Prediction of the next medication order to assist prescription verification by pharmacists in a health care center

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A project of URPP – Unité de Recherche en Pratique Pharmaceutique

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Disclaimer

We are pharmacists, not computer scientists

Outline

- Health system pharmacy
- Our data
- Our project
- Previous work
- Methods and results
- Perspectives
- Questions and discussion

Our data

CHU Sainte-Justine

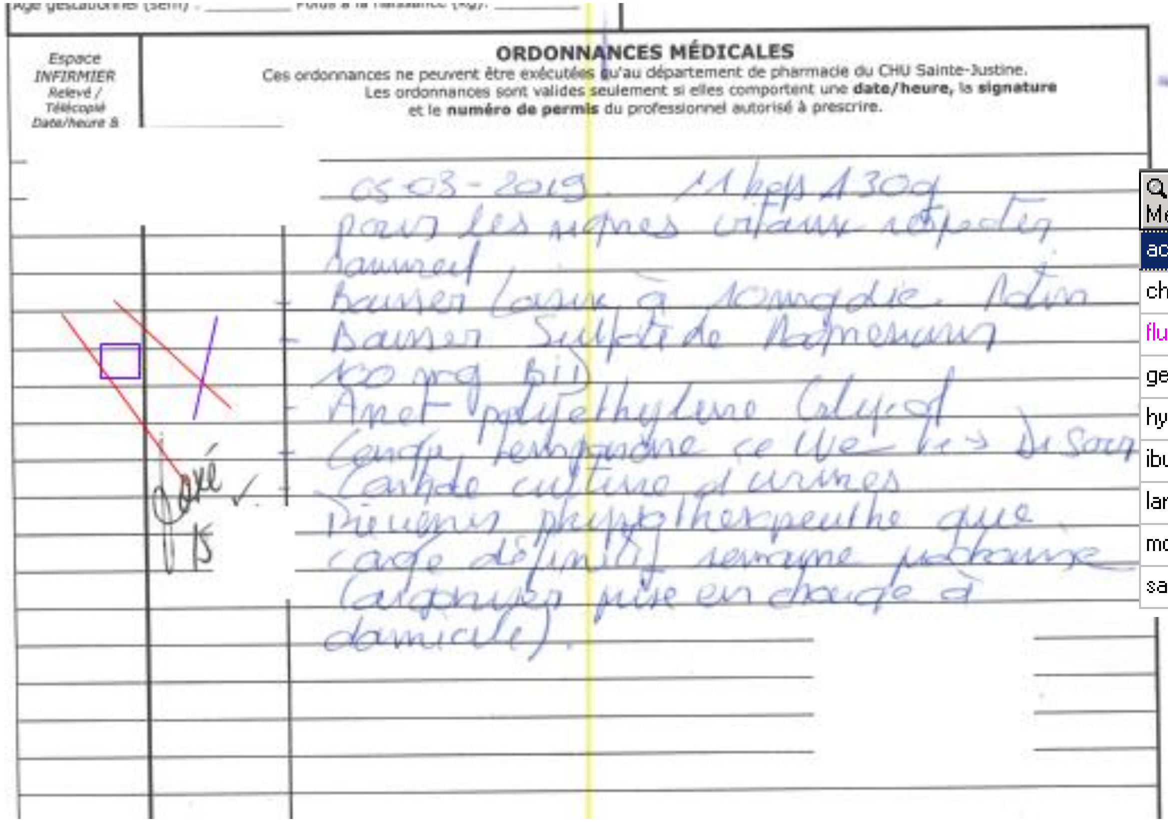
- 500 bed, mother-child tertiary care academic hospital center

- Pharmacy departement in 2018
  - > 130 employees, students and residents, 36 pharmacists
  - 201 730 orders entered (552 per day)
  - 10 611 medication reconciliations on patient admission
  - 7798 instances of patient counseling
  - 6759 hours spent rounding patients with MDs

- Unité de recherche en pratique pharmaceutique
  - 17 years

Medication order data

Orders



Médicament	Dose	Voie	Posologie	Début validité	Fin validité
acétaminophène 80 mg/mL so	200 mg	po/ir	q4p	19-02-25 11:20	21-11-20 16:00
cholécalciférol (vit D3) 400 ui/mL ser so fab	400 ui	po9	die	19-03-01 14:56	21-11-24 16:00
fluticasone 125 mcg/dose 60 doses inh buc	125 mcg	inb1	bid	19-02-20 16:11	21-11-15 16:00
gelee de petrole +huile minerale 3.5g tube ong oph	0	ouong	dieh	19-02-20 17:02	21-11-15 16:00
hydroxypropylmethylcellulose 0.5% 15mL bout gt oph	1 gtte	ougtt	bid	19-02-20 17:04	21-11-15 16:00
ibuprofene 20 mg/mL so	138 mg	po5	q8p	19-02-25 18:37	21-11-20 16:00
lansoprazole 15 mg co la (désintégration rapide)	7.5 mg	po20	bid	19-02-22 12:20	21-11-17 16:00
mometasone 50 mcg dose 140 doses vap nas	50 mcg	vap3	bid	19-03-05 08:34	21-11-28 16:00
salbutamol 100 mcg/dose 200 doses inh buc	200 mcg	inb1	q46p	19-03-01 14:57	21-11-24 16:00

Medication order data

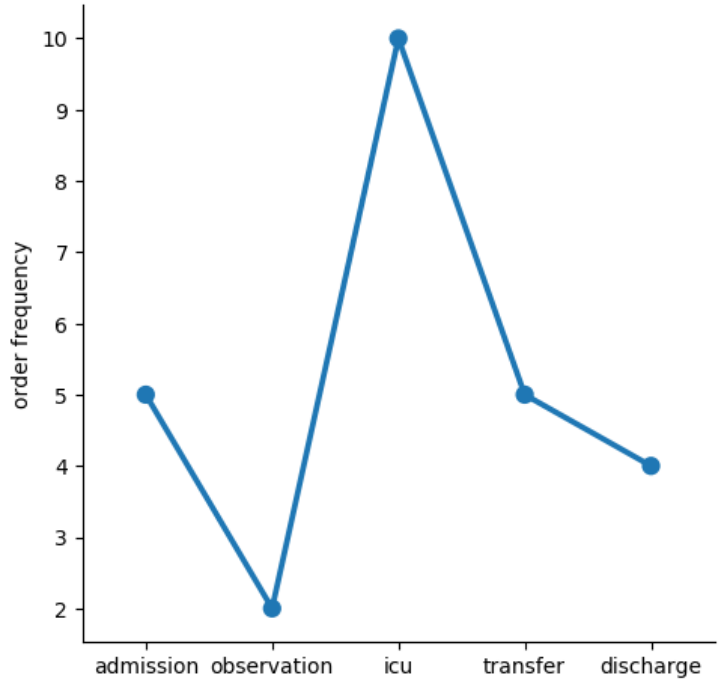
- Medication orders may refer to
  - Starting a new drug ***(our project will focus on this type of order)***
  - Modifying an existing order (ex: modifying the dose)
  - Stopping a drug

Medication order data

- Medication order:
  - « Acetaminophen 200 mg PO/IR q4h PRN »

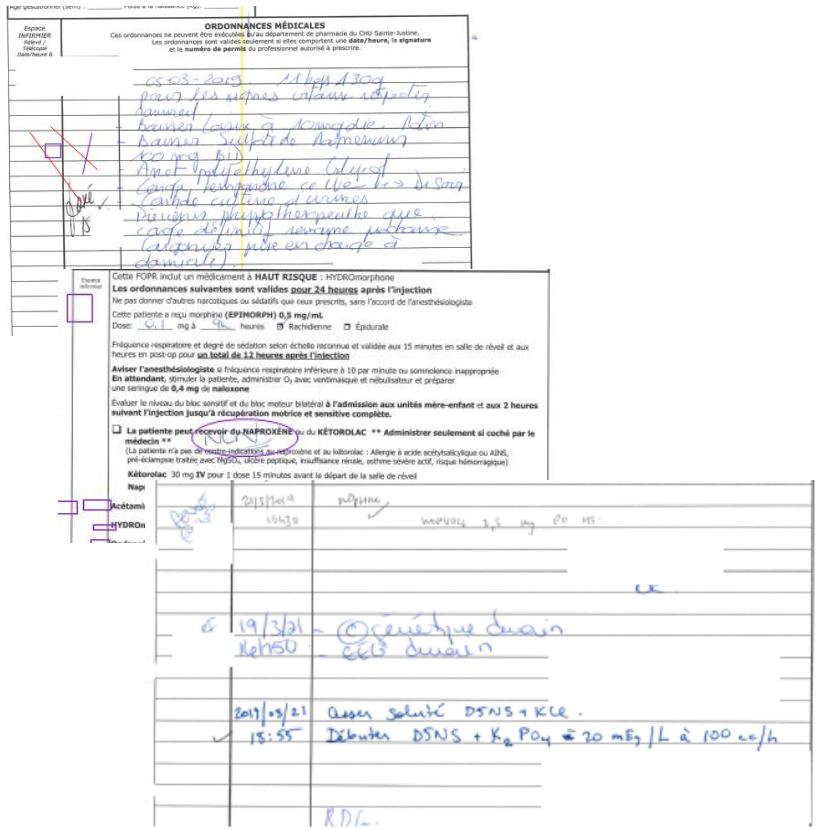
Médicament	Dose	Voie	Posologie	Début validité	Fin validité
acétaminophène 80 mg/mL so	200 mg	po/ir	q4p	19-02-25 11:20	21-11-20 16:00

