Signal Detection

Detecting Increases in Frequency of Adverse Events in Pharmacovigilance Database

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I Pharmacovigilance and Signal Detection

II Bayesian Algorithm for Increase in Frequency

III Approaches and Methods Comparison

IV Algorithm Evaluation on Different Patterns

V Conclusion and Propositions

Agenda

I **Pharmacovigilance and Signal Detection**

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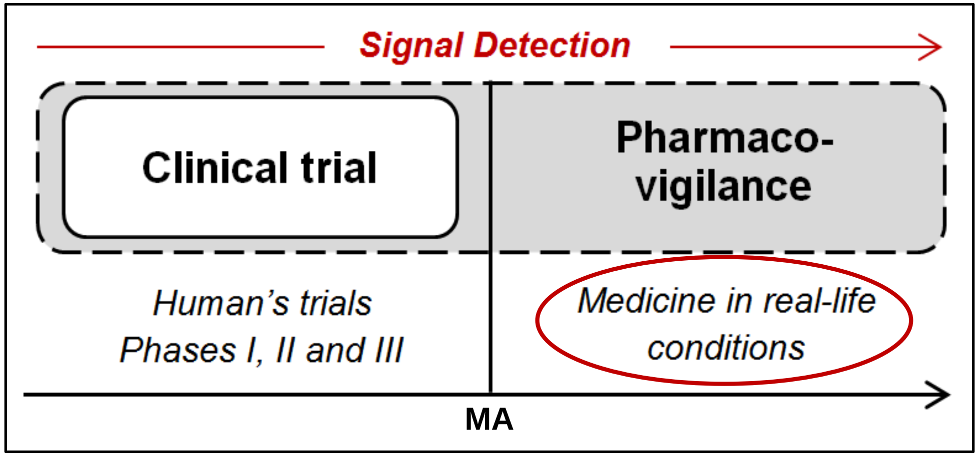
According to the World Health Organization: *"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem"*

Mission

Control the presence of Adverse Drug Reaction *(ADR)*

Identify phenomena influencing the health of patients → Evaluate the relationship between product and AE → Prevent the danger related to a side effect and update the RCP



According to the World Health Organization: *"A signal is a possible causal relationship between an adverse event and a drug, previously unknown or incompletely documented"*

Only information source

Spontaneous Report

=

Doctor *(Primary Source)* + Patient *(Identifiable)* + Adverse Event *(AE)* + Medical Product *(Drug)*

Received from different sources for Servier products

Organized in the Argus database
(430 000 cases in April 2016)

Individual control by the Therapeutic Safety Department

Article R.5144.19 code de santé publique

"déclaration obligatoire des effets indésirables graves ou inattendus (médecins, chirurgiens-dentistes, sages-femmes, pharmaciens)"

Take advantage of the information by statistical methods to prioritize the analysis of reported cases

Objective: activate alerts for some crossing ***Drug-Event Combination (DEC)*** corresponding to the presence of a suspected association

Drug | *AE*

DEC

Automated method for signal detection

Limits to keep in mind

No real nominator

Individual cases, Anonymous patient in the base

No known denominator

No rate of incidence

Sensitive bias

Underestimate possible

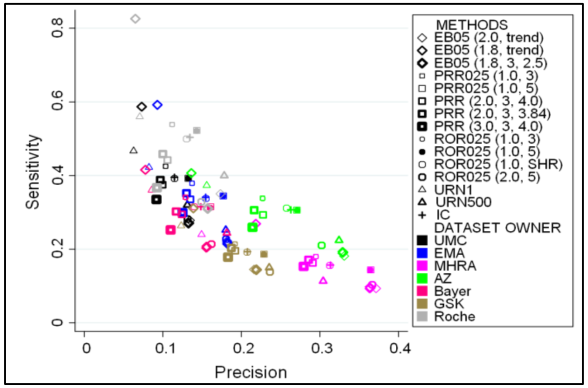
Identify a DEC with a statistical association measure using frequency of other crossings as comparator

Disproportionality Algorithm (DPA)			
Frequentist method		*Bayesian method*	
Proportional Reporting Ratio (PRR)	Reporting Odds Ratio (ROR)	Gamma Poisson Shrinker (GPS)	Bayesian Confidence Propagation Neural Network (BCPNN)

Algorithm precision: Alert for a maximum potential dangers *(sensitivity)* and for a minimum absence of dangers *(specificity)*

"A good signal detection method would detect ADRs at the earliest opportunity and produce a low number of false positives."

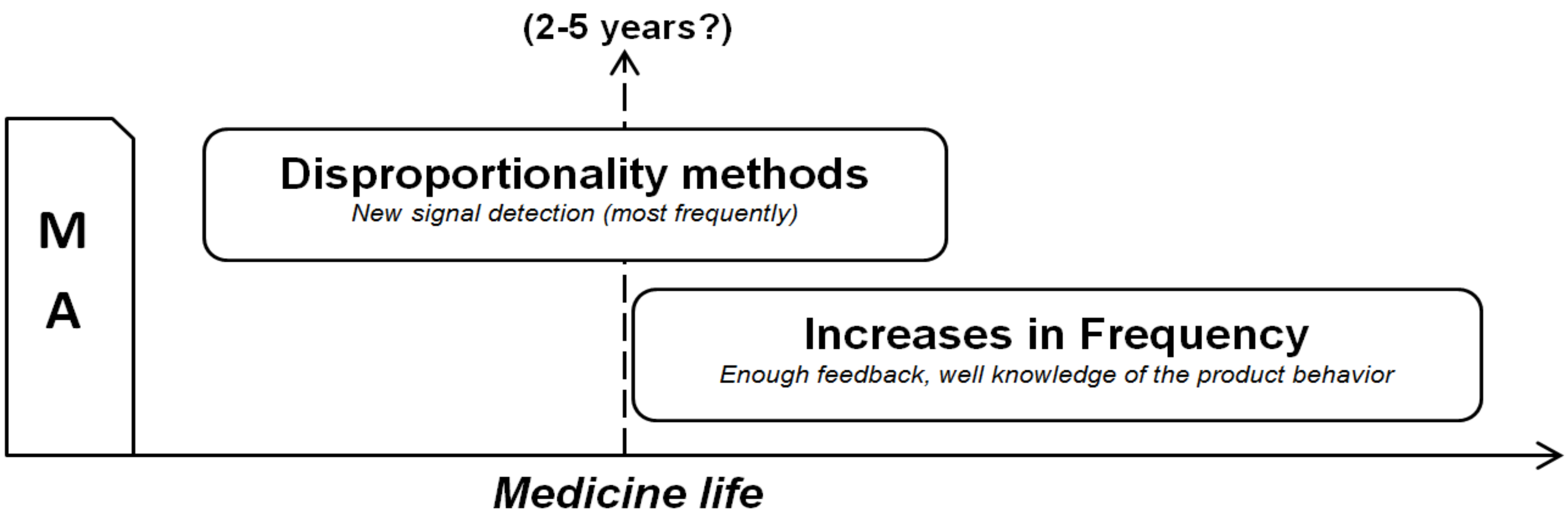
Comparison of Statistical Signal Detection Methods Within and Across Spontaneous Reporting Databases. **Candore & Al.**



The high frequency of some DEC can mask important AE less common

Internship problematic

What detection approach would be appropriate for modeling and for predicting spontaneous report evolution across time ?



