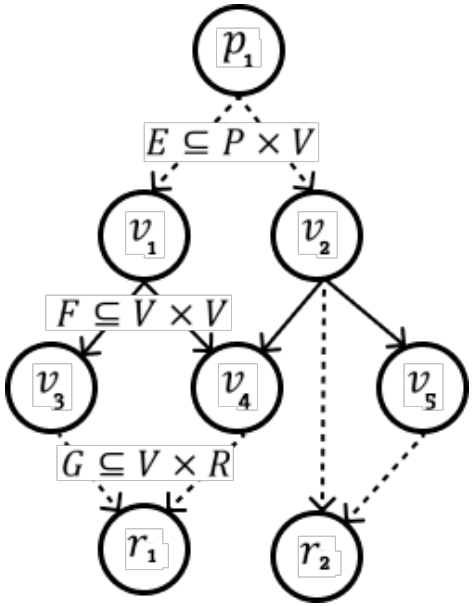
CONSTRUCTING BAYSIAN NETWORKS TO DETERMINE THE RISKS OF DRUG INTERACTIONS BASED ON INSTRUCTIONS.



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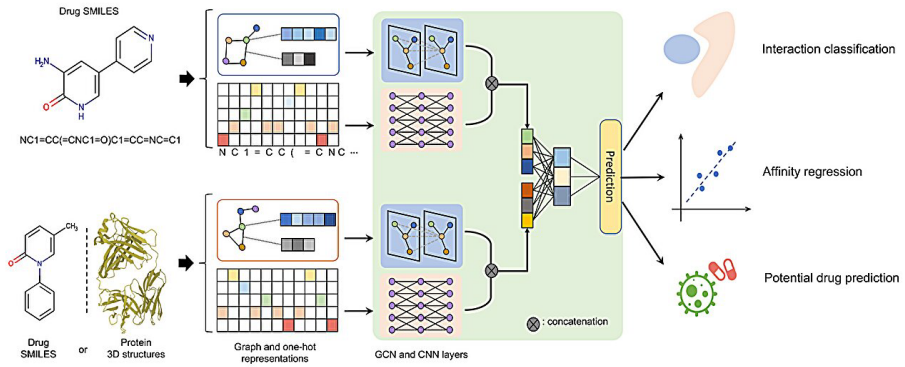
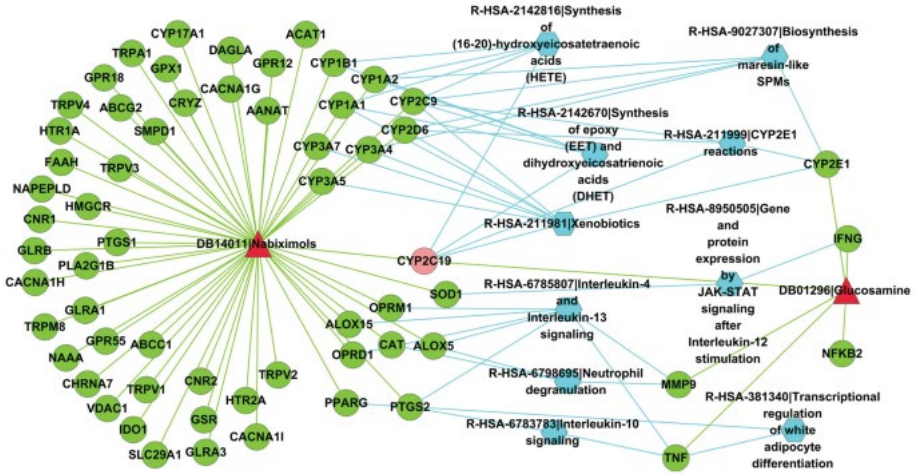
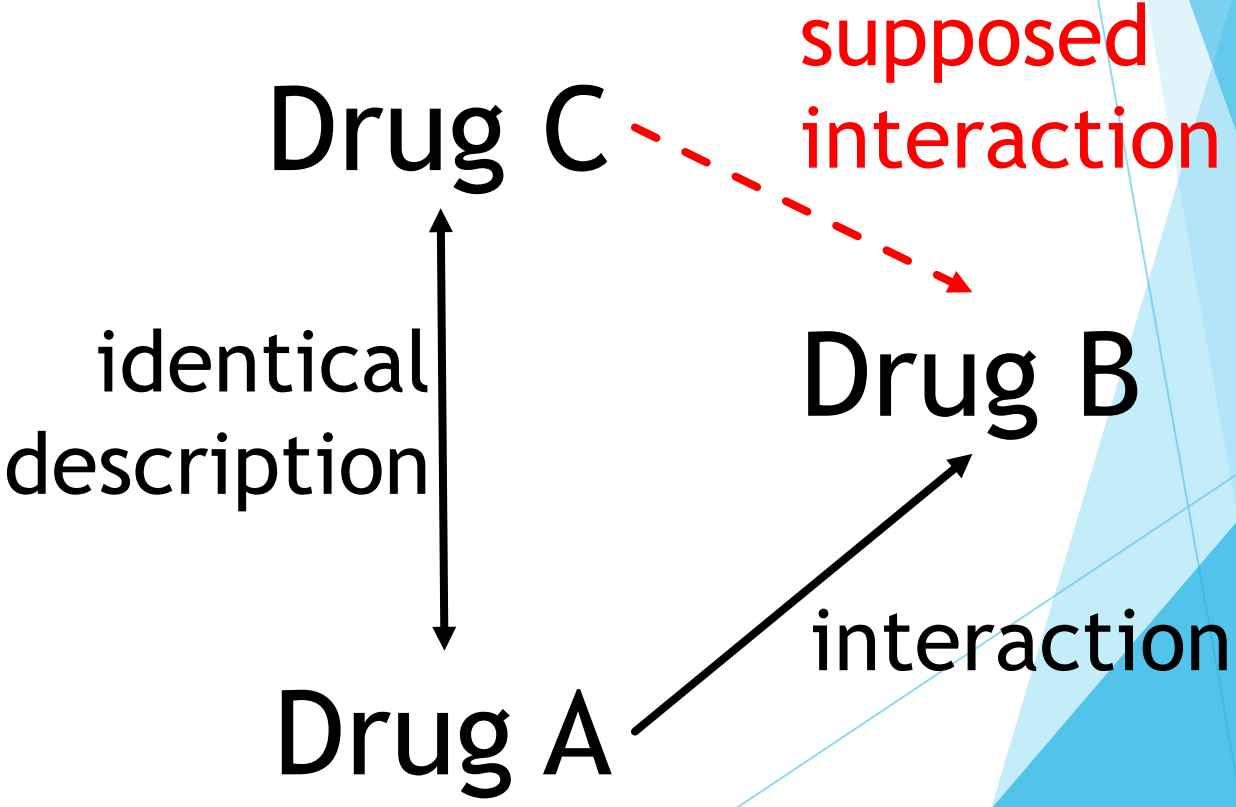
DDI - drug-drug interactions



