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FREQUENTIST AND BAYESIAN META-ANALYSIS: AN EXAMPLE OF A COMBINED MODEL

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ABSTRACT
The philosophy behind frequentist and Bayesian paradigms essentially differs. However, at the methodology level there are attempts to combine the two, since not only that both have advantages and disadvantages, but can be essential for each others development. The methodology in focus in this research is meta-analysis, for authors' opinion is that it can benefit from both methodologies.
The research's purpose is to offer a meta-analysis methodology that combines frequentist and Bayesian paradigms, without entering the debate which one is "correct". The model will then be used to summarize the prevalence of steatosis in HCV infection.
Key words: meta-analysis, frequentist, bayesian, steatosis, HCV

1. INTRODUCTION
One of the new methods arisen from the accessibility of published research is the meta-analysis (MA). Introduced in 1976 by Gene Glass as a research philosophy, it is in fact a collection of statistical and scientific methods deployed together to summarize results form different studies on the same topic. In focus of this paper are three statistical methods for MA, two frequentist, fixed effect model (FEM), and random effect model (REM) and bayesian approach.
An old scientific approach that benefited a lot from IT development is the so-called Bayesian paradigm. Its theoretical background dates from the 18th century, and is based on Bayes' theorem on conditional probabilities. Practical implementation is impossible without IT, and it relies on Monte Carlo Markov Chain (MCMC) estimation and sampling method, and on Gibbs or Metropolis-Hasting sampling algorithms. It involves definition of prior distribution (prior belief of the researcher), and updating it using MCMC in order to obtain posterior distribution. Clearly, its strength lies in the posterior distribution as complete information on parameter of interest, but potential weakness (and source of most critiques) is subjectivity in choice of prior.
The ever-growing interest in Bayesian paradigm drew critics from the so-called frequentist approach statisticians (but in this paper, we will leave arguments of both aside). Frequentist approach became popular in the 20th century, and is based on the work of Neumann and Pearson. It is a set of the well-defined and vastly used statistical techniques.

Recently, there appeared a number of voices advocating in favor of combining the two methods (see for example Efron, 2005). In accordance with this, the purpose of this paper is to present a combined model for MA, which will benefit most from both Bayesian and frequentist approach, avoiding the philosophical arguments on their differences. In order to check the model, we will present a case study on prevalence of steatosis in HCV patients.

2. META-ANALYSIS: A COMBINED MODEL – BACKGROUND

Typically, the steps in MA are the following: formulation of the research's purpose and hypotheses, collection and systematic review of published studies (the most time-consuming step), statistical synthesis of the results, and interpretation and publishing of the results. The second step can furthermore be divided as: definition of inclusion/exclusion criteria, extensive search of available databases, study quality assessment and inclusion/exclusion, and data and meta-data acquisition. These steps are mutual for both frequentist and Bayesian approach.

Frequentist MA can further deploy either FEM or REM approach. In FEM the collected data are the population and one only has to take into account the study variance. In REM selected studies are a sample from an unknown population and one has to take into account the between-study variance as well. Very important issues in frequentist MA are heterogeneity and publication bias assessment.

On the other hand, for Bayesian MA, after the selection of studies and data acquisition, one has to choose a prior, model the posterior and run simulations using the existing data in order to asses parameters of the posterior distribution. Regardless of philosophical differences in approaches, REM and Bayesian estimates as a rule have quite close values.

The model authors are suggesting uses the clear advantage of the Bayesian approach, and that is obtaining the distribution for parameters of interest. In order to avoid subjectivity, authors deploy frequentist approach as input into prior selection (FEM), and in sensitivity analysis (FEM).

2.1. A combined model

The following model is a proposal from authors after the long and thorough study of MA: determination of the research's topic, excessive systematical search of the published studies on the topic and data acquisition, definition of research's goal and hypotheses, heterogeneity analysis, FEM MA as input for prior selection, Bayesian MA, sensitivity analysis which includes REM meta analysis.

