Thesis: 02/12/2021

Analysing LUMC Dataset

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December 3, 2021

Data

	ID	severity_score_pseudo	day_no	Cytokine_1	Cytokine_2	Cytokine_3
1	1	2.00	11.00	92.03	1053.03	244.03
2	1	3.00	13.00	106.68	1011.68	214.68
3	1	7.00	15.00	49.19	1010.19	183.19
4	1	0.00	18.00	77.63	1473.63	269.63
5	1	1.00	20.00	38.73	1129.73	259.73
6	2	15.00	38.00	152.03	727.03	347.03
7	2	15.00	43.00	199.81	987.81	350.81

- Missing data: only in variable day_no
  - For 2 patients: ID 46 (11 measurements) & ID 98 (8 measurements), both all time points

Transformations

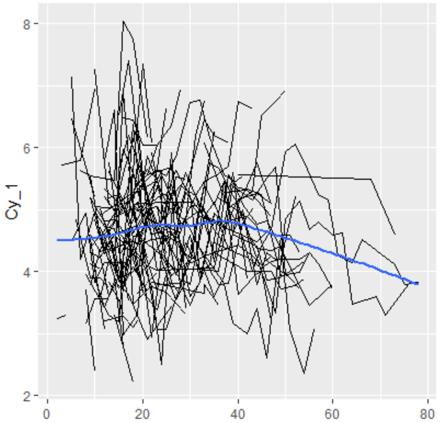
- In the table we see the correlations with severity score for different transformations of the cytokines

	NO	ln	sqrt
Cytokine 1	0.22	0.38	0.31
Cytokine 2	0.04	0.07	0.05
Cytokine 3	0.32	0.34	0.34

- We thus take a log transformation for all Cytokines
- As Cytokine 1 has highest correlation with severity score we focus on Cytokine 1

Time-Transformations

- We have only data about days when patient was at the ICU?
  - Average time-span per patient: 13 days.
    - RIVM: Average time at ICU: 13 days
  - Minimum: 0 days, Maximum: 47 days
- We see that time-patterns are very different

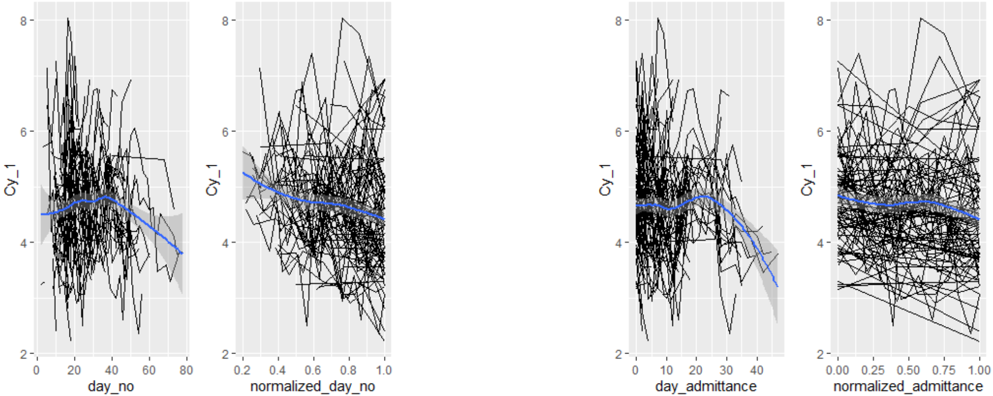


Different Time-scales

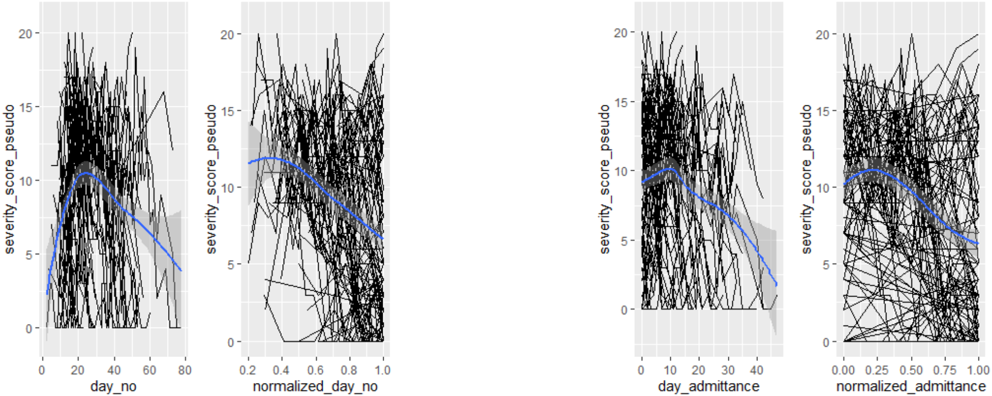
- Thus I tried different time-scales
  - Time since infection (day_no)
  - Nomalized time since infection
  - Time since admittance
  - Normalized time since admittance
- Below correlation table: However, correlation measures only linear association

