Spontaneous Reporting System Modelling for Data Mining Methods Evaluation in Pharmacovigilance

E. Roux[1], F. Thiessard[2], A. Fourrier[2], B. Bégaud[2] and P. Tubert-Bitter[1]
[1]INSERM U472 Epidémiologie et Biostatistique, Villejuif, France
[2]Université Victor Segalen, Bordeaux, France

Abstract

The pharmacovigilance aims at detecting adverse effects of marketed drugs. It is based on the spontaneous reporting of events that are supposed to be adverse effects of drugs. The Spontaneous Reporting System (SRS) is supplying huge databases that pharmacovigilance experts cannot exhaustively exploit without any data mining tools. Data mining methods have been proposed in the literature but none of them is the object of a consensus in terms of applicability and efficiency. It is especially due to the difficulties to evaluate the methods on real data.

In this context, the aim of this paper is to propose the SRS modelling in order to simulate realistic data that would permit to complete the methods evaluation and comparison, with the perspective to help in defining surveillance strategies. In fact, as the status of the drug-event relations is known in the simulated dataset, the signal generated by the data mining methods can be labelled as "true" or "false".

Spontaneous Reporting process is viewed as a Poisson process depending on the drugs exposure frequency, on the delay from the drugs launch, on the adverse events background incidence and seriousness and on a reporting probability. This reporting probability, quantitatively unknown, is derived from the qualitative knowledge found in literature and expressed by experts. This knowledge is represented and exploited by means of a fuzzy characterisation of variables and a set of fuzzy rules.

Simulated data are described and two Bayesian data mining methods are applied to illustrate the kind of information, on methods performances, that can be derived from the SRS modelling and from the data simulation.

1 Introduction

The aim of the pharmacovigilance is to detect adverse effects of marketed drugs. Pharmacovigilance is based on the spontaneous reporting of events that are supposed to be adverse effects of drugs.

In France, the Spontaneous Reporting System (SRS) is supplying a database that gathers about 200000 reports. Since 1985, the yearly reports number has been on the steady increase and has reached 20000 in 2001 [10]. In 1997, 35000 new reports were added quarterly in the World Health Organisation (WHO) database [2]. The generation of signals, i.e. the fact that drug-event couples suspected to be causally related are bringing out, is currently human based or supported by some heuristic rules implemented in basic software [1]. Due to the mass of the data and to the fact that useful features are lost in this mass, these methods cannot effectively exploit the whole information contained in the database. Data mining methods have been proposed to automatically generate signals and support pharmacovigilance experts, but none of them is used routinely. These methods are based on different association measures associated with detection thresholds. Measures are all intended to evaluate the difference between the observed number of reports and the expected one under the drug-event independance assumption. The methods have been proposed for different databases: the Proportional Reporting Ratio (PRR) [7] for the Medical Control Agency (MCA) of the UK, the Information Component (IC) [2] for the WHO database, the Empirical Bayes Method (EB) [4; 5] for the Food and Drugs Administration (FDA), etc. These methods have been evaluated on real data, i.e. on pharmacovigilance databases [2; 4; 8; 14].

Lack of knowledge

All the questions concerning the methods reliability cannot be totally answered with the evaluations as they are performed in the literature, explaining in part the fact that the methods are not routinely used. In fact, the Spontaneous Reporting System (SRS) is based on the subjective appreciation of the medical community and does not provide an exhaustive report-

ing of the adverse effects. At first the adverse event has to be diagnosed and next, it has to be judged new and serious enough to be reported [13]. It is impossible to know the proportion of adverse events that is reported. Moreover, the reported events are supposed to be causally related to the prescribed drugs but the simultaneous presence of an adverse event and of a drug can be coincidental. In other words, all the adverse effects are not reported (and the proportion of reported events is unknown), and the adverse events reported are not all adverse drug reactions. Moreover, the numbers of patients exposed to the drugs as well as the background incidence of the adverse events in the whole population are ill-known. To access this knowledge would require deep investigations that are not conceivable at the database scale. That is preventing to determinate reliable estimations of the expected numbers of reports that would allow to compare the reports frequencies for the drug-event couples and to reliably determine the nature of the drug-event relations. Eventually, the drug-event relative risk in the real database is unknown.