Yin Q , Fan R , Cao X , Liu Q , Jiang R , Zeng W . DeepDrug: A general graph-based deep learning framework for drug-drug interactions and drug-target interactions prediction. Quant. Biol. 2023; 11(3): 260–274. https://doi.org/10.15302/J-QB-022-0320



Mei, S., Zhang, K. A machine learning framework for predicting drug–drug interactions. Sci Rep 11, 17619 (2021). https://doi.org/10.1038/s41598-021-97193-8



Problems of polypharmacotherapy

no contraindications	Amiodarone	Acetylsalicylic acid		
no contraindications	Amiodarone	Amoxicillin		
under medical supervision	Amiodarone	Dabigatran		
no contraindications	Amoxicillin	Acetylsalicylic acid		
no contraindications	Amoxicillin	Dabigatran		
no contraindications	Dabigatran	Acetylsalicylic acid		
???	Amiodarone	Acetylsalicylic acid	Amoxicillin	
???	Amiodarone	Acetylsalicylic acid	Dabigatran	
???	Amiodarone	Amoxicillin	Dabigatran	
???	Amoxicillin	Acetylsalicylic acid	Dabigatran	
???	Amiodarone	Acetylsalicylic acid	Amoxicillin	Dabigatran

under medical supervision

- Can three or more drugs with unknown interactions have a significant risk of causing adverse effects?
- If a pair of interacting drugs has a minor interaction, could the risk be increased by taking a large number of drugs?

no contraindications	Amiodarone	Ketoprofen		
no contraindications	Amiodarone	Clopidogrel		
no contraindications	Amiodarone	Aspirin		
under medical supervision	Ketoprofen	Clopidogrel		
under medical supervision	Ketoprofen	Aspirin		
under medical supervision	Clopidogrel	Aspirin		
???	Amiodarone	Ketoprofen	Clopidogrel	
???	Amiodarone	Ketoprofen	Aspirin	
???	Amiodarone	Clopidogrel	Aspirin	
???	Ketoprofen	Clopidogrel	Aspirin	
???	Amiodarone	Ketoprofen	Clopidogrel	Aspirin

System structure

System

Natural Language Processing, NLP

Stage 1. Processing instruction texts
Stage 2. Construction of a Bayesian network
Stage 3. Probability assessment
Stage 4. Activation of vertices.