  - Orders are entered into a pharmacy information system which supports drug preparation and distribution, as well as medication administration by nurses (eMAR) and other systems
  - The frequency of orders varies during hospitalization
    - From 0-2 orders/day (observation) to multiple orders per hour (icu)
    - Acute care: scale of orders per day to orders per hour depending on the department and patient context



Medication order data

Time



Sequence of orders

É..	V..	P..	P..	L...	# Ordo.	Médicament	Dose	Voie	Posologie	Début validité	Fin validité	Dernière opération	Dosage
	✓				398	baclofen 10 mg/mL ser so fab	5 mg	sto9	die	19-02-27 11:28	19-03-15 13:48	SU	5
	✓				399	melatonine 3 mg caps	9 mg	po2	die	19-03-01 19:57	19-03-01 20:39	SU	3
	✓				400	melatonine 3 mg/mL ser so fab	9 mg	sto9	die	19-03-01 20:39	21-11-24 16:00	RE	9
	✓				401	acétaminophène 80 mg/mL so	260 mg	po5	q4	19-03-09 19:10	19-03-11 17:00	SU	80
	✓				402	acétaminophène 80 mg/mL so	345 mg	po5	q4p	19-03-11 21:07	21-12-04 16:00	NO	80
	✓				403	baclofen 10 mg/mL ser so fab	10 mg	po9	bid	19-03-15 13:48	21-12-08 16:00	RE	10
	✓				404	ibuprofene 200 mg co	200 mg	po1	q6p	19-03-15 13:49	19-03-21 17:26	SU	200
	✓				405	tetrahydrocannabinol+cannabidiol 90 doses vap buc	1 vap	vap1	chevet	19-03-15 15:17	21-12-08 16:00	NO	90
	✓				406	polyETHYLene glycol en ass. 15% 30 g tube gel	0	nas5	p	19-03-19 17:26	19-03-21 08:15	SU	0
	✓				407	héparine * 10 unités/mL* 3 mL SER inj HR	25 ui	iv1	diep	19-03-21 08:08	21-12-14 16:00	NO	30
	✓				408	polyETHYLene glycol en ass. 15% 30 g tube gel	0	nas5	q1p	19-03-21 08:15	21-12-14 16:00	NO	0
	✓				409	hydrocortisone (base) 1% cr	0	top2	bid	19-03-21 08:22	19-03-21 11:28	SU	0
	✓				410	lidocaine liposomale 4% 30 g tube cr	0	top1	diep	19-03-21 11:23	19-03-21 11:24	SU	0
	✓				411	lidocaine liposomale 4% 5 g tube cr	0	top1	diep	19-03-21 11:24	21-12-14 16:00	NO	0
	✓				412	hydrocortisone (base) 1% cr	0	top2	bidp	19-03-21 11:27	21-12-14 16:00	NO	0
	✓				413	diclofenac 1.16% 100 g tube gel	0 tube	top1	q8p	19-03-21 11:30	21-12-14 16:00	NO	0
	✓				414	lidocaine 2% + chlohexidine 0.05 % 6 mL ser gel	0	top1	diep	19-03-21 11:48	19-03-21 12:24	SU	0
	✓				415	HYDROmorphone 2 mg/mL ser inj fab (F:0140) HR	0.5 mg	iv1	pro59	19-03-21 12:20	19-03-21 16:20	SU	0.5
	✓				416	lidocaine 2% chlorhexidine 0.05% ser top 6 ml	0	top1	diep	19-03-21 12:24	21-12-14 16:00	NO	0
	✓				417	LORazepam 4 mg/mL 1 mL fio inj	2.5 mg	iv1	p	19-03-21 13:05	19-03-21 16:24	SU	4
	✓				418	fentaNYL 25 mcg/heure timbre HR	1 timbr	top8	q3j-tif	19-03-21 13:45	19-03-21 14:24	SU	1
	✓				419	HYDROmorphone 2 mg/mL ser inj fab (F:0140) HR	0.7 mg	iv1	pro59	19-03-21 16:21	21-12-14 16:00	RP	0.7
	✓				420	LORazepam 4 mg/mL 1 mL fio inj	3 mg	iv1	p	19-03-21 16:24	19-03-21 17:06	SU	4
	✓				421	LORazepam 4 mg/mL 1 mL fio inj	3 mg	iv1	p	19-03-21 17:05	21-12-14 16:00	RP	4
	✓				422	ibuprofene 200 mg co	200 mg	po1	q6	19-03-21 17:26	21-12-14 16:00	NO	200

Our project

Predicting the next medication order

Our project

- Pharmacist verification of drug order entry
  - Final step before drug preparation and administration
  - Pharmacist needs to catch any problem that has made it up to this point
    - Administrative error (wrong patient !)
    - Prescription error (MD wrote the wrong thing)
    - Pharmacological problems (drug interactions, contra-indication, etc.)
    - Order entry error

Ordre des Pharmaciens du Québec. Standards de pratique. https://www.opq.org/doc/media/290_38_fr-ca_0_standards_pratique_vf.pdf ISBN 978-2922438-76-5

Our project

- Pharmacists want to concentrate on clinical tasks
- Verifying every single order we process is necessary to catch errors
  (and it's required by law)

Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: Prescribing and transcribing-2016. Am J Health Syst Pharm 2017;74:1336-52.
Schneider PJ, Pedersen CA, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: Dispensing and administration-2017. Am J Health Syst Pharm 2018;75-1203-26.
Bussières JF, Tanguay C, Bonnici A. Perspective québécoise et canadienne de la pratique pharmaceutique en établissement de santé pour 2016-2017. Pharmactuel 2018;51:105-42.

Our project

- Pharmacists get distracted while verifying
  - Interruption decreases chance of detecting error
    - OR 0.149, CI 0.042-0.525
- There are *a lot* of orders to verify
  - Chances of making an error increase as the number of orders increases
    - OR 1.4 per 1000 orders; 95% CI 1.06-1.7

Orders per shift	Error rate
100-200	2.6
201-400	8.4
>400	11.1

Thibault M, Porteils C, Goulois S et al. The Impact of Phone Interruptions on the Quality of Simulated Medication Order Validation Using Eye Tracking: A Pilot Study. Simul Healthc 2018. doi: 10.1097/SIH.0000000000000350
Gorbach C, Blanton L, Lukawski BA, Varkey AC, Pitman EP, Garey KW. Frequency and risk factors for medication errors by pharmacists during order verification in a tertiary care medical center. Am J Health Syst Pharm 2015;72:1471-4.

Our project

Long term: automate *(at least part of)* drug order verification

Short term: focus pharmacist attention on potential problems

Objective: identify orders deviating from usual patterns

Can we predict the next medication order ?

Similar work

Woods, Mulherin, Flynn et al.

J Am Med Inform Assoc 2014, doi: 10.1136/amiajnl-2013-002008

- 961 bed tertiary care academic hospital, Chicago, 2012
- Atypical order alert
  - Pop-up alert based on « order sentences », no other context
  - Statistical frequency of « order sentences » for 5 low variability drugs
- Pre-post study
  - Pre: 13 164 orders of 77 sentences
  - Post: 18 019 orders of 63 sentences
- 68 alerts
  - 74% overriden
  - 41% potentially averted problems
  - Specificity 41-90%

Wright, Wright, McCoy et al.

