Beta-binomial-models that respect randomization for meta-analysis of the odds ratio in case of very few events

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Introduction

- Standard beta-binomial (BB) model has shown good statistical properties for meta-analyses of binary outcomes, in challenging situations with a low number of studies or (very) few events [1, 2,3,4]
- However it ignores the randomisation level (arm-based)
- **Aim**: To introduce BB models that respect randomization and compare these models in a simulation study in case of (very) few events

Standard (common-*rho)* beta-binomial model (**BBST**)

- $E(\pi_i) = \mu_i = \alpha/(\alpha + \beta)$
- $Var(\pi_i) = \mu_i(1 - \mu_i)\ \vartheta/(1 + \vartheta)$, where $\vartheta = 1/(\alpha + \beta)$
- Assumption correlation equal between study groups, $corr(z_{ij}, z_{ik}) = \rho = 1/(\alpha + \beta + 1)$, is the same for all observations

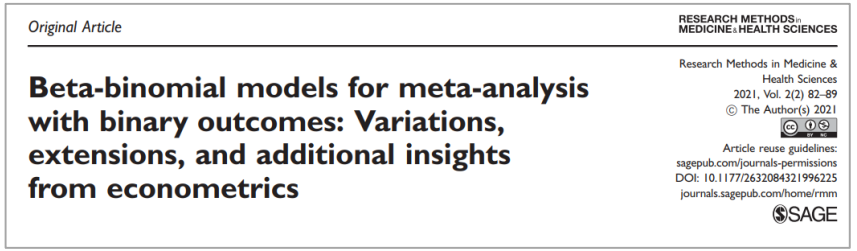
→ $(\alpha_C+\beta_C) = (\alpha+\beta) = (\alpha_T+\beta_T)$

BBST estimation of treatment effect

- The treatment effect $\theta = b_T = g^{-1}(\mu_T)/g^{-1}(\mu_C)$ is modelled via the link function
$$g(\mu_i) = b_0 + b_T \times i$$

→ ignores the randomization level

Common-*beta* beta-binomial model (**BBCB**)



Original Article

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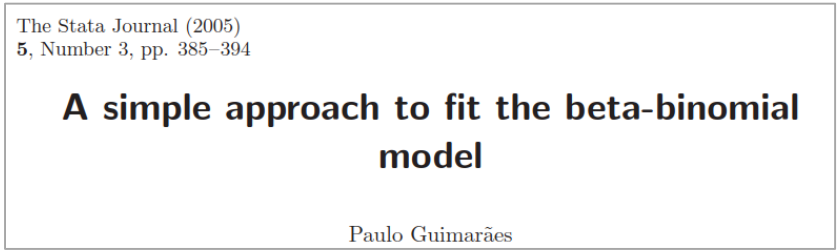
- Alternative assumption is that β is the same across studies/groups, so that $\beta_C = \beta_T = \beta$ but the alphas (α_C, and α_T) differ between studies/groups

Common-*beta* beta-binomial model



- Suppose a fixed-effects negative binomial regression (FE-NegBin) with response y, an intercept c_0, a binary indicator c_1, and the interaction of c_1 and the treatment effect c_T
- If we set $\beta = \exp(c_0)$, $\alpha_T = \exp(c_0 + c_1 + c_T)$, and $\alpha_C = \exp(c_0 + c_1)$, then the likelihood of the common-*beta* FE-NegBin and the common-*beta* BB coincide, if the FE-NegBin is estimated by conditional maximum likelihood [5]

Estimating CBBBs using panel count data models

The ML estimation can be conditioned on the counts in each study_group (ignores randomization) [6] or each study (respects randomisation)

Study	Treatment	Study Group	Success	y	BBCB_ignor	BBCN_resp	BBST
1	1	1	1	16	Σ	Σ	Σ
1	1	1	0	8			
1	0	2	1	17	Σ		Σ
1	0	2	0	11			
2	1	3	1	12	Σ	Σ	Σ
2	1	3	0	0			
2	0	4	1	7	Σ		Σ
2	0	4	0	3			