	score	Cy_1	day_no	nor_day_no	day_admit	nor_admit
severity_score_pseudo	1.00	0.38	-0.07	-0.34	-0.20	-0.31
Cy_1	0.38	1.00	-0.04	-0.18	-0.07	-0.14
day_no	-0.07	-0.04	1.00	0.40	0.81	0.48
normalized_day_no	-0.34	-0.18	0.40	1.00	0.39	0.84
day_admittance	-0.20	-0.07	0.81	0.39	1.00	0.64
normalized_admittance	-0.31	-0.14	0.48	0.84	0.64	1.00

Different Time-scales



Different Time-scales



Different Time-scales

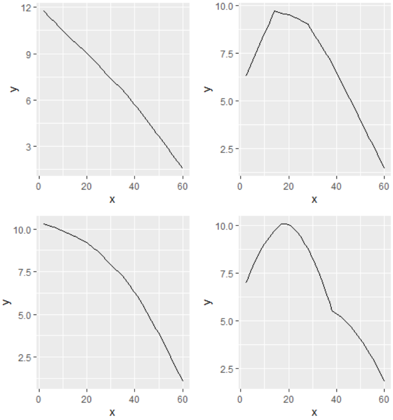
- I decided to focus on days since infection
  - Day since infection is most interesting for a doctor
  - Normalized days can not be used as a prediction model (can be useful for etiology).
- Here you do not account for different disease progression speeds in individuals.
  - Random breakpoints?

Possible Time-models

- For days since infection time is clearly not linear!
    - There are several ways in which to account for this
        - Quadratic change
        - Piecewise linear change (with breakpoints)
        - Quadratic Splines model (with breakpoints)
    - I also added Linear change model as reference
- Piecewise linear change: How to get breakpoints?
    - MARS (Multivariate adaptive regression spline)
        - For Cytokine 1: breakpoints 28 & 40
        - For Severity Score: breakpoints 14 & 28
- Quadratic Splines: location of breakpoints less important
    - I set bp to 1st and 3rd quartiles

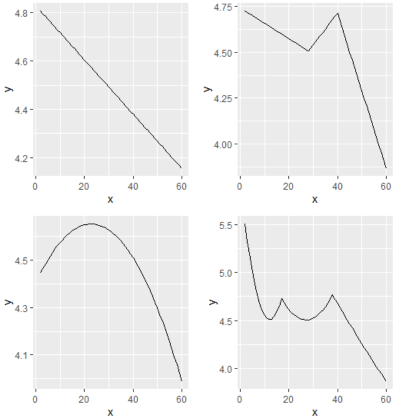
Time-models Severity Score

	Linear	Piecewise	Quadratic	Cubic
AIC	3088	3033	3083	3074
BIC	3109	3072	3109	3117
logLik	-1539	-1507	-1536	-1527



Time-models Cytokine 1

	Linear	Piecewise	Quadratic	Cubic
AIC	1333.00	1318.00	1324.00	1319.00
BIC	1350.00	1344.00	1345.00	1358.00
logLik	-662.00	-653.00	-657.00	-651.00



Modelling time: Conclusion

- I decided to stick with piecewise linear time-model
  - Breakpoints as given by MARS
- Applied Models 0 & 2 & 3 in INLA using piecewise time
  - First without breakpoints (simply linear)
  - No breakpoints within random effects
  - Only breakpoint 28 as random effects
  - All breakpoints as random effects
- Breakpoint 28 is more important than the other because:
  - Cy: Few patients have data further than bp 40 (only 25/99)
  - Score: The breakpoint at 28 seems much stronger than that at 14 (judging by loess fit)

