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Document-level adverse drug reaction event extraction on electronic health records in Spanish *

Extracción a nivel de documento de reacciones adversas a medicamentos en informes médicos electrónicos en español

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Resumen: Presentamos un sistema de extracción de Reacciones Adversas a Medicamentos (RAMs) para Informes Médicos Electrónicos escritos en español. El objetivo del sistema es asistir a expertos en farmacia cuando tienen que decidir si un paciente padece o no una o más RAMs. El núcleo del sistema es un modelo predictivo inferido de un corpus etiquetado manualmente, que cuenta con características semánticas y sintácticas. Este modelo es capaz de extraer RAMs de parejas enfermedad-medicamento en un informe dado. Finalmente, las RAMs extraidas automáticamente son post-procesadas usando un heurístico para presentar la información de una forma compacta. Esta fase ofrece los medicamentos y enfermedades del documento con su frecuencia, y también une las parejas relacionadas como RAMs. En resumen, el sistema no sólo presenta las RAMs en el texto sino que también da información concisa a petición de los expertos en farmacia (los usuarios potenciales del sistema).
Palabras clave: Extracción de Eventos; Reacciones Adversas a Medicamentos; Minería de Textos.

Abstract: We outline an Adverse Drug Reaction (ADRs) extraction system for Electronic Health Records (EHRs) written in Spanish. The goal of the system is to assist experts on pharmacy in making the decision of whether a patient suffers from one or more ADRs. The core of the system is a predictive model inferred from a manually tagged corpus that counts on both semantic and syntactically features. This model is able to extract ADRs from disease-drug pairs in a given EHR. Finally, the ADRs automatically extracted are post-processed using a heuristic to present the information in a compact way. This stage reports the drugs and diseases of the document together with their frequency, and it also links the pairs related as ADRs. In brief, the system not only presents the ADRs in the text but also provides concise information on request by experts in pharmacy (the potential users of the system).
Keywords: Event Extraction; Adverse Drug Reactions; Text Mining.

1 *Introduction*

In the era of digitalization, the documentation on patients of health systems is also being stored in electronic format. Because of this fact the volume of digital information generated in the hospitals is growing exponentially. Professionals often have to manage an excess of data and different kinds of information. The manner in which this sensitive information is presented to the doctors can help in the decision-making process and also alleviate the workload of several services within a hospital. All these facts make the creation of a robust system an important challenge for the Natural Language Processing research community.

In this context the goal of this work is to obtain the Adverse Drug Reactions (ADRs)

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that are stated in the Electronic Health Records (EHRs) in a robust way. This need arises when experts have to prescribe a drug, since before that, they have to know if the patient has suffered from adverse reactions to substances or drugs. The final system should present the ADRs in the given EHR, showing the drug-disease pairs that triggered each ADR event. For example, the system should be capable of extracting ADRs such as *"As a result of the steroidal treatment, hyperglycemic decompensation was produced which requires treatment with insulinization"* from a given EHR, showed in the figure 1. In this case, the disease *"hyperglycemic decompensation"* has been caused by the *"steroidal treatment"*.

The challenge of the problem lies in the nature of the documents because they are written using unstructured free-text and a wide diversity of data-types (e.g. clinical analysis, personal antecedents, or treatments). With the aim of making progress in the extraction of ADRs, we have developed a system that extracts all possible drug-disease pairs and represents them with different features. These features are the input of a predictive model that determines if each pair represents an ADR. Finally, a post-process is carried out for each document to get a consistent representation of the drugs, diseases and ADRs presented in the EHR.

As a second challenge, we should mention the fact that the EHRs are written in Spanish and so far the clinical literature has focused primarily in English while there are some preliminary works, as well, in Spanish social media (de la Peña et al., 2014; Segura-Bedmar et al., 2015).