Simulation setup

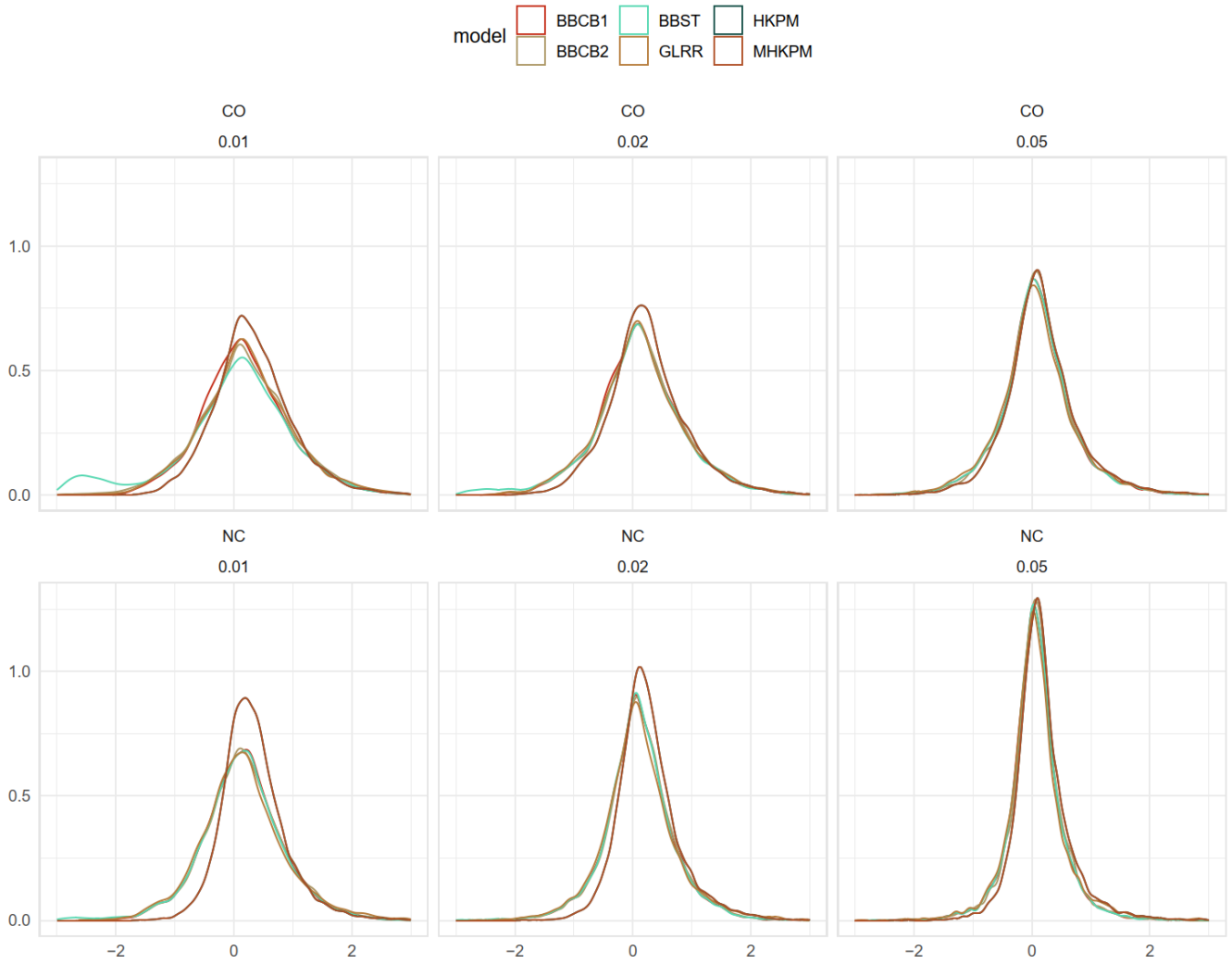
- Design factors based on real-world meta-analyses [7, 8]
- Mirrors non-Cochrane (median number of studies=8) and Cochrane (median number of studies=3) meta-analyses
- Median **odds ratio (OR)** under H1=0.69
- Event probabilities: 0.01; 0.02; 0.05
- Data were generate from an inverse variance model
- 10,000 meta-analyses

