Towards Confidence Estimation for Typed Protein-Protein Relation Extraction

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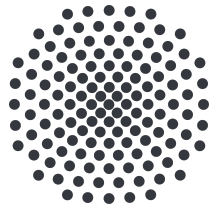

Motivation

IL-6	positive regulation	STAT-3
⋮	⋮	⋮
TIPE2	negative regulation	Snail2
⋮	⋮	⋮
growth factor	positive regulation	WSC domain
⋮	⋮	⋮

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Motivation

IL-6	positive regulation	STAT-3	true
⋮	⋮	⋮	
TIPE2	negative regulation	Snail2	
⋮	⋮	⋮	
growth factor	positive regulation	WSC domain	
⋮	⋮	⋮	

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Motivation

IL-6	positive regulation	STAT-3	true
⋮	⋮	⋮	
TIPE2	negative regulation	Snail2	interesting!
⋮	⋮	⋮	
growth factor	positive regulation	WSC domain	false
⋮	⋮	⋮	

▷ The middle fact is not in the STRING database, but PubMed/MEDLINE abstract 28186089 mentions it:

> *"(...) TIPE2 (...) downregulated (...) Snail2 (...)"*

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Motivation

c_1	IL-6	positive regulation	STAT-3	true
		⋮	⋮	
c_i	TIPE2	negative regulation	Snail2	interesting!
		⋮	⋮	
c_{i+k}	growth factor	positive regulation	WSC domain	false
		⋮	⋮	

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> *"(...) TIPE2 (...) downregulated (...) Snail2 (...)"*

▷ Requirements: $c_i \leq c_{i+1}$, $c_i \in [0, 1]$, for $i \geq 0$

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Strategies

We hypothesize that relation discovery confidence scores rely on three main kinds of sources:

S1: The (aggregated) confidence scores of the individual modules of RE pipelines

S2: The internal graph structure of the discovered relations

S3: Evidence gathered from external knowledge sources, such as textual evidence or knowledge retrieved or inferred from structured knowledge sources (biomedical ontologies and databases)

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▷ In this work, we focus on strategy S1

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Datasets

MEDLINE English-only, protein- and gene-centered subset of from May 1992 to May 2017

PMIDs 1376980 to 28211214
40,911,675 tokens in 1,939,915 abstracts
https://www.nlm.nih.gov/bsd/pmresources.html

STRING Human gene/protein subset of STRING database, which integrates many biomedical databases

20,458 unique genes/proteins with 6,013,567 unique typed interactions
https://string-db.org/

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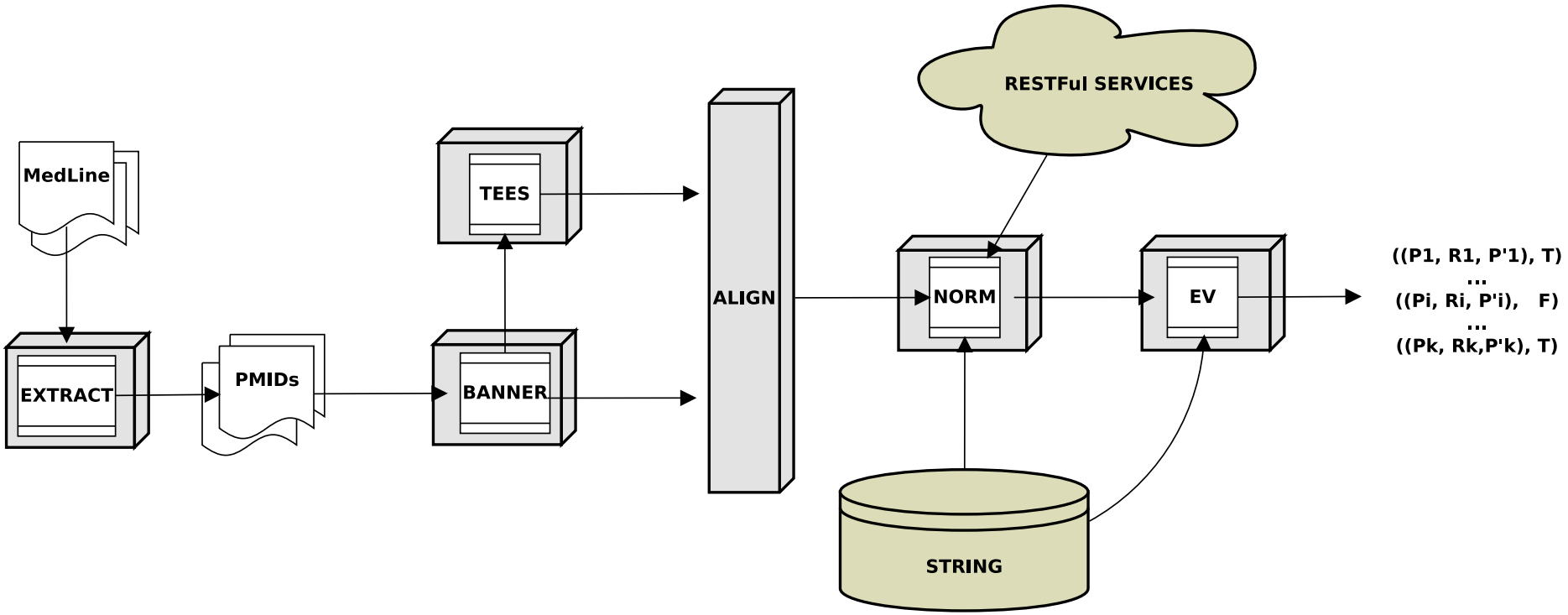
System Architecture



