Side Effects Analysis Based On Action Sets for Medical Treatments

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Abstract. Side effects result from the application of treatments to patients. They are commonly negative and therefore undesirable. Side effects are one of the major causes of readmissions in hospitals and generate additional expenses and poor healthcare quality. One of the main challenges in side effects study is their unexpectedness and the lack of predictability in a multi-factor environment. In this paper, we strive to extract negative side effects patterns from multivalued features. We also present a patients clustering scheme based on similar negative side effects (negative action sets). We evaluated our approach using the Florida State Inpatient Databases (SID), which is a part of the Healthcare Cost and Utilization Project (HCUP) [1]. Our results show that we are highly effective in extracting negative side effects.

Keywords: Side effects, Meta-actions, Action rules, Action sets, Action terms, Actionable knowledge

1 Introduction

Treatments' negative side effects discovery is a very challenging problem that has not been given a lot of attention from knowledge discovery researchers in the healthcare domain. Side effects are often resulting from the application of treatments modeled as Meta-actions [2]. Meta-actions represent actions triggering certain changes in objects' states that will execute action rules [3]. These changes are commonly referred to as meta-action effects that affect certain properties of the examined objects and are used for better personalization [4]. Meta-actions effects can be positive or neutral [5], and in some cases negative. Positive effects help objects positively to transition them into a more desired state. Neutral meaning does not introduce any effects on the overall state of the objects. Negative effects that may possibly harm or move the object into an undesired state. These effects can be seen as side effects when they are not intended by users.

There has been several work for treatment patterns recognition. Kolibaba et. al. [6] and Ramey et. al. [7] explored treatment patterns and outcomes. Lorigan et. al. [8] also explored treatment patterns and outcomes for patients with

metastatic melanoma in the U.K. In [9], the authors mine medical articles for the disease and treatments as well as underlying side effects. However, they did not extract treatment negative side effects patterns in terms of results.

Treatment effects are not only related to the applied meta-actions, but also to the patient's initial state. In our previous work on extracting treatment effects, we extracted only positive and neutral side effects because we can analyze them based on the patient initial state. In fact, the union of the neutral and positive effects constitute the patient's initial state. However, treatment's side effects are unknown before applying the treatments. For this reason, it is important to study the objects in hand and anticipate the possible side effects when applying specific meta-actions. In this paper, we focus on the extraction and evaluation of potential negative side effects given an object and the applicable meta-actions. We also cluster patients based on the negative action sets extracted and evaluate them for the Florida State Inpatient Databases (SID) [1]. Our results show that action sets extracted are effectively the negative side effects for the treatments.

2 Background

In this section, we define the concepts used in actionable knowledge discovery that will help extract patterns of treatment effects. These concepts are used to extract any type of effects; however, we are interested in negative side effects.

Definition 1 (Information System) *By information system [10] we mean a triple of the form $S = (X, F, V)$ where:*

1. *X is a nonempty, finite set of objects.*
2. *F is a nonempty, finite set of features of the form $f : X \to 2^{V_f}$, which is a function for any $f \in F$, where V_f is called the domain of f.*
3. *V is a finite set of feature values such as: $V = \bigcup\{V_f : f \in F\}$.*

Definition 2 (Stable and Flexible features) *Stable features are object properties that we do not have control over in the context of an information system. For example, a birth date is a stable feature. On the other hand, flexible features are object properties that can transition from one value to another triggering a change in the object state. For instance, blood pressure is a flexible features.*

In the following, we will define the Atomic Action Terms that are the foundational expressions in actionable knowledge.

Definition 3 (Atomic action term in S) *also called elementary action term in S, is an expression that defines a change of state for a distinct feature in S.*

For example, $(f, v_1 \to v_2)$ is an atomic action term which defines a change of value for feature f in S from v_1 to v_2, where $v_1, v_2 \in V_f$. In the case when there is no change, we omit the right arrow sign; so for example, (f, v_1) means that the value of feature f in S remains v_1, where $v_1 \in V_f$.

Atomic action terms model value transition patterns for a single feature, but they do not model the association between feature values transition patterns. We augment the definition of atomic action terms to action terms by associating several transitions of feature values.