- no contraindications
- minor
- under medical supervision
- major
- prohibited

Stage 1. Processing instruction texts

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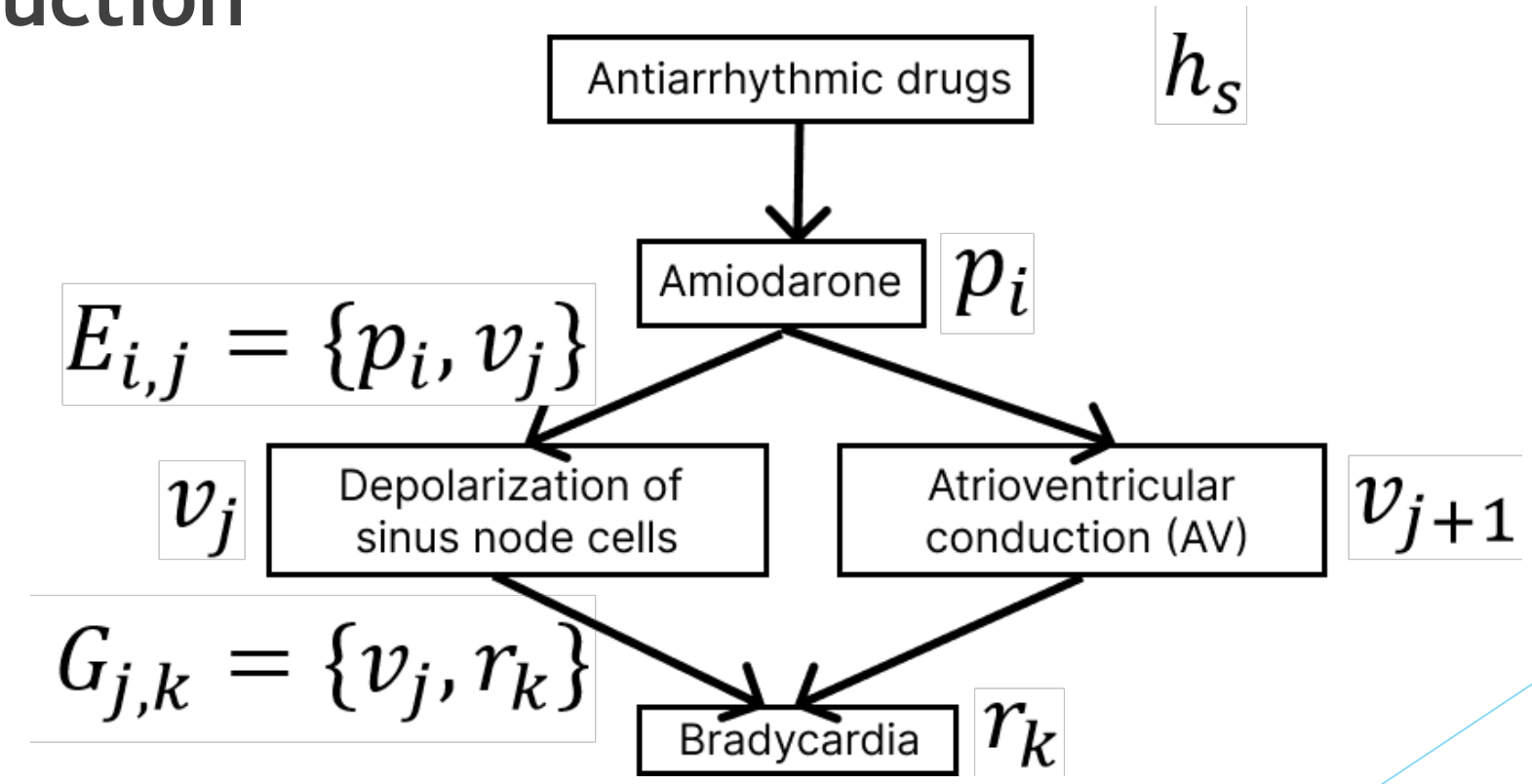
Model Name	Accuracy	Precision	Recall	F1	AUC
saved_model_mark_sent_2_rubert-base-cased_3	0.89091	0.73684	0.7	0.71795	0.89924
saved_model_mark_sent_2_RuBioBERT_3	0.86818	0.67241	0.65	0.66102	0.88716
saved_model_mark_sent_2_rubert-base-cased_4	0.9	0.74576	0.73333	0.7395	0.90276
saved_model_mark_sent_2_RuBioBERT_4	0.92727	0.85246	0.86667	0.8595	0.92377
saved_model_mark_sent_2_rubert-base-cased_5	0.92273	0.82258	0.85	0.83607	0.91571
saved_model_mark_sent_2_RuBioBERT_5	0.91364	0.7377	0.75	0.7438	0.91478
saved_model_mark_sent_2_rubert-base-cased_6	0.93182	0.86885	0.88333	0.87603	0.91996
saved_model_mark_sent_2_RuBioBERT_6	0.90909	0.72581	0.75	0.7377	0.91392
saved_model_mark_sent_2_rut5-base_3	0.65396	0.48214	0.29032	0.36242	0.62422
saved_model_mark_sent_2_rut5-base-multitask_3	0.70088	0.53333	0.43011	0.47619	0.72582
saved_model_mark_sent_2_rut5-base_4	0.70674	0.5	0.44086	0.46857	0.74104
saved_model_mark_sent_2_rut5-base-multitask_4	0.70381	0.45238	0.4086	0.42938	0.75598
saved_model_mark_sent_2_rut5-base_5	0.69501	0.4878	0.43011	0.45714	0.74004
saved_model_mark_sent_2_rut5-base-multitask_5	0.71261	0.47619	0.43011	0.45198	0.74818
saved_model_mark_sent_2_rut5-base_6	0.68915	0.42529	0.39785	0.41111	0.73733
saved_model_mark_sent_2_rut5-base-multitask_6	0.69795	0.46429	0.41935	0.44068	0.74205

Stage 2. Construction of a Bayesian network

- Amiodarone: Inhibits slow (diastolic) **depolarization of the sinus node cell** membrane, causing **bradycardia** and decreased **atrioventricular (AV) conduction**



Stage 2. Construction of a Bayesian network

$$W = \{H, P, V, R, E, F, G\}$$

- Groups of drugs

$$H = \{h_1, h_2 \dots h_s, \dots h_S\}, \forall p_i \; \exists h_s: \; p_i \in h_s$$

- Medicine / drugs

$$P = \{p_1, p_2 \dots p_i, \dots p_n\}; p_i \in \{A_{0,i}, A_{1,i} \dots A_{q_i,i}\}$$

