Using State Space Models for Longitudinal Neuropsychological Outcomes

Zach Baucom

Introduction

- Zach Baucom, 4th year Biostatistics PhD student at Boston University.
- Working with Professor Yorghos Tripodis PhD.
  - Data and Biostatistics Director of the Boston University Alzheimer's Disease Center
- Interested in modeling subject level cognitive decline over time/cognitive trajectories.

Dementia is a Problem

- According to the World Health Organization dementia effects around 50 million people in the world today
    - 60-70% of those due to Alzheimer's disease (AD)
- We want to create a model that can be used to,
    - Illuminate how and why dementia progresses.
    - Assist in early disease diagnosis.
    - Determine intervention effectiveness.

Motivating Data

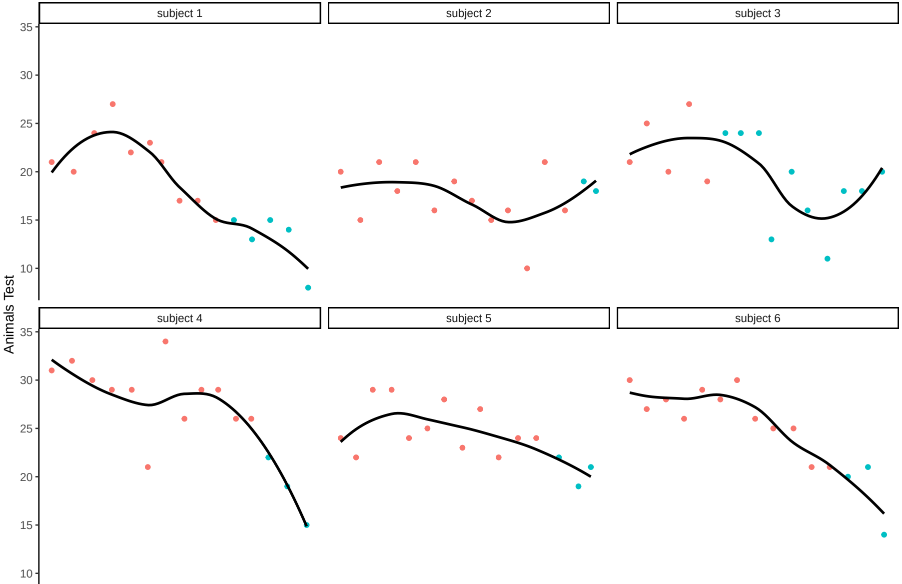
- Data collected by the National Alzheimer's Coordinating Center (NACC).
  - Established by the National Institute of Aging in 1990.
  - Centralizes neuropsychological data from 34 different research facilities.
  - Neuropsychological data include a number of cognitive tests repeated over time.

Model of Interest

- Studying the cognitive trajectory among those who transitioned from cognitively normal to MCI or Dementia during follow-up.
  - Interested in the effect of the APOE e4 allele on cognition.
  - 1,643 subjects in the analysis with a median of 6 visits.

$$\text{Animals} \sim (1 + \text{I}\{\text{Transitioned to MCI or Dementia}\} + \text{APOE} + \text{Sex} + \text{APOE*Sex} + \text{Race} + \text{Age} + \text{Education}) * \text{Time}$$

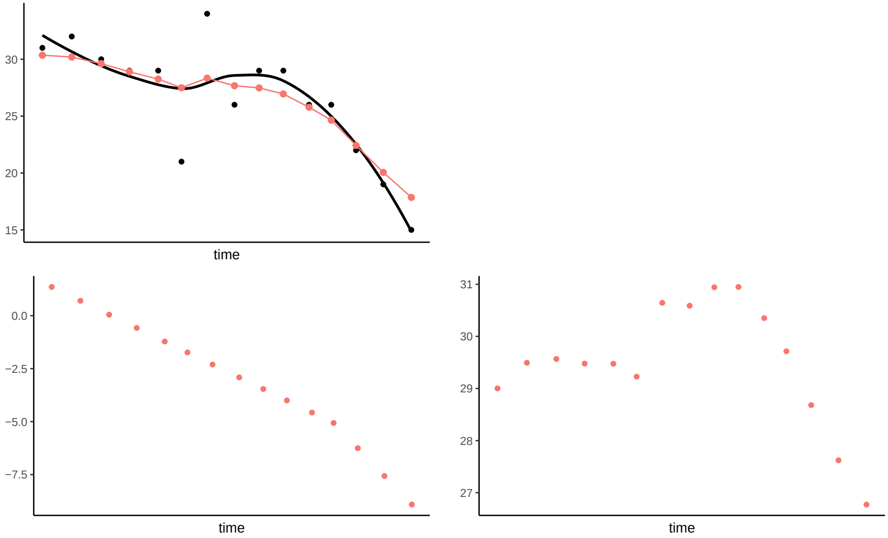
Data Characteristics



We Want a Model That...

- Captures general trajectory.
- Has the subject specific heterogeneity shown by the non-parametric method.
- We are able to interpret and make inference on effects of interest.

Welcome to the State Space Model



State Space Model Introduction

- State Space Models have been primarily used for time series data with a large number of time points and only a small number of chains observed.
- We are working to apply these models to a small number of time points and a large number of subjects.
  - Small t and large n are typically what we see in observational data.
- We wish to show that the State Space Model can be more acomodating than the commonly used linear mixed effect models (LMEM)(Laird and Ware, 1983; Diggle, Liang and Zeger, 1994).

Computation Consideration

- State space models can be computationally intensive.
- We will compare different state space model estimation methods to find the best balance of computational efficiency and accuracy.
    - State space model in matrix form.
    - Partitioned state space model.
    - Bayesian state space model.

State Space Model

A general linear state space model can be denoted as:

$$
\begin{aligned}
y_t &= F_t \mu_t + v_t \\
\mu_t &= G_t \mu_{t-1} + w_t
\end{aligned}
$$

where at time t,

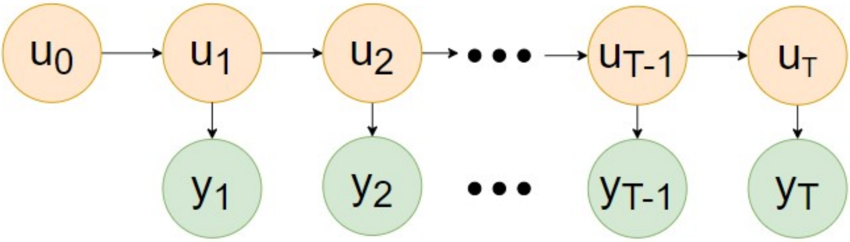
- y_t is the an $n \times 1$ observation vector.
- μ_t is the $q \times 1$ latent state vector, where q is the number of latent states.
- F_t is the $n \times q$ observation matrix.
- G_t is the $q \times q$ state transition matrix.

We assume v_t and w_t are independent identically distributed with distributions $v_t \sim N(0, V)$ and $w_t \sim N(0, W)$ respectively (Harvey, 1990; Durbin and Koopman, 2012) .

State Space Model Illustration

General Model:

$$y_t = F_t \mu_t + v_t$$
$$\mu_t = G_t \mu_{t-1} + w_t$$



Proposed Model

We wish to model the data according to a specific SSM, the Local Linear Trend Model (LLT),

$$y_{it} = \alpha_{it} + x_{it}^T \beta_t + \varepsilon_t$$

$$\mu_{it} = \begin{bmatrix} \alpha_{it} \\ \beta_t \end{bmatrix} = \begin{bmatrix} \alpha_{i(t-1)} \\ \beta_{(t-1)} \end{bmatrix} + \begin{bmatrix} \eta_{it} \\ 0_{p\times 1} \end{bmatrix}$$

Where $\alpha_0 \sim N(a_0, P_0)$, $\beta_0 \sim N(\beta, 0)$, $\varepsilon_{it} \sim N(0, \sigma_\varepsilon^2)$, and $\eta_{it} \sim N(0, \sigma_\eta^2)$.

- y_t is an $n \times 1$ observation vector where n indicates the number of subjects.
- α_t is an $n \times 1$ latent state vector.
  - Variation in α_t over time creates a dynamic moving average auto-correlation between observations y_t.
- X_t is an $n \times p$ matrix of time varying covariates (can be $X_t = t * X$ where X are baseline covarties).

What is α_t

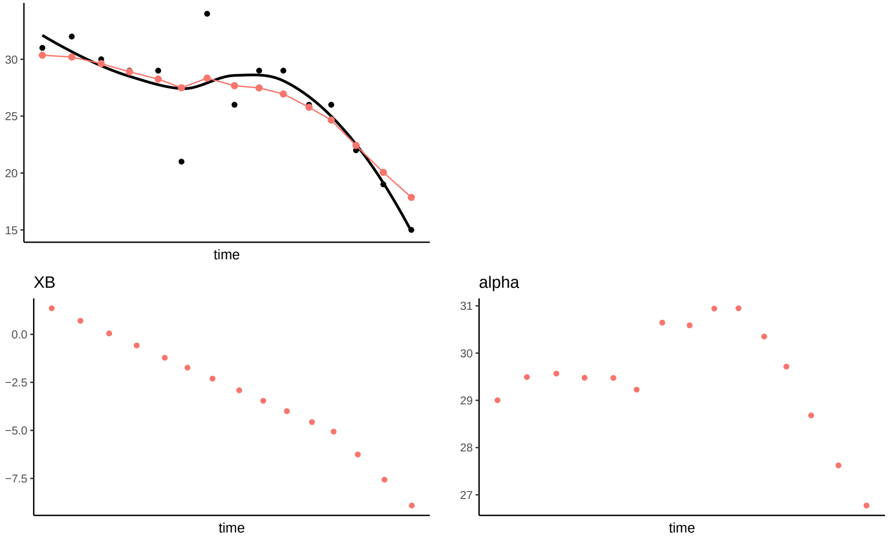
Consider the model,

$$y_{it} = \alpha_{it} + x_{it}^T \beta_t + \varepsilon_t$$
$$\mu_{it} = \begin{bmatrix} \alpha_{it} \\ \beta_t \end{bmatrix} = \begin{bmatrix} \alpha_{i(t-1)} \\ \beta_{(t-1)} \end{bmatrix} + \begin{bmatrix} \eta_{it} \\ 0_{p\times 1} \end{bmatrix}$$

We can think of α_t as the underlying cognitive state not accounted for by covariates X_t. The α_t is there to capture unobserved effects on the outcome.

Notice $\alpha_t|\alpha_{t-1} \sim N(\alpha_{t-1}, \sigma_\eta^2)$. This means our next underlying cognitive state will be centered at the previous underlying cognitive state.

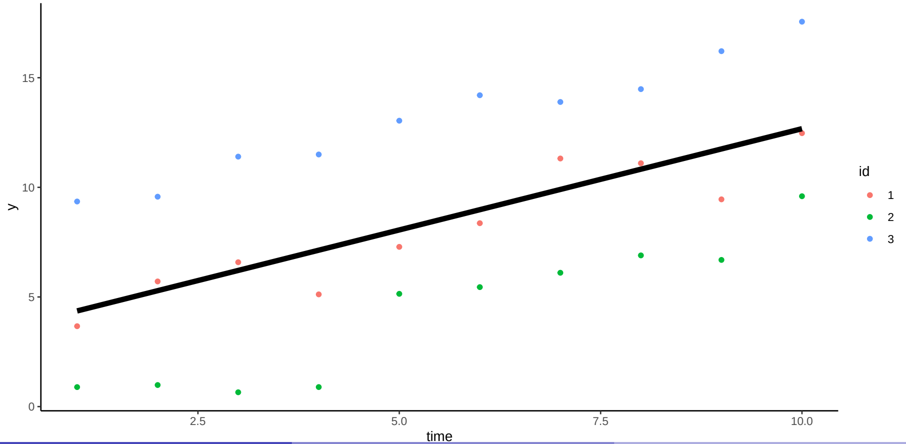
Revisited Plot



LME with Random Intercept

Consider the model: $y_{it} = b_{i0} + t * \beta + \epsilon_{it}$ where $b_{i0} \sim iid\ N(0, \sigma_b^2)$ and $\epsilon_{it} \sim iid\ N(0, \sigma^2)$.

Let $\beta = 1$, $\sigma_b^2 = 10$, and $\sigma^2 = 1$.



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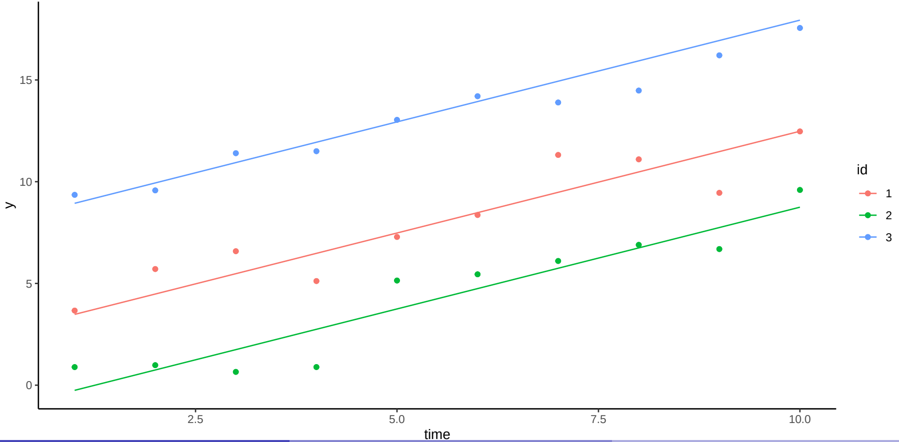
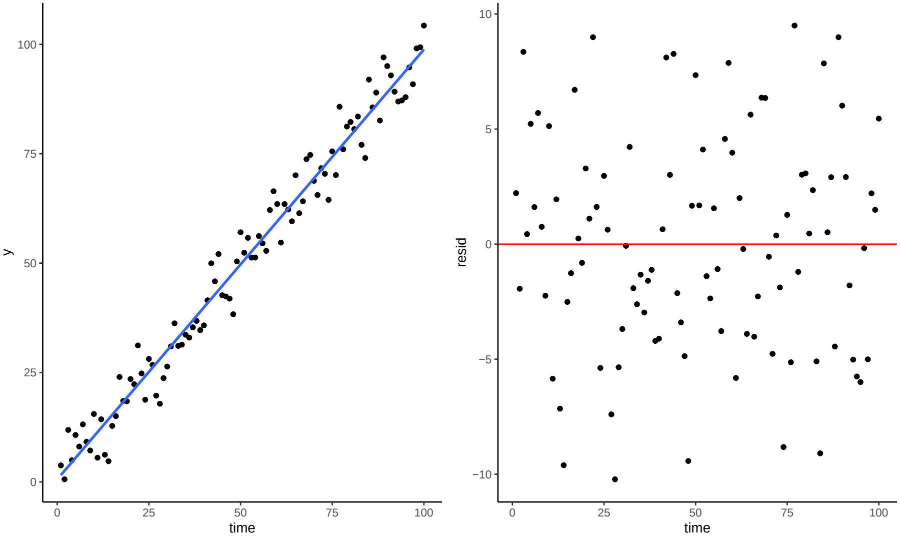
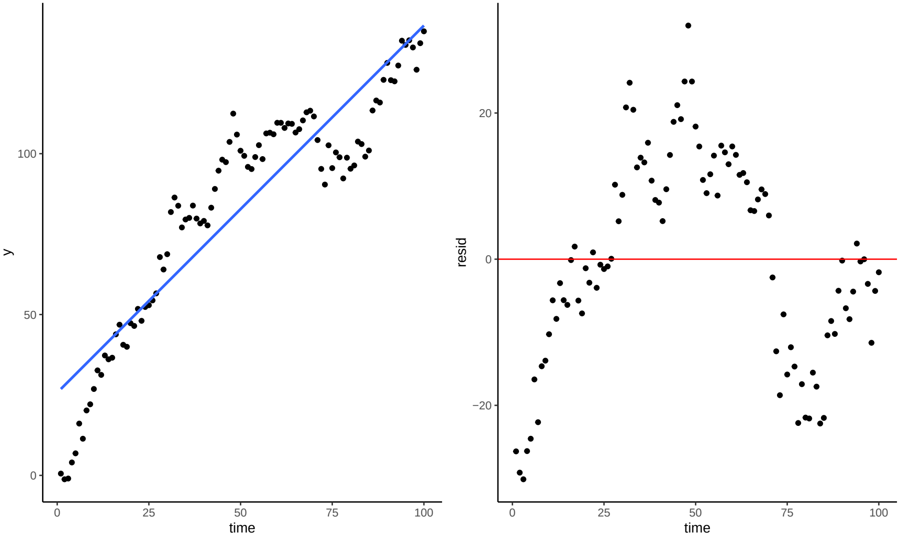


Single subject from a LMEM



Single subject from an LLT



Auto-correlation

The correlation between observations at any two time points is called the auto-correlation.

