Bayesian Hierarchical Temporal Modeling and Targeted Learning with Application to Reproductive Health

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June 27, 2022

UMassAmherst

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- Which interventions are effective in improving health outcomes?
  - Chapter 3: methods for estimating the effect of interventions on family planning outcomes.

Outline

1. Chapter 1: Temporal models for demographic and global health outcomes in multiple populations
2. Chapter 2: Flexible Modeling of Transition Processes with B-splines
3. Chapter 3: Automatic Bayesian Targeted Likelihood Estimation of Marginal Structural Models

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- Comparing across models can be difficult.
- **This chapter:** an overarching model class called *Temporal Models for Multiple Populations* (TMMPs).

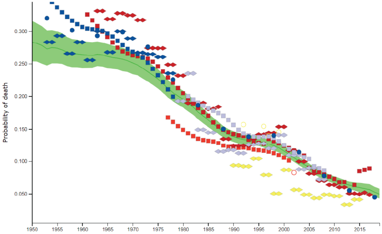
Background

- Published in *International Statistical Review*:
    - Susmann, Herbert, Monica Alexander, and Leontine Alkema. "Temporal Models for Demographic and Global Health Outcomes in Multiple Populations: Introducing a New Framework to Review and Standardise Documentation of Model Assumptions and Facilitate Model Comparison." *International Statistical Review* (2022).

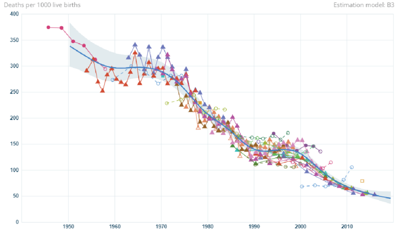
Under-5 Mortality Rate (U5MR) Models

Under-five Mortality Rate Estimates in Senegal, 1950-2019

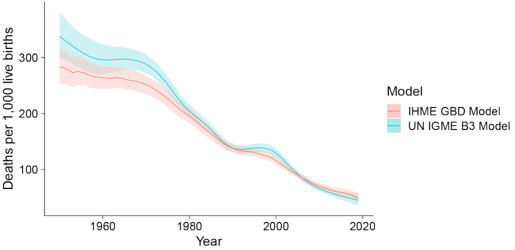
(A) IHME Data and Estimates



(B) UN IGME Data and Estimates



(C) Comparison of Estimates



The model for GPR was

$$\mu_t = f(t) + S_t$$

$$f(t) \sim GP(M, C)$$

Where

μ_t is the true $\log_{10}(5q0)$ at time t

$f(t)$ is the baseline mortality risk

S_t is excess mortality due to fatal discontinuities estimated independently of $f(t)$

M is the mean for the Gaussian process

C is the covariance for the Gaussian process

Spatiotemporal smoothing

The spatiotemporal stage smooths the residuals between the predicted time series of 5q0 and the adjusted raw data over time and across countries in the same GBD region. The predicted time series for this smoother was obtained from the equation below; no random effects or survey type fixed effects were included.

$$predicted_5 m_{0,cy} = \exp[\beta_1 * \log(LDI_{cy}) + \beta_2 * education_{cy} + \alpha_{intercept}] + \beta_3 * HIV_{cy}$$

We first found the residuals between the predicted time series, above, and the adjusted points. We then applied a combination of smoothing functions to these residuals. For each country-year, we weighted all

A glance at the UN IGME model...

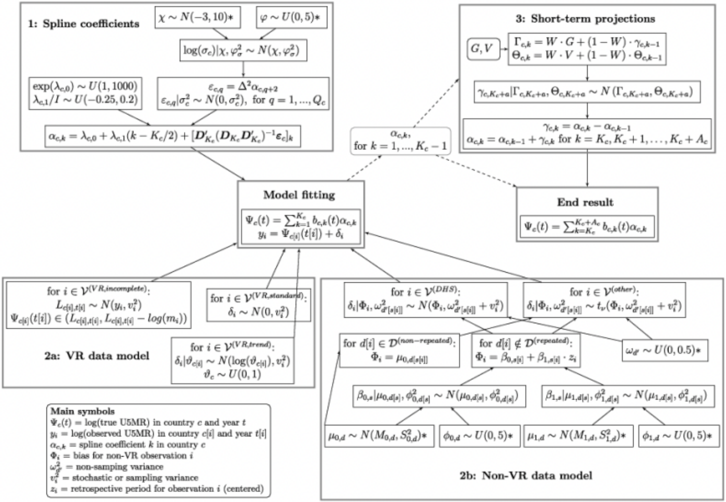


FIG. 3. *Model overview. This chart summarizes the model used to estimate the U5MR. In the center is the description of the "Model fitting" part, where $\Psi_c(t)$ refers to the true U5MR on the log-scale, which was modeled with a Bayesian penalized spline regression model, as summarized in block 1 (see Section 3.1). The models for the error term δ_i for observed log(U5MR) are described separately for VR and non-VR data in blocks 2a and 2b (see Section 3.2). Short-term projections are summarized in block 3 (see Section 3.3).*

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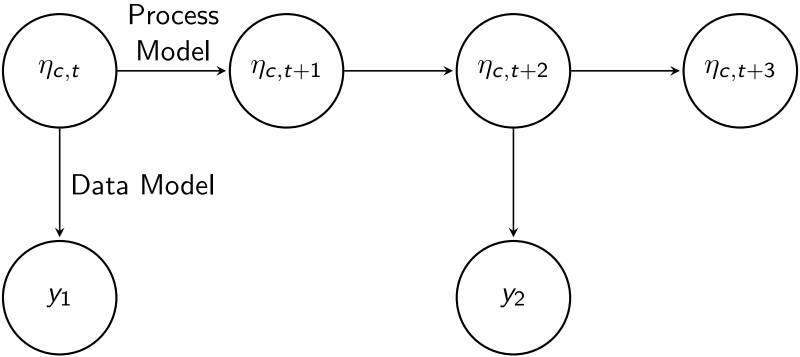
- *Data model* describes relationship between y_i and $\eta_{c[i],t[i]}$.

Modeling Framework



Data Model Examples

Examples of data models:

- Normal:

$$y_i | \eta_{c[i],t[i]}, \sigma_i^2 \sim N(\eta_{c[i],t[i]}, \sigma_i^2)$$

  where $y_i \in \mathbb{R}$ and σ_i^2 is the sampling variance.

- Binomial:

$$y_i | \eta_{c[i],t[i]} \sim \mathrm{Binom}(n_i, \eta_{c[i],t[i]})$$

  where y_i, n_i are integers.

Process Model

$$g_1(\eta_{c,t}) = \underbrace{g_2(X_{c,t}, \boldsymbol{\beta}_c)}_{\text{covariate}} + \underbrace{g_3(t, \eta_{c,s\neq t}, \boldsymbol{\alpha}_c)}_{\text{systematic}} + \underbrace{a_{c,t}}_{\text{offset}} + \underbrace{\epsilon_{c,t}}_{\text{smoothing}}$$

Covariate component

$$g_1(\eta_{c,t}) = \underbrace{g_2(X_{c,t}, \beta_c)}_{\text{covariate}} + \underbrace{g_3(t, \eta_{c,s \neq t}, \alpha_c)}_{\text{systematic}} + \underbrace{a_{c,t}}_{\text{offset}} + \underbrace{\epsilon_{c,t}}_{\text{smoothing}}$$

- Regression function for incorporating covariates.