- «Mechanism»: chemical structures, transporters, enzymes and carriers

$$V = \{v_1, v_2 \dots v_j, \dots v_m\}; v_j \in \{B_{0,j}, B_{1,j}\}$$

- Side effects

$$R = \{r_1, r_2 \dots r_k, \dots r_z\}; \; r_k \in \{C_{0,k}, C_{1,k}\}$$

Stage 2. Construction of a Bayesian network

$$W = \{H, P, V, R, E, F, G\}$$

- arcs connecting drugs and mechanisms

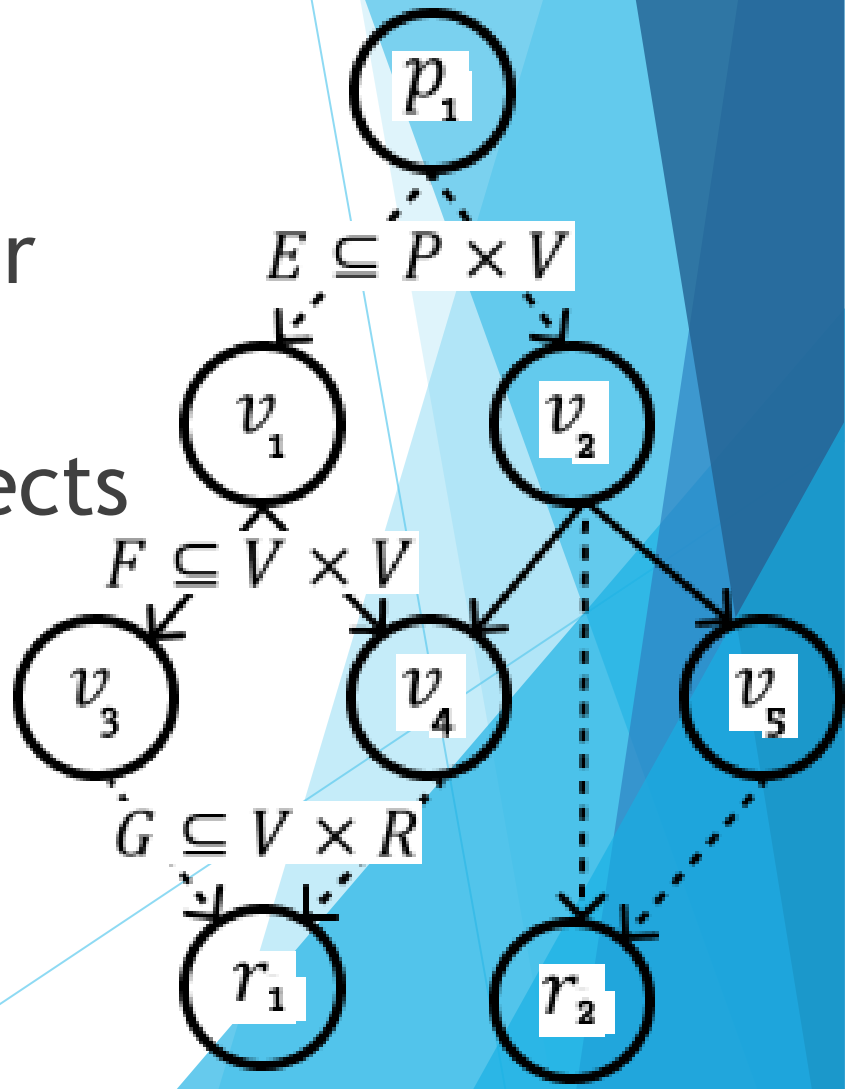
$$E \subseteq P \times V$$

- arcs connecting mechanisms to each other

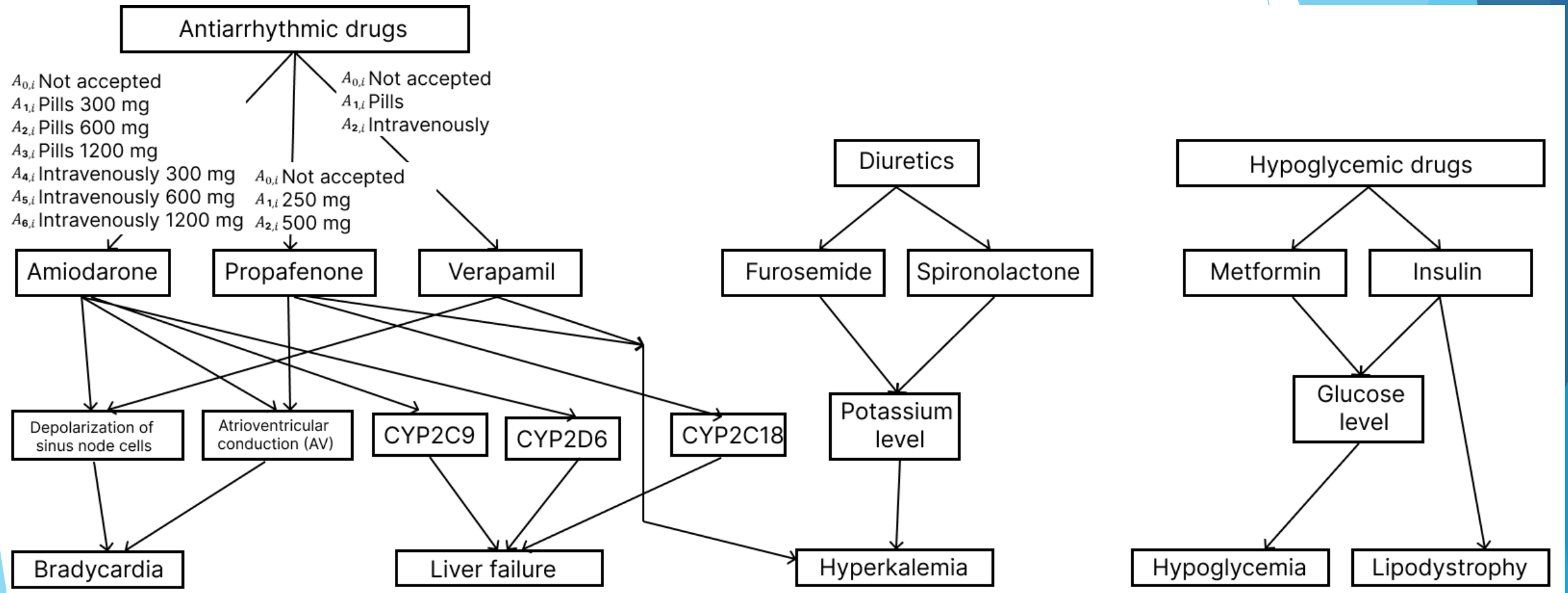
$$F \subseteq V \times V$$

- arcs connecting mechanisms and side effects

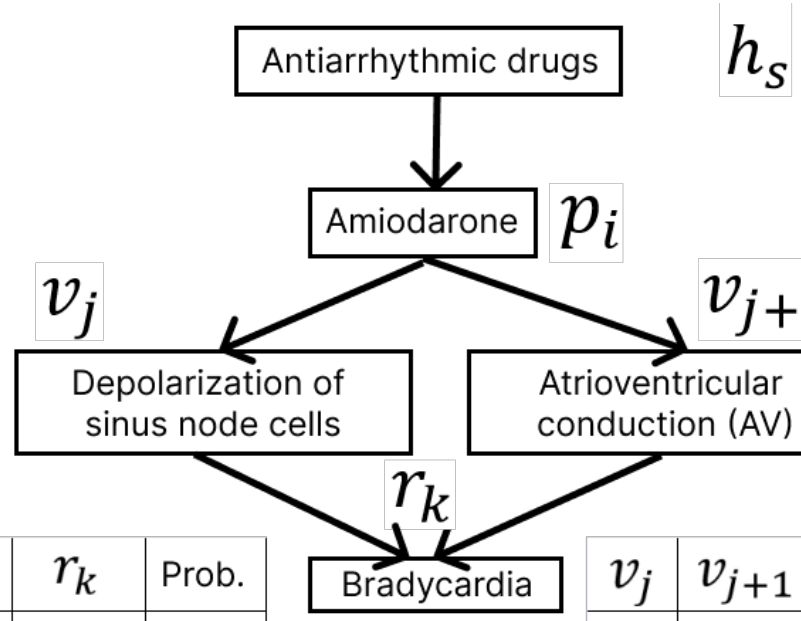
$$G \subseteq V \times R$$



Stage 2. Construction of a Bayesian network



Stage 3. Probability assessment



p_i	v_j	Prob.
