, Q_n^*, g_n) = D_2^*(\bar{Q}_n^2, g_n) + D_1^*(\bar{Q}_n^2, \bar{Q}_n^{1s}, g_n) + D_0^*(\bar{Q}_n^{1s}, \bar{Q}_n^{0s}).
$$

The typical TMLE solves the compatible efficient influence curve equation $0 = P_n D^*(Q_n^*, g_n)$, where

$$
D^*(Q_n^*, g_n) = D_2^*(Q_n^2, g_n) + D_1^*(Q_n^2, Q_n^{1s}, g_n) + D_0^*(Q_n^{1s}, Q_n^{0s}).
$$

Let’s now prove that this incompatible efficient influence curve still allows the desired second order expansion the asymptotic linearity and efficiency proof relies upon. By the general representation theorem for the efficient influence curve in CAR-censored data models (Robins and Rotnitzky, 1992; van der Laan and Robins, 2003) we have

$$
D^*(Q^*, g) = D_{IPTW}(g, \bar{Q}_0) + D_{CAR}(Q^*, g),
$$

where $D_{IPTW}(g, \bar{Q}_0) = I(\bar{A} = \bar{d}/\bar{y})Y - \bar{Q}_0$, and $D_{CAR}(Q^*, g)$ is a score of the censoring mechanism, thereby, being a function of $O$ that has conditional mean zero w.r.t. $g$ (for every value of $Q$). Thus the incompatible efficient influence curve $D^*(\bar{Q}_n^2, Q_n^*, g_n)$ can be represented as $D_{IPTW}(g, \bar{Q}_n^{0s}) + D_{CAR}(Q, g)$, where $\bar{Q} \neq \bar{Q}_n^{0s}$. We have

$$
P_0 D^*(\bar{Q}_n^2, Q^*, g) = P_0\{D_{IPTW}(g, \bar{Q}_n^{0s}) + D_{CAR}(Q, g)\}
$$

$$
= P_0\{D_{IPTW}(g, \bar{Q}_n^{0s}) + D_{CAR}(Q^*, g)\}
$$

$$
+ P_0\{D_{CAR}(Q^*, g) - D_{CAR}(Q, g)\}
$$

$$
= \Psi(Q_0) - \Psi(Q^*) + R_2(Q^*, Q_0, G, G_0)
$$

$$
+ P_0\{D_{CAR}(Q^*, g) - D_{CAR}(Q, g)\}.
$$

So we need to show that the last term is a second order term. But this last term equals:

$$
R_{2a}(Q_0, Q, g, g_0) = P_0\{D_{CAR}(Q^*, g) - D_{CAR}(Q, g) - D_{CAR}(Q^*, g_0) + D_{CAR}(Q, g_0)\}.
$$

Thus, we conclude that

$$
P_0 D^*(\bar{Q}_n^2, Q^*, g) = \Psi(Q_0) - \Psi(Q^*) + R_2(Q^*, Q_0, g, g_0) + R_{2a}(\bar{Q}_n^2, \bar{Q}_n^{2s}, g, g_0),
$$

which thus yields a desired double robust second order remainder term defined as the sum of $R_2$ and $R_{2a}$. Since the compatible TMLE generates a second order term
$R_2$, it might be the case that for finite samples the second order term $R_2 + R_{2a}$ of the incompatible TMLE is larger.

**Case II: Updating the loss function with $\epsilon$.** The universal least favorable submodels are defined as above:

\[
\begin{align*}
\logit \tilde{Q}^2_{\epsilon} &= \logit \hat{Q}^2 - \epsilon H_2(g) \\
\logit \tilde{Q}^1_{\epsilon} &= \logit \hat{Q}^1 - \epsilon H_1(g)
\end{align*}
\]