Our proposed SSM model has the following auto correlation structure.

$$corr(y_{it}, y_{i(t+\tau)}) = \frac{t\sigma_\eta^2}{\sqrt{\sigma_\varepsilon^2 + t\sigma_\eta^2}\sqrt{\sigma_\varepsilon^2 + (t+\tau)\sigma_\eta^2}}$$

This is equivalent to a dynamic moving average covariance structure. If $\sigma_\eta^2 = 0$ then auto-correlation is 0 and our proposed model boils down to a LMEM.

$$y_t = \alpha_0 + X_t\beta + \varepsilon_t$$

Accounting for Autocorrelation in LMEM Framework

- Many different autocorrelation techniques have been used.
- The a common practices has been to model an AR(1) covariance structure on the errors.

$$y_t = b_0 + X_t\beta + e_t, \quad b_0 \sim N(0, \sigma_b^2)$$
$$e_t = \rho e_{t-1} + \eta_t, \quad \eta_t \sim N(0, \sigma_\eta^2), \quad -1 < \rho < 1$$

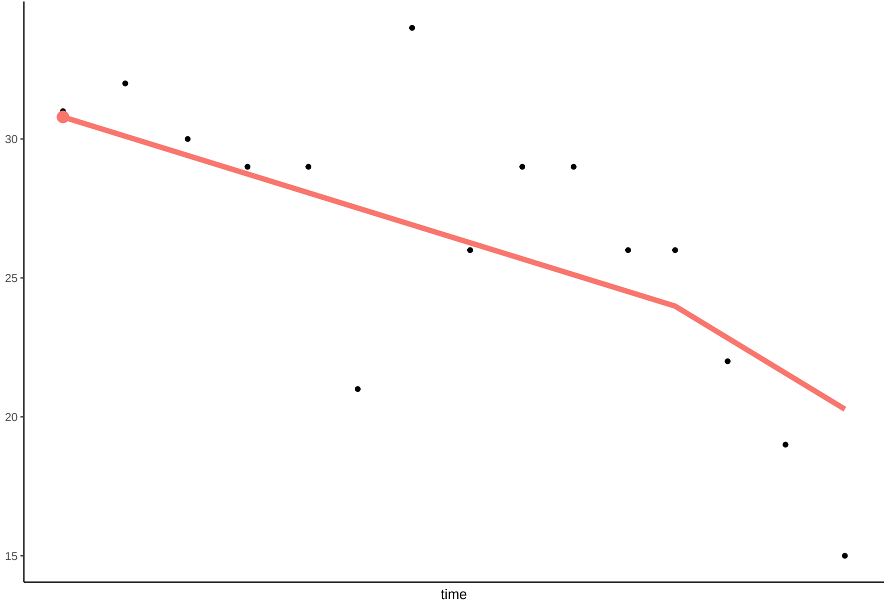
Recap

- We can think of autocorrelation as the effect of unobserved time-varying variables (UTV).
- Different modeling techniques make different assumptions on the behavior of the UTV
  - LMEM: There is not effect over time of UTV.
  - LMEM AR(1): The UTV effect will revert back to their levels at baseline.
  - LLT: The UTV can vary freely overtime for each subject.

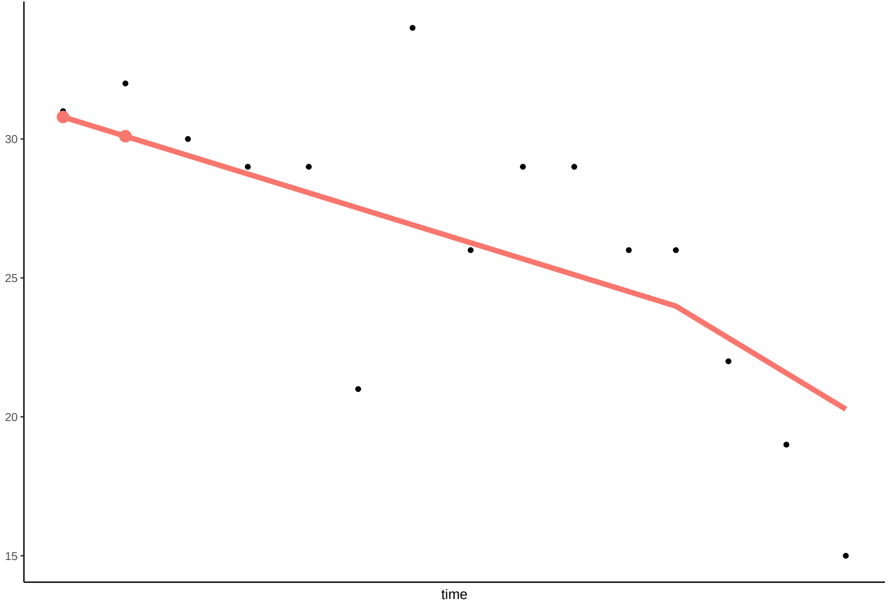
Lots of Plots

- The next few plots show the $E(Y_{t+\tau}|Y_t, \beta, X)$.
- Illustrates the LLT allows for dynamic changes in predicted trajectory while the LMEM and LMEM with AR(1) are very restrictive.