$A_{0,i}$	$B_{0,j}$	0,88
$A_{0,i}$	$B_{1,j}$	0,12
$A_{1.i}$	$B_{0,j}$	0,27
$A_{1.i}$	$B_{1,j}$	0,73

p_i	v_{j+1}	Prob.
$A_{0,i}$	$B_{0,j+1}$	0,67
$A_{0,i}$	$B_{1,j+1}$	0,33
$A_{1.i}$	$B_{0,j+1}$	0,08
$A_{1.i}$	$B_{1,j+1}$	0,92

v_j	v_{j+1}	r_k	Prob.
$B_{0,j}$	$B_{0,j+1}$	$C_{1,k}$	0,09
$B_{1,j}$	$B_{0,j+1}$	$C_{1,k}$	0,16
$B_{0,j}$	$B_{1,j+1}$	$C_{1,k}$	0,31
$B_{1,j}$	$B_{1,j+1}$	$C_{1,k}$	0,48

v_j	v_{j+1}	r_k	Prob.
$B_{0,j}$	$B_{0,j+1}$	$C_{0,k}$	0,91
$B_{1,j}$	$B_{0,j+1}$	$C_{0,k}$	0,84
$B_{0,j}$	$B_{1,j+1}$	$C_{0,k}$	0,69
$B_{1,j}$	$B_{1,j+1}$	$C_{0,k}$	0,52

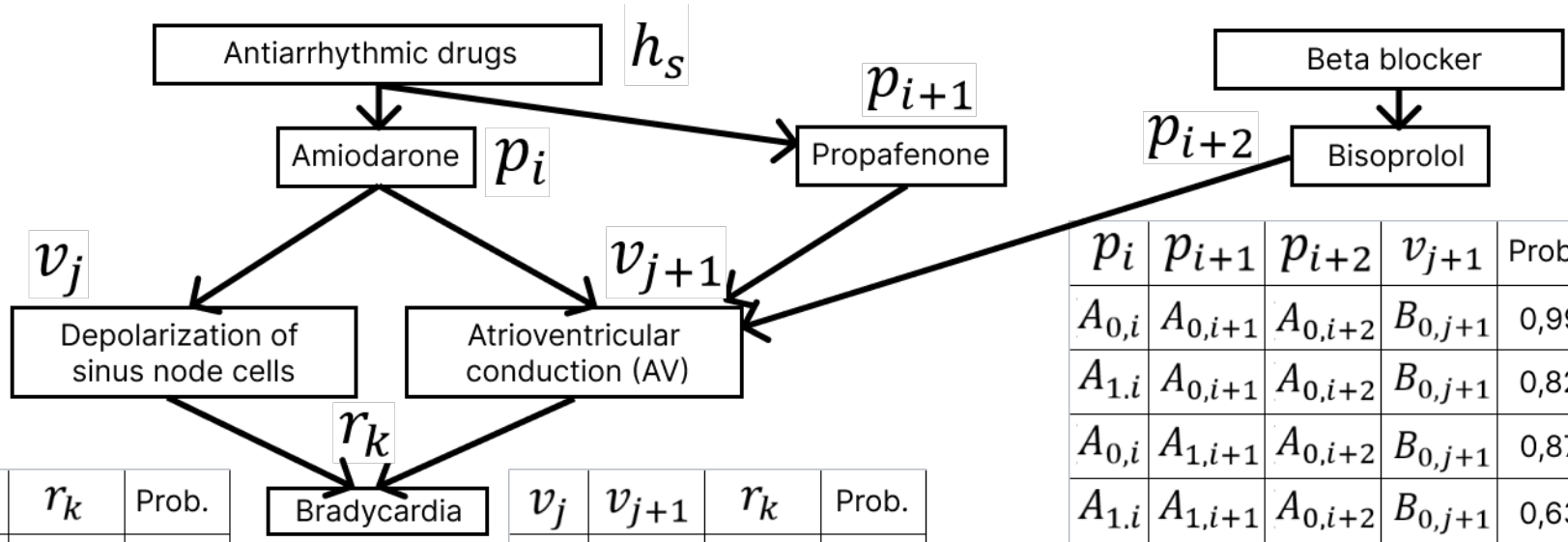
$$P(A_{1,i}, B_{1,j}, B_{1,j+1}, C_{1,k}) = P(C_{1,k}/\, B_{1,j}, B_{1,j+1})P(B_{1,j}/A_{1,i})P(B_{1,j+1}/A_{1,i})P(A_{1,i}) = \ 0.48 * 0.73 * 0.92 * 1 = 0.3223.$$