Indeed, it has the following key property with respect to the loss function $L_{\tilde{Q}}(\bar{Q})$:

\[
\left. \frac{d}{dh} L_{\tilde{Q}^2}(\bar{Q}_{\epsilon + dh}) \right|_{h=0} = H_2(g)(Y - \bar{Q}^2_{\epsilon}) + H_1(g)(\bar{Q}^2_{\epsilon} - \bar{Q}^1_{\epsilon}) \\
\equiv D^*_2(\bar{Q}_{\epsilon}, g) + D^*_1(\bar{Q}_{\epsilon}, g).
\]

Let’s assume that we determined that the empirical risk $P_n L_{\tilde{Q}^2}(Q_{n, \epsilon})$ is decreasing at $\epsilon = 0$, so that we need to determine the desired $\epsilon_n > 0$. The solution $\epsilon_n$ is defined by the smallest $\epsilon > 0$ for which

\[
\left. \frac{d}{dh} P_n L_{\tilde{Q}^2_{n, \epsilon}}(Q_{n, \epsilon + dh}) \right|_{h=0},
\]

or, equivalently, the smallest $\epsilon > 0$ for which

\[
P_n D^*(Q_{n, \epsilon}, g_n) = 0,
\]

where

\[
Q_{n, \epsilon} = (\bar{Q}^2_{n, \epsilon}, \bar{Q}^1_{n, \epsilon}, \bar{Q}^0_{n, \epsilon} = P_n \bar{Q}^1_{\epsilon}).
\]

The TMLE of $\psi_0$ is now defined by $\Psi(Q_{n, \epsilon_n}) = P_n \bar{Q}^1_{n, \epsilon_n}$, and it solves $P_n D^*(Q_{n, \epsilon_n}, g_n) = 0$.

To obtain some insight in solving for $\epsilon_n$, note that it requires solving:

\[
0 = \frac{1}{n} \sum_{i=1}^{n} \{ \bar{Q}^1_{n, \epsilon}(L_i(0)) - P_n \bar{Q}^1_{n, \epsilon} \} \\
+ \frac{1}{n} \sum_{i=1}^{n} I(A_i(0) = d_0(L_i(0))) \frac{g_{A(0), n}(O_i)}{g_{A(0), n}(O_i)} (\bar{Q}^2_{n, \epsilon} - \bar{Q}^1_{n, \epsilon}) \\
+ \frac{1}{n} \sum_{i=1}^{n} I(\tilde{A}_i(1) = \tilde{d}(\tilde{L}_i(1))) \frac{g_{A(1), n}(O_i)}{g_{A(1), n}(O_i)} (Y_i - \bar{Q}^2_{n, \epsilon}).
\]

Since $\tilde{Q}^i_{n, \epsilon}$ is a simple adjustment of the initial estimator $\bar{Q}^i_n$ (just adding $\epsilon H_j(g_n)$ on the logistic scale), $j = 2, 1$, this estimator is very easy to compute.
This implementation of TMLE is quite different from the current implementation of TMLE that carries out the TMLE update step by fitting a separate $\epsilon$ for updating each $\bar{Q}^j$, and sequentially carrying out these updates starting with $\bar{Q}^2$ and going backwards. In addition, it involves first targeting the regression before defining it as outcome for the next regression backwards in time. For example, if there are many treatment nodes over time, then the TMLE presented above still only relies on fitting a single $\epsilon$, while the current TMLE would require iteratively fitting many $\epsilon_j$’s. We suspect that the TMLE proposed here could be significantly more stable in finite samples.

C Universal canonical one-dimensional submodel for targeted minimum loss-based estimation of a multidimensional target parameter when the loss function depends on nuisance parameters