2 Related work and contributions

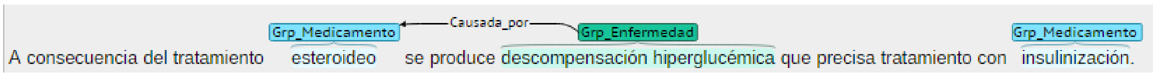
Friedman, Geiger, and Goldszmidt (1997) were amongst the first researchers in discovering adverse events in EHRs automatically. They proposed the automatic extraction of associations between clinical entities, such as disease-symptom and disease-drug pairs using statistical associations and knowledge, as well as statistical and theoretical processes to remove incorrect associations. This proposal was put in practice by Wang et al. (2009) for narrative reports. Their experiments were centred on a set of seven drugs with known adverse events that were selected for evaluation and they achieved a precision of 0.75 and a recall of 0.31. By contrast, our proposal is not limited to a restricted set of drugs, but to any ADR that was annotated in the training corpus, that contained more than 800 distinct drugs, making it a more challenging task.

Aramaki et al. (2010) presented a system that extracted ADRs from medical records. The extraction task was divided in two steps: 1) identification of drugs and symptoms; 2) association of symptoms with drugs. For the second step, they compared a pattern-based methodology and Support Vector Machines. The support vector machine algorithm was trained with four features and their system presented a precision of 0.301 and a recall of 0.597. In our approach, we also carry out a two-step process to recognize medical entities first, and next guess the relationships, but we describe these thoroughly with 54 syntactic and semantic features.

Sohn et al. (2011) presented two approaches for extracting adverse drug events from EHRs. The first approach was based on rules and the second one consisted of a hybrid method including both rules and machine learning. Their system was tested in a limited domain corresponding to psychiatry and psychology and it was centred only in intra-sentence ADRs.

Karlsson et al. (2013) explained a model that can be used for the detection of adverse drug reactions using structured data in order to avoid mistakes such as the detection of ADRs that occurred in the past. The EHRs in Spanish in our corpus are non structured. Trying to find the underlying structure is still an open problem in the field of semantics applied to Biomedicine (Cohen and Demner-Fushman, 2014). Karlsson et al. evaluated the performance of different machine learning algorithms with six feature sets, concluding that Random Forest yielded highly accurate models. These encouraging results led us make use of Random Forests.

Most of the analysed studies had English as their target language, and fewer works have been carried out for other languages. In Deléger, Grouin, and Zweigenbaum (2010) and Li et al. (2013) it is reported the implementation of a medication extraction system which extracts drugs and related information in the domain of tele-cardiology from EHRs written in French. Grigonyte et al. (2014) tried to improve the readability of electronic health records in Swedish detecting the out-



A consecuencia del tratamiento esteroideo se produce descompensación hiperglucémica que precisa tratamiento con insulinización.

Figure 1: Example of ADR in a given EHR.

of-dictionary words. Laippala et al. (2009) presented the steps taken towards an automated processing of clinical Finnish, focusing on daily nursing notes in a Finnish Intensive Care Unit (ICU). de la Peña et al. (2014) and Segura-Bedmar et al. (2015) wrote some works that we are aware of that tackle adverse effects for Spanish. Contrary to our work, they process texts from social media streams. Their work implemented the identification of drug and disease entities by a dictionary-matching approach. Besides, they also tackle the extraction of drug indications.

To sum up, our contribution is a consistent system to assist doctors and experts on pharmacy in making the decision of whether a specific patient suffers from one or more adverse drug reactions, and consequently, to help them making prescriptions to treat that patient. Besides, this work makes use of non structured EHRs written in Spanish in an attempt to make progress on biomedical NLP for this language.

3 *Text mining strategy*

The system developed in this work, depicted in figure 2, is composed of the following parts (each of which shall be described in sections 3.1, 3.2 and 3.3 respectively):

1. **Pre-process:** the input corpus, consisting of a set of manually annotated EHRs. The text is morpho-syntactically analysed and all the drug-disease pairs extracted as ADR candidates.
2. **Inference:** given the aforementioned ADR candidates, we resorted to Naïve Bayes and Random Forest algorithms to infer two different predictive models.
3. **Post-process:** having the classifiers established the potential ADR events as either positive or negative, next, a heuristic is applied to all the ADRs found in each document in order to get a sub-set through a simple coercion post-process.