$$P(A_{1,i}, B_{1,j}, B_{1,j+1}, C_{0,k}) = 0.52 * 0.73 * 0.92 * 1 = 0.3493$$

Stage 3. Probability assessment

A_i	B_j	B_{j+1}	C_k	Probability	A_i	B_j	B_{j+1}	C_k	Probability
$A_{0,i}$	$B_{0,j}$	$B_{0,j+1}$	$C_{0,k}$	0	$A_{0,i}$	$B_{0,j}$	$B_{0,j+1}$	$C_{1,k}$	0
$A_{1,i}$	$B_{0,j}$	$B_{0,j+1}$	$C_{0,k}$	0,0196	$A_{1,i}$	$B_{0,j}$	$B_{0,j+1}$	$C_{1,k}$	0,0019
$A_{0,i}$	$B_{1,j}$	$B_{0,j+1}$	$C_{0,k}$	0	$A_{0,i}$	$B_{1,j}$	$B_{0,j+1}$	$C_{1,k}$	0
$A_{1,i}$	$B_{1,j}$	$B_{0,j+1}$	$C_{0,k}$	0,0491	$A_{1,i}$	$B_{1,j}$	$B_{0,j+1}$	$C_{1,k}$	0,0093
$A_{0,i}$	$B_{0,j}$	$B_{1,j+1}$	$C_{0,k}$	0	$A_{0,i}$	$B_{0,j}$	$B_{1,j+1}$	$C_{1,k}$	0
$A_{1,i}$	$B_{0,j}$	$B_{1,j+1}$	$C_{0,k}$	0,1714	$A_{1,i}$	$B_{0,j}$	$B_{1,j+1}$	$C_{1,k}$	0,0771
$A_{0,i}$	$B_{1,j}$	$B_{1,j+1}$	$C_{0,k}$	0	$A_{0,i}$	$B_{1,j}$	$B_{1,j+1}$	$C_{1,k}$	0
$A_{1,i}$	$B_{1,j}$	$B_{1,j+1}$	$C_{0,k}$	0,3493	$A_{1,i}$	$B_{1,j}$	$B_{1,j+1}$	$C_{1,k}$	0,3223
Summ			$C_{0,k}$	0,5894	Summ			$C_{1,k}$	0,4106

Stage 3. Probability assessment



v_j	v_{j+1}	r_k	Prob.
$B_{0,j}$	$B_{0,j+1}$	$C_{1,k}$	0,09
$B_{1,j}$	$B_{0,j+1}$	$C_{1,k}$	0,16
$B_{0,j}$	$B_{1,j+1}$	$C_{1,k}$	0,31
$B_{1,j}$	$B_{1,j+1}$	$C_{1,k}$	0,48

v_j	v_{j+1}	r_k	Prob.
$B_{0,j}$	$B_{0,j+1}$	$C_{0,k}$	0,91
$B_{1,j}$	$B_{0,j+1}$	$C_{0,k}$	0,84
$B_{0,j}$	$B_{1,j+1}$	$C_{0,k}$	0,69
$B_{1,j}$	$B_{1,j+1}$	$C_{0,k}$	0,52

p_i	p_{i+1}	p_{i+2}	v_{j+1}	Prob.
$A_{0,i}$	$A_{0,i+1}$	$A_{0,i+2}$	$B_{0,j+1}$	0,99
$A_{1.i}$	$A_{0,i+1}$	$A_{0,i+2}$	$B_{0,j+1}$	0,82
$A_{0,i}$	$A_{1,i+1}$	$A_{0,i+2}$	$B_{0,j+1}$	0,87
$A_{1.i}$	$A_{1,i+1}$	$A_{0,i+2}$	$B_{0,j+1}$	0,63
$A_{0,i}$	$A_{0,i+1}$	$A_{1.i+2}$	$B_{0,j+1}$	0,95
$A_{1.i}$	$A_{0,i+1}$	$A_{1.i+2}$	$B_{0,j+1}$	0,75
$A_{0,i}$	$A_{1,i+1}$	$A_{1.i+2}$	$B_{0,j+1}$	0,79
$A_{1.i}$	$A_{1,i+1}$	$A_{1.i+2}$	$B_{0,j+1}$	0,69