This model starts from the research topic, not from a narrow goal, for the authors strongly believe that it is impossible to know in advance if there exist enough published relevant study for a valid MA. After that, it follows the usual step of defining the inclusion/exclusion criteria. The further proposal is to do the excessive systematical search and data acquisition first, and then to define the research's goal and hypotheses.

The heterogeneity analysis provides insight into the selected data. If there are obvious clinical or other sources of heterogeneity, and data can be stratified following the valid reasoning, then one should repeat this step with stratified data. If some studies have to be excluded, one has to go back to check the inclusion/exclusion criteria. If they are consistent, one can either proceed with cautious interpretation of the results, or re-consider the goal.

Next, authors deploy FEM MA as input for the informative prior selection. In this model, FEM results are initial opinion on the observed data, and the basis to compare to expert opinion.

The next step is the Bayesian MA, followed by the sensitivity analysis, which includes REM. In this mode, REM is the basis of the sensitivity analysis, for, as mentioned earlier, it should give similar results to Bayesian MA. Apart from REM, the authors suggest the usual sensitivity analysis with skeptical and optimistic priors, and (if they significantly differ) FEM and expert opinion inputs to prior choice. In the following case-study, we follow the steps of the combined model.

2.2. Case study - prevalence of steatosis in hcv patients

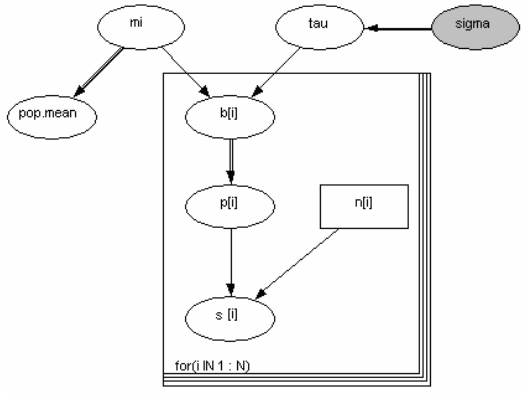
The association of steatosis, characterized by the accumulation of lipids in hepatocytes, with HCV infection has been extensively studied recently. Steatosis is considered one of the etiological markers of infection due to its high frequency in the range 34.8%-81.2% in chronic hepatitis (Matos et al. 2006). This meta-analysis is predominantly based on the work of Lonardo et al. (2006) for two reasons: obtaining information that is more accurate (then proportion of 55.5% ranging from 34.8% to 81.2%), and inability of BIH authors to easily access knowledge bases due to lack of institutional

support. The studies included in the analysis are in Table 1. For frequentist MA we used MIX Version 1.7 (Bax er al. 2008), and for Bayesian WinBUGS version 1.4.3 (Lunn et al. 2000).

Table 1: Studies included into meta-analysis on steatosis prevalence in HCV patients.

References	Prevalence of steatosis	n	References	Prevalence of steatosis	n
Scheuer et al. 1992	29	54	Latorre et al. 2002	33	69
Fiore et al.1996	73	121	Hui et al. 2002	90	122
Czaja et al. 1998	31	60	Akuta et al.2002	320	394
Hourigan et al. 1999	91	148	Romero-Gomez et al. 2003	63	131
Adinolfi et al. 1999	65	158	Asselah et al. 2003	135	290
Fujie et al. 1999	21	43	Ohata et al.2003	56	161
R.-Brandt et al.2000	41	101	Poynard et al. 2003	935	1428
Clouston et al.2001	56	80	Cholet et al. 2003	182	314
Hwang et al. 2001	55	106	Hu et al. 2004	214	324
Adinolfi et al. 2001	86	180	R.-Brandt et al. 2004	315	755
Petit et al.2001	66	123	Sharma et al. 2004	90	225
Serfaty et al. 2001	60	142	Patton et al. 2004	277	574
Monto et al. 2002	171	297	Matos et al. 2006	60	90
			Total	**3615**	**6490**