Definition 4 (Action terms) *are defined as the smallest collection of expressions for an information system S, such that:*

- *If t is an atomic action term in S, then t is an action term in S.*
- *If t_1, t_2 are action terms in S and $\wedge$ is a 2-argument functor called composition, then $t_1 \wedge t_2$ is a candidate action term in S.*
- *If t is a candidate action term in S and for any two atomic action terms $(f, v_1 \rightarrow v_2), (g, w_1 \rightarrow w_2)$ contained in t we have $f \neq g$, then t is an action term in S.*

Action terms provide an actionable knowledge; however, we still need the actions to perform in order to trigger these action terms. To do so, we use meta-actions which, when executed, trigger changes in values of some flexible features in S [2].

More formally, let us define $\mathbf{M}(S)$ as a set of meta-actions associated with an information system S. Let $f \in F$, $x \in X$, and $M \subset \mathbf{M}(S)$, then, applying the meta-actions in the set M on an object x will result in $M(f(x)) = f(y)$, where object x is converted to object y by applying all meta-actions in M to x. Similarly, $M(F(x)) = F(y)$, where $F(y) = \{f(y) : f \in F\}$ for $y \in X$, and object x is converted to object y by applying all meta-actions in M to x for all $f \in F$.

2.1 Side Effects Based on Action Terms

As stated before, the main goal of meta-actions is to trigger action rules. However, it is often the case that when applying meta-actions for the purpose of executing a specific action rule, a set of additional unrelated and potentially harmful atomic action terms is triggered. The additional action terms resulting from the meta-action application are called side effects. Meta-actions might move the values of some object's features from negative to positive (desirable positive side effects), and values of some object's features from positive to negative values (undesirable negative side effects). Even though the features transitioning from positive to negative values might result in catastrophic situations, they were not fully investigated in previous work involving action rules discovery [4]. In the following, we depict two types of side effects based on action terms and we give a brief description for each type.

Meta-actions Side Effects. Side-effects based on action terms in the context of meta-actions alone are the effects that occur for specific small clusters of objects. This type of side effects is discovered in the meta-action extraction process. It is represented by the action terms that exhibit very low or unusual likelihood of occurrence. In fact, this type of action term is very rare in our

dataset, and it was extracted from a very small number of objects. We can think of this type of effects as minor effects of a meta-action that do not represent the core goal of applying this meta-action. Detecting this type of side effects is done by setting a minimum number of occurrence for the action terms (cardinal of support), or setting a minimum jump in values of cardinal of supporting set between the action terms.

Action Rules Side Effects. Side-effects based on action terms in the context of action rules are the unintended changes in the values of some flexible features that meta-actions trigger on objects. In other words, those effects are triggered by meta-actions but are outside of the intended action rule scope. To discover those side effects, we can perform two set operations. We start by performing a set difference operation between the antecedent side of the action rule and the meta-actions' action terms reported in the influence matrix. The result is then intersected with the object's precondition to get the final set of side effects.

2.2 Action Sets

The changes in flexible features, triggered by meta-actions, are commonly represented by action terms for the respective features, and reported by an influence matrix presented in [2]. However, when an information system contains multivalued features where the same feature takes a set of values at any given object state and transitions to another set of values in a different object state, it is best to represent the transitions between the feature initial set of values and another set of values by action sets [5] that are defined as:

Definition 5 (Action Set) *An action set in an information system S is an expression that defines a change of state for a distinct feature that takes several values (multivalued feature) at any object state.*

For example, $\{f_1, f_2, f_3\} \rightarrow \{f_1, f_4\}$ is an action set that defines a change of values for feature $f \in F$ from the set $\{f_1, f_2, f_3\}$ to the set $\{f_1, f_4\}$ where $\{f_1, f_2, f_3, f_4\} \subseteq V_f$. Action sets are used to model meta-action effects for information systems with multivalued features. In addition, the usefulness of action sets is best captured by the set intersection, between the two states involved, that models neutral action sets, and set difference, between the two states involved, that models positive action sets. In the previous example, neutral and positive action sets are respectively computed as follow: $\{f_1, f_2, f_3\} \rightarrow [\{f_1, f_2, f_3\} \cap \{f_1, f_4\}]$ and $\{f_1, f_2, f_3\} \rightarrow [\{f_1, f_2, f_3\} \setminus \{f_1, f_4\}]$.

