rijksuniversiteit groningen

Network analysis of IADB dataset

Implementing a drug prescription network to evaluate psychiatric polypharmacy

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A bit about me

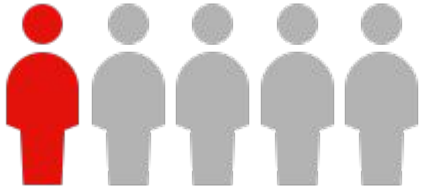
Aly Lamuri Murdani

MSc of Computational Neuroscience and Neuroinformatics. Currently pursuing a doctoral degree in Universitas Indonesia and Rijksuniversiteit Groningen. Proficient in scripting with R also comfortable in scripting with python and Google script. **Highly interested in researching psychology and medicine.**

Introduction

Chronic psychiatric disorders lead to polypharmacy

1 in 5 people



has mental disorders[1]

Polypharmacy

13–90%

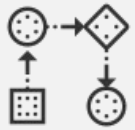
Worldwide prevalence[2]

What influences drug prescription?

Physician's prescribing habits

Patient-physician relationship

Pharmaceutical market



Decision-making process

Challenges in medication surveillance[3]

Group results by demographic factors

Identify increased mortality/morbidity

Relate to health outcomes and services

Describe the importance of polypharmacy

[1]Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Üstün TB, Wang PS. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. Epidemiology and Psychiatric Sciences. 2009 Mar;18(1):23–33.
[2]Delara M, Murray L, Jafari B, Bahji A, Goodarzi Z, Kirkham J, Chowdhury M, Seitz DP. Prevalence and factors associated with polypharmacy: a systematic review and meta-analysis. BMC geriatrics. 2022 Jul 19;22(1):601.
[3]Sirois, C., Tannenbaum, C., Gagnon, ME. et al. Monitoring polypharmacy at the population level entails complex decisions: results of a survey of experts in geriatrics and pharmacotherapy. Drugs Ther Perspect 32, 257–264 (2016).

Polypharmacy is a complex and interlinked medication use

Daily prescription data

Patient	Medication
P1	Fluoxetine
P1	Metformin
P1	Amlodipine
P2	Fluoxetine
P2	Metformin
P3	Fluoxetine

Adjacency Matrix

P1

	[1]	[2]	[3]
Fluoxetine [1]	0	1	1
Metformin [2]	1	0	1
Amlodipine [3]	1	1	0

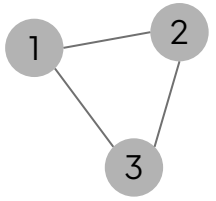
P2

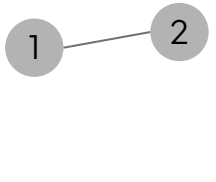
	[1]	[2]	[3]
Fluoxetine [1]	0	1	0
Metformin [2]	1	0	0
Amlodipine [3]	0	0	0

P3

	[1]	[2]	[3]
Fluoxetine [1]	1	0	0
Metformin [2]	0	0	0
Amlodipine [3]	0	0	0

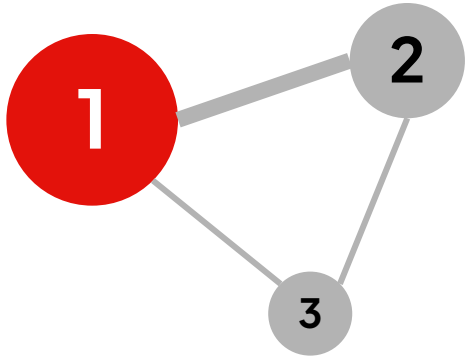
Graph





Drug Prescription Network

	[1]	[2]	[3]
Fluoxetine [1]	1	2	1
Metformin [2]	2	0	1
Amlodipine [3]	1	1	0



Askar M, Cañadas RN, Svendsen K. An introduction to network analysis for studies of medication use. Research in Social and Administrative Pharmacy. 2021 Dec 1;17(12):2054–61.
Bazzoni G, Marengoni A, Tettamanti M, Franchi C, Pasina L, Djade CD, Fortino I, Bortolotti A, Merlino L, Nobili A. The drug prescription network: A system-level view of drug co-prescription in community-dwelling elderly people. Rejuvenation Research. 2015 Apr 1;18(2):153–61.
Cavallo P, Pagano S, Boccia G, De Caro F, De Santis M, Capunzo M. Network analysis of drug prescriptions. Pharmacoepidemiology and drug safety. 2013 Feb;22(2):130–7.

What can a network-based approach offer?

