

Negation and uncertainty detection in clinical texts written in Spanish: a deep learning-based approach

Oswaldo Solarte Pabón^{1,2}, Orlando Montenegro², Maria Torrente³, Alejandro Rodríguez González¹, Mariano Provencio³ and Ernestina Menasalvas¹

¹ Centro de Tecnología Biomédica, Universidad Politécnica de Madrid, Madrid, Spain

² Escuela de Ingeniería de Sistemas y Computación, Universidad del Valle, Cali, Colombia

³ Hospital Universitario Puerta de Hierro, Madrid, Spain

ABSTRACT

Detecting negation and uncertainty is crucial for medical text mining applications; otherwise, extracted information can be incorrectly identified as real or factual events. Although several approaches have been proposed to detect negation and uncertainty in clinical texts, most efforts have focused on the English language. Most proposals developed for Spanish have focused mainly on negation detection and do not deal with uncertainty. In this paper, we propose a deep learning-based approach for both negation and uncertainty detection in clinical texts written in Spanish. The proposed approach explores two deep learning methods to achieve this goal: (i) Bidirectional Long-Short Term Memory with a Conditional Random Field layer (BiLSTM-CRF) and (ii) Bidirectional Encoder Representation for Transformers (BERT). The approach was evaluated using NUBES and IULA, two public corpora for the Spanish language. The results obtained showed an F-score of 92% and 80% in the scope recognition task for negation and uncertainty, respectively. We also present the results of a validation process conducted using a real-life annotated dataset from clinical notes belonging to cancer patients. The proposed approach shows the feasibility of deep learning-based methods to detect negation and uncertainty in Spanish clinical texts. Experiments also highlighted that this approach improves performance in the scope recognition task compared to other proposals in the biomedical domain.

Subjects Data Mining and Machine Learning, Data Science, Natural Language and Speech **Keywords** Negation and Uncertainty detection, Deep learning, Text mining, Natural Language Processing, Clinical texts

INTRODUCTION

Narrative medical records can provide valuable information to support clinical research, but frequently this information contains uncertain and negated findings (*Vincze et al., 2008*). Detecting negation and uncertainty is important for medical text mining applications because extracted findings can be incorrectly identified as real or factual events. However, due to the complexity of natural language, automatic identification of negated and uncertain events in clinical texts is not an easy task (*Agarwal & Yu, 2010a; Agarwal & Yu, 2010b*).

Submitted 26 October 2021 Accepted 10 February 2022 Published 7 March 2022

Corresponding author Oswaldo Solarte Pabón, oswaldo.solartep@alumnos.upm.es

Academic editor Sebastian Ventura

Additional Information and Declarations can be found on page 29

DOI 10.7717/peerj-cs.913

© Copyright 2022 Solarte Pabón et al.

Distributed under Creative Commons CC-BY 4.0

OPEN ACCESS

Moreover, clinical texts are written by highly skilled physicians and nurses using domainspecific terms, under time pressure, with a rich and complex jargon, which makes these texts differ from those of other domains (*Dalianis*, 2018a).

Negation changes the meaning of an affirmative sentence, phrase, or word in a negative way. While uncertainty is used to describe ambiguous or suspected events where their truth value cannot be determined due to a lack of information (*Jean et al., 2016*; *Szarvas et al., 2012*). In the medical field, it must be known whether the patient definitely suffers, probably suffers, or does not suffer from an illness (*Vincze, 2014*). In the sentence "A 74-year-old patient with suspected lung carcinoma.", the truth value of the clinical finding "*lung carcinoma*" cannot be confirmed, as this finding is uncertain, suspicious, or speculative. Uncertainty detection has also been studied in terms of modality, and it involves related concepts such as subjectivity, hedging, and speculation (*Morante & Sporleder, 2012*; *Cruz Díaz et al., 2012*; *Solarte Pabón et al., 2021*). Furthermore, uncertainty is inherent in many medical decisions, as physicians face uncertain results when they are diagnosing or treating patients (*Nikfarjam, Emadzadeh & Gonzalez, 2014*). The breadth and complexity of possible diagnoses in medical practice make uncertainty very common in clinical narratives (*Alam et al., 2017*; *Bhise et al., 2018*). Consequently, both negation and uncertainty detection are crucial tasks for information extraction in the medical domain.

Negation and uncertainty detection is commonly divided into two sub-tasks: (i) *cue identification* and (ii) *scope recognition*. Cues are words or terms that express negation (*e.g.*, not, without, denies) or uncertainty (*e.g.*, possible, probable, suggest) (*Cruz Díaz & Maña López*, 2019). The scope is the text fragment affected by the corresponding cue in a sentence (*De Albornoz et al.*, 2012). In the sentence: "*Probable lung carcinoma with high fever since yesterday, biopsy test will be taken on 25-07-2018*.", the cue is shown in bold and the scope is underlined.

The natural language processing (NLP) community has paid considerable attention to uncertainty and negation detection (*Farkas et al., 2010, Morante & Blanco, 2012*). Moreover, several corpora annotated for negation and uncertainty have been proposed in the biomedical domain (*Vincze et al., 2008; Vincze, 2010b; Uzuner, Zhang & Sibanda, 2009*). However, most of these proposals have focused on the English language, while information extraction in the medical domain represents its own challenges in languages other than English (*Névéol et al., 2018a*). Most proposals developed for medical texts written in Spanish (*Santiso et al., 2018; Santiso et al., 2020; Cotik et al., 2016; Costumero et al., 2014*), have been focused only on negation detection. Uncertainty detection for Spanish medical texts has not yet been sufficiently addressed and can be improved.

Negation and uncertainty detection have been widely addressed using rule-based approaches (*Chapman et al., 2001; Harkema et al., 2009; Kesterson et al., 2015*), and classical machine learning-based approaches (*Cruz Díaz et al., 2012; Morante & Daelemans, 2009b; Jimnez-Zafra et al., 2021*). Rule-based methods can suffer from a lack of flexibility and universality (*Zhou et al., 2018*). While classical machine learning methods depend on hand-crafted features, and they often require a complex and time-consuming feature engineering process and analysis to obtain a good performance (*Minaee et al., 2020*). Recently, deep learning approaches have been shown to improve performance at processing natural

language texts in several tasks such as named entity recognition (NER) (*Lample et al., 2016*), question answering (*Bordes, Chopra & Weston, 2014*), and language translation (*Sutskever, Vinyals & Le, 2014*). One of the advantages of deep learning approaches is they can automatically learn features from data, instead of adopting handcrafted features. Embedding models such as Word2Vec (*Mikolov et al., 2013*), Glove (*Pennington, Socher* & *Manning, 2014*), and FasText (*Bojanowski et al., 2017*) have been popularly used in text processing applications. These models also have been applied in the biomedical field (*Wang et al., 2018*; *Soares et al., 2019*). Moreover, the development of contextual embeddings (*Peters et al., 2018*) and transformer-based models (*Devlin et al., 2019*) have shown that such representations are able to improve performance on a wide range of natural language processing tasks (*Liu, Kusner & Blunsom, 2020*; *Gu et al., 2020*; *Pires, Schlinger & Garrette, 2019*). Recently, deep learning-based approaches have also been proposed for negation and uncertainty detection (*Dalloux, Claveau & Grabar, 2019*; *Britto* & *Khandelwal, 2020*; *Fei, Ren & Ji, 2020*; *Zavala & Martinez, 2020*), showing promising results that will allow to advance in the field.

Motivated by improvements in deep learning methods to process natural language texts, in this paper we propose an approach for negation and uncertainty detection in clinical texts written in Spanish. This approach explores two deep learning methods to perform negation and uncertainty detection: (i) Bidirectional Long-Short Term Memory with a Conditional Random Field layer (BiLSTM-CRF) and (ii) Bidirectional Encoder Representation for Transformers (BERT). The proposed approach takes advantage of transfer learning techniques to perform uncertainty and negation detection in clinical texts. Transfer learning aims to transfer knowledge from pre-trained resources to improve the performance on a new target task (*Liu et al., 2019a; Peng et al., 2020; Ortiz Suarez, Romary & Benoit, 2012; Panigrahi, Nanda & Swarnkar, 2021*). In this approach we exploit pre-trained resources such as word embeddings (*Soares et al., 2019; Mikolov et al., 2013*) and contextualized embeddings (*Devlin et al., 2019*) to perform negation and uncertainty detection as a sequence labeling task. The most significant contributions of this paper are:

- A deep learning-based approach for negation and uncertainty detection in clinical texts written in Spanish. The main advantage of this approach is the use of word embeddings and contextual embeddings to automatically represent text features, avoiding the time-consuming feature engineering process. In the Spanish language, most of the previous studies have focused only on negation detection. Meanwhile, our approach goes further and in addition to negation, it also performs uncertainty detection. Code developed in this approach is public accessible from GitHub (https://github.com/solarte7/NegationAndUncertainty).
- Exploiting transfer learning techniques to perform negation and uncertainty detection in Spanish clinical texts. In particular, transfer learning exploitation is applied in two ways: (i) Creating pre-trained clinical embeddings and (ii) Fine-tuning the BERT model. The generated clinical embeddings improve the performance of the BiLSTM-CRF neural model for detecting uncertainty and negation. Furthermore, the BERT model is fine-tuned with a classification layer on top. To the best of our knowledge, this is the

first approach that uses a transformer-based method to perform both uncertainty and negation detection in clinical text written in Spanish.

- Improvement of performance in the scope recognition task, compared to other proposals in the biomedical domain for the Spanish language. Results obtained with both BiLSTM-CRF and BERT models have shown an improvement over other studies. Performed tests were evaluated using NUBES (*Lima Lopez et al., 2020*) and IULA (*Marimon, Vivaldi & Bel, 2017*), two public corpora for the Spanish language. Obtained results in the scope recognition task have shown an F-score of 92% and 80% for negation and uncertainty detection, respectively.
- Validation of the proposed approach with a real-life dataset which contains annotations of patients diagnosed either with lung or breast cancer. To perform this validation, we used trained models on the NUBES corpus (*Lima Lopez et al., 2020*) to predict negation and uncertainty in this new dataset. The validation process shows the ability of deep learning-based models to predict negation and uncertainty in a different dataset to the one they were trained on.

The remainder of this paper is organized as follows: 'Related works' shows previous studies about uncertainty and negation detection in the biomedical domain. In 'Materials and methods' datasets and proposed methods to perform negation and uncertainty detection are described. 'Experimentation and Results' explains the experiments carried out to validate our approach, and 'Discussion', provides a discussion of the results obtained. Finally, 'Conclusions' includes conclusions and future work.

RELATED WORKS

The high percentage of uncertain and negated sentences within clinical texts has motivated more research on this field. In particular, 12% of the sentences contained in Medline abstracts are uncertain, and 20% are negated (*Vincze, 2014*). Several annotated corpora have been proposed in the biomedical domain (*Vincze et al., 2008; Vincze, 2010b; Uzuner, Zhang & Sibanda, 2009*). In the Bioscope corpus (*Vincze et al., 2008*), 18% of the sentences contain uncertain findings (*Szarvas et al., 2012*). Moreover, *Jiménez-Zafra et al. (2020b*) describes a comprehensive review of different corpora annotated with negation. This review includes the analysis of several corpus in different languages including English and Spanish.

In what follows, we will address the three approaches that have been found in the literature for negation and uncertainty detection: (i) rule-based, (ii) machine learning-based, and (iii) deep learning-based.

Rule-based approaches

Rule-based approaches use declarative methods for creating manually crafted rules that extract uncertain and negated findings. One of the most widely used rule-based algorithm to detect negation in medical records is NegEx (*Chapman et al., 2001*). This algorithm has been recognized as one of the most useful approaches for the detection of negated medical concepts. However, several studies have been proposed to improve NegEx's performance (*Elazhary, 2017; Harkema et al., 2009*), Deepend2015. In particular,

the ConText algorithm (*Harkema et al., 2009*) extends NegEx for determining whether clinical conditions mentioned in clinical reports are negated, hypothetical, historical, or experienced by someone other than the patient. The proposal described in *Wu et al. (2011)* also extends the NegEx algorithm to detect uncertainty by adding a separate category of uncertainty terms. In *Velupillai et al. (2014)*, the authors proposed ConTextSwe, an adaptation of the ConText algorithm to Swedish. Several proposals have also been presented to adapt the NegEx algorithm to Spanish (*Costumero et al., 2014*; *Stricke, Ignacio & Cotik, 2015*; *Santamaria, 2019*), but these proposals have only focused on negation detection.