Method from literature, Dr. DuMouchel approach

Predict the average frequency in view of the past data and compare the real frequency with the prediction (Bayesian Gamma-Poisson model)

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Bayesian Approach

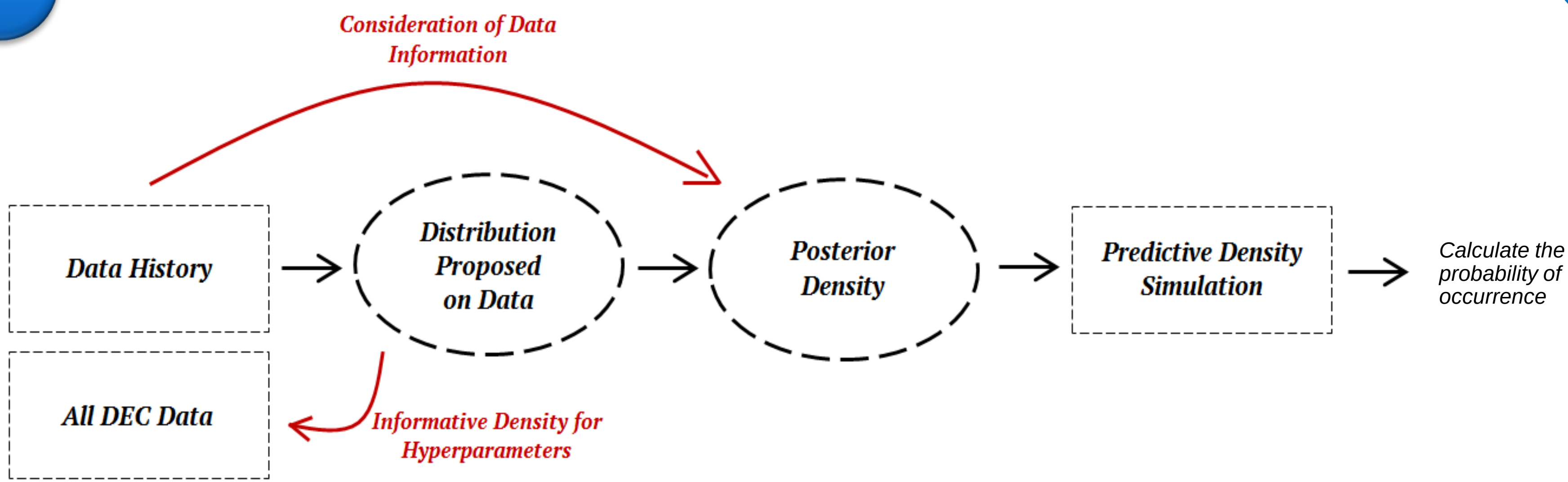
For a given DEC …

1

Choice of a known distribution on past data

Choice of a distribution on parameters

1



Bayesian Approach

For a given DEC …

1 Choice of a known distribution on past data

Choice of a distribution on parameters

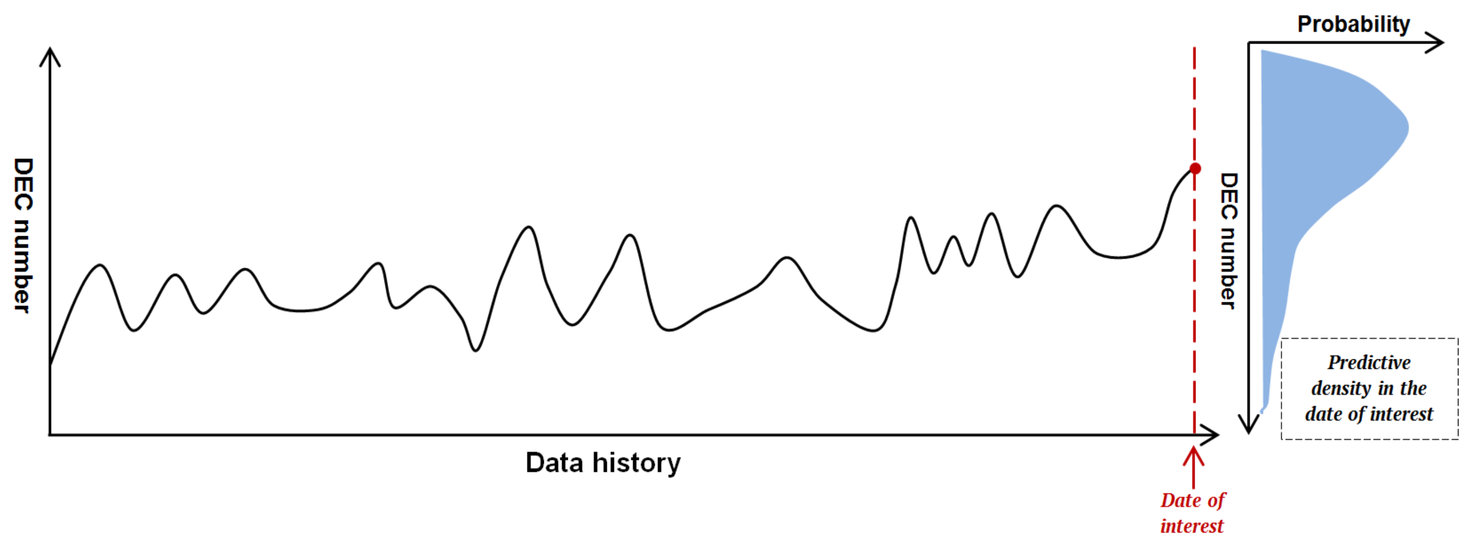
2 **Simulate the predictive density**

A large number of possibilities for the frequency to the date of interest

3 **Submit the real value to the predictive density**

Activate an alert if the probability of occurrence is lower than a given threshold

2-3



Gamma-Poisson model with known posterior distribution

X_k *History for DEC k*

Z *History mean for all DEC*

Y_k *Predictive simulation for DEC k*

Assumed distribution $\Rightarrow$ $\begin{cases} X_k \mid \lambda_k \sim P(\lambda_k) \\ \lambda_k \sim G(\alpha_k, \tau_k) \end{cases}$

Posterior distribution $\Rightarrow$ $[\lambda \mid X_1,\dots,X_n] \sim G(\alpha_k^p = \alpha_k + \sum_1^n x_i, \tau_k^p = \tau_k + n)$

Predictive formulae $\Rightarrow$ $[X = x^* \mid X_1,\dots,X_n] = \int_0^{+\infty} [X = x^* \mid \lambda][\lambda \mid X_1,\dots,X_n]\, d\lambda$

Law of interest $\Rightarrow$ $[X = x^* \mid X_1,\dots,X_n] \sim BinNeg(r_k^p = \alpha_k + \sum_1^n x_i, p_k^p = \dfrac{\tau_k + n}{\tau_k + n + 1})$

Predictive simulation

$$\begin{cases} \alpha_k \sim U[0, 2\hat{\alpha}] \\ \tau_k \sim U[0, 2\hat{\tau}] \\ \alpha_k^p = \alpha_k + \sum_1^n x_i \\ \tau_k^p = \tau_k + n \\ \lambda_k^p \sim G(\alpha_k^p, \tau_k^p) \\ Y_k \sim P(\lambda_k^p) \end{cases}$$

Gamma-Poisson model with unknown posterior distribution

Assumed distribution $\Rightarrow$ $\begin{cases} X_k \mid \lambda_k \sim P(\lambda_k) \\ \lambda_k \sim G(\alpha_k, \tau_k) \end{cases}$

Posterior distribution $\Rightarrow$ SUPPOSED UNKNOWN

X_k *History for DEC k*

Y_k *Predictive simulation for DEC k*

MCMC approach (Rstan)

Simulation of 2 Markov Chains for the parameters estimation

```
modelString <- "
 data{
  int<lower=0> N;
  int<lower=0> y[N];
 }

 parameters{
  real<lower=0> lambda[N];     // rate of Poisson
  real<lower=0> m;             // mode of Gamma
  real<lower=0> v;             // variance of Gamma
 }

 transformed parameters{
  real<lower=0> a;             // shape of Gamma
  real<lower=0> b;             // rate of Gamma
  b <- (m + sqrt(m^2 + 4 * v)) / (2 * v);  ------> τ_k^p
  a <- 1 + m * b;  ---------------------------> α_k^p
 }

 model{
  lambda ~ gamma(a, b);
  for(i in 1:N){
   increment_log_prob(poisson_log(y[i], lambda[i]));
  }        └-> λ_k^p
 }
"
```