Cavallo (2013)

- Complement inferential statistics in pharmacoepidemiology
- Extract and isolate co-prescription for detailed analysis
- Demonstrate that high connections only occur in a few medications
- Evaluate physician's prescription habit

Future Direction

Encourage network science application for public health evaluation

Bazzoni (2015)

- Highlight dynamic changes in medication uses
- Reflect changes in physician's prescription habit
- Display the co-prescription trends of selected medications
- Extract and isolate distinct clusters in a network

Future Direction

Evaluate medicine prescription and expenditure using a network-based approach

Askar (2021)

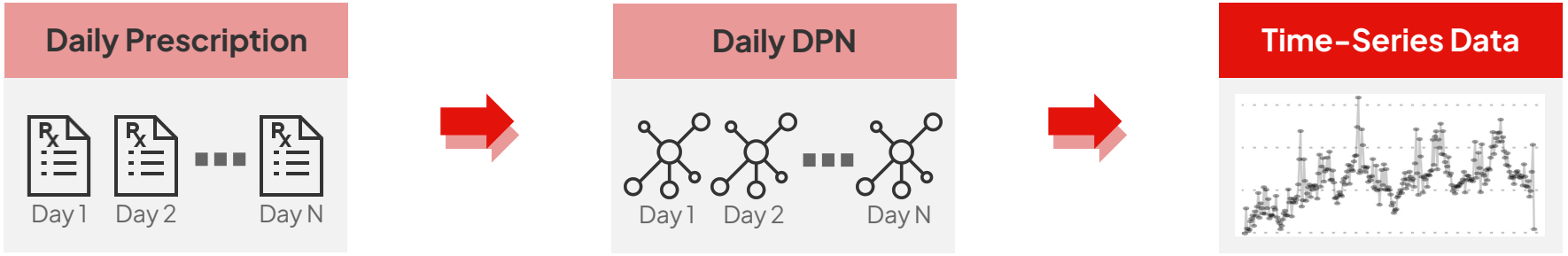
- Observe the influence of multiple drugs using centrality measures
- Suggest centrality measures for variable selection
- Identify clusters of patients with similar co-prescription patterns
- Detect topological differences by comparing different networks

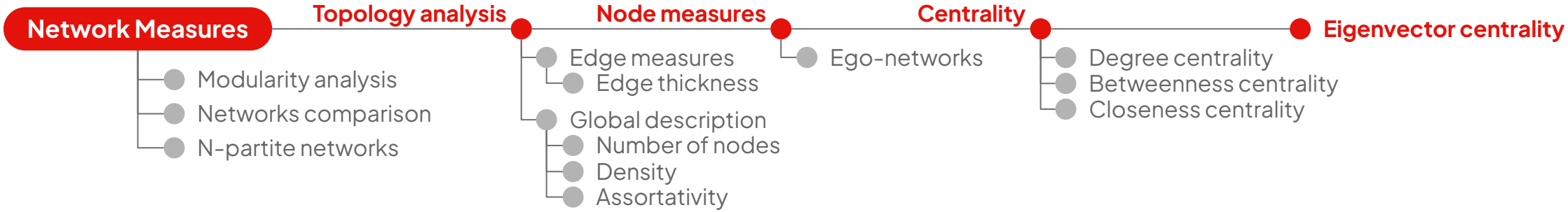
Future Direction

Apply network analysis in social pharmacy and pharmacoepidemiology

Askar M, Cañadas RN, Svendsen K. An introduction to network analysis for studies of medication use. Research in Social and Administrative Pharmacy. 2021 Dec 1;17(12):2054–61.
Bazzoni G, Marengoni A, Tettamanti M, Franchi C, Pasina L, Djade CD, Fortino I, Bortolotti A, Merlino L, Nobili A. The drug prescription network: A system-level view of drug co-prescription in community-dwelling elderly people. Rejuvenation Research. 2015 Apr 1;18(2):153–61.
Cavallo P, Pagano S, Boccia G, De Caro F, De Santis M, Capunzo M. Network analysis of drug prescriptions. Pharmacoepidemiology and drug safety. 2013 Feb;22(2):130–7.

DPN captures the dynamic of polypharmacy regimens





"What does eigenvector centrality tell us about polypharmacy in psychiatric disorders?"

Askar M, Cañadas RN, Svendsen K. An introduction to network analysis for studies of medication use. Research in Social and Administrative Pharmacy. 2021 Dec 1;17(12):2054–61.

Methods

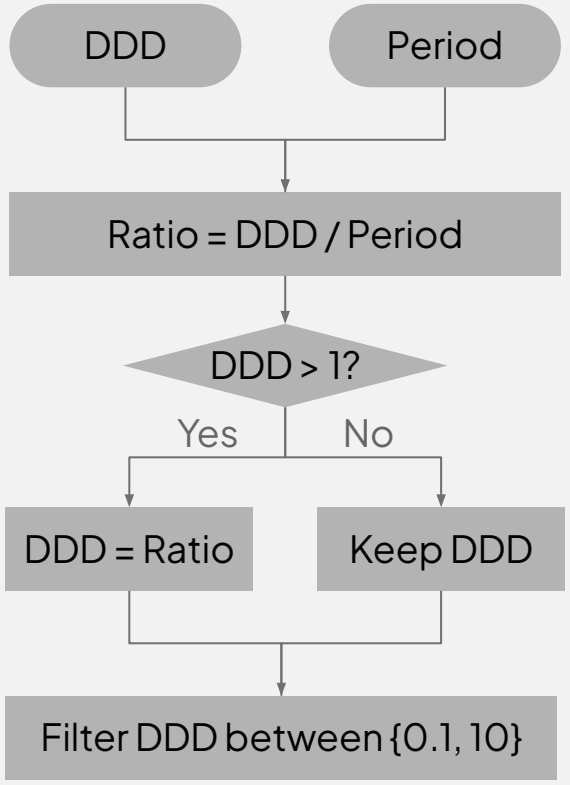
Source of data and pre-processing steps

Data from IADB.nl

ID	ATC	DDD	Date	Period
P1	A07EC02	1	2018-01-01	15
P1	G02BA03	1800	2018-01-01	1800
P1	B03BA03	0.8	2018-01-01	13
P2	A07EC02	0.7	2018-01-01	12
P2	B03BA03	100	2018-01-01	5
...	...	...	...	...
PN	A11CC05	0.9	2022-12-31	10