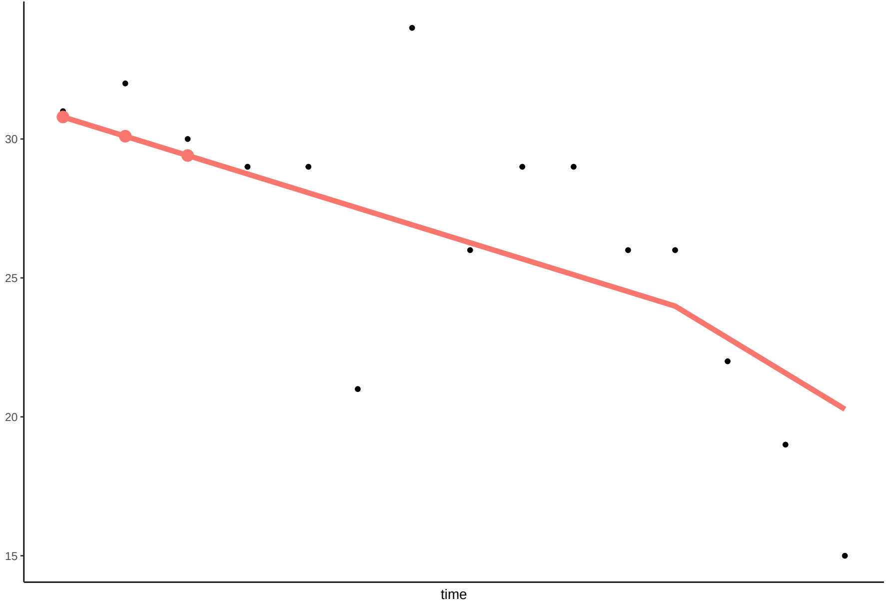
LMEM: Observation = 1



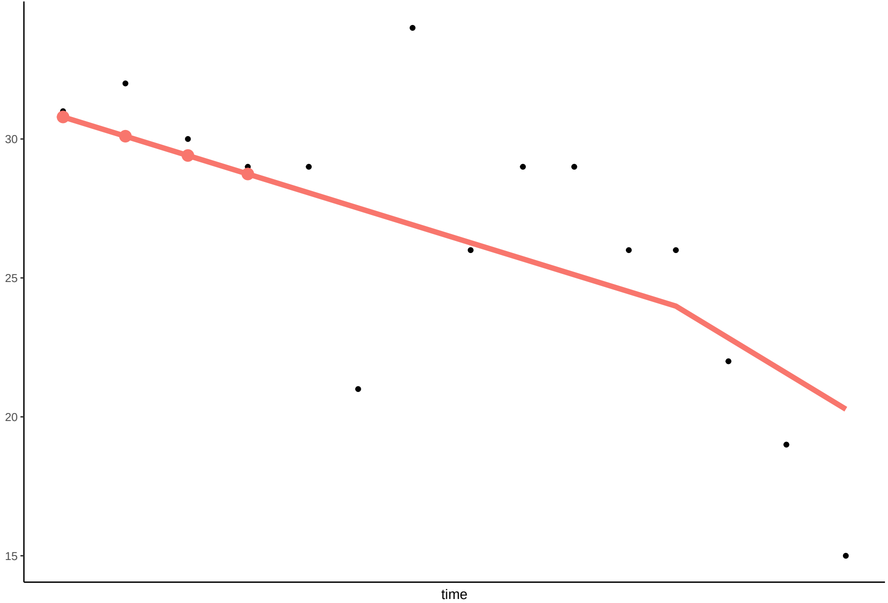
LMEM: Observation = 2



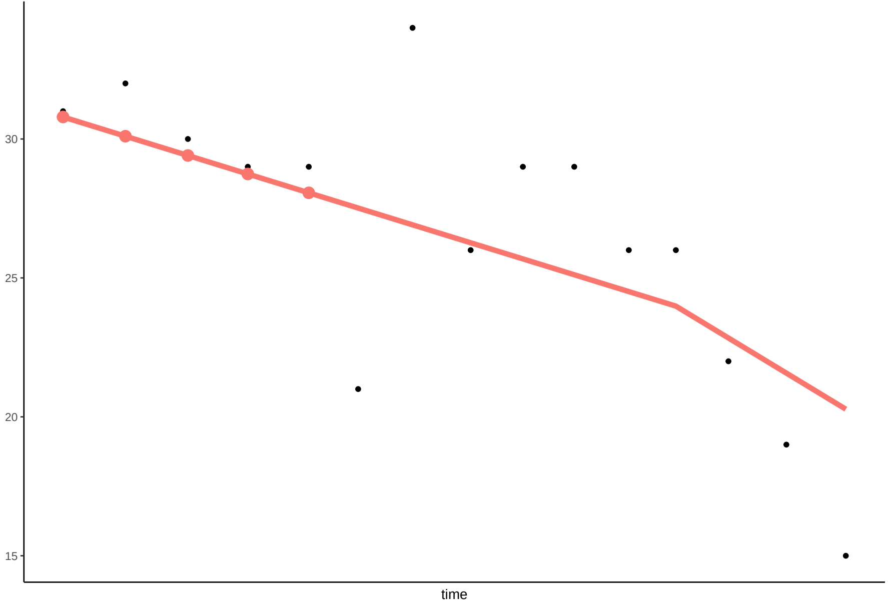
LMEM: Observation = 3

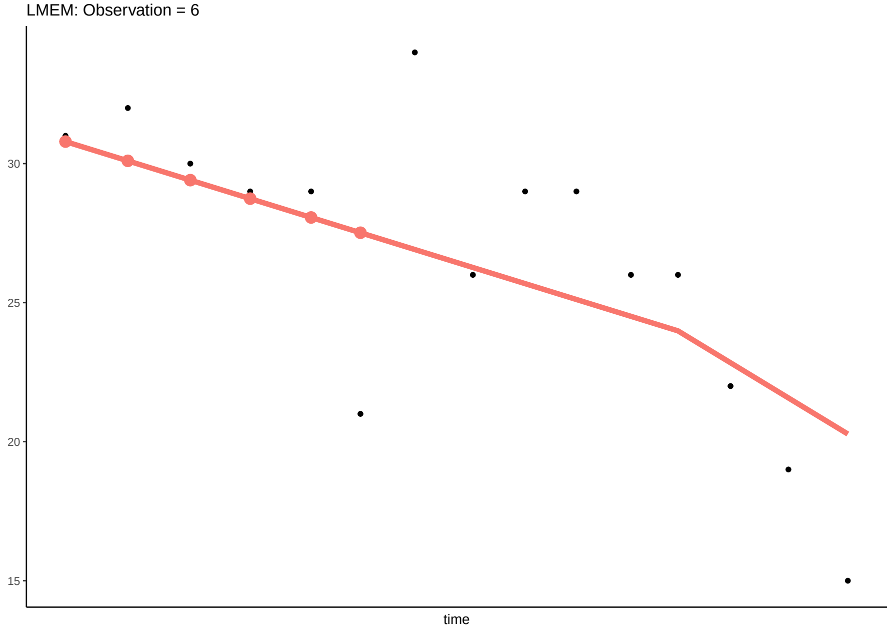


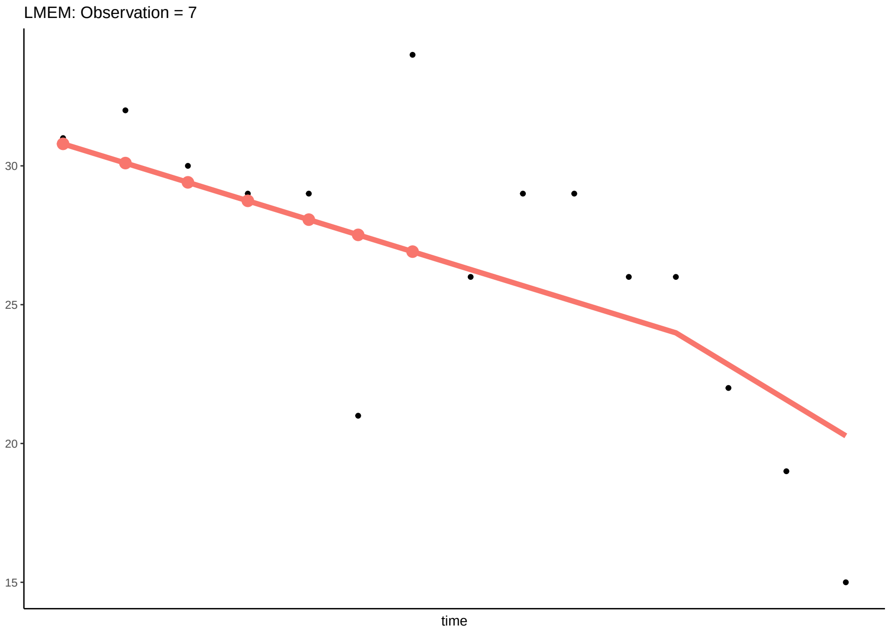
LMEM: Observation = 4



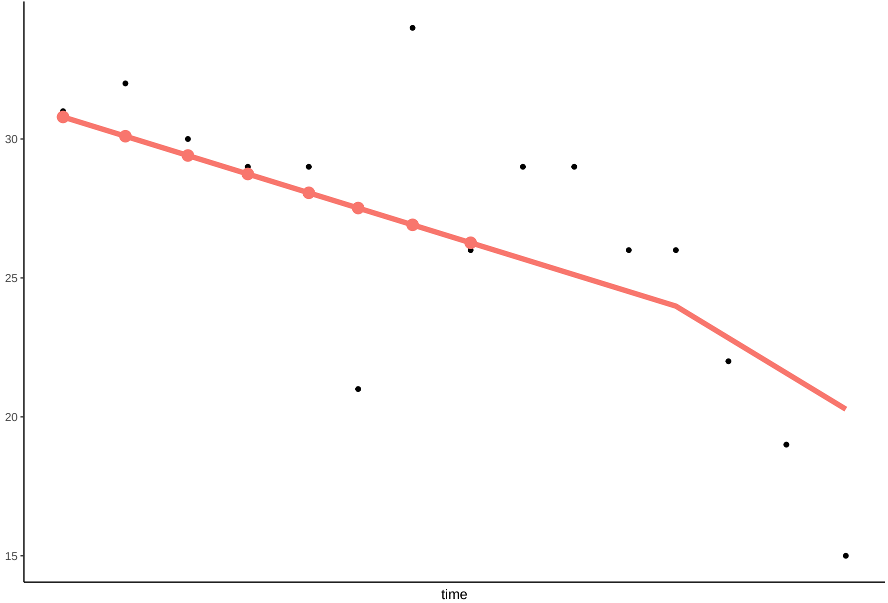
LMEM: Observation = 5

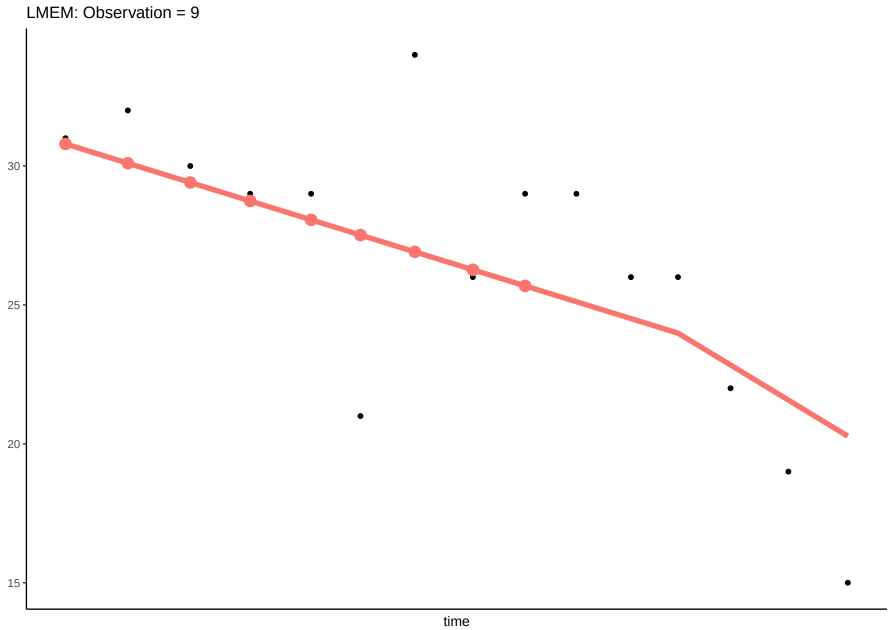


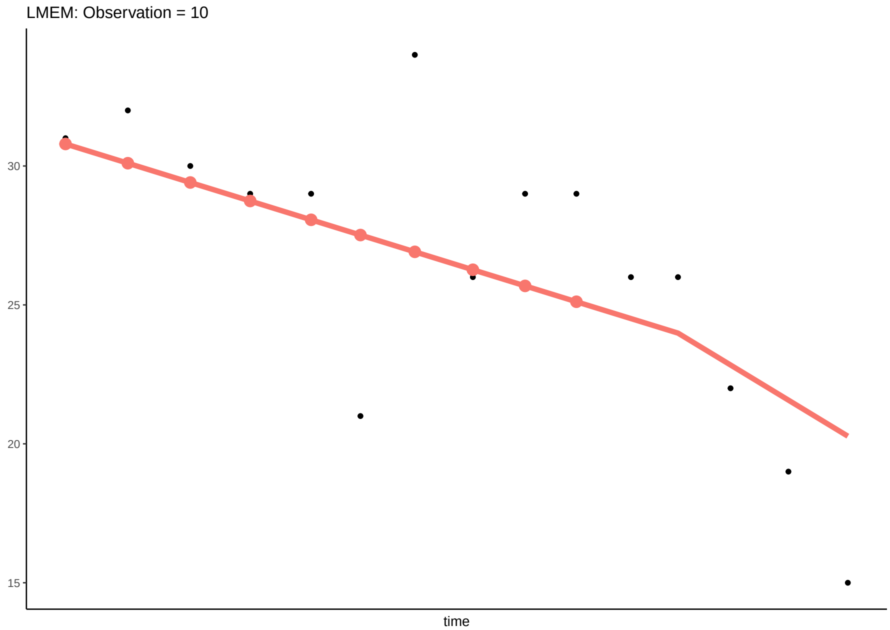

LMEM: Observation = 6
30
25
20
15
time


LMEM: Observation = 7
30
25
20
15
time

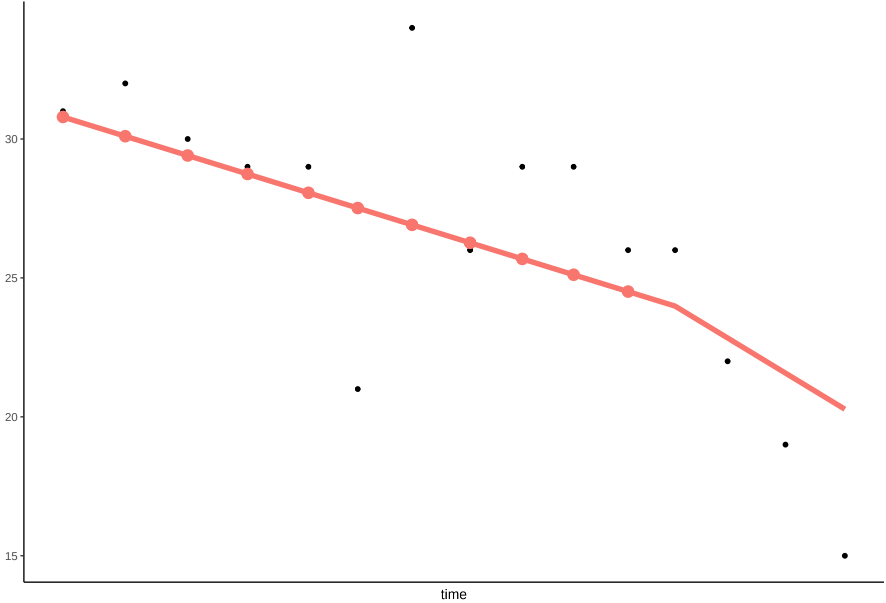
LMEM: Observation = 8

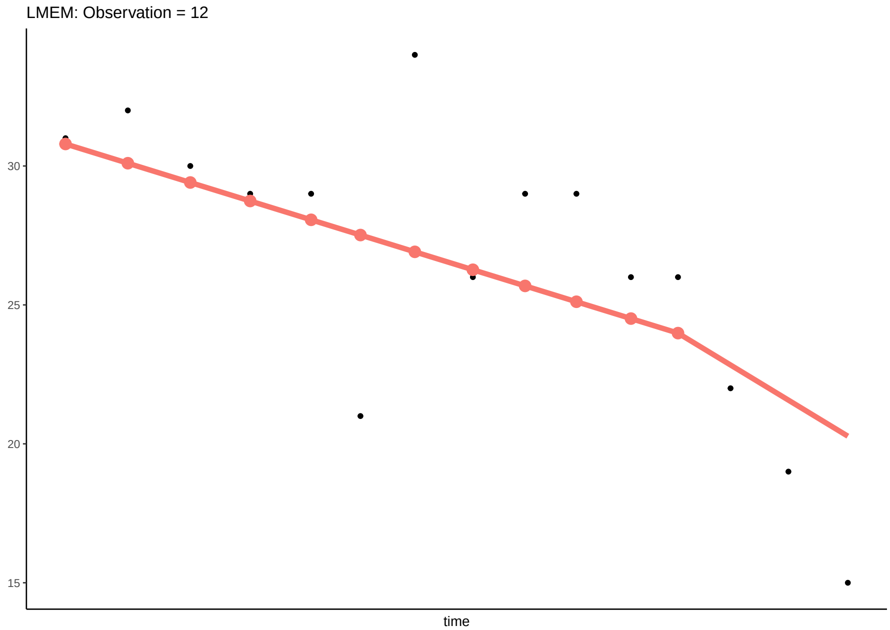


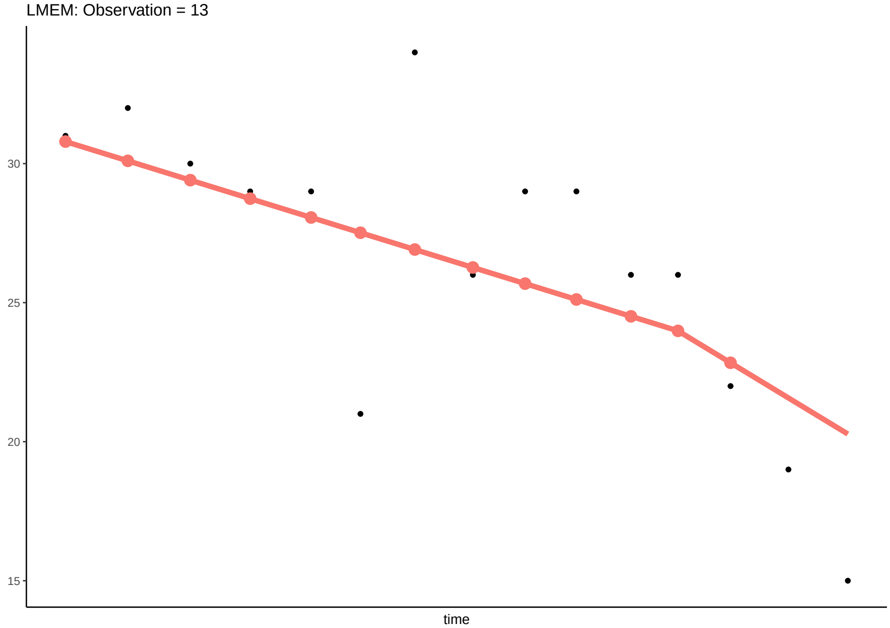

LMEM: Observation = 9
30
25
20
15
time

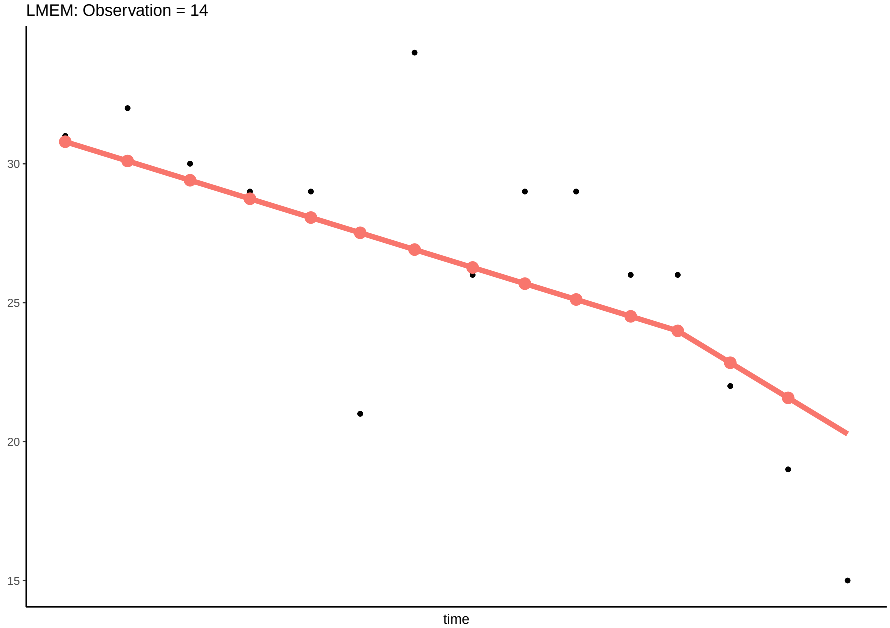

LMEM: Observation = 10
30
25
20
15
time

LMEM: Observation = 11

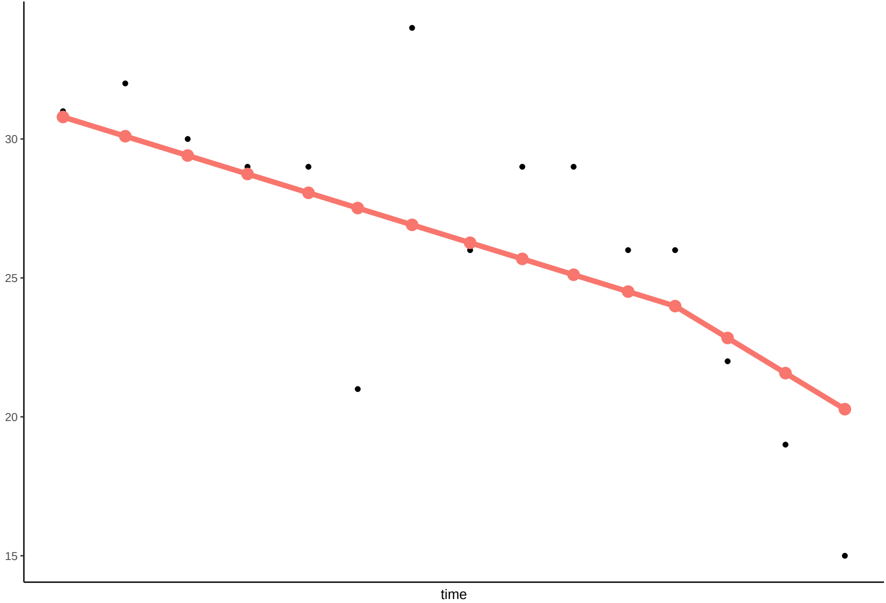


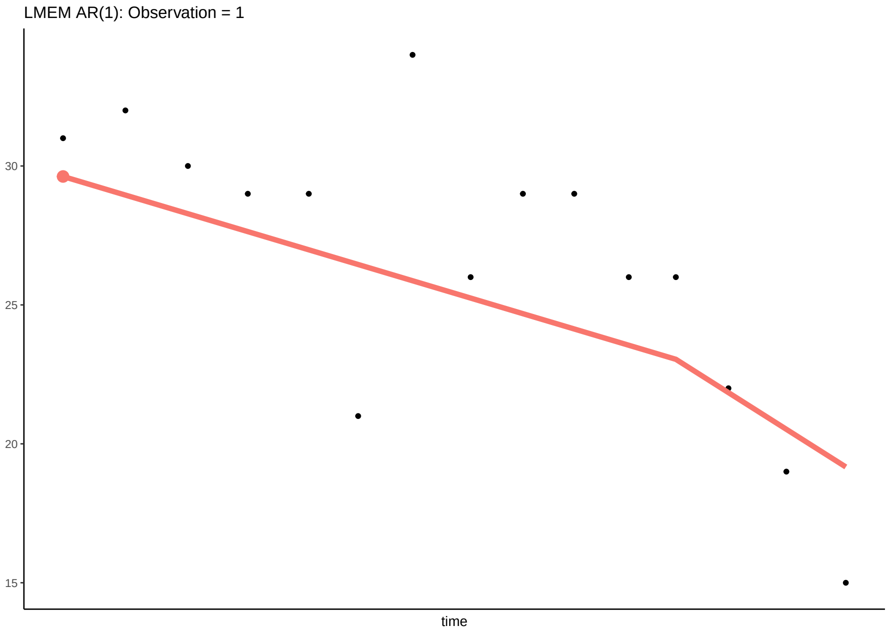

LMEM: Observation = 12
30
25
20
15
time


LMEM: Observation = 13
30
25
20
15
time

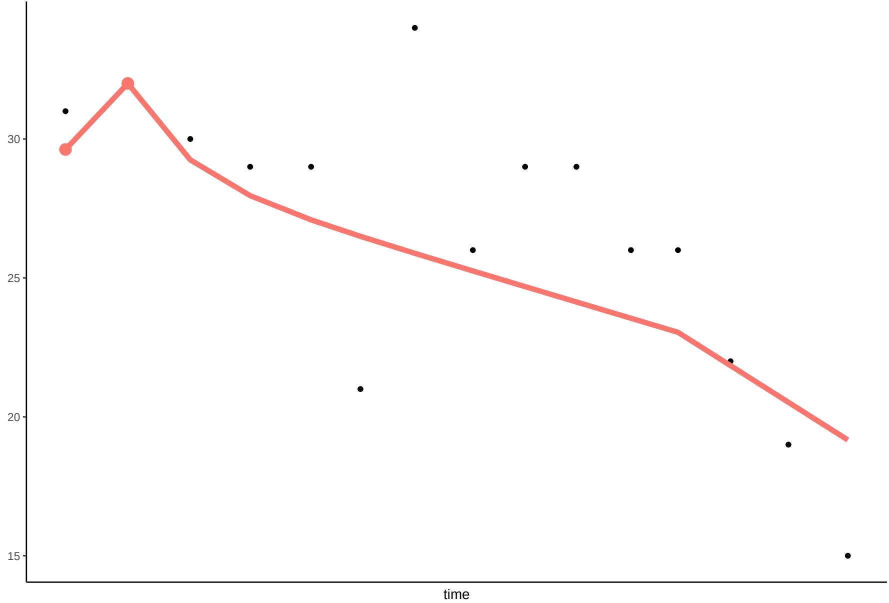

LMEM: Observation = 14
30
25
20
15
time

LMEM: Observation = 15

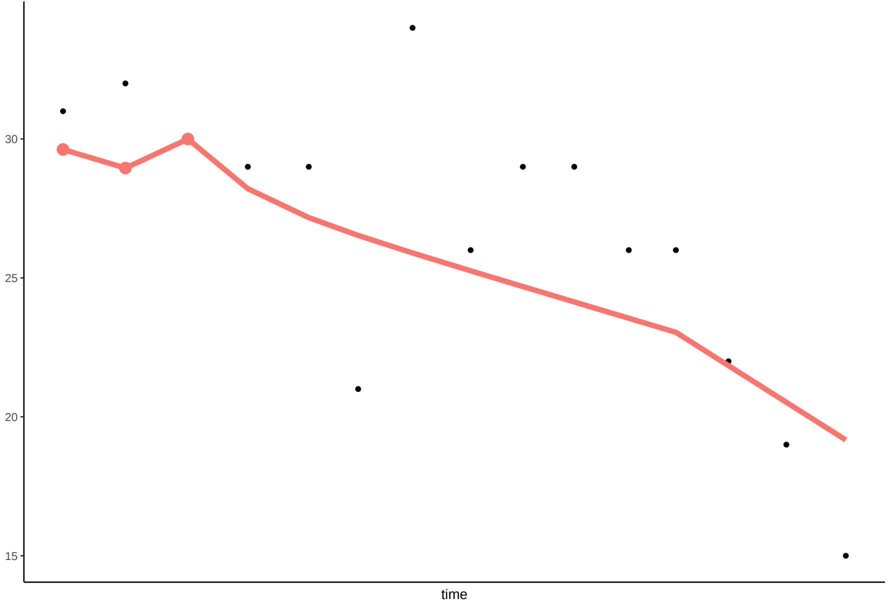


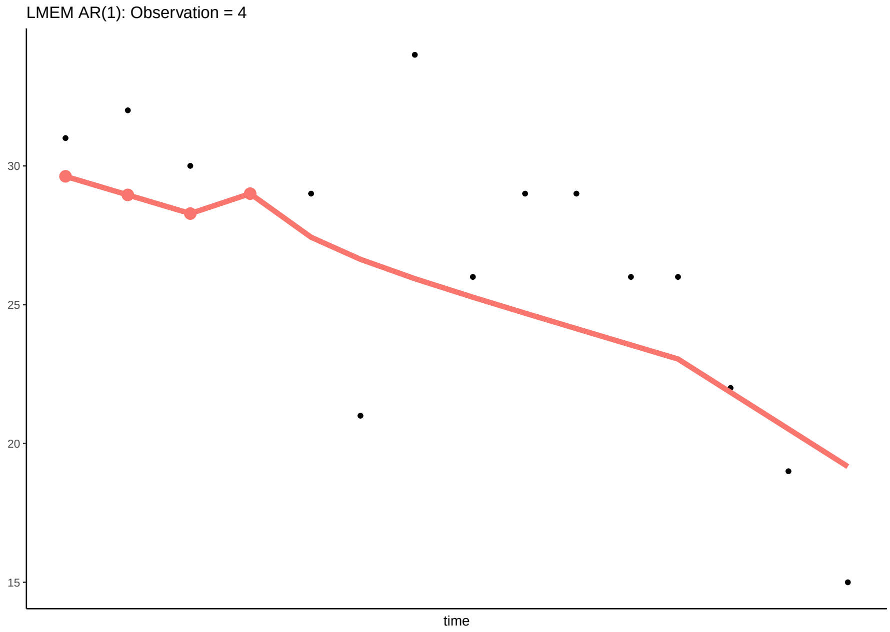

LMEM AR(1): Observation = 1
30
25
20
15
time

LMEM AR(1): Observation = 2

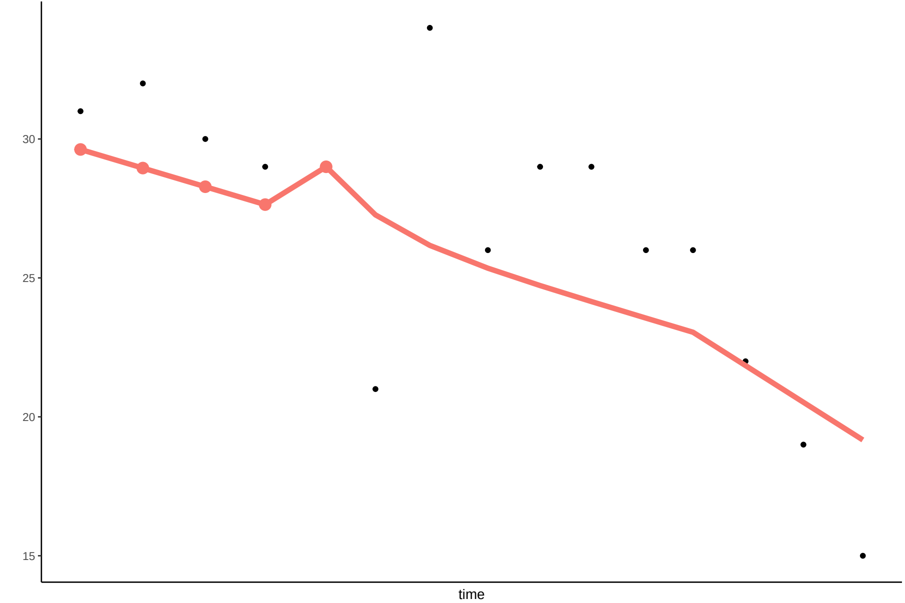


LMEM AR(1): Observation = 3

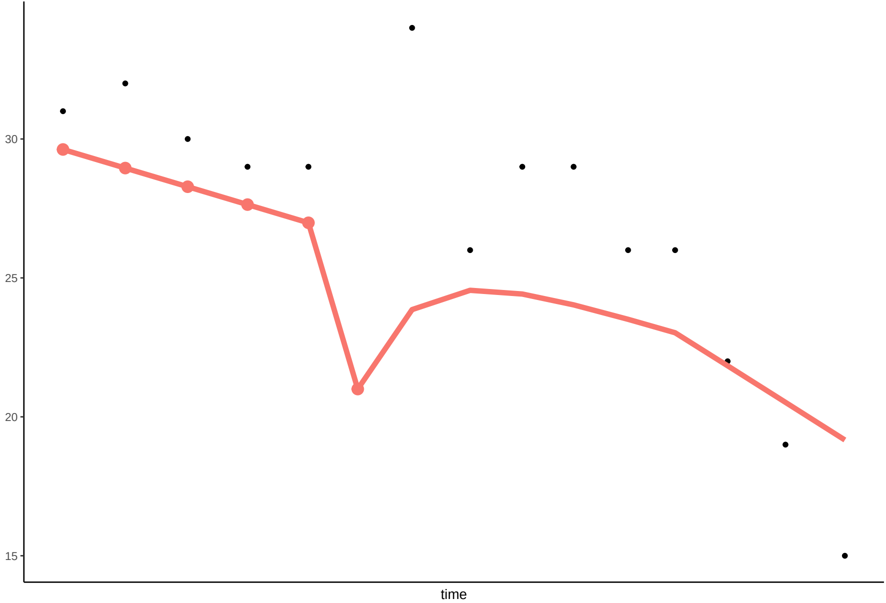



LMEM AR(1): Observation = 4
30
25
20
15
time

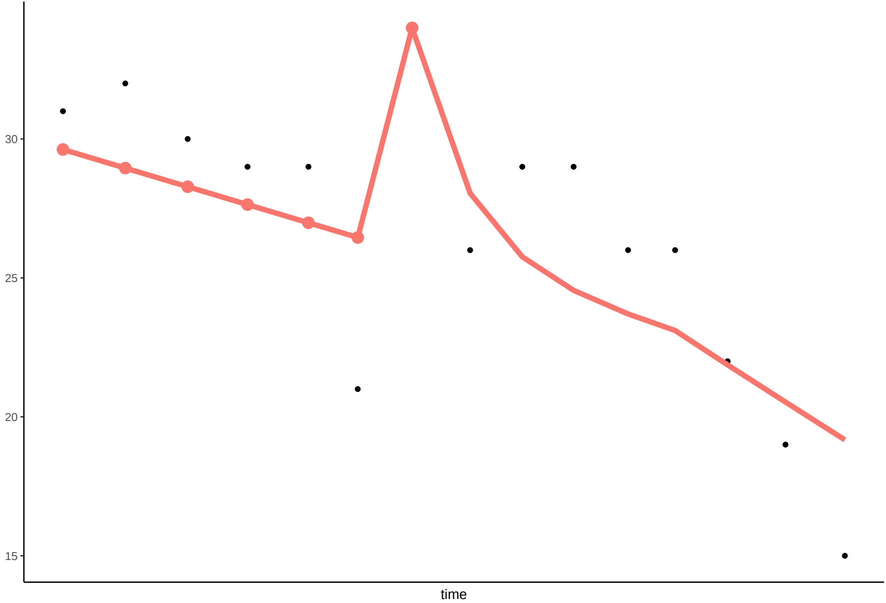
LMEM AR(1): Observation = 5



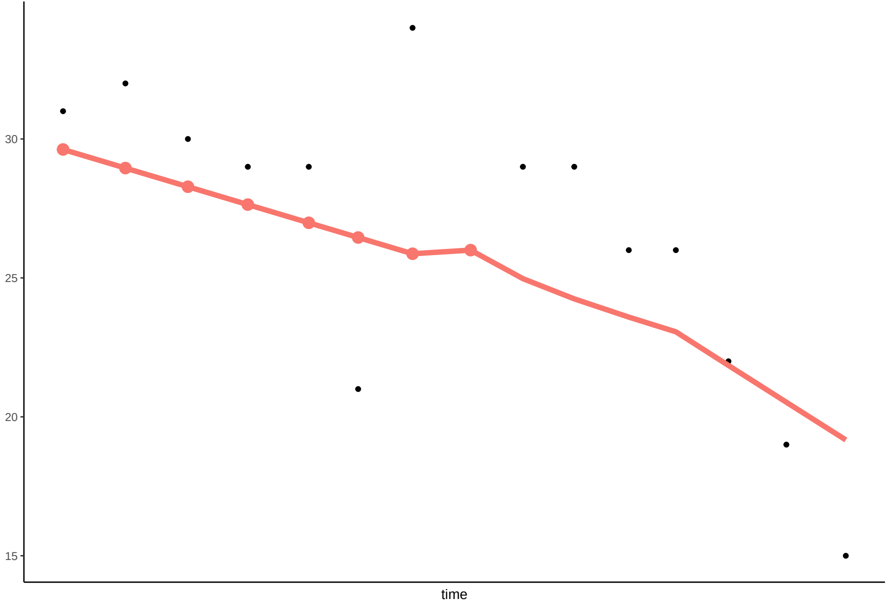
LMEM AR(1): Observation = 6

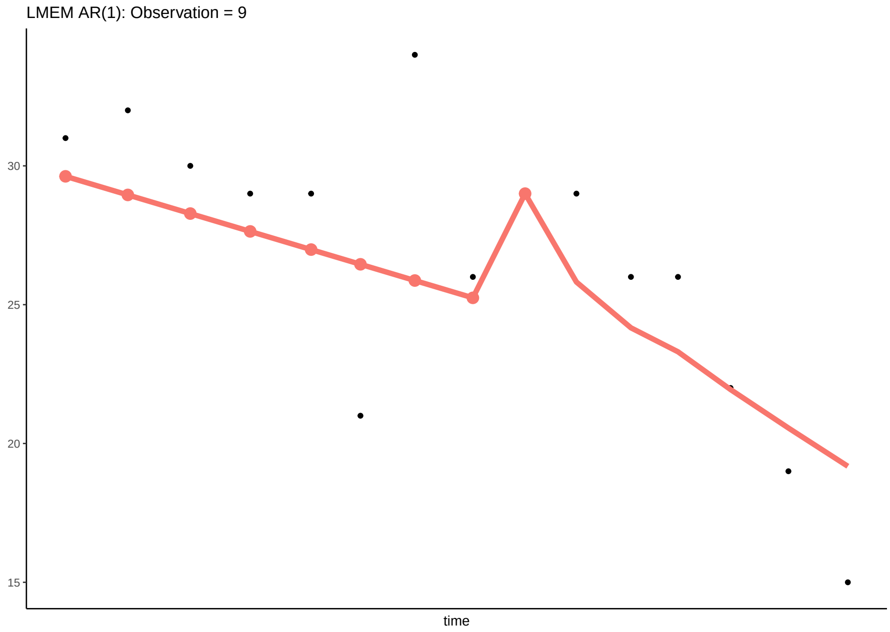


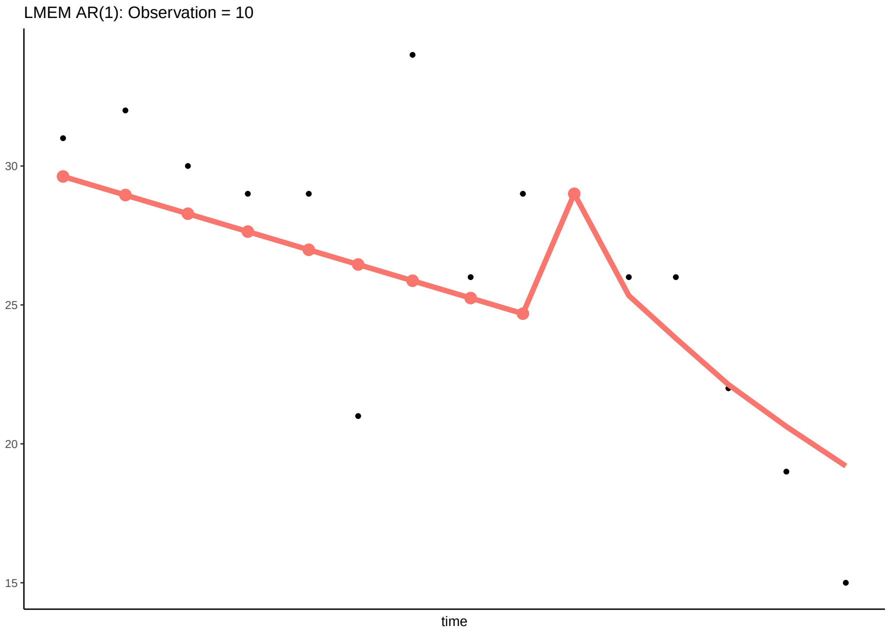
LMEM AR(1): Observation = 7



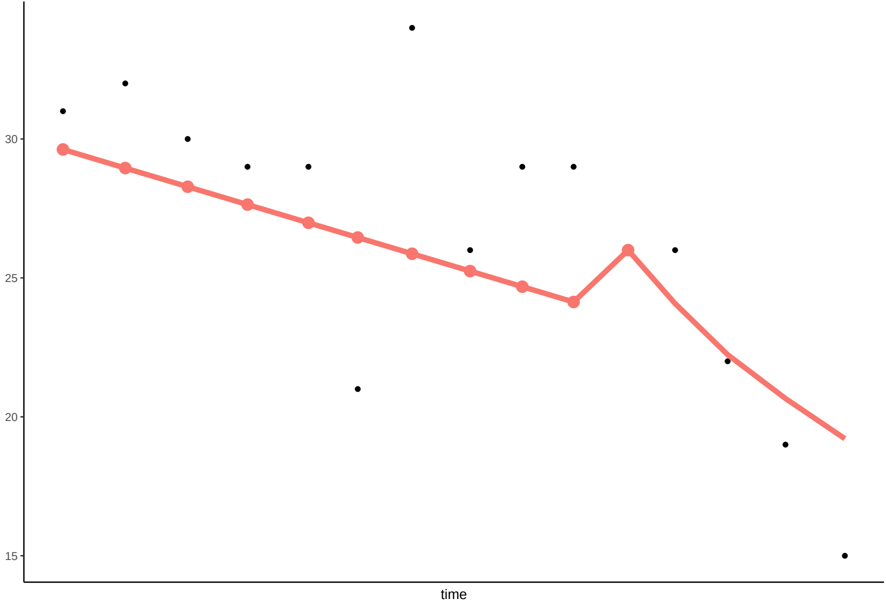
LMEM AR(1): Observation = 8

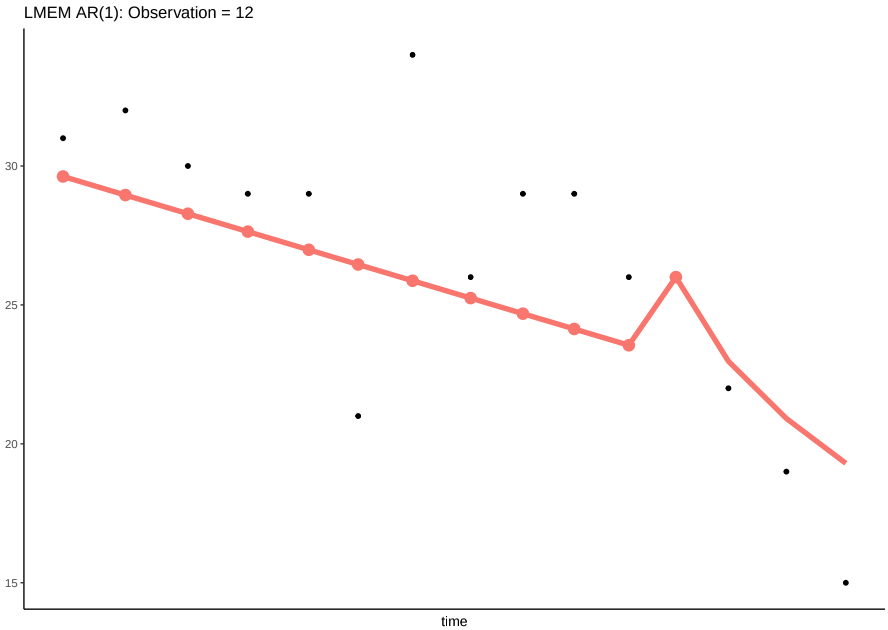