Systematic component

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- Parametric function for modeling systematic temporal trends.

Offset

$$g_1(\eta_{c,t}) = \underbrace{g_2(X_{c,t}, \beta_c)}_{\text{covariate}} + \underbrace{g_3(t, \eta_{c,s\neq t}, \alpha_c)}_{\text{systematic}} + \underbrace{a_{c,t}}_{\text{offset}} + \underbrace{\epsilon_{c,t}}_{\text{smoothing}}$$

- The offset term incorporates external information, for example from a separate modeling step.

Smoothing Component

$$g_1(\eta_{c,t}) = \underbrace{g_2(X_{c,t}, \beta_c)}_{\text{covariate}} + \underbrace{g_3(t, \eta_{c,s\neq t}, \alpha_c)}_{\text{systematic}} + \underbrace{a_{c,t}}_{\text{offset}} + \underbrace{\epsilon_{c,t}}_{\text{smoothing}}$$

- The smoothing component allows data-driven deviations from the other components, while still enforcing smoothness.
- Many choices B-splines, Gaussian processes, AR(p), RW(p), spatio-temporal smoothing, ...

Hierarchical Modeling

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- Example: hierarchical model with one level of hierarchy for a country-specific parameter θ_c:

$$\theta_c \mid \theta_w, \sigma_\theta \sim N(\theta_w, \sigma_\theta^2)$$

Comparing the example models...

	GBD	**B3**
$\eta_{c,t}$	U5MR	U5MR
$g_1(\cdot)$	$\log_{10}$	log
Process model formula	$g_1(\eta_{c,t}) = g_2(\boldsymbol{X}_{c,t}, \boldsymbol{\beta}) + a_{c,t} + \epsilon_{c,t}$	$g_1(\eta_{c,t}) = g_3(t, \boldsymbol{\alpha}_c) + \epsilon_{c,t}$
Covariate Component		
$g_2(\cdot)$	non-linear regression formula (Equation 1.4.1)	·
Covariates	LDI, EDU, HIV	·
Systematic Component		
$g_3(\cdot)$	·	$\alpha_{c,0} + \alpha_{c,1}(t - t_c^*)$, with $t_c^* \approx$ middle of observation period
$\boldsymbol{\alpha}_c$	·	intercept $\alpha_{c,0}$ and slope $\alpha_{c,1}$
Offsets		
$a_{c,t}$	offsets obtained from smoothed residuals of a mixed-effects regression model fit	·
Stochastic smoothing Component $\boldsymbol{\epsilon_c} = \boldsymbol{B}_c \boldsymbol{\delta}_c$		
$\boldsymbol{B}$	$\boldsymbol{B} = \boldsymbol{I}$	$B_{c,k}$ = cubic B-splines, knots every 2.5 years
$s(t_1, t_2)$	Matérn	indep. $s(t_1, t_2) = \sigma^2_{\tau,c} 1(t_1 = t_2)$
r	0	2
$\mathcal{K}_{d,c}$	·	$\mathcal{K}_{0,c} = \{k^*\}$, $\mathcal{K}_{1,c} = \{2, \cdots, K_c\}$

Contributions

- A model class, Temporal Models for Multiple Populations (TMMPs), that encompasses many existing demographic and health models.
    - Model class makes a clear distinction between the *process model* and the *data model*.
    - Process model is split into building blocks: covariates, systematic trends, offsets, and smoothing components.
- Detailed description of six existing models using TMMP notation, and templates provided for documenting additional models as TMMPs.

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- **This chapter:** We propose a new type of model, called *B-spline Transition Models*, for flexibly estimating indicators that follow transitions.

Case Study

- Modern Contraceptive Prevalence Rate (mCPR) for married or in-union women: proportion of married or in-union women of reproductive age using (or with partner using) a modern contraceptive method.

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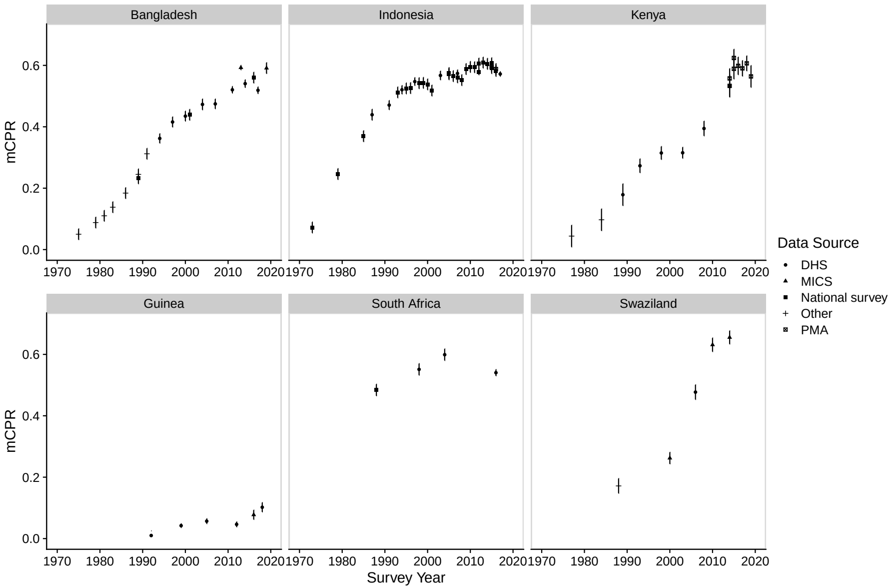
- Goal: estimate and project mCPR in countries from 1970-2030.
- Dataset aggregated by United Nations Population Division (UNPD) from surveys conducted by governments or international organizations.

Case Study



Bangladesh
Indonesia
Kenya
Guinea
South Africa
Swaziland
mCPR
0.0
0.2
0.4
0.6
1970
1980
1990
2000
2010
2020
Survey Year
Data Source
DHS
MICS
National survey
Other
PMA

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- The systematic component has the following form:

$$g_3(t, \boldsymbol{\eta}_{c,s\neq t}, \boldsymbol{\alpha}_c) = \begin{cases} \Omega_c, & t = t_c^*, \\ g_1(\eta_{c,t-1}) + f(\eta_{c,t-1}, P_c, \beta_c), & t > t_c^*, \\ g_1(\eta_{c,t+1}) - f(\eta_{c,t+1}, P_c, \beta_c), & t < t_c^*, \end{cases}$$

where $\boldsymbol{\alpha}_c = \{\Omega_c, P_c, \beta_c\}$.

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- The function f is called the *transition function*.