Positive and neutral action sets were previously studied in [5]. In this paper, we are mainly interested in the study of negative action sets extracted from information systems with multivalued features. These negative action sets represent negative side effects when medical meta-actions are applied, and they are best captured by the reverse set difference between the two states involved. In the previous example, negative action sets are captured as follows: $\{f_1, f_2, f_3\} \rightarrow [\{f_1, f_4\} \setminus \{f_1, f_2, f_3\}]$

3 Negative Side Effects

In healthcare, the study of side effects is mainly related to treatments and patients' conditions. In this section, we study the mining and representation of negative action sets (negative side effects) resulting from the application of meta-actions. We also show how to cluster patients based on these negative action sets and analyze the clusters.

3.1 Negative Action Sets Representation and Mining

Negative side effects are represented by action sets which model the appearance of certain diagnoses when applying a meta-action on specific patients. These diagnoses were not intended by the physician and can be harmful to the patient. The negative action sets are part of the meta-action effects, and they are best captured by the reverse set difference between the prior and posterior state of the patient. For instance, applying meta-action treatment m to patient x who is diagnosed with $F(x)_t = \{Dx_1, Dx_2, Dx_3\}$ at the prior state time t might transition the patient to a new state with the following diagnoses $F(x)_{t+1} = \{Dx_1, Dx_4\}$ at the posterior time $t+1$. This transition introduces a new diagnosis condition Dx_4 that was not present before applying m. The action set resulting is described by: $\{Dx_1, Dx_2, Dx_3\} \rightarrow [\{Dx_1, Dx_4\} \setminus \{Dx_1, Dx_2, Dx_3\}]$, where $[\{Dx_1, Dx_4\} \setminus \{Dx_1, Dx_2, Dx_3\}] = Dx_4$ represents the reverse set difference between the left hand side of the action set and its right hand side. In this example Dx_4 is seen as a negative side effect that appeared as a result of applying m to x.

Meta-actions effects extracted from information systems with multivalued features are commonly represented by an ontology that include neutral $\overline{As}$, and positive $\underline{As}$ action sets. We augment this representation by including negative action sets labeled $\overline{\underline{As}}$ and represented in red in Figure 1.

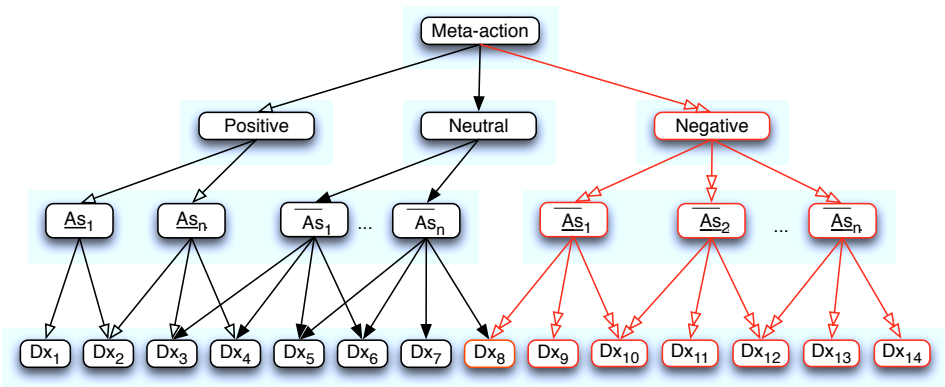

Fig. 1. Ontology representation of a meta-action with negative effects.

Once we define the format of negative action sets, we use the same action set mining technique described in [5]. In fact, we order patients by visit date, and create pairs containing two consecutive visits for each patient. The negative action sets are then extracted from those pairs for each patient and a power set is then generated to extract all possible combinations.

3.2 Patients' Clustering Based on Side Effects

Patients react similarly to some treatments that result in the same negative side effects. Therefore, it is important to keep track of the meta-actions side effects and cluster the patients who experience similar negative side effects. Clustering the patients based on the negative side-effects is done using the negative action sets. The negative action sets are supported by patients that reacted negatively to the treatments (meta-actions) applied with the respective side effects. The supporting patients for a specific negative action set constitute a cluster of patients; hence, the clustering is done by grouping those patients.

