# Applying Drug and Critical Term Ontologies to Australian Drug Safety Data for Adverse Event Signalling (AES) and Comparison with the Bayesian AES method MGPS

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# Outline

- Drug Safety Data (Australian Adverse Drug Reaction Advisory Committee (ADRAC) database)
- Develop new Adverse Event Signalling (AES) method
  - Using Ontologies
    - Reaction Terms (System organ class—SOC, Critical Terms)
    - Drug Terms (anatomical-therapeutic-chemical classification—ATC codes)
- Comparison with the Bayesian AES method mulit-item gamma Poisson shrinker —MGPS

# Motivation

- Existing signal detection methods
  - Proportional ratios – too sensitive
  - Bayesian
    - too insensitive,
    - lack transparency
    - signal leakage
    - signal masking

# Aims

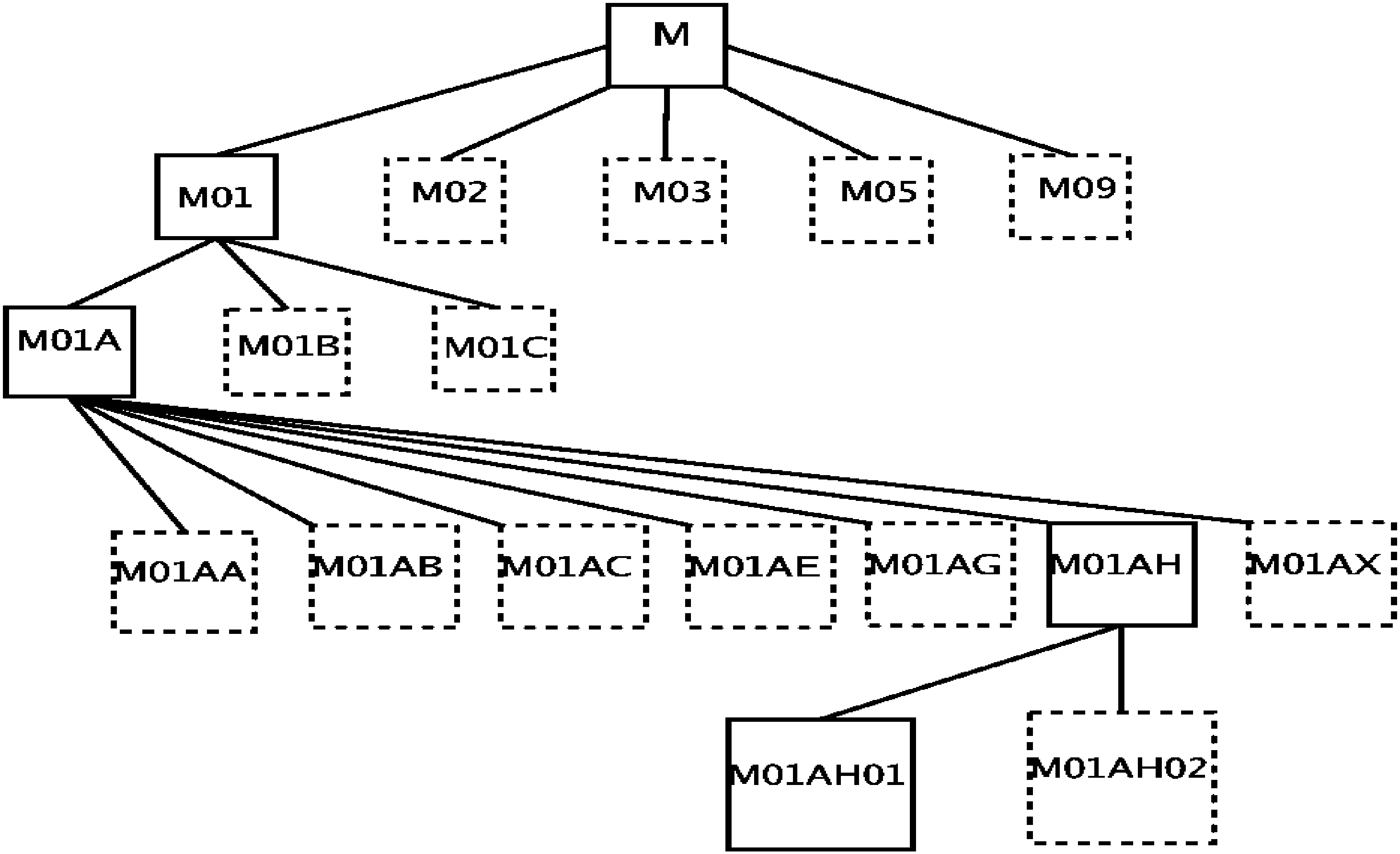
- Develop a signal method based on ontology for drugs and reactions
- Use critical reaction terms to increase signal intensity
- Exploit ATC drug classification hierarchy
- Follow significant drug-reaction associations, by traversal of the ATC tree where reaction frequencies are significant based on Chi-Square ($\chi^2$) test

