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PM-TOM: A Method for Finding Personalized Polypharmacy Therapies with Minimal Adverse Drug-Drug, Drug-Gene and Drug-Condition Interactions

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Abstract. Polypharmacy therapies, quite frequent in older populations, pose significant health risks for patients due to a high possibility of their cumulative adverse drug reactions. We present Personalized Medicine Therapy Optimization Method (PM-TOM) for the discovery of polypharmacy therapies with minimal drug- drug interactions, drug-gene interactions, and drug-condition interactions. The inputs of the PM-TOM heuristic algorithm are the patient's conditions, genome, and the drug products and therapy considered by a clinician. Its output is a comprehensive report that explains details of the optimal therapies for considered drug products and all drugs that treat the patient's conditions. PM-TOM was developed by using the Electronic Medical Records repository of the Personal Genome Project (PGP), and the public repositories: DrugBank and Comprehensive Toxicogenomics Database (CTD). Testing of PM-TOM showed potential for significant reduction of the cumulative adverse drug interactions in personalized polypharmacy therapies. In the group of patients with 8 to 17 conditions, PM-TOM reduced the average cumulative drug interactions from 22 to 5.83, and the group with 6 to 7 conditions from 11.17 to 3. These results encourage further research and development of clinical decision support tools like PM-TOM.

Keywords. Personalized Medicine, Electronic Medical Records, Polypharmacy Therapies, Clinical Decision Support, Adverse Drug Reactions, Drug-Drug Interactions, Drug-Gene Interactions, Drug-Condition Interactions.

1. Introduction

Multiple studies show that polypharmacy therapies can lead to dangerous adverse drug reactions (*ADR*) and high healthcare costs due to their cumulative drug-drug interactions *(DDI)*, drug-gene interactions (*DGI*), and contraindicated drug-condition interactions (*DCI)*. Paper [1] reports that the average patient in the examined cohort was prescribed with 12 medications; significant *DGIs* were found in 73% of tested patients and *DDIs* in 87% of patients. In the study explained in paper [2], *DDIs* accounted for 66.1% of the total interactions, and the remaining 33.9% were *DGIs*. In Canada, among patients aged 65 years and older with polypharmacy (>5 drugs) admitted to hospital, the prevalence of potential drug interactions is 80% [3]. The study described in the paper [4] states that in 1994 some 2,216,000 hospitalized patients had

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severe *ADRs* with 106,000 fatal outcomes, making these reactions between the fourth and sixth leading cause of death in the US that year.

Our research is motivated by the urgency of finding solutions to these troubling facts. In this paper, we present the Personalized Medicine Therapy Optimization Method *(PM- TOM)* for the discovery of polypharmacy therapies with minimal *DDIs*, *DGIs*, and *DCIs* (referred to in the paper as cumulative adverse interactions - *CADIs*). In Section 2, we explain the inputs, outputs, and the database of the *PM-TOM* method, and in Section 3, its heuristic algorithm. In the development, testing, and validation of *PM-TOM*, we used the public data repositories of the *Personal Genome Project (PGP)* [5], *DrugBank* [6], and *Comparative Toxicogenomics Database (CTD)* [7]. Results, presented in Section 4, show that *PM-TOM* has the potential to aid in the significant reduction of the cumulative drug interactions in polypharmacy therapies.

2. PM-TOM Database, Inputs and Outputs

The components of the ***PM-TOM* database** are *(i)* Electronic Medical Records (*EMR*) repository (denoted as *EMR)*, *(ii)* Drug Repository *(DRG)*, and *(iii)* Gene-Drug Repository *(GDR)*. The current version of *PM-TOM* requires from *EMR* only the patient conditions, drug product prescriptions, and genome (gene variations that could be pathogenic or affect drug behavior, i.e., found to be pharmacogenetic). Other *EMR* elements, such as the patient's gender, race, blood type, drug dosages, etc., will be used in the future *PM-TOM* versions. Formally, $EMR \subset PID \times \mathbb{P}(C) \times \mathbb{P}(G) \times \mathbb{P}(P)$, where *PID* is a set of patient *ID*s, *C* the set of all conditions, *G* the set of all genes and their variants, *P* set of all commercial drug products, and $\mathbb{P}$ powerset symbol.

The drug repository *(DRG)* includes data about the active drug ingredients (referred to as "drugs" in this paper), commercial drug products (referred to as "drug products"), drug-drug interactions, and drug-condition contraindications. The database keeps drug interactions by referencing active drug ingredients (drugs) rather than drug products. If *D* denotes the set of all drugs, then the set of drug products *P* can be defined as $P \subset D \times N$ (*N* is the set of product names). Set *DC* describes the drug indications, $DC \subset D \times C$. Set $DDI \subset D \times D \times DDS$ defines the drug-drug interactions, where set $DDS = \{1, 2...\}$ quantifies their relative severities. Similarly, set $DCI \subset D \times C \times DCS$ describes the drug contraindications, where set *DCS* quantifies their severities. Gene-Drug Repository *(GDR)* keeps data about drug-gene interactions and their severities, denoted as set $DGI \subset D \times G \times DGS$ (*DGS* is a set of their severities).

