Encoding Breast Cancer patients' medical pathways from reimbursement data using representation learning: a benchmark for clustering tasks

M. Guyomard, AD. Bouhnik, L. Tassy, R. Urena

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SESSTIM, Faculté des Sciences Médicales et Paramédicales, Aix-Marseille Université, Marseille, France

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Table of Contents

Electronical Health Records

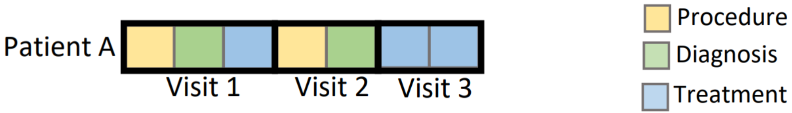

Figure: An example of EHR.

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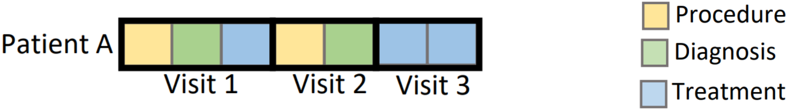

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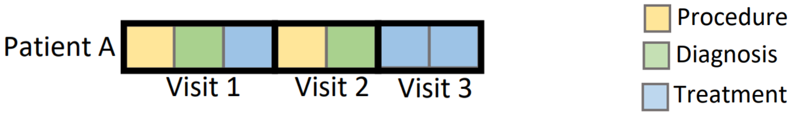
Challenges

- Temporal Dynamic: temporal dependencies;

Electronical Health Records



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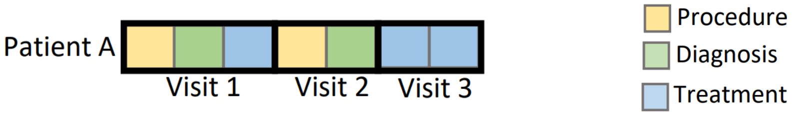
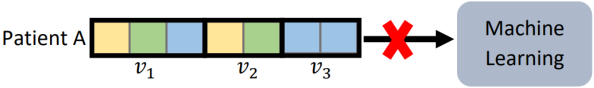


Figure: An example of EHR.

Challenges

- Temporal Dynamic: temporal dependencies;
- Multi-modality: a single visit contains multiple medical codes;
- Unstructured data;
- Highly dimensional: thousands of unique medical codes.

Representation Learning



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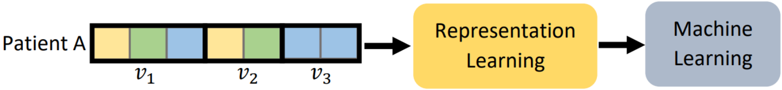

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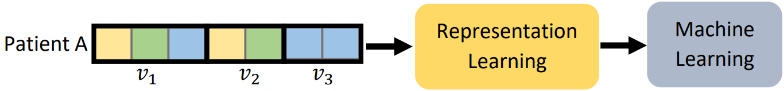

Definition (Representation Learning Task)

Patient Representation Learning task involves extracting meaningful information from the dense mathematical representation of a patient within an embedding space or latent space.

$$f_C : \mathbb{R}^L \to \mathbb{R}^m. \quad (1)$$

[Si, 2021], [Shickel, 2017]

Representation Learning

3 main Deep Learning strategies

- Natural Language Processing [Y. Choi, 2016], [E. Choi, 2016a-d]
- Autoencoders [Miotto, 2016], [Landi, 2020], [Baytas, 2017]
- Transformers [Li, 2020], [Rasmy, 2021]

Representation Learning

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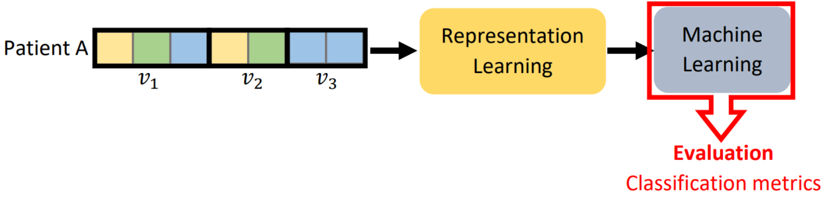
3 types of representation