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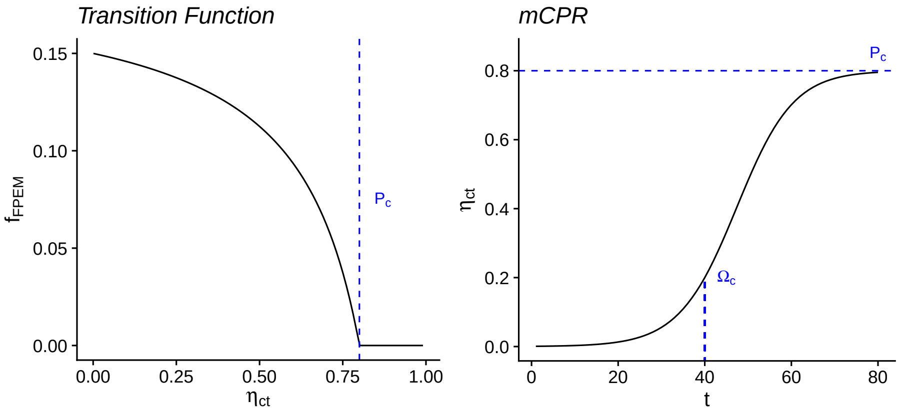
- The FPEM transition function was chosen such that mCPR follows a logistic growth curve:

$$f(\eta_{c,t-1}, P_c, \boldsymbol{\beta}_c) = \begin{cases} \frac{(\eta_{c,t-1} - P_c)\omega_c}{P_c(\eta_{c,t-1} - 1)}, & \eta_{c,t-1} < P_c, \\ 0, & \text{otherwise.} \end{cases}$$

where $\boldsymbol{\beta}_c = \{\omega_c\}$, and the parameters can be interpreted as

- ω_c: rate parameter,
- P_c: asymptote parameter.

FPEM Example



B-spline Transition Model

- **Our contribution:** estimate the transition function f while making weaker functional form assumptions.
- Approach: estimate f using B-splines.

B-spline Example

B-spline Transition Model

- Define a transition function f_b as:

$$f_b(\eta_{c,t}, P_c, \beta_c) = \sum_{j=1}^{J} \underbrace{h_j(\beta_{c,j})}_{\text{coefficient}} \cdot \underbrace{B_j(\eta_{c,t}/P_c)}_{\text{basis function}},$$

where P_c is an asymptote parameter.

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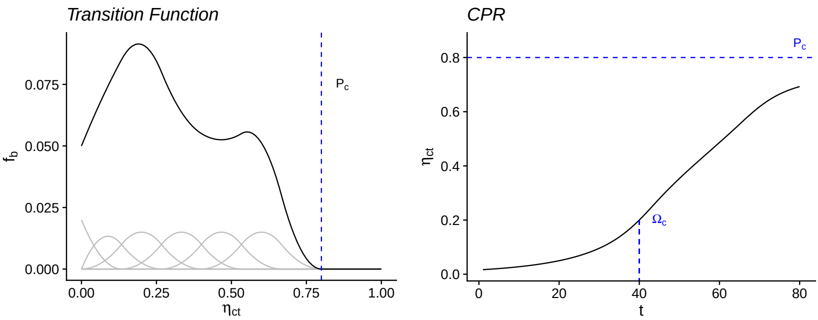
  where P_c is an asymptote parameter.
- Flexibility of f_b can be tuned through the spline degree and number and positioning of knots.

Example B-spline Transition Function



Sharing information on shape of transition function

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- Spline coefficients $\beta_{c,j}$ are nested within sub-regions, regions, and world.
- Hierarchical model on the spline coefficients $\beta_{c,j}$ for $j = 1, \ldots, J$:

$$\beta_{c,j} \mid \beta^{(s)}_{s[c],j}, \sigma^{(c)}_{\beta,j} \sim N\left(\beta^{(s)}_{s[c],j}, \left(\sigma^{(c)}_{\beta,j}\right)^2\right),$$

$$\beta^{(s)}_{s,j} \mid \beta^{(r)}_{r[s],j}, \sigma^{(s)}_{\beta,j} \sim N\left(\beta^{(r)}_{r[s],j}, \left(\sigma^{(s)}_{\beta,j}\right)^2\right),$$

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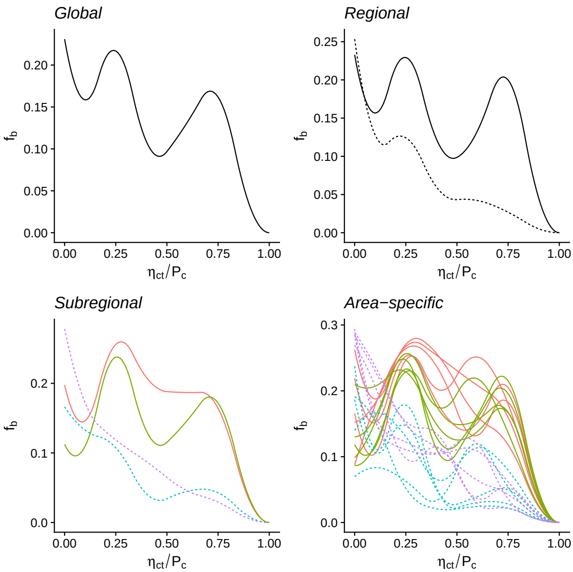


Smoothing component

- Recall the process model has two components:

$$g_1(\eta_{c,t}) = \underbrace{g_3(t, \boldsymbol{\eta}_{c,s\neq t}, \boldsymbol{\alpha}_c)}_{\text{systematic}} + \underbrace{\epsilon_{c,t}}_{\text{smoothing}} .$$

- Smoothing component: AR(1) process of the form

$$\epsilon_{c,t} | \epsilon_{c,t-1}, \tau, \rho \sim N(\rho * \epsilon_{c,t-1}, \tau^2)$$

Smoothing component

Data Model: connection to observed data

- Let y_i, $i = 1, \ldots, n$ be the observed mCPR for country $c[i]$ and year $y[i]$ from data source $d[i]$.
- For each observation we have an estimate s_i^2 of the sampling error.
- We also expect each data source to have additional non-sampling error $\sigma^2_{d[i]}$.
- Truncated normal data model:

$$y_i | \eta_{c[i],t[i]}, \sigma^2_{d[i]} \sim N_{(0,1)}\left(\eta_{c[i],t[i]}, s_i^2 + \sigma^2_{d[i]}\right).$$

Computation

- Model fit with full Bayesian inference
- Implementation in Stan, including a fast B-spline algorithm in C++

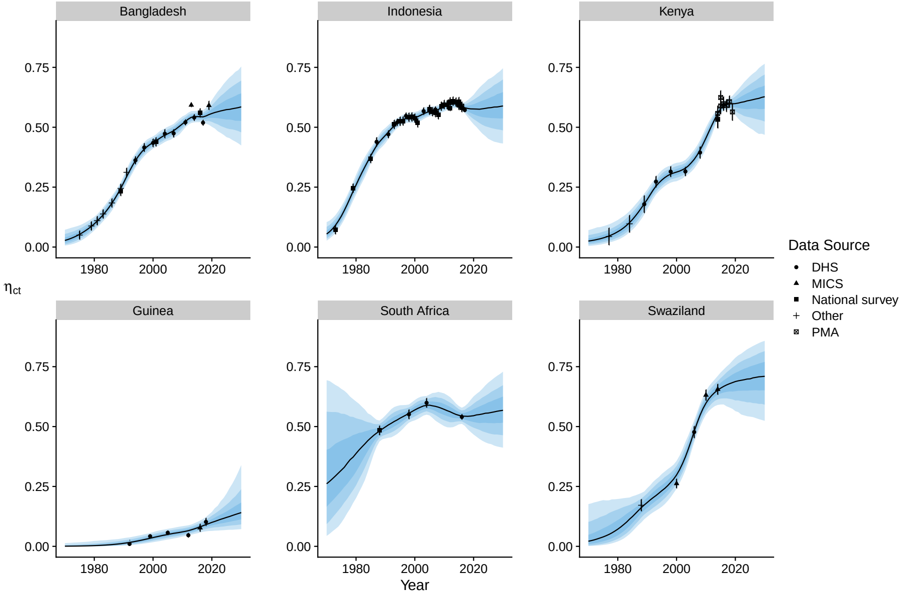
Choosing a spline specification

Validation exercise: hold out all observations after a cutoff year $L = 2010$.