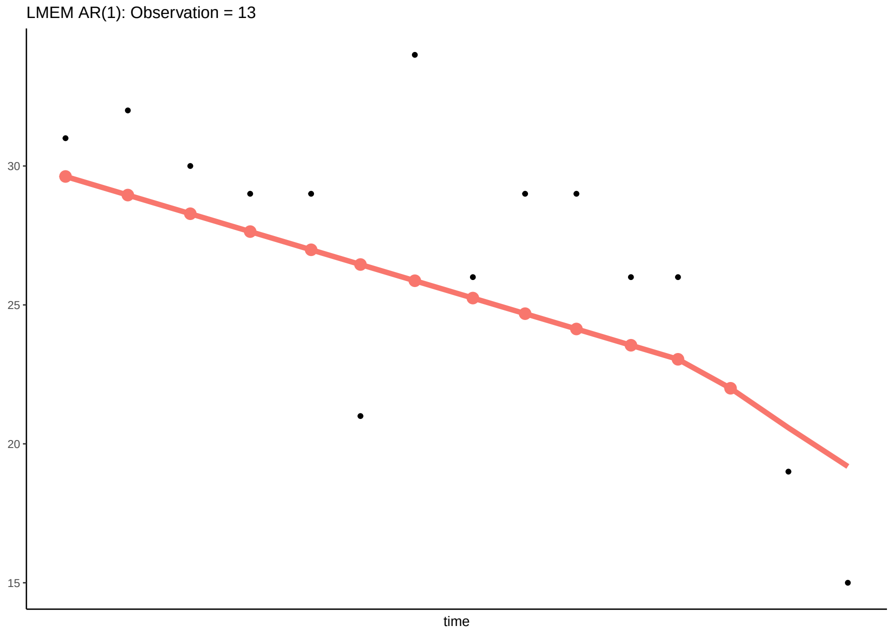

LMEM AR(1): Observation = 9
30
25
20
15
time


LMEM AR(1): Observation = 10
30
25
20
15
time

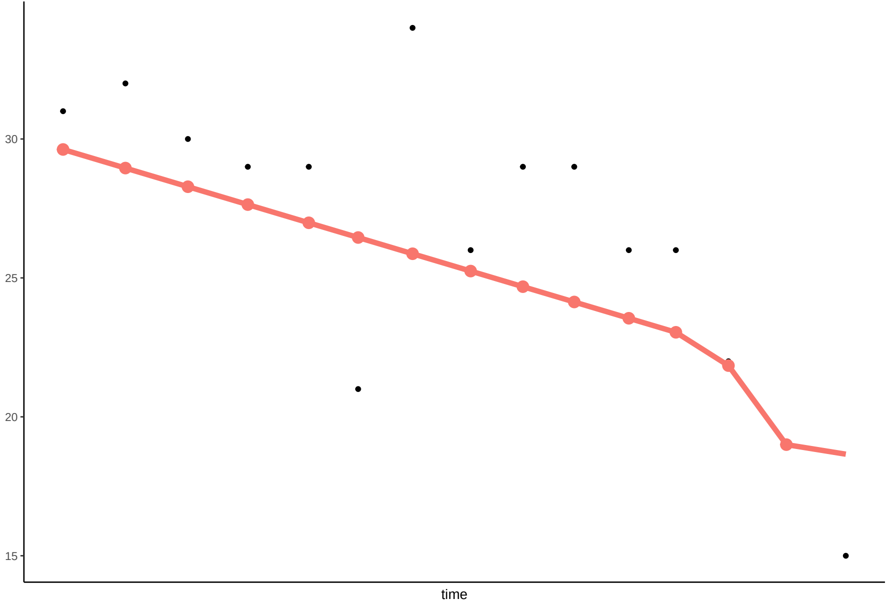
LMEM AR(1): Observation = 11

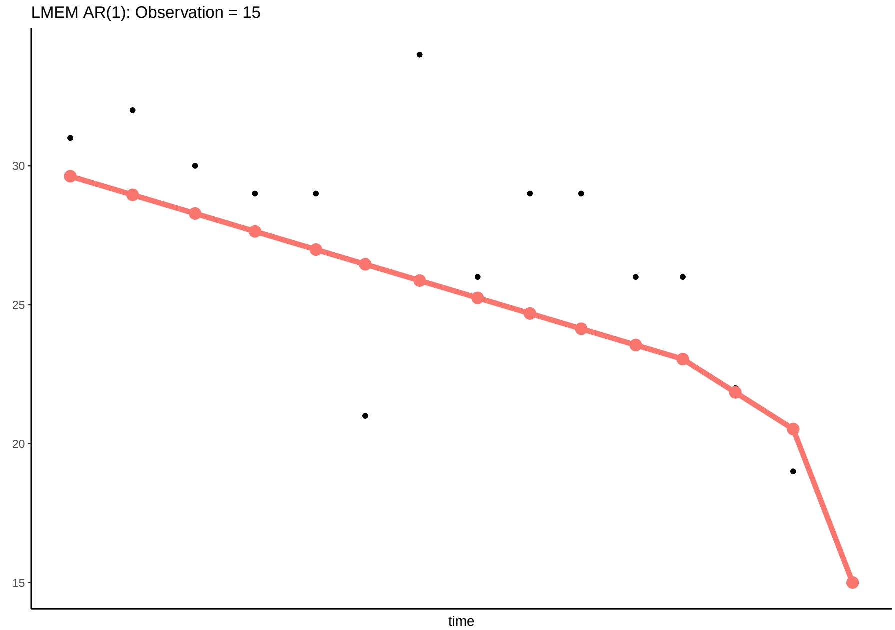


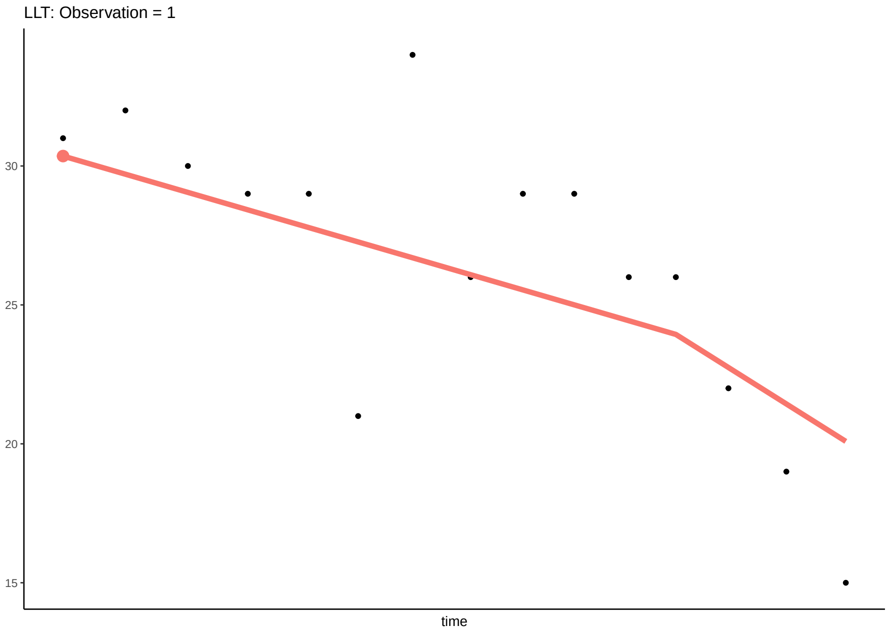

LMEM AR(1): Observation = 12
30
25
20
15
time

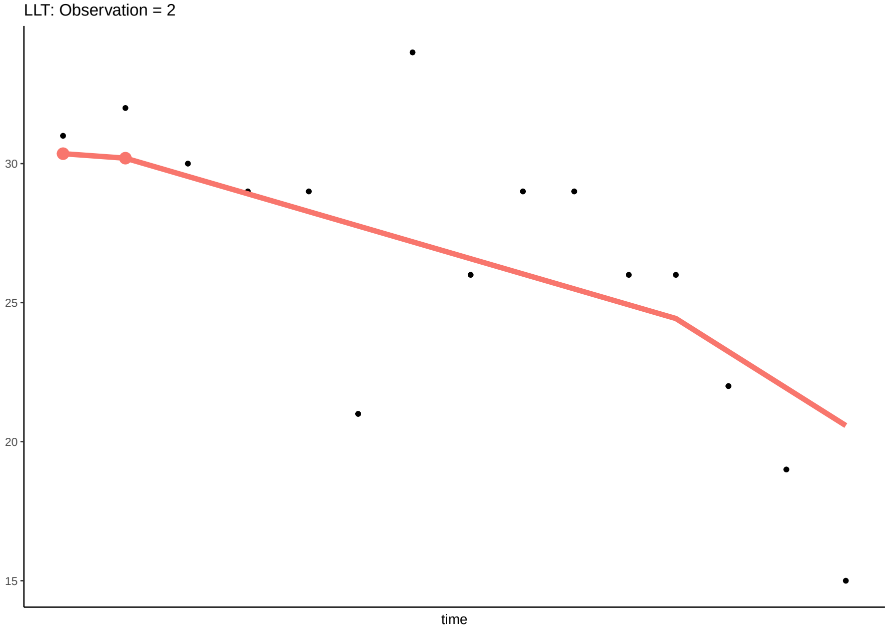

LMEM AR(1): Observation = 13
30
25
20
15
time

LMEM AR(1): Observation = 14

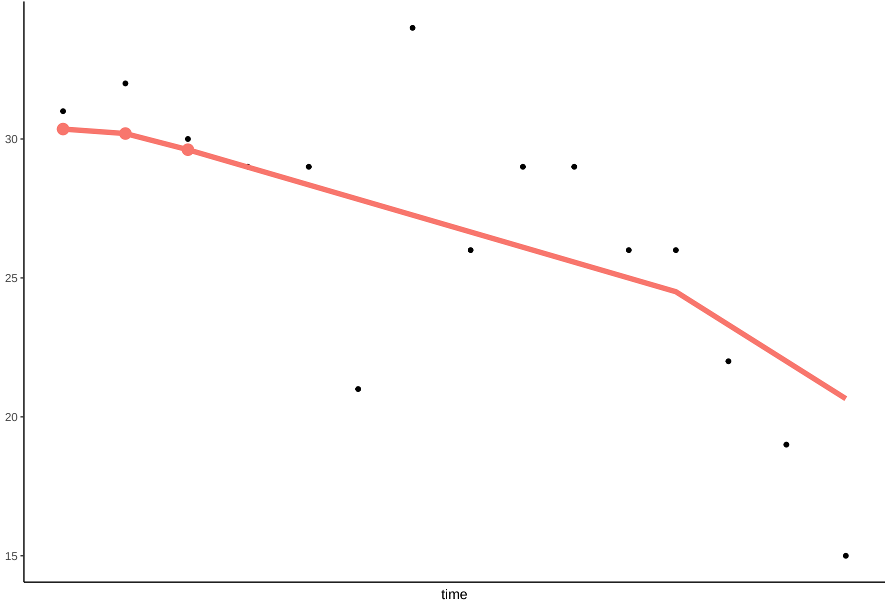



LMEM AR(1): Observation = 15
30
25
20
15
time

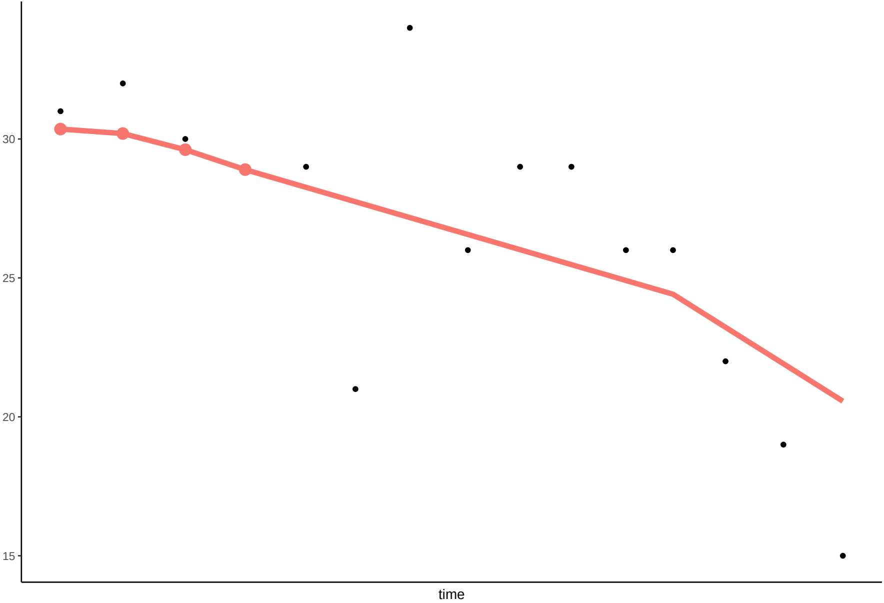

LLT: Observation = 1
30
25
20
15
time


LLT: Observation = 2
30
25
20
15
time

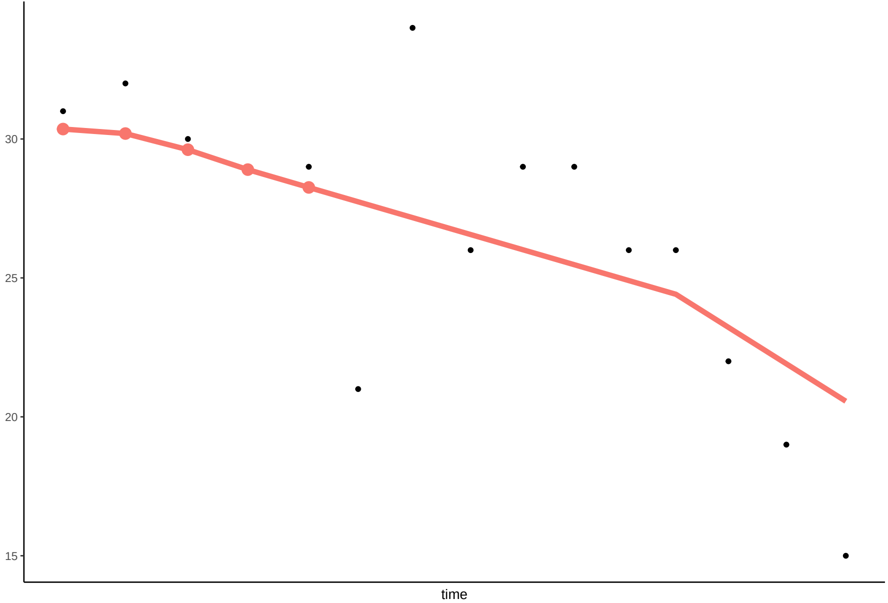
LLT: Observation = 3

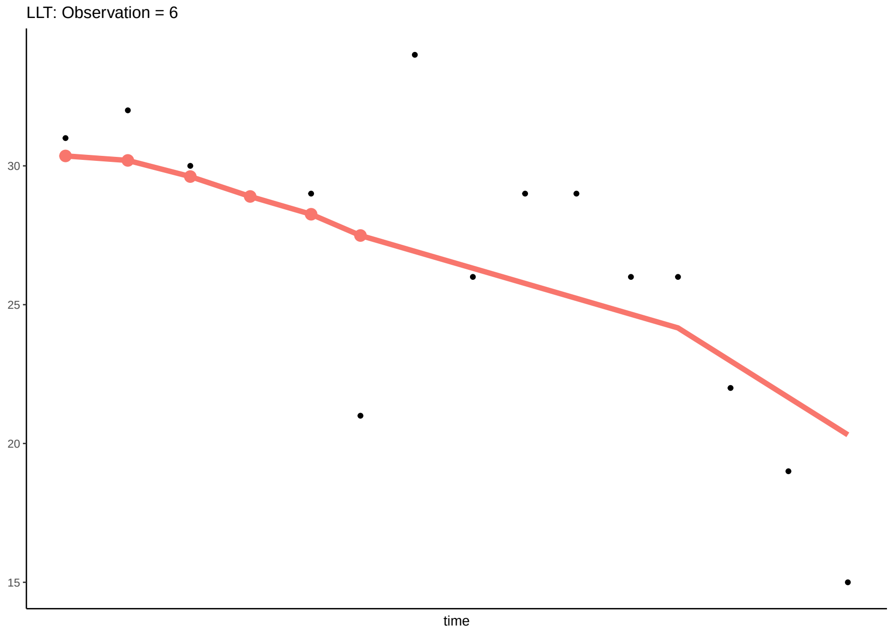


LLT: Observation = 4

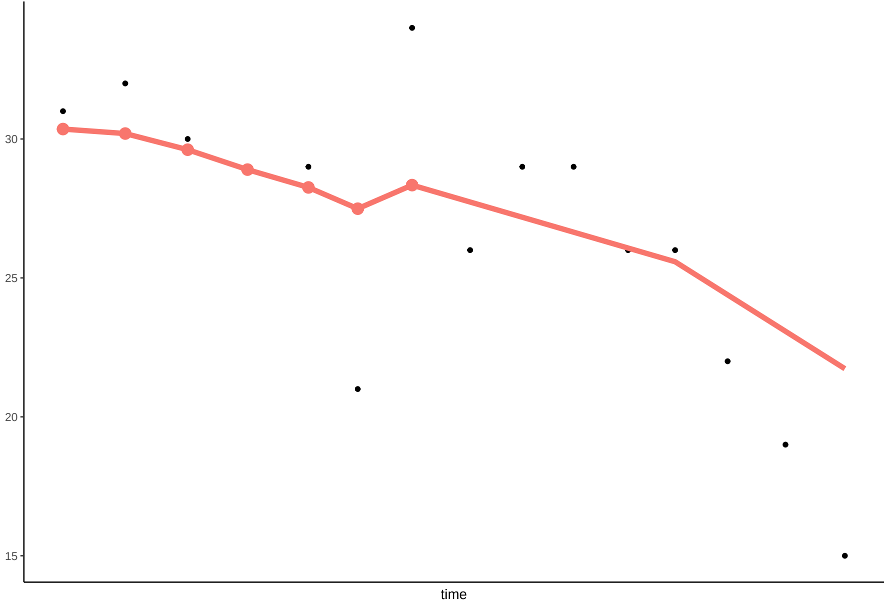


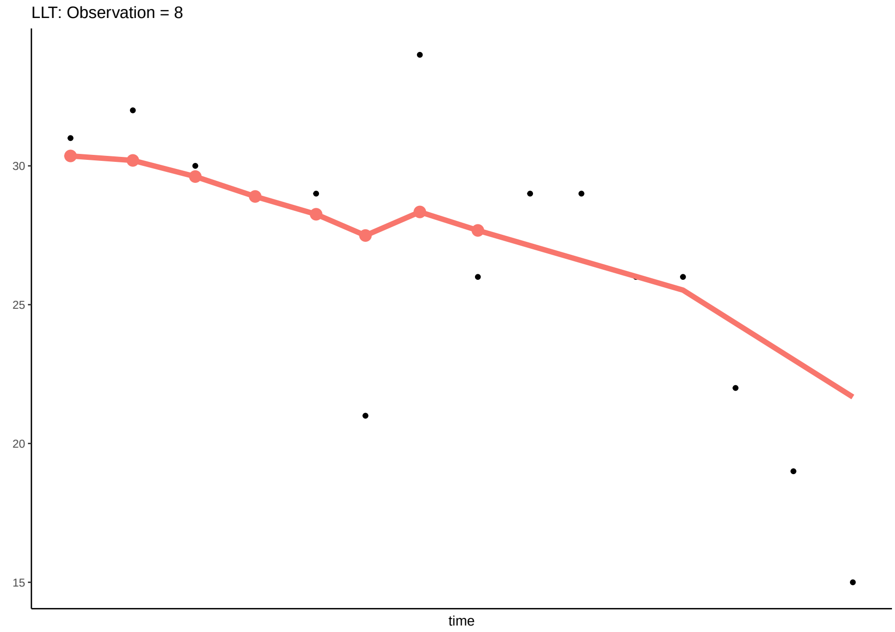
LLT: Observation = 5



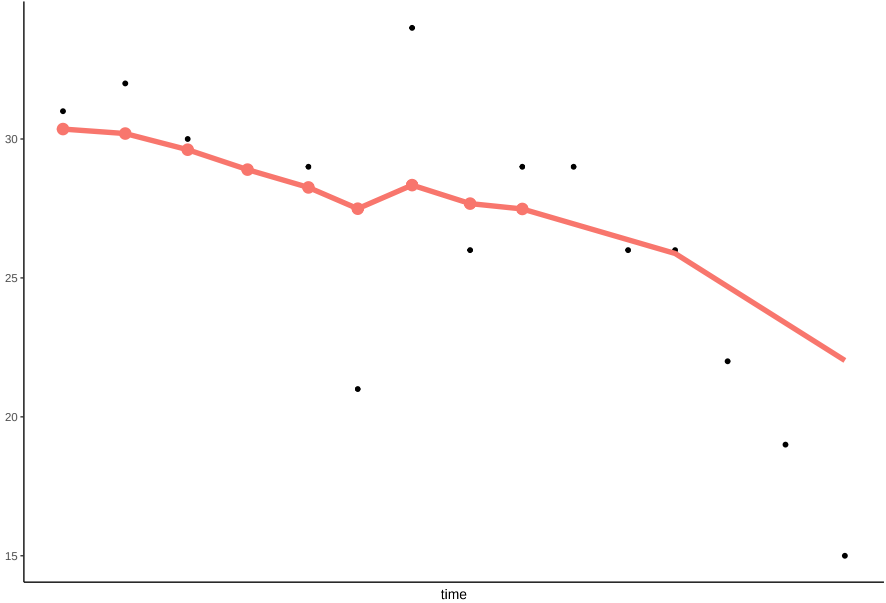

LLT: Observation = 6
30
25
20
15
time

LLT: Observation = 7

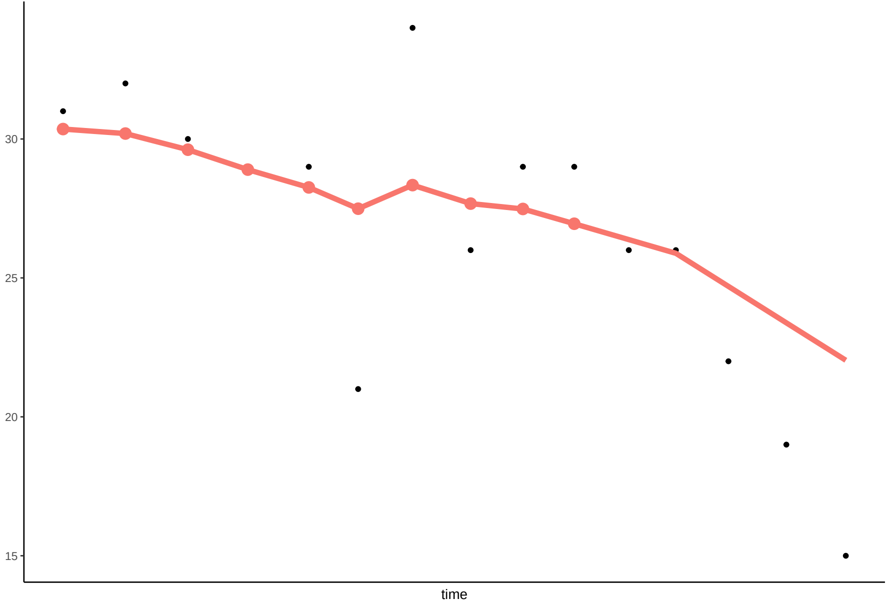



LLT: Observation = 8
30
25
20
15
time

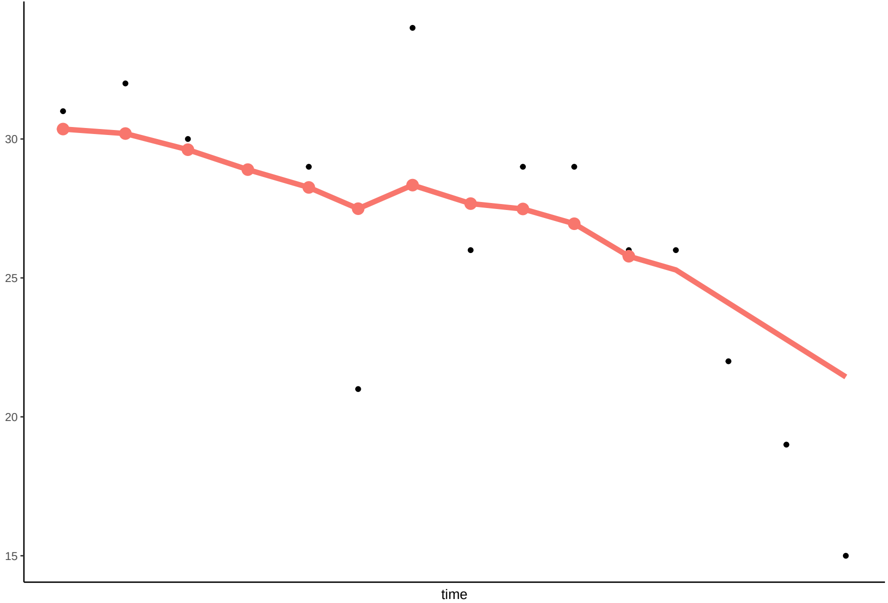
LLT: Observation = 9

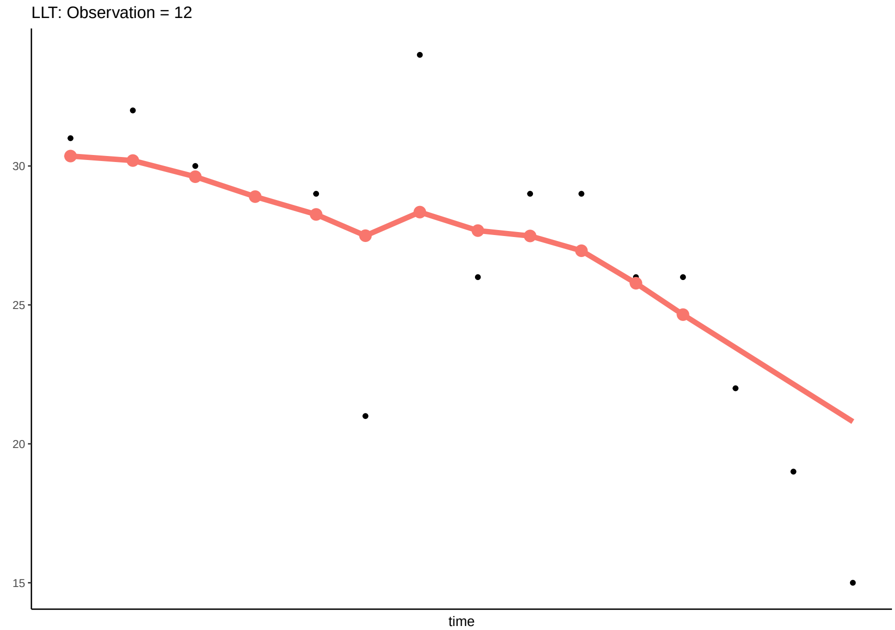


LLT: Observation = 10

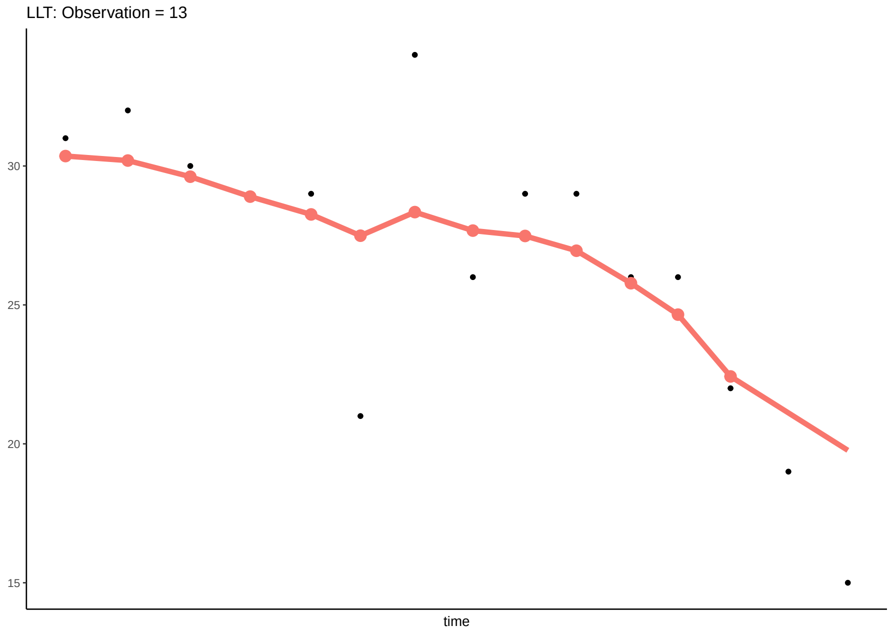


LLT: Observation = 11



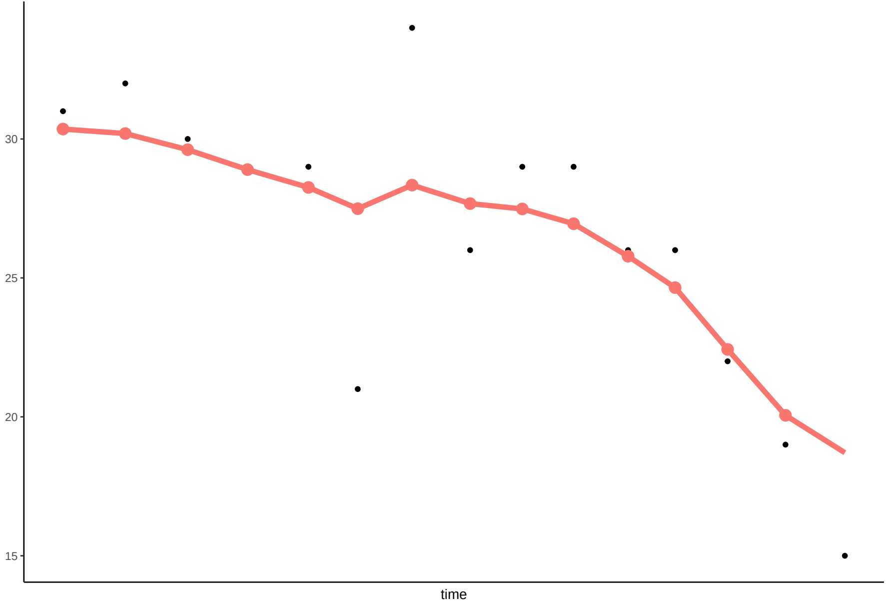


LLT: Observation = 12
30
25
20
15
time

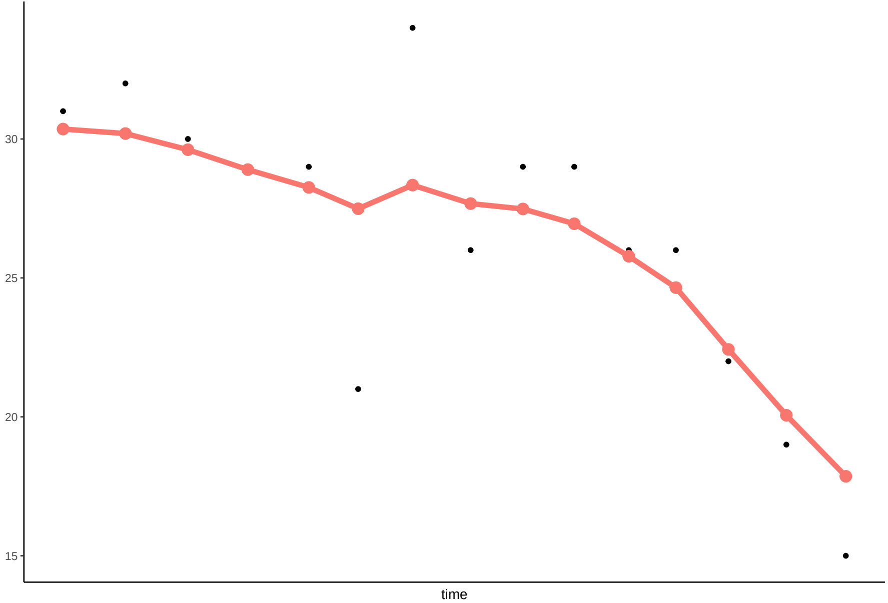


LLT: Observation = 13
30
25
20
15
time

LLT: Observation = 14



LLT: Observation = 15



Summary

Consider the model,

$$
\begin{aligned}
y_t &= \alpha_t + X_t \beta_t + \varepsilon_t \\
\alpha_t &= \alpha_{t-1} + \eta_t \\
\beta_t &= \beta_{t-1}
\end{aligned}
$$

We can think of α_t as the underlying cognitive state not accounted for by the covariates X_t.