Inclusion:
- Aged 18–65 years old
- Received N05B/N06A at least once
- Data from 2018 to 2022

Cleaning the DDD



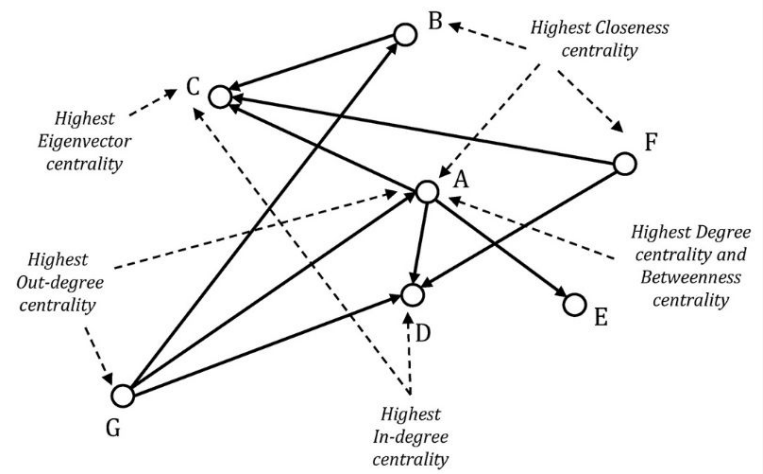
Grouping by ATC level 1 3 4

Alimentary & Metabolism	Blood	Cardiovascular
Dermato-logicals	Genito-urinary	Systemic Hormonal
Anti-infectives	Anti-neoplastic	Musculo-skeletal
Anti-parasitic	Respiratory	Sensory
Others	Anesthetic	Analgesics
Anti-epileptics	Anti-parkinsons	Other Neuro Drugs
Anti-psychotics	Anxiolytics	Hypnotics
Anti-depressants	Psycho-stimulants	Anti-dementia

Network centrality as a score for each medication

- **Network Measures**
  - Modularity analysis
  - Networks comparison
  - N-partite networks
- **Topology analysis**
  - Edge measures
    - Edge thickness
  - Global description
    - Number of nodes
    - Density
    - Assortativity
- **Node measures**
  - Ego-networks
- **Centrality**
  - Degree centrality
  - Betweenness centrality
  - Closeness centrality
- **Eigenvector centrality**

Evaluating Medication in DPN



Operational Definition

Centrality
Indicates how influential a medication is in a network

Eigenvector Centrality
Measures how well-connected a medication is to highly co-prescribed medications

Centrality measures the relative importance of the medications by assigning a score to each of them

$$\lambda c_i = \sum_{j \neq i} v_{j,i} \cdot c_j$$

$$\sum_{i \in N} c_i = 1$$

λ : Associated eigenvalue

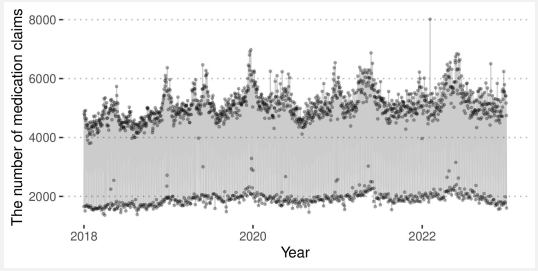
c_i : Eigenvector centrality of node i

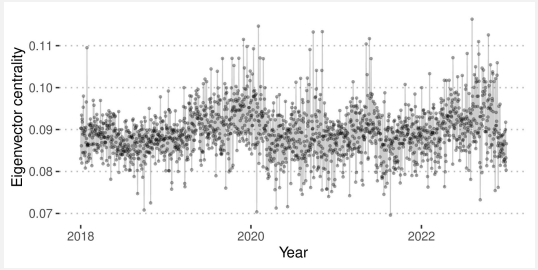
$v_{j,i}$: Connection from j to i

Askar M, Cañadas RN, Svendsen K. An introduction to network analysis for studies of medication use. Research in Social and Administrative Pharmacy. 2021 Dec 1;17(12):2054–61.