J Biomed Inform 2014, doi: 10.1016/j.jbi.2014.09.003

- Outpatients: 161 497 patients of an insurer in Texas, 2008-2011
- 10 classes, 37 drugs used for diabetes
- Sequential pattern mining (cSPADE) to predict pattern of drugs and classes followed by a patient over time
- 90% train, 10% test
- Top 3 accuracy for next class : 89.1-90.5%
- Top 3 accuracy for next drug: 64.1%

Helagson

MIT Master's degree 2008, http://hdl.handle.net/1721.1/43873

- Inpatients and outpatients from hospitals in Nordjylland, Denmark
- CPOE « pick lists »
- 2004-2008: 1,059,750 prescriptions from 80,177 encounters
- Active ingredient only: 978 classes
- K-Nearest Neighbors, 1st order Markov chains, LCS, WFBS, SVMs
- 20 000 orders random sample and 5-fold cross-validation (K-Fold)

- WFBS: Top 20 accuracy 70.2%, recall 95%

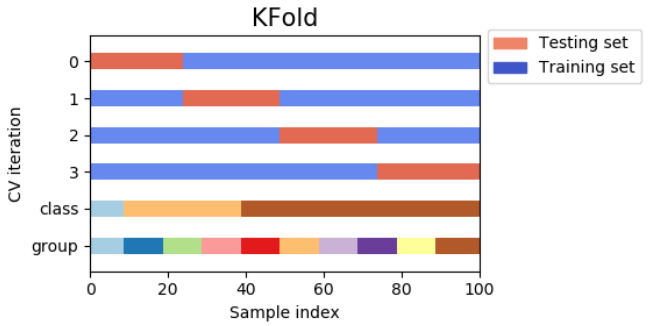


Image taken from the Scikit-learn user guide. https://scikit-learn.org/stable/modules/cross_validation.html#cross-validation

Chen, Goldstein, Asch et al.

J Am Med Inform Assoc 2016, doi: 10.1093/jamia/ocw136

- Stanford University Hospital STRIDE data for 2013
- LDA topic modeling of clinical orders in the first 24 hours
  - Medication (active ingredient and route)
  - Labs (binned as low, normal or high)
  - Admission diagnosis ICD9 codes (3 digit hierarchy)
  - Other clinical orders (diet, nursing, etc.)
- Filtered infrequent orders: 1512 items selected
- Training set: 10 655 patients
- Validation set: 4820 patients

Chen, Goldstein, Asch et al. (cont'd)

J Am Med Inform Assoc 2016, doi: 10.1093/jamia/ocw136

- At every instance of order set use, simulate orders from LDA model
  - Order sets: groups of orders that exist as a defined entity in CPOE

- Best model: 32 topics
- Prediction of orders in the next 24 hours:
  - Order sets: ROC-AUC 0.81, precision 16%, recall 35%
  - LDA model: ROC-AUC 0.90, precision 25%, recall 47%

Methods and results

Word2vec, doc2vec, neural network

Methods

- Access to the data was authorized (DAMU/DSP)

- Data extraction
  - Training set: 2013-2017 (5 years)
    - 1 022 272 orders from 96,590 encounters, mean ± sd of 11.3 ± 22.7 orders per encounter
    - 3145 drugs
  - Test set: Jan-July 2018
    - 95 310 orders from 9,978 encounters, mean ± sd of 10.2 15.3 orders per encounter
    - 1843 drugs

- Anonymized patient encounter identifier, departement
- Drug (identification, AHFS class)
- Date and time of order entry and discontinuation

Methods

- Data was cleaned up
  - Test patients
  - Test entries
  - Entry errors

- Preprocessing
  - Label: each individual order
  - Features
    - Sequence of drug orders leading to label
    - Active drugs and classes at the time the label was prescribed
  - Sorted by time: by hospitalization start date then order start date and time

Methods

- Drug identification
  - Active ingredient
    - « Acétaminophène »
  - Database entry
    - « acétaminophène 80 mg/mL so »
    - « acétaminophène 325 mg co »
    - « acétaminophène 325 mg co (gmo) »
    - Acetaminophen has 19 database entries used in different contexts
    - Database entry models route up to a certain point

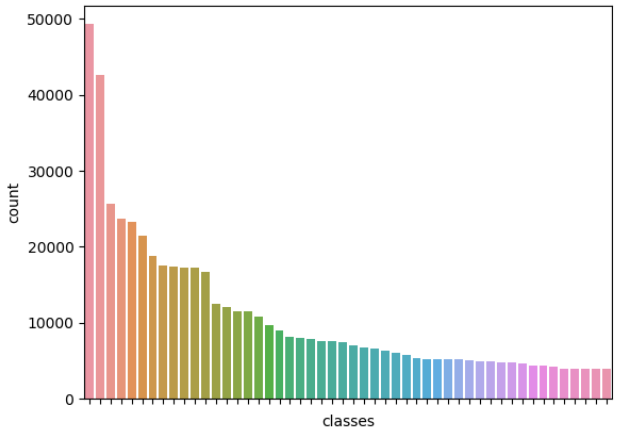
We want to predict the database entry, not the active ingredient

Results

- Baseline
  - Dummy classifier: top 1, top 10 and top 30 drugs by frequency

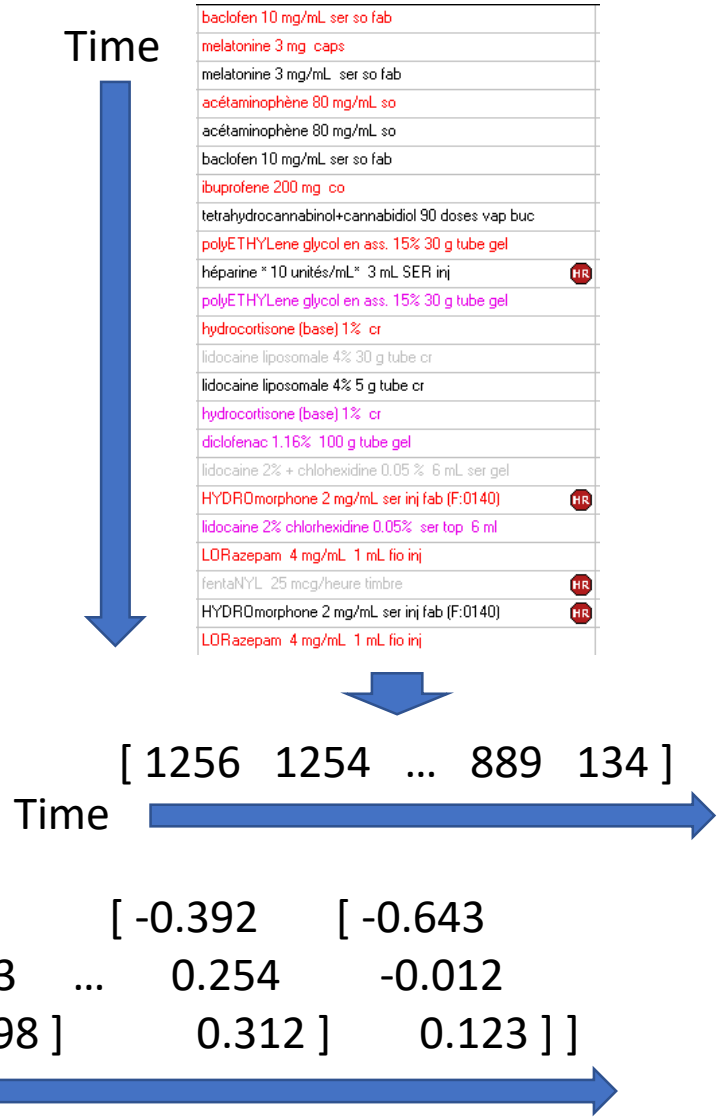
	2013-2017 set	2018 set
Top 1	4.5%	5.1%
Top 10	23.6%	21.0%
Top 30	41.1%	44.5%

Targets distribution in 2013-2017 set, top 50



Methods

- >3000 classes: embedding
- Drugs are related to one another like words
  - The sequence of drugs carries meaning
  - The clinical context influences the choice of drugs
- Sequence of orders: **word2vec**
- Entire profile: **doc2vec**



Methods

The sequence of all orders is interesting…

But what about orders that got discontinued along the way ?

What about drug characteristics?

What about patient characteristics ?