- Results are only presented for H1

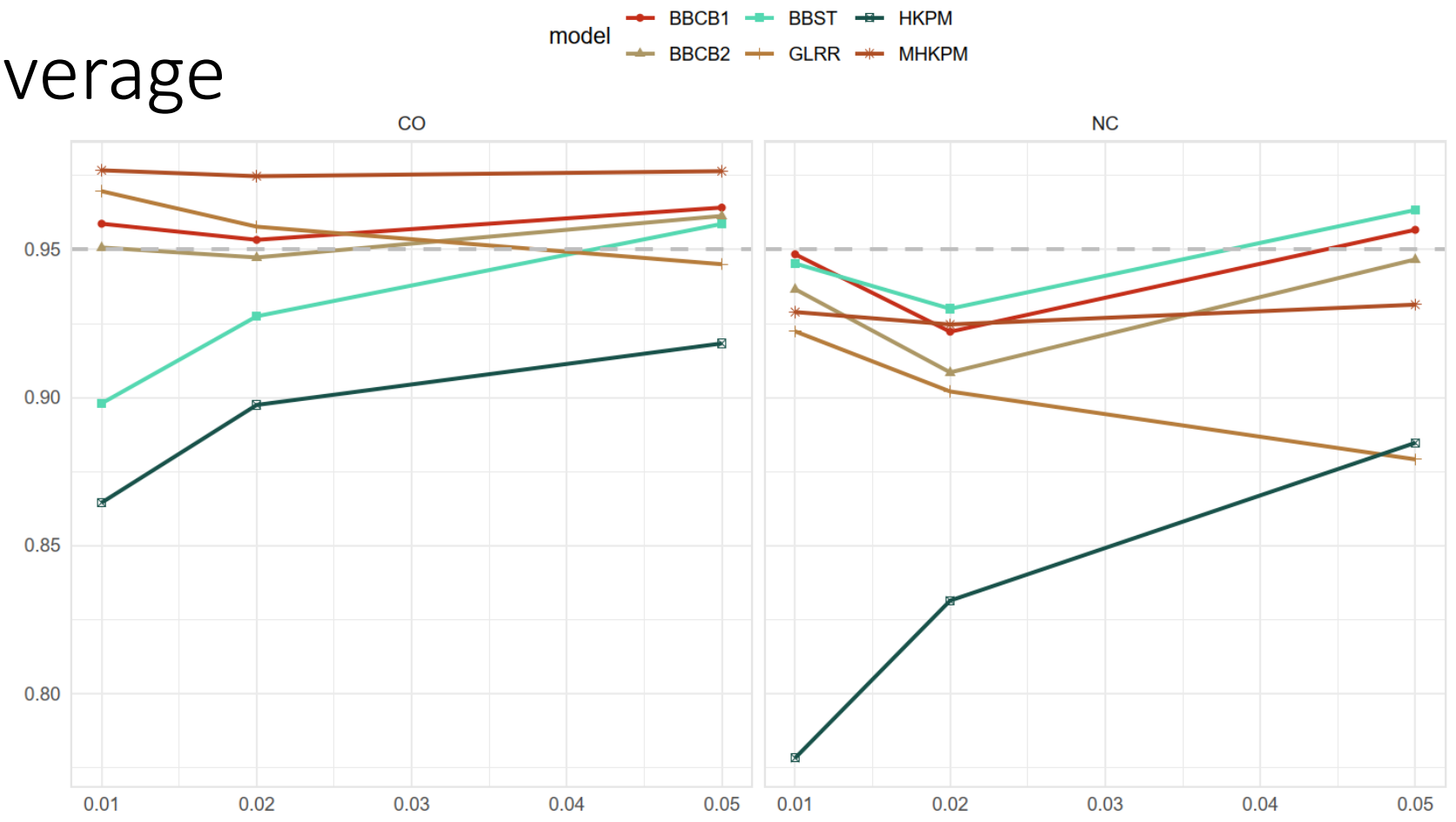
Comparator models

- Generalized linear mixed model with a random intercept and random treatment effect (**GLRR**) [9]: $g(\pi_{ki}) = \gamma_k + i \times \theta + i \times \epsilon_k$
- Inverse variance random-effects model
  - Heterogeneity variance estimated using the Paule-Mandel method
    - Hartung-Knapp-Sidik-Jonkman 95%CIs (**HKPM**)
    - Refined version of Hartung-Knapp-Sidik-Jonkman 95%CIs (**MHKPM**): variance correction is only applied if the 95%CIs of the original HKSJ-method are smaller than the Wald-type 95%CIs