C.1 A universal canonical one-dimensional submodel

Let’s now generalize this construction of a universal canonical submodel in the previous section to a parameter $Q$ whose loss-function depends on a nuisance parameter. As in the previous section we assume that $\Psi(P) = \Psi_1(Q(P)) \in \mathbb{R}^d$ for some target parameter $Q : \mathcal{M} \to Q(\mathcal{M})$ defined on the model and real valued function $\Psi_1 : Q(\mathcal{M}) \to \mathbb{R}^d$. Let $L_{\Gamma(P)}(Q|O)$ be a loss-function for $Q(P)$ in the sense that $Q(P) = \arg\min_{Q \in Q(M)} PL_{\Gamma(P)}(Q)$, where $\Gamma : \mathcal{M} \to \Gamma(\mathcal{M})$ is some nuisance parameter. Let $D^*(P) = D^*(Q(P), G(P))$ be the canonical gradient of $\Psi$ at $P$, where $G : \mathcal{M} \to G(\mathcal{M})$ is some nuisance parameter. We consider the case that the linear span of the components of the efficient influence curve $D^*(P)$ is in the tangent space of $Q$, so that a least favorable submodel does not need to fluctuate $G$: otherwise, one just includes $G$ in the definition of $Q$. One will have that $\Gamma(P)$ only depends on $P$ through $(Q(P), G(P))$, so that we will also use the notation $\Gamma(Q, G)$. Given $(Q, G)$, let $\{Q_{\delta}^{\text{lm}} : \epsilon\} \subset Q(M)$ be a local $d$ dimensional least favorable model w.r.t. loss function $L_{\Gamma(Q, G)}(Q)$ at $\delta = 0$ so that

$$\left.\frac{d}{d\delta} L_{\Gamma(Q, G)}(Q_{\delta}^{\text{lm}})\right|_{\epsilon=0} = D^*(Q, G).$$

The dependence of this submodel on $G$ is suppressed in this notation.

Consider the empirical risk $P_n L_{\Gamma(Q, G)}(Q_{\delta}^{\text{lm}})$, and note that its gradient at $\delta = 0$ equals $P_n D^*(Q, G)$. For a small number $dx$, we want to minimize the empirical risk over all $\delta$ with $\|\delta\| \leq dx$, and locally, this corresponds with maximizing its linear gradient approximation:

$$\delta \to (P_n D^*(Q, G))^\top \delta.$$
By the Cauchy-Schwarz inequality, it follows that this is maximized over $\delta$ with $\|\delta\| \leq dx$ by

$$\delta_n^*(Q, dx) = \frac{P_nD^*(Q, G)}{\|P_nD^*(Q, G)\|} dx \equiv \delta_n^*(Q)dx,$$

where we defined $\delta_n^*(Q) = P_nD^*(Q, G)/\|P_nD^*(Q, G)\|$. We can now define our update $Q_{dx} = Q_{\delta_n^*(Q, dx)}$. This process can now be iterated by applying the above with $Q$ replaced by $Q_{dx}$ and $\Gamma(Q, G)$ replaced by $\Gamma(Q_{dx}, G)$, resulting in an update $Q_{2dx}$, and in general $Q_{Kdx}$. So at the $k$-th step, we have

$$Q_{kdx} = Q_{\delta_n^*(Q_{(k-1)dx})dx},$$

where

$$\delta_n^*(Q_{(k-1)dx}) = \frac{P_nD^*(Q_{(k-1)dx}, G)}{\|P_nD^*(Q_{(k-1)dx}, G)\|.}

So this updating process is defined by the differential equation:

$$Q_{x+dx} = Q_{\delta_n^*(Q_{x})dx},$$

where $Q_{\delta_n^*(Q_{x})dx}$ is the local least favorable multidimensional submodel above but now through $Q_x$ instead of $Q$.

Assume that for some $\dot{L}_\Gamma(Q)(O)$, we have

$$\left. \frac{d}{dh} L'_{\Gamma_x}(Q_{x,h}) \right|_{h=0} = \dot{L}_\Gamma_x(Q_x) \left. \frac{d}{dh} Q_{\delta_n^*(Q_{x})dx} \right|_{h=0}, \quad (8)$$

where we used the notation $\Gamma_x = \Gamma(Q_x, G)$. Then,

$$\left. \frac{d}{dh} Q_{x,h} \right|_{h=0} = \frac{D^*(Q_x, G)}{L_{\Gamma_x}(Q_x)}.$$