p_i	p_{i+1}	p_{i+2}	v_{j+1}	Prob.
$A_{0,i}$	$A_{0,i+1}$	$A_{0,i+2}$	$B_{1,j+1}$	0,01
$A_{1.i}$	$A_{0,i+1}$	$A_{0,i+2}$	$B_{1,j+1}$	0,18
$A_{0,i}$	$A_{1,i+1}$	$A_{0,i+2}$	$B_{1,j+1}$	0,13
$A_{1.i}$	$A_{1,i+1}$	$A_{0,i+2}$	$B_{1,j+1}$	0,37
$A_{0,i}$	$A_{0,i+1}$	$A_{1.i+2}$	$B_{1,j+1}$	0,05
$A_{1.i}$	$A_{0,i+1}$	$A_{1.i+2}$	$B_{1,j+1}$	0,25
$A_{0,i}$	$A_{1,i+1}$	$A_{1.i+2}$	$B_{1,j+1}$	0,21
$A_{1.i}$	$A_{1,i+1}$	$A_{1.i+2}$	$B_{1,j+1}$	0,31

Stage 3. Probability assessment

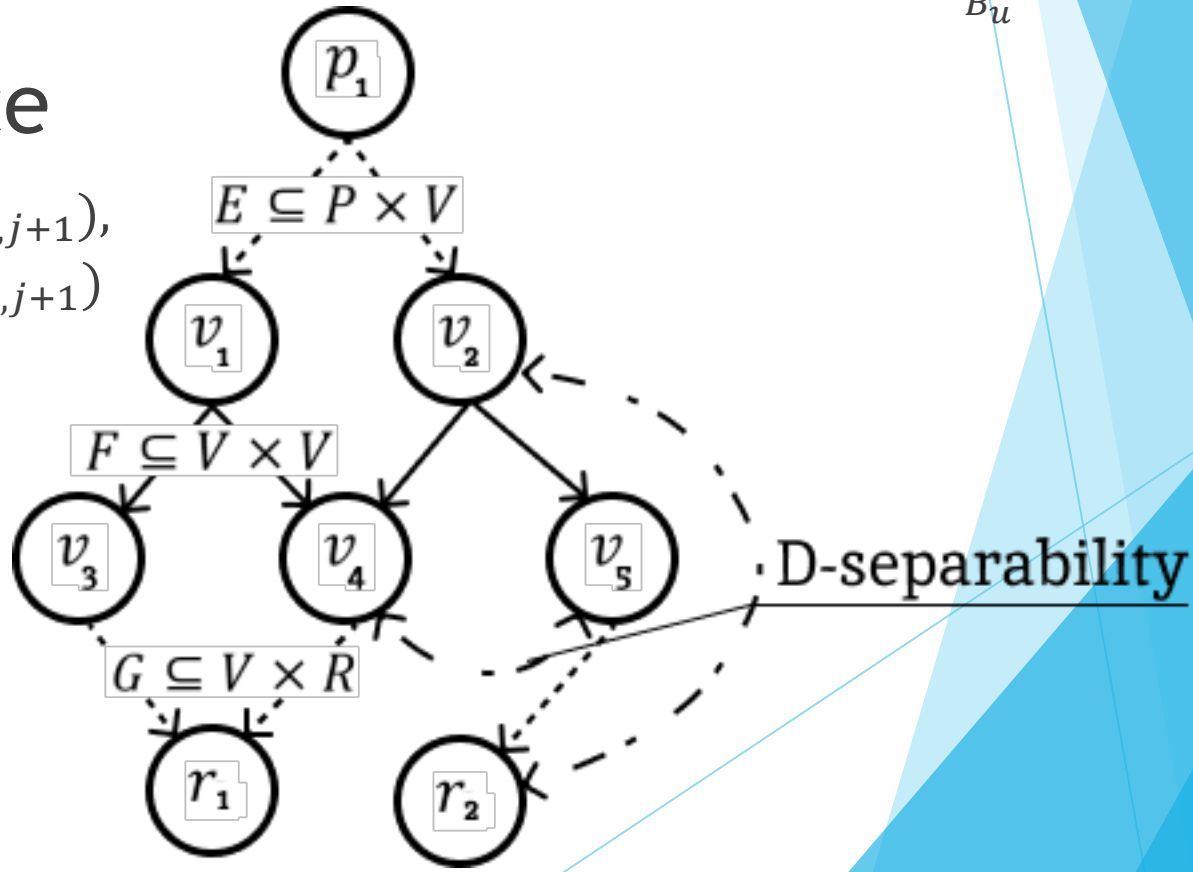
- Early marginalization

$$P(B_1) = \sum_{A} [P(B_1/A)P(A)]\,; P(B_i) = \sum_{B_{i-1}} [P(B_i/B_{i-1})P(B_{i-1})]\,, i \in (2 \ldots u);\ P(C) = \sum_{B_u} P(C/B_u)P(B_u)\,;$$

- Conditional independence

$$P(B_{0,k}/\,B_{0,j}, B_{0,j+1}) \sim P(B_{0,k}/\,B_{0,j})P(B_{0,k}/\,B_{0,j+1}),$$
$$P(B_{0,k}/\,A_{0,j}, A_{0,j+1}) \sim P(B_{0,k}/\,A_{0,j})P(B_{0,k}/\,A_{0,j+1})$$

- D-separability



Stage 3. Probability assessment

Training samples:

$X^l = (p_i, r_k, P(C_{1,k}))^l$, Text of instructions: side effects when using drugs;

$X^s = (p_i, r_{k_1}, r_{k_2}, P(C_{1,k_1})/P(C_{1,k_2}))^s$, Frequency of side effects from VigiAccess;

$X^z = (p_i, p_j, r_k, P(C_{1,k}))^z$, Text of instructions: drug-drug interactions.

