A Safety Signal Analysis with Three-Level Hierarchical Mixture Model

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Introduction

Some background

1. trials with treatment and control group (two arms);
2. want to understand if treatment (or drug) cause adverse effects;
3. we have many adverse effects categorized under different body systems.

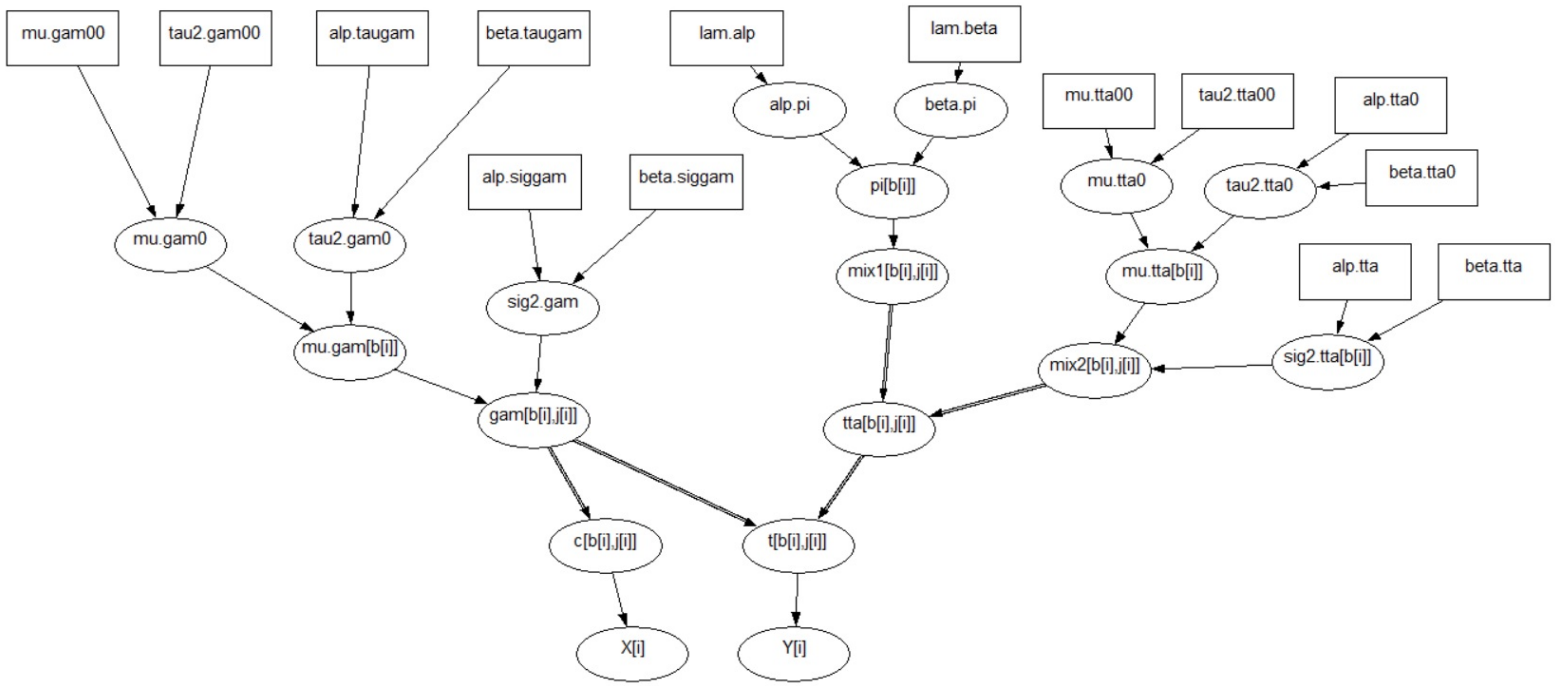
Introduction

b	j	Type of SAE A_{bj}	Treatment (N_T=320) Y_{bj}	Rate	Control (N_C=320) X_{bj}	Rate
1	1	Arrhythmia	0	0.000	1	0.003
1	2	Increased BP	3	0.009	3	0.009
1	3	Other CB AEs	0	0.000	2	0.006
1	4	Pre-eclampsia	8	0.025	6	0.019
2	1	Emesis	0	0.000	1	0.003
2	2	Other GI AEs	0	0.000	1	0.003
3	1	Depression	0	0.000	1	0.003
3	2	Headache	0	0.000	1	0.003
3	3	Other HNMB AEs	1	0.003	0	0.000
4	1	Gestational Diabetes Mellitus	2	0.006	0	0.000
4	2	Other MAN AEs	0	0.000	1	0.003
5	1	Chorioamnionitis	0	0.000	2	0.006
5	2	Decreased Fetal Movement	1	0.003	2	0.006
5	3	Endomyometritis	1	0.003	0	0.000
5	4	Miscarriage	0	0.000	1	0.003
5	5	Other PD AEs	3	0.009	1	0.003
5	6	Postpartum Hemorrhage	1	0.003	0	0.000