This lack of knowledge makes difficult to labelled the signal generated by the data mining methods as "true" or "false". Gould [8] circumvented this difficulty by comparing methods results with the results of one of them, considered as the reference one. By this way, methods can be compared in a relative manner. However, it is still impossible to verify the signals ranking pertinence, i.e. the fact that the higher the drug-event relative risk is, the stronger the signal has to be. Moreover, the sensitivity of the methods results according to the drug and/or event characteristics cannot be study easily. Indeed, it is interesting to establish if the methods tend to bring out recently marketed drug or older ones, serious events or mild ones, etc.

Objectives

In this context, this paper proposes the SRS modelling in order to simulate realistic data. Data mining methods can then be applied on these data and it is possible to complete the previously described evaluations, as the status of the drug-event relations and as the drugs and events characteristics are known. It is important to obtain data as realistic as possible in order to study the data mining methods behaviour according to the model parameters and to be able to derive knowledge on their efficiency with real data.

The SRS modelling is described in the first section. This modelling phase exploits qualitative knowledge expressed by pharmacovigilance experts and found in literature, by means of a fuzzy representation of knowledge and a fuzzy inference system. Then, the Application section proposes a set of simulation parameters values that aims at obtain some characteristic situations of the French pharmacovigilance database and describes two Bayesian data mining methods [2; 4; 5]. Generated data are described and performances of the data mining methods are presented in the Results section. The data mining methods evaluation is not the main issue tackled by this paper but it is presented as an illustration of what information can be derived from simulations.

2 Spontaneous reporting system modelling

In the present study, a pharmacovigilance database is simply viewed as a two entries table: one entry for the events and the other for the drugs. The cell corresponding to the (drug i, event j) couple contains the cumulated reports number, N_{ij}, associated to this couple.

The probability distribution of the numbers of reports n_{ij}, during a given period Δ_t, is assumed to be Poisson with a mean reports' number δ_{ij} [11; 12]:

$$\delta_{ij} = RR_{ij} \cdot I_j \cdot T_i \cdot p_{ij} \quad (1)$$

RR_{ij} is the Risk Ratio of a (drug i, event j) combination. When RR_{ij}=1, the (drug i, event j) association is only coincidental and the reports are "false" reports. I_j is the background incidence of the event j and T_i the exposure frequency, i.e. the number of patients exposed to the drug i during the given period Δ_t. Assuming that the probability to observe the event without the exposure to the drug is comparable to the probability to observe the event in the whole population, i.e. the background incidence of the event, the product $RR_{ij} \cdot I_j \cdot T_i$ represents the expected number of events j associated to the drug i during Δ_t.

As seen before, even if an adverse event occurs when a patient is exposed to a drug, the case is not systematically reported. So a reporting probability, p_{ij}, completes the spontaneous reporting system modelling. The reporting probability is known to be very variable from a drug-event couple to another. The pharmacovigilance experts have only general and/or qualitative knowledge on its order of magnitude, on the factors that influence it and on the effects of these factors. In order to obtain realistic data, this knowledge has to be exploited and has to be easily updated if a change occurs in it. Fuzzy set theory and fuzzy logic permit to represent such knowledge and to exploit them to perform human like deductive reasoning. A set of fuzzy rules is derived from literature and pharmacovigilance experts advices. These fuzzy rules represent three basic intuitions of the experts concerning the reporting probability, that have been confirmed by quantitative analysis of real data [13]: 1) the more serious the event is and the more reported it is 2) The more unknown the causal drug-event association is, the more reported it is 3) the more recent the drug is, the more reported the event is. These rules impose to distinguish serious and mild events, to characterise the knowledge on the causal drug-event association and the delay since the drug launch.

Seriousness of the events

We considered the seriousness of an event as a binary variable with two modalities: serious and mild.

Knowledge on the drug-event association

The knowledge the medical community has on a given drug-event association is assumed to be characterised by the cumulative sum of the reports number, for the considered drug-event couple, from the launch date of the drug. This cumulative sum is then fuzzified by means of the membership functions described in Figure 1.

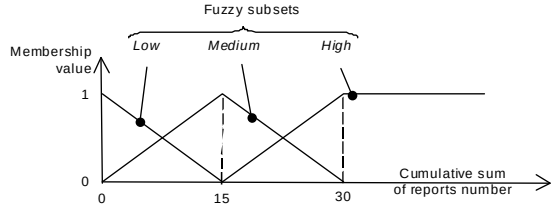

Figure 1: Membership functions to characterise the cumulative sum of reports

Delay from the drug launch

The delay from the drug launch is characterised by the membership values of the periods of the drug life cycle. This cycle is supposed to be a classical product life cycle with five periods (that are fuzzy in our study): "launch", "growth", "maturity", "decline", and "end of life" (Figure 2).