The above-mentioned proposals use a similar approach to recognize the scope; that is the search for a termination term in a lexicon which indicates the end of the scope. However, one disadvantage of this approach occurs when the sentence does not contain any termination term. In these cases, the scope recognition fails because all tokens in a sentence can be taken as the scope. To deal with this problem, other studies have included the use of syntactic properties of the sentence to extract the scope (*Cotik et al., 2016; Zhou et al., 2015; Peng et al., 2018*). Although rule-based approaches have been widely used in the biomedical domain, their main disadvantages are the large amount of time it takes to create rules manually, and the lack of flexibility and universality (*Zhou et al., 2018*).

Machine learning-based approaches

In machine learning-based approaches, negation and uncertainty detection is formulated as a classification problem where both cues and scope detection are considered as sequence labeling tasks. These approaches commonly follow two steps: in the first step, hand-crafted features are extracted from documents and, in the second step those features are used to train a classifier to perform predictions. Early machine learning-based proposals deal only with recognizing negation and uncertainty at the sentence level (*Clausen, 2010; Skeppstedt,* Paradis & Kerren, 2016; Velupillai, Dalianis & Kvist, 2011; Shaodian et al., 2016). In these cases, the complete sentence is considered an uncertain or negated fact. However, it is necessary to identify what tokens in the sentence are affected and which are not. One of the firsts machine learning proposals which deal with scope recognition is described in Morante & Daelemans (2009b). This study uses four classifiers for negation detection using approaches such as Support Vector Machines (SVM) and Conditional Random Fields (CRF) (Lafferty, McCallum & Pereira, 2001). The approach was evaluated using the Bioscope corpus (Vincze et al., 2008) and obtained an F1-score of 80.4% in the scope recognition task. In Morante & Daelemans (2009a), the above proposal was extended to deal with uncertainty detection.

Another proposal for negation detection is described in *Agarwal & Yu (2010a)*. In this work, negation cues and their scope are detected in clinical notes and biological literature using CRF as a machine learning algorithm. With the goal of detecting both negation and uncertainty, *Cruz Díaz et al. (2012)* proposed a two phases machine learning model. The first phase classifies the cues, and the second predicts the scope. Reported results showed an F1-score of 91% and 72% for negation and uncertainty scope, respectively. All the machine learning-based proposals mentioned above use the BioScope corpus (*Vincze et al., 2008*), which is focused on the English language. In the case of the Spanish language, *Santiso*

et al. (2018) proposed a CRF-based classification model for negation detection in clinical records. This study was evaluated using IULA (*Marimon, Vivaldi & Bel, 2017*), a corpus annotated with negation in clinical text written in Spanish, and obtains an F1-score of 81% in scope recognition.

Although classical machine learning-based approaches have addressed limitations of rule-based methods, one disadvantage of these approaches is the reliance on the hand-crafted features that require tedious, time-consuming feature engineering along with analysis to obtain good performance (*Minaee et al., 2020*). This fact can be seen in studies such as the ones reported in *Jiménez-Zafra et al. (2020a)* and *Jiménez-Zafra et al. (2020b)*, where a CRF-based system is trained with a considerable set of hand-crafted features to perform negation detection.

Deep learning-based approaches

The core component of these approaches is the use of word embedding models that map a set of texts into a low-dimensional continuous space (*Mikolov et al., 2013; Pennington, Socher & Manning, 2014; Bojanowski et al., 2017*). Contextualized embeddings such as ELMO (*Peters et al., 2018*) and BERT (*Devlin et al., 2019*) have also shown that such representations are able to improve performance on sequence labeling tasks. Recurrent neural networks(RNN) (*Goldberg & Hirst, 2017; Hochreiter & Schmidhuber, 1997*), and Convolution Neural Networks(CNN) (*Lopez & Kalita, 2017*) have also been used to process text in the biomedical domain.

In *Qian et al.* (2016), the authors proposed a Convolutional Neural Network-based model to extract negation and uncertainty scope from biomedical texts written in English. This model first extracts path and position features from syntactic trees with a convolutional layer whose features are concatenated into one feature vector. This vector is finally fed into the softmax layer to obtain the output vector. Tests and validation are conducted using the Bioscope corpus, showing the ability of the deep neural approaches to deal with negation and uncertainty detection. In Fancellu et al. (2017) is proposed a Bidirectional Long-Short Term Memory (BiLSTM) model to extract negation scope from English and Chinese texts. The performance shows an F-score of 89% for English and 79% for Chinese using the CNeSp corpus (Zou, Zhou & Zhu, 2016). The conclusion of that research is a suggestion to use more training data to make progress on negation detection. In Taylor & Harabagiu (2018), the authors proposed a BiLSTM neural model for negation detection from electroencephalography reports written in English. Reported results show an F-score of 88% for the scope recognition task using the Bioscope corpus. In Bhatia, Celikkaya Khalilia (2018), an encoder-decoder neural architecture that combines a shared encoder and different decoding schemes to jointly extract entities and negations is proposed. Reported results show 90% in F-score for negation detection using data from the 2010 i2b2/VA challenge task (Uzuner et al., 2011).

An attention mechanism to perform uncertainty cue identification using data from CoNLL2010 shared task (*Farkas et al., 2010*) is developed in *Adel & Schütze (2017*). Reported results have shown that combining attention layers with RNN and CCN models increases the performance for uncertainty detection in the English language, showing 85%

in F1-score. The attention layer helps the model to recognize which part of the input data is important during the training, allowing the networks to focus on specific information by generating a weight vector. Another proposal that combines an attention layer with an RNN for detecting negated, possible and hypothetical medical findings from clinical notes is described in *Chen* (2019). In *Khandelwal & Sawant* (2020), the authors proposed NegBert, a model for negation detection using BERT contextual embeddings. NegBert has been trained for the English language using three corpora from different domains, including the BioScope corpus for the biomedical domain (*Vincze et al.*, 2008). Reported results have shown an improvement in the scope resolution task with 93% in F1-score and comparable results in the cue identification task. In *Shaitarova, Furrer & Rinaldi (2020b)*, the authors extended the *Khandelwal & Sawant* (2020) proposal to deal with both uncertainty and negation detection using transformer-based architectures such as BERT (*Devlin et al.*, 2019), XLNet (*Yang et al.*, 2019) and Roberta (*Liu et al.*, 2019b). This study was also focused on the English language using the Bioscope corpus and the SFU Review corpus (*Konstantinova et al.*, 2012).

In recent years, the interest in processing negation and uncertainty has also grown in languages other than English. In *Dalloux, Claveau & Grabar (2019)*, a BiLSTM-CRF model focused on the French language is presented. The approach was validated using a dataset from the National Cancer Institute in France (NCI (https://en.e-cancer.fr/)) and obtained an F-score of 90% and 86% for negation and uncertainty scope detection, respectively. *Al-khawaldeh (2019)* proposed an Attention-based BiLTSM model to perform speculation detection in Arabic medical texts. This proposal obtained an F-score of 73.5% in the scope recognition task using the BioArabic corpus (*Al-khawaldeh, 2016*).

In the case of the Spanish language, Santiso et al. (2018) proposes a CRF-based model combined with word embeddings to perform negation scope detection. That proposal depends on several hand-crafted features to increase the performance of the proposed model. In Santiso et al. (2020) is described a BiLSTM-based proposal that uses word embeddings and lexical properties of the sentence such as word-forms and lemmas to identify negated medical concepts. This proposal uses the IxaMed-GS corpus (Oronoz et al., 2015), a private dataset consisting of 75 clinical notes written in Spanish. Reported results showed 83% in F-score for the scope recognition task. Zavala & Martinez (2020) evaluate the impact of embeddings on different deep learning-based models to perform negation and speculation detection using several corpora from English and Spanish. In particular, for the Spanish language, the performed tests were conducted using IULA (Marimon, Vivaldi & Bel, 2017) and SFU ReviewSP-NEG (Jiménez-Zafra et al., 2018), two corpora focused only on negation annotation. Moreover, the BiLSTM-based approach proposed in Zavala & Martinez (2020) uses general domain word embeddings for Spanish (Cardellino, 2019), and several annotated features such as Part of Speech (POS) tagging and information about overlapping entities to perform negation detection. The above proposals for Spanish share two features: (i) they perform only negation detection but not uncertainty detection. (ii) They use hand-crafted features, syntactic properties, or lexical information of the sentence to detect negation in clinical documents.

Proposal	Approach	Language	Corpus	Negation	Uncertainty
Qian2016	CCN	English	Bioscope	yes	yes
Fancellu2017	BiLSTM	English & Chinese	Bioscope & CNeSp	yes	no
Taylor2018	BiLSTM	English	BioScope	yes	no
Uzuner2011	Encoder- Decoder	English	i2b2/VA NLP challenge	no	yes
Attention2017	RNN + Attention	English	Bioscope	yes	yes
Attention_Chen_2019	RNN + Attention	English	i2b2/VA NLP challenge	yes	no
NegBERT2020	BERT	English	Bioscope	yes	no
Dalloux2019	BiLSTM	French	NCI - France	yes	yes
Al-khawaldeh2019	Attention + BiLSTM	Arabic	Bio Arabic	no	yes
Santiso2018	Embeddings + CRF	Spanish	IULA	yes	no
Santiso2020	BiLSTM	Spanish	IxaMed-GS	yes	no
Zavala2020	BiLSTM, BERT	Spanish	IULA	yes	no
Lima2020	BiLSTM	Spanish	NUBES	yes	yes

 Table 1
 Summary of Deep learning-based approaches.

The first study that can be found for Spanish to perform negation and uncertainty detection is the one presented in *Lima Lopez et al. (2020)* in which the NUBES corpus is presented. This corpus contains both negation and uncertainty annotations from clinical notes written in Spanish. Moreover, in that proposal, the authors provide a BiLSTM-based model whose results showed a 90% and 78% in F1-score for negation and uncertainty scope detection, respectively. Although this study has shown promising results, the main disadvantage is that it relies on several hand-crafted features and syntactic properties of the sentence to feed the system, making the feature engineering process time-consuming.

Table 1 shows a summary of the most relevant deep learning-based approaches to perform negation and uncertainty detection. From this table, it is important to highlight the following facts: (i) Most of the proposals have focused on the English language, as a result of the availability corpora (*Vincze et al., 2008; Uzuner et al., 2011; Farkas et al., 2010*); (ii) Most of the existing proposals developed for the Spanish language concentrate only on negation detection, (iii) Although the proposal described in *Lima Lopez et al. (2020)* aims to detect uncertainty and negation in Spanish, its main weakness is the dependence on hand-crafted features. These facts suggest that uncertainty and negation detection in Spanish can be improved.

Thus, in this paper, we propose a deep learning-based approach that also relies on BERT and BiLSTM as other proposals reviewed in the literature. However, the proposed approach in this paper presents the following differences and advantages over other proposals for the Spanish language:

• We propose using suitable biomedical word embeddings and contextual embeddings for Spanish, which can represent text features automatically. In our approach, we only use information from word embeddings and contextual embeddings to train deep learning-based models. These embeddings allow us to obtain competitive results for both uncertainty and negation detection, which avoids relying on a manual feature engineering process. In addition, this approach does not depend on the syntactic or lexical properties of the sentence.

- We compare the performance of the BiLSTM and BERT models analyzing the advantages and shortcomings of each model. To the best of our knowledge, this is the first study that compares the performance of these models for uncertainty and negation detection in Spanish.
- We perform a validation process in an external dataset that is not used to train the deep learning-based models. Previous approaches for the Spanish language only report results for the same corpus used in the training process. The proposed approach uses trained models on the NUBES corpus (*Lima Lopez et al., 2020*) and validates them in the Cancer dataset section 'Datasets'. It is important to note that this validation has been required to annotate a new corpus (The Cancer dataset) which is a time-consuming task. In summary, our approach leverages the NUBES corpus to train models and use them to detect uncertainty and negation in the Cancer dataset. To our knowledge, this is the first study that reports results obtained after applying models trained with the NUBES corpus in another dataset. The results obtained show the potential of models trained this way to be applied to detect negation and uncertainty on external datasets in the biomedical domain.

MATERIALS AND METHODS

In this section, we first show the datasets used for training, testing, and validating the proposed approach. Next, we will describe the deep learning-based methods for negation and uncertainty detection.