Exploratory data analysis procedure

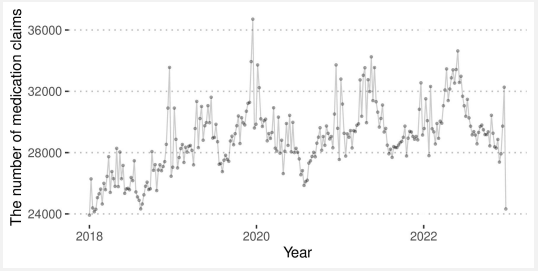
Daily Metrics

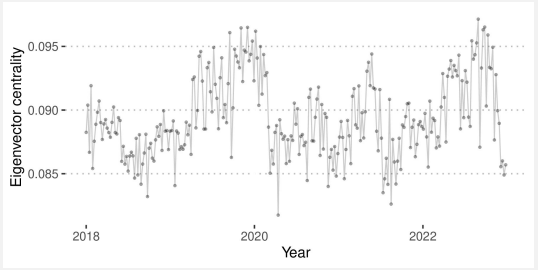




The time points present with daily cyclical patterns

Weekly Aggregate

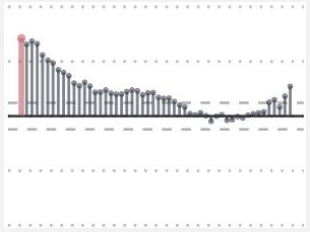




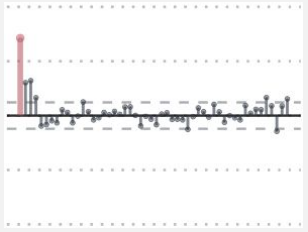
Aggregating the data to remove daily cyclical patterns

Univariate Analysis

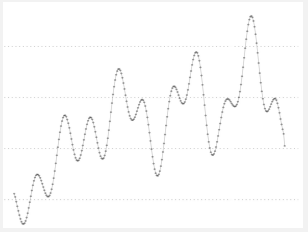
	Number of Claims	Eigenvector Centrality
Mean	…	…
STD	…	…
Median	…	…
IQR	…	…



ACF



PACF



SSA Decompose

Determining relative importance of each medications

1 **The sum of all eigenvector centralities = 1**

$$\lambda c_i = \sum_{j \neq i} v_{j,i} \cdot c_j$$

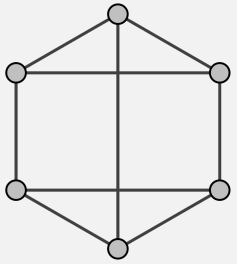
$$\sum_{i \in N} c_i = 1$$

λ : Associated eigenvalue

c_i : Eigenvector centrality of node i

$v_{j,i}$: Connection from j to i

2 **Hypothesized regular graph**



In a regular graph, all nodes have the same centrality, i.e. 1/N

3 **Parameterize 1/N as a normal distribution**

$$\bar{c}_i \sim \mathcal{N}\left(\frac{1}{N}, \sigma\right)$$

$\bar{c}_i$: The mean of eigenvector centrality at node i

n : Total number of nodes

σ : Standard deviation

The mean of eigenvector centrality follows normal distribution

4 **One-sample Student's T-Test**

- Assess how much the observed eigenvector centrality differs from the expected value (1/N)
- If > 1/N → High
- If < 1/N → Low

Rationale and the general ideas

- Regular graph is the null reference
- In a DPN, regular graph implies that all medications are highly likely to be co-prescribed
- The sum of all eigenvector centralities is 1
- In a regular graph, the eigenvector centrality is equal for all nodes, i.e., 1/N
- Null hypothesis: The eigenvector centrality follows 1/N
- One-sample Student's T-Test was performed to test the hypothesis