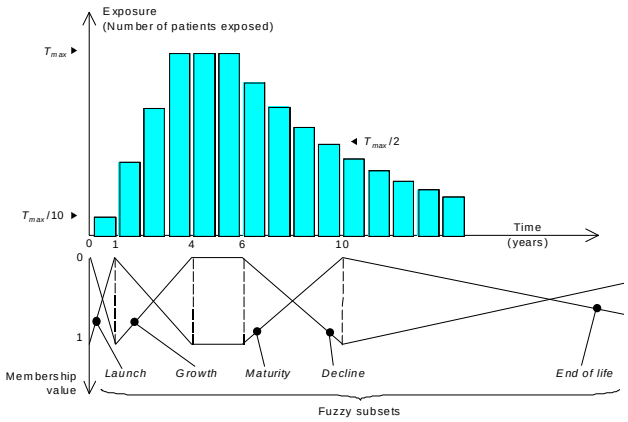

Figure 2: Drug life cycle and fuzzy characterising of drug life cycle

Reporting probability (p_{ij})

The reporting probability is assumed to be at most equal to 0.1 [12; 15]. p_{ij} is characterised by five fuzzy subsets as described in Figure 3.

Fuzzy rules definition

Given the three basic rules previously stated and the coding of the variables, the rule base presented in Figure 4 is defined.

The fuzzy conclusions associated to the cells of the table (Figure 4) are chosen to represent the gradual

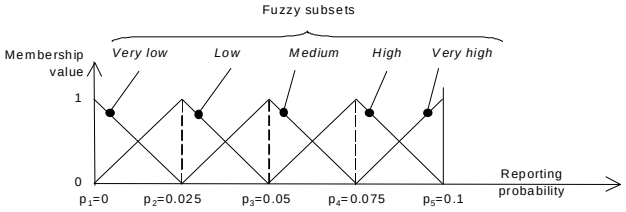

Figure 3: Membership functions defining fuzzy subsets for the reporting probability

Drug life cycle periods	Cumulative number of reports: Low	Medium	High
Launch	VH / H	VH / H	VH / H
Growth	VH / VH	VH / H	H / M
Maturity	VH / H	H / M	M / L
Decline	H / M	M / L	L / VL
End of life	M / L	L / VL	VL / VL

The more recent, the more reported

The more known, the less reported

Figure 4: Fuzzy rule base for the reporting probability determination. In each cell of the table are given the conclusions associated to a serious event (upper part of the cell) and to a mild event (lower part of the cell). VH is for "Very high", H for "High", M for "Medium", L for "Low" and VL for "Very low"

knowledge of the type "the higher (resp. "lower") [...] is, the higher (resp. "lower") the reporting probability is". The only exceptions are the rules associated to the fuzzy subset "Launch", for which the reporting probability is "Very high" (or "High") whatever the cumulative sum of the reports number is. This is justified by the fact that during the launch period, the causal drug-event association is unknown. Another exception is the increase of the reporting probability when moving up from the "Launch" to the "Growth" period and while keeping with a "Low" cumulative sum of reports number. This increase of the reporting probability is supposed to model, before the "Maturity" period, a learning phase during which medical community and pharmacovigilance experts are more focalised on the new drug couple, when the drug-event association is not known yet [11].

Rules activation

The fuzzy implication is performed by the min operator. The generalised modus ponens operator is the min operator too and the fuzzy conclusions are aggregated with the max operator [3]. At this stage, the conclusion is still fuzzy and cannot be exploited directly by the formula (1). It has to be defuzzified. This operation is realised by the Height Method (HM) [6], consisting in computing the weighting average of

the reporting probability corresponding to the maxima of the membership functions, p_k (k∈[1,5], cf. Figure 3 and Figure 5), by μ_k^{ij} (k∈[1,5]), the heights of the fuzzy subsets of the conclusion (cf. Figure 5).

$$p_{ij} = \frac{\sum_{k=1}^{5} \mu_k^{ij} \cdot p_k}{\sum_{k=1}^{5} \mu_k^{ij}} \quad (2)$$