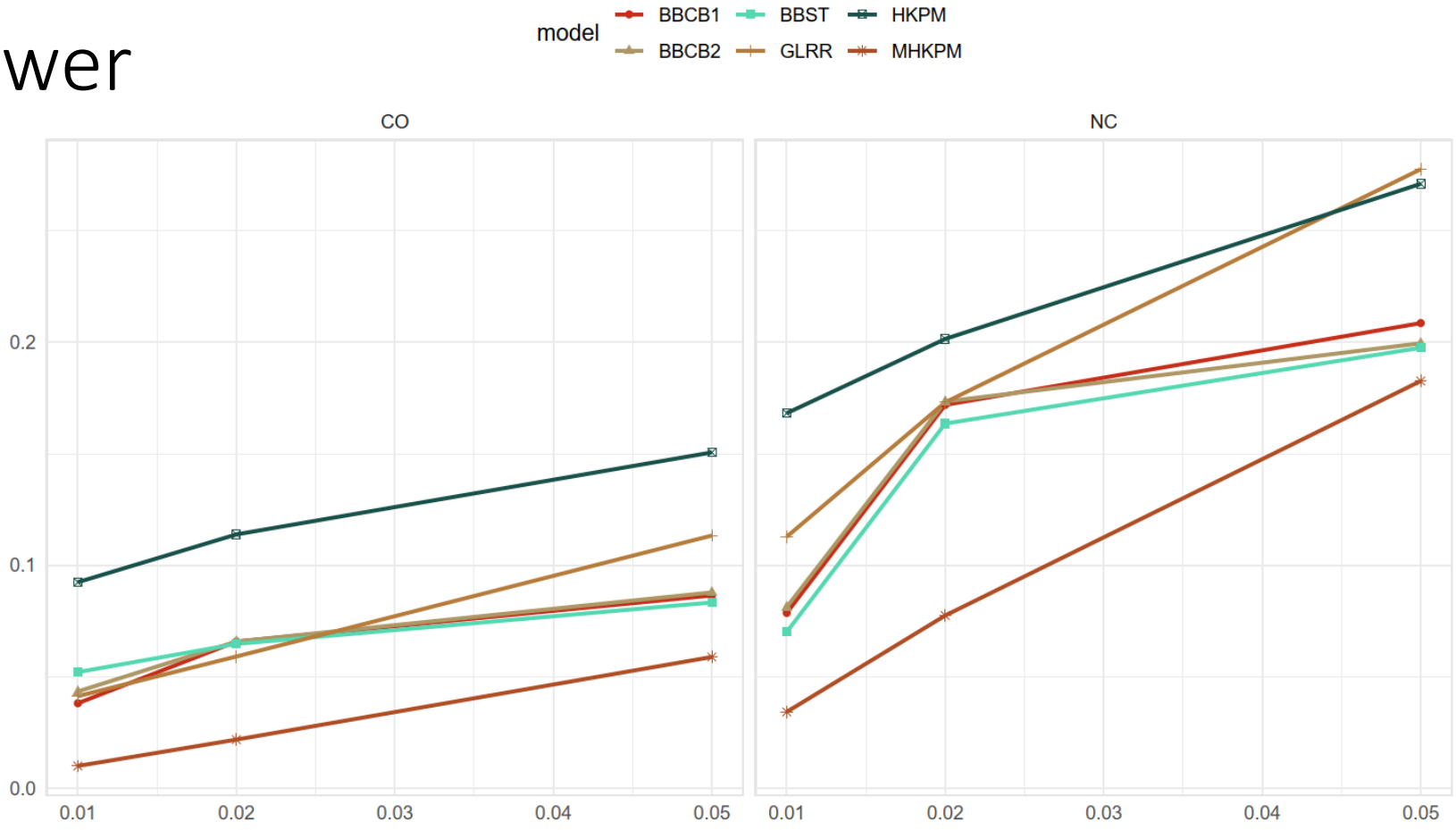
Bias


model
BBCB1
BBCB2
BBST
GLRR
HKPM
MHKPM
CO
0.01
CO
0.02
CO
0.05
NC
0.01
NC
0.02
NC
0.05
1.0
0.5
0.0
−2
0
2

Coverage

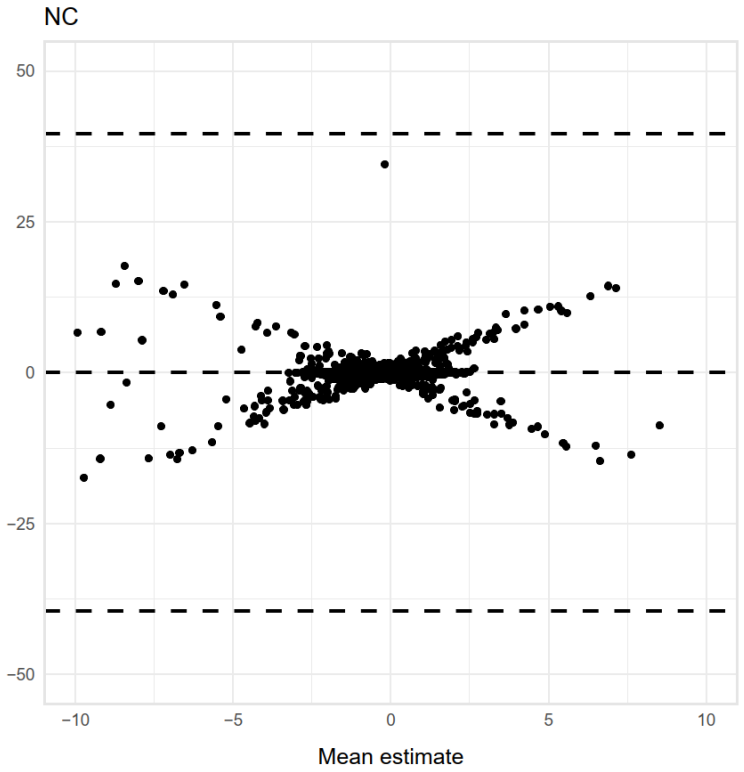

model
BBCB1
BBCB2
BBST
GLRR
HKPM
MHKPM
CO
NC
0.95
0.90
0.85
0.80
0.01
0.02
0.03
0.04
0.05

Power


model
BBCB1
BBST
HKPM
BBCB2
GLRR
MHKPM
CO
NC
0.0
0.1
0.2
0.01
0.02
0.03
0.04
0.05

Agreement of treatment effect

- In situations were models disagreed ORs were often unrealistic high in consideration of the data
- BBCB_resp tends to show implausible results when sample sizes between studies varied strongly
- BBCB_ignor tends to show implausible results when there was (very) large heterogeneity



Conclusion

- Theoretical advantage: no continuity correction is necessary and never falls back to a fixed-effect model
- The preliminary results of this simulation study indicate that the BBCB respecting randomization might be a promising candidate for pooling studies in the case of very rare events
- The BBCBs have a closed-form and can be conveniently implemented using standard procedures from statistical software as used in econometrics (e.g. PROC COUNTREG SAS, plm package in R, xtnbreg in Stata)
- The idea of using panel count data estimation routines opens the door for using any panel data model that has been introduced previously, e.g. zero inflated Poisson-regression, random-effects negative binomial regression

References

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Description simulation study

Parameter	Distributional assumption and parameter specification	Description of resulting data set
Sample size of single study n_k	Generated from a log-normal distribution with μ_{ND} = 4.615 and σ_{ND} = 1.1	Q1 = 50.0, median = 102.0, mean = 185.7, Q3 = 213.0