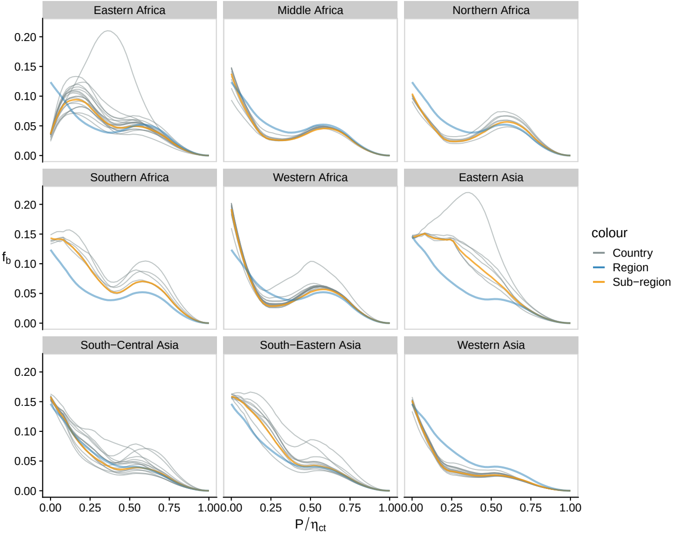
	95% UI				Error	
	% Below	% Included	% Above	CI Width $\times 100$	ME $\times 100$	MAE $\times 100$
Model Check 2 ($L = 2010$), $n = 133$						
B-spline ($d = 2,\ K = 5$)	3.76%	94.7%	1.5%	32.0	-1.670	4.64
B-spline ($d = 2,\ K = 7$)	6.02%	91.7%	2.26%	31.5	-1.260	4.68
B-spline ($d = 3,\ K = 5$)	3.76%	94.7%	1.5%	32.4	-1.630	4.48
B-spline ($d = 3,\ K = 7$)	3.76%	94%	2.26%	31.6	-0.965	4.57

95% UI: 95% uncertainty interval. ME: median error. MAE: median absolute error. Measures calculated using the last held-out observation within each area.

Illustrative Fits from B-spline Model



Trends can be seen in regional and subregional transition functions

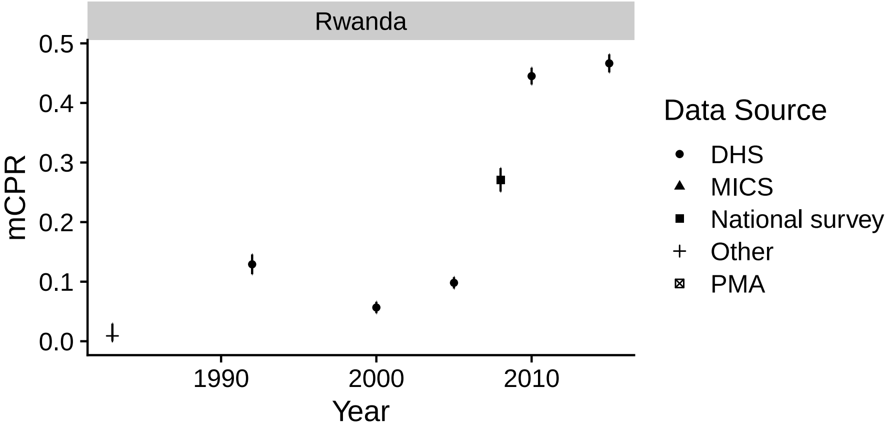


Comparison to a logistic type model

Validation exercise: hold out all observations after a cutoff year $L = 2010$.

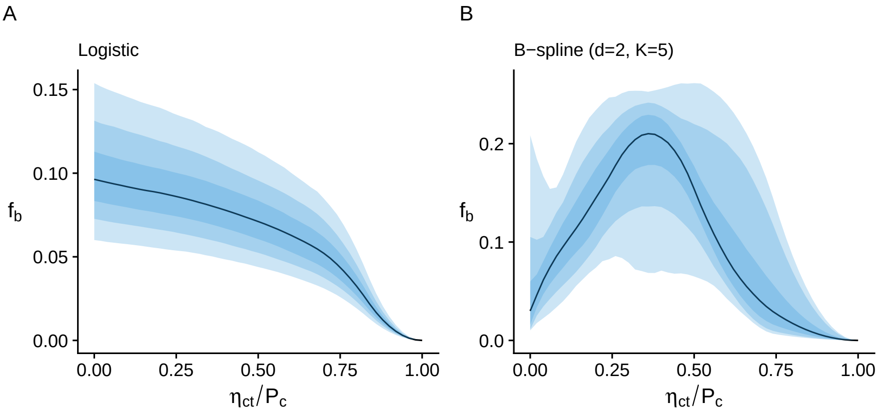
	95% UI				Error	
	% Below	% Included	% Above	CI Width $\times 100$	ME $\times 100$	MAE $\times 100$
Model Check 2 ($L = 2010$), $n = 133$						
B-spline ($d = 2,\ K = 5$)	3.76%	94.7%	1.5%	32.0	-1.670	4.64
Logistic	6.77%	92.5%	0.752%	32.7	-2.850	4.82

95% UI: 95% uncertainty interval. ME: median error. MAE: median absolute error.
Measures calculated using the last held-out observation within each area.


Rwanda
mCPR
0.0
0.1
0.2
0.3
0.4
0.5
1990
2000
2010
Year
Data Source
DHS
MICS
National survey
Other
PMA