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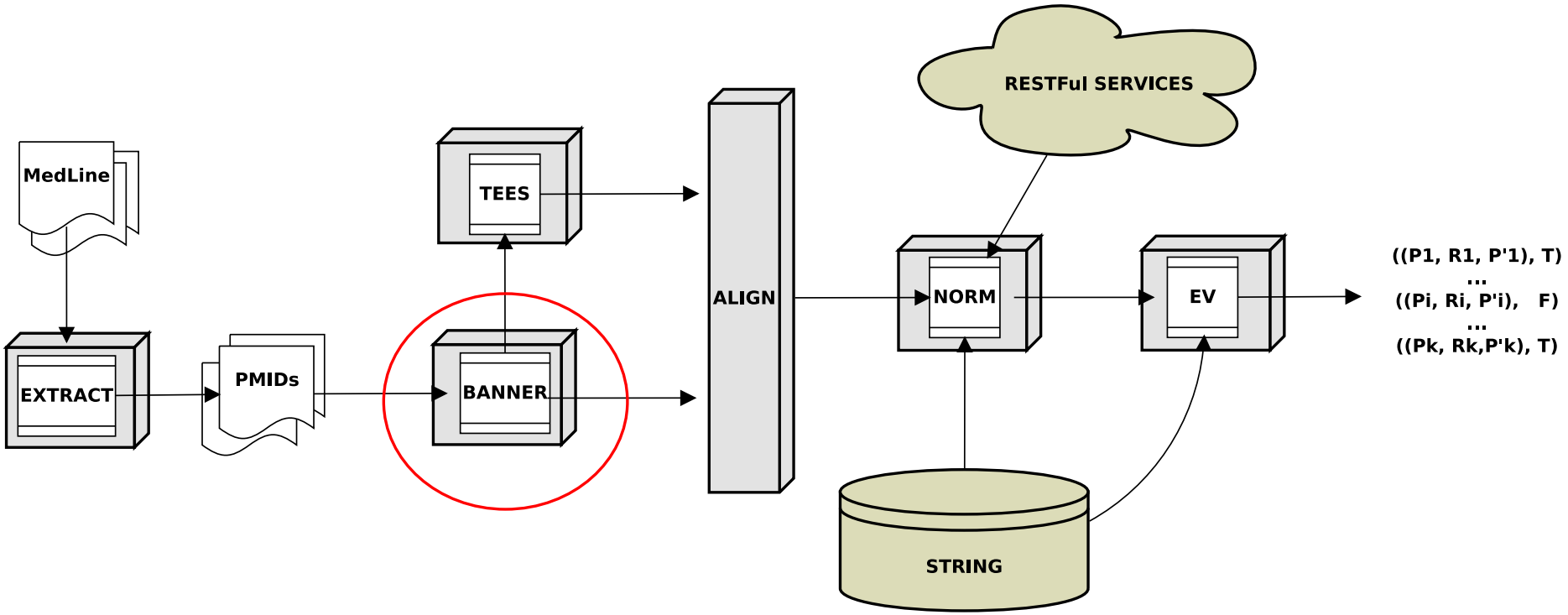

BANNER [LG08] for protein/gene recognition (CRF-based biomedical entity recognition tool)