Datasets

NUBES (*Lima Lopez et al., 2020*) and IULA (*Marimon, Vivaldi & Bel, 2017*) are two public corpora available for the Spanish language that will be used to train models. Additionally, an in-house annotated dataset with real-life data of cancer patients was manually annotated and will be used for validation purposes. Details about each dataset are given as follows:

- NUBES (https://github.com/Vicomtech/NUBes-negation-uncertainty-biomedicalcorpus): a public corpus which consists of 29,682 sentences obtained from anonymized health records annotated with negation and uncertainty (*Lima Lopez et al., 2020*). NUBES is the largest publicly available corpus for negation in Spanish clinical records, and the first corpus that also incorporates the annotation of uncertainty. This corpus contains annotations for syntactic, lexical, and morphological negation cues.
 - Syntactic negation: are cues represented by function words or adverbs, for instance: not, without, never ("no, sin, nunca")
 - Lexical negation: are words or multi-word expressions which indicate negation depending on the context. They include verbs, adjectives or noun phrases, for example: negative, denies, withhold ("negativo, niega, suspender").
 - Morphological Negation: are words which refer to negation by means of affixes, for instance: afebrile, asymptomatic (*"Afebril, Asintomático"*).



In the case of uncertainty, the NUBES corpus contains annotations for lexical and syntactic cues. Lexical cues are words that express uncertainty depending on the context. Lexical cues include words such as "probable", "possible", and "compatible with" ("*Probable, posible, compatible con*"). Syntactic cues include only the disjunctions words "Versus", "Vs", "Or" ("*Versus, vs, o*"). These cues were only annotated when they appeared by themselves in a context of uncertainty.

IULA (http://eines.iula.upf.edu/brat/#/NegationOnCR_IULA/): a public corpus which contains 3,194 sentences extracted from anonymized clinical records and manually annotated with negation cues and their scopes (*Marimon, Vivaldi & Bel, 2017*). This corpus was extracted from clinical notes from one hospital in Barcelona (Spain) and contains annotations only with negation. Syntactic negation, and lexical negation cues have been annotated in this corpus, but not morphological negation.

Cancer dataset: an in-house manually annotated dataset with data from patients either suffering with lung or breast cancer. This dataset was extracted from real-life clinical notes belonging to cancer patients from "Hospital Universitario Puerta de Hierro, Madrid Spain". The dataset contains 2,700 sentences annotated with both negation and uncertainty. We have received informed consent from participants of our study before annotating this dataset. The Cancer dataset was annotated with syntactic, lexical and morphological negation. In the case of uncertainty, this dataset contains syntactic and lexical cues with their respective scopes. In the Cancer dataset, negation was more frequently found in sentences that describe symptoms, medical tests results, and treatments. On the other hand, uncertainty was more frequently found in sentences that describe cancer diagnosis.

Table 2 Inter-amotator agreement for the Cancer dataset.								
	Token level IAA	Entity level IAA						
Negation cue	0.96	0.95						
Negation scope	0.94	0.92						
Uncertainty cue	0.94	0.93						
Uncertainty scope	0.92	0.90						

able 2	Inter-annotator agreement for the Cancer dataset.
--------	---

Figure 1 shows a set of sentence examples extracted from the Cancer dataset. These sentences show negation and uncertainty cues and their scopes.

The Cancer dataset was manually annotated by two clinicians using the BRAT annotation tool (https://brat.nlplab.org/). These annotators were guided by a data scientist who prepared documents and explained the BRAT tool functionalities. The annotation process was performed in four steps, as follows:

- 1. Training: This step aimed to train annotators to manually annotate cues (negation and uncertainty) and their scopes in clinical notes.
- 2. Pre-annotation: Annotators started with the annotation of 20% of the sentences in the dataset. Once they finished, they met the data scientist to resolve questions regarding the annotation process.
- 3. Annotation: In this step, the clinicians annotated 100% of the sentences independently and performed the annotation process separately.
- 4. Disagreement resolution: The annotators met with a linguist who reviewed the cases where there were disagreements and guided the clinicians to resolve them.

The inter-annotator agreement (IAA) measures the quality of annotations and the reliability of an annotated corpus. Although, both Kappa statistic (Cohen, 1960) and F-measure (Hripcsak & Rothschild, 2005) have been used to calculate de IAA between annotators, it has been argued that using the F-measure is more suitable than Kappa in contexts where annotated entities might have different token spans (Campillos-Llanos et al., 2021; Brandsen et al., 2020; Dalianis, 2018b; Pradhan et al., 2015; Ogren, Savova & *Chute*, 2008). This is because obtaining the Kappa value requires calculating the probability of agreement by chance. This can be very small or close to zero (Oronoz et al., 2015) in contexts such as annotating the negation and uncertainty, as most tokens in the dataset do not receive any annotation.

Thus, in a similar way to the one proposed for the Bioscope corpus (Vincze et al., 2008) and the IxaMed corpus (Oronoz et al., 2015), we calculate the IAA for the Cancer dataset using the F-measure (Hripcsak & Rothschild, 2005). In particular, to calculate the IAA between annotator pairs, one annotator is considered as the gold standard. Precision is the percentage of correct positive annotations made by the second annotator, and Recall is the percentage of positive cases annotated by the second annotator (Alnazzawi, Thompson & Ananiadou, 2014). The F-measure is the harmonic mean between Precision and Recall. We calculate the IAA after the annotation step is finished. Table 2 shows the IAA using the F-measure, which was obtained at token level and entity level, as follows:

Indicators	NUBES	IULA	Cancer dataset
Number of sentences	29,682	3,194	2,700
Sentences with negation	25.5%	34%	27%
Sentences with uncertainty	7.5%	-	12%
Maximum number of tokens	210	159	181
Mean (Number of tokens)	18	14	15
Median (Number of tokens)	14	10	12
First quartile	9	6	7
Third quartile	23	19	18

Table 3 A summary of the datasets used in the proposed approach.

Table 4 A summary of cues and scopes in the datasets.

Indicators	NUBES	IULA	Cancer dataset
Number of distinct negation cues	345	46	52
Number of distinct uncertainty cues	303	_	70
Total negation cues	9318	1145	804
Total uncertainty cues	2529	_	345
Syntactic negation cues	85%	92%	83%
Lexical negation cues	6%	8%	10%
Morphological negation cues	9%	7%	2%
Syntactic uncertainty cues	2%	_	1%
Lexical uncertainty cues	98%	_	99%
Continuous scopes	95%	96%	97%
Discontinuous scopes	5%	4%	3%

- Token level agreement: the IAA for each token is calculated separately. When a cue or a scope contains several tokens, a pair of annotators can annotate different spans. In this case, correct annotations are those tokens where both annotators agree. For instance, in the sentence "*Sin dolor toráxico agudo*" (No acute chest pain), the scope annotated by one annotator is shown underlined. If the second annotator annotates only the tokens *dolor toráxico*", then these two tokens are considered an agreement and the other token is considered a disagreement.
- Entity level agreement: the IAA is measured at cue or scope level. In this case, the correct annotations are those cues or scopes where both annotators agree in all annotated tokens. In the above example, an annotation is considered an agreement when the two annotators annotate the same tokens in the scope "*dolor toráxico agudo*". Otherwise, it is considered a disagreement.

Tables 3 and 4 show a descriptive analysis of the datasets previously mentioned. This analysis aims to check how sentences, cues and scopes behave in Spanish clinical texts. The analysis has shown that negation and uncertainty have specific features as follows:

• Sentence length: is the number of tokens in sentences where uncertainty or negation appears. According to Table 3, the analyzed datasets have similar values in indicators

such as median, first quartile, and third quartile. In the case of the NUBES corpus, the value of median is 14, which indicates that 50% of the sentences have 14 tokens or fewer. Similar behavior occurs in the IULA corpus and the Cancer dataset, where the median is 10 and 12, respectively. This fact suggests that in clinical texts written in Spanish negation and uncertainty can frequently occur in short sentences. However, there are also large and more complex sentences where several cues can appear as well as negation as uncertainty. In fact, negation and uncertainty can appear in the same sentence. According to Fig. 1, in the fourth example there is a short sentence, while the fifth example shows a large and more complex sentence.

- **Cues:** are distributed as follows; in the NUBES corpus 85% of negation annotations contain syntactic negation, 6% lexical, and 9% morphological negation. Similar values can be found in the IULA and the Cancer datasets. In the case of uncertainty, 98% of annotations contain lexical uncertainty and only 2% syntactic uncertainty, for the case of the NUBES corpus. Similar values can be found in the Cancer dataset (See Table 4).
- Scopes: can behave in a continuous or discontinuous way. A continuous scope occurs when the tokens affected by a specific negation or uncertainty cue are continuous in the sentence. On the other hand, a discontinuous scope occurs when the sequence of tokens affected by a cue are separated in different positions of the text sentence. In Fig. 1, the first and the fourth sentences contain continuous scopes. In contrast, the third sentence contains a discontinuous scope. According to Table 4, most cases are continuous scopes. In the NUBES corpus, 95% of annotations correspond to continuous scopes and only 5% to discontinuous scopes. Similar behavior can be seen in the IULA and the Cancer datasets. Additionally, the scope can appear after the cue, before the cue, or on both sides. According to Fig. 1, in the fourth sentence the scope appears to the right (after) of the cue "Sin". In the second sentence, the scope is in both sides of the cue.

Deep learning-based methods for negation and uncertainty detection The proposed approach addresses negation and uncertainty detection as a sequence-labeling

task, where each token in a sentence is classified as being part of the cue or the scope. The BIO (short for Beginning, Inside, Outside) tagging format is used to labeled each token. This approach recognizes cues and their scopes in a single stage for both negation and uncertainty. To perform negation and uncertainty detection from clinical text written in Spanish, we explore two deep learning-based models: BiLSTM-CRF and BERT.

We chose these models as they have shown to be widely used to perform sequencelabeling tasks. In particular, the BiLSTM-CRF model has shown its ability to use previous and future information in a text sequence to predict the state of a current input (*Giorgi* & *Bader*, 2019). This ability can be useful to resolve the scope, because in clinical texts written in Spanish, the scope can appear after and before the cue, as was shown in section 'Datasets'. Thus, analyzing the context that is before and after a cue in the sentence can help in the scope recognition. On the other hand, the BERT model is based on transformer architectures which also have been improved sequence-labeling tasks in the biomedical domain (*Lee et al.*, 2020). Transformers are able to learn long-range dependencies between



Full-size DOI: 10.7717/peerjcs.913/fig-2

words using a self attention mechanism (*Vaswani et al., 2017*). This mechanism can be useful to learn dependencies between cues and their scope.

In this section, we first show how the corpora mentioned in section 'Datasets' is pre-processed, and then how the BiLSTM-CRF and BERT models were trained, as follows:

Corpus pre-processing

The corpus pre-processing aims to transform the annotated corpora into a matrix representation of data which will be used to train the deep learning-based models. Pre-processing a corpus includes four steps (See Fig. 2), as follows:

- 1. Annotations to BIO format: this step generates two matrices (T, L) using the BIO tagging format. The matrix T contains one row for each sentence in the corpus and the columns are the tokens of the sentence. On the other hand, the matrix L contains one row per sentence in which columns represent the BIO labels for each token of the sentence. Let i be the the number of sentences in the corpus, and j be the maximum length of tokens in the sentences. Since the sentences do not have the same number of tokens, padding tokens are added to the matrices.
- 2. *Dictionary creation:* in this step two dictionaries (*DT*, *DL*) are created to represent tokens and BIO labels using unique identifiers. The dictionary *DT* contains the set



Figure 3 Negation and uncertainty detection using the BiLSTM-CRF model. Full-size DOI: 10.7717/peerjcs.913/fig-3

of unique tokens in the corpus and their numeric identification. The dictionary DT contains the set of BIO labels in the corpus. The size of DT is the total number of different tokens in the corpus and the size of DL is the number of different BIO labels in the corpus.

- 3. Matrix codification according to dictionaries: this step uses the dictionaries DT and DL to generate two new matrices (T', L'). Matrix T' contains a numeric representation for each token using the identifications from DT. Matrix L' contains a numeric representation for each BIO label using the identifications from DL.
- 4. One hot vector creation: this step generates matrix H which contains a one hot vector representation for each token and its BIO label for each sentence. The size of the matrix H is $i \times j$, where i represents the number of sentences in the corpus, and j is the maximum length of tokens of all sentences. Each position $H_{i,j}$ contains one hot vector representation which represents the BIO label for the token in $T_{i,j}$ position.