Sample size of treatment (control) arm of single study n_{kT} (n_{kC})	For n_{kT}: Generated from a binomial distribution with event probability 0.5 (1:1 randomisation) and n_k as number of experiments For n_{kC}: $n_k - n_{kT}$	Based on Fleishman power transformation
Event probability in control group $\pi_{C,true}$	Generated from a beta distribution with α = 0.42 and β = 1.43	Q1 = 0.024, median = 0.129, mean = 0.230, Q3 = 0.369
Variation σ^2 within study	Is implicitly given by random sample size of single study and event probability in control group	
Heterogeneity τ^2 between the studies (for θ = log OR)	Generated from a log normal distribution with μ_{ND} = –1.47, σ_{ND} = 1.65 and skewness = –0.55 using Fleishman's power transformation to generate the skewed distribution[44, 45]	τ^2: Q1 = 0.079, median = 0.273, mean = 0.621, Q3 = 0.802
Effect size of θ = log OR under H_1	Generated from a log normal distribution with μ_{ND} = –0.59, σ_{ND} = 0.61, skewness = –1.28 and kurtosis = 3.68	OR: Q1 = 0.527, mean = 0.673, median = 0.694, Q3 = 0.838
OR: odds ratio; SD: standard deviation; Q1: 1st quartile; Q3: 3rd quartile		

Number of zero studies

Scenario			Proportion of zero studies			
Number of studies in meta-analysis	Effect	Baseline probability in the control arm	Proportion of zero studies in treatment arm	Proportion of zero studies in control arm	Proportion of single zero studies in either control or treatment arm	Proportion of double zero studies
"CO"	"H0"	0.01	0.54	0.55	0.73	0.36
"CO"	"H0"	0.02	0.38	0.37	0.55	0.2
"CO"	"H0"	0.05	0.19	0.17	0.29	0.06
"CO"	"H1"	0.01	0.62	0.55	0.77	0.4
"CO"	"H1"	0.02	0.47	0.37	0.61	0.24
"CO"	"H1"	0.05	0.26	0.16	0.35	0.08
"NC"	"H0"	0.01	0.54	0.55	0.73	0.36
"NC"	"H0"	0.02	0.38	0.37	0.55	0.2
"NC"	"H0"	0.05	0.19	0.16	0.29	0.06
"NC"	"H1"	0.01	0.62	0.55	0.77	0.4
"NC"	"H1"	0.02	0.47	0.37	0.6	0.24
"NC"	"H1"	0.05	0.27	0.16	0.35	0.08