- State of patient profile at time of label prescription: **multi-hot vector**
  - Active drugs [1 0 1 0 … 1 1 0 0]
  - AHFS Class (4 level hierarchical class for drugs, similar to ICD codes)

    Ex: ***cefazolin*** **-> 08 : 12 : 06 . 04**

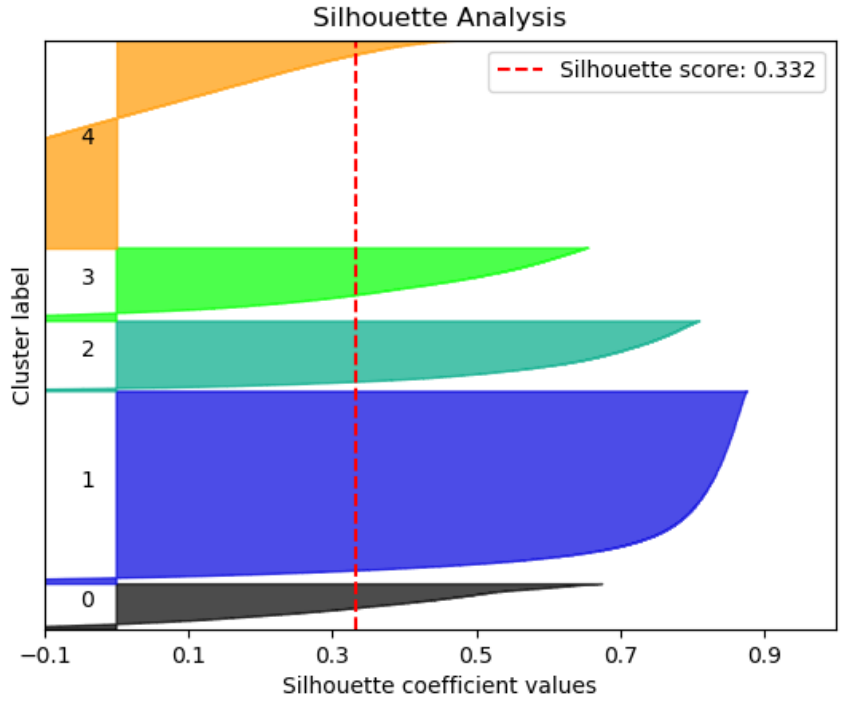
    Anti-infective agents — Anti-bacterials — Cephalosporins — First generation cephalosporins
  - Department

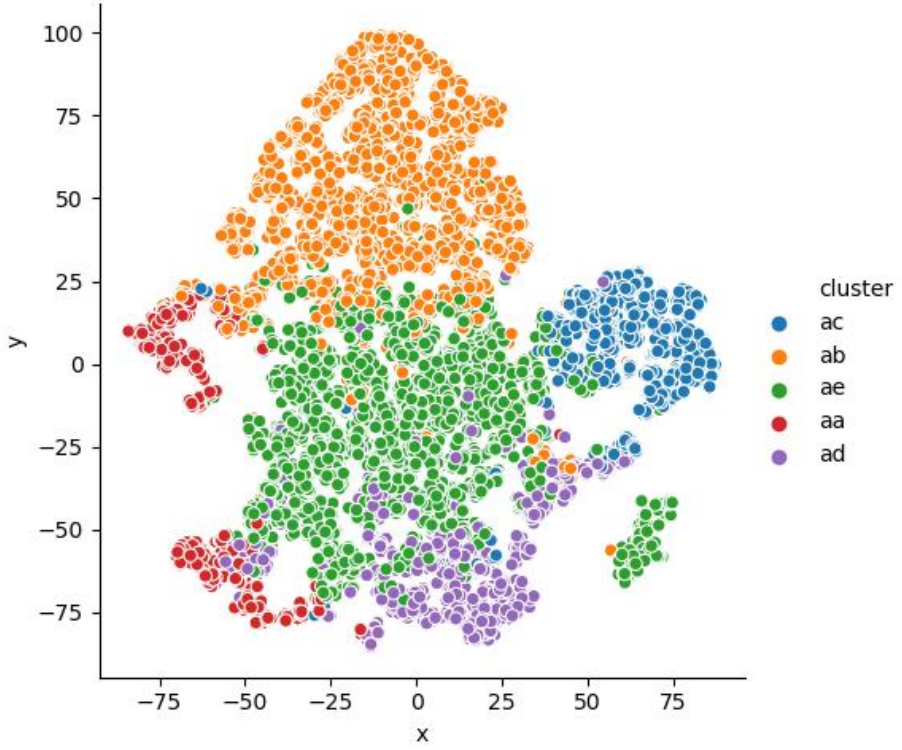
Methods

- Initial word2vec and doc2vec optimization alone
- Mini-batch K-means clustering using random search then grid search
- Based on optimizing silhouette score of resulting clusters
- Best hyperparameters were used when training neural network
- Done with Gensim and Scikit-learn