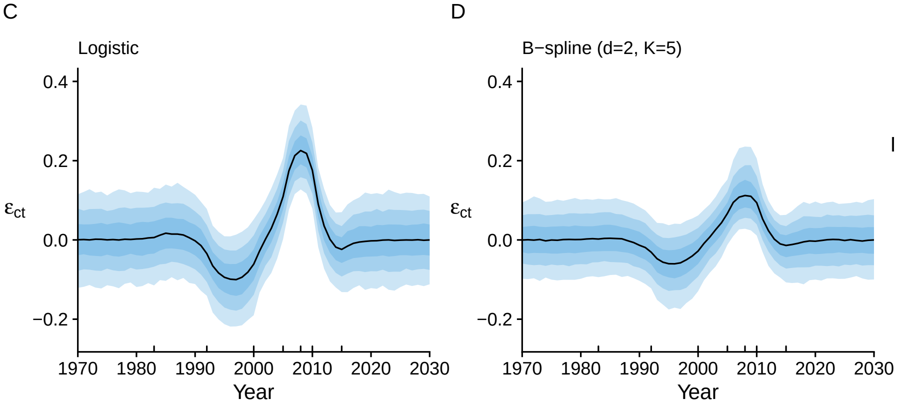
Detailed Example: Rwanda

Transition Functions



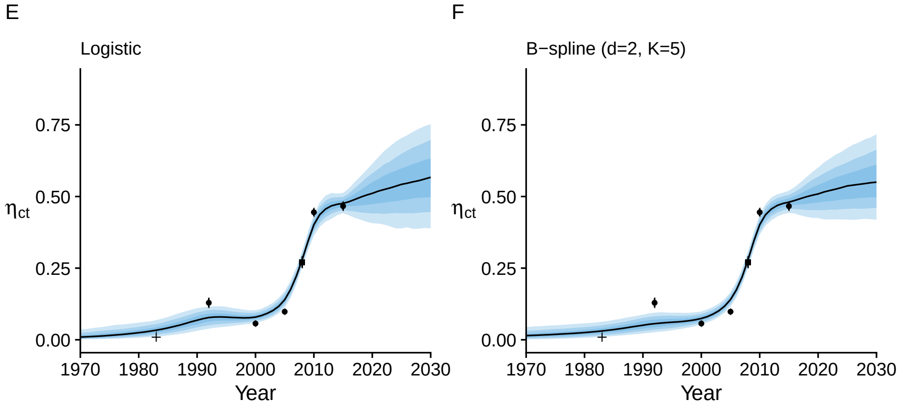
Detailed Example: Rwanda

Smoothing component



Detailed Example: Rwanda

Modern Contraceptive Prevalence Rate



Contributions

- Subclass of *Transition Models* for indicators that follow transitions.
- B-spline Transition Model: flexible modelling approach based on B-splines.
- Generated estimations and projections of mCPR in countries from 1970-2030.
- Found systematically different transitions in countries across regions.
- Flexible model framework that can be easily extended to new settings and use cases.

Background

- Which interventions are effective in improving health outcomes?
- *Marginal Structural Models* provide one a way to summarize how the effect of an intervention on an outcome changes within subgroups.
- **This Chapter**: We introduce a novel targeted Bayesian estimator for the parameter of a Marginal Structural Model in a general setting.

Motivating Example

- Randomized field experiment conducted in Lilongwe, Malawi, to investigate effect of family planning intervention on contraceptive use (Karra et al., 2020, 2022).

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- Outcome: contraceptive use two years after intervention.

Scientific question

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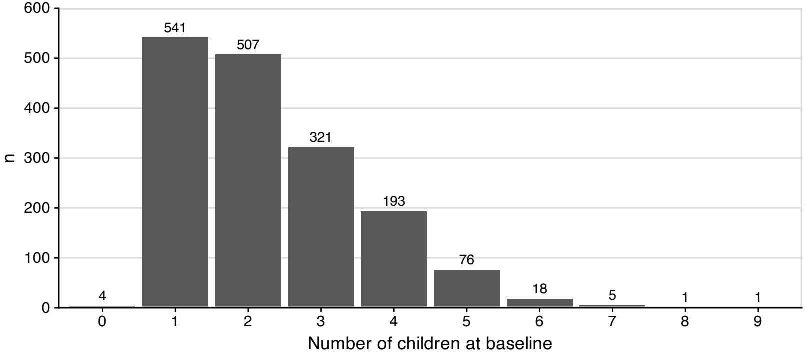
- Marginal distribution of number of children:



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- For each participant, we have:
  - X: set of 11 covariates measured at baseline, including number of children X_c;
  - A: indicator of randomization into intervention group;
  - Y: indicator of contraceptive use at endline.
- Let $O_1, \ldots, O_n$ be n i.i.d. draws of the generic variable $O = (X, A, Y)$ from the law P_0 of the experiment.

Conditional Average Treatment Effect

- *Conditional Average Treatment Effect* (CATE):

$$\begin{aligned}\Psi_P^{\mathrm{CATE}}(x) &= \mathbb{E}_P[Y \mid A=1, X=x] - \mathbb{E}_P[Y \mid A=0, X=x], \\ &= \bar{Q}_P^{(1)}(x) - \bar{Q}_P^{(0)}(x)\end{aligned}$$

- Causally identifiable under "standard causal assumptions" (consistency, positivity, no unmeasured confounders).

An example of a Marginal Structural Model

- Approach: summarize the relationship between potential *treatment effect modifiers* (X_c) and conditional treatment effects ($\Psi_P^{\mathrm{CATE}}(X)$) using a user-supplied working model.
- For instance, let $B(P) \in \mathbb{R}^2$ be the solution to the following optimisation problem:

$$B(P) = \arg\min_{\boldsymbol{\beta} \in \mathbb{R}^2} \mathbb{E}_P \left[\left(\Psi_P^{\mathrm{CATE}}(X) - (1, X_c)\beta \right)^2 \right].$$

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$$B(P) = \underset{\boldsymbol{\beta} \in \mathbb{R}^2}{\arg\min}\, \mathbb{E}_P \left[\left(\underbrace{\boxed{\Psi_P^{\mathrm{CATE}}(X)}}_{\text{conditional average treatment effect}} - (1, X_c)\boldsymbol{\beta} \right)^2 \right]$$

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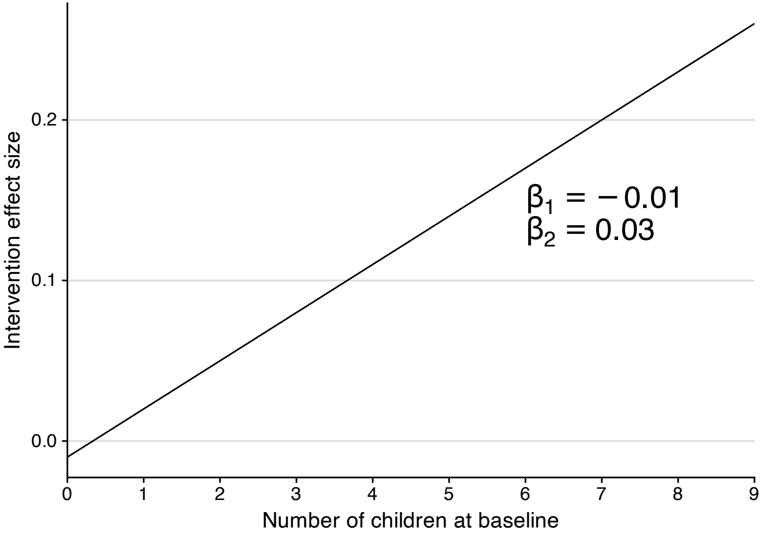
defined in terms of P

What a plot of the results will look like



General Setting for MSMs

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- For the motivating example:
    - $O = (Y, A, X)$, $Z = (Y, A)$, $X = X$.
    - $\Psi_P(X) = \mathbb{E}_P[Y \mid A = 1, X] - \mathbb{E}_P[Y \mid A = 0, X]$, the CATE
      $= \bar{Q}_P^{(1)}(X) - \bar{Q}_P^{(0)}(X)$.

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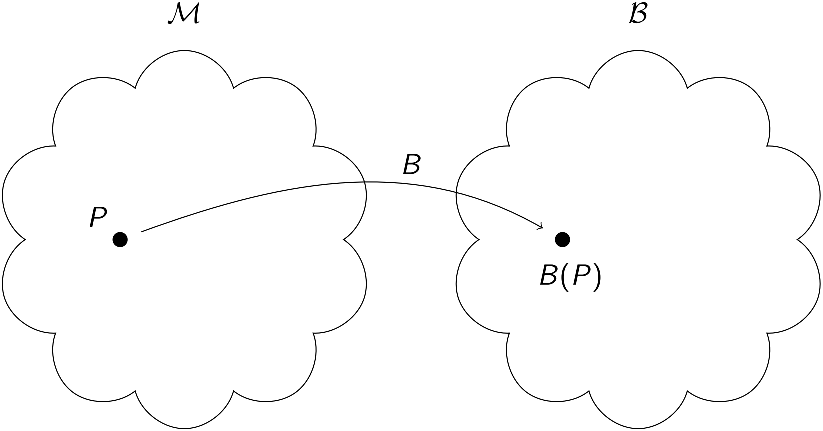
- **Our contribution:** a general framework for MSMs.