BiLSTM-CRF

The first model is a Bidirectional Long-Short Term Memory with a CRF layer(BiLSTM-CRF) neural net. This model is based on neural architectures described in *Lample et al.* (2016); *Huang, Xu & Yu* (2015); *Collobert et al.* (2011) and consist of three layers: Embedding layer, BiLSTM layer, and CRF layer (see Fig. 3). To train the BiLSTM-CRF

model, the approach uses pre-processed information from matrices T and H section 'sub-preprocessing'.

- Embedding layer: This layer allows the approach to automatically represent text features using dense vector representations. In these vectors, words with a similar context in the text have a similar representation. The Embedding layer enables the approach to represent each word into a fixed length vector of defined size. We use two different word embeddings in this approach:
 - Biomedical embeddings: These embeddings were trained using full-text medical papers written in Spanish (*Soares et al., 2019*). The papers were taken from Scielo (a scientific electronic library (https://scielo.isciii.es/scielo.php)), and a subset of Wikipedia articles related to Pharmacology, Medicine, and Biology.
 - *Clinical embeddings*: We create in-house embeddings trained with more than 1 million clinical notes written in Spanish. These clinical documents were provided in a raw format by two public hospitals in Madrid (Spain) and Cali(Colombia). We use the FasText (*Bojanowski et al., 2017*) method for creating word embeddings using a vector size of 300 positions by default.
- **BiLSTM layer**: the Bidirectional LSTM (BiLSTM) layer captures both left and right contexts of words to produce a vector representation of text sequences. Given a sentence $(w_1, w_2, w_3, \dots, w_n)$ as input, where *n* is the number of words, this layer processes the sentence using two steps:
 - A Forward step processes the sentence from left to right, where each element f_i represents the value of the left context for the word w_i in the sentence.
 - A Backward step processes from right to left where each element b_i represents the value of the right context for the word w_i in the sentence.

As an output, the BiLSTM layer generates a vector representation h_i for each word by concatenating the values f_i and b_i . The output vector h_i contains a sequence of probabilities for each label to be predicted. The BiLSTM layer computes the Forward and Backward steps separately. Therefore, the values f_i and b_i are calculated independently.

• CRF layer: this layer predicts the label sequence with the highest prediction score from all sequences generated by the BiLSTM layer. Although the BiLSTM layer generates probabilities for each label to be predicted, these probabilities are calculated independently. For sequence labeling tasks it is crucial to consider correlations and dependencies across output labels. Therefore, this layer uses an implementation of the CRF algorithm (*Lafferty, McCallum & Pereira, 2001*) to improve the predictions for each label. The CRF algorithm considers correlations between other labels and jointly decodes the best chain of labels for a given input text sentence.

Bidirectional Encoder Representation for Transformers (BERT)

BERT (*Devlin et al., 2019*) uses a transformer-based architecture to learn representation of texts in a bidirectional way by considering both the left and the right context of words. In the proposed approach, the BERT model is fine-tuned with a classification layer on



top. We use multilingual BERT as contextualized embeddings to perform negation and uncertainty detection in clinical notes written in Spanish. Multilingual BERT has been pre-trained on data in 104 languages with the same training objectives as BERT: masked language modeling and next-sentence prediction.

Figure 4 shows the process for detecting negation and uncertainty using multilingual BERT. This process uses information from the matrices T and L section 'Corpus preprocessing', and processes each sentence using three steps: Tokenization, BERT Processing, and Classification & Post-processing.

1. **Tokenization:** the goal of this step is to take a raw text sentence as input and tokenize it using a WordPiece Tokenization method (*Wu et al., 2016*). This method relies on the idea that the most frequent used words should not be divided into smaller sub-words, but rare words should be split into meaningful sub-words. The tokenization method used by BERT was previously trained on a raw text dataset to learn vocabulary with

most frequent words. In the example of Fig. 4, the words "*muestra*" and "*células*" have not been split into sub-words because the WordPiece tokenization method considers these words as frequent words in its vocabulary. In contrast, the words "*biopsia*" and "*cancerígenas*" are considered rare words by the algorithm because they are not in its vocabulary. Consequently, these words have been split in sub-words and the characters "##" are used to separate these tokens. The WordPiece Tokenization algorithm uses a Byte Pair Encoding strategy (*Schuster & Nakajima, 2012*) to generate new sub-words. This tokenization method aims to improve the handling of rare and unseen words in a dataset by providing a balance between the flexibility of character-delimited tokenizers and the efficiency of word-delimited tokenizers. Finally, in this step, two special tokens are added to the sentence: [CLS] and [SEP]. The [CLS] token always appears at the beginning of a sentence, and the [SEP] token is used to separate segments of a sentence.

- 2. **BERT Processing:** In this step, the approach takes the tokenized sentence as input from the previous step and process it as follows:
 - An embedding representation (E_i) for each token in the sentence is obtained. This representation is composed of three embeddings: token, segment, and position. The token embedding contains a vector representation for each token representing the relation of this token with other tokens in the text. The segment embedding is used to distinguish the vector representation for two sentences in a sentence pair. The position embedding is used to specify the position of words in the text sentence. Thus, the embedding representation (E_i) is the concatenation of token, segment and position embeddings.
 - The BERT Transformer Blocks takes the embedding representation (E_i) as input, and calculates a score that represents the contextualized value for each specific token in relation to all other tokens. This score is represented as (R_i) for each token in the processed sentence.
- 3. Classification & Post-Processing: In this step, the approach takes each predicted BERT representation (R_i) as input and feeds them into a dense layer with a softmax activation function. This layer obtains a BIO label for each token in the sentence, calculating a probability *P* for each label using the softmax function, as follows:

$$P(l|R_i) = Softmax(W_oR_i + b_o)$$

(1)

where the label l belongs to the set of BIO labels to be predicted. In addition, W_o is a matrix of weight parameters and b_o is a bias vector, both learned by the dense layer. Finally, the special tokens '[CLS], [SEP], [PAD]' are removed to obtain the final BIO labels at the end of post-processing step.

EXPERIMENTATION AND RESULTS

In this section, we describe experiments carried out to evaluate the proposed approach for negation and uncertainty detection. We will first describe the evaluation methodology, then the experiments that were carried out, followed by the results that were obtained.

Evaluation methodology

The evaluation methodology depends on the dataset used, as follows:

- NUBES corpus: this corpus was split by their authors into three subsets: training (75%), developing(10%), and testing (15%). Models trained with the NUBES corpus were executed just once. The testing subset was used to calculate the performance metrics.
- IULA corpus: this corpus does not provide an explicit division for training and testing subsets. Therefore, in this case we followed a cross-validation strategy with k = 5. The performance was calculated as the average of all five folds executed by the cross-validation strategy.

To evaluate the performance of the proposed approach, we used the following standard metrics: Precision (P), Recall (R), and F-score (F1). The F-score is calculated as a weighted average of the Precision and Recall measurements. A token is correctly classified when the predicted label is equal to the label indicated by the annotated corpus. The performance for the cue identification task and the scope recognition task is analyzed separately.

$$Precision = \frac{\text{Number of tokens correctly predicted}}{\text{Number of predicted tokens}}$$
(2)

$$Recall = \frac{Number of tokens correctly predicted}{Number of tokens in the dataset}$$
(3)

$$F-score = 2 * \frac{Precision * Recall}{Precision + Recall}$$
(4)

Experiments

The BiLSTM-CRF model proposed by *Huang*, Xu & Yu (2015) was used as baseline system to perform negation and uncertainty detection. Next, we performed the following experiments:

- 1. Experiment 1: Spanish biomedical embeddings proposed by *Soares et al. (2019)* were added to the BiLSTM-CRF model. The goal of this experiment was to analyze the impact of adding biomedical embeddings to the BiLSTM-CRF model.
- 2. Experiment 2: the goal of this experiment was to test the impact of using embeddings trained on clinical notes written in Spanish. Consequently, in-house clinical embeddings section 'BiLSTM-CRF' were added to the BiLSTM-CRF model.
- 3. Experiment 3: the goal of this experiment was to analyze the impact of using multilingual BERT embeddings to perform negation and uncertainty detection in Spanish. To perform this experiment, we used the BERT model as described in section 'Bidirectional Encoder Representation for Transformers (BERT)'.

Validation

The Cancer dataset described in section 'Datasets' is used for validating the performance of trained models on the NUBES corpus. We used these models for validation because the

Linocaanigs).				
Label name	Р	R	F1	Support
-PAD-	1.0	1.0	1.0	474126
B-NEG	0.95	0.93	0.94	1423
B-NSCO	0.93	0.91	0.92	1322
B-UNC	0.86	0.84	0.85	400
B-USCO	0.84	0.79	0.81	400
I-NEG	0.89	0.86	0.87	120
I-NSCO	0.92	0.88	0.90	3901
I-UNC	0.85	0.75	0.80	168
I-USCO	0.82	0.77	0.79	1513
0	0.98	0.99	0.98	41977

Table 5Results for each BIO label using the NUBES corpus (BiLSTM-CRF + BiomedicalEmbeddings).

NUBES corpus contains annotations for both negation and uncertainty (the IULA corpus cannot be used as it does not contain uncertainty annotations). This validation aims to measure the performance of trained models on the NUBES corpus to predict negation and uncertainty in a new dataset.

Implementation and Hyperparameters setting

To perform the previously explained experiments Python 3.7, TensorFlow (https: //www.tensorflow.org/?hl=es-419) and Keras (https://keras.io/) were used. For the BiLSTM-CRF model the following parameters were settled: learning rate as 0.001, dropout as 0.5, the number of epochs was set to 60, the BiLSTM hidden size was set to 300, and the batch size to 512. For the BERT model, the fine-tuning was performed with a sequence length of 256 tokens, a batch size of 64, and five epochs. These values were established after training the models different times, and checking the best performance for these parameters. Data and code of the proposed approach can be found in GitHub (https://github.com/solarte7/NegationAndUncertainty).

Results

This section shows first the support and the performance metrics for each BIO label. Once the results of each label are shown, we will also describe the global performance for cue identification and scope recognition. We will conclude the section showing the validation results for the Cancer dataset.

Table 5 depicts the results obtained for each BIO label using the BiLSTM-CRF model and biomedical embeddings in the NUBES corpus (*Lima Lopez et al., 2020*). These kinds of tables have also been calculated for each model.

The values of Table 5 will be used later to calculate the performance for cue detection and scope recognition as the weighted average between the "B" and "I" labels. In particular, the performance of the negation cue detection is obtained as the weighted average between "B-NEG" and "I-NEG" labels. On the other hand, the negation scope is obtained as the weighted average between "B-NSCO" and "I-NSCO". In the same way, we calculate the

Table 6 Results for cue identification (Partial match).

	Negation				Uncertaint	у		Negation		
	Р	R	F1	Р	R	F1	Р	R	F1	
BiLSTM-CRF	0.86	0.82	0.83	0.79	0.76	0.77	0.82	0.78	0.80	
BiLSTM-CRF + Biomedical Embbedings	0.94	0.92	0.93	0.85	0.81	0.83	0.91	0.90	0.90	
BiLSTM-CRF + Clinical Embbedings	0.93	0.91	0.92	0.84	0.80	0.82	0.90	0.88	0.89	
Multilingual BERT	0.95	0.93	0.95	0.86	0.83	0.84	0.92	0.93	0.92	

performance for uncertainty detection labels. This procedure has been followed for each model and for each corpus.

Moreover, results are obtained using partial and exact match, as follows:

- Partial match: Refers to the performance at token level. When a cue or scope contains several tokens, the performance for each token is independently measured. For instance, in the sentence "*La biopsia no muestra células cancerígenas*", the scope annotated in the corpus is underlined. However, the model could predict just the tokens "*muestra*" and "*células*". In this case, these tokens are considered as correctly predicted. In contrast, the token "*cancerígenas*" is considered as an error as it does not match with the annotated token in the corpus.
- Exact match: Refers to the performance at cue and scope level. An exact match is then only considered in the case when the complete set of tokens predicted by the model corresponds to the set of tokens annotated by the experts in the corpus. In the above example, the scope is considered a correct prediction if the model predicts all the tokens annotated in the corpus (*muestra células cancerígenas*)", otherwise, it is considered an error.

The following shows the results of experiments for cue identification, scope recognition, and validation with the Cancer dataset.