Utilizing that the local least favorable model $h \rightarrow Q_{x,h}^{\text{lm}}$ is continuously twice differentiable with a score $D^*(Q_x, G)$ at $h = 0$, we obtain a second order Taylor expansion

$$Q_{x,\delta_n^*(Q_x)dx} = Q_x + \left. \frac{d}{dh} Q_{x,h}^{\text{lm}} \right|_{h=0} \delta_n^*(Q_x)dx + O((dx)^2)$$

$$= Q_x + \frac{D^*(Q_x, G)}{L_{\Gamma_x}(Q_x)} \delta_n^*(Q_x)dx + O((dx)^2).$$

This implies the following recursive analytic definition of the universal least favorable model through $Q$:

$$Q_x = Q + \int_0^\infty \frac{D^*(Q_x, G)^\top}{L_{\Gamma_x}(Q_x)} \delta_n^*(Q_x)dx. \quad (9)$$
Let’s now explicitly verify that this submodel defined by (9) indeed satisfies the desired condition that the one-step TMLE $Q_{\epsilon_n}$ with $\epsilon_n$ defined as the value closest to zero for which

$$\left. \frac{d}{dh} P_n L_{\Gamma}(Q_{\epsilon}, G) (Q_{\epsilon+h}) \right|_{h=0} = 0$$

solves $\| P_n D^*(Q_{\epsilon_n}, G) \| = 0$. Only assuming (8) it follows that

$$\left. \frac{d}{dh} P_n L_{\Gamma}(Q_{\epsilon}, G) \right|_{h=0} = \left. P_n \frac{d}{dh} L_{\Gamma}(Q_{\epsilon+h}) \right|_{h=0} = P_n L_{\Gamma}(Q_{\epsilon}) \frac{d}{d\epsilon} Q_{\epsilon}$$

$$= P_n L_{\Gamma}(Q_{\epsilon}) \frac{D^*(Q_{\epsilon}, G)}{L_{\Gamma}(Q_{\epsilon})} \delta_n^*(Q_{\epsilon})$$

$$= P_n D^*(Q_{\epsilon}, G) \delta_n^*(Q_{\epsilon})$$

$$= \left\{ P_n D^*(Q_{\epsilon}, G) \right\}^{\top} \left\| P_n D^*(Q_{\epsilon}, G) \right\|$$

$$= \left\| P_n D^*(Q_{\epsilon}, G) \right\| .$$

This proves that this submodel and the corresponding one-step TMLE (which updates the loss through $\Gamma_{\epsilon}$ when moving along $\epsilon$) indeed solves $\| P_n D^*(Q_{\epsilon_n}, G) \| = 0$.

In addition, under some regularity conditions, so that the above derivation in terms of the local least favorable submodel applies, it also follows that $Q_{\epsilon} \in Q(M)$. This proves the analogue of Theorem 5.

C.2 Example: One-step TMLE of parameters of marginal structural working model for multiple time-point interventions

In this subsection we develop a new one-step TMLE based on the universal canonical one-dimensional submodel, while the previous closed form TMLE developed in Petersen et al. (2013) was based on a local least favorable submodel with $d$-parameters at each time point.