Marginal Structural Models



Danger! Infinite dimensional space visualized in two dimensions!

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- The semi-parametric efficiency bound for estimating β_0 is given by $\mathrm{var}_{P_0}(D^*(P_0)(O))$

Efficient Influence Function of $B(P)$

Our contribution: we derived the EIF for the MSM parameter $P \mapsto B(P)$ in a general setting.

Theorem (Efficient Influence Function)

(Simplified) The target functional $P \mapsto B(P)$ is pathwise differentiable at every $P \in \mathcal{M}$, with an efficient influence function $D^*(P)$ given by

$$D^*(P)(O) = M^{-1}\left[D_1^*(P)(O) + D_2^*(P)(X)\right],$$

where $D_1^*(P), D_2^*(P) \in L_0^2(P)$ are given by

$$D_1^*(P)(O) = \nabla \dot{L}(\Psi_P(X), B(P))(X) \times \Delta^*(P)(O),$$
$$D_2^*(P)(X) = \dot{L}(\Psi_P(X), B(P))(X),$$

and the normalizing matrix M is given by

$$M = -\mathbb{E}_P\left[\ddot{L}_m(\Psi_P(X), B(P))(X)\right].$$

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For our motivating example:

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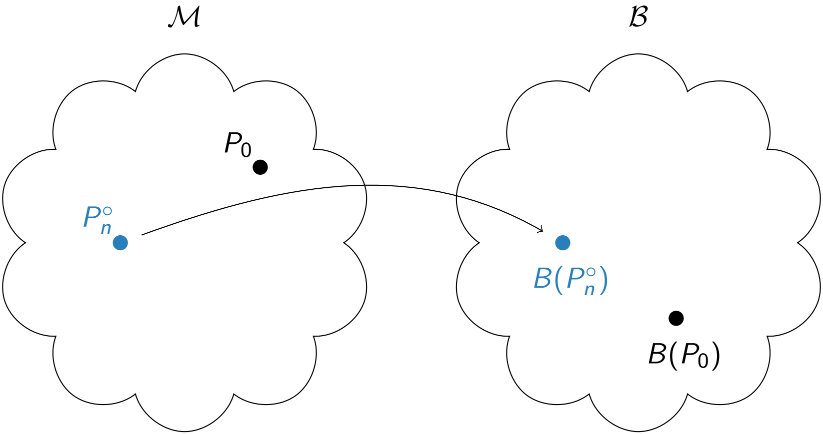
- The plug-in estimator is biased!

Plug-in estimation is biased



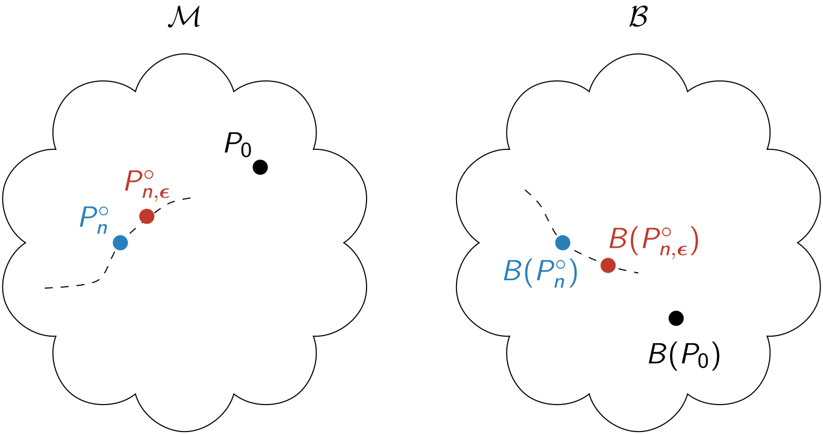
Targeted Minimum Loss-Based Estimation

- Targeted Minimum Loss-Based Estimation (TMLE): plug-in estimator of the form

$$\hat{\boldsymbol{\beta}}^{TMLE} = B(P_n^\circ(\boldsymbol{\epsilon}_n^*))$$

where $\{P_n^\circ(\boldsymbol{\epsilon}) : \boldsymbol{\epsilon} \in \mathbb{R}^p\} \subset \mathcal{M}$ is a *fluctuation* of an initial estimator P_n° of the pieces of P_0 relevant to $\boldsymbol{\beta}$, and $\boldsymbol{\epsilon}_n^*$ is chosen by minimising the empirical risk induced by a well-chosen loss function $\mathcal{L}$.

TMLE: update initial estimate in direction of truth



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- Core idea: some choices of TMLE loss function $\mathcal{L}$ can be interpreted as defining a likelihood for the data O conditional on the parameter ϵ under the fluctuation submodel.
- We can then use Bayesian inference to estimate ϵ! (Diaz et al., 2011; Díaz et al., 2020)

Bayesian TMLE

- Basic application of Bayes rule: posterior distribution of ϵ is given by

$$\Pi_{\epsilon}(\epsilon \mid O_1, \ldots, O_n) \propto \pi_{\epsilon}(\epsilon) \prod_{i=1}^{n} p_n^{\circ}(O_i \mid \epsilon)$$

where π_{ϵ} is a prior distribution for ϵ and $p_n^{\circ}(O \mid \epsilon)$ is the likelihood of O under $P_n^{\circ}(\epsilon)$.

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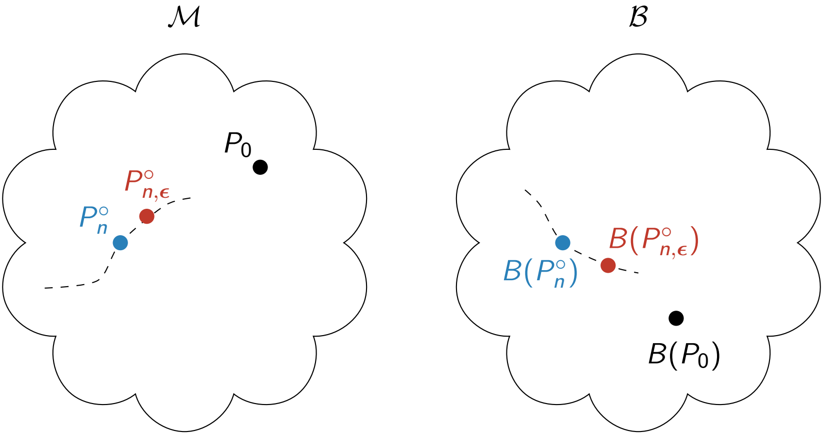
- Once we have a posterior distribution for ϵ we can map it to a posterior distribution for β.