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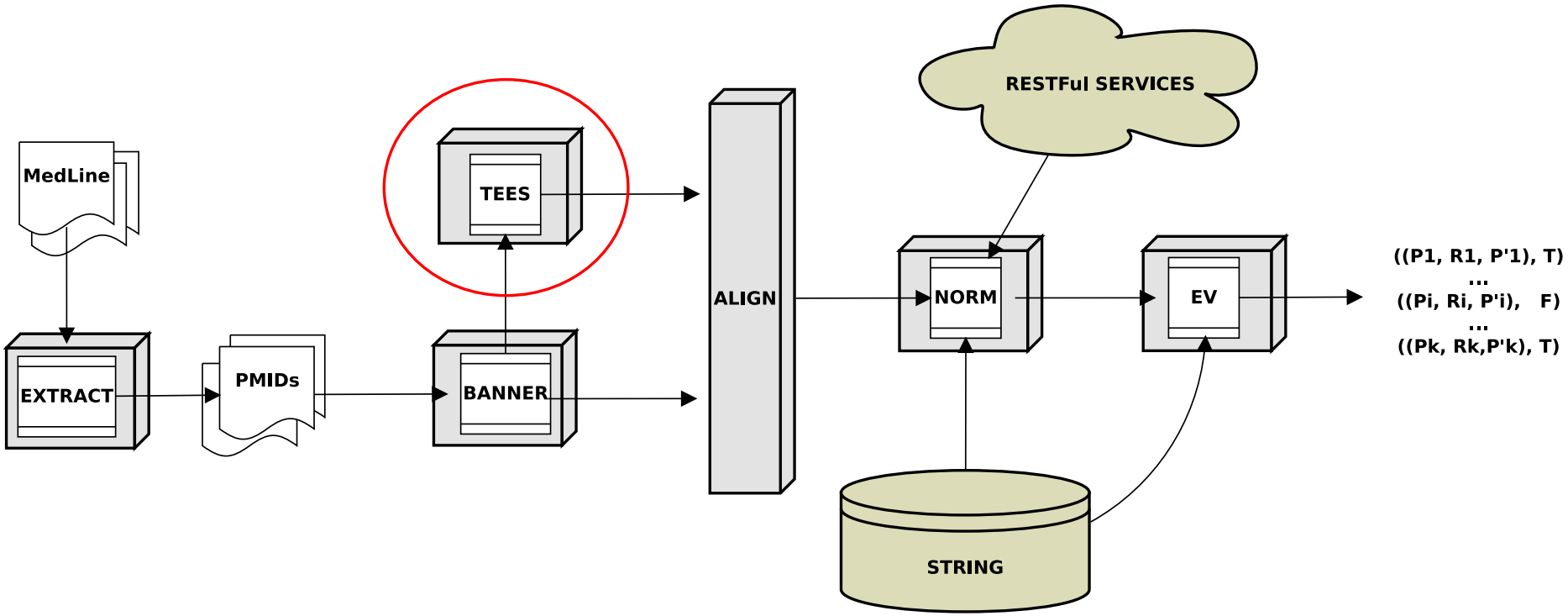
System Architecture



TEES [BS15] for protein-protein typed event recognition

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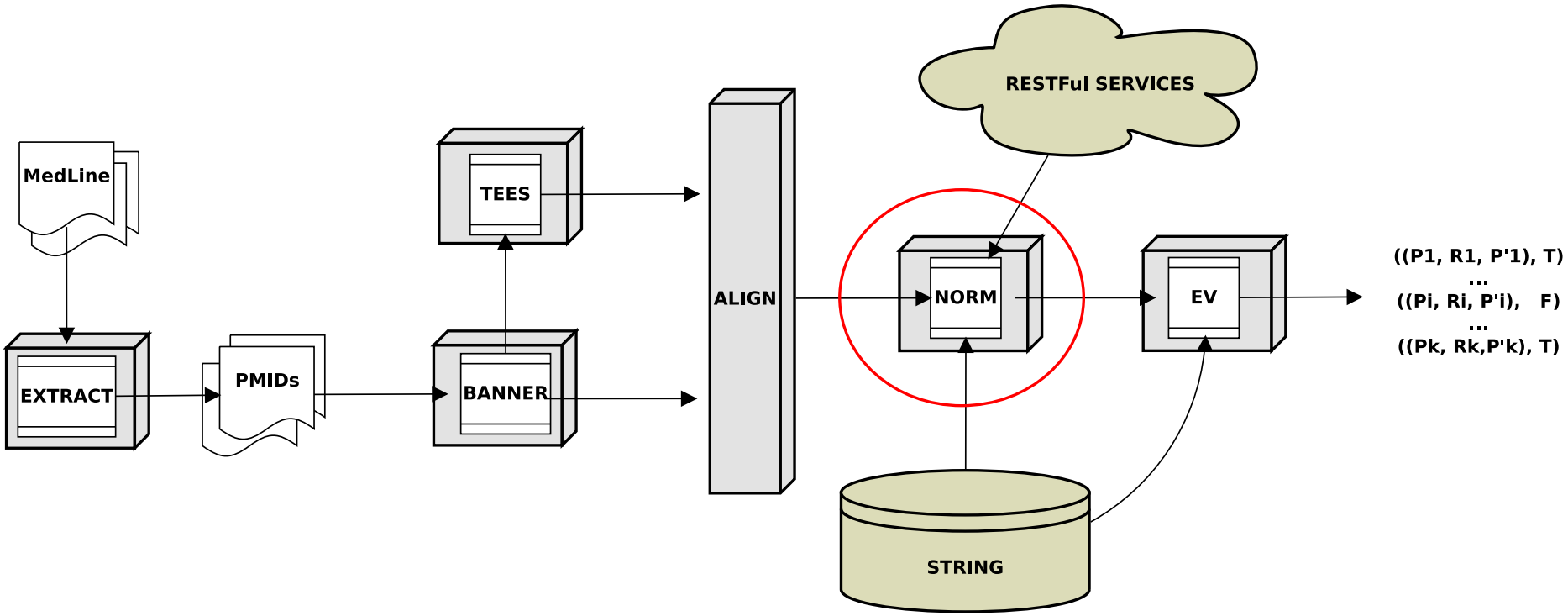
System Architecture