Results

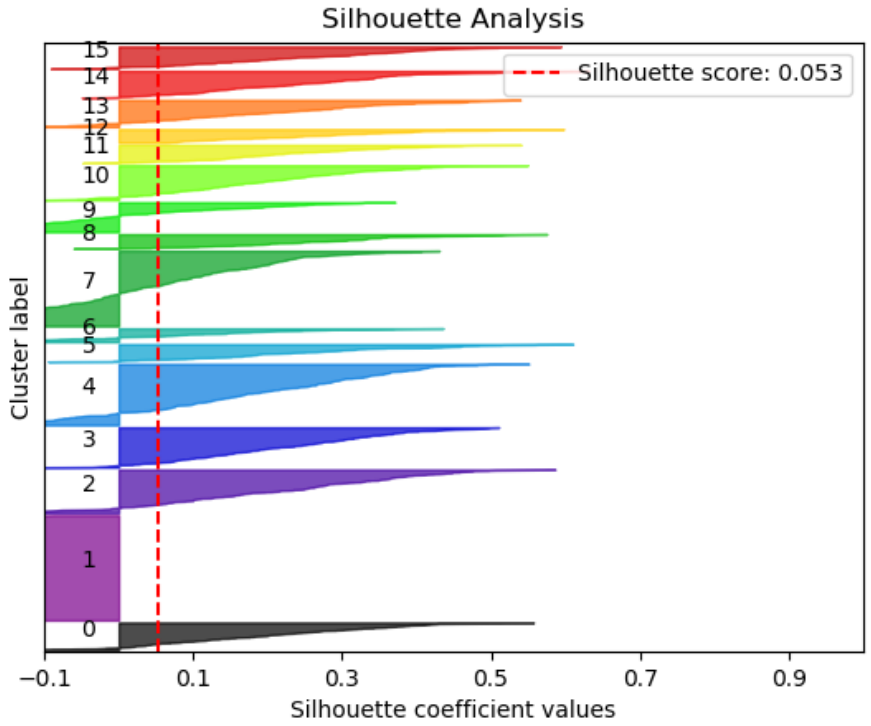
doc2vec

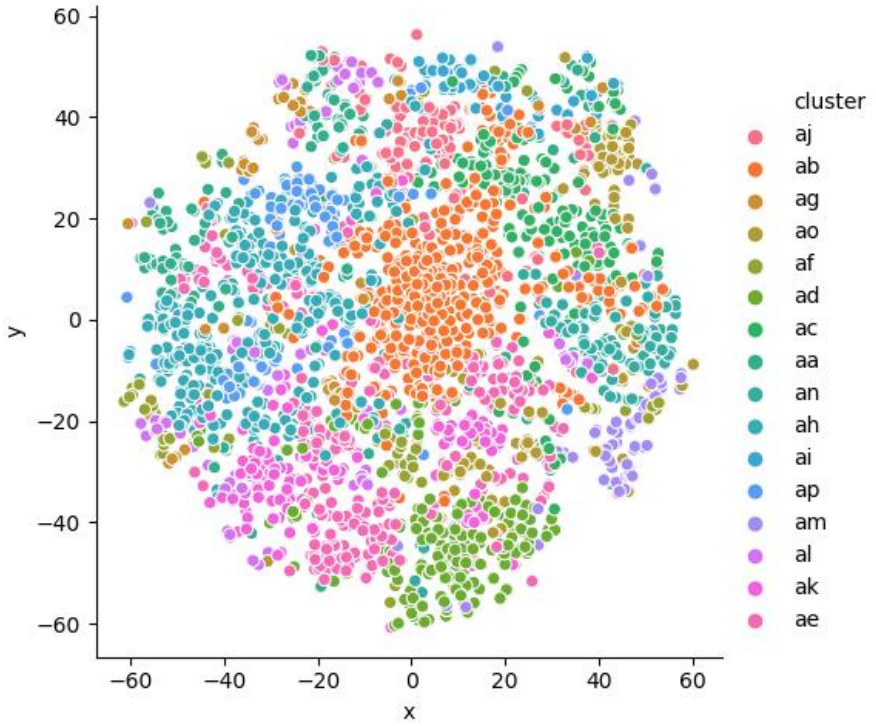




Results

word2vec





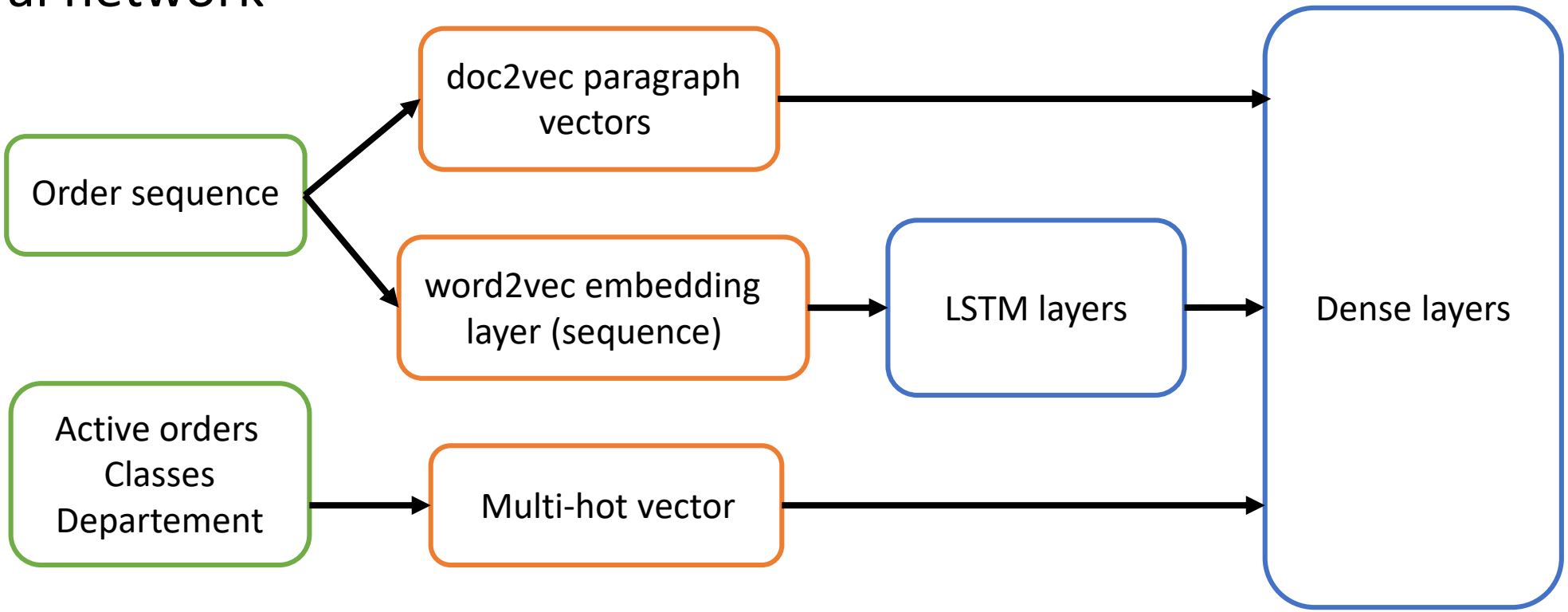
Results

3D t-SNE projection of word2vec drug embeddings

Tensorflow embedding projector

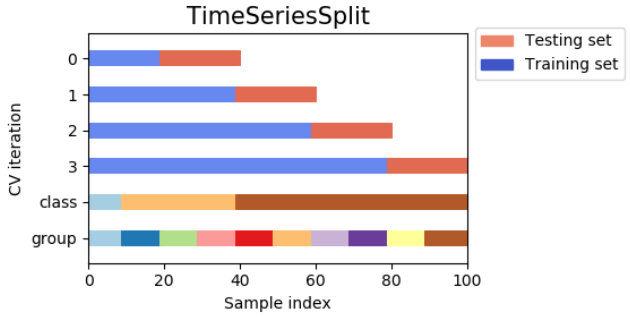
Methods

Neural network



Methods

- Tests for model size and configuration
- Tests for features
- Tests for handling word2vec embeddings
- Learning curve: behaviour with increasing data volume

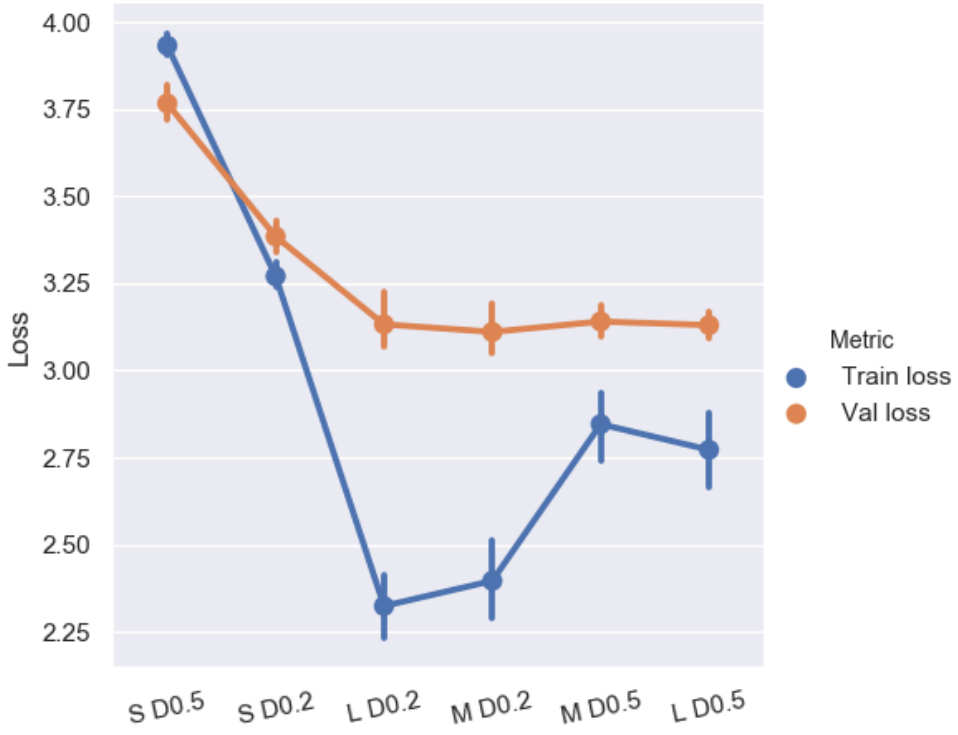


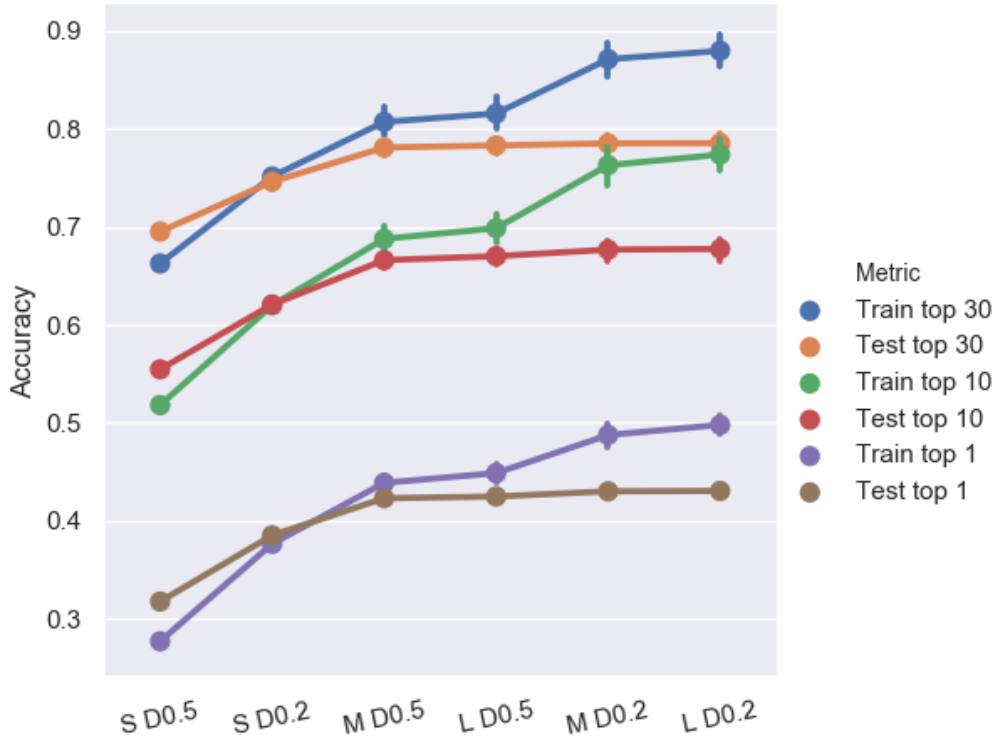
- 5-fold cross-validation with time series split
- Loss: categorical crossentropy
- Optimizer: Adam
- Early stopping when validation loss decrease < 0.005 over 3 epochs
- Done with Keras with Tensorflow backend and Scikit-learn