Cue identification

Table 6 shows the results obtained for the cue identification task in the experiments previously described. These results show the feasibility of both BiLSTM-CRF and BERT models to perform negation and uncertainty cue identification in clinical texts written in Spanish. As can be seen, the best performance was obtained in the third experiment in which the model was trained using multilingual BERT. Using the NUBES corpus, this model obtained an F-score of 95% and 84% for negation and uncertainty detection, respectively. While for the IULA corpus, the model obtained an F-score of 92% for negation detection.

In addition, Table 6 shows that when the BiLSTM-CRF model is combined with biomedical and clinical embeddings, it obtains competitive results in the cue identification task. In the first experiment, the BiLSTM-CRF model obtained an F-score of 93% and 83% for negation and uncertainty, respectively. In the second experiment an F-score of 92% and 82% were obtained. These results suggest that using biomedical and clinical embeddings is a useful approach to improve the performance of the BiLSTM-CRF model

Table 7 Results for scope recognition (Partial match).

			NUBES	IULA corpus					
	Negation				Uncertaint	у	Negation		
	Р	R	F1	Р	R	F1	Р	R	F1
BiLSTM-CRF	0.84	0.76	0.79	0.72	0.69	0.70	0.77	0.74	0.75
BiLSTM-CRF + Biomedical Embbedings	0.92	0.89	0.90	0.82	0.77	0.79	0.88	0.84	0.86
BiLSTM-CRF + Clinical Embbedings	0.92	0.87	0.89	0.81	0.75	0.78	0.87	0.83	0.85
Multilingual BERT	0.93	0.90	0.92	0.82	0.79	0.80	0.91	0.86	0.88

to detect negation and uncertainty in Spanish clinical texts. Moreover, using biomedical and clinical embeddings also improved the performance of the BiLSTM-CRF model in the IULA corpus.

According to Table 6, negation detection showed better performance than uncertainty detection. In the first experiment, the BiLSTM-CRF model obtained an F-score of 93% for negation detection and 83% for uncertainty detection. Meanwhile, models trained using multilingual BERT obtained an F-score of 95% for negation detection and 84% for uncertainty detection. Thus, these results highlight the fact that uncertainty detection is more difficult than negation detection in clinical texts written in Spanish.

The cue identification task measured using the exact match also shows competitive results. The best performance was also achieved using multilingual BERT. For the NUBES corpus, this model obtains an F-score of 95% and 83% for negation and uncertainty, respectively. The BiLSTM-CRF combined with biomedical embeddings obtains an F-score of 92% and 80% for negation and uncertainty. These results are similar to those shown in Table 6. This is because most of the negation and uncertainty cues contain only one annotated token, and consequently, the partial and exact matches have similar behavior.

Scope recognition

Table 7 describes the results obtained in the scope recognition task using a partial match. These results show the feasibility of deep learning-based methods to perform the scope recognition task for both negation and uncertainty detection. The best performance was obtained by using the BERT model. A 92% F-score for negation and 80% F-score for uncertainty were obtained using the NUBES corpus. Using the IULA corpus, this model obtained an F-score of 89% for negation detection.

The BiLSTM-CRF model combined with biomedical and clinical embeddings also showed a competitive performance in the scope recognition task. In the first experiment, it obtained an F-score of 90% for negation and 79% for uncertainty detection using the NUBES corpus. In the second experiment, 89% and 78% were obtained for negation and uncertainty, respectively. Results obtained suggest that adding clinical and biomedical embeddings increases the ability of the BiLSTM-CRF model to perform the scope recognition task. Results obtained in the IULA corpus also show that using biomedical and clinical embeddings has a positive impact on the performance of the BiLSTM-CRF model.

 Table 7 shows that negation detection performs better than uncertainty detection

 in experiments carried out with the NUBES corpus. This suggests that extracting the

Table 8 Results for scope recognition (Exact match).

	NUBES corpus							IULA corpus			
	Negation				Uncertaint	у	Negation				
	Р	R	F1	Р	R	F1	Р	R	F1		
1. BiLSTM-CRF	0.81	0.73	0.76	0.67	0.63	0.64	0.74	0.72	0.73		
2. BiLSTM-CRF + Biomedical Embbedings	0.88	0.85	0.86	0.73	0.70	0.71	0.84	0.83	0.84		
3. BiLSTM-CRF + Clinical Embbedings	0.86	0.84	0.84	0.71	0.68	0.69	0.84	0.80	0.82		
4. Multilingual BERT	0.90	0.86	0.88	0.75	0.70	0.72	0.89	0.84	0.86		

uncertainty scope is more difficult than extracting the negation scope. This behavior can be explained by the fact that negation also performs better than uncertainty in the cue identification task. Therefore, the difficulties in extracting uncertainty cues can also affect scope recognition, since cue identification and scope recognition are related tasks.

Table 8 describes the results obtained in the scope recognition task measured with an exact match. Using the NUBES corpus, the best performance was obtained with the BERT model. This model obtained an F-score of 88% for negation and 72% for uncertainty detection, respectively. These results show a decrease in the performance compared to those results from partial matches. The decrease percentage is 4% for negation and 8% for uncertainty detection, respectively. Regarding the IULA corpus, the BERT model obtained an F-score of 86%, which is 2% lower compared to results from partial matches. The performance decrease can also be seen in the BiLSTM-based models. The performance decrease is due to the fact that the scope commonly consists of several tokens in the sentence. Therefore, correctly predicting all annotated tokens by experts is a difficult task. Note that the decrease percentage is smaller in negation detection than uncertainty detection. This behavior can be explained by the following facts:

- Predicting the exact scope when it finishes at the end of the sentence is easier than predicting the scope when it ends in any other part of a sentence. Moreover, negation has more scopes that finish with the end of the sentence than uncertainty. Predicting these scopes generates fewer errors than predicting scopes that do not finish at the end of the sentence. In the NUBES corpus, 27% of the negation scopes finish at the end of the sentence. On the other hand, only 7% of the uncertainty scopes finish at the end of the sentence. In the IULA corpus (annotated only with negation), 33% of the scopes finish with the sentence.
- Predicting the scope in a short sentence is easier than predicting it in a long sentence. The percentage of sentences whose number of tokens is below the first quartile (Q1) is higher in negation than in uncertainty. We consider these sentences as short sentences. For instance, the sentence "*Paciente sin dolor toráxico.*" (patient without chest pain.) is considered as a short sentence, and the scope is shown underlined. In the NUBES corpus, 19% of sentences annotated with negation are below Q1, and only 7% of the sentences annotated with uncertainty are below Q1.
- Predicting the scope in a long sentence produces more errors than predicting it in a short sentence. The percentage of sentences whose number of tokens is above the third

		· ·	,									
		Cue detection					Scope recognition					
	Negation Uncertainty		Negation			Uncertainty						
	Р	R	F1	Р	R	F1	Р	R	F1	Р	R	F1
BiLSTM-CRF + Biomedical Embbedings	0.89	0.87	0.88	0.75	0.80	0.78	0.86	0.83	0.84	0.79	0.74	0.76
BiLSTM-CRF + Clinical Embbedings	0.91	0.88	0.89	0.80	0.81	0.80	0.87	0.85	0.86	0.79	0.76	0.77
Multilingual BERT	0.91	0.89	0.90	0.84	0.80	0.82	0.89	0.86	0.87	0.79	0.78	0.78

Table 9 Validation results with the Cancer dataset (Partial match).

quartile (Q3) is greater in uncertainty than in negation. In the NUBES corpus, 52% of sentences annotated with uncertainty are above Q3. On the other hand, only 30% of the sentences annotated with negation are above Q3.

Transferring results to the cancer dataset

Table 9 shows obtained results for the validation process with the Cancer dataset using a partial match. These results show the performance of trained models with the NUBES corpus for predicting cues and scopes on the Cancer dataset. Table 9 shows that the best performance was obtained by using the BERT model. In the cue identification task, this model obtained an F-score of 90% and 82% for negation and uncertainty, respectively. In the scope recognition task, the BERT model obtained an F-score of 87% and 78% for negation and uncertainty, respectively. In addition, the performance of the BiLSTM-CRF model combined with biomedical and clinical embeddings also showed competitive results. For instance, the model that uses clinical embeddings obtained an F-score of 89% and 80% in cue identification for negation and uncertainty, respectively. In the scope recognition task, this model obtained an F-score of 86% and 77% for negation and uncertainty, respectively.

Although results from Table 9 show a lower performance compared to those described in Tables 6 and 7, results are still promising. The validation process showed the ability of the deep learning-based models trained with the NUBES corpus to predict negation and uncertainty in a different dataset. This fact suggests that models trained with the NUBES corpus can be used to detect negation and uncertainty in new clinical texts.

On the other hand, Table 10 shows results for validation with the Cancer dataset using an exact match. These results also show that in the cue detection task the performance is similar to those results from partial matching. However, in the scope detection task, a decrease in the performance can be seen compared to those results obtained in a partial match. The BERT model obtained an F-score of 84% and 74% for negation and uncertainty, respectively. The decrease percentage was 3% for negation and 4% for uncertainty detection.

If we compare the performance of the proposed approach with other studies in the literature, we found that for the cue identification task, this approach obtains competitive results compared to those reported by *Lima Lopez et al.* (2020), as shown in Table 11. A direct comparison with other proposals such as the one in *Santiso et al.* (2018) is not possible because it reports results for negated entities within the scope, but not for negation cues. Other proposals such as *Santiso et al.* (2020), *Costumero et al.* (2014) and *Cotik et al.*

Table 10 Validation results with the Cancer dataset (Exact match).

		Cue detection						Scope recognition				
	Negation		U	Incertain	ity	Negatic			n Unc		certainty	
	Р	R	F1	Р	R	F1	Р	R	F1	Р	R	F1
BiLSTM-CRF + Biomedical Embbedings	0.87	0.86	0.87	0.75	0.80	0.78	0.81	0.80	0.80	0.71	0.69	0.70
BiLSTM-CRF + Clinical Embbedings	0.91	0.88	0.89	0.80	0.81	0.80	0.82	0.83	0.75	0.72	0.71	0.71
Multilingual BERT	0.91	0.89	0.90	0.82	0.80	0.81	0.85	0.84	0.84	0.75	0.73	0.74

 Table 11
 Comparison with other proposals in the cue identification task.

	Cue detection - NUBES corpus									
		Negation			Uncertainty	7				
	Р	R	F1	Р	R	F1				
Lima Lopez et al. (2020)	0.96	0.95	0.95	0.87	0.83	0.85				
Our approach (BiLSTM-based)	0.94	0.92	0.93	0.85	0.81	0.83				
Our approach (BERT-based)	0.95	0.95	0.95	0.86	0.83	0.84				

 Table 12
 Comparison with other proposals in the scope recognition task (F-score).

	NUBES corpus		IULA corpus
Proposal	Negation	Uncertainty	Negation
Santiso et al. (2018)	_	-	0.83
Zavala & Martinez (2020)	_	-	0.85
Lima Lopez et al. (2020)	0.90	0.78	_
Our approach (BiLSTM-based)	0.90	0.79	0.84
Our approach (BERT-based)	0.92	0.80	0.86

(2016) use private corpora which are not publicly available so a direct comparison is also not possible. Moreover, those proposals focused only on negation detection, but not on uncertainty.

In the scope recognition task, the proposed approach outperforms previous studies both for negation and uncertainty detection in Spanish. Table 12 shows the performance of the proposed approach in comparison with other proposals for the scope detection task. If one further analyzed the results from the NUBES corpus, the approach presented in this paper outperforms the *Lima Lopez et al.* (2020) proposal in both tasks (improvement of 2% in the case of uncertainty and 2% in the case of negation) using a partial match. If one analyzes the IULA corpus, the approach presented in this paper outperforms the results reported in *Santiso et al.* (2018) and *Zavala & Martinez* (2020) by 3% and 1%, respectively. In the IULA corpus, the performance was compared using an exact match. In addition, the approach proposed in this paper presents the following advantages over other studies:

• The proposed approach takes advantage of transfer learning techniques, biomedical word embeddings, and pre-trained models to automatically represent text features using dense vector representations. These representations are used for negation and uncertainty

detection. In contrast, other proposals such as *Lima Lopez et al. (2020)*; *Santiso et al. (2018)* require a considerable set of hand-crafted features to obtain comparable results. The process of manual feature extraction can be time-consuming and costly. Moreover, the proposal described in *Zavala & Martinez (2020)* depends on the syntactic properties of a sentence and other word-level annotated features to perform negation detection. On the contrary, the approach proposed in this paper only uses suitable biomedical word embeddings and contextual embeddings without depending on any other annotated features.