GNAT [HGH+11] and GNorm [WKL15] for protein normalization

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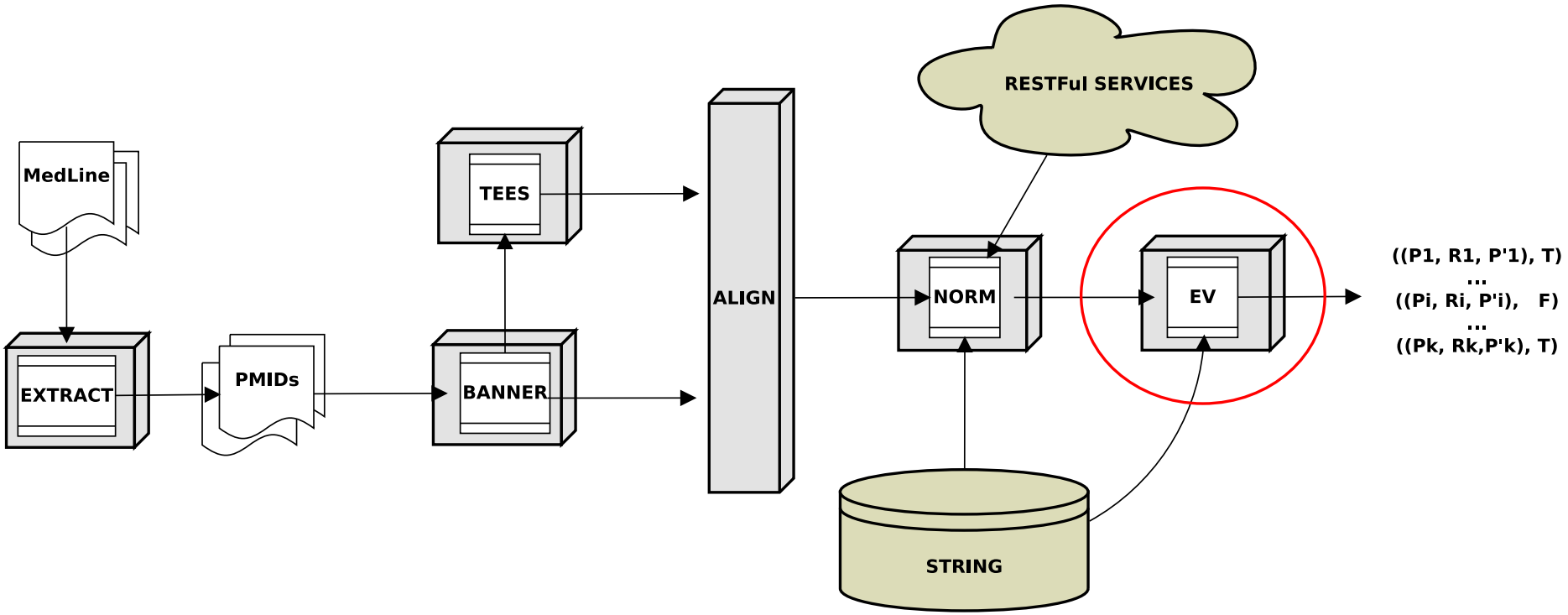
System Architecture



