



BAYESIAN NETWORK META-ANALYSIS: WHAT, HOW, AND WHY?

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Special Thanks

- Keith Abrams
- Tony Ades
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Workshop Summary

- Introduction to Bayesian Methods
- Bayesian Approaches to Meta-Analysis
- Gibbs Sampling
- Indirect Comparisons (frequentist)
- Mixed Treatment Comparisons
- Examples



Bayes' Theorem

- Simple Manipulation of Conditional Probabilities

$$P(A \text{ and } B) = P(A|B)P(B) = P(B|A)P(A)$$

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

$$P(A|B) = \frac{P(B|A)P(A)}{P(B|A)P(A) + P(B|A')P(A')}$$



Bayes' Theorem

- Example with diagnostic testing:
- If the prevalence of a disease in a population is 1 in a 1000, and a specific test has a 99% chance of being correct (positive or negative), what is the probability a patient has the disease after testing positive?

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Bayes' Theorem

$$P(D | +ve) = \frac{P(+ve | D)P(D)}{P(+ve | D)P(D) + P(+ve | D')P(D')}$$

$$P(D | +ve) = \frac{(.99)(.001)}{(.99)(.001) + (.01)(.999)} = 0.09 = 9\%$$

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General Bayesian Formulation

- Want to estimate some parameter θ given data y .
- Frequentist statistical methods do this by using the data to find “best” estimate of θ by some manipulation of the data.
- This estimate will have desirable properties such as unbiasedness and low variance.

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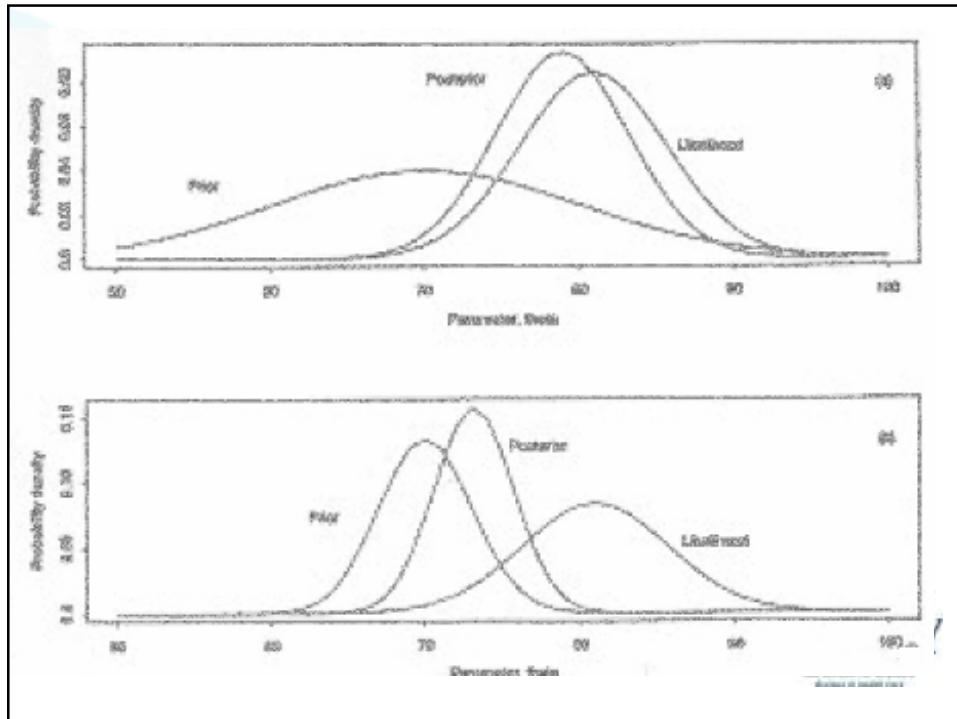
General Bayesian Formulation

$$p(\theta | y) = \frac{p(y | \theta)p(\theta)}{p(y)}$$

$$p(\theta | y) \propto L(y | \theta)p(\theta)$$

Posterior \propto Likelihood(Data)*Prior

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Prior Distributions

- Vague or Non-informative
 - Contain Little Information Relative to Likelihood
- Sceptical
 - Centred at no difference with a specified probability of showing a difference
- Enthusiastic
 - Initially favour one side
- Subjective
 - Elicited from experts or groups
- Based on previous evidence/studies
 - Adjusted and/or down-weighted for potential biases.