Results and Discussion

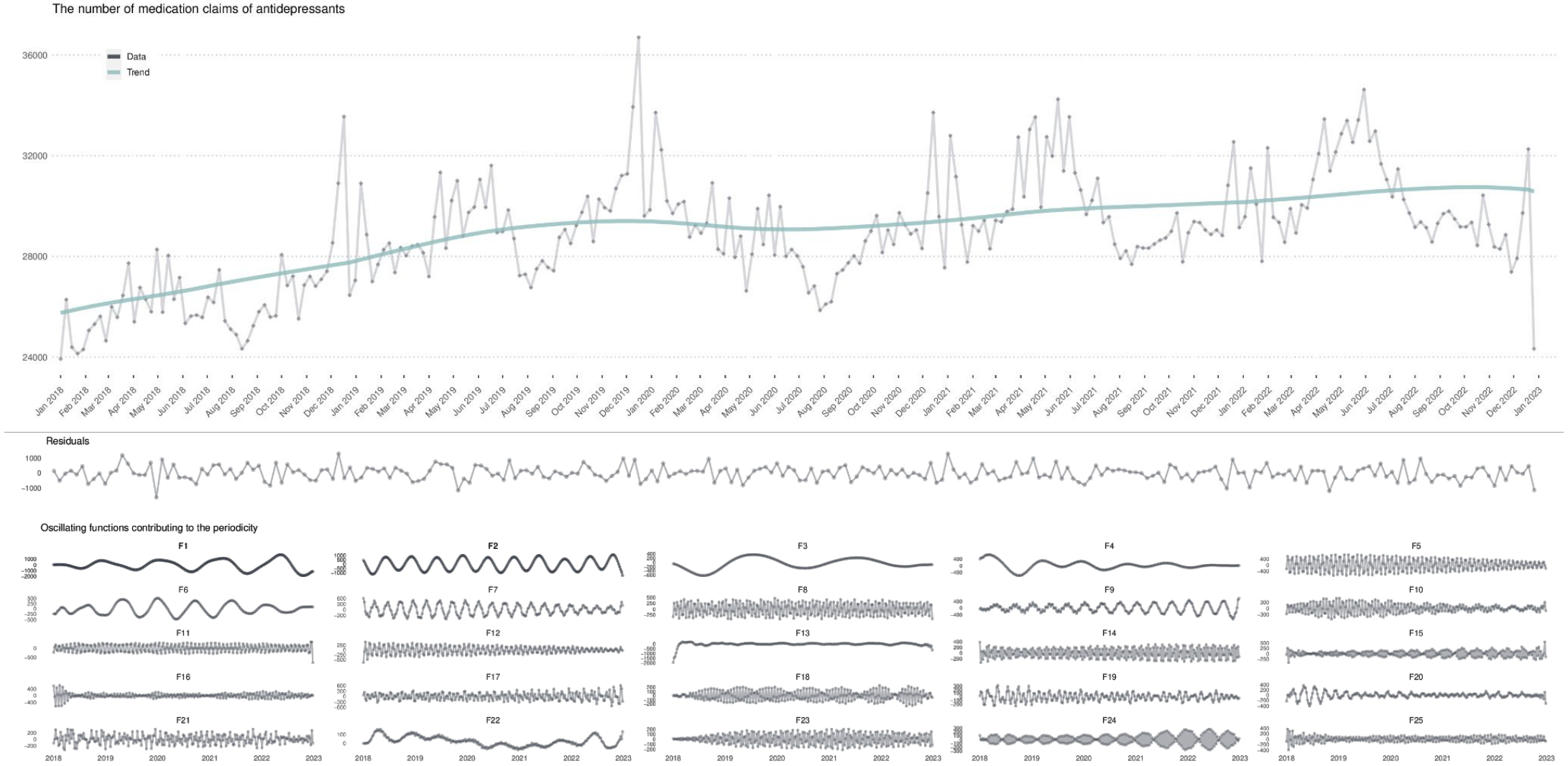
Patients with at least one claim of N05B/N06A from 2018 to 2022

Year	Number of Patients		Age Mean		Age SD	
	Male	Female	Male	Female	Male	Female
2018	42,164 (36.6 %)	73,124 (63.4 %)	48.72	48.02	12.33	12.80
2019	42,427 (36.7 %)	73,109 (63.3 %)	49.26	48.54	12.62	13.02
2020	42,010 (36.6 %)	72,700 (63.4 %)	49.77	49.15	12.79	13.16
2021	42,016 (36.7 %)	72,532 (63.3 %)	50.15	49.55	13.04	13.42
2022	39,464 (36.7 %)	67,930 (63.3 %)	50.82	50.38	13.12	13.50

Distribution of prescription claim from 2018 to 2022

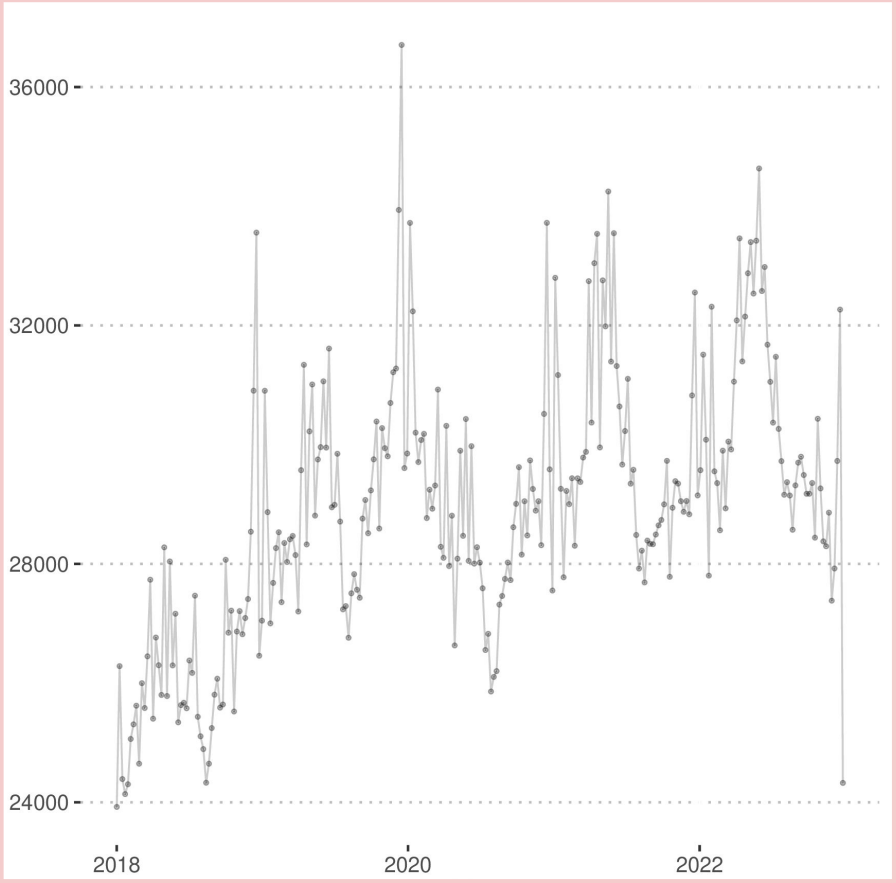
Day	Number of Claims			
	Mean (SD)	Median (IQR)	Min	Max
Monday	7,222.42 (999.8)	7400 (524.0)	2935	9194
Tuesday	6,793.16 (640.8)	6821 (483.0)	3164	8620
Wednesday	6,865.45 (601.1)	6852 (566.0)	3915	8503
Thursday	7,109.15 (592.1)	7136 (579.0)	4156	8608
Friday	6,726.46 (535.5)	6771 (597.0)	3589	8712
Saturday	2,807.73 (174.1)	2803 (169.0)	2293	4533
Sunday	2,990.58 (166.4)	3009.5 (161.3)	2381	3478