- Medical Codes [Y. Choi, 2016], [E. Choi, 2016a,b,d], [Li, 2020], [Rasmy, 2021]
- Visit [E. Choi, 2016b-d], [Rasmy, 2021]
- Patient [E. Choi, 2016a], [Miotto, 2016], [Landi, 2020], [Baytas, 2017]

Representation Learning

Evaluation Method

Quality and **Reliability** are assessed through the performance resulting from the prediction task fitted on the embedding space by the mean of **classification metrics mostly**.



[Choi, 2016c], [Choi, 2016d], [Miotto, 2016]

Representation Learning

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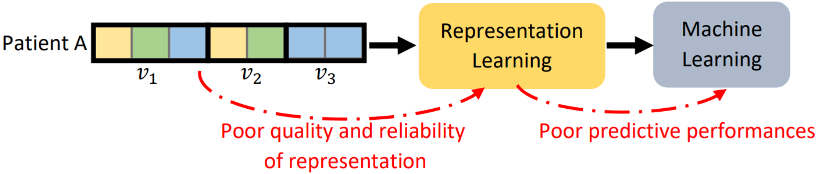

[Choi, 2016c], [Choi, 2016d], [Miotto, 2016]

Objectives

- Validation of state of the art Representation Learning tools
  - Quantify their accuracies
  - Analyse their reliability

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1. Fit general latent spaces (unsupervised tools)

Strategy / Types	NLP	Autoencoder	Transformer
Medical code	**Skip-Gram** [Y.Choi, 2016], [E.choi, 2016a] [E.Choi, 2016d]	-	*Out of scope* *Supervised Tools*
Visit	**Med2Vec** [E.Choi, 2016b], [E.choi, 2016c]	-	
Patient	-	**Deep Patient** [Miotto, 2016]	

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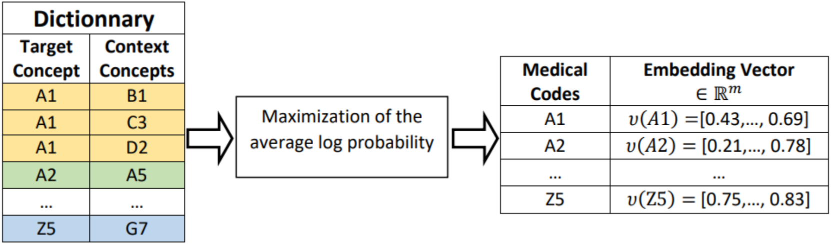
Visit	**Med2Vec** [E.Choi, 2016b], [E.choi, 2016c]	-	*Supervised Tools*
Patient	-	**Deep Patient** [Miotto, 2016]	

2. Clustering task

Table of Contents

Skip-Gram

- Natural Language Processing
- Medical Code Representation [Y.Choi, 2016]

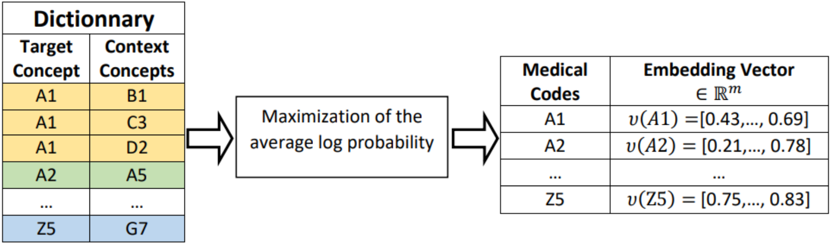


Schema of Skip-Gram.

**Theoretical information are provided in Appendix.*

Skip-Gram

- Natural Language Processing
- Medical Code Representation [Y.Choi, 2016]



Schema of Skip-Gram.