Model 0_3: General Model structure in INLA

Model 0_3

$$\begin{cases} Cy_{i,j} = & (\beta_0^{(Cy)} + u_{0,i}^{(Cy)}) + \beta_{Sc}^{(Cy)} Score_{i,j} + (\beta_t^{(Cy)} + u_{t,i}^{(Cy)}) t_{i,j} + \\ & (\beta_t^{(Cy),28} + u_{t,i}^{(Cy),28})(t_{i,j} - 28)_+ + \\ & (\beta_t^{(Cy),40} + u_{t,i}^{(Cy),40})(t_{i,j} - 40)_+ + \epsilon_{i,j}^2 \\ Sc_{i,j} = & (\beta_0^{(Sc)} + u_{0,i}^{(Sc)}) + \beta_{Cy}^{(Sc)} Cy_{i,j} + (\beta_t^{(Sc)} + u_{t,i}^{(Sc)}) t_{i,j} + \\ & (\beta_t^{(Sc),28} + u_{t,i}^{(Sc),28})(t_{i,j} - 28)_+ + \\ & (\beta_t^{(Sc),14} + u_{t,i}^{(Sc),14})(t_{i,j} - 14)_+ + \epsilon_{i,j}^2 \end{cases}$$

$$\left(u_{0,i}^{(Cy)}, u_{t,i}^{(Cy)}, u_{t,i}^{(Cy),28}, u_{t,i}^{(Cy),40}\right) \sim \mathcal{N}(0, unstructured)$$

$$\left(u_{0,i}^{(Sc)}, u_{t,i}^{(Sc)}, u_{t,i}^{(Sc),28}, u_{t,i}^{(Sc),14}\right) \sim \mathcal{N}(0, unstructured)$$

Model 0_0: No breakpoints

$$
\begin{cases}
Cy_{i,j} = & (\beta_0^{(Cy)} + u_{0,i}^{(Cy)}) + \beta_{Sc}^{(Cy)} Score_{i,j} + (\beta_t^{(Cy)} + u_{t,i}^{(Cy)})t_{i,j} + \\
& \cancel{(\beta_t^{(Cy),28} + u_{t,i}^{(Cy),28})(t_{i,j} - 28)_+ +} \\
& \cancel{(\beta_t^{(Cy),40} + u_{t,i}^{(Cy),40})(t_{i,j} - 40)_+} + \epsilon_{i,j}^2 \\
Sc_{i,j} = & (\beta_0^{(Sc)} + u_{0,i}^{(Sc)}) + \beta_{Cy}^{(Sc)} Cy_{i,j} + (\beta_t^{(Sc)} + u_{t,i}^{(Sc)})t_{i,j} + \\
& \cancel{(\beta_t^{(Sc),28} + u_{t,i}^{(Sc),28})(t_{i,j} - 28)_+ +} \\
& \cancel{(\beta_t^{(Sc),14} + u_{t,i}^{(Sc),14})(t_{i,j} - 14)_+} + \epsilon_{i,j}^2
\end{cases}
$$

$$\left(u_{0,i}^{(Cy)}, u_{t,i}^{(Cy)}, \cancel{u_{t,i}^{(Cy),28}, u_{t,i}^{(Cy),40}}\right) \sim \mathcal{N}(0, unstructured)$$

$$\left(u_{0,i}^{(Sc)}, u_{t,i}^{(Sc)}, \cancel{u_{t,i}^{(Sc),28}, u_{t,i}^{(Sc),14}}\right) \sim \mathcal{N}(0, unstructured)$$

Model 0_1: No breakpoints as random effects

$$
\begin{cases}
Cy_{i,j} = & (\beta_0^{(Cy)} + u_{0,i}^{(Cy)}) + \beta_{Sc}^{(Cy)} Score_{i,j} + (\beta_t^{(Cy)} + u_{t,i}^{(Cy)})t_{i,j} + \\
& (\beta_t^{(Cy),28} + \cancel{u_{t,i}^{(Cy),28}})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Cy),40} + \cancel{u_{t,i}^{(Cy),40}})(t_{i,j} - 40)_+ + \epsilon_{i,j}^2 \\
Sc_{i,j} = & (\beta_0^{(Sc)} + u_{0,i}^{(Sc)}) + \beta_{Cy}^{(Sc)} Cy_{i,j} + (\beta_t^{(Sc)} + u_{t,i}^{(Sc)})t_{i,j} + \\
& (\beta_t^{(Sc),28} + \cancel{u_{t,i}^{(Sc),28}})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Sc),14} + \cancel{u_{t,i}^{(Sc),14}})(t_{i,j} - 14)_+ + \epsilon_{i,j}^2
\end{cases}
$$