The variable β_t is the effect of the covariates X_t. It has the same interpretation as with a LMEM.

LLT Estimation

We can rewrite the proposed model to fit the state space model as follows,

$$y_t = \begin{bmatrix} I_n & X_t \end{bmatrix} \begin{bmatrix} \alpha_t \\ \beta_t \end{bmatrix} + \varepsilon_t$$

$$\begin{bmatrix} \alpha_t \\ \beta_t \end{bmatrix} = \begin{bmatrix} I_{(n+p)\times(n+p)} \end{bmatrix} \begin{bmatrix} \alpha_{t-1} \\ \beta_{t-1} \end{bmatrix} + \begin{bmatrix} \eta_t \\ 0_{p\times 1} \end{bmatrix}$$

- $F_t = \begin{bmatrix} I_n & X_t \end{bmatrix}$
- $v_t = \varepsilon_t$
- $w_t = \begin{bmatrix} \eta_t \\ 0_{p\times 1} \end{bmatrix}$
- $\mu_t = \begin{bmatrix} \alpha_t \\ \beta_t \end{bmatrix}$
- $G_t = I_{(n+p)\times(n+p)}$

Kalman Filter

The Kalman filter is a recursive algorithm to estimate the unobserved states conditioned on the observed data (Kalman, 1960; Durbin and Koopman, 2012). Let $\hat{\mu}_{i|j} = E(\mu_i|y_{1:j})$ and $P_{i|j} = var(\mu_i|y_{1:j})$.

Predicted state: $\hat{\mu}_{t|t-1} = G_t\hat{\mu}_{t-1|t-1}$

Predicted state covariance: $P_{t|t-1} = G_t P_{t-1|t-1} G_t' + W$

Innovation covariance: $S_t = F_t P_{t|t-1} F_t' + V$

Kalman Gain: $K_t = P_{t|t-1} F_t' S_t^{-1}$

Innovation: $\tilde{f}_t = y_t - F_t\hat{\mu}_{t|t-1}$

Updated state estimate: $\hat{\mu}_{t|t} = \hat{\mu}_{t|t-1} + K_t\tilde{f}_t$

Updated state covariance: $P_{t|t} = (I - K_t F_t)P_{t|t-1}$

Updated innovation: $\tilde{f}_{t|t} = y_t - F_t\hat{\mu}_{t|t}$

Kalman Smoother

Let $J_t = P_{t|t} G'_{t+1} + P^{-1}_{t+1|t}$. We can then calculate $E(\mu_t | y_{1:T})$ and $var(\mu_t | y_{1:T})$ using the following Kalman smoother equations.

$$
\begin{aligned}
E(\mu_t | y_{1:T}) &= \hat{\mu}_{t|t} + J_t(\hat{\mu}_{t+1|T} - \hat{\mu}_{t+1|t}) \\