Suppose that the observed data structure is $O = (L(0), A(0), L(1), A(1), Y) \sim P_0$, where $Y \in \{0, 1\}$ or continuous with $Y \in (0, 1)$. Let $V = f(L(0))$ be some potential baseline effect modifier of interest. Suppose that our statistical model $M$ only makes assumptions about $g_0 = (g_{0,A(0)}, g_{0,A(1)})$. Consider a set of dynamic treatment regimens $D$, and for a $d \in D$, let $E_d(Y_d \mid V)$ be the conditional mean of $Y_d$, given $V$, under the $G$-computation formula $p_0 = q_{L(0)} q_{L(1)} q_Y d_{A(0)} d_{A(1)}$ obtained by replacing $g_{0,A(0)}, g_{0,A(1)}$ in the factorization of the density $p_0$ of $P_0$ by the degenerate conditional distributions $d_{A(0)}$ and $d_{A(1)}$. Here $Y_d$ is the counterfactual marginal mean outcome under an intervention that sets treatment according to some rule, $d$, $Q_{L(0)}$ is the marginal distribution of $L(0)$, and $Q_{L(1)}, Q_Y$ are the conditional distributions of $L(1)$, given $A(0), L(0)$, and of $Y$, given $L(1), A(1)$, respectively,
where the overbar denotes the entire covariate history through time point 1, and \( q_{L(0)}, q_{L(1)}, q_Y \) are their respective densities. Given a working model \( \{m_\beta : \beta \in \mathbb{R}^d\} \) for \( E_0(Y_d \mid V) \), and weight function \( (d, V) \rightarrow h(d, V) \), the target parameter \( \Psi : \mathcal{M} \rightarrow \mathbb{R}^d \) is defined by

\[
\Psi(P) = \arg \min_{\psi} E_P \sum_{d \in D} h(d, V) L^F(m_\psi(d, V))(Y_d, V),
\]

where \( L^F(m)(Y_d, V) = -\{Y_d \log m(d, V) + (1 - Y_d) \log(1 - m(d, V))\} \) is the full-data log-likelihood loss function for \( E(Y_d \mid V) \). This can also be represented as:

\[
\Psi(P) = \arg \min_{\psi} E_P \sum_{d \in D} h(d, V) L^F(m_\psi(d, V))(E_P(Y_d \mid L(0)), V),
\]

i.e., where \( Y_d \) is replaced by \( E_P(Y_d \mid L(0)) \) in the loss function. By the sequential regression representation of \( E_P(Y_d \mid V) \) (Bang and Robins, 2005), it follows that \( \Psi(P) = \Psi_1(Q_{1L(0)}, \bar{Q}) \), where \( \bar{Q} = (\bar{Q}^1, \bar{Q}^2) = (\bar{Q}^{1,d}, \bar{Q}^{2,d} : d \in D) \), and

\[
\bar{Q}^{d,1}(\bar{L}(1)) = E_P(Y \mid \bar{L}(1), \bar{A}(1) = \bar{d}(\bar{L}(1))),
\]

\[
\bar{Q}^{d,0}(L(0)) = E_P(\bar{Q}^{d,1}(\bar{L}(1)) \mid L(0), A(0) = d_{A(0)}(L(0))).
\]

We assume that \( \text{Logit}m_\beta(d, V) = \beta^\top \phi(d, V) \) for some vector of basis functions \( \phi = (\phi_1, \ldots, \phi_d) \). The efficient influence curve of \( \Psi \) at \( P \) is given by \( D^*(Q, G) = c(\Psi(Q))^{-1}D(Q, G) \), where

\[
D(Q, G)(O) = \sum_{d \in D} h_1(d, V)(\bar{Q}^{d,1}(d, L(0)) - m_\psi(Q)(d, V))
\]

\[
+ \sum_{d \in D} h_1(d, V) \frac{I(A(0) = d_{A(0)}(L(0)))}{g_{A(0)}(O)} (\bar{Q}^{d,1}(\bar{L}(1)) - \bar{Q}^{d,0}(L(0)))
\]

\[
+ \sum_{d \in D} h_1(d, V) \frac{I(\bar{A}(1) = \bar{d}(\bar{L}(1)))}{g_{A(0)}g_{A(1)}(O)} (Y - \bar{Q}^{d,1}(\bar{L}(1)))
\]

\[
\equiv D^0(Q) + D^1(\bar{Q}, G) + D^2(\bar{Q}, G),
\]

and

\[
h_1(d, V) = h(d, V)\phi(d, V)
\]

\[
c(\psi) = E_P \sum_{d \in D} h(d, V)\phi(d, V)\phi(d, V)^\top m_\psi(1 - m_\psi)(d, V).
\]