3.1 Pre-process: operational description of ADR events

The corpus counts on several medical entities and relations (events) between them, manually annotated by consensus of two experts from the pharmacy and pharmacosurveillance departments of a hospital. The IAA (Inter Annotator Agreement) was 90.53% for entities and 82.86% for events (Oronoz et al., 2015).

For this problem, the context in which the pair appears is crucial. To describe the drug-disease pairs we use the following 54 features:

- **Morphosyntax:** part of speech, lemma and word-form for the drug or disease entities and their context. The context-window was set to 3 terms (often a term is formed by more than one word-form). For this task, a morphosyntactic analyser is required. As a general-purpose analyser would be of little use, due to the use of medical language, we resorted to FreeLing-Med, an analyser adapted to the clinical domain, operating both in Spanish and English (Oronoz et al., 2013; Gojenola et al., 2014).
- **Distance:** the distance from the drug to the disease entity in two scales: number of characters and number of sentences. These features turned out of much help: typically, the furtherer the lower the probability to form an ADR event.
- **Trigger words:** presence of trigger-words between the drug and the disease entities. As an example of trigger words, we consider the following ones: “due to”, “secondary to”, “caused by”, etc. To get the list of trigger words, we extracted from the training set the terms between the entities, and the experts manually selected a sub-set on the basis of two criteria: high frequency and reliability.
- **Modifiers:** two types of modifiers are taken into account: on the one hand, the presence of other drugs in the context of the ADR event; on the other hand, the presence of either negation or speculation modifiers regarding the drug and disease entities (e.g. “afebrile” as the negation of “febrile”, “dubious allergy” as an speculation for “allergy”).