var(\mu_t | y_{1:T}) &= P_{t|t} - J_t G_{t+1} P_{t|t}
\end{aligned}
$$

Setting Parameters

We assume $\mu_0 \sim N(u_0, P_0)$, however u_0 and P_0 are unknown.

- By initializing $u_0 = 0$ and $P_0 = \infty$ we are essentially putting a flat prior on μ_0.
- It has been shown $\hat{\mu}_{0|T}$ and $P_{0|T}$ quickly converge to u_0 and P_0 respectively for even small T (Kalman, 1960; Durbin and Koopman, 2012).

In our proposed model, $\mu_t = \begin{bmatrix} \alpha_t \\ \beta_t \end{bmatrix}$.

- $\hat{\beta}_{0|T}$ is then our estimate for β and has variance covariance $P_{\hat{\beta}} = [P_{0|T}]_{(n+1):(n+p),(n+1):(n+p)}$.
- We can then use $\hat{\beta}_{0|T}$ and $P_{\hat{\beta}}$ for inference on β.
  - $\hat{\beta} \overset{asym}{\sim} N(\beta, P_{\hat{\beta}})$.

Estimation of σ_ε^2 and σ_η^2

- We get proper estimates for β given we have correctly specified our model, including σ_ε^2 and σ_η^2.
- The parameters σ_ε^2 and σ_η^2 are unknown, but can be estimated using Maximum Likelihood Estimation (MLE).

$$\ell(\sigma_\varepsilon^2, \sigma_\eta^2) = -\frac{np}{2} log(2\pi) - \frac{1}{2} \sum_{i=1}^{t} \left(log|\tilde{S}_i| + \tilde{f}_i{`} S_i^{-1} f_i \right)$$

- To maximize the log-likelihood we used a Newton-Raphson method with a limited memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) method (Liu and Nocedal, 1989; Zhou and Li, 2007).

Missing Data

If a subject is missing an observation at time t we can set

- $y^* = W_t y_t$ where W_t is a subset of rows of I_n corresponding to those with observed data.
- $F_t^* = W_t F_t$
- $\varepsilon_t^* = W_t \varepsilon_t$

then carry out the same Kalman filter and smoother replacing y with y^*, Z with Z^*, and ε_t^* with ε_t. Doing this modification still allows us to get the smoothed values for α_t and β_t.