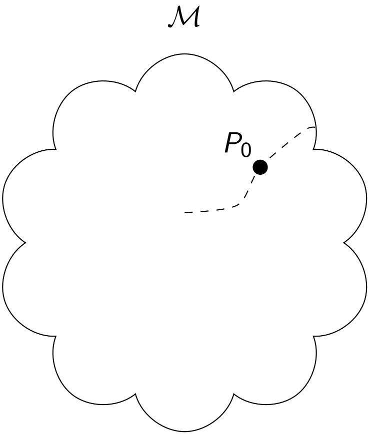
Bayesian TMLE

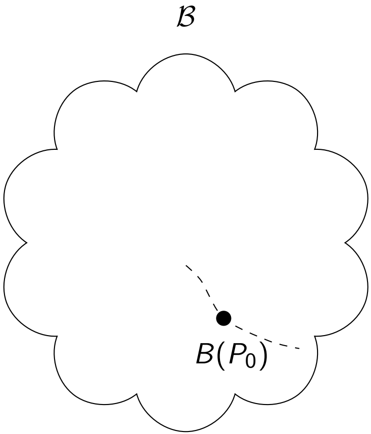


Bernstein von-Mises

- Desired result: the posterior distribution for β converges to a normal distribution centered on the frequentist TMLE with variance given by the variance of the efficient influence function.
- **Our contribution:** We prove an *oracular* version that provides conditions under which the posterior distribution based on fluctuation of P_0 will converge to the optimal distribution.

Bayesian TMLE





Bernstein von-Mises

- Let $p_n^0(O \mid \epsilon)$ be the likelihood of the submodel fluctuating P_0.
- Key conditions:
  - The gradient satisfies

$$\left.\frac{\partial}{\partial \boldsymbol{\epsilon}} \log p_n^0(O|\boldsymbol{\epsilon})\right|_{\boldsymbol{\epsilon}=0} = D^*(P_0)(O).$$

  - The Hessian satisfies

$$P_0\left[\left.\frac{\partial^2}{\partial \boldsymbol{\epsilon}^2} \log p_n^0(O|\boldsymbol{\epsilon})\right|_{\boldsymbol{\epsilon}=0}\right] = P_0[D^*(P_0)D^*(P_0)^\top].$$

Bernstein von-Mises

Theorem (Oracular Bernstein von-Mises)

(Simplified) Let $N(\mu, \Sigma)$ denote the multivariate normal distribution with mean vector μ and covariance matrix Σ. Then, under certain assumptions,

$$\|\Pi_{\boldsymbol{\beta}}^{0}(\cdot \mid O_1, \ldots, O_n) - N\left(\Delta_n^0, P_0[D^*(P_0)D^*(P_0)^\top]\right)\|_1 = o_P(1)$$

where

$$\Delta_n^0 = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} P_0[\lambda^*(P_0)]^{-1} D^*(P_0)(O_i). \tag{1}$$

Universal Algorithm

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Universal Algorithm

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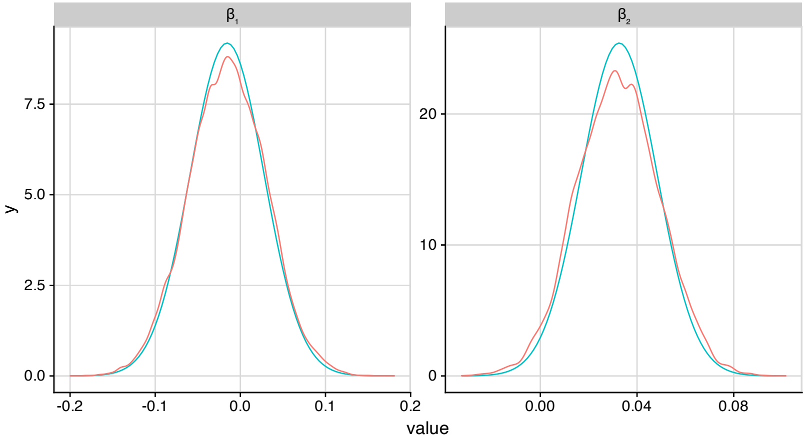
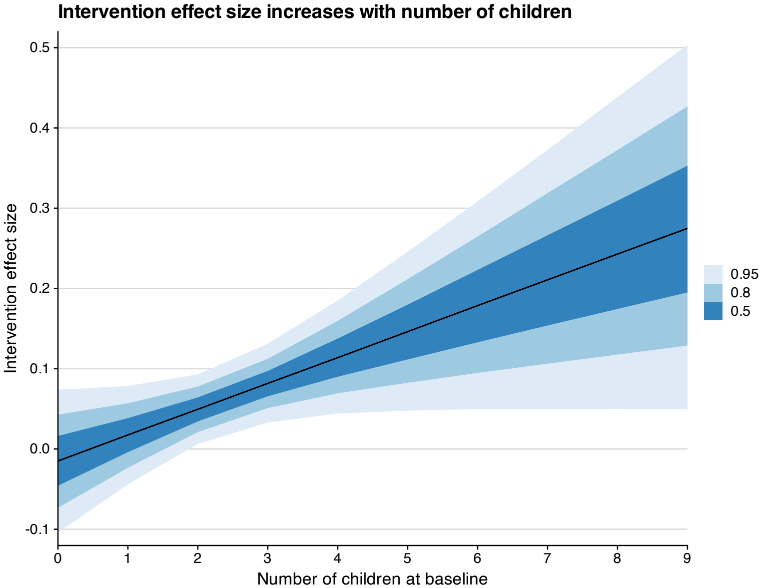
- We could anticipate this and choose several working models and loss functions and hand-code the required derivatives. But what if a user wants to use something we haven't implemented?
- An alternative is to use *automatic differentiation* to compute the required derivatives automatically.
- **Our contribution:** We implemented a universal algorithm in Julia that uses auto-differentiation to automatically adapt the fluctuation model and efficient influence function to arbitrary well-chosen working models and loss functions.

Motivating Example: Results



Posterior density (red) and a normal density (blue) centered on the frequentist MLE with variance given by the estimated variance of the efficient influence function.

Motivating Example: Results



Contributions

- Definition of MSMs in a general setting.
- Derivation of efficient influence function for general MSM parameters.
- Novel Bayesian TMLE for MSMs.
- Universal algorithm implemented in Julia using autodifferentiation.
- Application to estimate relationship between effect of intervention on contraceptive use with number of children as an effect modifier in a randomized field experiment.

Future Work

- Strengthening Bernstein von-Mises result
- Developing methods for choosing between multiple working models.

Summary

Where is improvement needed?

- Chapter 1: Temporal Models for Multiple Populations
- Chapter 2: B-spline Transition Model

Which interventions are effective in improving health outcomes?

- Chapter 3: Bayesian targeted learning for Marginal Structural Models

Acknowledgements

Questions?