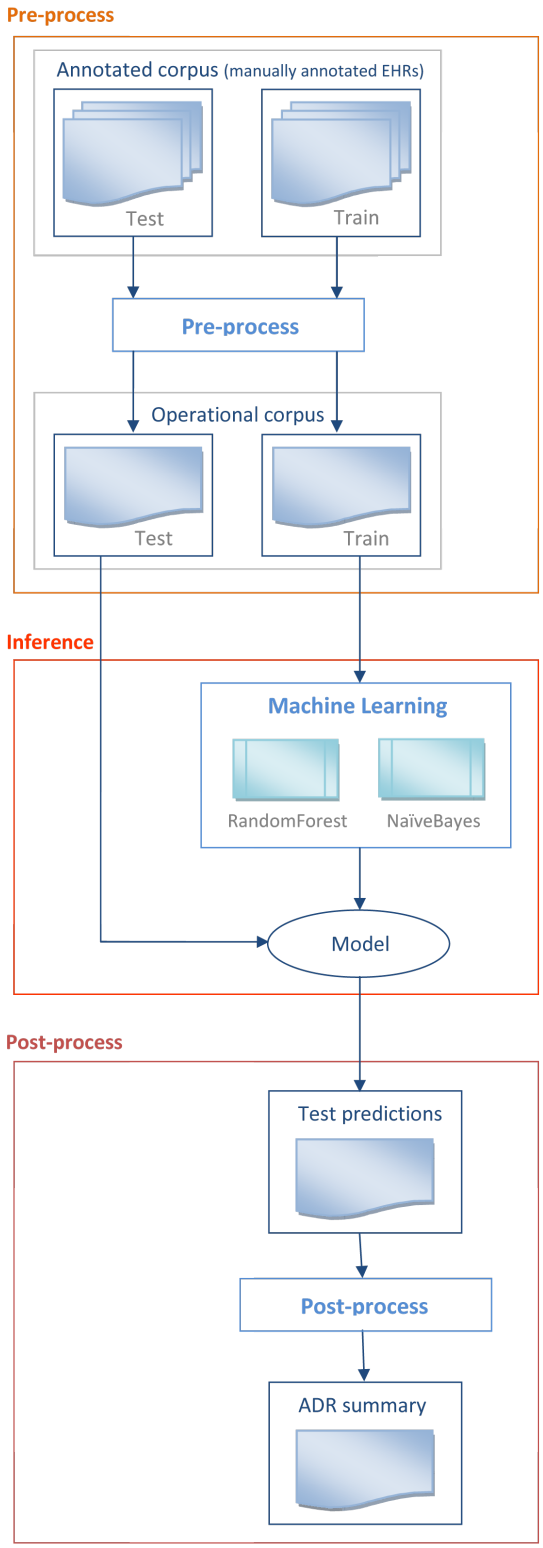


Figure 2: ADR event extraction system.

3.2 Inference of ADR event extraction model

For the ADR extraction system, in the literature there are references to a few well known supervised classification techniques. Gurulingappa et al. used Naïve Bayes (NB), as a baseline and a Decision Tree algorithm in the identification of ADR events in a restricted context of assertive sentences from medical case reports (Gurulingappa et al., 2011). Sohn et al. also used a decision tree together with a rule based strategy in a drug side-effect extraction task from clinical narratives (Sohn et al., 2011). We opted for Random Forests (RFs) as an extension of Decision Trees, and we also explored Naïve Bayes as a baseline. Both of them are available within the Weka-3.6.9 libraries (Hall et al., 2009).

Needless to say, many approaches could have been used, such as Support Vector Machines (SVMs). Nevertheless, motivated by the high-dimensional space and due to the fact that SVMs tend to be computationally expensive, we explored RFs. The use of RFs stands on the fact that it is more general than a single decision tree which by its side resulted useful in ADR detection tasks (Gurulingappa et al., 2011; Sohn et al., 2011).

3.3 Post-process: document-level coercion of ADR events

The prediction system tries to guess whether a given drug-disease pair represents an ADR or not. Hence, so far, the search focuses on a particular drug and a particular disease both in a given position of the EHR. As a result, it might happen that the same pair can appear more than once in the text. Nevertheless, for the purpose of presenting the information in a compact way, the experts requested not only having marked each pair in its corresponding position in the document, but also providing them with an overall result. The underlying motivation is simply to save reading time.

In addition, we want to note that one pair in one position might represent an ADR but not in another part of the document. For example, it might happen, in the family background, that anybody else used that drug to combat a disease, while for the patient itself the drug resulted in an adverse reaction. In any case, the personnel in the hospital is interested in having the chance to get also the overall summary.

In order to produce the compact version of the information in the text, as presented in algorithm 1, we carried out a cautious post-process that aims at reducing the false negative rate.

Let $\mathcal{E} = \{(adr, \hat{c})_i\}_{i=1}^{N}$ be a set of candidate ADR instances from an EHR together with their estimated class. Let us denote each component from $\mathcal{E}$: $\mathcal{A}_{\mathcal{E}} \times \mathcal{C}_{\mathcal{E}}$ where $\mathcal{A}$ denotes the set of candidate ADRs explored by the system and $\mathcal{C} = \{\ominus, \oplus\}$ the set of available predicted classes.

Algorithm 1 Coercion post-process

```
Require: $\mathcal{E} = \mathcal{A}_{\mathcal{E}} \times \mathcal{C}_{\mathcal{E}} = \{(adr, \hat{c})_i\}_{i=1}^{N}$
Ensure: $\mathcal{S} \subseteq \mathcal{E}$
Begin
$\mathcal{A} \leftarrow$ Unique($\mathcal{A}_{\mathcal{E}}$)
for each $adr \in \mathcal{A}$ do
    CoerceToAvoidFNs(adr,$\mathcal{E}$)
end for
$\mathcal{S} \leftarrow$ Unique($\mathcal{E}$)
End
```

What we expect in return is the sub-set $\mathcal{S} \subseteq \mathcal{E}$ without inconsistencies. That is, although different instances of a pair can appear as positive and negative in the document, by means of the coercion post-process the positive class is selected for the pair. In this sense, the approach adopted is conservative, since it avoids the false negatives. The inconsistencies are coerced to the positive class by the so-called CoerceToAvoidFNs() routine. As a by-product, this routine provides information about the inconsistencies, that is, pairs in the text detected as both positive and negative (which might be perfectly correct, for example, in the case that the instance appeared in both familiar antecedents and also current treatment of the patients). Note that, should the documents were structured, this task would not be as tough as it is.