- Patient Representation: sum all the medical codes' embedded vectors appearing for a patient [E.Choi, 2016a].

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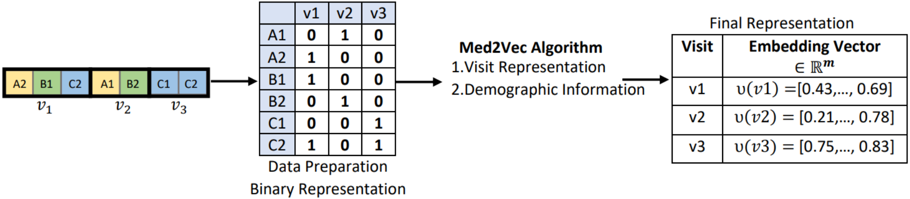
Med2Vec

- Multi-Layer Perceptron x Natural Language Processing
- Visit Representation [E.Choi, 2016b]



Schema of Med2Vec Algorithm.

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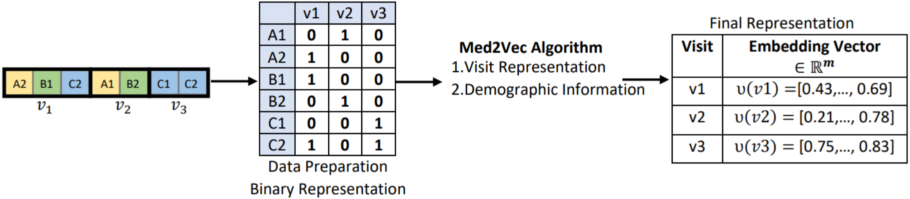

Schema of Med2Vec Algorithm.

- Patient Representation: sum all the visit representations.

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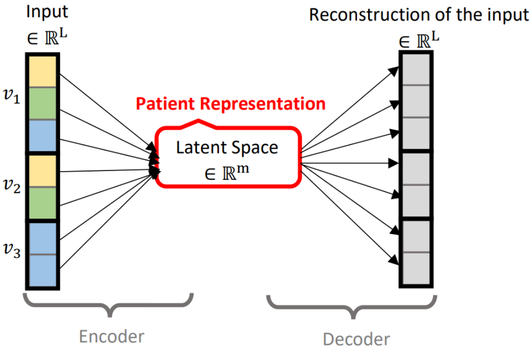
Deep Patient

- Denoising Stacked Autoencoder
- Patient Representation [Miotto, 2016b]



Schema of an Autoencoder.

**Theoretical information are provided in Appendix.*

Evaluation of Patient Representations

Clustering

- Clustering Methods
  1. K-means
  2. Gaussian Mixture Model

- Performance:
  1. Metric: silhouette score and Davies-Bouldin index
  2. Visualization: PCA and t-SNE

- Reliability: Chi-squared test on the clusters

Table of Contents

Settings

Data

- VICAN study [Bouhnik, 2015]
- Female patients with Breast Cancer
- 1,304,361 events, 6111 patients (213 visits in average)
- 3407 unique medical codes

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Need of Representation Learning Tools !

Settings

Learning

1. Representation Learning
   - Gridsearch of the hyperparameters
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Settings

Learning

1. Representation Learning
   - Gridsearch of the hyperparameters
   - Training of the hyperparameters
2. Clustering Task
   - Gridsearch of the optimal number of clusters
     - 10-folds CV
     - Maximization of the silhouette score on validation sample
   - Training of the clusters
     - 10-folds CV

Performance

	Training Sample		Validation Sample	
	Silhouette Score ↑	Davies-Bouldin ind. ↓	Silhouette Score ↑	Davies-Bouldin ind. ↓
Skip-Gram	0.6 (0.005)	0.34 (0.005)	0.6 (0.006)	0.344 (0.02)
Med2Vec	0.55 (0.004)	0.3 (0)	0.54 (0.006)	0.31 (0.005)
Deep Patient	0.98 (0)	0.13 (0.005)	0.98 (0.002)	0.13 (0.007)

Average metrics (std) over the 10-folds for the k-means clustering task.