Example of Bayesian Formulation

- Previous experience suggests success rate of an intervention is between 20% and 60%.
- Prior \sim Beta ($\alpha=9.2$, $\beta=13.8$)
mean=0.4, SD=0.1.
- Data: Observe 15 successes out of 20.
- Posterior: Beta($\alpha=24.2$, $\beta=18.8$)
Posterior mean = 0.56.



Fundamental Differences Between Bayesian and Frequentist Formulations

- Prior Distribution
- Bayesian analysis treats unknown parameters as random variables, while frequentist analysis treats them as fixed but unknown quantities. (semantics?).



Review: Frequentist Methods of Meta-analysis

- Parameters are estimated on the study level first (i.e. parameter estimate with standard error).
- Studies are combined by weighting each by inverse variance (or other method) plus perhaps a function of between study variance (random effects).



Bayesian Approaches to Meta-Analysis

- Models are created using Bayesian methods.
- Prior distributions are specified for parameters and study results act as data for the likelihood.
- Parameters are defined by joint posterior distributions combined with prior distributions.



Example: Fixed Effects Model

$$Y_i \sim \text{Normal}(d, V_i)$$

$$d \sim \text{Normal}(0, 10^5) \text{ (vague prior)}$$

- The distribution of the assumed common mean difference of the studies (d) is derived from a vague prior and the study data.



Example: Random Effects Model

$$Y_i \sim \text{Normal}(\delta_i, V_i)$$

$$\delta_i \sim \text{Normal}(d, \tau^2)$$

$$d, \tau^2 \sim \text{prior distributions}$$

- Same as fixed effects, except each study is now allowed to have a different mean difference, that is presumably randomly distributed around a common study level mean.
- Note: Watch specification of prior distribution for between studies variance (τ^2).



Advantages of Bayesian Methods

- Can make direct probability statements.
- All evidence regarding a specific problem can be taken into account.
- Predictive statements can be easily made.
- Elicitation of prior belief forces investigators into more careful consideration.
- RE meta-analyses “borrow strength” from one another.
- Decision theoretic framework allows for easy accounting of cost/utilities in making decisions.

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Disadvantages of Bayesian Methods

- Use of prior beliefs undermines objectivity
- Elicitation of priors is non-trivial with few guidelines.
- Computationally complex to implement and time consuming to perform.
- Software limitations.

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Differences from Frequentist Meta-analysis

- Effects of prior distribution
- Between study variance (τ^2) treated as random variable rather than constant in Bayesian analysis (random effects only).
- Study level estimates are “shrunk” towards overall mean due to borrowing of information across studies.



Implementation: Gibbs Sampling

- Direct computation of posterior distributions is usually not feasible.
- By sampling from full conditional distributions we can get estimates of marginal (unconditional) distributions.
- This is known as Gibbs sampling—a Markov Chain Monte Carlo simulation.



Gibbs Sampling

$$(\theta_1 | \theta_2^0, \theta_3^0 \dots \theta_p^0, x) \sim [-, -] \Rightarrow \theta_1^1$$

$$(\theta_2 | \theta_1^1, \theta_3^0 \dots \theta_p^0, x) \sim [-, -] \Rightarrow \theta_2^1$$

⋮

$$(\theta_p | \theta_1^1, \theta_2^1 \dots \theta_{p-1}^1, x) \sim [-, -] \Rightarrow \theta_p^1$$

$$\underline{\theta}_1 \sim (\theta_1^1 \dots \theta_1^m)$$

⋮

$$\underline{\theta}_p \sim (\theta_p^1 \dots \theta_p^m)$$

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Indirect Comparisons (Bucher et al)

- When no or little direct evidence is available for comparing two interventions, they can be compared indirectly using the methods of Bucher et al.
- This method preserves the randomisation preserves idea inherent in meta-analysis that we should compare directly only with studies.