Loss function: Q quantile for X^l и X^z, and quadratic for X^s.

Model – bayesian network, under the hypothesis of independence of conditional probabilities, D-separability and node activation.

Training in the model – selection of optimal values of conditional probabilities for all states of vertices v_j, r_k.

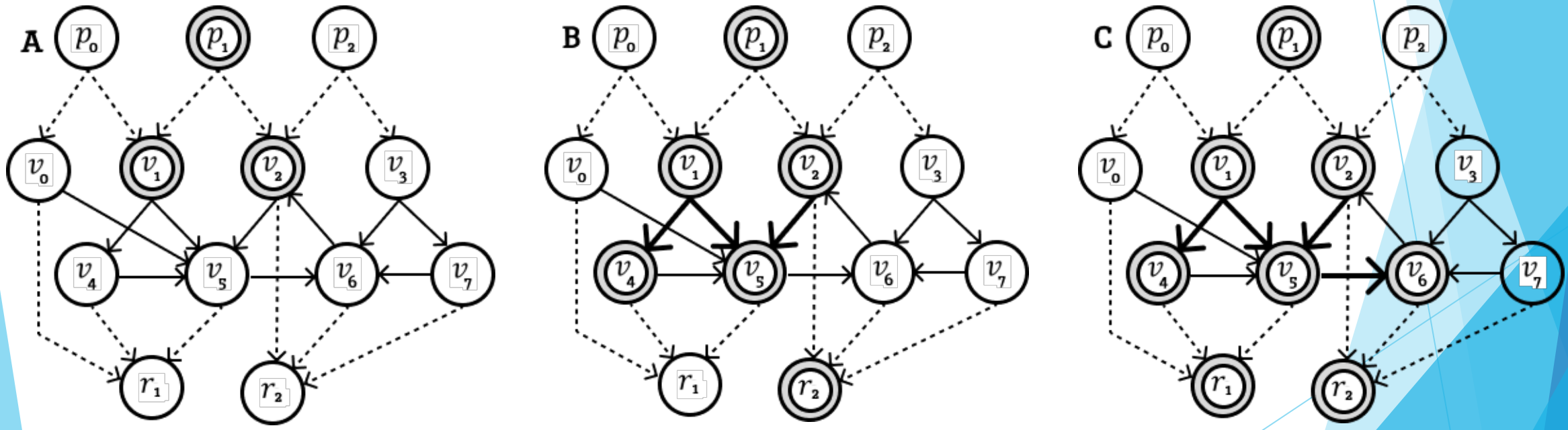
Teaching method – application of a variety of ensemble methods to minimize the loss function Q.

Test **verification** of the trained model is carried out through interaction with medical personnel via the corresponding web interfaces..

Optimization of hyperparameters: the number of states at the vertices of the v_j mechanisms and the parameters of the quantile loss function, using cross-validation methods, such as hold-out or LOO (leave one out).

Stage 4. Activation of vertices.

- A wave algorithm is used. A wave is launched from the selected drug peaks to the peaks of side effects



Conclusion

- The developed model was tested on drugs prescribed for chronic heart failure.
- More than 17 thousand documents on 54 international nonproprietary names of drugs: Aliskeren, Alprazolam, Amisulpiride, Amitriptyline, Apalutamide, Apomorphine, Aripiprazole, Aspirin, Avanafil, Baclofen, Betamethasone, Bexpiprazole, Brimonidine, Bromfenac, Budesonide, Buprenorphine, Buspirone, Butorphanol, Valsartan, Veroshpiron, Cabergoline, Canagliflozin, Captopril, Hypothiazide, Alprostadil, Atenolol, Minoxidil, Indomethacin, Allopurinol, Novocainamide, Insulin, Epoetin, Digoxin, Azathioprine, Cyclophosphamide, Dexamethasone, Propranolol, Temsirolimus, Sirolimus, Everolimus, Biseptol, Vildagliptin, Sitagliptin, Racecadotril, Neutralax, Bisoprolol, Carvedilol, Metoprolol, Nebivolol, Eplerenone, Lisinopril, Hydrochlorothiazide, Potassium chloride, Cyclosporine, Verapamil, Amlodipine, Celecoxib, Ephedrine, Nimesulide, Meloxicam, Lithium carbonate, Gastrasan, Glibenclamide, Gliclazide, Metformin, Repaglinide, Levonorgestrel, Allopurinol, Diazoxide, Moxonidine, Cardiket, Nitroglycerin, Amisulpride, Guanfacine, Chlorpromazine, Nifedipine, Phenobarbital, Enalapril, Heparin, Torasemide, Methyldopa, Indapamide, Betaxolol, Imipramine, Amitriptyline, Chlorpromazine, Levomepromazine, Fluphenazine, Trifluoperazine, Fentanyl, Temsirolimus, Sirolimus, Everolimus, Sitagliptin
- Based on the results of processing the data from the documents, a Bayesian network was created, with more than 1000 different mechanisms.
- The criterion for the “correctness” of the system’s operation is compliance with all instructions for medicinal products
- **In a further study**, it is planned to add antibiotics with the aim of selecting a suitable antibiotic for a group of drugs in terms of instructions

Thank you for your attention