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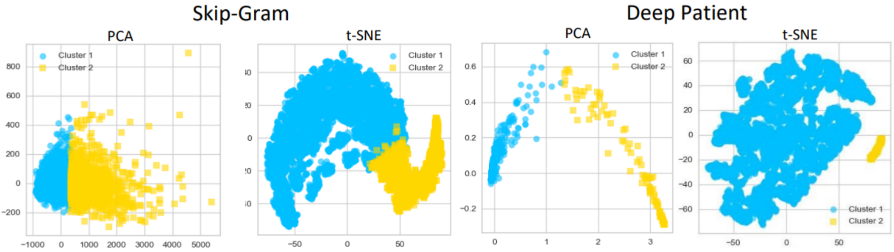

Visualization through PCA and t-SNE of the k-means clusters.

Clinical Reliability

	Skip-Gram	Med2Vec	Deep Patient
Partial Mastectomy	<0.05 (0)	0.07 (0.04)	<0.05 (0.02)
Mastectomy	<0.05 (0)	0.37 (0.13)	<0.05 (0.01)
Axillary Surgery	<0.05 (0)	<0.05 (0)	0.7 (0.23)
Chemotherapy Y/N	<0.05 (0)	<0.05 (0)	0.5 (0.27)
Chemotherapy Setting	<0.05 (0)	<0.05 (0)	<0.05 (0.03)
Chemotherapy Regimen	<0.05 (0)	<0.05 (0)	0.1 (0.22)
Targeted Therapy Y/N	0.87 (0.12)	<0.05 (0)	0.6 (0.31)
Targeted Therapy Setting	0.7 (0.01)	<0.05 (0)	0.7 (0.2)
Targeted therapy Regimen	0.34 (0.12)	<0.05 (0)	0.6 (0.31)
Radiotherapy Y/N	<0.05 (0.03)	<0.05 (0)	0.4 (0.23)
Radiotherapy Setting	<0.05 (0.21)	<0.05 (0)	<0.05 (0)
Endocrine Therapy Y/N	<0.05 (0.01)	<0.05 (0)	0.2 (0.2)
Endocrine Therapy Setting	<0.05 (0.03)	<0.05 (0)	<0.05 (0)
Endocrine Therapy Regimen	<0.05 (0)	<0.05 (0)	<0.05 (0)
BC Sub Type	<0.05 (0)	<0.05 (0)	0.2 (0.12)
Nodal status	<0.05 (0.01)	<0.05 (0)	0.06 (0.07)
Metastatic	<0.05 (0)	<0.05 (0)	<0.05 (0)

Average (std) of Chi-squared test p-values between the k-means clusters and the BC characteristics obtained on 5 *random sub samples.*

Table of Contents

Conclusion

- Assessing the quality of RL tools only on empirical metrics is not sufficient;
- Unsupervised study: methods with higher value of silhouette score does not necessarily align with patients' clinical reality;
- Need of evaluation metrics assessing both the performance and the consistency of patient RL tools.

Conclusion

- Assessing the quality of RL tools only on empirical metrics is not sufficient;
- Unsupervised study: methods with higher value of silhouette score does not necessarily align with patients' clinical reality;
- Need of evaluation metrics assessing both the performance and the consistency of patient RL tools.

Future works

1. Develop an empirical metric to evaluate both performance and reliability of RL tools;
2. Develop an intrinsically interpretable RL tool.

References

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Table of Contents

EHR

Notation

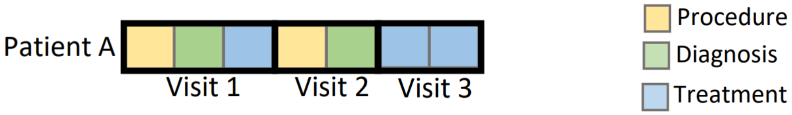

Figure: An example of EHR.