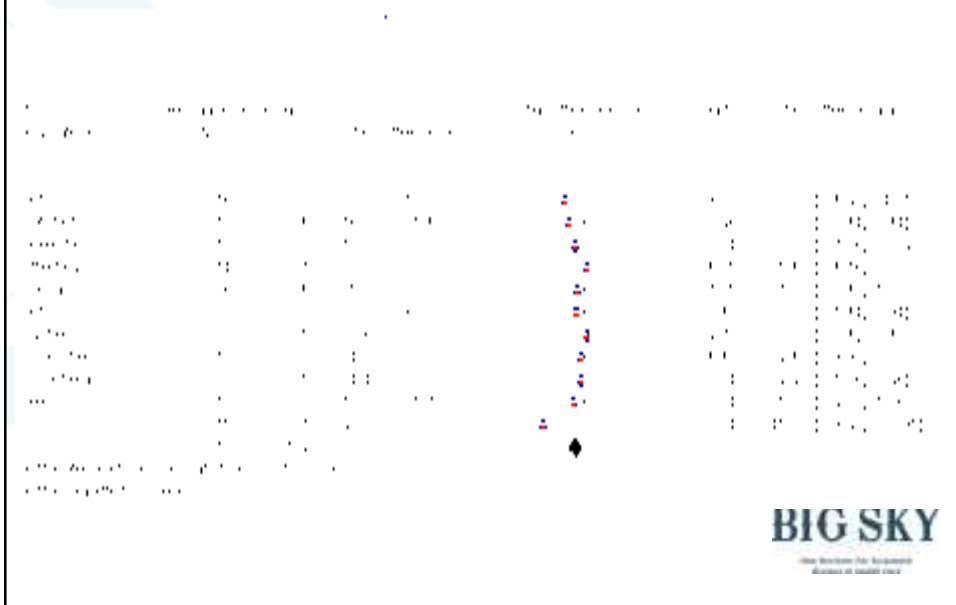
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Basic Formulation

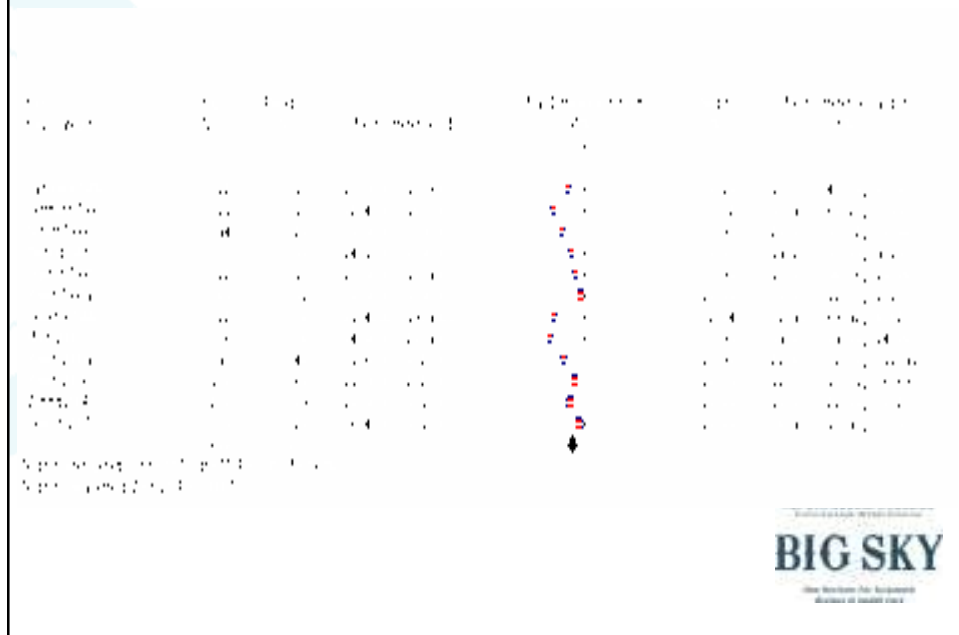
- No direct evidence comparing A with B, yet estimate of A-B (d_{AB}) is desired.
- Direct evidence exists comparing A with C (d_{AC}) as well as evidence comparing B with C (d_{BC}).
- $d_{AB} = d_{AC} - d_{BC}$
- $\text{Var}(d_{AB}) = \text{Var}(d_{AC}) + \text{Var}(d_{BC})$

THESE RESULTS ARE BASED ON THE ASSUMPTION THAT THE DATA ARE INDEPENDENT AND THAT THE VARIANCES ARE KNOWN.
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THESE RESULTS ARE BASED ON THE ASSUMPTION THAT THE DATA ARE INDEPENDENT AND THAT THE VARIANCES ARE KNOWN.