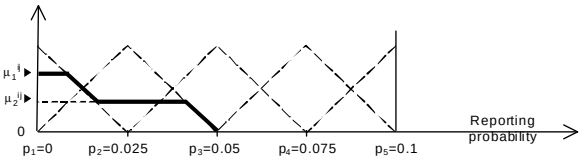

Figure 5: Fuzzy conclusion (thick lines) and values used for defuzzification

This defuzzification method does not require to define the membership functions for all the values of p_{ij} but only to determine the parts of the fuzzy subset supports that correspond to the maximum (or maxima in the case of trapezoidal membership function for example) of the membership functions. Such a defuzzification method is simple and fast. Moreover, it permits to reach the maximal values of p_{ij}, i.e. 0 and 0.1, unlike the centre of gravity method.

At this stage of the SRS modelling, only p_{ij} is defined. T_i, RR_{ij} and I_j have now to be defined so that they represent at best realistic situations.

Exposure (T_i)

T_i is time dependent and is defined, in our study, by the drug life cycle presented Figure 2. The only parameter required for defining the whole cycle is the maximal exposure, T_{imax}, corresponding to the exposure during the maturity phase. T_i is supposed to reach $\frac{T_{imax}}{10}$ at the end of the Launch period, to reach its maximal value after four years and decline exponentialy from the sixth years, so that at ten years, $T_i = \frac{T_{imax}}{2}$.

Relative risk (RR_{ij})

A proportion of coincidental drug-event associations that will give "false" reports, i.e. with RR_{ij}=1, is defined. The remaining couples, with RR_{ij} >1, are associated to "true" reports and are supposed to generate a signal. In order to observe all the possible situations according to the different values of the model parameters, the subset of drug-event couples having the same values for the drug exposure, the delay since the drug launch, the event incidence and seriousness, have to described the whole range of the chosen RR_{ij} values. For each of these subsets, the chosen RR_{ij} are randomly attributed to the drug-event couples.

No particular constraint is imposed for the definition of I_j in the present version of the SRS modelling and the choice of the I_j values will be presented further.

Data generation process

Data are generated sequentially. A total duration of the reporting process, corresponding to the maximal delay since the drug launch we want to consider, must be defined. The period Δ_t between two successive generations has to be chosen too. As a new drug can be launched during the generation process, it is possible to have, at the same time, drugs with different delays since launch.

3 Application

Data generation

We considered 60 drugs and 40 effects. The following parameters values have been chosen in order to represent some characteristic situations of the French pharmacovigilance. Two maximal exposures (T_{imax}) have been chosen: 300000 (one half of the drug) and three millions (the other half). Concerning the delays since the drug launch, we chose to have three different cases: one, five and ten years, corresponding to one third of the drugs each. So, ten years of the reporting process have been simulated. Moreover, a six months generation period (Δ_t) has been chosen. In the present study, data are considered at the end of the generation process, i.e. at the end of a ten-year spontaneous reporting process. Two values have been chosen for the events background incidences (I_j): 1/10000 (one half of the events) and 1/50000. Moreover, one half of the events are considered as serious, the remaining events being mild. This repartition corresponds approximatively to the one in the french pharmacovigilance database, where 46% of the events are labelled serious [10]. Eventually, 90% of the drug-event associations are assumed to be coincidental, i.e. with RR_{ij}=1. The set of RR_{ij} >1 is assumed to be exponentially distributed so that RR_{ij} ∈[1.2,10]. Indeed DuMouchel [4] supposed that 1/3 of the drug-event couples are dependent but found, in the FDA database, 1/10 of dependent couples by means of his mixture model (cf. application section and [4]). The figure 6 summarises the previous choices for the parameters and their values.