- The proposed approach deals with negation and uncertainty detection in a single step, improving those approaches (*Zavala & Martinez*, 2020; *Santiso et al.*, 2018; *Santiso et al.*, 2020; *Costumero et al.*, 2014; *Cotik et al.*, 2016) that only deal with negation detection in Spanish clinical texts.
- This approach improves performance in the scope recognition task in comparison with approaches *Lima Lopez et al. (2020)* dealing both with negation and uncertainty in Spanish, as one can see in Table 12.

DISCUSSION

The proposed approach has shown the feasibility of deep learning-based methods to perform negation and uncertainty detection from clinical texts written in Spanish. We found that both BiLSTM-CRF and BERT models obtained competitive results for both tasks: cue identification and scope recognition. The use of biomedical embeddings for Spanish and contextualized embeddings from multilingual BERT results in an improvement of the negation and uncertainty detection process. The proposed approach automatically represents text features using word embeddings and contextual embeddings, and uses them to detect uncertainty and negation. This is an advantage over previous proposals that require complex hand-crafted rules (*Costumero et al., 2014*; *Cotik et al., 2016*; *Solarte-Pabón, Menasalvas & Rodriguez-González, 2020*) or a considerable set of hand-crafted features (*Lima Lopez et al., 2020*) to obtain comparable results.

Obtained results showed that scope recognition is a more complex task than cue identification. This could be because in most cases negation and uncertainty cues consist of a single token. However, the scope frequently contains a longer sequence of tokens which makes it more difficult to detect it properly. As Table 7 shows, the proposed approach in this paper obtained competitive results for the scope recognition task, outperforming previous studies available for this task (*Santiso et al., 2018; Lima Lopez et al., 2020*).

The proposed approach performs better negation detection than uncertainty detection. Specifically, in the cue identification task, the best performance showed an F-score of 95% and 84% for negation and uncertainty detection, respectively (See Table 6). This behavior can be explained by two facts:

• The number of annotations with negation is higher than with uncertainty in the NUBES corpus. In this corpus, there are more than 7,500 sentences annotated with negation and only 2,219 sentences annotated with uncertainty, which affects the training of the models.

• Negation cues have less variability than uncertainty cues. Only five negation cues are used in the NUBES corpus ("no, sin, negativo, negativos, niega") to express 87% of all negation annotations. However, the set of words used to express uncertainty is much broader. The five more frequent uncertainty cues ("probable, posible, compatible con, sospecha de, parece") are used only in less than 48% of all uncertainty annotations. This fact once again affects the training process, reducing the performance of the models to perform uncertainty detection.

Although both BiLSTM-CRF and BERT models have shown feasibility to perform negation and uncertainty detection in Spanish, BERT obtains better results than BiLSTM-CRF in some specific cases. In particular, we observed that the BERT model tends to learn the scope better in those cases in which it appears before the cue, such as in the sentence:

"Mujer con cáncer de pulmón, <u>HER2</u> negativo" (Woman with lung cancer, HER2 negative).

In this sentence, the scope is underlined and the negation cue is in bold. In this case, the BERT model is able to learn that the scope is before the cue. The BiLSTM-CRF model failed in most of these cases. The BERT model also showed better performance than the BiLSTM-CRF model in those cases where the scope appears in both directions of the cue, as in the following sentence:

"<u>TAC cerebral</u> *negativo* <u>para células tumorales.</u>" (Negative brain CT scan for tumor cells.)

In this sentence, we can see that the scope (underlined) is before and after the cue (showed in bold). In these cases, the BERT model recognizes the scope in both directions (after and before the cue). On the other hand, the BiLSTM-CRF model tends to recognize only the part of the scope that appears after the cue.

The BERT model also outperforms the BiLSTM-CRF model when predicting labels with fewer annotations in the annotated corpus. In particular, the NUBES corpus contains more than 6,500 annotations for *syntactic negation*, and only 460 for *lexical negation*. In the syntactic negation, both BiLSTM-CRF and BERT models perform accurately. However, for lexical negation, the BiLSTM model fails to recognize some lexical cues with a low number of annotations in the corpus, while the BERT model recognizes them properly.

In 'Related works', we analyzed that syntactic properties of the sentence have been used in rule-based approaches for negation detection. Nevertheless, these properties can also be used in the context of deep learning methods and particularly for sequence-labeling tasks. In the context of negation and uncertainty detection in Spanish, several proposals (*Lima Lopez et al., 2020; Zavala & Martinez, 2020*) have used syntactic properties such as Part of Speech (POS) tagging and dependence relations between words as input features to the deep learning models. However, in the approach presented in this paper, we propose using suitable biomedical and clinical embeddings for the Spanish language instead of syntactical properties, and we have shown that this achieves competitive results. However, it will be interesting to explore additional syntactic properties in future works to improve the performance of negation and uncertainty detection in Spanish. The deep learning-based approach proposed in this paper relies on the availability of annotated corpora which is a time-consuming task. Fortunately, for the Spanish language, in recent years, great efforts have been made to create manually annotated corpora (*Lima Lopez et al., 2020; Marimon, Vivaldi & Bel, 2017*). We want to acknowledge the efforts to annotate these public corpora that have made it possible to propose and validate new approaches such as the one we have presented in this paper. For those languages in which annotated corpora are not available, researchers have to dedicate a large amount of time to obtain a manually annotated corpus.

Despite the promising results in this study, there are still some limitations that need to be addressed. In particular, we identify the following causes of error which can affect the performance of the proposed approach in both: BiLSTM-CRF and BERT-based models:

- Those cues that appear rarely are not detected. These cases mainly occur in uncertainty detection where some syntactic cues such as "Versus" and "O" (or), are annotated as uncertainty cues. However, the NUBES corpus has very few annotations using these words which means the approach does not recognize them as cues. As a consequence, the approach fails in sentences such as these examples: (Cue shown in bold):
 - "Cáncer pulmonar Versus inflamación del lóbulo derecho". (Lung cancer Versus right lobe inflammation).
 - "Carcinoma estadio IV o estadio IIIB". (Stage IV or stage IIIB carcinoma.)
- In the scope recognition task, most errors are caused by discontinuous scopes. This occurs when the sequence of tokens affected by a negation cue or an uncertainty cue are separated in different positions of the text sentence. In the next example, the scope (shown underlined) is discontinuous. We show the sentence annotated in the gold standard compared to that predicted by the system.

Gold: "*Paciente parcialmente <u>orientado</u> (si en tiempo, no <u>en espacio</u>)" (Partially oriented patient (in time, not in space)*

Predicted: "Paciente parcialmente orientado (si en tiempo, no en espacio)"

Another case of discontinuous scopes occurs when a sentence contains a sequence of cues, but some tokens in the sentence are not affected by any cue. A sequence of cues is more frequent in negation detection, as one can see in the following examples:

i) **Gold:** "*No hipertensión arterial*, *no* <u>vómito</u>, *no* <u>sangrado</u>." (No high blood pressure, no vomiting, no bleeding.)

i) Predicted: "No hipertensión arterial, no vómito, no sangrado."

ii) **Gold:** "**No** <u>dolor</u>, fiebre alta desde la noche anterior, **no** <u>sangrado</u>, **no** <u>vomito</u>." (No pain, high fever since last night, no bleeding, no vomiting.)

ii) **Predicted:** "**No** <u>dolor, fiebre alta desde la noche anterior</u>, **no** <u>sangrado</u>, **no** <u>vomito</u>." Note that in the first sentence (*i*), each token is affected by a negation cue. In this case, the approach correctly predicts the scope for each cue. However, in the second example (*ii*), the tokens "*fiebre alta desde la noche anterior*" are not negated, but the approach classifies them as negated. A possible cause of error when predicting discontinuous scopes may be associated with the fact that these scopes are not frequent in the annotated corpora. For instance, in the NUBES corpus, only about 5% of annotated scopes are discontinuous. However, these cases should be analyzed further in the future to improve performance.

CONCLUSIONS

In this paper, we proposed a deep learning-based approach for negation and uncertainty detection in clinical texts written in Spanish. Results obtained have shown the ability of deep learning methods to perform both cue identification and scope recognition tasks. The proposed approach takes advantage of transfer learning techniques, word embeddings, and pre-trained models to automatically represent text features, thus avoiding the time-consuming feature engineering process. This approach is useful for medical text mining applications because it can recognize negation and uncertainty in a single step. Moreover, the approach improves previous studies, as has been shown.

Both BiLSTM and BERT models have shown promising results for negation and uncertainty detection in clinical texts written in Spanish. The BERT model performed better than the BiLSTM model in some specific cases. In the cue identification task, the BERT model performed better at predicting labels that have fewer annotations in a corpus. In the scope recognition task, this model worked better at extracting the scope that appears before the cue, or when it appears on both sides of the cue. These facts increased the performance of the BERT model over the BiLSTM-CRF model.

In this paper, we also conducted a validation process using real-life clinical data which showed promising results. Deep learning models trained on the NUBES corpus have shown the ability to predict negation and uncertainty in datasets that are different from those on which they were trained. In future studies, we will explore more transformer-based architectures to perform negation and uncertainty detection.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

This paper is supported by European Union's Horizon 2020 research and innovation program under grant agreement No. 875160, project CLARIFY (Cancer Long Survivors Artificial Intelligence Follow Up). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures

The following grant information was disclosed by the authors: European Union's Horizon 2020 research and innovation program: 875160. CLARIFY (Cancer Long Survivors Artificial Intelligence Follow Up).

Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Oswaldo Solarte Pabón conceived and designed the experiments, performed the experiments, analyzed the data, performed the computation work, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Orlando Montenegro conceived and designed the experiments, performed the experiments, performed the computation work, prepared figures and/or tables, and approved the final draft.
- Maria Torrente, Alejandro Rodríguez González and Mariano Provencio analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.
- Ernestina Menasalvas conceived and designed the experiments, performed the experiments, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

The data and code of the proposed approach are available at GitHub: https://github.com/solarte7/NegationAndUncertainty.

Two datasets were used for training our models: NUBES and IULA. They are available at:

- http://eines.iula.upf.edu/brat/#/NegationOnCR_IULA
- https://github.com/Vicomtech/NUBes-negation-uncertainty-biomedical-corpus.

The Cancer dataset contains real-life data from patients treated with lung and breast cancer in "Hospital Puerta de Hierro" in Madrid, (Spain). This dataset is governed by the General Data Protection Regulation (GDPR) (EU) 2016/679 of the European Parliament. The Cancer dataset is available upon request and can be accessible for research purposes after an evaluation by the hospital's ethics committee. Researchers can request a copy of the Cancer dataset by contacting Dr. Cristina Avendaño Solá, Director of the hospital's ethics committee at Hospital Universitario Puerta de Hierro (Spain): cristina.avendano@uam.es.

REFERENCES

- Adel H, Schütze H. 2017. Exploring different dimensions of attention for uncertainty detection. In: 15th conference of the European chapter of the association for computational linguistics, EACL 2017 proceedings of conference. 22–34 DOI 10.18653/v1/e17-1003.
- Agarwal S, Yu H. 2010a. Biomedical negation scope detection with conditional random fields. *Journal of the American Medical Informatics Association* 17(6):696–701 DOI 10.1136/jamia.2010.003228.
- **Agarwal S, Yu H. 2010b.** Detecting hedge cues and their scope in biomedical text with conditional random fields. *Journal of Biomedical Informatics* **43(6)**:953–961 DOI 10.1016/j.jbi.2010.08.003.
- Al-khawaldeh FT. 2016. Speculation and negation annotation for arabic biomedical texts
 : BioArabic corpus. World of Computer Science and Information Technology Journal (WCSIT) 6(1):8–11.