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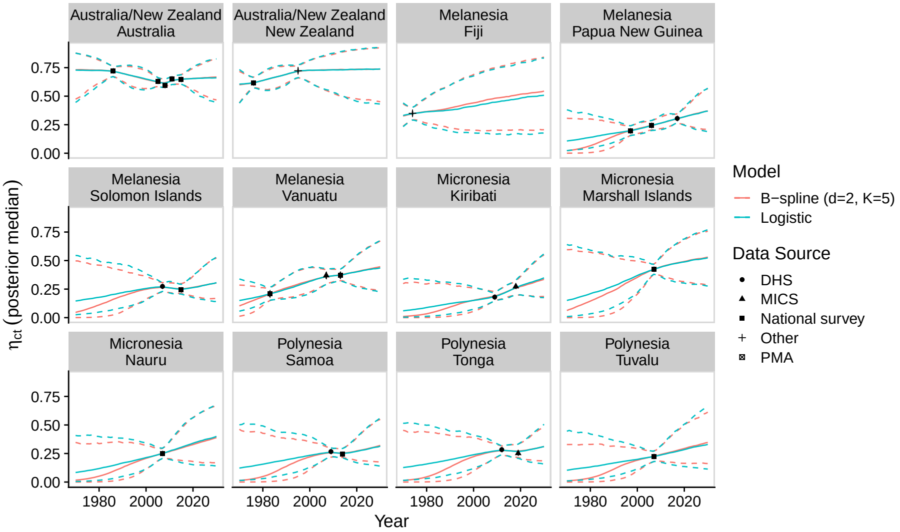
Difference between B-splines and logistic model



Estimation

- Let's analyze the properties of the plug-in estimator.
- We can write

$$\begin{aligned}\sqrt{n}\,(\beta_n^\circ - \beta_0) = & \underbrace{\sqrt{n}(P_n - P_0)D^*(P_0)}_{\rightsquigarrow N(0, P_0 D^*(P_0)^2)} \\ & - \underbrace{\sqrt{n}P_n D^*(P_n^\circ)}_{\text{bias term}} \\ & + \underbrace{\sqrt{n}(P_n - P_0)(D^*(P_n^\circ) - D^*(P_0)) + o_p(1)}_{\text{negligible}}.\end{aligned}$$

- We want to construct an estimator with a bias term of zero.

A glimpse at how TMLE works

- The fluctuation and loss function are chosen to satisfy (among other things) a key property:

$$D^*(P_n^\circ) \in \mathrm{Span}\left(\frac{\partial}{\partial \epsilon} \mathcal{L}\left(P_n^\circ(\epsilon)\right) \Big|_{\epsilon=0} \right).$$

- Importantly, the TMLE solves the EIF of the target parameter:

$$\mathbb{E}_{P_n}[D^*(P_n^\circ(\epsilon_n^*))(O)] = 0.$$

- Under certain conditions, $\hat{\beta}^{TMLE}$ is asymptotically normal and efficient.

Blueprint for fluctuation model

How do we choose the form of the fluctuation model $P_n^\circ(\epsilon)$? **Our contribution:** a blueprint for the fluctuation model.

TMLE Blueprint. The following choice of loss functions and fluctuation model satisfy the conditions (L1), (L2), and (M1).

- For any $P \in \mathcal{M}$ with corresponding ψ_P, $\bar{Q}_P = \{\bar{Q}_P^{(1)}, \dots, \bar{Q}_P^{(J)}\}$, Q_P, and η_P, define the parametric fluctuation model as

$$\bar{Q}_{P,\epsilon}^{(1)}(O) = \bar{Q}_P^{(1)}(O) + H_1(O)\boldsymbol{\epsilon}^\top \nabla \dot{L}(\psi_P(X), B(P))(X),$$
$$\vdots$$
$$\bar{Q}_{P,\epsilon}^{(J)}(O) = \bar{Q}_P^{(J)}(O) + H_J(O)\boldsymbol{\epsilon}^\top \nabla \dot{L}(\psi_P(X), B(P))(X),$$
$$Q_{P,\epsilon}(X) = C \exp\left(\boldsymbol{\epsilon}^\top \dot{L}(\psi_P(X), B(P))(X)\right) Q_P(X).$$

- Choose $\mathcal{L}_j$ and H_j for $j = 1, \dots, J$ such that

$$\sum_{j=1}^{J} \dot{\mathcal{L}}_j(\bar{Q}_P^{(j)}(O), O) H_j(O) = \Delta^*(P)(O).$$

Back to the motivating example

- First, we need to find the parts of P relevant to B and D^*.
- Recall the definition of $B(P)$ and Ψ_P^{CATE}:

$$
\begin{aligned}
B(P) &= \arg\min_{\beta \in \mathcal{B}} \mathbb{E}_P \left[\Psi_P^{\mathrm{CATE}}(X) - (1, X)\beta\right] \\
\Psi_P^{\mathrm{CATE}}(x) &= \bar{Q}_P^{(1)}(x) - \bar{Q}_P^{(0)}(x) \\
&= \mathbb{E}_P[Y \mid A = 1, X = x] - \mathbb{E}_P[Y \mid A = 0, X = x]
\end{aligned}
$$

- In addition, $D^*(P)$ depends on $g_P(a, x) = P(A = a | X = x)$.
- The relevant parts of P are therefore Q_P (the marginal distribution of X), $\bar{Q}_P^{(1)}$, $\bar{Q}_P^{(0)}$, and g_P.

Back to the motivating example

- Suppose we have initial estimators of each part of P_0 relevant to B and D^*.
    - To estimate Q_{P_0}, the marginal distribution of X under P_0, we use the empirical distribution of X, which we call Q_n°.
    - To estimate $\bar{Q}_{P_0}^{(0)}$, $\bar{Q}_{P_0}^{(1)}$, and g_{P_0}, we use estimators $\bar{Q}_n^{\circ,(0)}$, $\bar{Q}_n^{\circ,(1)}$, and g_n°.

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- Let $P_n^\circ \in \mathcal{M}$ be any law such that its relevant features coincide with $\{Q_n^\circ, \bar{Q}_n^{\circ,(0)}, \bar{Q}_n^{\circ,(1)}, g_n^\circ\}$.

Back to the motivating example

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- Now we need to build a fluctuation submodel of each of the parts of P relevant to B.
- Fluctuation indexed by $\boldsymbol{\epsilon} \in \mathbb{R}^p$:

$$\bar{Q}_{n,\boldsymbol{\epsilon}}^{\circ,(1)}(x) = \bar{Q}_n^{\circ,(1)}(x) + \frac{1}{g_P^\circ(1,x)}\boldsymbol{\epsilon}^\top(1,X)^\top$$

$$\bar{Q}_{n,\boldsymbol{\epsilon}}^{\circ,(0)}(x) = \bar{Q}_n^{\circ,(0)}(x) - \frac{1}{g_P^\circ(0,x)}\boldsymbol{\epsilon}^\top(1,X)^\top$$

$$Q_{n,\boldsymbol{\epsilon}}^\circ(x) \propto \exp(\boldsymbol{\epsilon}^\top D_{2,\mathrm{CATE}}^*(P_n^\circ)(x))Q_n^\circ(x)$$

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$$\bar{Q}_{n,\boldsymbol{\epsilon}}^{\circ,(0)}(x) = \bar{Q}_{n}^{\circ,(0)}(x) - \frac{1}{g_P^{\circ}(0,x)}\boldsymbol{\epsilon}^{\top}(1,X)^{\top}$$
$$Q_{n,\boldsymbol{\epsilon}}^{\circ}(x) \propto \exp(\boldsymbol{\epsilon}^{\top} D_{2,\mathrm{CATE}}^{*}(P_n^{\circ})(x)) Q_n^{\circ}(x)$$

- Negative log-likelihood loss function:

$$\mathcal{L}(\bar{Q}_{n,\boldsymbol{\epsilon}}^{\circ,(0)}, \bar{Q}_{n,\boldsymbol{\epsilon}}^{\circ,(1)}, Q_{n,\boldsymbol{\epsilon}}^{\circ}, O) = \left(Y - \bar{Q}_{n,\boldsymbol{\epsilon}}^{\circ,(A)}\right)^2 - \log Q_{n,\boldsymbol{\epsilon}}^{\circ}(X).$$