Image taken from the Scikit-learn user guide. https://scikit-learn.org/stable/modules/cross_validation.html#cross-validation

Results

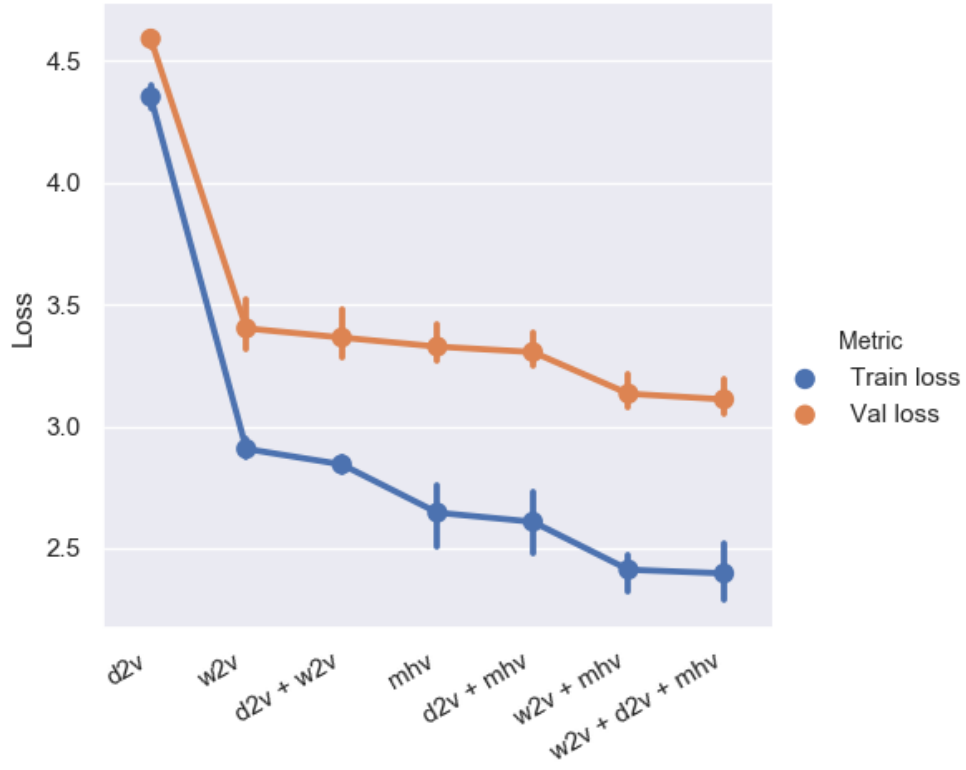
Network size and configuration

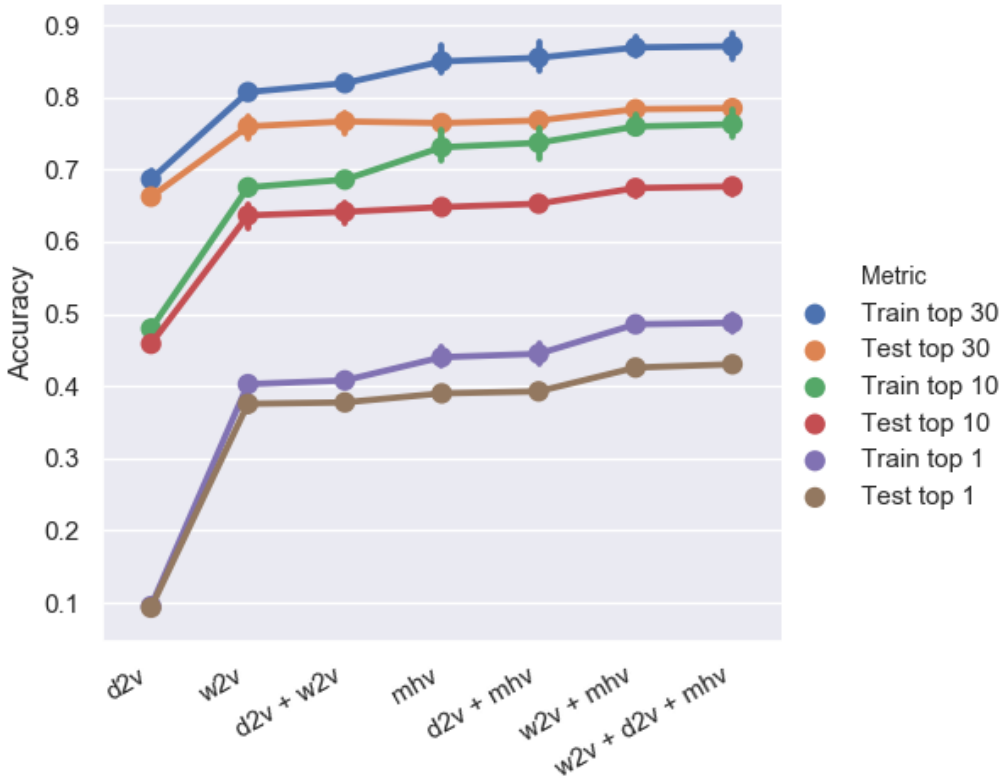




Results

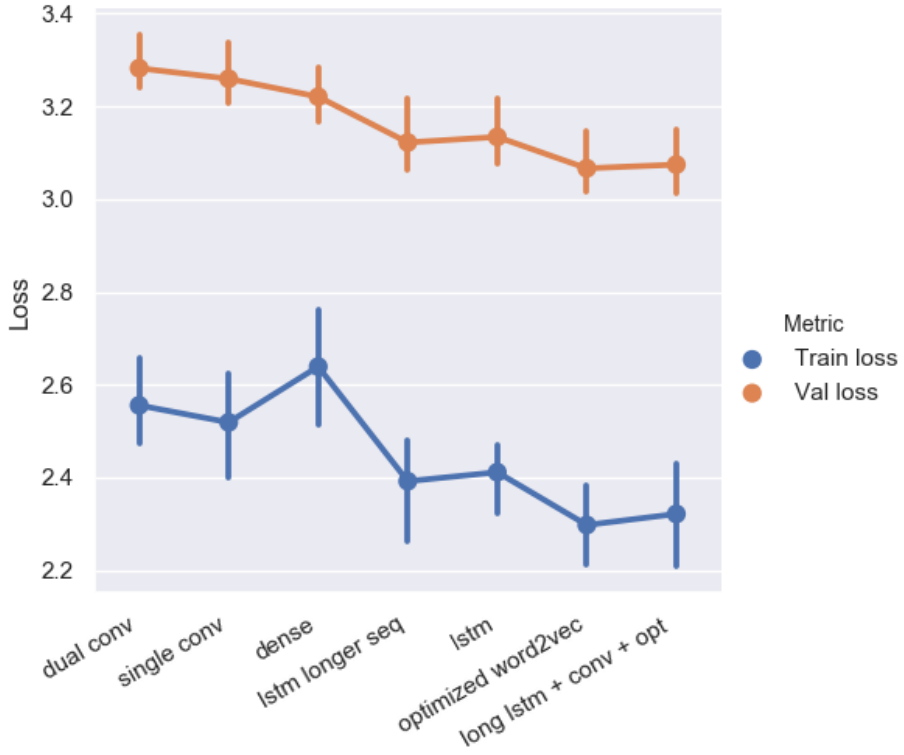
Model features

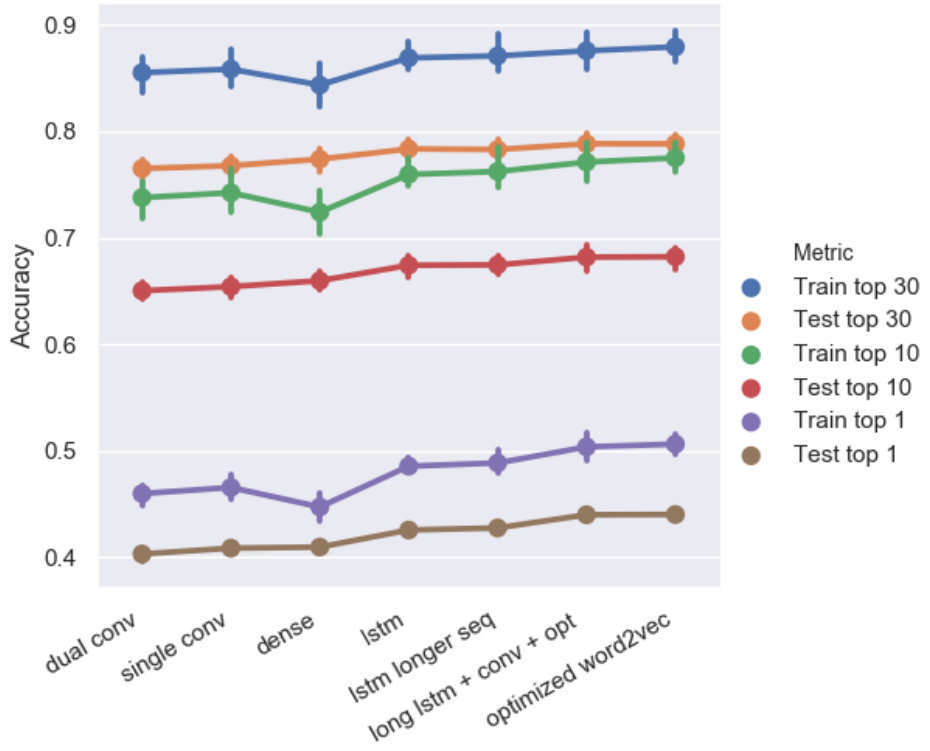




Results