Example



Example



Example

- Indirect estimate of benzos versus non-benzos can be obtained through their respective direct comparisons with placebo:
- $\text{diff} = 2.81 (-4.91, 10.52)$ (using variance formula to compute 95% CI).
- Confidence interval wider than either direct comparison.

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Combining

- Indirect evidence can also be combined with direct evidence.



Bayesian Network Meta-Analysis (or Mixed Treatment Comparison)

- Also known as mixed treatment comparison (MTC).
- What is it?
- When can/should it be used?
- How do we perform it?

What is MTC?

- Generalisation of meta-analysis.
- Direct and indirect evidence are combined using Bayesian meta-analysis formulations.
- Accommodates any number of interventions as long as all interventions are connected in a network of studies.

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When Can It Be Used?

- When all interventions are connected in network of studies:

Eg. if we have 7 interventions (A, B, C, D, E, F, G) and we have the following sets of pairwise studies: AB, AC, BC, CD, EF, EG, FG; we can only do an MTC on the A, B, C, D group and E, F, G groups separately, since there is no connecting link

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How is it performed?

- Method sets one treatment as a reference and compares all other treatments to this reference. These are basic parameters and are given prior distributions.
- All other contrasts can be defined as functional parameters of the base parameters.



Formulation

Four treatments A, B, C, and D. A is baseline treatment:

$$d_{AB}, d_{AC}, d_{AD} \sim N(0, 10000)$$

$$d_{BC} = d_{AC} - d_{AB}$$

$$d_{BD} = d_{AD} - d_{AB}$$

$$d_{CD} = d_{AD} - d_{AC}$$



Advantages

- Easily incorporates multi-arm trials.
- Easy to incorporate cost-effectiveness into analysis.
- Easy to compute rank statistics.

Disadvantages

- More assumptions required.
- Between studies variance can be difficult to prioritize (random effects only).



Example: Procedural Sedation

- Four interventions: Midazolam, Etomidate, Propofol and Ketofol.
- 6 trials: M vs E (2 trials)

M vs E vs P

M vs P

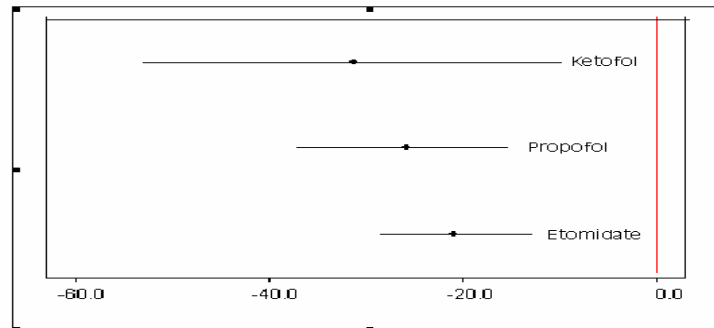
E vs P

P vs K



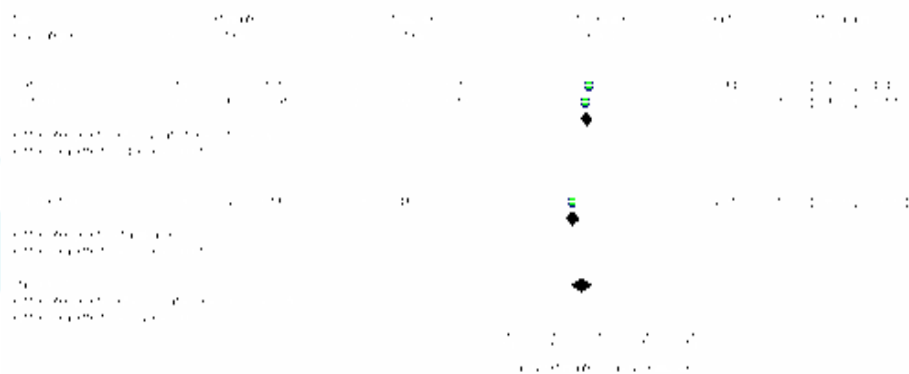
Procedure Time compared to Midazolam (standard care) (minutes)

Intervention	Point Estimate	95% Credible Interval	Probability of "best"
<u>Ketofol</u>	-31.4	-52.9, -9.8	73%
<u>Propofol</u>	-25.7	-36.9, -15.5	24%
<u>Etomidate</u>	-21.2	-28.6, -12.8	3%