By the supporting set for a negative action set $\overline{\underline{As}} = [F(x)_{t+1} \setminus F(x)_t]$ of the form $F(x)_t \rightarrow [F(x)_{t+1} \setminus F(x)_t]$ in an information system $S = (X, F, V)$, where $F(x)_t = \{f(x)_t : f \in F\}$, we mean the set of patients $x \in X$ represented by the expression $sup(\overline{\underline{As}}) = \{x \in X : (\forall f(x) \in \overline{\underline{As}})\ [(f(x) \in F(x)_{t+1}) \wedge (f(x) \notin F(x)_t)]\ \}$. Now, $sup(\overline{\underline{As}})$ represents the set of the objects affected by the negative action set. This way each supporting set of patients represents a different cluster $sup(\overline{\underline{As_i}})$ labeled by $\overline{\underline{As_i}}$.

4 Negative Side Effects Evaluation

The negative actions sets are evaluated and analyzed using the confidence and the cardinal of supporting set -*CardSup*- that are similar to the evaluation of neutral and positive action sets. In fact, for each negative action set $\overline{\underline{As}}$, we can compute the cardinal of the support $CardSup(\overline{\underline{As}})$ as follows:

$$CardSup(\overline{\underline{As}}) = card(sup(\overline{\underline{As}})) \tag{1}$$

The $CardSup(\overline{\underline{As}})$ is a good measure of the spread or dominance of this negative side effect for a specific meta-action.

Of course, we can also compute the negative action set confidence $ActionConf(\overline{\underline{As}})$ as follows:

$$ActionConf(\overline{\underline{As}}) = \frac{CardSup(\overline{\underline{As}})}{card(\{x_i \in X : [\overline{\underline{As}} \subseteq F(x_i)_{t+1}]\})} \tag{2}$$

where $F(x_i)_t$ represents the initial state of the object or patient x_i. Note here that the $ActionConf(\overline{\underline{As}})$ does not model the confidence of predicting that patients with the initial state $F(x_i)_t$ will react with negative side effects to the meta-action; it rather models the confidence of the action set being a negative

action set $\overline{As}$ and not a neutral one. In other words, it does not model correlation between $F(x_i)_t$ and $\overline{As}$.

In previous work [5], we computed the meta-action confidence $MetaConf(m)$ for m to acquire a general idea on its stability with regards to patients initial states and the positive and neutral action sets. However, we did not include the negative side effects because the purpose of the meta-action is to cure the initial diagnoses of the patients. On the other hand, the negative side effects may have originated from the correlation between the applied meta-action and some stable or unknown features and not necessarily from the initial state of the patient.

$$NegMetaConf(m) = \frac{\sum_{i=1}^{n} [CardSup(\overline{As_i}) \cdot ActionConf(\overline{As_i})]}{\sum_{i=1}^{n} CardSup(\overline{As_i})} \tag{3}$$

where n is the number of extracted negative action sets. The negative meta-action confidence informs us about how the initial state of the patient is correlated with the negative action sets.

5 Evaluation

5.1 HCUP Dataset Description

In this paper, we used the Florida State Inpatient Databases (SID) that is part of the Healthcare Cost and Utilization Project (HCUP). The Florida SID dataset contains records from several hospitals in the Florida State. It contains over 2.5 million visit discharges from over 1.5 million patients. The dataset is composed of five tables, namely: AHAL, CHGH, GRPS, SEVERITY, and CORE. The main table used in this work is the *Core* table. The *Core* table contains over 280 features; however, many of those features are repeated with different codification schemes. In the following experiments, we used the Clinical Classifications Software (CCS) that consists of 262 diagnosis categories, and 234 procedure categories. This system is based on ICD-9-CM codes. In our experiments, we used fewer features that are described in this section. Each record in the *Core* table represents a visit discharge. A patient may have several visits in the table. One of the most important features of this table is the $VisitLink$ feature, which describes the patient's ID. Another important feature is the Key, which is the primary key of the table that identifies unique visits for the patients and links to the other tables. As mentioned earlier, a $VisitLink$ might map to multiple Key in the database. This table reports up to 31 diagnoses per discharge as it has 31 diagnosis columns. However, patients' diagnoses are stored in a random order in this table. For example, if a particular patient visits the hospital twice with heart failure, the first visit discharge may report a heart failure diagnosis at diagnosis column number 10, and the second visit discharge may report a heart failure diagnosis at diagnosis column number 22. Furthermore, it is worth mentioning that it is often the case that patients examination returns less than

Table 1. Mapping between features and concepts features.

features	**Concepts**
VisitLink	Patient Identifier
DaysToEvent	Temporal visit ordering
DXCCSn	n^{th} Diagnosis, flexible feature
PRCCSn	n^{th} Procedure, meta-action
Race, Age Range, Sex,..	Stable features
DIED	Decision Atribute