**Reaction Ontology—SOC terms:**
Classified into 18 reaction classes

**Drug Ontology—ATC Embeded Code:**
X99XX99 (pattern)

| | |
|---|---|
| Level 0 – A (Alimentary tract) | 14 |
| Level 1 – A01 | 92 |
| Level 2 – A01A | 227 |
| Level 3 – A01AA | 602 |
| Level 4 – A01AA01 | 1809 |

# Tree Traversal for Musculo-skeletal system (M)



# Signal Method

- **Step 1**: Select drug and reaction class of interest
  - E.g., Musculo-skeletal system (M) and cardiovascular (SOC 1000)
- **Step2**: Find set of children in drug tree; test to see if any children have significantly more reactions (based on Chi-Square ($\chi^2$)
- **Step 3**: continue **Step 2** at next level down

# Signal Level

- **OK** – ≤ 15% critical terms
- **Notice** – 15 – 30%
- **Strong notice** – 30 – 40%
- **Warning** – 40 – 50%
- **Strong warning** – 50 – 60%
- **Alert** – > 60%

# Results:

Our algorithm produced a total of 62 warnings: 42 **OK**, 9 **NO**, 4 **WA**, 3 **SW**, 4 **AL**

The results of MGPS were ordered by **EBGM** with the highest value of 37.585

**Definition of MGPS values:**

**EBGM**—Empirical Bayesian Geometric Mean. A more stable estimate than RR; the shrinkage estimate, computed as the geometric mean of the posterior distribution of the true RR

**RR**—Relative Ratio. (The same as N/E.) Observed number of cases with the combination divided by the expected number of cases with the combination

**N**—Observed number of cases with the combination of items

**E**—The expected number of cases with the combination

**Table 1: Alert** Warning Level

| N | E | RR | EBGM | ATCcode | SOC | Drug_name | No_Sig* |
|---|---|---|---|---|---|---|---|
| 29 | 32.875 | 0.882 | 0.886 | A01AB03 | Nervous | Chlorhexidine | 26 |
| 401 | 103.919 | 3.859 | 3.842 | B01AB01 | Haemic&lymph | Heparin | 220 |
| 229 | 124.574 | 1.838 | 1.794 | C02AB01 | Haemic&lymph | Methyldopa | 177 |
| 27 | 4.301 | 6.278 | 5.644 | G02BA01 | Foetal | Plastic IUD | 26 |

* Number of signals with our algorithm for ATC/SOC pairs

**Table 2: Strong Warning** Level

| N | E | RR | EBGM | ATCcode | SOC | Drug_name | No_Sig |
|---|---|---|---|---|---|---|---|
| <2887 | | | ≤0.026 | M01AH01 | Haemic&lymph | Celecoxib | 105 |
| 123 | 76.476 | 1.608 | 1.546 | N05AH02 | Cardiovascular | Clozapine | 236 |
| 322 | 113.291 | 2.842 | 2.829 | V08AA20 | Respiratory | Meglumine diatrizoate | 188 |

**Table 3: Warning** Level

| N | E | RR | EBGM | ATCcode | SOC | Drug_name | No_Sig |
|---|---|---|---|---|---|---|---|
| 236 | 210.479 | 1.121 | 1.113 | J06BB30 | Nervous | Comb. Specific immunoglobulins | 690 |
| 537 | 113.134 | 4.747 | 4.727 | J01CF05 | Liver | Flucloxacillin | 267 |
| <2887 | | | ≤0.026 | M01AH01 | Cardiovascular | Celecoxib | 282 |
| 264 | 35.842 | 7.366 | 7.265 | N05AH02 | Haemic&lymph | Clozapine | 587 |

# Conclusion

- There is no correspondence between the signal levels we defined and the values produced by MGPS
- Our AES method is quite simplistic in its present form
- Problem could be in the SOC reaction system does not have enough levels of granularity for both AES methods
- Next plan is to make more use of association rules and the use of medical ontology, e.g., employ the MedDRA for reaction ontology, make use of a medical ontology

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