Predictive simulation

$$\{\ Y_k \sim P(\lambda_k^p)$$

Model limit

$$\left.\begin{aligned} E[X] &= \frac{r(1-p)}{p} = \frac{\alpha}{\tau} = \lambda \\ V[X] &= \frac{r(1-p)}{p^2} = E[X]\frac{\tau+1}{\tau} = \lambda\frac{\tau+1}{\tau} \end{aligned}\right\} X \sim GP\left(\lambda = \frac{\alpha}{\tau}, \sigma = \frac{\tau+1}{\tau}\right)$$

- ✓ **σ > 1**, *overdispersion,* ***GP*** *adapted*
- ✓ **σ = 1**, *impossible with* ***GP***, ***P*** *adapted*
- ✓ **σ < 1**, *underdispersion, no solution*

$\Rightarrow$ ***Constraint for GP :*** $E[X] \leq V[X]$

Poisson-Uniform model with unknown posterior distribution

X_k	*History for DEC k*
Y_k	*Predictive simulation for DEC k*

Assumed distribution $\Rightarrow$ $\begin{cases} X_k \mid \lambda_k \sim P(\lambda_k) \\ \lambda_k \sim U(0,100) \end{cases}$

Posterior distribution $\Rightarrow$

MCMC approach (Rstan)

Simulation of 2 Markov Chains for the parameters estimation

```
modelP <- "
  data{
    int<lower=0>N;
    int<lower=0>y[N];
  }

  parameters{
    real<lower=0>lambda[N]; // mean of Poisson
  }

  model{
    lambda ~ uniform(0,100);
    for(i in 1:N){
      increment_log_prob(poisson_log(y[i],lambda[i]));
    }
  }
"
```

$\Rightarrow \lambda_k^p$

Predictive simulation

$$\{\ Y_k \sim P(\lambda_k^p)$$

Without MCMC ?

Frequentist approach

Law on past data		Modeling the variations of λ_k		Predictive simulation
$\{\ X_k \sim P(\lambda_k)$	$\Rightarrow$	$E[X_k] = \hat{\lambda}_k$	$\Rightarrow$	$\{\ Y_k \sim P(\hat{\lambda}_k)$

Bayesian Algorithm for Increase in Frequency
Bayesian Proposition (6/6)

4 models with this approach

2 Gamma-Poisson models
For series with overdispersion
- 1 with known posterior distribution
- ~~1 with MCMC approach~~

2 Poisson models
For series without overdispersion
- 1 with frequentist estimations
- 1 with MCMC approach

Algorithmic approaches
(Bayesian context)

Classic Bayesian
Frequentist Poisson model
G-P with known distribution

MCMC Bayesian
Poisson MCMC model

Composite Bayesian
Poisson MCMC model
G-P with known distribution

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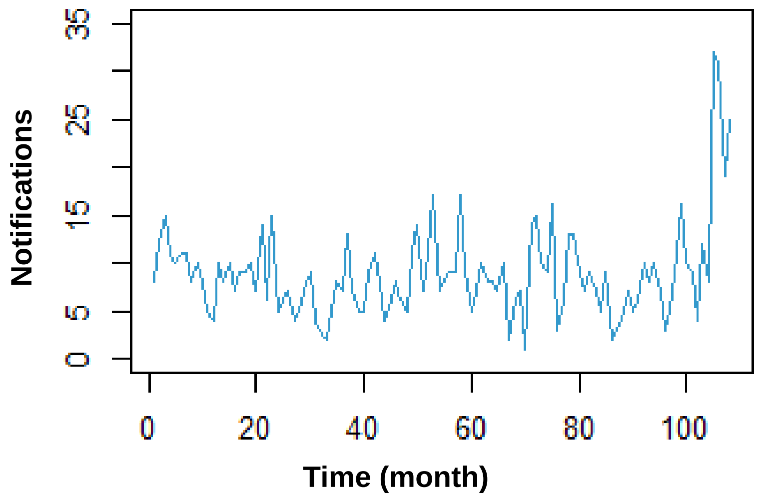
DEC simulation with signal at the end of the series

Example with a DEC



500 DEC $(k = 1, \dots, K)$

Obs. based on Poisson law

24 & 60 history values

10 DEC with signal at the end of the series
(4 times)

Signal : ${\lambda^{k}}^{sig.} = \lambda_k + Z\sqrt{\lambda_k}$

5 signal coefficients $(Z \in \{1,3,5,9,12\})$

200 simulations

500 000 series generated

DuMouchel method
- ✓ 3 regression models,
- ✓ 4 thresholds.

Bayesian method
- ✓ 3 approaches,
- ✓ 3 probabilities thresholds
  (1%, 0.5%, 0.1%).

Decision algorithm

Sensibility > 10%	Specificity > 50%	Yule Q. > 0.5	➡	Best VPP
✓ Enough true signals detected	✓ Acceptable quantity of false signals	✓ Acceptable compromised between true and false signals		✓ Final evaluation with true signals proportion among alarms

	Objective	
	Best results	**Best compromise**
Low signal	Composite bayesian *1%* *Time-consuming*	Classic bayesian *0.5%*
Moderate signal	Composite bayesian *0.1%* *Time-consuming*	Classic bayesian *0.1%*
Important signal	Composite bayesian *0.1%* *Time-consuming*	Classic bayesian *0.1%*

Algorithm calculation
(without parallelization)

- ***Classic Bayesian method***
  10 minutes
- ***DuMouchel method***
  10 hours
- ***Composite Bayesian method***
  2 days

⇒ Next steps

Classic Bayesian in a second set of simulations

Classic, Composite & MCMC Bayesian on real data

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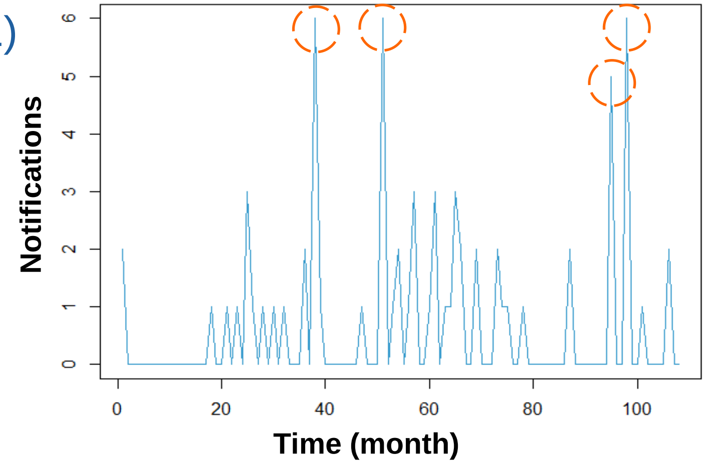
Algorithm Evaluation on Different Patterns
Second Set of Simulation

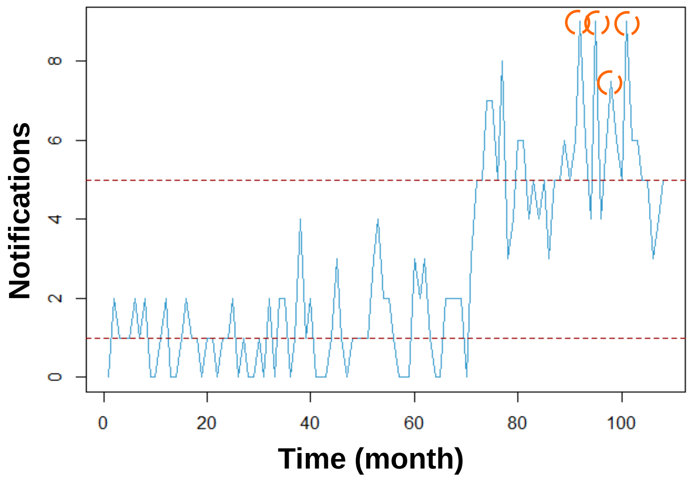
Signal during the series | *Break during the series* | *Signal after a break*

Example with 2 DEC

(1)



(2)