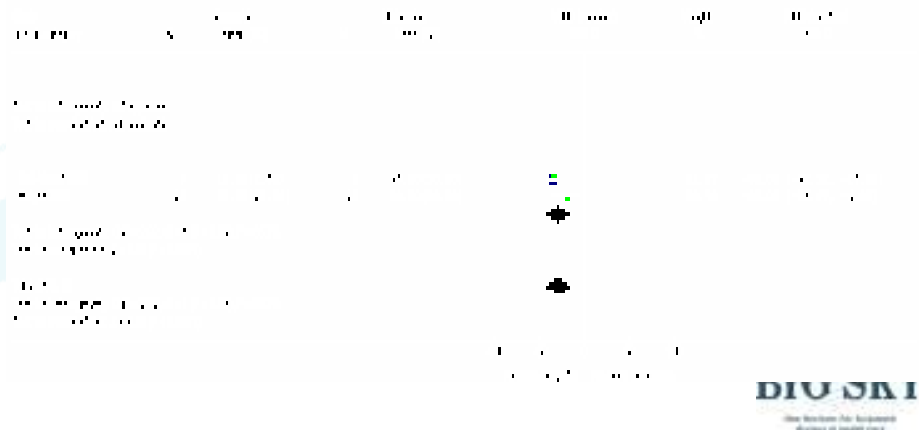
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Compare to Frequentist Results



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Compare to Frequentist Results



Example 2 Meditation Review

15 interventions:

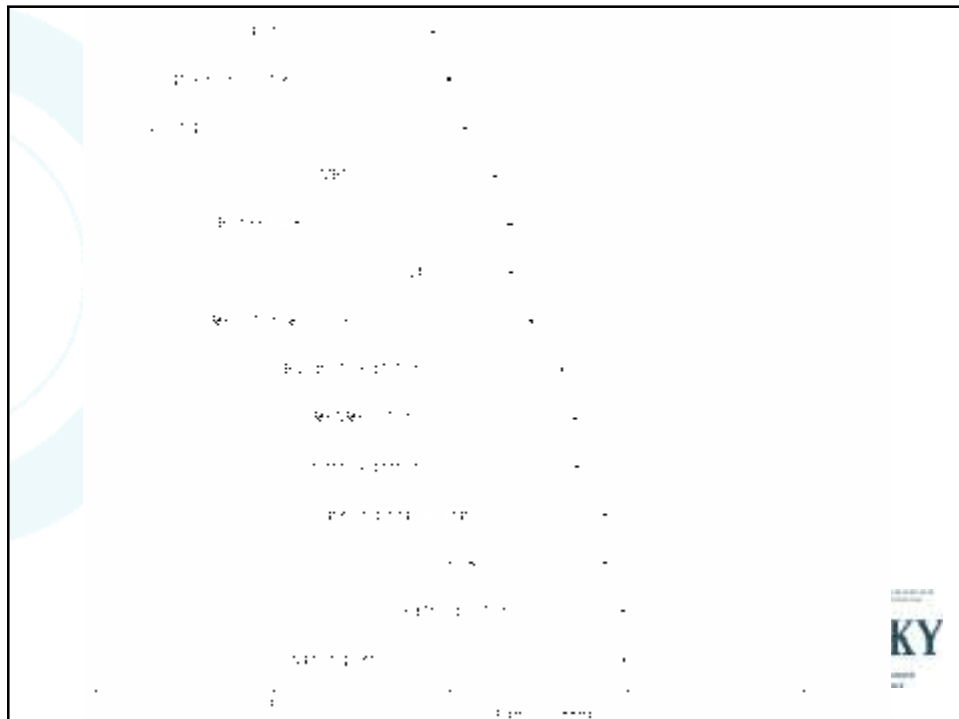
- | | |
|------------------------------|------------------------|
| 1. No Intervention | 8. PMR |
| 2. Education | 9. Tai Chi |
| 3. Yoga | 10. MBCT |
| 4. Relaxation Response | 11. Mantra Meditation |
| 5. Transcendental Meditation | 12. Rest/Relaxation |
| 6. Buddhist Meditation | 13. Yoga + Biofeedback |
| 7. Biofeedback | 14. Waiting List |
| | 15. Qi Gong |