Extended the normalizers to normalize event types as well

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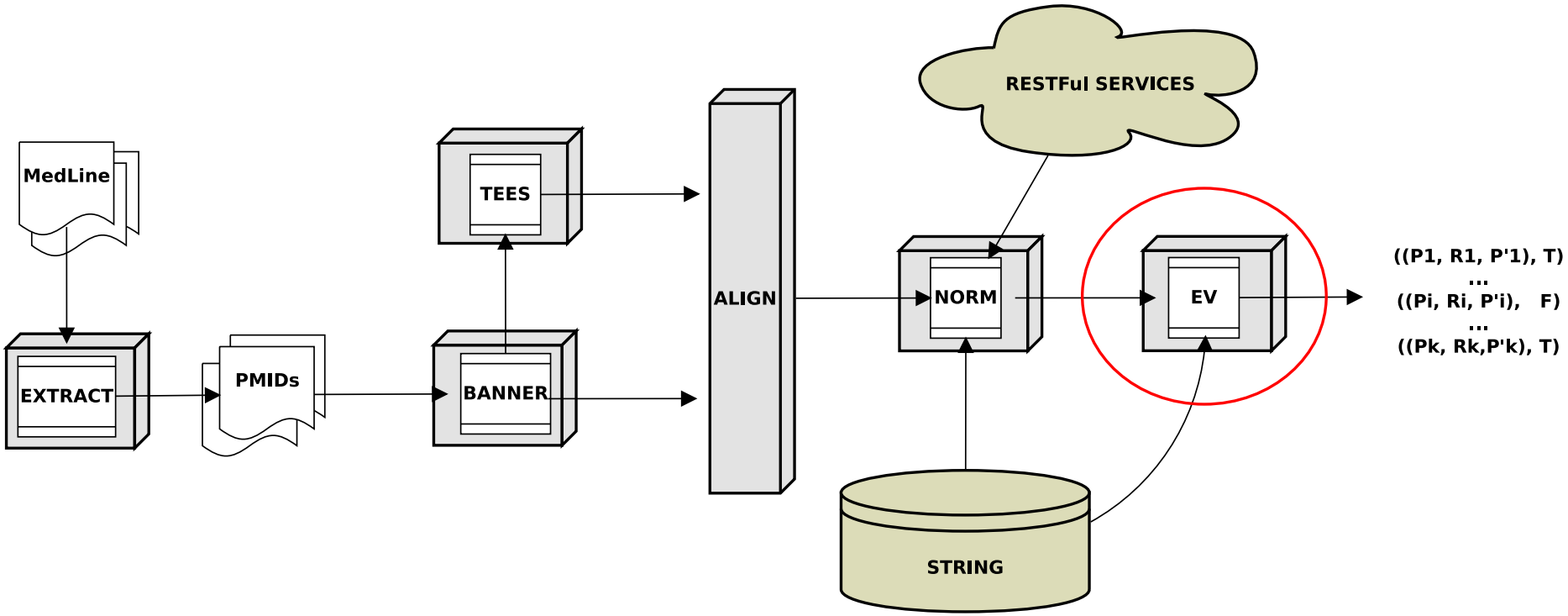
System Architecture



≈ 20,000 relations from ≈ 10,000 PMIDs

≈ 10,000 normalized relations per normalizer (GNAT, GNorm)

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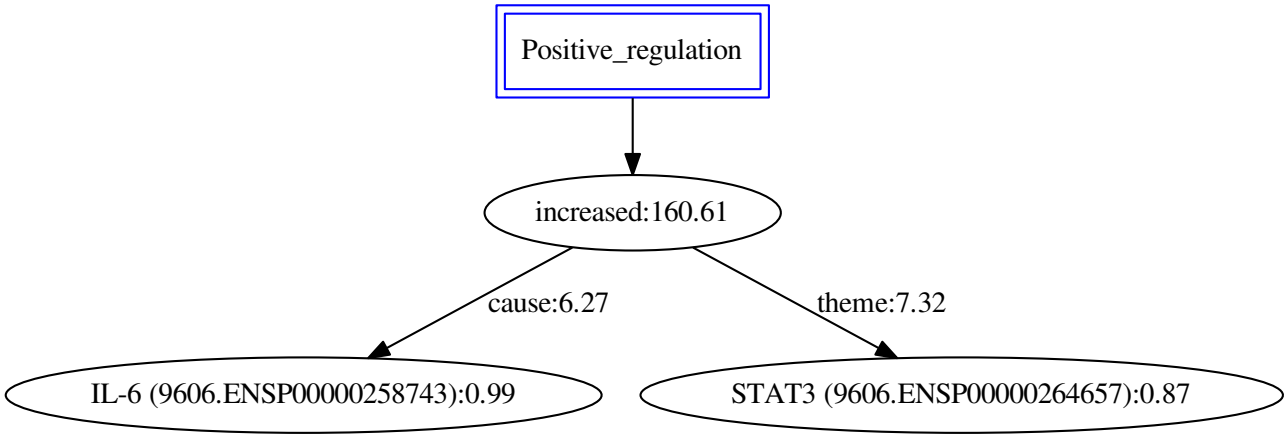
Typed Protein-Protein Relations

A typed interaction is a triple $rel = (p_1, r, p_2)$ denoting a directed relation r between proteins p_1 and p_2



Western blot analysis showed that IL-6 **increased** JKA, STAT3, p-STAT3 and VEGF-C protein levels in the gastric cancer cells. (pmid 26750536)

(typed interaction extracted by the pipeline
for the first relation from the motivating example)