$$
\left(u_{0,i}^{(Cy)}, u_{t,i}^{(Cy)}, \cancel{u_{t,i}^{(Cy),28}, u_{t,i}^{(Cy),40}}\right) \sim \mathcal{N}(0, unstructured)
$$

$$
\left(u_{0,i}^{(Sc)}, u_{t,i}^{(Sc)}, \cancel{u_{t,i}^{(Sc),28}, u_{t,i}^{(Sc),14}}\right) \sim \mathcal{N}(0, unstructured)
$$

Model 0_2: Only breakpoint 28 as random effect

$$
\begin{cases}
Cy_{i,j} = & (\beta_0^{(Cy)} + u_{0,i}^{(Cy)}) + \beta_{Sc}^{(Cy)} Score_{i,j} + (\beta_t^{(Cy)} + u_{t,i}^{(Cy)}) t_{i,j} + \\
& (\beta_t^{(Cy),28} + u_{t,i}^{(Cy),28})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Cy),40} + \cancel{u_{t,i}^{(Cy),40}})(t_{i,j} - 40)_+ + \epsilon_{i,j}^2 \\
Sc_{i,j} = & (\beta_0^{(Sc)} + u_{0,i}^{(Sc)}) + \beta_{Cy}^{(Sc)} Cy_{i,j} + (\beta_t^{(Sc)} + u_{t,i}^{(Sc)}) t_{i,j} + \\
& (\beta_t^{(Sc),28} + u_{t,i}^{(Sc),28})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Sc),14} + \cancel{u_{t,i}^{(Sc),14}})(t_{i,j} - 14)_+ + \epsilon_{i,j}^2
\end{cases}
$$

$$
\left(u_{0,i}^{(Cy)}, u_{t,i}^{(Cy)}, u_{t,i}^{(Cy),28}, \cancel{u_{t,i}^{(Cy),40}}\right) \sim \mathcal{N}(0, unstructured)
$$

$$
\left(u_{0,i}^{(Sc)}, u_{t,i}^{(Sc)}, u_{t,i}^{(Sc),28}, \cancel{u_{t,i}^{(Sc),14}}\right) \sim \mathcal{N}(0, unstructured)
$$

Model 2_3: General Model structure in INLA

Model 2_3

$$
\begin{cases}
Cy_{i,j} = & (\beta_0^{(Cy)} + u_{0,i}^{(Cy)}) + \beta_{Sc}^{(Cy)} Score_{i,j} + (\beta_t^{(Cy)} + u_{t,i}^{(Cy)}) t_{i,j} + \\
& (\beta_t^{(Cy),28} + u_{t,i}^{(Cy),28})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Cy),40} + u_{t,i}^{(Cy),40})(t_{i,j} - 40)_+ + \epsilon_{i,j}^2 \\
Sc_{i,j} = & (\beta_0^{(Sc)} + u_{0,i}^{(Sc)}) + \beta_{Cy}^{(Sc)} Cy_{i,j} + (\beta_t^{(Sc)} + u_{t,i}^{(Sc)}) t_{i,j} + \\
& (\beta_t^{(Sc),28} + u_{t,i}^{(Sc),28})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Sc),14} + u_{t,i}^{(Sc),14})(t_{i,j} - 14)_+ + \epsilon_{i,j}^2
\end{cases}
$$

$$
\left(u_{0,i}^{(Cy)}, u_{t,i}^{(Cy)}, u_{0,i}^{(Sc)}, u_{t,i}^{(Sc)}\right) \sim \mathcal{N}(0, unstructured)
$$

$$
\left(u_{t,i}^{(Cy),28}, u_{t,i}^{(Cy),40}, u_{t,i}^{(Sc),28}, u_{t,i}^{(Sc),14}\right) \sim \mathcal{N}(0, unstructured)
$$