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23 studies

- 1 vs 3
- 1 vs 3 vs 6
- 1 vs 3 vs 8
- 1 vs 3 vs 13
- 1 vs 5
- 1 vs 9
- 1 vs 10
- 1 vs 11
- 2 vs 3 (2 studies)
- 2 vs 4
- 2 vs 5 (3 studies)
- 2 vs 5 vs 8 (2 studies)
- 3 vs 12
- 4 vs 7 (2 studies)
- 4 vs 7 vs 14
- 12 vs 13
- 14 vs 15 (2 studies)

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Practical Example

Component	Autumn 2002	Standard Deviation		CSD (%)		ICD (%)		CSD (%) + ICD (%)	
		K ₁	g	K ₂	g	K ₃	g	K ₄	g
1	0.000000	0	0	0	0	0	0	0	0
2	0.000000	0	0	0	0	0	0	0	0
3	0.000000	0	0	0	0	0	0	0	0
4	0.000000	0	0	0	0	0	0	0	0
5	0.000000	0	0	0	0	0	0	0	0
6	0.000000	0	0	0	0	0	0	0	0
7	0.000000	0	0	0	0	0	0	0	0
8	0.000000	0	0	0	0	0	0	0	0
9	0.000000	0	0	0	0	0	0	0	0
10	0.000000	0	0	0	0	0	0	0	0
11	0.000000	0	0	0	0	0	0	0	0
12	0.000000	0	0	0	0	0	0	0	0
13	0.000000	0	0	0	0	0	0	0	0
14	0.000000	0	0	0	0	0	0	0	0
15	0.000000	0	0	0	0	0	0	0	0
16	0.000000	0	0	0	0	0	0	0	0
17	0.000000	0	0	0	0	0	0	0	0
18	0.000000	0	0	0	0	0	0	0	0
19	0.000000	0	0	0	0	0	0	0	0
20	0.000000	0	0	0	0	0	0	0	0
21	0.000000	0	0	0	0	0	0	0	0
22	0.000000	0	0	0	0	0	0	0	0
23	0.000000	0	0	0	0	0	0	0	0
24	0.000000	0	0	0	0	0	0	0	0
25	0.000000	0	0	0	0	0	0	0	0
26	0.000000	0	0	0	0	0	0	0	0
27	0.000000	0	0	0	0	0	0	0	0
28	0.000000	0	0	0	0	0	0	0	0
29	0.000000	0	0	0	0	0	0	0	0
30	0.000000	0	0	0	0	0	0	0	0
31	0.000000	0	0	0	0	0	0	0	0
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35	0.000000	0	0	0	0	0	0	0	0
36	0.000000	0	0	0	0	0	0	0	0
37	0.000000	0	0	0	0	0	0	0	0
38	0.000000	0	0	0	0	0	0	0	0
39	0.000000	0	0	0	0	0	0	0	0
40	0.000000	0	0	0	0	0	0	0	0
41	0.000000	0	0	0	0	0	0	0	0
42	0.000000	0	0	0	0	0	0	0	0
43	0.000000	0	0	0	0	0	0	0	0
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69	0.000000	0	0	0	0	0	0	0	0
70	0.000000	0	0	0	0	0	0	0	0
71	0.000000	0	0	0	0	0	0	0	0
72	0.000000	0	0	0	0	0	0	0	0
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79	0.000000	0	0	0	0	0	0	0	0
80	0.000000	0	0	0	0	0	0	0	0
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83	0.000000	0	0	0	0	0	0	0	0
84	0.000000	0	0	0	0	0	0	0	0
85	0.000000	0	0	0	0	0	0	0	0
86	0.000000	0	0	0	0	0	0	0	0
87	0.000000	0	0	0	0	0	0	0	0
88	0.000000	0	0	0	0	0	0	0	0
89	0.000000	0	0	0	0	0	0	0	0
90	0.000000	0	0	0	0	0	0	0	0
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92	0.000000	0	0	0	0	0	0	0	0
93	0.000000	0	0	0	0	0	0	0	0
94	0.000000	0	0	0	0	0	0	0	0
95	0.000000	0	0	0	0	0	0	0	0
96	0.000000	0	0	0	0	0	0	0	0
97	0.000000	0	0	0	0	0	0	0	0
98	0.000000	0	0	0	0	0	0	0	0
99	0.000000	0	0	0	0	0	0	0	0
100	0.000000	0	0	0	0	0	0	0	0