Time-series decomposition results

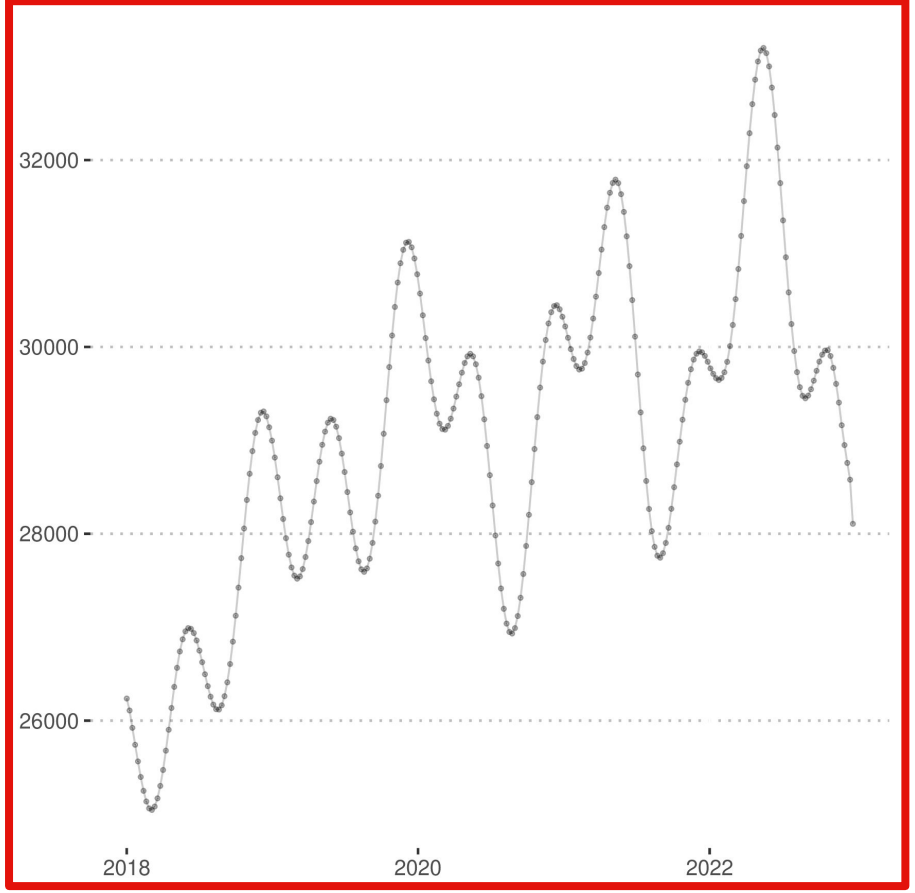


Why is it necessary to decompose the time-series?