Computational Challenges

For each iteration of the Kalman filter we must invert $var(Y_t|y_{1:(t-1)}) = S_t$.

- S_t is non-sparse as calculating $var(Y_t|y_{1:(t-1)})$ is a function of β_{t-1} which is shared between all observations.
- S_t is an $n \times n$, so as n increases there is an exponential increase in computation time.

Solution 1: Partitioning

A solution to solving inversion computational inefficiencies is to partition:

- Partition the subjects into k groups.
- Run the Kalman filter and smoother on each group independently to extract $\hat{\beta}^{(i)}_{0|T}$ and $P^{(i)}_{\beta}$ for i in $1, ..., k$.
- Use the estimate $\bar{\beta} = \frac{\sum_{i=1}^{k} \hat{\beta}^{(i)}_{0|T}}{k}$.
  - $\bar{\beta} \sim N(\beta, \frac{\sum_{i=1}^{k} P_{\hat{\beta}^{(i)}}}{k^2})$

Solution 2: Bayesian Gibb's Sampling Approach

- For the Bayesian approach we use a Gibb's sampler.
- Instead of calculating β in the Kalman filter, we can estimate it separately.
- The model,

$$
\begin{aligned}
y_t &= \alpha_t + X_t\beta + \varepsilon_t \\
\alpha_t &= \alpha_{t-1} + \eta_t
\end{aligned}
$$

Gibb's Sampling

- Gibb's sampling is a method to gain an approximate sample from a posterior distribution for a given variable (Gelfand-Smith, 1990).
- It works by:
  - calculating the distribution of a variable conditioned on all other unknown variables, known as the posterior distribution.
  - sampling from the posterior distribution and assigning the new sample to the variable.
  - calculate the posterior of the next variable and continue to sample, update, and recalculate the other posteriors.
  - The process is commonly repeated thousands of times.
- We need to calculate the posterior for $\alpha_{1:T}, \beta, \sigma_\varepsilon^2, \sigma_\eta^2$.