1 000 DEC $(k = 1, \ldots, K)$

Obs. based on Argus *(SOC & HLT)*

10 DEC with signal during the series (1),

10 DEC with break of the series and signal after the break (2),

24 & 60 history values

Monthly & trimester history

200 simulations

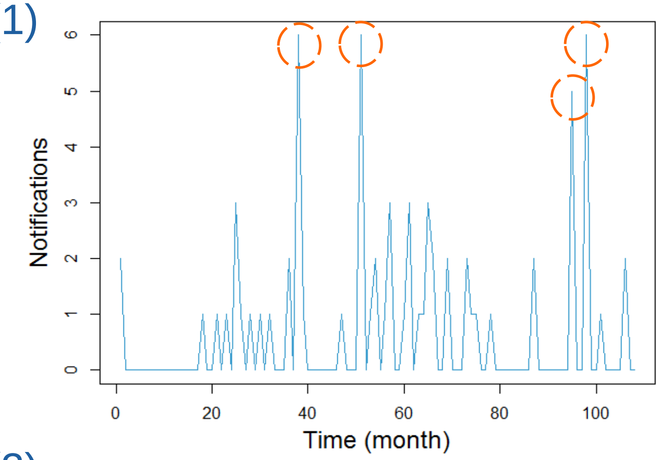
Bayesian method

- ✓ Model GP bay. & P freq.
- ✓ 4 probabilities thresholds (5%, 1%, 0.5%, 0.1%)

200 000 series generated

Algorithm Evaluation on Different Patterns
Different Situations Results

(1)



Result for signal detection during the series…

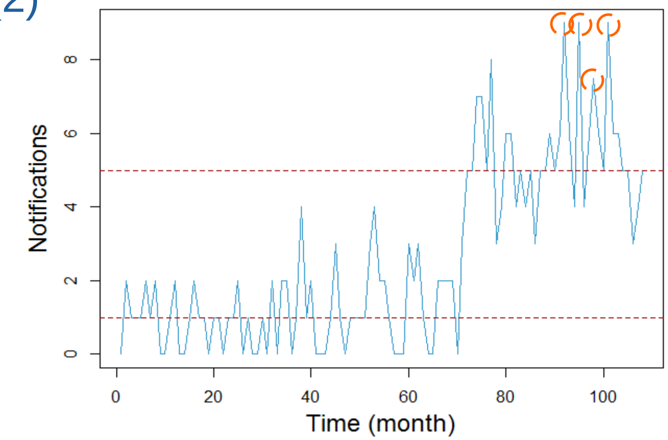
Recommendations

- ✓ 60 history values
- ✓ Monthly data
- ✓ Strict threshold

…after a break during the series

Same recommendations with less performance than (1)

(2)

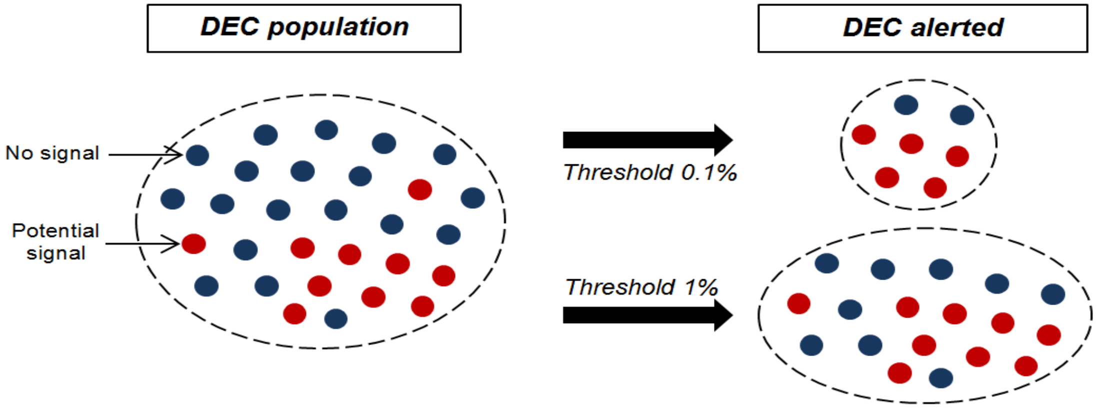


Result for break detection during the series

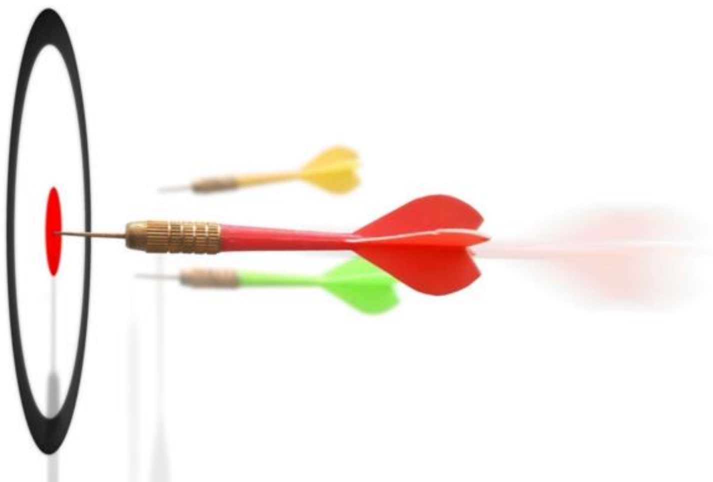
Recommendations

- ✓ 60 history values
- ✓ Quarterly data
- ✓ Strict threshold

Thresholds situations



Algorithm Evaluation on Different Patterns
Thresholds & Decision



⇒ Final Decision

- Bayesian approach validated
- Analyze on monthly & quarterly data
- Strict threshold (0.1%)

Evaluation on a Servier's antihypertensive drug

Analyze available for 23 years

- Analyses on levels SOC & HLT from MedDRA (AE classification)
- A restricted number of alerts initiated = focus possible for the PV
- Success in finding historical alerts concerning this product

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Conclusion and Propositions
Conclusion

Results & Decisions

2 methods compared, 1 from literature, 1 innovative

Different algorithms compared, with their own characteristics

Many simulations sets, take into account of uncertainties for robustness

- ✓ Bayesian composite algorithm presents best theoretical results
- ✓ Combine monthly and quarterly data with 60 months of history and strict threshold

Approach interest

Useful to complete the exhaustive cases study and detect the impact of new phenomena
⇒ Give the priority to some DEC

Show the Bayesian method potential
⇒ Bayesian Counting model validated

Increase in Frequency Detection Method is only a ***decision helper*** *for* ***generate alerts*** *and not a* ***tool to validate signals***

Limits in practice

In fine, exhaustive cases analysis is necessary

⇒ Non detectable situations could be missed

Go farther into the matter of series' overdispersion

⇒ Binomial negative hypothesis is enough ?

For more knowledge

Algorithms evaluation on different products

⇒ Validation for other therapeutic areas, with more confirmed signals and different trends