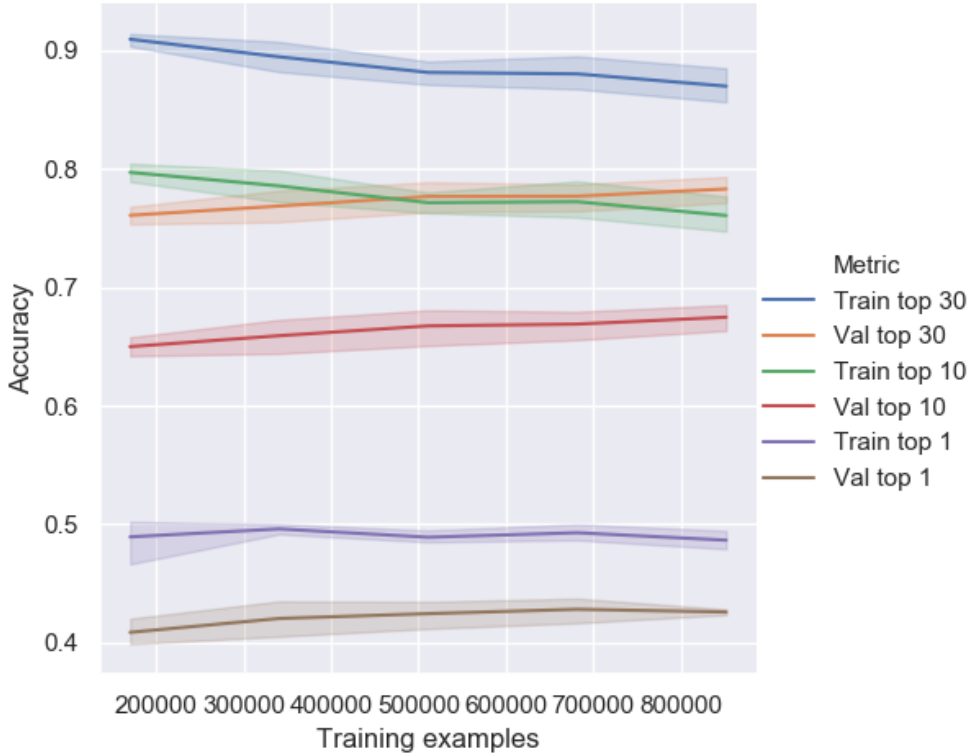
Handling word2vec embeddings



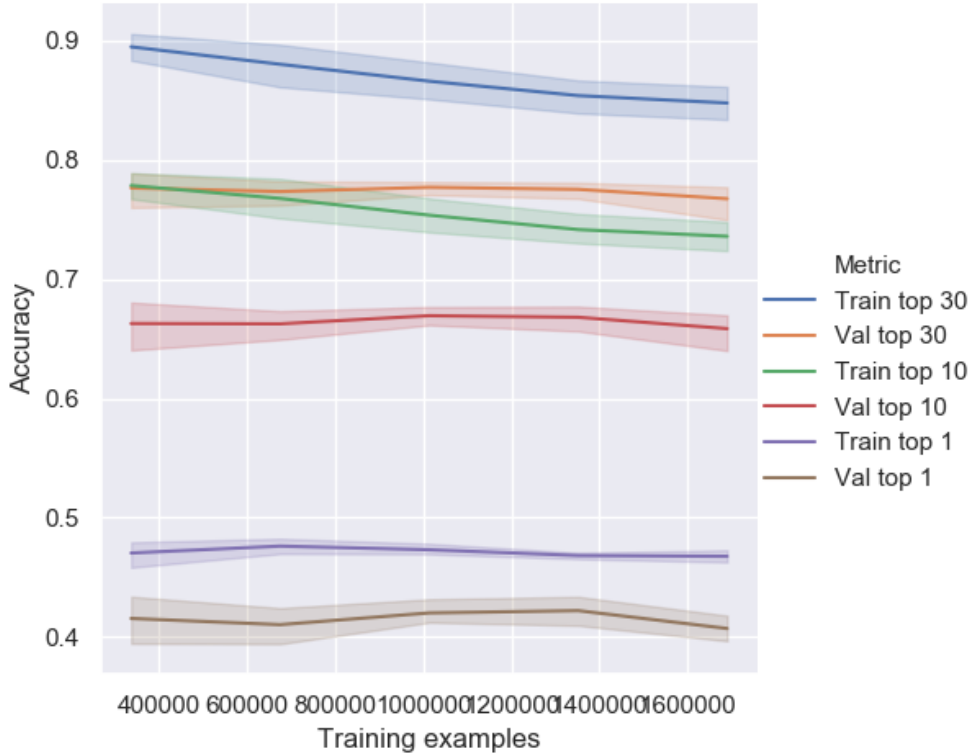


Results

Learning curve



5 years



10 years

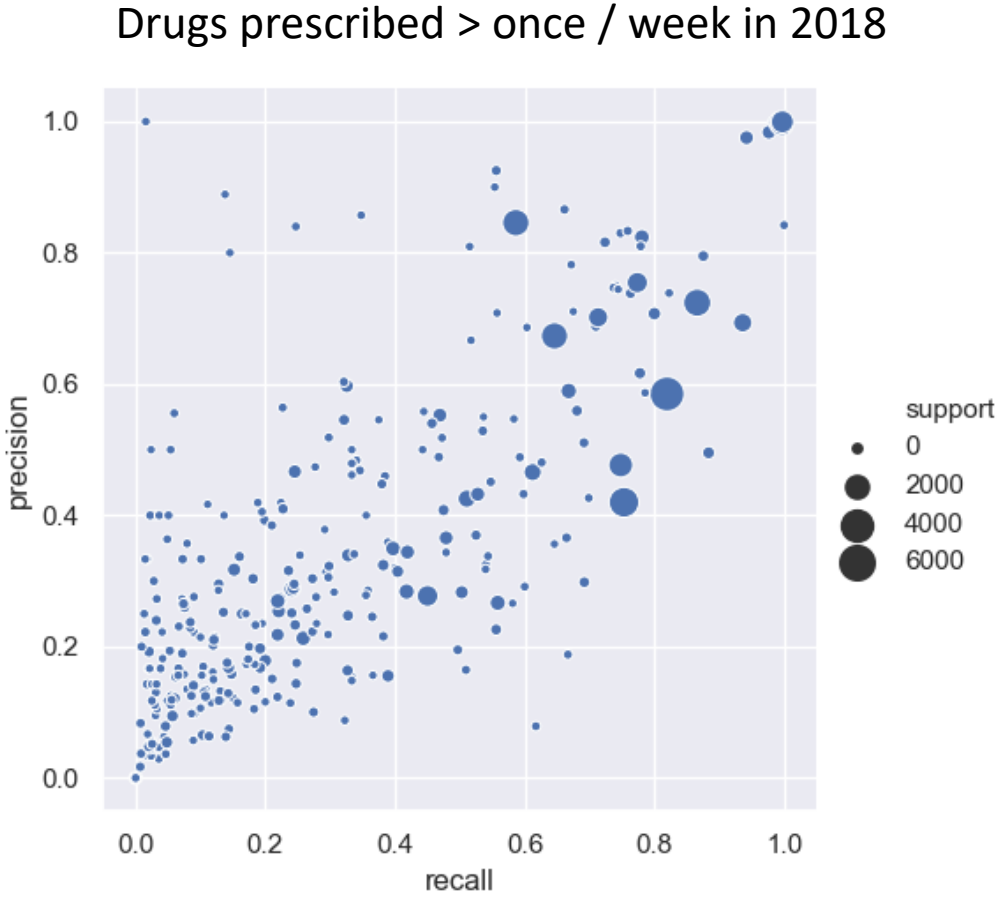
Chen JH, Alagappan M, Goldstein MK, Asch SM, Altman RB. Decaying relevance of clinical data towards future decisions in data-driven inpatient clinical order sets. Int J Med Inform 2017;102:71-9.