Consider the following loss functions for the components of \( \bar{Q} = (\bar{Q}^1, \bar{Q}^2) = (\bar{Q}^{d,1}, \bar{Q}^{d,2} : d \in D) \):

\[
L_2(\bar{Q}^2) = - \sum_{d \in D} I(\bar{A}(1) = \bar{d}(\bar{L}(1)))\{Y \log \bar{Q}^{2,d} + (1 - Y) \log(1 - \bar{Q}^{2,d})\}
\]

\[
L_1, \bar{Q}^2(\bar{Q}^1) = - \sum_{d \in D} I(A(0) = d_{0}(L(0)))\{\bar{Q}^{2,d} \log \bar{Q}^{1,d} + (1 - \bar{Q}^{2,d}) \log(1 - \bar{Q}^{1,d})\}.
\]
We will estimate the marginal distribution of $L(0)$ in the representation (10) of $\Psi(P)$ with the empirical distribution. As a consequence, we only need a TMLE of $\bar{Q}_0^2$ and $\bar{Q}_0^1$.

We can now define the sum loss function for $\bar{Q}$:

$$L_{\bar{Q}^2}(\bar{Q}) \equiv L_2(\bar{Q}^2) + L_{1,\bar{Q}^2}(\bar{Q}^1),$$

which is indexed by nuisance parameter $\bar{Q}^2$ itself. For notational convenience, let’s denote this nuisance parameter with $\Gamma(\bar{Q}) = \bar{Q}^2$. Then, this loss-function can also be represented as:

$$L_\gamma(\bar{Q}^2, \bar{Q}^1) = L_2(\bar{Q}^2) + L_{1,\gamma}(\bar{Q}^1),$$

Indeed, we have $L_{\gamma_0}(\bar{Q})$ is a valid loss function for $\bar{Q}_0 = \arg\min_Q P_0 L_{\gamma_0}(Q)$.

Consider the following local least favorable $d$-dimensional submodel through $\bar{Q} = (\bar{Q}^2, \bar{Q}^1)$:

$$\text{Logit} \bar{Q}^2, d, lfm = \text{Logit} \bar{Q}^2 - \delta^\top H_2(d,g),$$

$$\text{Logit} \bar{Q}^1, d, lfm = \text{Logit} \bar{Q}^1 - \delta^\top H_1(d,g),$$

where $H_2(d,g) = h_1(d,V) I(\bar{A}(1) = \bar{d}(\bar{L}(1)))/(g_{A(0)} g_{A(1)}(O))$, and $H_1(d,g) = h_1(d,V) I(A(0) = d_0(L(0)))/(g_{A(0)}(O))$. Indeed, we have

$$\frac{d}{d\delta} L_{\bar{Q}^2}(\bar{Q}_{\delta}^2(\bar{Q})) \bigg|_{\delta=0} = \bar{D}(\bar{Q}, G) \equiv D^1(\bar{Q}, G) + D^2(\bar{Q}, G).$$

Let $dx$ be given. Define the $d$-dimensional vector

$$\delta^*_n(\bar{Q}) = \frac{P_n \bar{D}(\bar{Q}, G)}{\| P_n \bar{D}(\bar{Q}, G) \|}.$$

We can now define our first update $\bar{Q}_{dx} = \bar{Q}_{\delta^*_n(\bar{Q})dx}$. In other words, for each $d \in D$, we have

$$\text{Logit} \bar{Q}^2, d, dx = \text{Logit} Q^2, d - \delta^*_n(\bar{Q}) dx H_2(d,g),$$

$$\text{Logit} \bar{Q}^1, d, dx = \text{Logit} Q^1, d - \delta^*_n(\bar{Q}) dx H_1(d,g).$$