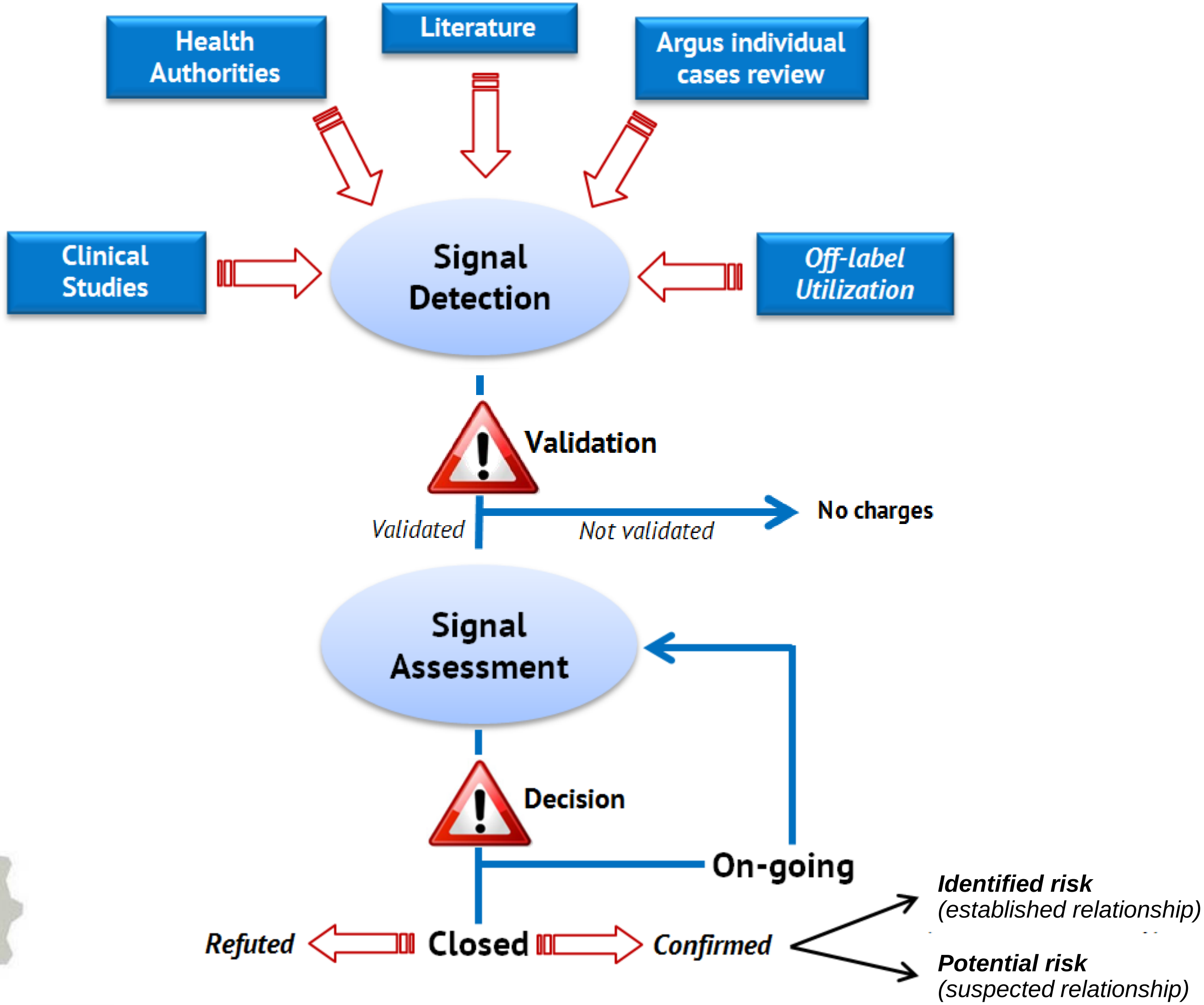
Compare our results with disproportionality approach

⇒ When each approach should be used precisely ?

Thank for your attention

Back up

According to the World Health Organization: *"A signal is a possible causal relationship between an adverse event and a drug, previously unknown or incompletely documented"*



Detection algorithm – Increase in Frequency
DuMouchel Proposition

D. W. DuMouchel approach, *Validated on GSK database*

(Automated method for detecting increases in frequency of spontaneous adverse event reports over time)

1 **Predict the average frequency in view of the past data**

Regression model (3 evaluated)

2 **Compare the real frequency with the prediction**

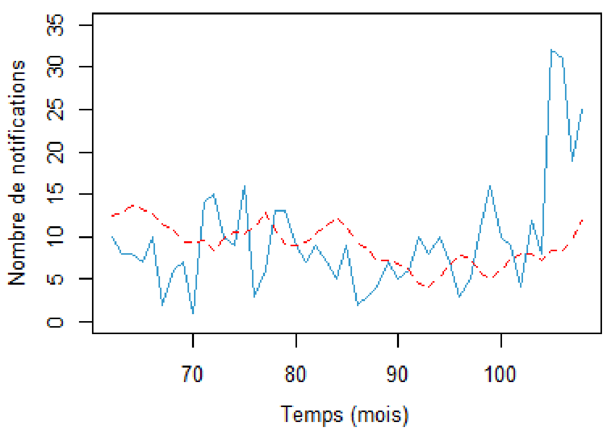
Bayesian Gamma-Poisson model

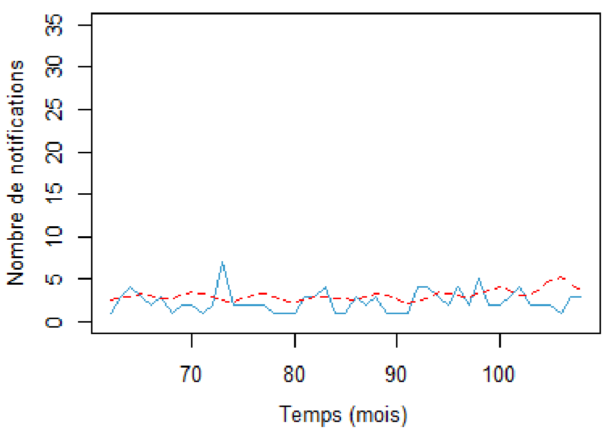
3 **Activate an alert if thresholds are exceeded**

Use of indicators

Observed data

Predicted data





⇒ No package available, method implemented during the internship

Detection algorithm – Increase in Frequency
DuMouchel Proposition (1/4)

D. W. DuMouchel approach, *Validated on GSK database*

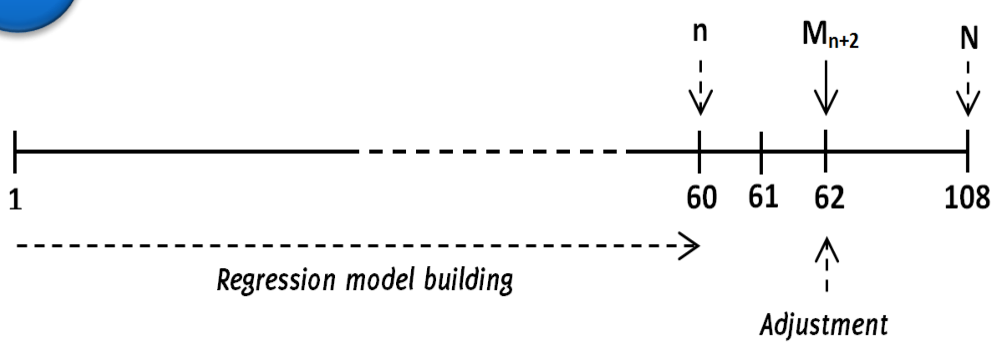
(Automated method for detecting increases in frequency of spontaneous adverse event reports over time)

1

Predict the average frequency in view of the past data

Regression model

1



For time $T \Rightarrow M_{n+2}$

- Model built on monthly data [n-60;n] or [n-24;n] *(Regression),*
- Model correction with errors truncation *(Interval [-1;1]),*
- Time weighting *(Tukey triweight function).*

⇒ Predicted adjusted value estimation

Harmonic regression	Spline regression	Local polynomial regression

Detection algorithm – Increase in Frequency
DuMouchel Proposition (2/4)

D. W. DuMouchel approach, *Validated on GSK database*

(Automated method for detecting increases in frequency of spontaneous adverse event reports over time)

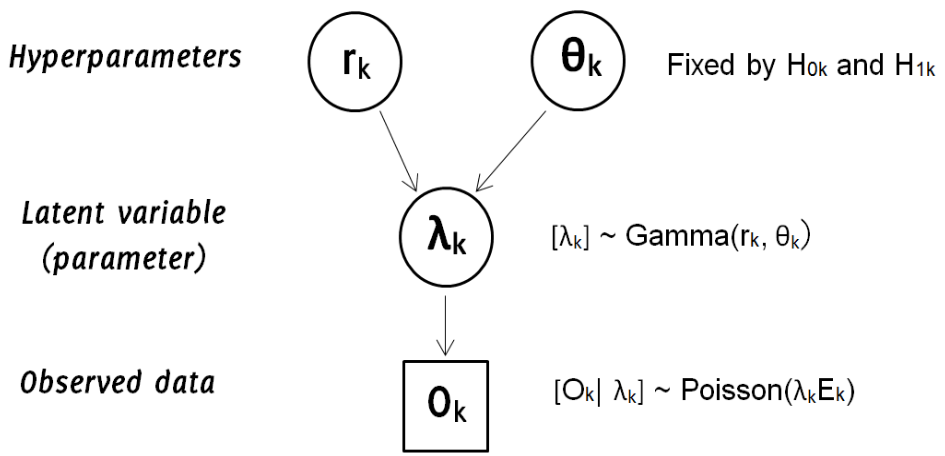
1 – **Predict the average frequency in view of the past data**

Regression model

2 – **Compare the real frequency with the prediction**

Bayesian Gamma-Poisson model

2



⇒ Gap evaluation between observation O_k and prediction E_k

For an event k in a given time T

- Law on data: $O_k | \lambda_k \sim P(\lambda_k E_k)$,
- Prior hypothesis λ_k:

  H_0: *no gap*, $\lambda_k \sim Gamma(E_k, E_k)$

  H_1: *gap*, $\lambda_k \sim Gamma(r_k, \theta_k)$
- p_1 : proba. a priori to be under H_1,
- Marginal distribution, proba. and density a posteriori.