Posterior of α

- Notice, if we are conditioning on β for the posterior $\alpha_{1:T}|...$ then each y_{it} is independent and we can run the Kalman filter chains independently.
- Let $y_t^* = y_t - X_t\beta$, then the model becomes

$$y_t^* = \alpha_t + \varepsilon_t$$
$$\alpha_t = \alpha_{t-1} + \eta_t$$

- We can then run a forward Kalman filter with a backward sampler to sample from the posterior of $\alpha_{1:T}$ (Fruhwirth-Schnatter, 1994)

Posterior of β

- We let $\beta \sim N(\theta, \sigma_\beta^2)$
- The posterior is $\beta|... \sim N(\Sigma^{-1}B, \sigma_\varepsilon^2\sigma_\beta^2\Sigma^{-1})$ where,
- $B = \sigma_\beta^2\big(\sum_{t=1}^T y_t - \alpha_t\big)' X_t - \sigma_\varepsilon^2\theta$
- $\Sigma = (\sigma_\beta^2 \sum_{t=1}^T X_t' X_t) + \sigma_\varepsilon^2 I_p$

The Gibbs Sampling Algorithm

1. Select prior parameters for $\theta, \sigma_\beta^2, a_0, b_0, c_0, d_0$.
2. Let $\beta^{(0)} = \theta$, $\sigma_\eta^{2(0)} = \frac{d_0/2}{1+c_0/2}$, and $\sigma_\varepsilon^{2(0)} = \frac{b_0/2}{1+a_0/2}$.
3. Run a forward-filtering backward sampling procedure as described above conditioning on $\beta^{i-1}, \sigma_\eta^{2(i-1)}, \sigma_\varepsilon^{2(i-1)}$ and set the samples equal to $\alpha^{(i)}$ for the i^{th} iteration.
4. Sample σ_η^{2*} from $IG(\frac{nT+a_0}{2}, \frac{\sum_{t=1}^{T}(\alpha_t^{(i)} - \alpha_{t-1}^{(i)})^2 + b_0}{2})$ and set $\sigma_\eta^{2(i)} = \sigma_\eta^{2*}$.
5. Sample σ_ε^{2*} from $IG(\frac{nT+c_0}{2}, \frac{d_0 + \sum_{t=1}^{T}(y_t - X_t\beta^{(i-1)} - \alpha_t^{(i)})^2}{2})$ and set $\sigma_\varepsilon^{2(i)} = \sigma_\varepsilon^{2*}$.
6. Sample β^* from $N(\Sigma^{-1}B, \sigma_\varepsilon^2\sigma_\beta^2\Sigma^{-1})$ where $\alpha = \alpha^{(i)}, \sigma_\eta^2 = \sigma_\eta^{2(i)}, \sigma_\varepsilon^2 = \sigma_\varepsilon^{2(i)}$ and set $\beta^{(i)} = \beta^*$.
7. Repeat steps 3-6 for i in 1, 2, . . . , M.

Estimating β

- After throwing out a number of initial samples from the Gibb's sampler we can estimate β by taking the mean of the posterior samples.
- We create a 95 credibility interval (as a pseudo-confidence interval) by calculating the 97.5^{th} and 2.5^{th} percentiles of the posterior draws.

Simulation Analyses

- Conducted two separate simulation analyses.
  1. Fully simulated data controlling the underlying data generation process.
  2. Adding and estimating an effect on the Animals outcome where the underlying data generation process is unknown.
- The most desirable model is one that,
  - Maintains 95% coverage of true parameter.
  - Is unbiased.
  - Has small parameter variance (small 95% confidence intervals)

Simulation Study 1

We sampled from the models,

$$\begin{aligned} y_t &= \alpha_t + X_t\beta + \varepsilon_t, \quad && \varepsilon_t \sim N(0, \sigma_\varepsilon^2 I_n) \\ \alpha_t &= \alpha_{t-1} + \eta_t, && \eta_t \sim N(0, \sigma_\eta^2 I_n) \end{aligned} \tag{1}$$

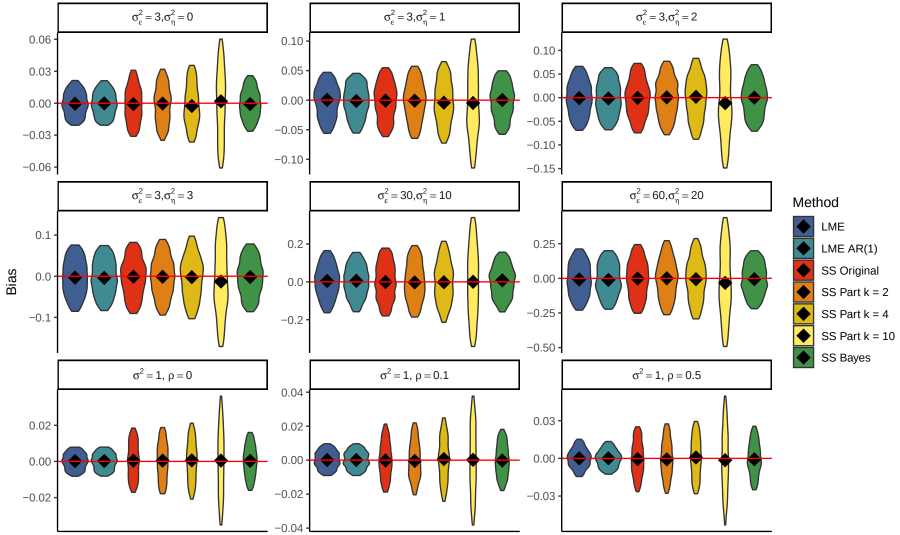
$$\begin{aligned} y_t &= b_0 + X_t\beta + e_t, \quad b_0 \sim N(0, \sigma_b^2) \\ e_t &= \rho e_{t-1} + \eta_t, \quad \eta_t \sim N(0, \sigma_\eta^2) \end{aligned} \tag{2}$$

We simulated 100 subjects to have between 3-10 observations. X was simulated to mirror our initial model of interest from the NACC. The variables σ_ε^2, σ_η^2, and ρ varied between simulations. We compared 95% CI coverage, bias, and estimate variance between 1. LMEM with a random intercept, 2. LMEM with a random intercept and AR(1) error correlation structure, the matrix formulation of the state space model, the Bayesian estimated state space model, the a state space model partitioned into 2, 4, and 10 groups.

95% Coverage

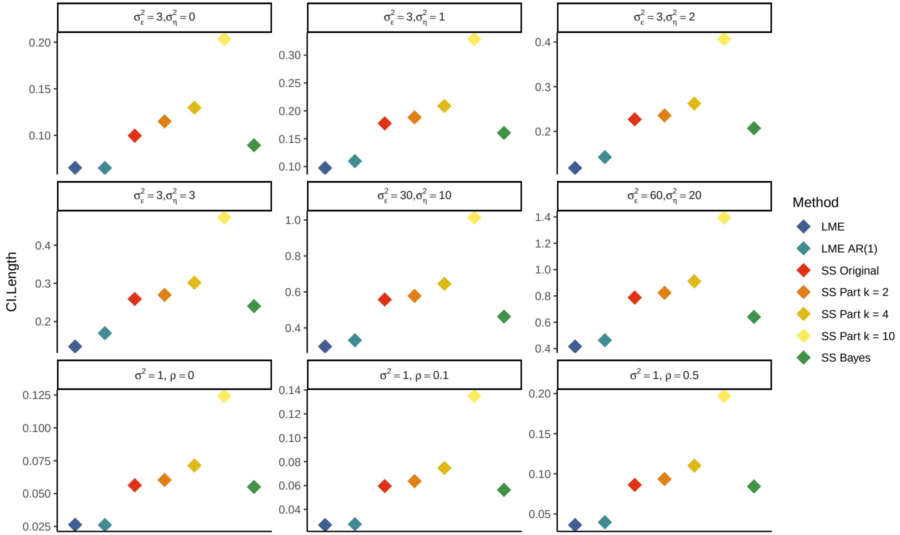
Variance Parameters		Traditional Methods		State Space Methods				
σ_ε^2	σ_η^2	LME	AR(1)	LLT	Part2	Part4	Part10	Bayes
3	0	0.941	0.940	0.945	0.966	0.968	0.977	0.958
3	1	0.788	0.848	0.945	0.949	0.954	0.968	0.941
3	2	0.733	0.837	0.947	0.942	0.950	0.969	0.932
3	3	0.715	0.838	0.946	0.939	0.947	0.968	0.928
30	10	0.771	0.836	0.942	0.940	0.945	0.969	0.940
60	20	0.780	0.840	0.944	0.944	0.945	0.967	0.944
$\rho = 0$	1	0.954	0.953	0.947	0.951	0.961	0.984	0.964
$\rho = 0.1$	1	0.938	0.947	0.945	0.953	0.961	0.983	0.955
$\rho = 0.5$	1	0.889	0.944	0.965	0.967	0.977	0.987	0.962

Bias



$\sigma^2_\varepsilon = 3, \sigma^2_\eta = 0$
$\sigma^2_\varepsilon = 3, \sigma^2_\eta = 1$
$\sigma^2_\varepsilon = 3, \sigma^2_\eta = 2$
$\sigma^2_\varepsilon = 3, \sigma^2_\eta = 3$
$\sigma^2_\varepsilon = 30, \sigma^2_\eta = 10$
$\sigma^2_\varepsilon = 60, \sigma^2_\eta = 20$
$\sigma^2 = 1, \rho = 0$
$\sigma^2 = 1, \rho = 0.1$
$\sigma^2 = 1, \rho = 0.5$
Bias
Method
LME
LME AR(1)
SS Original
SS Part k = 2
SS Part k = 4
SS Part k = 10
SS Bayes

CI Length



$\sigma^2_\varepsilon = 3, \sigma^2_\eta = 0$
$\sigma^2_\varepsilon = 3, \sigma^2_\eta = 1$
$\sigma^2_\varepsilon = 3, \sigma^2_\eta = 2$
$\sigma^2_\varepsilon = 3, \sigma^2_\eta = 3$
$\sigma^2_\varepsilon = 30, \sigma^2_\eta = 10$
$\sigma^2_\varepsilon = 60, \sigma^2_\eta = 20$
$\sigma^2 = 1, \rho = 0$
$\sigma^2 = 1, \rho = 0.1$
$\sigma^2 = 1, \rho = 0.5$
CI.Length
Method
LME
LME AR(1)
SS Original
SS Part k = 2
SS Part k = 4
SS Part k = 10
SS Bayes

Key Take-aways

- The state space methods give unbiased estimates while maintaining near 0.95 coverage probability for the 95% CIs.
  - While the LME methods are unbiased, they do not maintain 0.95 coverage probability under model mispecification.
- If the number of subjects in each partition is reasonable compared to the number of coefficients to estimate, then partitioning returns very similar results to not partitioning.
- Of the state space models, the Bayesian method has the least amount of variability in the estimates, the smallest variability in the estimate variances, all while maintaining 0.95 coverage probability.

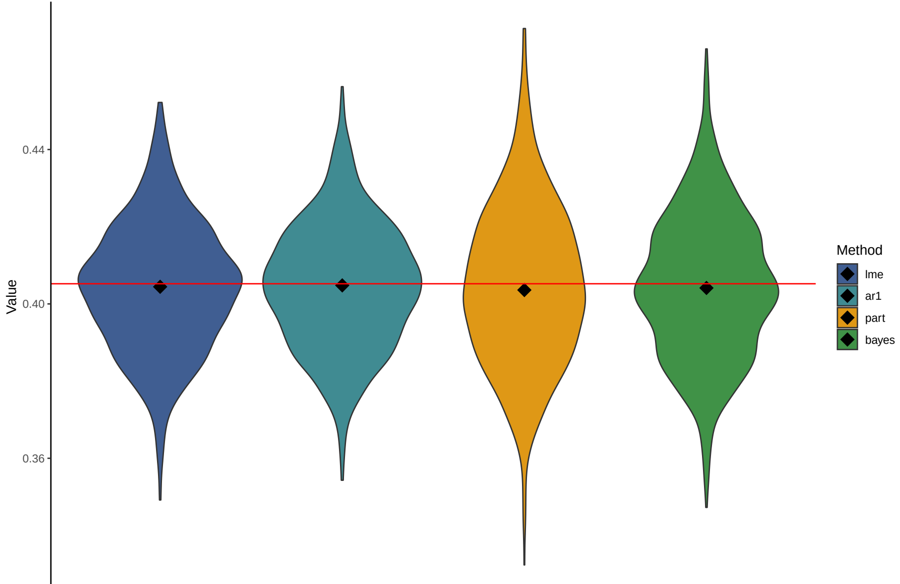
Real Data Simulation

- Add a linear effect on the Animals outcome for half the subjects.
- Estimate the model:

$$\begin{aligned}\textbf{Updated Animals} \sim & (1 + \mathrm{I}\{\text{Transitioned to MCI or Dementia}\} + \text{APOE} \\ & + \text{Sex} + \text{APOE*Sex} + \text{Race} + \text{Age} + \text{Education} \\ & + \textbf{Randomized Group}) * \text{Time}\end{aligned}$$

- Estimate the linear effect using the different models,
- LMEM, LMEM AR(1), Partitioned LLT with group size 100, and Bayesian LLT.

Bias



Coverage

lme	ar1	part	bayes
0.816	0.908	0.946	0.944

- When the underlying data generation process is unknown, the LLT models do a much better estimating the effect of interest.

Analysis

On the NACC data set we fit the model:

$$\text{Animals} \sim (1 + \text{I}\{\text{Transitioned to MCI or Dementia}\} + \text{APOE} + \text{Sex} \\ + \text{APOE*Sex} + \text{Race} + \text{Age} + \text{Education}) * \text{Time}$$

Using the LMEM, LMEM AR(1), and the Bayesian LLT Model.

Results

	APOE	APOE x Sex
lme	-0.088 (-0.166, -0.009)	-0.049 (-0.146, 0.049)
ar1	-0.077 (-0.176, 0.022)	-0.076 (-0.198, 0.046)
bayes	-0.089 (-0.201, 0.042)	-0.07 (-0.238, 0.081)

Summary

- The LLT shows proper 95% coverage for the fully simulated, even under model misspecification, and for the real NACC data.
- When compared to the full data LLT, the partitioned LLT shows very similar results as long as the number of parameters estimated is reasonable for the group size.
- The Bayesian LLT is the most desirable of the fitted models as it maintains 95% coverage, is unbiased, and has the smallest parameter variance.

Thank you!

Questions?