Application to the evaluation of data mining methods in pharmacovigilance

The next section presents some results relative to two Bayesian data mining methods, the Information Component method (IC) [2] and the Empirical Bayes Method (EB) [4; 5], in order to illustrate what kind of information we can derived from simulated data. IC method exploits the IC measure of association defined as followed:

$$IC_{ij} = log_2 \frac{w_{ij}}{u_i \cdot v_j} \quad (3)$$

u_i is the probability of having the drug i, v_j the probability to observe the j^{th} event and w_{ij} is the probability of having the drug-event association given the observed number of reports. u_i, v_j and w_{ij} are supposed to be, *a priori*, beta distributed. So u_i, v_j and w_{ij} are, *a posteriori*, beta distributed too. Then,

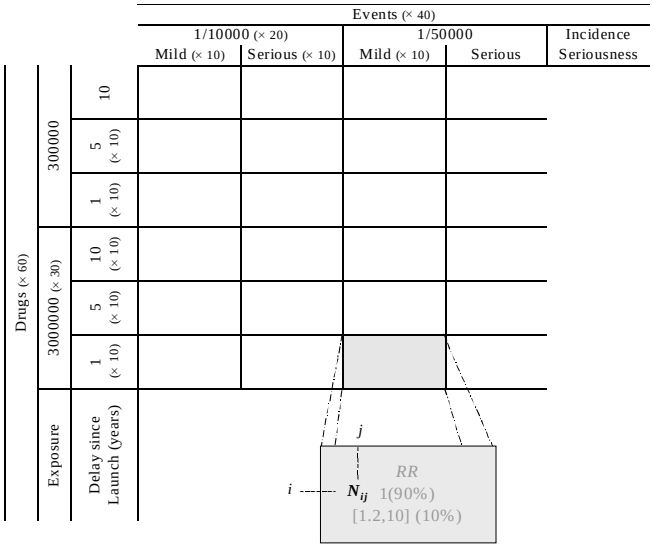

Figure 6: Model parameters and associated values

Bate defines a criterion in order to make a decision. He proposes to generate a signal when the lower limit of the 95% credible interval, $IL95_{ij}$, is positive. $IL95_{ij}$ is estimated with the formula:

$IL95_{ij}$=Posterior expectation of IC_{ij} - 1.96 · Posterior standard deviation of IC_{ij}

DuMouchel [4] assumes a Poisson distribution for the number of reports, with a mean μ_{ij} for the (drug i, event j) couple. Then he considers the rate $\lambda_{ij} = \mu_{ij}/(n_{i.} \cdot n_{.j}/N)$, where $n_{i.}$ and $n_{.j}$ are the total reports number for the drug i and for the event j, respectively. N is the total reports number in the database and $(n_{i.} \cdot n_{.j})/N$ is the expected reports number for the (drug i, event j) couple, assuming the statistical independence between drug i and event j. A prior mixture of two gamma distributions is assumed for λ_{ij}:

$$\lambda_{ij} \overset{a\ priori}{\sim} P \cdot \Gamma_1(\alpha_1, \beta_1) + (1-P) \cdot \Gamma_2(\alpha_2, \beta_2) \quad (4)$$

The "empirical" character of the method comes from the estimation of the prior distribution parameters $\Theta = \{P, \alpha_1, \beta_1, \alpha_2, \beta_2\}$, by means of a maximum likelihood estimation from the data. The posterior distribution is a mixture of two gamma distributions too. It is then possible to obtain the exact posterior mean of λ_{ij}, denoted $EBAM_{ij}$. DuMouchel proposes to use this value (in fact, DuMouchel uses the geometric mean derived from $log_2(\lambda_{ij})$) to rank the drug-event couples and does not recommend a threshold. Gould [8] chose to apply a decision criterion comparable to Bate's one [2], by computing the lower bound of the 95% credible interval. This lower bound can be approached with a predefined precision. Indeed, Gamma quantiles are tabulated in marketed software and a basic optimisation procedure can easily find the probability corresponding to a given quantile of the posterior mixture.

The objective of the present study is not properly the methods description and evaluation but the SRS modelling. We refer to the following articles for a more detailed description of the methods [2; 4; 8].

4 Results

1000 datasets have been generated. Figure 7 shows the reporting probability and the cumulative number of reports in three different cases and as a function of the time.