Detection algorithm – Increase in Frequency
DuMouchel Proposition (3/4)

D. W. DuMouchel approach, *Validated on GSK database*

(Automated method for detecting increases in frequency of spontaneous adverse event reports over time)

1 Predict the average frequency in view of the past data

Regression model

2 Compare the real frequency with the prediction

Bayesian Gamma-Poisson model

3 Activate an alert if thresholds are exceeded

Use of indicators

3

Indicators :

- $-log_{10}Pvalue$
- $log_{10}BayesFactor$
- $Proba\ Posteriori\ q_k$

⇒ Alert activated if at least one threshold is crossed

Decision algorithm

Sensibility > 10% | Specificity > 50% | Yule Q. > 0.5 → Best VPP

- ✓ Enough true signals detected
- ✓ Acceptable quantity of false signals
- ✓ Acceptable compromised between true and false signals
- ✓ Final evaluation with true signals proportion among alarms

Harmonic regression with DuMouchel approach

Signal	Hyp.	Sample	24 month Alerted rate	24 month VPP (Threshold)	60 month Alerted rate	60 month VPP (Threshold)
Z1	H_0	98000	12.05	4.97	X	X
	H_1	2000	32.05	(S1)	X	
Z3	H_0	98000	12.36	9.71	11.01	10.92
	H_1	2000	65.10	(S2)	66.10	(S1)
Z6	H_0	98000	11.24	13.50	0.00	100
	H_1	2000	85.95	(S4)	63.35	(S4)
Z9	H_0	98000	0.08	95.29	0.01	99.61
	H_1	2000	74.80	(S4)	75.80	(S4)
Z12	H_0	98000	0.10	94.08	0.01	99.81
	H_1	2000	81.10	(S4)	80.35	(S4)

Spline regression with DuMouchel approach

VPP (threshold)		Z1		Z3		Z6	
Se.	1-Sp.						
24 month		5.73 (S2)		12.00 (S4)		14.56 (S4)	
		30.35	10.19	65.50	9.81	82.85	9.92

Z6 : *signal coefficient*

(S4) : *best threshold*

Approaches and Methods Comparison
Bayesian Approach Results

Z6 : *signal coefficient*

Classic Bayesian Model (60 past data)

Signal	Hyp.	Sample	*Threshold 0.001* Alerted rate	*Threshold 0.001* VPP	*Threshold 0.005* Alerted rate	*Threshold 0.005* VPP	*Threshold 0.01* Alerted rate	*Threshold 0.01* VPP
Z1	H_0	98000	0.03	33.33	0.21	28.17	0.46	21.99
	H_1	2000	0.80		4.00		6.30	
Z3	H_0	98000	0.04	90.62	0.23	79.64	0.50	69.20
	H_1	2000	19.80		43.80		55.15	
Z6	H_0	98000	0.04	96.75	0.22	87.46	0.49	77.00
	H_1	2000	62.45		76.00		79.85	
Z9	H_0	98000	0.04	97.24	0.21	89.48	0.47	79.95
	H_1	2000	77.60		87.65		92.10	
Z12	H_0	98000	0.02	98.75	0.21	90.39	0.47	80.98
	H_1	2000	87.20		95.50		97.50	

Composite Bayesian Model (60 past data)

Signal	Hyp.	Sample	*Threshold 0.001* Alerted rate	*Threshold 0.001* VPP	*Threshold 0.005* Alerted rate	*Threshold 0.005* VPP	*Threshold 0.01* Alerted rate	*Threshold 0.01* VPP
Z1	H_0	19600	0,01	66,67	0,03	57,14	0,05	59,09
	H_1	400	1,00		2,00		3,25	
Z3	H_0	19600	0,01	96,00	0,03	94,92	0,05	94,12
	H_1	400	12,00		28,00		36,00	
Z6	H_0	19600	0,01	99,27	0,03	98,08	0,05	97,26
	H_1	400	67,75		76,50		80,00	
Z9	H_0	19600	0,01	99,44	0,03	98,42	0,05	97,68
	H_1	400	89,00		93,25		94,75	
Z12	H_0	19600	0,01	99,46	0,03	98,48	0,05	97,77
	H_1	400	91,25		97,50		98,50	

DuMouchel Approach Results

Signal	Hyp.	Alerted rate	VPP
Z1	H_0	10.19	5.73
	H_1	30.35	*(Spline 24m, S2)*
Z3	H_0	9.81	12.00
	H_1	65.50	*(Spline 24m, S4)*
Z6	H_0	0.00	100
	H_1	63.35	*(Harmo. 60m, S4)*
Z9	H_0	0.01	99.61
	H_1	75.80	*(Harmo. 60m, S4)*
Z12	H_0	0.01	99.81
	H_1	80.35	*(Harmo. 60m, S4)*

Algorithm Evaluation on Real Data
Drug tested & MedDRA Dictionary

Analyse on antihypertensive drug

AE alerted for tested drug
(SER Information)

Orthostatic hypotension
Blood creatinine increased
Renal failure
Bradycardia
Malaise
Fall

Marketing Authorization

1st case notification

1st detection

Extracted data

Apr 1987 — ***Aug 1988*** — ***Aug 1993*** — ***Oct 2011*** — ***May 2012*** — ***Nov 2012*** — ***Apr 2016***

With 60 history data, analyze on 23 years

26 SOC & 337 HLT notified

26 SOC & 50 HLT studied

MedDRA, *AE classification & hierarchy*

System Organ Class (SOC)	Ex. Cardiac disorders
High Level Term (HLT)	Ex. Rate & rhythm dis.
Preferred Term (PT)	Ex. Arrhythmia

SER : *Safety Evaluation Report*

Automatic Detection on 23 years

- ✓ SOC & HLT levels
- ✓ Monthly & Quarterly data
- ✓ 60 past data
- ✓ Threshold 0.1%

Classic algorithm	*MCMC algorithm*	*Composite algorithm*
11 alerts concerning 9 SOC 62 alerts concerning 42 HLT	20 alerts concerning 10 SOC 16 alerts concerning 9 HLT	25 alerts concerning 12 SOC 41 alerts concerning 16 HLT
3 SOC notified in SER alerted 3 HLT notified in SER alerted	3 SOC notified in SER alerted 4 HLT notified in SER alerted	5 SOC notified in SER alerted 2 HLT notified in SER alerted
$SOC : \frac{3}{9} = 33\%^{*}$ $HLT : \frac{3}{42} = 7\%^{*}$	$SOC : \frac{3}{10} = 30\%^{*}$ $HLT : \frac{4}{9} = 44\%^{*}$	$SOC : \frac{5}{12} = 42\%^{*}$ $HLT : \frac{2}{16} = 12\%^{*}$

$$^{*}\ \frac{DEC\ notified\ in\ SER\ alerted}{DEC\ alerted}$$

Algorithm Evaluation on Real Data
Hyperium & MedDRA Dictionary

Tested drug
(antihypertensive drug)