31 diagnoses. The *Core* table also contains 31 columns describing up to 31 procedures that the patient went through. Even though a patient might have gone through several procedure in a given visit, the primary procedure that occurred at the visit discharge is assumed to be the first procedure column. The *Core* table also contains an feature called $DaysToEvent$, which describes the number of days that passed between the admission to the hospital and the procedure day. This field is anonymized in order to hide the patients' identity. Furthermore, the *Core* table also contains a feature called *DIED*, that informs us on whether the patient died or survived in the hospital for a particular discharge. There are several demographic data that are reported in this table as well, such as: Race, Age Range, Sex, living area, ...etc. Table 1 maps the features from the *Core* table to the concepts and notations used in this paper.

5.2 Experiments

We performed several experiments regarding mining negative action sets and analyzing patients' clusters based on negative side effects. We used four meta-actions to extract and analyze side effects. The four meta-actions used are referenced by the following procedure CCS codes [1]: 34, 43, 44, and 45.

We started by mining the negative action sets and evaluated them. We also give a few examples of the negative action sets mined in Table 2. For instance, coronary artery bypass graft (CCS:44) results in bacterial infection (CCS:3, ActionConf=98%). Patients were then grouped and analyzed based on side effects.

You can note from Table 3 that the $MetaConf$ is smaller than the average confidence since it reflects a better global confidence of the meta-actions with regard to $CardSup$. However, Figure 2 shows that more than 73% of action sets have over 90% confidence for all meta-acions. This shows that a threshold on the $ActionConf$ can be used to eliminate some negative action sets. The total number of clusters, the average $CardSup$, and the average cluster's negative action set size are also reported in Table 3 for descriptive reasons.

Table 4 shows that the number of clusters follows a Gaussian distribution [11] behavior with regard to their negative action sets sizes. In addition, the average $CardSup$ decreases when the size of the cluster's action sets increases. The action set cluster with size 0 indicates no side effects; in other words, patients in this cluster did not have any side effects as a result of applying the meta-action.

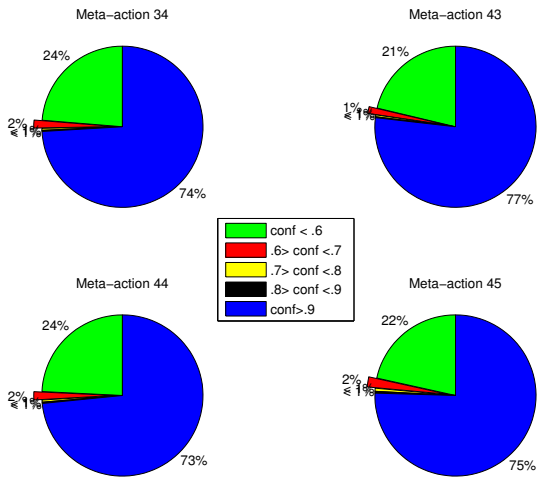

Fig. 2. Negative action sets confidence proportion.

Those tables show that increasing the size of the cluster action sets, in most of the cases, increases the average of $ActionConf$. This is due to introducing more constraints in the action sets.

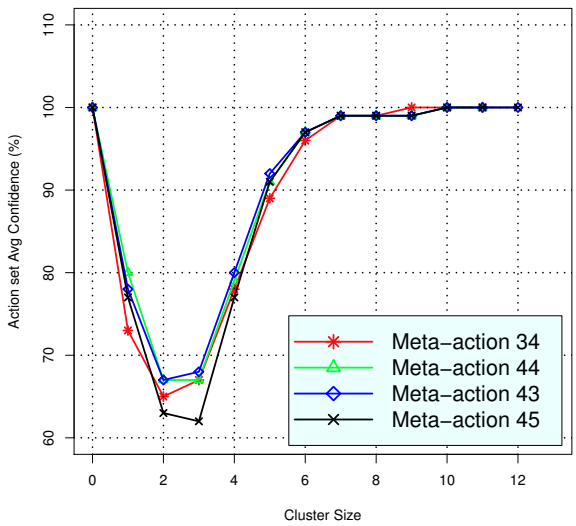

Fig. 3. Negative action sets confidence by size of clusters.