***PM-TOM* inputs** include a patient's *(i)* conditions, *(ii)* considered drug products, *(iii)* genome, and *(iv)* the initial therapy, which is composed of a single drug product for each condition. Formally, the input *PM-TOM* record is $r_i = (pid_i, C_i, G_i, P_i, t_i)$, where $pid_i \in PID$; C_i is the set of the patient's conditions, $C_i \subset C$; G_i is the patient's genome, $G_i \subset G$; P_i is the set of considered drug products, $P_i \subset P$; and t_i is the initial therapy, $t_i \subset C_i \times P_i$.

***PM-TOM* outputs** are *(i)* optimal therapy for considered drug products, *tc*, *(ii)* optimal therapy for all drugs, *to*, which *PM-TOM* creates after examining all drugs from *EMR* applicable to the patient's conditions, and *(iii)* a detailed personalized therapy report. The report elaborates both optimal therapies, indicating their *CADIs*, and explaining their drug-drug, drug-gene, and drug-condition interactions. It also includes the list of all available drug products for each drug suggested in *to*.

3. PM-TOM Algorithm

In Step 1, *PM-TOM* collects the patient's record. An example is a *PGP* record with patient's *ID* ='*huC29627*'; conditions *Ci= {Anxiety, ADHD, Depression}*; genome *Gi = {CBS, TGM1, MBL2, C3, BRCA2, COL41A, TP53, ITPA, KCNH2, DRD2, MBL2, CACNA1C}*; considered drug products *Pi= {Venlafaxine, Xanax, Zoloft, Escitalopram, Adderall, Ritalin, Celexa, Wellbutrin, Viibryd}*; and the initial therapy *ti = {(Anxiety, Zoloft), (ADHD, Adderall), (Depression, Celexa)}.*

PM-TOM identifies, in Step 2, the corresponding drug (drug ingredient) of each considered drug product. For example, the active drug ingredient of *Xanax* is *Alprazolam*. Next, as Step 3, *PM-TOM* prepares the set of pairs of conditions and considered drug products, called *CDi*. In the above example, *CDi= {(Anxiety, Venlafaxine), (Anxiety, Xanax), (Anxiety, Escitalopram), (Anxiety, Zoloft)*, (ADHD, Adderall)*, (ADHD, Ritalin), (Depression, Celexa)*, (Depression, Viibryd), (Depression, Wellbutrin)}.* The pairs marked with *** indicate the initial therapy (t_i).

In Step 4, *PM-TOM* uses set *CDi* to identify candidate therapies, t_k, for considered drug products. It forms candidate therapies by replacing only one drug in the initial therapy with another drug from set *CDi* applicable to the same condition. An example of a candidate therapy is *{(Anxiety, Xanax), (ADHD, Adderall) *, (Depression, Celexa) *}*, i.e., for *Anxiety*, *Xanax* replaced *Zoloft*. Note that *PM-TOM* does not evaluate all combinations of considered drug products so that it could miss the most effective therapy. However, the testing results show that this approach can lead to significant improvements in the initial treatments. If *d* is the average number of candidate drugs for *n* conditions, then the complexity of an algorithm that evaluates all drug combinations will be proportional to d^n. *PM-TOM* examines only *n*d* candidate therapies.

In Step 5, *PM-TOM* calculates *CADI* indicator *(w)* of each candidate therapy t_k after examining the following sets: *(i)* drug-drug interactions $DDI_k = \{ddi_k = (d_1, d_2, dds): \exists(c_1,d_1) \in t_k, \exists(c_2, d_2) \in t_k, ddi_k \in DDI\}$, *(ii)* drug-gene interactions $DGI_k = \{dgi_k = (d, g, dgs): \exists(c,d) \in t_k, g \in G_i, dgi_k \in DGI\}$, and *(iii)* drug-condition contraindications $DCI_k = \{dci_k = (d, c, dcs): \exists(c_1, d) \in t_k, \exists(c, d_1) \in t_k, \nexists (c_1, d_1) \in t_k, dci_k \in DCI\}$. $w(t_k)$ is calculated as

$$w(t_k) = DDIP * \sum_{ddi_k \in DDI_k} ddi_k[dds] + DGIP * \sum_{dgi_k \in DGI_k} dgi_k[dgs] + DCIP * \sum_{dci_k \in DCI_k} dci_k[dcs]. \quad (1)$$

DDIP, *DGIP*, and *DDIP* are the *PM-TOM* parameters that define relative weights of *DDIs*, *DGIs*, and *DCIs* (set to 1 by default). $ddi_k[dds]$, $dgi_k[dgs]$, and $dci_k[dcs]$ indicate severities of these interactions. As an example, the *CADI* indicator of the above initial therapy is $w(t_i) = 6$.