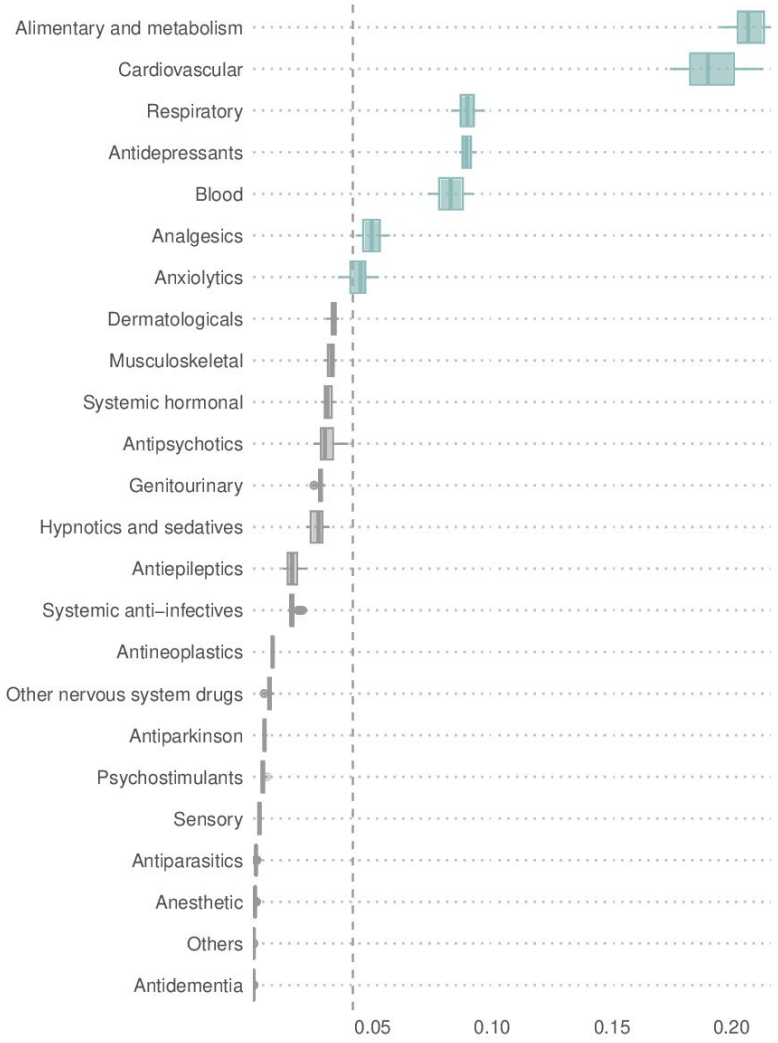
Before decomposition



After decomposition



Seven medications had a high relative importance



Medication Group	N Claims 2018 – 2022	Eigenvector Centrality	Dose
		Mean [95% CI]	Mean [SD]
Alimentary and metabolism	11,512,424	0.2074 [0.2066, 0.2081]	0.60 [0.33]
Cardiovascular	9,778,030	0.1914 [0.1901, 0.1926]	0.54 [0.31]
Respiratory	5,492,900	0.0895 [0.0890, 0.0899]	0.66 [0.33]
Antidepressants	6,108,776	0.0894 [0.0891, 0.0896]	0.54 [0.31]
Blood	2,908,944	0.0827 [0.0821, 0.0833]	0.69 [0.39]
Analgesics	2,557,528	0.0499 [0.0494, 0.0504]	0.42 [0.26]
Anxiolytics	2,644,309	0.0443 [0.0438, 0.0449]	0.46 [0.29]

What does this study offer?

Strength

- Network analysis is a complementary approach to the general practice of inferential statistics
- DPN is proven useful as a data exploration and variable selection strategy

Limitation

- IADB.nl provides prescription registry data, not drug administration nor diagnosis
- We need a way to standardize DDD when excluding the record
- Constructing a DPN is computationally expensive

Future Direction

- Extract entries with high eigenvector centrality to assess individual patient's period of use
- Formulate a bipartite network to link medication with diagnosis or prescribing habits

Take-home messages

DPN is a complementary approach to the general practice of inferential statistics

Network analysis methodology is a powerful tool to address highly connected data

More studies incorporating network analysis of medication uses are encouraged

QUERY?

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> SELECT question FROM slide WHERE slide_number = x
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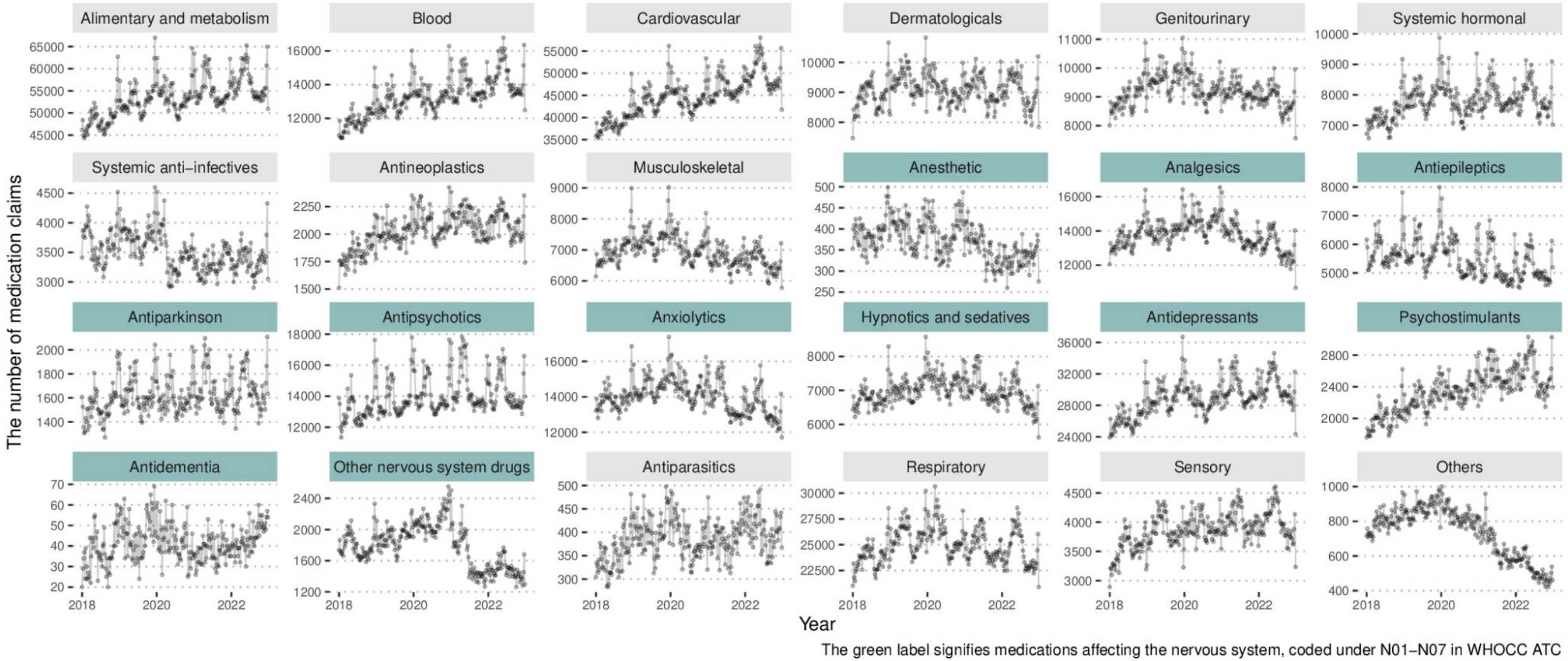
Appendix