Model 2_0: No breakpoints

$$
\begin{cases}
Cy_{i,j} = & (\beta_0^{(Cy)} + u_{0,i}^{(Cy)}) + \beta_{Sc}^{(Cy)} Score_{i,j} + (\beta_t^{(Cy)} + u_{t,i}^{(Cy)}) t_{i,j} + \\
& \cancel{(\beta_t^{(Cy),28} + u_{t,i}^{(Cy),28})(t_{i,j} - 28)_+ +} \\
& \cancel{(\beta_t^{(Cy),40} + u_{t,i}^{(Cy),40})(t_{i,j} - 40)_+} + \epsilon_{i,j}^2 \\
Sc_{i,j} = & (\beta_0^{(Sc)} + u_{0,i}^{(Sc)}) + \beta_{Cy}^{(Sc)} Cy_{i,j} + (\beta_t^{(Sc)} + u_{t,i}^{(Sc)}) t_{i,j} + \\
& \cancel{(\beta_t^{(Sc),28} + u_{t,i}^{(Sc),28})(t_{i,j} - 28)_+ +} \\
& \cancel{(\beta_t^{(Sc),14} + u_{t,i}^{(Sc),14})(t_{i,j} - 14)_+} + \epsilon_{i,j}^2
\end{cases}
$$

$$
\left(u_{0,i}^{(Cy)}, u_{t,i}^{(Cy)}, u_{0,i}^{(Sc)}, u_{t,i}^{(Sc)}\right) \sim \mathcal{N}(0, unstructured)
$$

$$
\cancel{\left(u_{t,i}^{(Cy),28}, u_{t,i}^{(Cy),40}, u_{t,i}^{(Sc),28}, u_{t,i}^{(Sc),14}\right) \sim \mathcal{N}(0, unstructured)}
$$

Model 2_1: No breakpoints as random effects

$$\begin{cases} Cy_{i,j} = & (\beta_0^{(Cy)} + u_{0,i}^{(Cy)}) + \beta_{Sc}^{(Cy)} Score_{i,j} + (\beta_t^{(Cy)} + u_{t,i}^{(Cy)}) t_{i,j} + \\ & (\beta_t^{(Cy),28} + \cancel{u_{t,i}^{(Cy),28}})(t_{i,j} - 28)_+ + \\ & (\beta_t^{(Cy),40} + \cancel{u_{t,i}^{(Cy),40}})(t_{i,j} - 40)_+ + \epsilon_{i,j}^2 \\ Sc_{i,j} = & (\beta_0^{(Sc)} + u_{0,i}^{(Sc)}) + \beta_{Cy}^{(Sc)} Cy_{i,j} + (\beta_t^{(Sc)} + u_{t,i}^{(Sc)}) t_{i,j} + \\ & (\beta_t^{(Sc),28} + \cancel{u_{t,i}^{(Sc),28}})(t_{i,j} - 28)_+ + \\ & (\beta_t^{(Sc),14} + \cancel{u_{t,i}^{(Sc),14}})(t_{i,j} - 14)_+ + \epsilon_{i,j}^2 \end{cases}$$

$$\left(u_{0,i}^{(Cy)}, u_{t,i}^{(Cy)}, u_{0,i}^{(Sc)}, u_{t,i}^{(Sc)}\right) \sim \mathcal{N}(0, unstructured)$$

$$\cancel{\left(u_{t,i}^{(Cy),28}, u_{t,i}^{(Cy),40}, u_{t,i}^{(Sc),28}, u_{t,i}^{(Sc),14}\right) \sim \mathcal{N}(0, unstructured)}$$

Model 2_2: Only breakpoint 28 as random effect

$$
\begin{cases}
Cy_{i,j} = & (\beta_0^{(Cy)} + u_{0,i}^{(Cy)}) + \beta_{Sc}^{(Cy)} Score_{i,j} + (\beta_t^{(Cy)} + u_{t,i}^{(Cy)}) t_{i,j} + \\
& (\beta_t^{(Cy),28} + u_{t,i}^{(Cy),28})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Cy),40} + \cancel{u_{t,i}^{(Cy),40}})(t_{i,j} - 40)_+ + \epsilon_{i,j}^2 \\
Sc_{i,j} = & (\beta_0^{(Sc)} + u_{0,i}^{(Sc)}) + \beta_{Cy}^{(Sc)} Cy_{i,j} + (\beta_t^{(Sc)} + u_{t,i}^{(Sc)}) t_{i,j} + \\
& (\beta_t^{(Sc),28} + u_{t,i}^{(Sc),28})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Sc),14} + \cancel{u_{t,i}^{(Sc),14}})(t_{i,j} - 14)_+ + \epsilon_{i,j}^2
\end{cases}
$$

$$
\left(u_{0,i}^{(Cy)}, u_{t,i}^{(Cy)}, u_{0,i}^{(Sc)}, u_{t,i}^{(Sc)}\right) \sim \mathcal{N}(0, unstructured)
$$

$$
\left(u_{t,i}^{(Cy),28}, u_{t,i}^{(Sc),28}, \cancel{u_{t,i}^{(Cy),40}, u_{t,i}^{(Sc),14}}\right) \sim \cancel{\mathcal{N}(0, unstructured)}
$$