FEM gives the proportion of 0.557, with CI lower bound 0.5487 and upper bound 0.5653. Additionally, FEM heterogeneity assessment (I^2=97.31, and τ^2=0.0701) support the assumption of no obvious heterogeneity.




```
model
{
        for( i in 1 : N ) {
                b[i] ~ dnorm(mi,tau)
                s[i] ~ dbin(p[i],n[i])
                logit(p[i]) <- b[i]
                }
        pop.mean <- exp(mi) / (1 + exp(mi))
        mi ~ dnorm(0.0,1.0E-6)
        # Choice of prior on random effects variance
        #Prior 1:
        tau ~ dgamma(1.0E-3, 1.0E-3);
        sigma <- 1/sqrt(tau); # s.d. of random effects
        # Prior 2: uniform on SD
        #sigma~ dunif(0,100)
        #tau<-1/(sigma*sigma)
}
```

Figure 1. The log-normal Bayesian model (left) and WINBugs code (right) for the prevalence of steatosis in HCV patients (source WinBUGS)

The Bayesian model starts from the assumption that the prevalence of steatosis across hospitals is similar in a way, which then corresponds to the following random effects model for the true failure probabilities p_i: $\text{logit}(p_i) = b_i$; $b_i \sim \text{Normal}(\mu, \tau)$. Then, a standard non-informative prior is specified for the population mean (logit) probability of failure, m, with a non-informative $\Gamma(0.001, 0.001)$ prior1 on the precision, τ, and an alternative uniform prior2 on the standard deviation for the random effects variance(Lunn et al. 2000).

A burn in of 1000 updates followed by the further 10000 updates give the estimates of Bayesian MA on prevalence of steatosis in HCV patients, as presented in Table 2.

As mentioned earlier, the sensitivity analysis involves non-informative prior and REM meta analysis. In order not to burden reader with too much information, we here present only the non-informative prior of the same model (with non-informative initial values) following the same procedure (Table 2). Additionally, REM estimate for the prevalence of steatosis in HCV patients is 0,5387 with CI lower bound 0.4867 and CI upper bound 0.5907.

From the results, it is obvious that FEM slightly overestimated the proportion of steatosis prevalence, compared to Bayesian estimate, unlike REM, which slightly underestimated it. Nevertheless, sensitivity analysis shows that even an enthusiastic prior can lead to an acceptable prior. Furthermore, Bayesian estimates are both greater than REM (but only by less then half of percent), with slightly smaller CI, removed to right.

Table 2: Results of Bayesian MA for steatosis prevalence in HCV patients for population mean and its variation. Informative prior (from FEM) and non-informative prior.

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
pop.mean	0.5417	0.02577	2,12E-01	0.4911	0.5418	0.5919	1	11000
sigma	0.4954	0.0812	6.653E-4	0.3637	0.487	0.6801	1	11000
tau	4.433	3.95	0.04147	2.163	4.217	7.559	1	11000
			Non-informative prior:					
pop.mean	0.542	0.02588	3,02E-01	0.491	0.542	0.5922	1	11000
sigma	0.4948	0.08101	9,76E-01	0.3642	0.4869	0.6757	1	11000
tau	4.477	5.408	0.08227	2.193	4.218	7.542	1	11000

3. CONCLUSION AND RECOMMENDATIONS

The results of the analysis presented in case-study show that, even though there exist philosophical differences between frequentist and Bayesian approach, both can lead to similar numerical values. This can lead to at least two conclusions: we do not have to bother with both approaches, just choose frequentist for it includes less modeling, but on the other hand, we can confirm the fact that Bayesian is not as subjective as critics say. Moreover, there still is the big and obvious advantage of the Bayesian approach: the posterior distribution with explicit density and estimated parameters.

Bearing all this in mind, authors strongly recommend the combined use of the two approaches, in order to use advantages of both: the simplicity and easiness of use of frequentist, and the complete information about results of Bayesian approach.

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