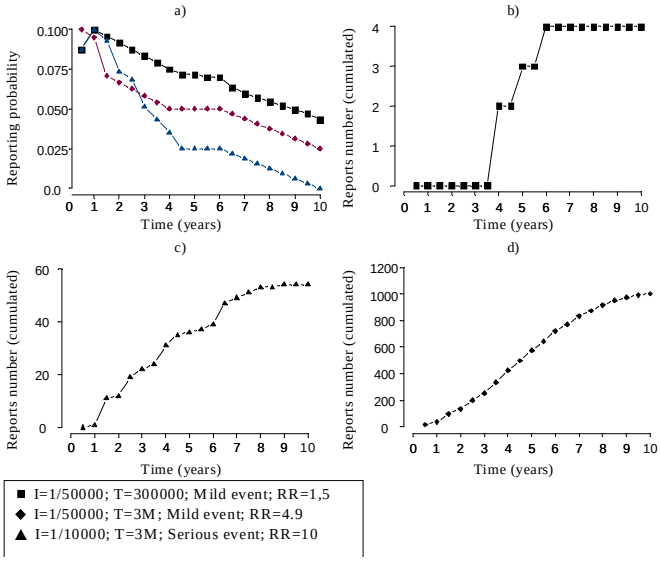

Figure 7: Reporting probabilities a) and cumulative number of reports b), c) and d)

Figure 8 shows the reports numbers distribution in average over the 1000 simulated datasets. The first bar refers to the drug-event couples without any reports. The maximal reports number associated to a drug-event couple is, in average, 994 (standard deviation: 32). In average, 51912 reports (N) are cumulated over 10 years in the whole dataset (stand. dev.: 197).

For each of the generated datasets, Bate and DuMouchel's methods have been applied. Table 1 shows the prior parameters of the DuMouchel's mixture model, obtained by means of maximum likelihood estimation. The average prior probability P=0.096, associated with the component which has a mean >1 (the 1^{st} one), corresponds well to the 10% of the drug-event couples with RR_{ij} >1.

Sensitivity and specificity have been computed with the decision thresholds that correspond to the following posterior distribution quantiles: 0.025, 0.05, 0.1, 0.2, ..., 0.9, 0.95, 0.975, for the two methods and for the 1000 simulated datasets. Computations have been performed after stratification according to the model

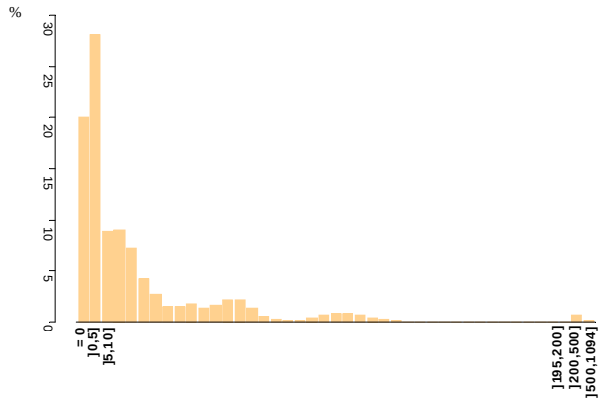

Figure 8: Reports number distribution in the whole dataset

	θ					1st mixture component		2nd mixture component	
						Mean	Variance	Mean	Variance
	α_1	β_1	α_2	β_2	P	$\frac{\alpha_1}{\beta_1}$	$\frac{\alpha_1}{(\beta_1)^2}$	$\frac{\alpha_2}{\beta_2}$	$\frac{\alpha_2}{(\beta_2)^2}$
Average	4.527	1.567	29.261	34.412	0.096	2.876	1.866	0.850	0.025
(Standard deviation)	(0.810)	(0.226)	(1.870)	(2.283)	(0.008)	(0.132)	(0.215)	(0.003)	(0.002)

Table 1: A priori parameters for the mixture model of DuMouchel

parameters. Then, over the 1000 datasets, the average and the standard deviation of the sensitivity and of the specificity corresponding to each quantile have been computed.

Results are shown Figure 9. IC and EB give comparable results in the majority of the situations but noticeable differences can be observed for a maximal exposure of 300000 and a delay of one year since drug launch. Even if the whole curves are not drawn given the chosen thresholds, EB clearly obtained better results. This situation corresponds to very low reports numbers (max=10, median=1 and max=4, median=1 for, respectively, an event incidence of 1/10000 and 1/50000), indicating the supremacy of EB for rare adverse drug effects. Conversely, results are similar and are the best ones for important reports numbers, i.e. for "old" and frequently used drugs.

Results show that a given threshold leads to very different results according to the different methods, inciting to define method specific thresholds and not an identical and arbitrary one.

Eventually, the signals pertinence according to the imposed Relative Risk has been evaluated by computing the linear correlation coefficient between the data mining measures and the imposed Relative Risk, for the whole set of drug-event couples of each simulated dataset (cf. Table 2). The correlation coefficient evaluates the ability of the methods to correctly rank the signal from the strongest to the weakest one according to the "true" RR_{ij} values. Results show that EB is the more effective method for couples ranking.