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Component-wise Confidences

For every candidate rel we compute component-wise confidence values

This gives rise to five confidence values for each rel

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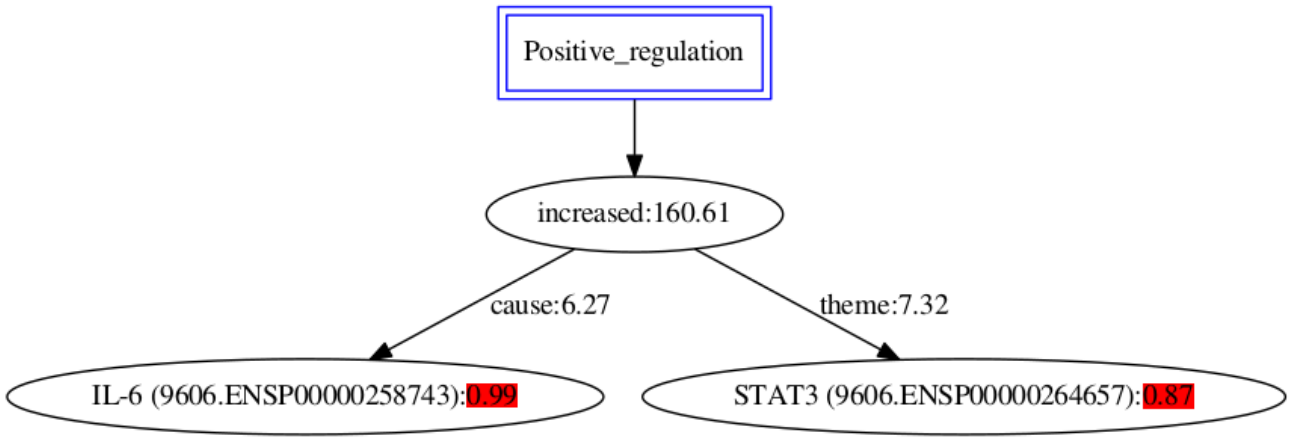
▷ BANNER (CRF) gamma probability [CM04] of protein entities:

$\text{cf}_{\gamma_c}(p1)$ and $\text{cf}_{\gamma_t}(p2)$



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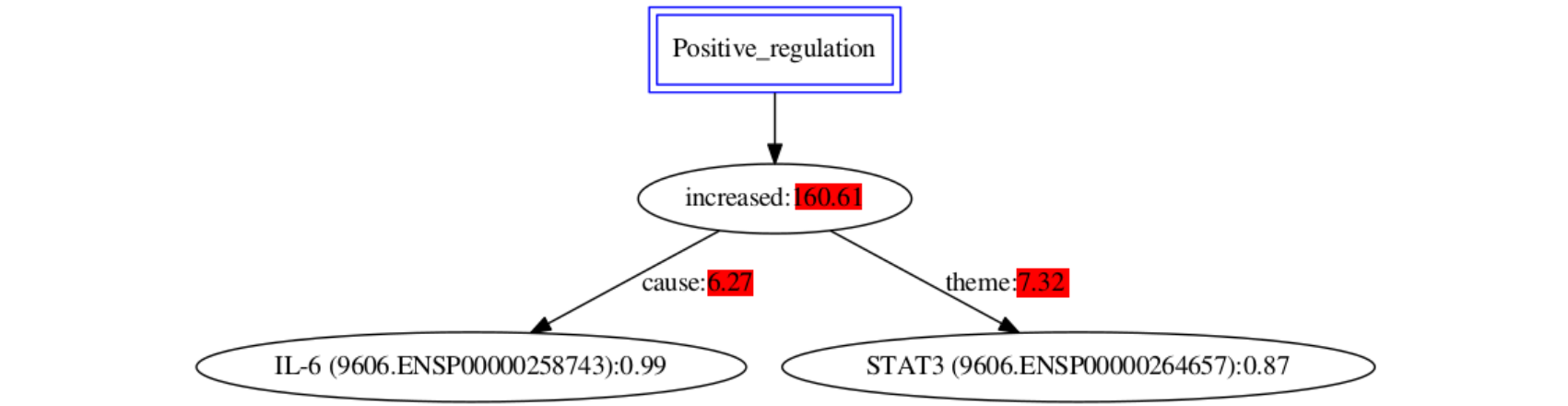
- ▷ TEES (SVM) margins for resp., events and their causes and themes:

$\text{cf}_c(p1)$ and $\text{cf}_t(p2)$ and $\text{cf}_{ev}(r)$



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Aggregation Methods

- Global confidence as a linear combination of component-wise confidences, namely, a (weighted) average:

$$\mathsf{cf}_{avg}^{(i)} = \frac{1}{5} \cdot \sum_{m} we_m \cdot \mathsf{cf}_{m}^{(i)}$$

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- Global confidence as a (weighted) product of component-wise confidences:

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- Weights $\bar{we} = (\mathsf{cf}_{ev}, \mathsf{cf}_c, \mathsf{cf}_t, \mathsf{cf}_{\gamma_t}, \mathsf{cf}_{\gamma_c})^T$ were learned from our silver data via logistic regression
- We considered unweighted versions of the aggregation models via unit weights $\bar{we} = (1, 1, 1, 1, 1)^T$

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Train and Test Datasets

- GNAT and GNorm give rise to two silver standards, heavily biased towards false relations ($> 80\%$)
- We oversampled positive relations and undersampled negative relations to derive two balanced training sets

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Train and Test Datasets

- GNAT and GNorm give rise to two silver standards, heavily biased towards false relations ($> 80\%$)
- We oversampled positive relations and undersampled negative relations to derive two balanced training sets
- For each silver standard, we extracted a test set (disjoint from training sets)

GNAT

Train: 2000 relations
(balanced via resampling)

Test: 1000 relations

GNorm

Train: 2000 relations
(balanced via resampling)

Test: 1000 relations

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Weight $\bar{we}$ Learning

- We learned logistic models from the training datasets

$$P(\ rel^{(i)} = \mathsf{True} \mid \bar{\mathsf{cf}}^{(i)}\ ) = (1 + \exp(-\sum_{m} \theta_m \cdot \mathsf{cf}_m^{(i)}))^{-1}$$

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- Cross-evaluated models over train/test pairs to choose best model

train dataset	test dataset	F_1
gnat_train	test_gnat	0.688
gnorm_train	test_gnat	0.658
gnat_train	**test_gnorm**	**0.766**
gnorm_train	test_gnorm	0.733

- Normalized AOD values to $[0, 1]$ to infer $\bar{we}$

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Correlation-based Evaluation of Aggregation Models

estimator	Kendall τ	p-value
cf_{prod} (unweig.)	0.041	0.127
cf_{prod}	0.041	0.127
cf_{avg} (unweig.)	0.032	0.210
cf_{avg}	**0.050**	**0.056**

- In **bold** the model with the highest τ value
- No test was statistically significant $\Rightarrow$ absence of correlation with linking judgments

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Confidence Feature Ranking - AOD

feature	deviance	p-value
cf_{ev}	6.200	0.013
$\mathbf{cf}_{t}$	**17.803**	$\mathbf{2.451 \cdot 10^{-05}}$
cf_{c}	4.858	0.028
cf_{γ_t}	2.370	0.124
$\mathbf{cf}_{\gamma_c}$	**22.667**	$\mathbf{1.926 \cdot 10^{-06}}$

- Analysis of deviance table for the best logistic model
- In **bold** the features with greater impact, and $p < 0.01$

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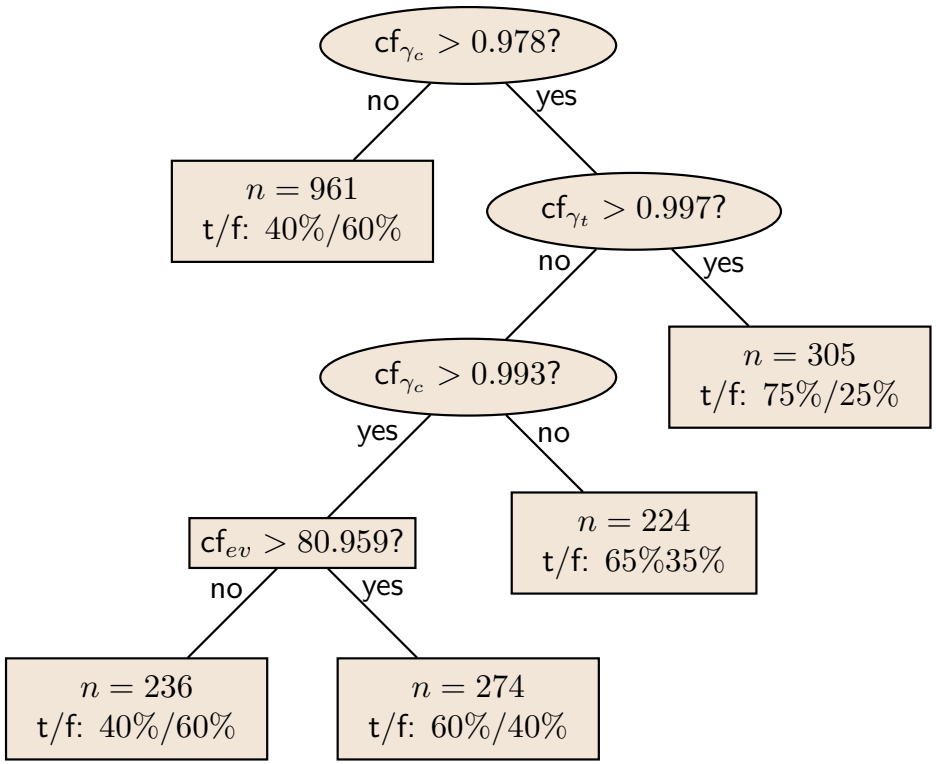
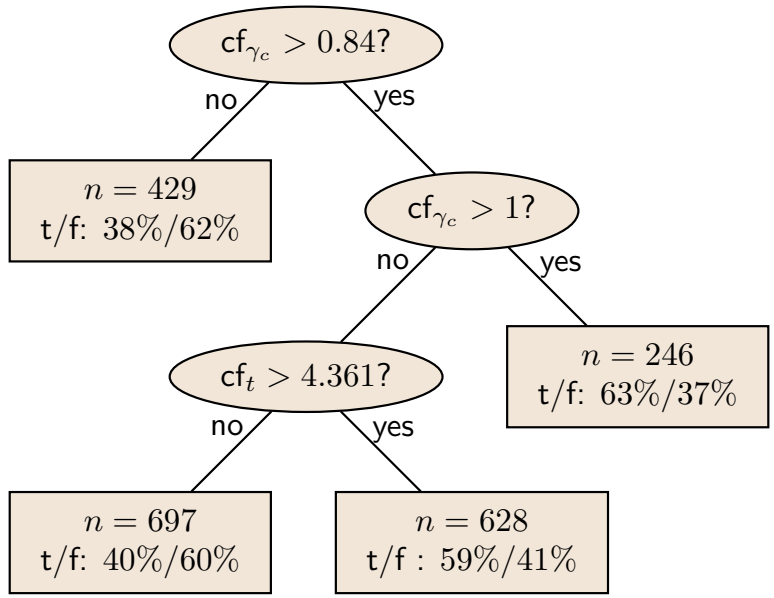
Confidence Feature Ranking - Decision Trees