The output of the algorithm is a sub-set that can be represented in a friendly front-end as depicted in figure 3. This summary shows the different entities (the drugs and the diseases) and which of them are related as ADR events.

4 *Experimental results*

4.1 Corpus

This work deals with 75 EHRs from a public hospital, that sum up to 41,633 word-forms, from which the train, development and test sets were randomly selected without replacement. The resulting partition is presented in table 1.

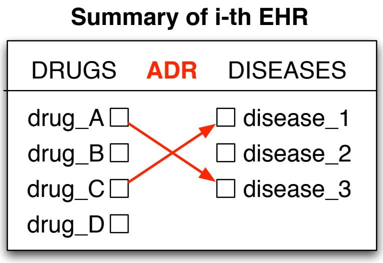


Figure 3: Given the i^{th} EHR, $\mathcal{E}_i$, the sub-set $\mathcal{S}_i$ is obtained through algorithm 1.

	Train	Dev	Test
EHRs	41	17	17
Word-forms	20,689	11,246	9,698
Drug Entity	280	183	181
Disease Entity	885	544	466
Total Entities	1,165	727	647
Event $\oplus$	69	45	33
Event $\ominus$	22,459	17,363	24,187
Total Events	22,528	17,408	24,220

Table 1: Quantitative description of the corpus: number of EHRs, different entities and ADRs.

In addition, table 1 provides the number of entities found in the corpus after having applied the pre-process. The candidate ADR events were formed by combining all the drug and disease entities present in each document.

The pre-process takes as input the corpus annotated by experts. In the annotation process, only those drug-disease pairs clearly stating about an ADR event were manually annotated once in an attempt to alleviate the workload of expert annotators and elude making redundant annotations. Since the data-set was created by inspecting all the drug-disease combinations in an EHR, and only those that were annotated by the experts were considered positives, then, we have realised that in the same EHR we accounted two drug-disease pairs occurring in different parts of the documents as positive and negative instances, respectively. That is, the operational corpus from which the inference is carried out might have some ambiguity because, for a given drug-disease pair within an EHR it might happen that it was manually tagged as an ADR in one part of the document but not in other parts. The same happens for the prediction system and, as a consequence, it might not classify all the instances in the document homogeneously. This fact represents a challenge for this task.

Each candidate ADR event has a class associated to denote whether it forms an ADR or not. Note that the corpus is highly unbalanced: the vast majority of the potential events found in the corpus are negative in a relation of 325 to 1 in the training set and even more striking in the test set. This is normal, because there are many more drug-disease pairs unrelated than those related as ADR. Tasks with imbalanced classes tend to be tough for automatic learning (Kubat and Matwin, 1997; Japkowicz and Stephen, 2002; Mollineda, Alejo, and Sotoca, 2007).

4.2 Performance

Several parameters of the RF model were fine tuned by means of 10-fold cross validation optimizing the averaged accuracy with the train set, to be precise, the number of trees and the number of features. The final model was trained on both training and development sets merged (this set is the eventual training set) and having set the optimal parameters obtained from a fine-tuning step. Besides, we resorted to an automatic feature subset selection technique in order to get rid of irrelevant or redundant attributes.

In an attempt to overcome the class imbalance, we turned to a stratification strategy that resampled the corpus so as to balance the number of instances in both classes. This produces a random sub-sample of the instances of the majority class and an over-sample of the instances of the minority class. Needless to say, the stratification was only applied to the eventual training set, since the test set must be kept as it was.