We can now iterate this updating process. So let

$$\delta^*_n(\bar{Q}_{dx}) = \frac{P_n \bar{D}(\bar{Q}_{dx}, G)}{\| P_n \bar{D}(\bar{Q}_{dx}, G) \|}.$$
We can now define our second update $Q_{2dx} = \tilde{Q}_{dx}^{dfm}(Q_{dx})dx$. In other words, for each $d \in D$, we have
\[
\text{Logit} \tilde{Q}^{2,d}_{2dx} = \text{Logit} \tilde{Q}^{2,d}_{dx} - \delta_n^*(\tilde{Q}_{dx})dx H_2(d, g) \\
= \text{Logit} \tilde{Q}^{2,d}_{dx} - \delta_n^*(\tilde{Q})dx H_2(d, g) - \delta_n^*(\tilde{Q}_{dx})dx H_2(d, g) \\
= \text{Logit} \tilde{Q}^{d,d}_d - \sum_{k=0}^{1} \delta_n^*(\tilde{Q}_{kd})dx H_2(d, g)
\]
\[
\text{Logit} \tilde{Q}^{1,d}_{2dx} = \text{Logit} \tilde{Q}^{1,d}_{dx} - \sum_{k=0}^{1} \delta_n^*(\tilde{Q}_{kd})dx H_1(d, g).
\]

So, by iteration it follows that the desired universal one-dimensional submodel is given by
\[
\tilde{Q}_\epsilon = \tilde{Q}_{dx}^{dfm}(\tilde{Q}_\epsilon dx).
\]

Let’s define the $d$-dimensional vector
\[
P_n \bar{D}(\tilde{Q}_\epsilon, G) = \int_0^\epsilon \frac{P_n \bar{D}(\tilde{Q}_x, G)}{\| P_n \bar{D}(\tilde{Q}_x, G) \|} dx.
\]

Then the desired universal canonical one-dimensional submodel can be presented as follows: for each $d \in D$, and $\epsilon > 0$,
\[
\text{Logit} \tilde{Q}^{2,d}_\epsilon = \text{Logit} \tilde{Q}^{2,d}_dx - C_n(\epsilon)^\top H_2(d, g) \\
\text{Logit} \tilde{Q}^{1,d}_\epsilon = \text{Logit} \tilde{Q}^{1,d}_dx - C_n(\epsilon)^\top H_1(d, g).
\]

Let’s now explicitly verify that the one-step TMLE indeed solves $P_n \bar{D}(\tilde{Q}_\epsilon, G) = 0$ at $\epsilon_n > 0$ defined by the smallest $\epsilon > 0$ for which $\frac{d}{dh} P_n \bar{L}(\tilde{Q}_{\epsilon+\epsilon_n}) \bigg|_{h=0} = 0$. Here we use that the empirical risk decreases in $\epsilon$. Let
\[
C'_n(\epsilon) = \frac{d}{d\epsilon} C_n(\epsilon) = \frac{P_n \bar{D}(\tilde{Q}_\epsilon, G)}{\| P_n \bar{D}(\tilde{Q}_\epsilon, G) \|}.
\]

We have
\[
\frac{d}{dh} P_n \bar{L}(\tilde{Q}_{\epsilon+\epsilon_n}) \bigg|_{h=0} = P_n \sum_{d \in D} h_1(d, V)C'_n(\epsilon)^\top H_1(d, g)(\tilde{Q}^{1,d} - \tilde{Q}^{0,d}) + P_n \sum_{d \in D} h_2(d, V)C'_n(\epsilon)^\top H_2(d, g)(Y - \tilde{Q}^{2,d}) \\
= \left( \frac{P_n \bar{D}(\tilde{Q}_\epsilon, G)}{\| P_n \bar{D}(\tilde{Q}_\epsilon, G) \|} \right)^\top P_n \bar{D}(\tilde{Q}_\epsilon, G) \\
= \| P_n \bar{D}(\tilde{Q}_\epsilon, G) \|.
\]

This proves that it is indeed a submodel that satisfies the desired condition so that the TMLE of $\Psi(P_0)$ is given by the one-step TMLE $\Psi_1(Q_{L(0),n}, \tilde{Q}_{\epsilon_n})$. 

20
References