Model 3_3: General Model structure in INLA

$$
\begin{cases}
m_{i,j} = & (\beta_0^{(Cy)} + u_{0,i}^{(Cy)}) + (\beta_t^{(Cy)} + u_{t,i}^{(Cy)})t_{i,j} + \\
& (\beta_t^{(Cy),28} + u_{t,i}^{(Cy),28})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Cy),40} + u_{t,i}^{(Cy),40})(t_{i,j} - 40)_+ \\
Cy_{i,j} = & m_{i,j} + \epsilon_{i,j}^2 \\
Sc_{i,j} = & \gamma m_{i,j} + (\beta_0^{(Sc)} + u_{0,i}^{(Sc)}) + \beta_{Cy}^{(Sc)} Cy_{i,j} + (\beta_t^{(Sc)} + u_{t,i}^{(Sc)})t_{i,j} + \\
& (\beta_t^{(Sc),28} + u_{t,i}^{(Sc),28})(t_{i,j} - 28)_+ + \\
& (\beta_t^{(Sc),14} + u_{t,i}^{(Sc),14})(t_{i,j} - 14)_+ + \epsilon_{i,j}^2
\end{cases}
$$

$$
\left(u_{0,i}^{(Cy)}, u_{t,i}^{(Cy)}, u_{t,i}^{(Cy),28}, u_{t,i}^{(Cy),40}\right) \sim \mathcal{N}(0, unstructured)
$$

$$
\left(u_{0,i}^{(Sc)}, u_{t,i}^{(Sc)}, u_{t,i}^{(Sc),28}, u_{t,i}^{(Sc),14}\right) \sim \mathcal{N}(0, unstructured)
$$

Models 3

- Similarly to Models 0 and 2 we also introduced Models 3_0, 3_1 and 3_2.
- A problem with Model 3 is that we can not put Score into the linear predictor of Cy
  - $Cy_{i,j} = \beta_{Sc}^{(Cy)} Score_{i,j}$ is not possible
  - INLA then simply ensures that $\gamma \cdot \beta_{Sc}^{(Cy)} = 1$, and all other terms are set to 0.
  - This problem can be averted when using Lagged values!
- Fitting these models takes a lot of computing power!
  - I therefore do a lot of the programming on the LUMC-test computer, is that allowed?
  - Can I install git on the LUMC computer?

General form of Model 3

- Association supplied via γ.

$$\begin{cases} m_{ij} = (\beta_0^{(x)} + u_{0,i}^{(x)}) + \beta_v^{(x)} \cdot v_i + \left(\beta_t^{(x)} + u_{t,i}^{(x)}\right) \cdot t_{i,j} \\ x_{i,j} = m_{ij} + \epsilon_{i,j}^{(x)} \\ y_{i,j} = \gamma \cdot m_{ij} + (\beta_0^{(y)} + u_{0,i}^{(y)}) + \beta_v^{(y)} \cdot v_i + \left(\beta_t^{(y)} + u_{t,i}^{(y)}\right) \cdot t_{i,j} + \epsilon_{i,j}^{(y)} \end{cases}$$

with

$$\begin{bmatrix} u_{0,i}^{(x)} \\ u_{t,i}^{(x)} \end{bmatrix} \sim \mathcal{N}_2 \left[\mathbf{0}, \begin{pmatrix} \sigma_{x,0}^2 & \sigma_{x,(0,t)} \\ \sigma_{x,(t,0)} & \sigma_{x,t}^2 \end{pmatrix} \right]; \quad \begin{bmatrix} u_{0,i}^{(y)} \\ u_{t,i}^{(y)} \end{bmatrix} \sim \mathcal{N}_2 \left[\mathbf{0}, \begin{pmatrix} \sigma_{y,0}^2 & \sigma_{y,(0,t)} \\ \sigma_{y,(t,0)} & \sigma_{y,t}^2 \end{pmatrix} \right];$$