- **Al-khawaldeh FT. 2019.** Speculation and negation detection for arabic biomedical texts. *World of Computer Science and Information Technology Journal (WCSIT)* **9(3)**:12–16.
- Alam R, Cheraghi-Sohi S, Panagioti M, Esmail A, Campbell S, Panagopoulou E. 2017. Managing diagnostic uncertainty in primary care: a systematic critical review. *BMC Family Practice* **18**(1):1–13 DOI 10.1186/s12875-017-0650-0.
- Alnazzawi N, Thompson P, Ananiadou S. 2014. Building a semantically annotated corpus for congestive heart and renal failure from clinical records and the literature. In: *Proceedings of the 5th international workshop on health text mining and information analysis (Louhi)*. Gothenburg, Sweden: Association for Computational Linguistics, 69–74 DOI 10.3115/v1/W14-1110.
- Bhatia P, Celikkaya B, Khalilia M. 2018. Joint entity extraction and assertion detection for clinical text. In: *Proceedings of the 57th Annual Meeting of the Association for Computational Linguistics*. Florence, Italy: Association for Computational Linguistics, 954–959 DOI 10.1007/978-3-030-24409-5.
- Bhise V, Rajan SS, Sittig DF, Morgan RO, Chaudhary P, Singh H. 2018. Defining and measuring diagnostic uncertainty in medicine: a systematic review. *Journal of General Internal Medicine* 33(1):103–115 DOI 10.1007/s11606-017-4164-1.
- **Bojanowski P, Grave E, Joulin A, Mikolov T. 2017.** Enriching word vectors with subword information. *Transactions of the Association for Computational Linguistics* **5**:135–146.
- **Bordes A, Chopra S, Weston J. 2014.** Question answering with subgraph embeddings. In: *Proceedings of the 2014 conference on empirical methods in natural language processing (EMNLP).* Doha, Qatar: Association for Computational Linguistics, 615–620 DOI 10.3115/v1/D14-1067.
- Brandsen A, Verberne S, Wansleeben M, Lambers K. 2020. Creating a dataset for named entity recognition in the archaeology domain. In: *Proceedings of the 12th language resources and evaluation conference*. Marseille, France: European Language Resources Association, 4573–4577.
- **Britto BK, Khandelwal A. 2020.** Resolving the scope of speculation and negation using transformer-based architectures. *ArXiv* 1–10.
- Campillos-Llanos L, Valverde-Mateos A, Capllonch-Carrión A, Moreno-Sandoval A. 2021. A clinical trials corpus annotated with UMLS entities to enhance the access to evidence-based medicine. *BMC Medical Informatics and Decision Making* 21(1):1–19 DOI 10.1186/s12911-021-01395-z.
- **Cardellino C. 2019.** Spanish billion words corpus and embeddings. *Available at https:* //crscardellino.github.io/SBWCE/ (accessed on 3 Sep 2021).
- Chapman WW, Bridewell W, Hanbury P, Cooper GF, Buchanan BG. 2001. A simple algorithm for identifying negated findings and diseases in discharge summaries. *Journal of Biomedical Informatics* 34(5):301–310 DOI 10.1006/jbin.2001.1029.
- **Chen L. 2019.** Attention-based deep learning system for negation and assertion detection in clinical notes. *International Journal of Artificial Intelligence and Applications (IJAIA)* **10(1)**:1–9.

- **Clausen D. 2010.** HedgeHunter: a system for hedge detection and uncertainty classification. In: *CoNLL-2010: shared task - fourteenth conference on computational natural language learning, proceedings of the shared task.* 120–125.
- **Cohen J. 1960.** A coefficient of agreement for nominal scales. *Educational and Psychological Measurement* **20**(1):37.
- Collobert R, Weston J, Bottou L, Karlen M, Kavukcuoglu K, Kuksa P. 2011. Natural language processing (almost) from scratch. *Journal of Machine Learning Research* 12(null):24932537.
- **Costumero R, Lopez F, Gonzalo-Martín C, Millan M, Menasalvas E. 2014.** Brain Informatics and Health. BIH 2014. In: Ślęzak D, Tan AH, Peters JF, Schwabe L, eds. *Lecture Notes in Computer Science*. vol. 8609. Cham: Springer, 366–375.
- Cotik V, Stricker V, Vivaldi J, Rodriguez H. 2016. Syntactic methods for negation detection in radiology reports in Spanish. In: *Proceedings of the 15th workshop on biomedical natural language processing*. Berlin, Germany: Association for Computational Linguistics, 156–165 DOI 10.18653/v1/W16-2921.
- **Cruz Díaz NP, Maña López MJ. 2019.** *Negation and speculation detection.* Amsterdam, The Netherlands: John Benjamins Publishing Company DOI 10.1075/nlp.13.
- **Cruz Díaz NP, Maña López MJ, Vázquez JM, Álvarez VP. 2012.** A machine-learning approach to negation and speculation detection in clinical texts. *Journal of the American Society for Information Science and Technology* **63**(7):1398–1410 DOI 10.1002/asi.22679.
- **Dalianis H. 2018a.** Clinical text mining. In: *Clinical text mining, secondary use of electronic patient records.* Cham: Springer Open DOI 10.1007/978-3-319-78503-5.
- **Dalianis H. 2018b.** Evaluation metrics and evaluation. In: *Clinical text mining: secondary use of electronic patient records.* Cham: Springer International Publishing, 45–53 DOI 10.1007/978-3-319-78503-5_6.
- **Dalloux C, Claveau V, Grabar N. 2019.** Speculation and negation detection in French biomedical corpora. In: *International conference recent advances in natural language processing, RANLP.* 223–232.
- **De Albornoz JC, Plaza L, Diaz A, Ballesteros M. 2012.** UCM-I: a rule-based syntactic approach for resolving the scope of negation. In: **SEM 2012 1st joint conference on lexical and computational semantics, volume 1.* 282–287.
- **Devlin J, Chang MW, Lee K, Toutanova K. 2019.** BERT: pre-training of deep bidirectional transformers for language understanding. In: *NAACL HLT 2019 - 2019 conference of the north american chapter of the association for computational linguistics: human language technologies - proceedings of the conference, 1(Mlm).* 4171–4186.
- **Elazhary H. 2017.** NegMiner: an automated tool for mining negations from electronic narrative medical documents. *International Journal of Intelligent Systems and Applications* **9(4)**:14–22 DOI 10.5815/ijisa.2017.04.02.
- Fancellu F, Lopez A, Webber B, He H. 2017. Detecting negation scope is easy, except when it isn't. In: Proceedings of the 15th conference of the european chapter of the association for computational linguistics: Volume 2, short papers. Valencia, Spain: Association for Computational Linguistics, 58–63.

- **Farkas R, Vincze V, Móra G, Csirik J, Szarvas G. 2010.** The CoNLL-2010 shared task: learning to detect hedges and their scope in natural language text. In: *Proceedings of the fourteenth conference on computational natural language learning –shared task.* Uppsala, Sweden: Association for Computational Linguistics, 1–12.
- Fei H, Ren Y, Ji D. 2020. Negation and speculation scope detection using recursive neural conditional random fields. *Neurocomputing* **374**:22–29 DOI 10.1016/j.neucom.2019.09.058.
- **Giorgi JM, Bader GD. 2019.** Towards reliable named entity recognition in the biomedical domain. *Bioinformatics* **36(1)**:280–286 DOI 10.1093/bioinformatics/btz504.
- **Goldberg Y, Hirst G. 2017.** *Neural network methods in natural language processing.* San Rafael, United States: Morgan and Claypool Publishers.
- Gu Y, Tinn R, Cheng H, Lucas M, Usuyama N, Liu X, Naumann T, Gao J, Poon H.
 2020. Domain-Specific language model pretraining for biomedical natural language processing. ArXiv preprint. arXiv:007.15779.
- Harkema H, Dowling JN, Thornblade T, Chapman WW. 2009. ConText: an algorithm for determining negation, experiencer, and temporal status from clinical reports. *Journal of Biomedical Informatics* **42**(5):839–851 DOI 10.1016/j.jbi.2009.05.002.
- **Hochreiter S, Schmidhuber J. 1997.** LSTM can solve hard long time lag problems. *Advances in Neural Information Processing Systems* 473–479.
- Hripcsak G, Rothschild AS. 2005. Agreement, the F-measure, and reliability in information retrieval. *Journal of the American Medical Informatics Association* 12(3):296–298 DOI 10.1197/jamia.M1733.
- Huang Z, Xu W, Yu K. 2015. Bidirectional LSTM-CRF models for sequence tagging. ArXiv preprint. arXiv:08.01991.
- Jean PA, Harispe S, Ranwez S, Bellot P, Montmain J. 2016. Uncertainty detection in natural language: a probabilistic model. In: *Proceedings of the 6th International Conference on Web Intelligence, Mining and Semantics (WIMS '16)*. New York: ACM, DOI 10.1145/2912845.2912873.
- Jiménez-Zafra SM, Morante R, Blanco E, Martín Valdivia MT, Ureña López LA. 2020a. Detecting negation cues and scopes in Spanish. In: *Proceedings of the 12th language resources and evaluation conference*. Marseille, France: European Language Resources Association, 6902–6911.
- Jiménez-Zafra SM, Morante R, Martín-Valdivia MT, Ureña-López LA. 2020b. Corpora annotated with negation: an overview. *Computational Linguistics* 46(1):1–52 DOI 10.1162/coli_a_00371.
- Jiménez-Zafra SM, Taulé M, Martín-Valdivia MT, Ureña-López LA, Martí MA. 2018. SFU ReviewSP-NEG: a Spanish corpus annotated with negation for sentiment analysis. A typology of negation patterns. *Language Resources and Evaluation* 52(2):533–569 DOI 10.1007/s10579-017-9391-x.
- Jimnez-Zafra SM, Cruz-Daz NP, Taboada M, Martn-Valdivia MT. 2021. Negation detection for sentiment analysis: a case study in Spanish. *Natural Language Engineering* 27(2):225248 DOI 10.1017/S1351324920000376.

- Kesterson J, Beesley C, Dexter P, Schmidt CM, Liu H. 2015. incorporating dependency relation into NegEx. *Journal of Biomedical Informatics* 54:213–219 DOI 10.1016/j.jbi.2015.02.010.DEEPEN.
- **Khandelwal A, Sawant S. 2020.** NegBERT: a transfer learning approach for negation detection and scope resolution. In: *LREC 2020 12th international conference on language resources and evaluation, conference proceedings.* 5739–5748.
- Konstantinova N, de Sousa SC, Cruz NP, Maña MJ, Taboada M, Mitkov R. 2012. A review corpus annotated for negation, speculation and their scope. In: *Proceedings of the eighth international conference on language resources and evaluation (LREC'12)*. Istanbul, Turkey: European Language Resources Association (ELRA), 3190–3195.
- Lafferty JD, McCallum A, Pereira FCN. 2001. Conditional Random Fields: probabilistic models for segmenting and labeling sequence data. In: *Proceedings of the eighteenth international conference on machine learning, ICML '01*. Williamstown, MA, USA: Morgan Kaufmann Publishers Inc., 282–289.
- Lample G, Ballesteros M, Subramanian S, Kawakami K, Dyer C. 2016. Neural architectures for named entity recognition. In: *Proceedings of the 2016 conference of the north american chapter of the association for computational linguistics: human language technologies*. San Diego, California: Association for Computational Linguistics, 260–270 DOI 10.18653/v1/N16-1030.
- Lee J, Yoon W, Kim S, Kim D, Kim S, So CH, Kang J. 2020. BioBERT: a pre-trained biomedical language representation model for biomedical text mining. *Bioinformatics* 36(4):1234–1240 DOI 10.1093/bioinformatics/btz682.
- **Lima Lopez S, Perez N, Cuadros M, Rigau G. 2020.** NUBes: a corpus of negation and uncertainty in Spanish clinical texts. In: *Proceedings of the 12th language resources and evaluation conference*. Marseille, France: European Language Resources Association, 5772–5781.
- Liu Q, Kusner MJ, Blunsom P. 2020. A survey on contextual embeddings. ArXiv preprint. arXiv:2003.07278.
- Liu R, Shi Y, Ji C, Jia M. 2019a. A survey of sentiment analysis based on transfer learning. *IEEE Access* 7:85401–85412 DOI 10.1109/ACCESS.2019.2925059.
- Liu Y, Ott M, Goyal N, Du J, Joshi M, Chen D, Levy O, Lewis M, Zettlemoyer L, Stoyanov V. 2019b. RoBERTa: a robustly optimized BERT pretraining approach. ArXiv preprint. arXiv:1907.11692.

Lopez MM, Kalita J. 2017. Deep learning applied to NLP. ArXiv preprint. arXiv:1703.03091.

- Marimon M, Vivaldi J, Bel N. 2017. Annotation of negation in the IULA Spanish clinical record corpus. In: *Proceedings of the workshop computational semantics beyond events and roles*. Valencia, Spain: Association for Computational Linguistics, 43–52 DOI 10.18653/v1/W17-1807.
- Mikolov T, Sutskever I, Chen K, Corrado GS, Dean J. 2013. Distributed representations of words and phrases and their compositionality. In: Burges CJC, Bottou L, Welling M, Ghahramani Z, Weinberger KQ, eds. *Advances in neural information processing systems 26*. Red Hook: Curran Associates, Inc., 3111–3119.