Marketing Authorization
April 23, 1987
29 years in the market

First notification case
August 26, 1988
28 years of history

26 SOC & 337 HLT notified
26 SOC & 50 HLT studied
(HLT retained : At least 1 case every 2 years on average)

⇒ ***With 60 history data, analyze on 23 years***

SER : *Safety Evaluation Report*

MedDRA, *AE classification & hierarchy*

- *System Organ Class (SOC)* — Ex. Cardiac disorders
- *High Level Group Term (HLGT)* — Ex. Cardiac arrhythmia
- *High Level Term (HLT)* — Ex. Rate & rhythm dis.
- *Preferred Term (PT)* — Ex. Arrhythmia
- *Lowest Level Term (LLT)* — Ex. Dysrhythmias

AE alerted for tested drug *(SER Information)*

PT	Date detected	Date closed	SOC	HLT
Blood creatinine increased	Oct-2011	Dec-2014	Investigations	Renal function analyses
Bradycardia	May-2012	Feb-2013	Cardiac disorders	Rate and rhythm disorders NEC
Fall	Nov-2012	Feb-2013	Injury, poisoning and procedural complications	Non-site specific injuries NEC
Malaise	Nov-2012	Feb-2013	General disorders and administration site conditions	Asthenic conditions
Orthostatic hypotension	Oct-2011	Dec-2014	Vascular disorders	Vascular hypotensive disorders
Renal failure	Oct-2011	Dec-2014	Renal and urinary disorders	Renal failure and impairment

Algorithm Evaluation on Real Data
Bayesian Algorithms with SOC & HLT

Automatic Detection Results (60 past data, 0.1%)

MedDRA level	SOC		HLT	
	Classic algorithm			
	Alerts	Concerned DEC	Alerts	Concerned DEC
Monthly data	7	5 (19%)	48	41 (76%)
Quarterly data	4	4 (15%)	14	11 (20%)
Algorithm conclusion	11	9 (34%)	62	42 (78%)
	MCMC algorithm			
	Alerts	Concerned DEC	Alerts	Concerned DEC
Monthly data	12	8 (31%)	2	2 (3%)
Quarterly data	8	4 (15%)	14	9 (17%)
Algorithm conclusion	20	10 (38%)	16	9 (17%)
	Composite algorithm			
	Alerts	Concerned DEC	Alerts	Concerned DEC
Monthly data	8	5 (19%)	19	11 (20%)
Quarterly data	17	10 (38%)	22	13 (24%)
Algorithm conclusion	25	12 (46%)	41	16 (30%)