Figure 3 summarizes the trend of the action sets average confidence in a better way. This figure shows that the average action set confidence is low for action sets' clusters with sizes ranging from 1 to 4. This is due to the small number of supporting patients for these clusters.

Table 2. Examples of negative action sets for all meta-actions.

Meta-action	Negative action set	Size	CardSup	ActionConf
34	[1]	1	404	0.99
	[238]	1	308	0.83
	[134]	1	719	0.88
	[155]	1	932	0.84
	[1 , 155]	2	187	0.89
	[134 , 155]	2	366	0.77
	[134 , 1 , 155]	3	54	0.87
	[134 , 59 , 155]	3	55	0.58
43	[257]	1	429	0.93
	[254]	1	399	1.00
	[155]	1	238	0.91
	[159]	1	227	0.81
	[259 , 254]	2	102	0.89
	[257 , 254]	2	72	0.96
	[113 , 159 , 254]	3	10	1.00
	[105 , 254 , 155]	3	8	1.00
44	[254]	1	403	1.00
	[102]	1	276	0.99
	[197]	1	272	0.93
	[3]	1	214	0.98
	[2 , 244]	2	111	0.86
	[197 , 238]	2	121	0.68
	[134 , 2 , 244 , 249 , 157]	5	3	1.00
	[2 , 52 , 249]	3	12	1.00
45	[102]	1	1532	0.97
	[130]	1	495	0.91
	[153]	1	456	0.91
	[60]	1	452	0.96
	[2 , 244]	2	252	0.90
	[153 , 60]	2	127	0.95
	[146 , 120]	2	68	0.96
	[2 , 244 , 249]	3	58	0.85

Table 3. Negative clusters analysis for all meta-actions.

Meta-action	Average clusters size	Total number of clusters	Average CardSup	Average ActionConf	MetaConf
45	4.84	405931	1.69	0.84	0.53
44	4.46	178446	1.49	0.83	0.55
43	4.70	194957	1.37	0.85	0.62
34	4.63	180372	1.44	0.83	0.58

Table 4. Negative clusters analysis for meta-action 43.

Meta-action	Action set clusters size	Number of clusters	Average CardSup	Average Action-Conf
43	0	1	2645	1
	1	213	64.12	0.78
	2	6277	5.46	0.67
	3	33158	1.64	0.68
	4	54737	1.10	0.80
	5	48576	1.01	0.92
	6	30447	1.00	0.97
	7	14476	1.00	0.99
	8	5275	1.00	0.99
	9	1457	1.00	0.99
	10	296	1.00	1
	11	41	1.00	1
	12	3	1.00	1
45	0	1	12076.0000	1
	1	225	225.2400	0.77
	2	8230	13.2682	0.63
	3	59864	2.4103	0.62
	4	111169	1.2360	0.77
	5	104193	1.0493	0.91
	6	70782	1.0130	0.97
	7	35255	1.0034	0.99
	8	12466	1.0006	0.99
	9	3143	1.0000	0.99
	10	542	1.0000	1
	11	58	1.0000	1
	12	3	1.0000	1
34	0	1	2264	1
	1	213	60.11	0.73
	2	5803	5.86	0.65
	3	29814	1.86	0.67
	4	52691	1.17	0.78
	5	47620	1.02	0.89
	6	28146	1.00	0.96
	7	11794	1.00	0.99
	8	3495	1.00	0.99
	9	703	1.00	1
	10	87	1.00	1
	11	5	1.00	1
44	0	1	3905	1
	1	219	82.39	0.80
	2	6912	5.99	0.67
	3	36008	1.67	0.67
	4	54893	1.11	0.79
	5	43770	1.01	0.91
	6	23878	1.00	0.97
	7	9463	1.00	0.99
	8	2700	1.00	0.99
	9	532	1.00	0.99
	10	66	1.00	1
	11	4	1.00	1

6 Conclusion

Mining negative side-effects allows us to cluster patients with similar negative action sets. This work is very helpful for the predictability of negative side effects, and personalized action rules extraction. We have shown in this paper how negative side effects based on action terms are represented, and demonstrated how negative action sets are structured and extracted. We then presented negative action sets evaluations metrics, and analyzed patients' clusters based on these metrics for the Florida State Inpatient Databases (SID)[1]. Our results show a high confidence for the negative action sets extracted and a high negative meta-action confidence for the meta-actions examined.

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