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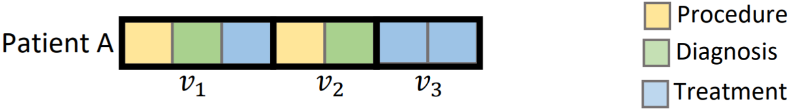

Figure: An example of EHR.

- $V = \{v_1, \ldots, v_n\}$;

$n = 3$

EHR

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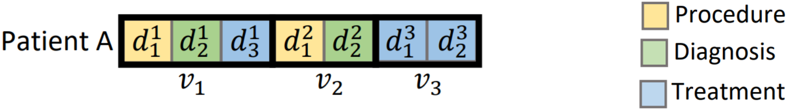


Figure: An example of EHR.

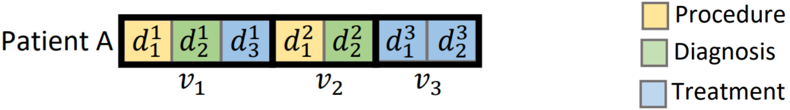
- $V = \{v_1, \ldots, v_n\}$;
- j-th visit: $v_j = \{d_1^j, d_2^j, \ldots, d_{k_j}^j\}$;

$n = 3$

$k_1 = 3, \ k_2 = k_3 = 2$

EHR

Notation



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- $v_j \subseteq \mathcal{C}, \quad \mathcal{C} = \{c_1, \ldots, c_{|\mathcal{C}|}\}$;

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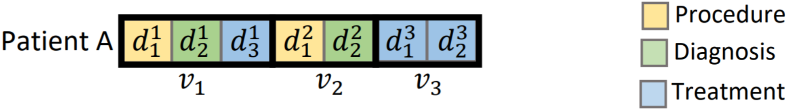

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- $v_j \subseteq \mathcal{C}, \quad \mathcal{C} = \{c_1, \dots, c_{|\mathcal{C}|}\}$;
- $L = \sum_{t=1}^{n} |v_t|$.

$n = 3$

$k_1 = 3, \; k_2 = k_3 = 2$

$L = 7$

Skip-Gram Algorithm

[Y.Choi, 2016]

- Medical representation: $\nu(c)$

$$\frac{1}{L}\sum_{l=1}^{L}\sum_{-w\leq j\leq w, j\neq 0}\log p(c_{t+j}|c_t), \tag{2}$$

with w representing the size of the context window and

$$p(c_{t+j}|c_t) = \frac{\exp(\nu(c_{t+j})^T\nu(c_t))}{\sum_{c=1}^{|\mathcal{C}|}\exp(\nu(c)^T\nu(c_t))}. \tag{3}$$

- Patient representation [E.Choi, 2016a]

$$e^{SG} = \sum_{t=1}^{n}\sum_{j=1}^{k_t}\nu(d_j^t) \in \mathbb{R}^m. \tag{4}$$

Med2Vec Algorithm

[E.Choi, 2016b]

- Visit representation
  1. Intermediate visit representation given a visit $\bar{v}_t \in \{0,1\}^{|\mathcal{C}|}$

$$u_t = \phi(W_c \bar{v}_t + b_c) \in \mathbb{R}^{m'}, \tag{5}$$

with $\phi(x) = \max\{0, x\}$, $W_c \in \mathbb{R}^{m' \times |\mathcal{C}|}$ and $b_c \in \mathbb{R}^{m'}$.

  2. Concatenation with demographic information $d_t \in \mathbb{R}^d$

$$\nu_t = \phi(W_v [u_t, d_t] + b_v) \in \mathbb{R}^m, \tag{6}$$

with $W_v \in \mathbb{R}^{m \times (m' \times d)}$ and $b_v \in \mathbb{R}^m$.