SOC : $\frac{3}{9} = 33\%$

HLT : $\frac{3}{42} = 7\%$

SOC : $\frac{3}{10} = 30\%$

HLT : $\frac{4}{9} = 44\%$

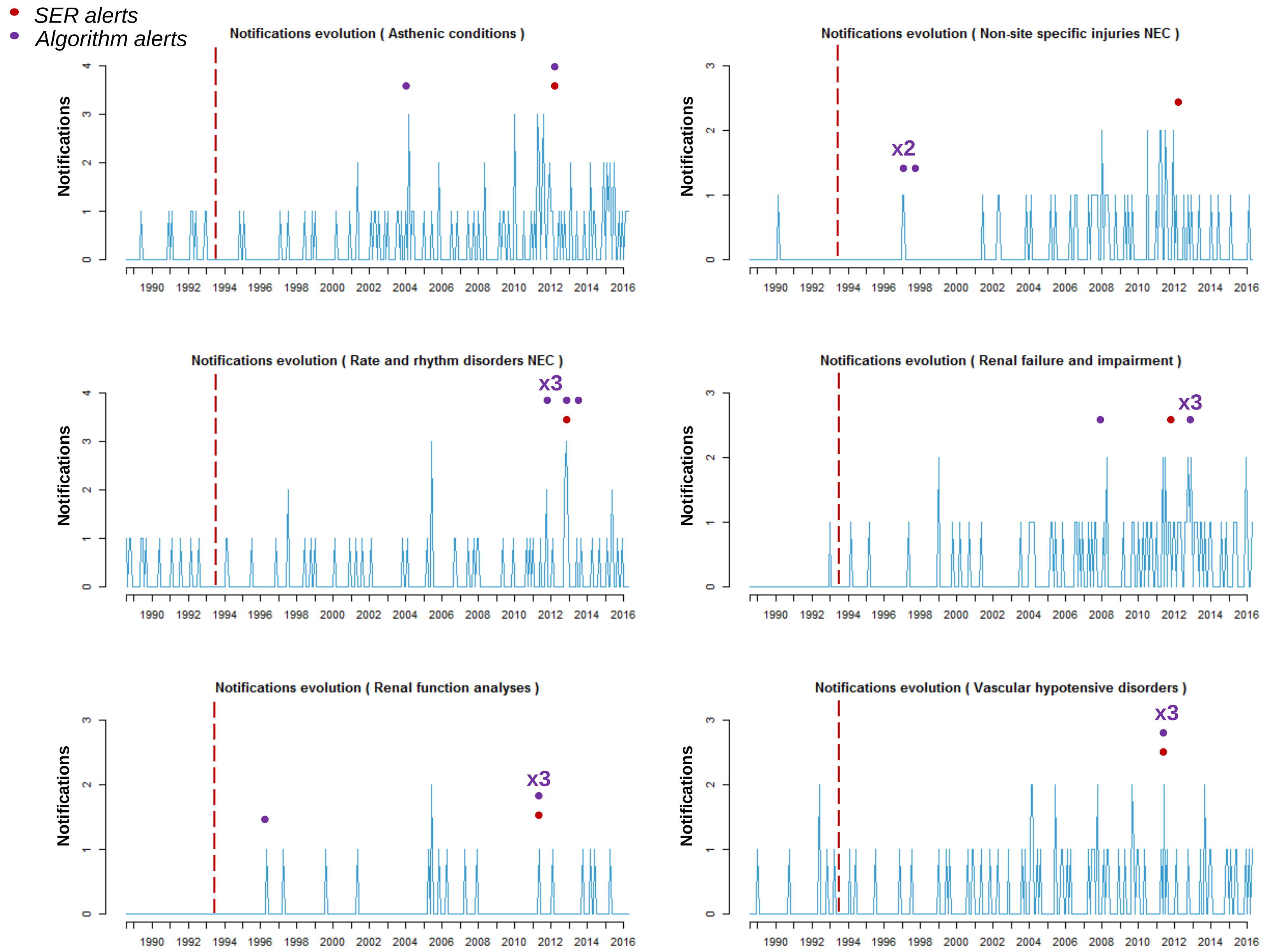
SOC : $\frac{5}{12} = 42\%$

HLT : $\frac{2}{16} = 12\%$

Comparison with SER alerts

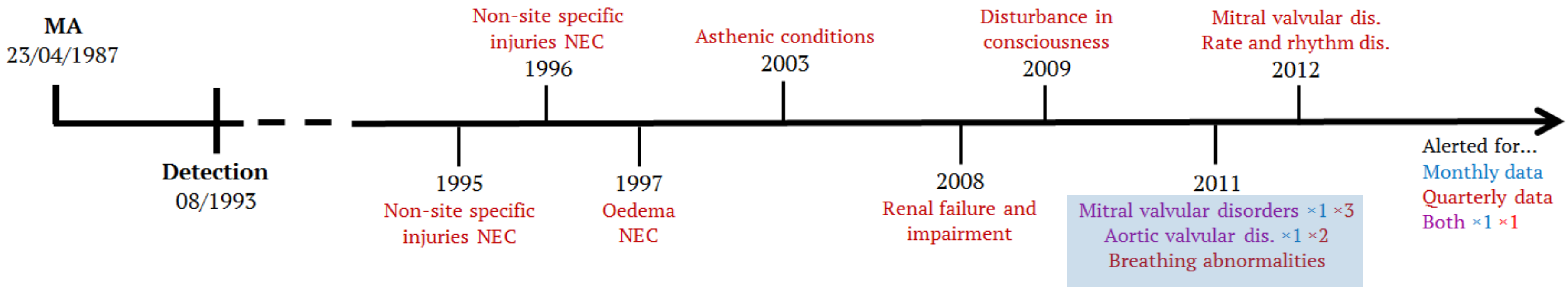
MedDRA level	SOC		HLT	
	Classic algorithm			
	Monthly data	Quarterly data	Monthly data	Quarterly data
Blood creatinine increased	/	/	1996 (1)	/
Bradycardia	/	2011 (1)	/	2013 (1)
Fall	/	/	1997 (1)	/
Malaise	/	2011 (1)	/	/
Orthostatic hypotension	/	2011 (1)	/	/
Renal failure	/	/	/	/
	MCMC algorithm			
	Monthly data	Quarterly data	Monthly data	Quarterly data
Blood creatinine increased	2010 (1)	/	/	/
Bradycardia	2011 (3)	/	2011 (3)	2012 (1)
Fall	/	2007 (1)	/	1995 (1) 1996 (2)
Malaise	/	/	2003 (1)	2012 (1)
Orthostatic hypotension	/	/	/	/
Renal failure	/	/	2012 (3)	2008 (1)
	Composite algorithm			
	Monthly data	Quarterly data	Monthly data	Quarterly data
Blood creatinine increased	/	2011 (1)	2011 (1)	2011 (2)
Bradycardia	2011 (4)	2011 (4)	/	/
Fall	/	/	/	/
Malaise	/	2011 (1)	/	/
Orthostatic hypotension	/	2011 (2)	2011 (1)	2011 (2)
Renal failure	2004 (1)	2012 (1)	/	/

Algorithm Evaluation on Real Data
Bayesian Algorithms with HLT

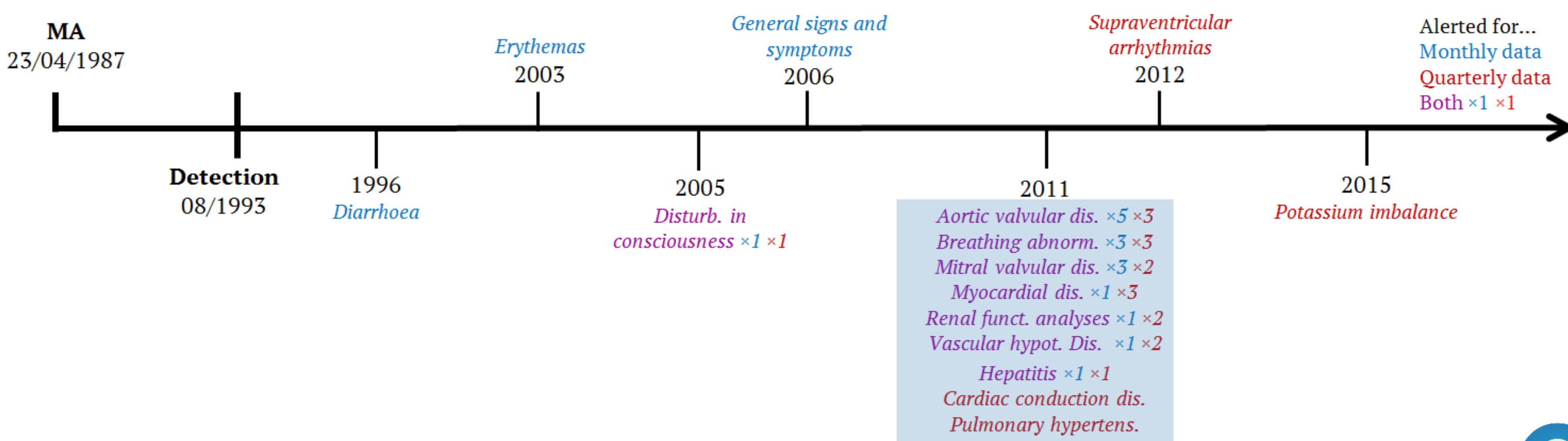


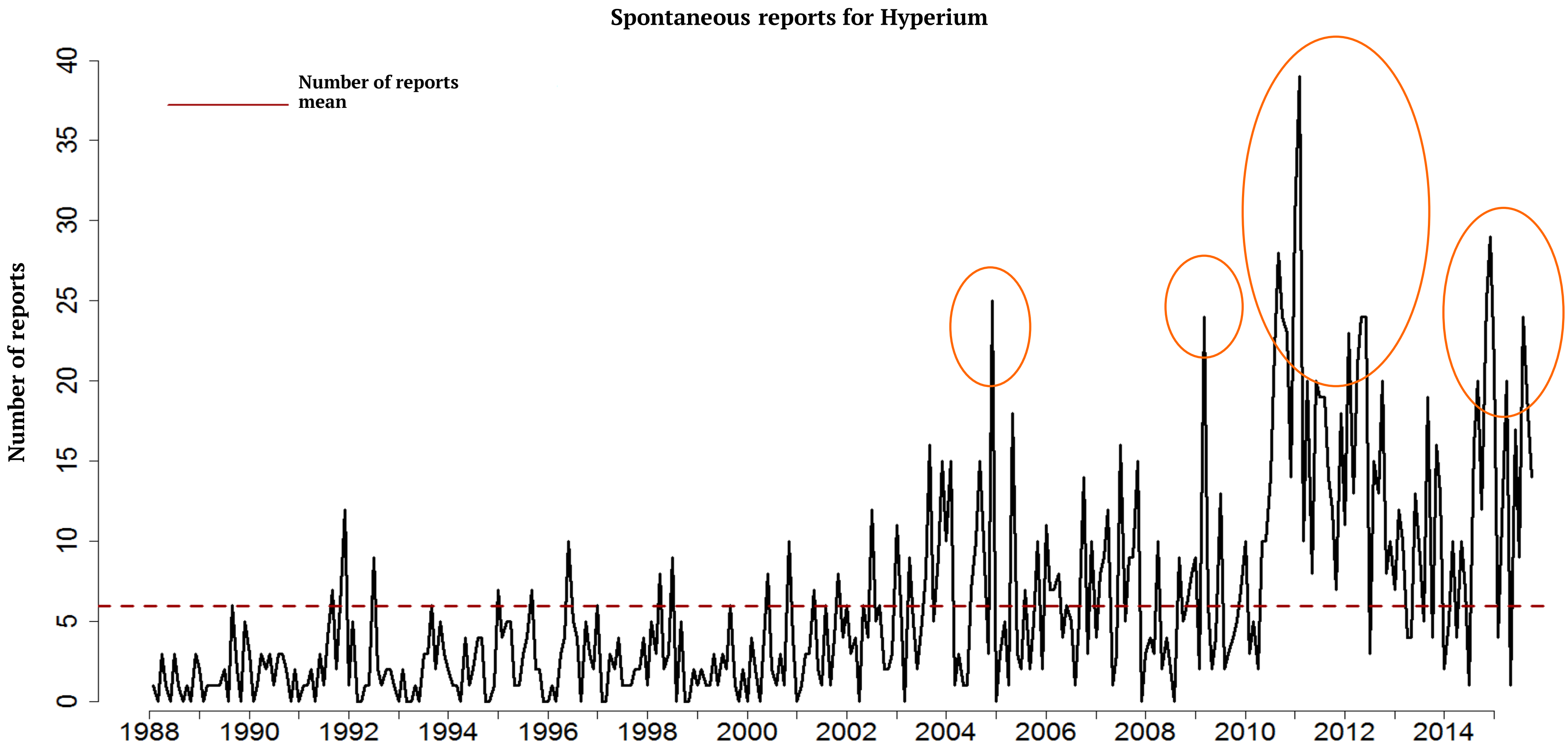
Algorithm Evaluation on Real Data
HLT Results across the time

Bayesian MCMC model on HLT data (60 past data, 0.1%)



Composite Bayesian model on HLT data (60 past data, 0.1%)





In 2011, **modification of Argus coding rules** leading to a global increase in frequency

Back up