Results

- Evaluation on 2018 test set
  - Top 1 accuracy: 44.4%
  - Top 10 accuracy: 69.9%
  - Top 30 accuracy: 80.4%

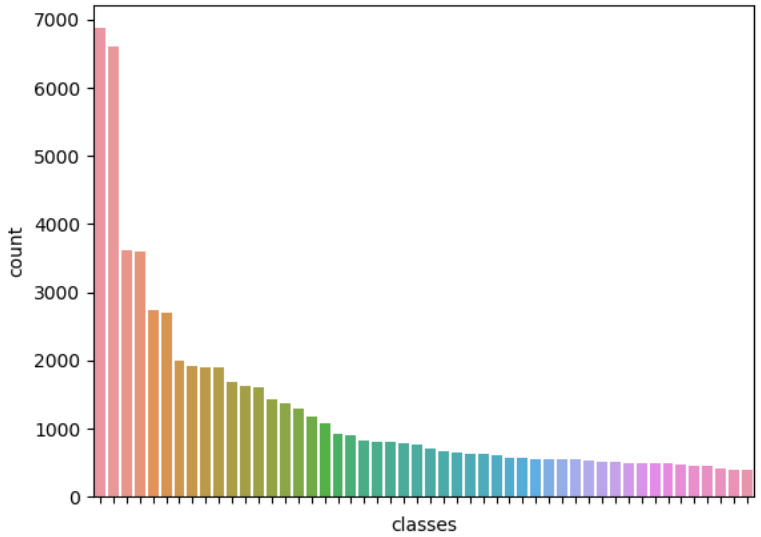
  - Weighted average precision: 0.415
  - Weighted average recall: 0.444

  - Weighted average AUROC: 0.959



Results

- Evaluation on 2018 test set
  - 1176 drugs predicted
  - Predictions distribution:



Prototype

Deployed on pharmacy intranet

Methods

- Survey sent to all pharmacists in departement (n=35)
- 20 orders to validate with same information as model
  - 16 actual orders (real, anonymized patient data)
  - 4 simulated entry errors
  - Balanced departements, prediction ranks
- Objective: rate each order on a 1 to 4 scale
  - 1 – Routine order
  - 4 – Extremely unusual order
- Bin prediction ranks based on pharmacist rating
- Evaluate if there was a correlation

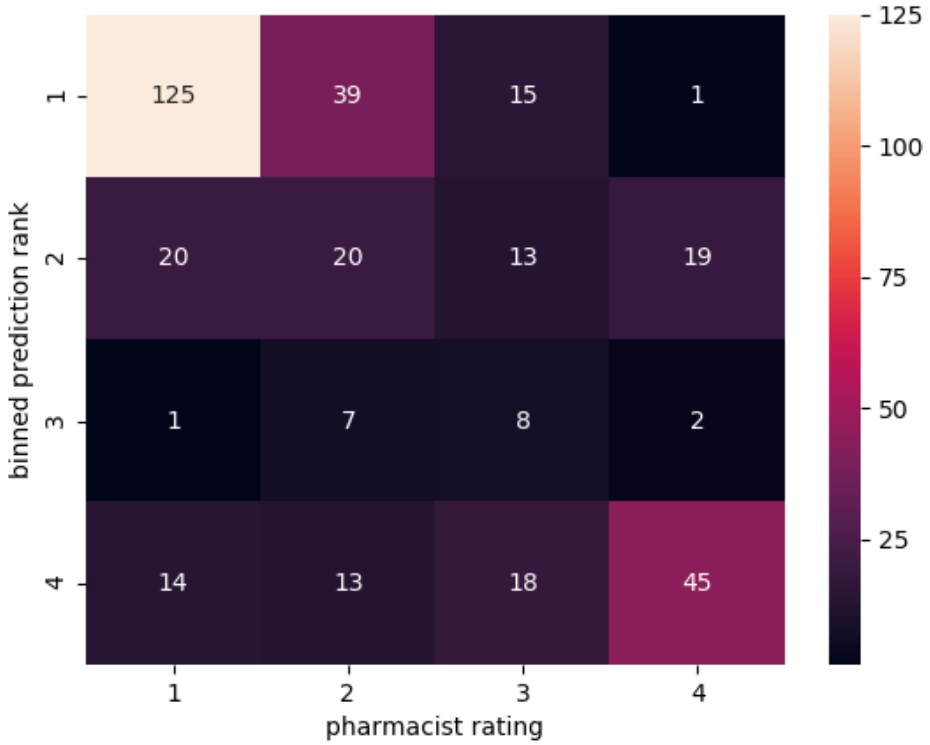
Results

- 18 pharmacists answered (51.4%)
- Inter-rater agreement between pharmacists was poor
  - Fleiss Kappa: 0.283 (March 25 talk: experts don't agree !)
- Prediction ranks binned into groups
  - Binning thresholds adjusted to maximize accuracy

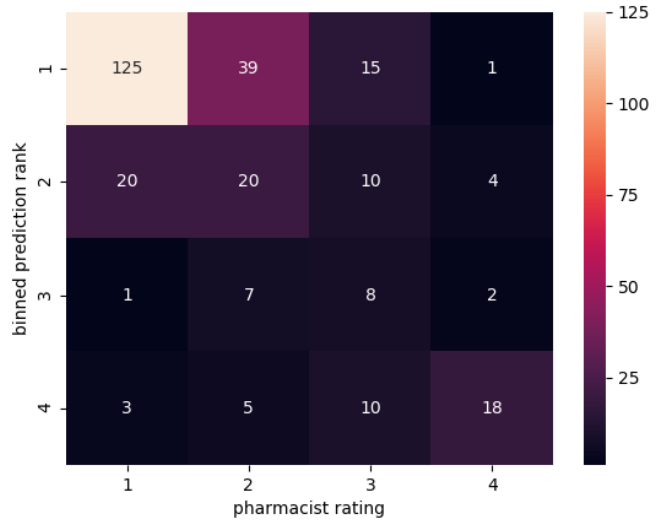
	Accuracy	Cohen Kappa	Precision (weighted avg)	Recall (weighted avg)
Overall	0.550	0.338	0.617	0.550
Real orders (excl. errors, n=16)	0.594	0.334	0.679	0.594
Experienced pharmacists (n=9)	0.550	0.345	0.623	0.550

Results

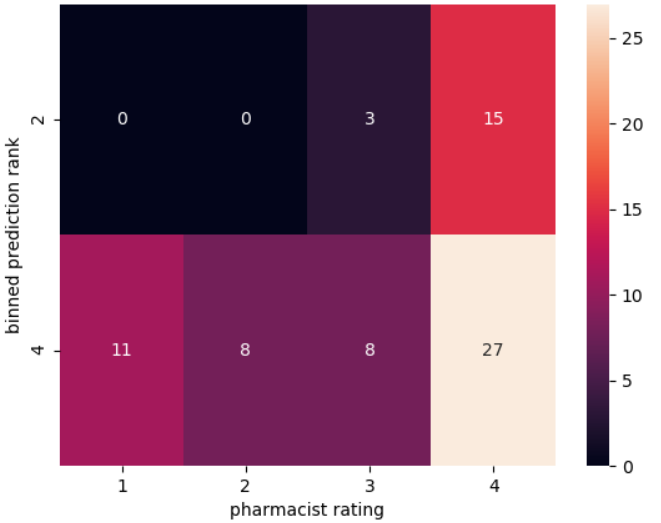
All



Real



Errors



Perspectives

Perspectives

- Results look promising
  - Modeling prescription patterns with acceptable accuracy appears feasible
  - Correlation with pharmacist ratings difficult to establish

- Limits
  - Exportability challenge: database entries for drugs are not standardized !
  - Single center: no data on how prescription patterns vary between centers
    - Applying as-is to MIMIC is not really feasible
      - Time resolution to the day, not minutes
      - Date shifting consistent for a patient, but not between patients
      - Pharmacological classes not in the dataset, matching is a challenge
  - Clinical advantage must be demonstrated

Perspectives

- Next steps
  - Optimize the approach, refine how predictions are used
  - Add clinical data beyond order sequence (difficult in Quebec !)
  - Validate the same model with data from another center and more
  - Validate usefulness during order validation
  - Validate usefulness in clinical practice

Thank you !

Questions ?