- Patient representation

$$e^{Med} = \sum_{t=1}^{n} \nu_t \in \mathbb{R}^m. \tag{7}$$

Deep Patient Algorithm

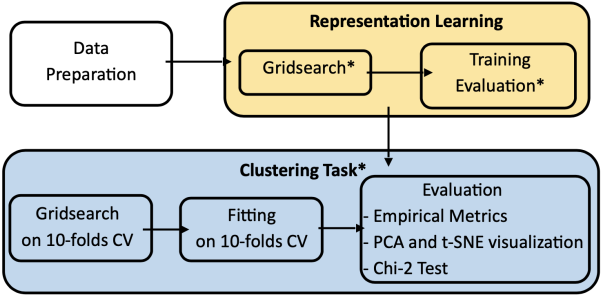
[Miotto, 2016b]

- Patient representation
- Denoising Stacked Autoencoder
  1. Masking Noise algorithm on the input $\tilde{V} \in \mathbb{R}^L$.
  2. Encoder
  $$y = f_\theta(\tilde{V}) = s(W\tilde{V} + b), \tag{8}$$
  with $s(\cdot)$ a non-linear transformation, $W \in \mathbb{R}^{m \times L}$ and $b \in \mathbb{R}^m$.
  3. Decoder
  $$z = g_{\theta'}(y) = s(W'y + b'), \tag{9}$$
  with $W' \in \mathbb{R}^{L \times m}$ and $b' \in \mathbb{R}^m$.

Data

- VICAN study [Bouhnik, 2015], a national survey on French cancer survivors
- Inclusion Criteria of patients : (i) Female, (ii) diagnosed with Breast Cancer, (iii) who have reached the age of majority and (iv) have undergone surgery
- Exclusion criteria of patients : affected by another form of cancer
- **1,304,361 events**, **6111 patients** with an average of 213 visits (min 4, max 1111)
- 3,407 medical codes at first
  - 2447 diagnosis (ICD-10 Classification)
  - 1977 procedures (Anatomical Therapeutic Chemical, ATC)
  - 1043 medications (Classification Commune des Actes Médicaux, CCAM)
- Grouping of the medical codes based on their hierarchical structure [Y.Choi, 2016], [E.Choi, 2016a]
  - 2 digits
  - It remains **3,407 unique medical codes**

Experimental Settings



Experimental settings. **The complementary tools provided on Github.*

Experimental Settings

	Epoch	Learning Rate	Tested Parameters
Skip-Gram	40	1e-3	Window Size: $\{\mathbf{5}, 10\}$ # False neighbors: $\{\mathbf{5}, 10\}$ Embedding Dim: $\{10, 20, \mathbf{50}, 100\}$
Med2Vec	5	1e-6	Temporary Dim: $\{20, \mathbf{50}, 100\}$ Final Dim: $\{\mathbf{20}, 50, 100\}$ Window Size: $\{\mathbf{1}, 3, 5\}$
Deep Patient	100	1e-3	Embedding Dim: $\{10, \mathbf{20}, 50, 100\}$ # Layers: $\{1, \mathbf{3}, 5\}$ Corruption Rate: $\{\mathbf{0.01}, 0.05, 0.01\}$

Settings for the Gridsearch step, optimal parameters are in bold.

Performance results

	Training Sample		Validation Sample	
	Silhouette Score	Davies-Bouldin ind.	Silhouette Score	Davies-Bouldin ind.
K-means				
SG	0.6 (0.005)	0.34 (0.005)	0.6 (0.006)	0.344 (0.02)
M2V	0.55 (0.004)	0.3 (0)	0.54 (0.006)	0.31 (0.005)
DP	0.98 (0)	0.13 (0.005)	0.98 (0 002)	0.13 (0.007)
Gaussian Mixture Model				
SG	0.37 (0.01)	0.52 (0.008)	0.35 (0.01)	0.52 (0.01)
M2V	0.06 (0.06)	1.1 (0.4)	0.3 (0.09)	0.8 (0.2)
DP	0.9 (0)	0.62 (0.01)	0.9 (0.005)	0.6 (0.09)

Average (standard deviation) results obtained on clustering over the $10-$*folds CV, for Skip-Gram (SG), Med2Vec (M2V) and Deep Patient (DP) algorithms.*