- Minaee S, Kalchbrenner N, Cambria E, Nikzad N, Chenaghlu M, Gao J. 2020. Deep learning based text classification: a comprehensive review. *ArXiv* 1(1):1–43.
- **Morante R, Blanco E. 2012.** SEM 2012 shared task: resolving the scope and focus of negation. In: *SEM 2012 1st joint conference on lexical and computational semantics, volume 1.* 265–274.
- **Morante R, Daelemans W. 2009a.** Learning the scope of hedge cues in biomedical texts. In: *Proceedings of the workshop on current trends in biomedical natural language processing, BioNLP '09.* 2836.
- Morante R, Daelemans W. 2009b. A metalearning approach to processing the scope of negation. In: *Proceedings of the thirteenth conference on computational natural language learning (CoNLL-2009)*. Boulder, Colorado: Association for Computational Linguistics, 21–29.
- Morante R, Sporleder C. 2012. Modality and negation: an introduction to the special issue. *Computational Linguistics* **38**(2):223–260 DOI 10.1162/COLL_a_00095.
- Névéol A, Dalianis H, Velupillai S, Savova G, Zweigenbaum P.. 2018. Clinical Natural Language Processing in languages other than English: opportunities and challenges. *Journal of Biomedical Semantics* 9(1):1–13 DOI 10.1186/s13326-018-0179-8.
- Nikfarjam A, Emadzadeh E, Gonzalez G. 2014. *Biomedical informatics insights*. vol. 5. Springer DOI 10.4137/BII.S8981.
- **Ogren P, Savova G, Chute C. 2008.** Constructing evaluation corpora for automated clinical named entity recognition. In: *Proceedings of the sixth international conference on language resources and evaluation (LREC'08)*. Marrakech, Morocco: European Language Resources Association (ELRA).
- **Oronoz M, Gojenola K, Pérez A, de Ilarraza AD, Casillas A. 2015.** On the creation of a clinical gold standard corpus in Spanish: mining adverse drug reactions. *Journal of Biomedical Informatics* **56**:318–332 DOI 10.1016/j.jbi.2015.06.016.
- **Ortiz Suarez P, Romary L, Benoit S. 2012.** A monolingual approach to contextualized word embeddings for mid-resource languages. In: *Proceedings of the 58th annual meeting of the association for computational linguistics.* 1703–1714.
- Panigrahi S, Nanda A, Swarnkar T. 2021. A survey on transfer learning. *Smart Innovation, Systems and Technologies* 194:781–789 DOI 10.1007/978-981-15-5971-6_83.
- Peng DL, Wang YR, Liu C, Chen Z. 2020. TL-NER: a transfer learning model for chinese named entity recognition. *Information Systems Frontiers* 22(6):1291–1304 DOI 10.1007/s10796-019-09932-y.
- **Peng Y, Wang X, Lu L, Bagheri M, Summers R, Lu Z. 2018.** NegBio: a high-performance tool for negation and uncertainty detection in radiology reports. In: *AMIA joint summits on translational science proceedings. AMIA joint summits on translational science*. 188–196.
- **Pennington J, Socher R, Manning CD. 2014.** GloVe: global vectors for word representation. In: *Empirical Methods in Natural Language Processing (EMNLP)*. 1532–1543.
- Peters ME, Neumann M, Iyyer M, Gardner M, Clark C, Lee K, Zettlemoyer L. 2018. Deep contextualized word representations. In: *NAACL HLT 2018 - 2018*

conference of the north american chapter of the association for computational linguistics: human language technologies - proceedings of the conference. 2227–2237 DOI 10.18653/v1/n18-1202.

- **Pires T, Schlinger E, Garrette D. 2019.** How multilingual is multilingual BERT? In: *Proceedings of the 57th annual meeting of the association for computational linguistics.* Florence, Italy: Association for Computational Linguistics, 4996–5001 DOI 10.18653/v1/P19-1493.
- Pradhan S, Elhadad N, South BR, Martinez D, Christensen L, Vogel A, Suominen H, Chapman WW, Savova G. 2015. Evaluating the state of the art in disorder recognition and normalization of the clinical narrative. *Journal of the American Medical Informatics Association* 22(1):143–154 DOI 10.1136/amiajnl-2013-002544.
- Qian Z, Li P, Zhu Q, Zhou G, Luo Z, Luo W. 2016. Speculation and negation scope detection via convolutional neural networks. In: *EMNLP 2016 conference on empirical methods in natural language processing, proceedings*. 815–825 DOI 10.18653/v1/d16-1078.
- **Santamaria J. 2019.** NegEx-MES: NegEx para textos Mdicos en ESpaol. *Available at https://github.com/PlanTL-SANIDAD/NegEx-MES*.
- Santiso S, Casillas A, Pérez A, Oronoz M. 2018. Word embeddings for negation detection in health records written in Spanish. *Soft Computing* 23(21):10969–10975 DOI 10.1007/s00500-018-3650-7.
- Santiso S, Pérez A, Casillas A, Oronoz M. 2020. Neural negated entity recognition in Spanish electronic health records. *Journal of Biomedical Informatics* 105(December 2019):103419 DOI 10.1016/j.jbi.2020.103419.
- **Schuster M, Nakajima K. 2012.** Wordpiece Tokenization. In: *ICASSP, IEEE international conference on acoustics, speech and signal processing - proceedings, volume 1.* Piscataway: IEEE, 5149–5152.
- Shaitarova A, Furrer L, Rinaldi F. 2020b. Cross-lingual transfer-learning approach to negation scope resolution. In: *CEUR Workshop proceedings, vol. 2624 (June)*.
- Shaodian Z, Tian K, Xingting Z, Dong W, Noemie E, Jianbo L. 2016. Speculation detection for Chinese clinical notes: impacts of word segmentation and embedding models. *Journal of Biomedical Informatics* 60(February):334–341 DOI 10.1016/j.jbi.2016.02.011.
- **Skeppstedt M, Paradis C, Kerren A. 2016.** Marker words for negation and speculation in health records and consumer reviews. *CEUR Workshop Proceedings* **1650**:64–69.
- Soares F, Villegas M, Gonzalez-Agirre A, Krallinger M, Armengol-Estapé J. 2019. Medical word embeddings for Spanish: development and evaluation. In: *Proceedings of the 2nd clinical natural language processing workshop*. Minneapolis, Minnesota, USA: Association for Computational Linguistics, 124–133 DOI 10.18653/v1/W19-1916.
- **Solarte-Pabón O, Menasalvas E, Rodriguez-González A. 2020.** Spa-neg: an approach for negation detection in clinical text written in Spanish. Cham: Springer International Publishing, 323–337.

- Solarte Pabón O, Torrente M, Provencio M, Rodríguez-Gonzalez A, Menasalvas E.
 2021. Integrating speculation detection and deep learning to extract lung cancer diagnosis from clinical notes. *Applied Sciences* 11(2):865 DOI 10.3390/app11020865.
- **Stricke rV, Ignacio I, Cotik V. 2015.** Negated findings detection in radiology reports in Spanish: an adaptation of NegEx to Spanish. In: *Workshop on replicability and reproducibility in natural language processing*. Buenos Aires, Argentina.
- **Sutskever I, Vinyals O, Le QV. 2014.** Sequence to sequence learning with neural networks. *Advances in Neural Information Processing Systems* **4**(January):3104–3112.
- Szarvas G, Vincze V, Farkas R, Mra G, Gurevych I. 2012. Cross-genre and crossdomain detection of semantic uncertainty. *Computational Linguistics* 38(2):335–367 DOI 10.1162/COLI_a_00098.
- **Taylor SJ, Harabagiu SM. 2018.** The role of a deep-learning method for negation detection in patient cohort identification from electroencephalography reports. 1018–1027.
- Uzuner Ö, South BR, Shen S, DuVall SL. 2011. 2010 i2b2/VA challenge on concepts, assertions, and relations in clinical text. *Journal of the American Medical Informatics Association* 18(5):552–556 DOI 10.1136/amiajnl-2011-000203.
- Uzuner O, Zhang X, Sibanda T. 2009. Machine learning and rule-based approaches to assertion classification. *Journal of the American Medical Informatics Association* 16(1):109–115 DOI 10.1197/jamia.M2950.
- Vaswani A, Shazeer N, Parmar N, Uszkoreit J, Jones L, Gomez AN, Kaiser L, Polosukhin I. 2017. Attention is all you need. In: *Proceedings of the 31st international conference on neural information processing systems*, *NIPS'17*. Red Hook, NY, USA: Curran Associates Inc., 6000–6010.
- Velupillai S, Dalianis H, Kvist M. 2011. Factuality levels of diagnoses in Swedish clinical text. Studies in Health Technology and Informatics 169:559–563 DOI 10.3233/978-1-60750-806-9-559.
- Velupillai S, Skeppstedt M, Kvist M, Mowery D, Chapman BE, Dalianis H, Chapman WW. 2014. Cue-based assertion classification for Swedish clinical text-Developing a lexicon for pyConTextSwe. *Artificial Intelligence in Medicine* 61(3):137–144 DOI 10.1016/j.artmed.2014.01.001.
- **Vincze V. 2010b.** Speculation and negation annotation in natural language texts: what the case of bioscope might (Not) reveal, NeSp-NLP '10. In: *Proceedings of the workshop on negation and speculation in natural language processing*. USA: Association for Computational Linguistics, 2831.
- **Vincze V. 2014.** Uncertainty detection in Hungarian texts. In: *COLING 2014 25th international conference on computational linguistics, proceedings of COLING 2014: technical papers.* 1844–1853.
- Vincze V, Szarvas G, Farkas R, Móra G, Csirik J. 2008. The BioScope corpus: biomedical texts annotated for uncertainty, negation and their scopes. *BMC Bioinformatics* 9(SUPPL. 11):1–9 DOI 10.1186/1471-2105-9-S11-S9.

- Wang Y, Liu S, Afzal N, Rastegar-Mojarad M, Wang L, Shen F, Kingsbury P, Liu H. 2018. A comparison of word embeddings for the biomedical natural language processing. *Journal of Biomedical Informatics* 87(April):12–20 DOI 10.1016/j.jbi.2018.09.008.
- Wu AS, Do BH, Kim J, Rubin DL. 2011. Evaluation of negation and uncertainty detection and its impact on precision and recall in search. *Journal of Digital Imaging* 24(2):234–242 DOI 10.1007/s10278-009-9250-4.
- Wu Y, Schuster M, Chen Z, Le QV, Norouzi M, Macherey W, Krikun M, Cao Y, Gao Q, Macherey K, Klingner J, Shah A, Johnson M, Liu X, Kaiser Ł., Gouws S, Kato Y, Kudo T, Kazawa H, Stevens K, Kurian G, Patil N, Wang W, Young C, Smith J, Riesa J, Rudnick A, Vinyals O, Corrado G, Hughes M, Dean J. 2016. Google's neural machine translation system: bridging the gap between human and machine translation. 1–23ArXiv preprint. arXiv:1609.08144.
- Yang Z, Dai Z, Yang Y, Carbonell J, Salakhutdinov R, Le QV. 2019. XLNet: Generalized autoregressive pretraining for language understanding. *Advances in Neural Information Processing Systems* 32(NeurIPS):1–18.
- Zavala RR, Martinez P. 2020. The impact of pretrained language models on negation and speculation detection in cross-lingual medical text: comparative study. *JMIR Medical Informatics* 8(12):1–21 DOI 10.2196/18953.
- Zhou H, Deng H, Huang D, Zhu M. 2015. Hedge scope detection in biomedical texts: an effective dependency-based method. *PLOS ONE* **10**(7):1–16 DOI 10.1371/journal.pone.0133715.
- **Zhou H, Ning S, Yang Y, Liu Z, Xu J. 2018.** Chinese hedge scope detection based on phrase semantic representation. In: *2017 international conference on asian language processing (IALP), volume 2018.* 285–288 DOI 10.1109/IALP.2017.8300599.
- Zou B, Zhou G, Zhu Q. 2016. Research on Chinese negation and speculation: corpus annotation and identification. *Frontiers of Computer Science* 10(6):1039–1051 DOI 10.1007/s11704-015-5101-2.