- ▷ Right: J48 decision tree for the GNAT silver standard (training set)
- ▷ Left: J48 decision tree for the GNorm silver standard (training set)

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Conclusions

- The prediction confidence of some modules seems to influence positive decisions
- Confidence aggregation is not enough to define estimation models satisfying our criteria
- Confidence alone does not provide sufficient evidence to rank relations
- In this work the confidence of normalization was not fully addressed
- As further work we plan to focus on more complex evidence gathering methods

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Appendix: Gamma Probability

- BANNER is a CRF-based protein recognizer
- We can leverage Viterbi matrix backward and forward probabilities to derive that of a complete entity span
- CRF gamma probability [CM04] of entity $p = w_i, \ldots, w_t$ starting at position t in a text with BIO labels $(s_t, \ldots, s_{t+k})$, $s_i \in \{\mathsf{B}, \mathsf{I}\}$ can be defined as

$$\mathrm{cf}_{\gamma_t}(p) = \prod_{i=t}^{k} \gamma_i(s_i) = \frac{\alpha_i(s_i) \cdot \beta_i(s_i)}{P(w_0, \ldots, w_i | \Lambda)}$$

this characterizes the likelihood that a given span of MEDLINE tokens is indeed a protein!

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Appendix: Matching

We match to STRING typed interaction as follows:

1. a protein mention p to a canonical form *i.e.*, STRING protein unique identifiers (UIDs)

$$\mathrm{norm}_{\mathsf{N}}(p) = \begin{cases} \mathrm{gn}_{\mathsf{N}}(p), & \text{if } \mathrm{gn}_{\mathsf{N}}(p)\downarrow \\ \mathrm{lk}(p), & \text{if } \mathrm{gn}_{\mathsf{N}}(p)\uparrow,\ \mathrm{lk}(p)\downarrow \\ \mathsf{NA}, & \text{if } \mathrm{gn}_{\mathsf{N}}(p)\uparrow,\ \mathrm{lk}(p)\uparrow \end{cases}$$

2. a relation/event type r to a STRING interaction type

$$\mathrm{ev}(r) = \begin{cases} \{\mathrm{inhibitits}\}, & \text{if } r \text{ is a neg. reg.} \\ \{\mathrm{expresses},\ \mathrm{activates}\}, & \text{if } r \text{ is a pos. reg.} \\ \{\mathrm{expresses},\ \mathrm{activates}\} \cup \{\mathrm{inhibits}\}, & \text{if } r \text{ is a reg.} \end{cases}$$

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Appendix: Pipeline Statistics

	Unit	Count
	PMIDs	11773
	Relations	21169
Elements	Proteins	11726
	Events	864
	Causes	5694
	Themes	6032
Regul.	General	4425
	Positive	9830
	Negative	6484

- "Events" refers to event trigger words
- "Relations" refers to a relational structure connecting typed events to cause–theme protein pairs by TEES

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