General form of Model 3

- This can be rewritten as:

$$
\begin{aligned}
y_{i,j} &= \gamma \cdot m_{ij} + (\beta_0^{(y)} + u_{0,i}^{(y)}) + \beta_v^{(y)} \cdot v_i + \left(\beta_t^{(y)} + u_{t,i}^{(y)}\right) \cdot t_{i,j} + \epsilon_{i,j}^{(y)} = \\
&= (\gamma\beta_0^{(x)} + \beta_0^{(y)}) + (\gamma\beta_v^{(x)} + \beta_v^{(y)})v_i + \left(\gamma\beta_t^{(x)} + \beta_t^{(y)}\right) \cdot t_{i,j} + (\gamma u_{0,i}^{(x)} + u_{0,i}^{(y)}) + \\
&\quad + (\gamma u_{t,i}^{(x)} + u_{t,i}^{(y)})t_{i,j} + \epsilon_{i,j}^{(y)} = \\
&= \beta_0^{(y)'} + \beta_v^{(y)'} v_i + \beta_t^{(y)'} t_{i,j} + u_{0,i}^{(y)'} + u_{t,i}^{(y)'} \cdot t_{i,j} + \epsilon_{i,j}^{(y)}
\end{aligned}
$$

with $\beta_0^{(y)'} = \gamma\beta_0^{(x)} + \beta_0^{(y)}$, $\beta_v^{(y)'} = \gamma\beta_v^{(x)} + \beta_v^{(y)}$ and $\beta_t^{(y)'} = \gamma\beta_t^{(x)} + \beta_t^{(y)}$.
For the random effects, they now have distribution:

$$
\begin{bmatrix} u_{0,i}^{(y)'} \\ u_{t,i}^{(y)'} \end{bmatrix} \sim \mathcal{N}_2 \left[\mathbf{0}, \begin{pmatrix} \gamma^2\sigma_{x,0}^2 + \sigma_{y,0}^2 & \gamma^2\sigma_{x,(0,t)} + \sigma_{y,(0,t)} \\ \gamma^2\sigma_{x,(t,0)} + \sigma_{y,(t,0)} & \gamma^2\sigma_{x,t}^2 + \sigma_{y,t}^2 \end{pmatrix} \right]
$$

General form of Model 3

- We obtain:

$$x_{i,j} = (\beta_0^{(x)} + u_{0,i}^{(x)}) + \beta_v^{(x)} \cdot v_i + \left(\beta_t^{(x)} + u_{t,i}^{(x)}\right) \cdot t_{i,j} + \epsilon_{i,j}^{(x)}$$

$$y_{i,j} = (\beta_0^{(y)'} + u_{0,i}^{(y)'}) + \beta_v^{(y)'} v_i + (\beta_t^{(y)'} + u_{t,i}^{(y)'}) t_{i,j} + \epsilon_{i,j}^{(y)}$$

with

$$\begin{bmatrix} u_{0,i}^{(x)} \\ u_{t,i}^{(x)} \end{bmatrix} \sim \mathcal{N}_2 \left[\mathbf{0}, \begin{pmatrix} \sigma_{x,0}^2 & \sigma_{x,(0,t)} \\ \sigma_{x,(t,0)} & \sigma_{x,t}^2 \end{pmatrix} \right],$$

$$\beta_0^{(y)'} = \gamma \beta_0^{(x)} + \beta_0^{(y)}, \quad \beta_v^{(y)'} = \gamma \beta_v^{(x)} + \beta_v^{(y)} \text{ and } \beta_t^{(y)'} = \gamma \beta_t^{(x)} + \beta_t^{(y)}$$

$$\begin{bmatrix} u_{0,i}^{(y)'} \\ u_{t,i}^{(y)'} \end{bmatrix} \sim \mathcal{N}_2 \left[\mathbf{0}, \begin{pmatrix} \gamma^2 \sigma_{x,0}^2 + \sigma_{y,0}^2 & \gamma^2 \sigma_{x,(0,t)} + \sigma_{y,(0,t)} \\ \gamma^2 \sigma_{x,(t,0)} + \sigma_{y,(t,0)} & \gamma^2 \sigma_{x,t}^2 + \sigma_{y,t}^2 \end{pmatrix} \right]$$