5	7	Premature Delivery	5	0.016	5	0.016
5	8	Premature ROM	2	0.006	10	0.031
5	9	Preterm Contractions	2	0.006	4	0.013
6	1	Other RESP AEs	0	0.000	1	0.003
6	2	Shortness of Breath	0	0.000	1	0.003
7	1	Other UG AEs	1	0.003	0	0.000
7	2	Pyelnephritis	1	0.003	4	0.013
7	3	Urinary Tract Infection	1	0.003	1	0.003
7	4	Vaginal Bleeding	1	0.003	1	0.003
8	1	Abdominal Pain	1	0.003	2	0.006
8	2	Other BODY AEs	0	0.000	3	0.009
8	3	PD012	2	0.006	0	0.000
8	4	Pelvic Pain	1	0.003	0	0.000
8	5	Polyhydramnios	0	0.000	1	0.003

Figur: data example

Model

We follow the three-level hierarchical model proposed in [**Berry04**]



Goal

We have the following goals:

1. Fit the original data from [**Berry04**](OpenBUGS and R) and compare
2. Fit the hierarchical model to the example data and compute posterior probabilities (OpenBUGS and R)
3. Fit another independent model to the example data and compare results with hierarchical model

OpenBUGS vs R vs Original Results

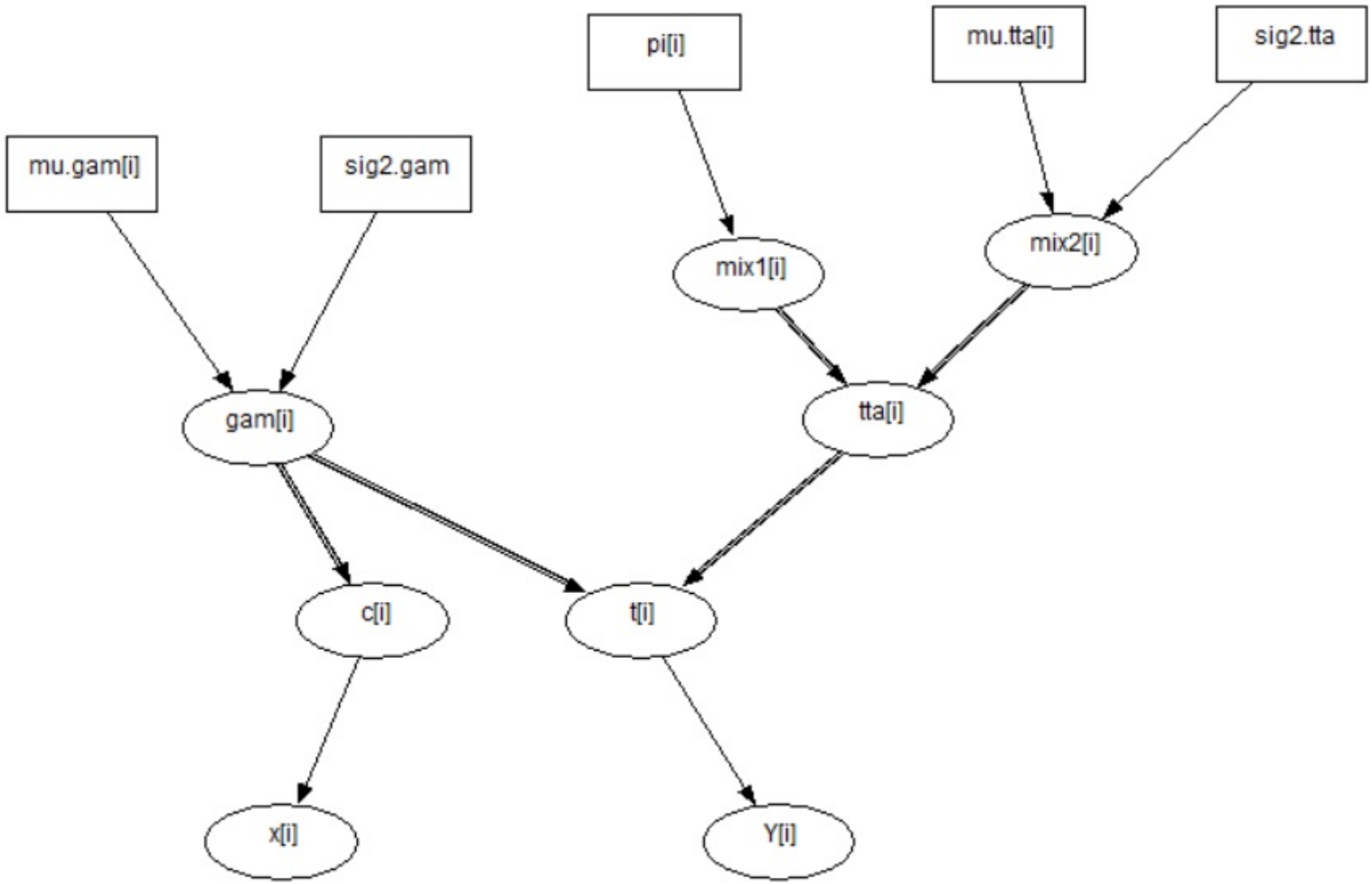
The following table compares results on the original data in [**Berry04**]:

		post $P(\theta > 0)$			
AEs	Type	Reference	OpenBugs	R	Fisher exact p
Irritability	$\theta_{8,3}$	0.78	0.978	0.984	0.003
Diarrhea	$\theta_{3,4}$	0.231	0.847	0.853	0.029
Rash	$\theta_{10,4}$	0.19	0.945	0.993	0.021
Rash, measles/rub-like	$\theta_{10,6}$	0.126	0.890	0.946	0.039

Tabel: OpenBugs and R results compare with reference

Independent Model

We compare hierarchical model with independent model when fitting the example data:



Results

	post $P(\theta > 0)$		
AE	R(Hierarchical)	OpenBUGS(Hierarchical)	OpenBUGS(Independent)
Arrhythmia	0.0207	0.0267	0.0496
Increased BP	0.0487	0.0591	0.0939
Other CB AEs	0.0136	0.0237	0.0227
Pre-eclampsia	0.0763	0.1102	0.1058
Emesis	0.0258	0.0264	0.0457
Other GI AEs	0.022	0.0249	0.0463
Depression	0.0229	0.0275	0.0464
Headache	0.0232	0.0301	0.0508
Other HNMB AEs	0.046	0.0529	0.2012
Gestational Diabetes Mellitus	0.0763	0.0961	0.2920
Other MAN AEs	0.0331	0.0341	0.0476
Chorioamnionitis	0.0061	0.0156	0.0240
Decreased Fetal Movement	0.0199	0.0281	0.0661
Endomyometritis	0.037	0.0413	0.1984
Miscarriage	0.0062	0.0194	0.0493
Other PD AEs	0.0634	0.0718	0.2238
Postpartum Hemorrhage	0.0309	0.0406	0.1871
Premature Delivery	0.0486	0.0671	0.0708
Premature ROM	0.0059	0.0109	0.0045
Preterm Contractions	0.0186	0.0331	0.0434
Other RESP AEs	0.0113	0.0232	0.0472
Shortness of Breath	0.0105	0.0251	0.0474
Other UG AEs	0.0466	0.0508	0.1887
Pyelnephritis	0.0254	0.0313	0.0272
Urinary Tract Infection	0.0466	0.0452	0.1047
Vaginal Bleeding	0.0402	0.0473	0.1046
Abdominal Pain	0.0335	0.0434	0.0616
Other BODY AEs	0.0125	0.0213	0.0118
PD012	0.0502	0.074	0.2885
Pelvic Pain	0.0414	0.0542	0.1897
Polyhydramnios	0.0198	0.0268	0.0483

References I

Berry, Scott M. and Berry, Donald A. (2004). Accounting for Multiplicities in Assessing Drug Safety: A Three-Level Hierarchical Mixture Model. *Biometrics* **60**, 418-426

Thank You!