Next, in Step 6, the algorithm iterates through all conditions, and for each condition, finds candidate therapy with minimal *CADI*. In Step 7, *PM-TOM* uses the drugs for each condition that form these candidate therapies to create the optimal therapy for considered drug products. In the above case, the optimal therapy is t_c= *{(Anxiety, Venlafaxine) #, (ADHD, Ritalin) #, (Depression, Celexa)#}*, with $w(t_c) = 4$.

As mentioned above, *PM-TOM* is an iterative method. It repeats the above steps, taking the optimal therapy found above as the initial therapy for the next iteration. If the new candidate optimal therapy shows no better *w(tc)*, the algorithm will stop (Step 8).

In the next phase, *PM-TOM* repeats Steps 3-8 to find the optimal therapy for all drugs *(to)* after *(i)* collecting all drugs from the *EMR* used to treat the patient's conditions and *(ii)* taking already found therapy *tc* as the starting point, instead of therapy *ti*. In the above example, *EMR* returned 33 applicable drugs. *to* was found as *{(Anxiety, Butabarbital)#, (ADHD, Dexmethylphenidate HCL) #, (Depression, SAM-E) #}*, with *w (to)=1*. The report for this *EMR* can be found at https://www.abs-info-age.com/project-1.

4. PM-TOM Validation and Testing

In the development, testing, and validation of *PM-TOM*, we used the *EMRs* of *PGP*, which include the patient conditions, genome, and administered drug products. *DrugBank* provided the drug product, drug-condition, and drug-drug interaction data, and *CTD* the drug-gene interaction data. We tested 286 *EMR*s. Table 1 lists in column *(A)* various categories of tested *EMRs*, which have the same number of conditions. Column *(B)* shows the count of cases and *(C)* the average number of genes in each category. Columns *(D)* and *(E)* display the average number of considered drug products and all drugs applicable to the patient's conditions.

Table 1. Average *CADI* of the optimal therapies for the considered drugs and all applicable drugs.

(A) Conditions	(B) Cases	(C) Genes	(D) Consid. drugs	(E) All drugs	(F) *CADI* - Consid. drugs	(G) *CADI* – All drugs
1	77	13.58	1.31	6.12	0.6	0.09
2	119	5.74	2.34	10.6	1.05	0.22
3	49	3.43	3.51	16.71	2.1	0.33
4	16	4.31	4.38	20.88	3.38	0.56
5	13	4.46	5.92	26	4.92	2.08
6..7	6	2.33	7.33	34	11.17	3
8-	6	10	12.83	42	22	5.83

Columns *(F)* and *(G)* display the average *CADIs* of the optimal therapies for considered drug products and all applicable drugs, which indicate a significant reduction of the average *CADI* between these two therapies (approximately three to six times, depending on the category). The algorithm required two iterations (Figure 1).

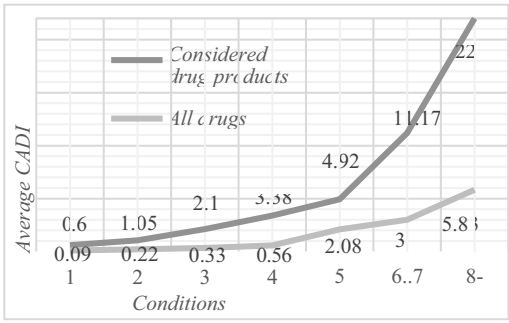

Figure 1. Average CADI for optimal therapies

5. Discussion

In paper [8], the author underlines the need for highly personalized drug selection by expert systems. To the best of our knowledge, *PM-TOM* is an original approach to do so. The testing results presented in Section 4 show that the method can identify possible treatments with significantly decreased *CADIs.* We also tested *EMR*s for some recurrent multi-diseases, like *{Hypertension, Diabetes Mellitus, Hyperlipidemia},* and their *CADI* reduction was approximately five times. A data mining algorithm for finding frequent multi-diseases, and their possible monogenic causes, is explained in paper [9].

Why do prescribed therapies typically have a high number of drug interactions? We speculate that the reasons are the lack of the patient's genetic data, which would enable finding highly personalized therapies, and the limitations of used tools, which are typically focused on *DDI* alerts. Also, according to the investigation in the US, reported in paper [10], these alerts are overridden for various reasons in about 90% of cases.

PM-TOM is an efficient iterative heuristic algorithm. Its testing confirmed that very few iterations lead to finding therapies with significantly decreased CADIs. The algorithm complexity is rather low as it evaluates a small subset of candidate therapies. For example, for seven candidate drugs for 12 conditions, PM-TOM will examine only 84 candidate therapies per iteration of possible 14 billion ones. Due to that feature, PM-TOM has room for extension with other features relevant for polypharmacy therapies, such as (i) rule-based medical guidelines, (ii) lab test results, (iii) drug dosages, (iv) patient's demographic data (age, race, gender, environment), (v) drug-drug-gene interactions (DDGIs), (vi) drug-food interactions, (vii) drug-microbiome interactions, and others.

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