Lagged effects

- Via multiple γ's
- Via history of outcome/endogenous covariate

Multiple γ's

$$
\begin{cases}
m_{ij} = (\beta_0^{(x)} + u_{0,i}^{(x)}) + \beta_v^{(x)} \cdot v_i + \left(\beta_t^{(x)} + u_{t,i}^{(x)}\right) \cdot t_{i,j} \\
x_{i,j} = m_{ij} + \epsilon_{i,j}^{(x)} \\
x_{i,(j-1)} = m_{i,(j-1)} + \epsilon_{i,(j-1)}^{(x)} \\
y_{i,j} = \gamma_1 \cdot m_{ij} + \gamma_2 \cdot m_{i,(j-1)} + (\beta_0^{(y)} + u_{0,i}^{(y)}) + \beta_v^{(y)} \cdot v_i + \left(\beta_t^{(y)} + u_{t,i}^{(y)}\right) \cdot t_{i,j} + \epsilon_{i,j}^{(y)}
\end{cases}
$$

- Here the same problem arises as in model with single γ.

Multiple γ's

- We obtain:

$$x_{i,j} = (\beta_0^{(x)} + u_{0,i}^{(x)}) + \beta_v^{(x)} \cdot v_i + \left(\beta_t^{(x)} + u_{t,i}^{(x)}\right) \cdot t_{i,j} + \epsilon_{i,j}^{(x)}$$

$$y_{i,j} = (\beta_0^{(y)'} + u_{0,i}^{(y)'}) + \beta_v^{(y)'} v_i + (\beta_t^{(y)'} + u_{t,i}^{(y)'}) t_{i,j} + \epsilon_{i,j}^{(y)}$$

with

$$\beta_0^{(y)'} = (\gamma_1 + \gamma_2)\beta_0^{(x)} + \beta_0^{(y)}, \quad \beta_v^{(y)'} = (\gamma_1 + \gamma_2)\beta_v^{(x)} + \beta_v^{(y)}$$

and $\beta_t^{(y)'} = (\gamma_1 + \gamma_2)\beta_t^{(x)} + \beta_t^{(y)}$

Variable History

- Can be implemented via e.g. AR process

$$\begin{cases} x_{i,j} = (\beta_0^{(x)} + u_{0,i}^{(x)}) + \beta_v^{(x)} \cdot v_i + \left(\beta_t^{(x)} + u_{t,i}^{(x)}\right) \cdot t_{i,j} + \sum_{t=1}^{p} \phi_t x_{j-t} + \epsilon_{i,j}^{(x)} \\ y_{i,j} = (\beta_0^{(y)} + u_{0,i}^{(y)}) + \beta_v^{(y)} \cdot v_i + \left(\beta_t^{(y)} + u_{t,i}^{(y)}\right) \cdot t_{i,j} + \sum_{t=1}^{p} \phi_t y_{j-t} + \epsilon_{i,j}^{(y)} \end{cases}$$

- One can set the depth of the history by varying p
- One can set requirements for ϕ, e.g: $\phi_t = \phi^t$.
- Can also be combined with model 3

Model comparison

- We see that overall Model 0_3 performs best
  - No association between the endogenous covariate and the outcome
  - Maximum number of breakpoints
  - Maximum number of random effects, maximum covariance between random effects

	0_0	0_1	0_2	0_3	2_0	2_1	2_2	2_3	3_0	3_1	3_2	3_3
MLIK	-2399	-2404	-2420	-2411	-2402	**-2394**	-2417	-2418	-2406	-2404	-2417	-2407
DIC_approx	4798	4808	4840	4821	4804	**4789**	4834	4836	4811	4809	4834	4813
DIC	4108	4088	4087	**4024**	4114	4074	4039	4040	4136	4137	4131	4060
WAIC	4103	4085	4081	**4013**	4109	4072	4034	4031	4129	4132	4123	4046
PIT	0.0394	0.0315	0.0255	0.0254	0.0380	0.0317	0.0324	0.0279	0.0290	**0.0252**	0.0277	0.0291
CPO	2083	2072	2074	**2046**	2081	2061	2049	2054	2093	2092	2092	2060
MSE	3.61	3.70	4.03	**3.52**	3.73	3.91	3.71	3.70	3.60	3.68	4.06	**3.52**

To-do

- Focus should be on lagged effects!
  - Using Lagged functional form
    - Using $\gamma_2 \cdot m_i(t_{i,j-1})$
    - Using autoregressive model?
  - Using other residual error covariance structures
- Inspect different time-scales and time-models

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