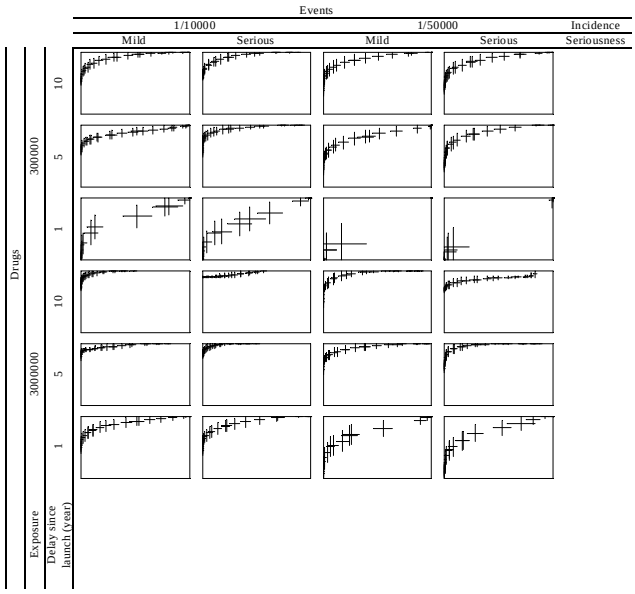

Figure 9: ROC curves for Bate and DuMouchel's data mining methods according to the model parameters values

	Linear correlation coefficient	
	IC	EB
Average (Standard deviation)	0.54 (0.014)	0.87 (0.012)

Table 2: Linear correlation coefficient between RR and IC and between RR and EB as an evaluation of the ranking pertinence

5 Discussion and Conclusion

Some SRS features have not been taken into account in the previously described model. The most important one is the drugs interactions, i.e. the fact that some events can be caused by the simultaneous exposure to two or more drugs and not by the drugs taken alone. DuMouchel proposes a method to identify the associations between an event and more than one drug by means of the "all-two-factor" model [5]. In order to evaluate such a method, it seems necessary to model drugs interactions in the simulated datasets.

SRS modelling permits not only to evaluate data mining methods but also to support pharmacovigilance experts in defining and testing surveillance strategies. A surveillance strategy is sequential and much information can be derived from the evolution of the reports number over the time [2; 8]. Moreover, it would be of particular interest to capitalise the experts knowledge when they interpret the signals generated and to use this knowledge for the subsequent signal generation. As the data generation process in the present study is sequential, surveillance strategies including time consideration could be easily tested.

The results presented in the present paper are obtained with a set of parameters values chosen in order to at best correspond to characteristic situations met in the French pharmacovigilance database. However, the choices are still quite arbitrary. A particular effort has to be done in order to make the distributions of the marginal numbers, i.e. $n_{i.}$ and $n_{.j}$, comparable with the real ones. Firstly these numbers are exploited by the data mining methods to determine the expected numbers of reports. Secondly, to study the distributions of these numbers is, to our knowledge, the only manner to quantitatively evaluate the SRS model. In fact, as the events incidences, the Relative Risks and the reporting probabilities are unknown in the real database, it would be useless to compare the real and the simulated number of reports at the drug-event couple level. The distributions of the marginal numbers are not only defined by the parameters values but also by the repartition of these values among the events, the drugs and the couples. As an example, it seems not realistic to have so many new drugs (1/3 of drugs with a delay of one year since the launch) in the database. So, the study of the French pharmacovigilance database, initiated in [10], has to be pursued to allow the simulation datasets to be as realistic as possible. However, results sensitivity according to the parameters values has to be studied too. Results in [9] show that methods sensitivity depends on the repartition of the causal/coincidental drug-event associations in the dataset. With a 40%/60% causal/coincidental associations repartition, relative methods results seem comparable but methods sensitivity are lower, for a given decision threshold.

Fuzzy set theory and fuzzy logic are not only interesting for modelling qualitative knowledge but also to actualise these knowledge by the pharmacovigilance experts themselves. They contribute to make the model intelligible for the experts and to make the results interpretable. So the Spontaneous Reporting System modelling participates to the knowledge discovery on the SRS itself and is of particular interest for the pharmacovigilance experts.

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