Table 2 shows the performance of the ADR extraction system using either Naïve Bayes (NB) or Random Forest (RF). With the final model, the 24,220 instances from the test set were classified and post-processed to obtain the aforementioned sub-set. The assessment was carried out by means of Precision, Recall and F-Measure. While the positive class turns out to be the most relevant one, for the sake of completeness, we also provide the results with respect to the negative class and the per-instance weighted average, denoted as “W.Avg.”.

	Prec	**Rec**	**F-M**	**Class**
NB	0.009	0.806	0.018	⊕
	0.999	0.789	0.882	⊖
	0.997	0.789	0.880	W.Avg.
RF	0.250	0.516	0.337	⊕
	0.999	0.996	0.998	⊖
	0.997	0.995	0.996	W.Avg.

Table 2: Naïve Bayes (NB) and Random Forest (RF) models.

4.3 Discussion

Looking at the positive class, the baseline system (NB) was by far less precise than the proposed model (RF). Both of them were precise at the negative class which is, indeed, the majority class. This fact was expected since the corpus is unbalanced towards the negative one, and hence, easier to learn. The challenge stands on achieving good results in the positive class with this kind of learning samples.

While we deal with manually annotated entities, FreeLingMed is able to recognise them automatically with high performance, needless to say, lower than human annotators (Oronoz et al., 2013). It would be interesting to measure the sensitivity of the ADR event classifier as the precision and recall of the recognised entities decrease.

Admittedly, higher performance would be desirable, and we believe that indeed it can be achieved by means of further effort in two directions. First, further corpus would be of much help, since the sample is of medium size. Nevertheless, this kind of corpora are scarce, amongst other reasons, for the evident reasons related with ethics and confidentiality (Bretonnel and Demmer-Fushman, 2014). Second, a light annotation process was to the detriment of the automatic pre-processing, or conversely, the pre-process did not deal with the annotation accurately. Let us explain this: we have realised that in the EHRs the same disease and the same drug might appear more than once in the document (e.g. in the antecedents and current treatment).

5 *Conclusions and future work*

This work presents an ADR detection system focusing on real EHRs in Spanish. The contribution of this work stands on: 1) the use of real EHRs written as free-text, an application rather different from ADR extraction on medical literature; 2) the focus on Spanish, a language on which little work has been made in biomedicine while it is widespread worldwide; and 3) a compact ADR extraction process at document level by means of the coercion post-process.

What we expect in return is the subset $\mathcal{S} \subseteq \mathcal{E}$ without inconsistencies. That is, although different instances of a pair can appear as positive and negative in the document, by means of the coercion post-process the positive class is selected for the pair. In this sense, the approach adopted is conservative, since it avoids the false negatives. That is, the inconsistencies are coerced to the positive class by the so-called CoerceToAvoidFNs() routine. As a by-product, this routine provides information about the inconsistencies, that is, pairs in the text detected as both positive and negative (which might be perfectly correct, for example, in the case that the instance appeared in both familiar antecedents and also current treatment of the patients). Note that, should the documents be structured, this task would not be as tough as it is.

The system was built on three consecutive stages: first, a pre-process that describes the candidate ADR instances; second, an inference stage that builds a classifier that explores all the ADRs within the document; the third stage tries to present the results consistently per each document.

Amongst the inference methods explored in the ADR extraction system, Random Forest resulted in a fast and flexible model, computationally cheap and accurate with respect to the baseline, Naïve Bayes. Experimental results show that the ADR event extraction problem is tough for the explored classifiers and further improvements are required. In the future, the operational description of the events will be benefited from other types of features, such as the section in which the entities were placed, e.g. clinical analysis or antecedents. That is, we mean to find the underlying structure of a given document. Even though trying to guess an structure in an unstructured document has proven to be a challenge (Bretonnel and Demmer-Fushman, 2014). Indeed, not all the EHRs follow the same sections while there is certain resemblance in the documents from the same department (e.g. intensive care, clinical pharmacy, cardiology, etc.). On the other hand, since the ADR events are imbalanced towards the negative class, a further effort shall be made to early filter and discard negative events.

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