Time-series decomposition with singular spectrum analysis

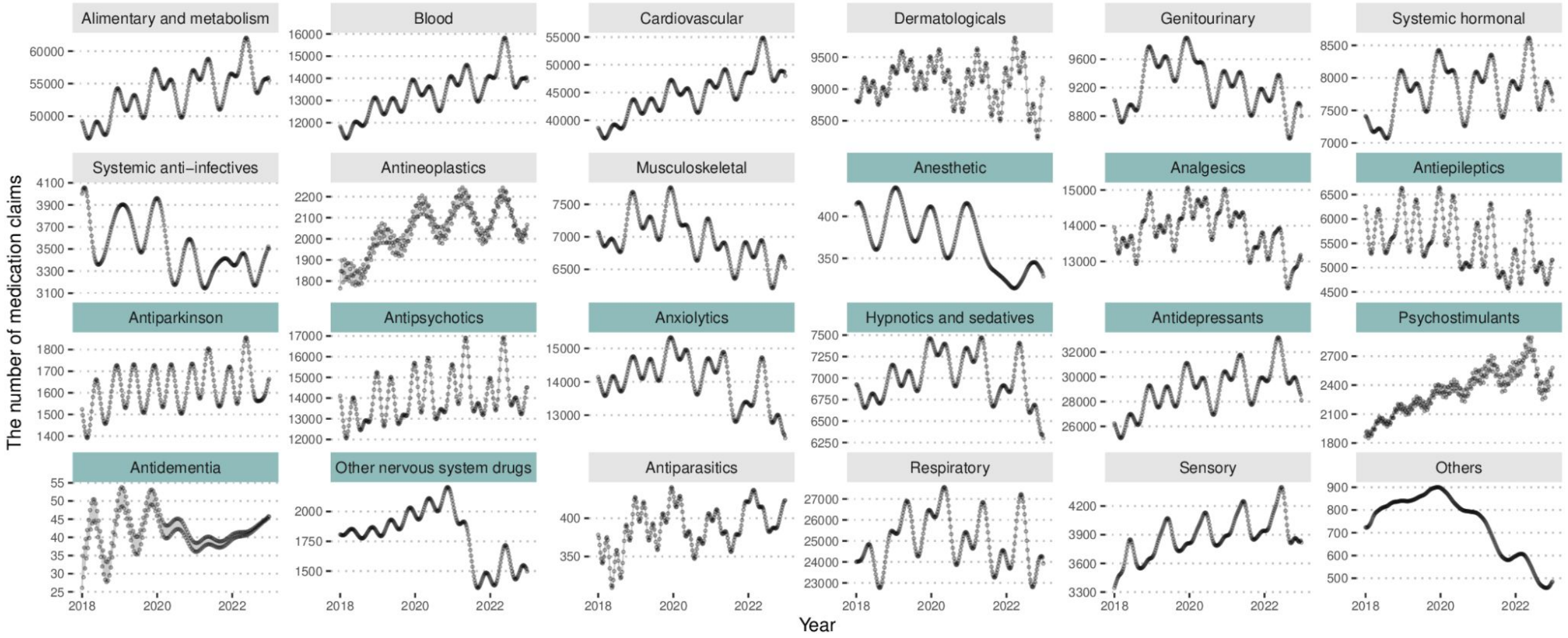
- The weekly time-series is embedded as a Hankel matrix
- The matrix is then decomposed using singular value decomposition
- SSA in a nutshell:
  - We can extract the eigenvalue and eigenvectors by performing matrix multiplication to its transposed form
  - Then we can extract the factor vectors
  - Finally, we get eigentriples as a row-wise decomposition of the Hankel matrix
- We performed a sequential SSA to decompose complex periodic patterns:
  - Fit SSA model to reconstruct the first eigentriple, use the lowest possible L, in our case L = 52
  - Extract the residual
  - Fit a second SSA model to the residual, use the highest possible L, theoretically L = N/2

Problems with raw time-series data



The green label signifies medications affecting the nervous system, coded under N01–N07 in WHOCC ATC

Reconstructing using the trend, F1, and F2



The green label signifies medications affecting the nervous system, coded under N01–N07 in WHOCC ATC