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Using *PM-TOM* for the Minimization of Adverse Drug and Gene Interactions in Therapies for Common Multi-Diseases

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Abstract. Multiple studies show that therapies for multi-diseases can lead to dangerous reactions and high healthcare costs due to their adverse drug-drug, drug-gene, and drug-condition interactions. In this paper, we present the results of using *PM-TOM* (*Personalized Medicine Therapy Optimization Method*) for finding therapies that minimize these interactions. The testing of the method was performed on the repository of electronic medical records of the *Harvard Personal Genome Project (PGP)*, and the public databases of the drug and genetic information: *DrugBank* and *Comprehensive Toxicogenomics Database (CTD)*. The results presented in this paper showed a significant potential of *PM-TOM* for reducing the cumulative adverse drug interactions in therapies for common multi-diseases.

Keywords. Personalized Medicine, Clinical Decision Support Systems (*CDSS*), Multi-diseases, Polypharmacy Therapies, Electronic Medical Records *(EMR)*, Adverse Drug Reactions *(ADR)*, Drug-Drug Interactions *(DDI)*, Drug-Gene Interactions *(DGI)*, Drug-Condition Interactions *(DCI*).

1. Introduction

Polypharmacy therapies for patients with multi-diseases pose significant health risks due to the possibility of their adverse drug-drug *(DDI)* drug-gene (*DGI*) and drug-condition (*DCI*) interactions, referred to as *CADI* (cumulative adverse drug interactions).

Studies [1] and [2] found *DDI*s in 66% and 87% of polypharmacy cases and *DGIs* in 33.9% and 73% of cases, respectively. In Canada [3], drug interactions are found in 80% of patients older than 65 years admitted to the hospital. Also, the study [4] reports that in 1994 some 2 million hospitalized patients had severe Adverse Drug Reactions *(ADR)* with more than 100k fatal outcomes, making these reactions between the fourth and sixth leading causes of death in the US that year.

Our research is motivated by the necessity of finding solutions to these worrying facts. In this paper, we present the results of applying the Personalized Medicine Therapy Optimization Method *(PM-TOM)* on cases of common multi-diseases. Its formal specification can be found in the paper [5]. Section 2 of this paper presents the *PM-TOM* method, data model and algorithm. In Section 3, we show the results of testing *PM-TOM* on *EMRs* with selected common multi-diseases. An exemplary multi-disease case is discussed in Section 4, along with the conclusions.

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2. *PM-TOM Data Model and Method*

Figure 1 shows the ***PM-TOM* Data Model**. Its core entities are *Patient, Condition, Gene, Drug Product,* and *Drug* (main drug product ingredient), which are associated via entities *Applied Drug*, *Drug Indication, Patient Condition,* and *Patient Gene*. Entities *Drug-Drug Interaction*, *Drug-Gene Interaction,* and *Drug-Condition Interaction* keep information about *DDIs*, *DGIs,* and *DCIs,* including their severities.

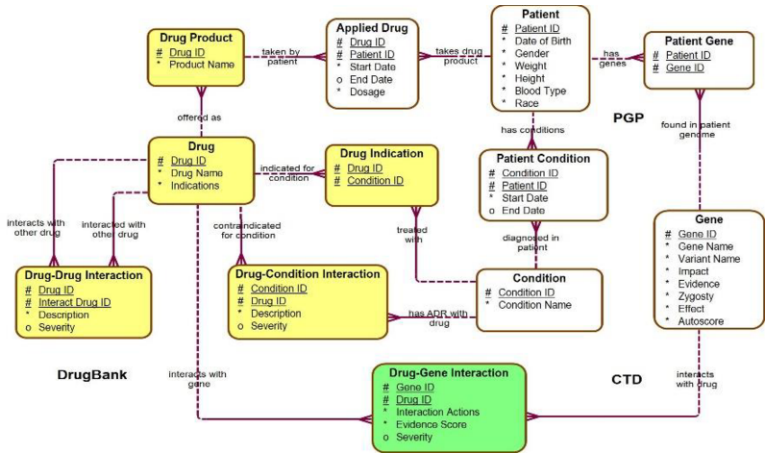

Figure 1. *PM-TOM* data model.

***PM-TOM* inputs** are *(i)* a patient's *EMR* record, composed of the patient's conditions and genome, *(ii)* one or many considered drug products *(CD)* for these conditions, and *(iii)* the initial therapy *(IT)*, composed of a single drug product for each condition.

***PM-TOM* outputs** are *(i)* optimal therapy for considered drugs (*OTCD*), *(ii)* optimal therapy for all applicable drugs (*OTAD*), and *(iii)* a detailed personalized therapy report *(PTR)*. *OTCD* has minimal *CADI* within the treatments formed of the considered drug products. On the other hand, *OTAD* has minimal *CADI* for therapies formulated from all medications prescribed to the patient's conditions in an *EMR* repository. *PTR* explains both optimal treatments, indicating their *CADIs*, and also describes their drug-drug, drug-gene, and drug-condition interactions. *PM-TOM* can also identify therapies with maximal *CADIs*, which suggest treatments with possible serious adverse effects.

To find *OTCD*, the ***PM-TOM* algorithm** [5] examines candidate therapies made from *IT* by replacing only one drug with another *CD* drug indicated for the same condition. For each candidate therapy, *PM-TOM* calculates *CADI* as a sum of its *DDI*s, *DGI*s, and *DCI*s, each interaction weighted by its severity (having values 1, 2, 3, etc.). In a special case, if the severities are not available, the *CADI* will be calculated as the sum of all *DDI*s, *DGI*s, and *DCI*s. *OTCD* is a candidate therapy with minimal *CADI*.

PM-TOM is an iterative method. In the next step, to find *OTAD*, it will examine all drugs from the *EMR* database prescribed for the patient's conditions. Instead of *IT*, the algorithm will now use its improved version, *OTCD*, created in the previous iteration. So, *PM-TOM* uses the expert knowledge of the physicians and clinical pharmacists expressed in the initial therapy, considered drugs and all prescribed drugs in *EMR*.

In the last step, *PM-TOM* generates *PTR*, which contains further details about both optimal therapies and their *CADI*s, including alternative drug products. Sample reports can be found at https://www.abs-info-age.com/projects.

3. *Testing Results*

We tested *PM-TOM* for finding treatments for common multi-diseases by using the database of the *Harvard Personal Genome Project (PGP)* [6], and public repositories *DrugBank* [7], and *Comparative Toxicogenomics Database (CTD)* [8].

In a cohort of 484 patients, we identified 16 most common diseases. Examples of these diseases are *Hypertension*, *Allergy*, *Hypercholesterolemia*, *Depression*, *Anxiety*, *Diabetes Mellitus, Asthma,* etc. We tested multi-disease patients that have at least three of these 16 conditions, for example: *(Allergy, Asthma, Rhinitis)* and *(Diabetes Mellitus, Hypercholesterolemia, Hypertension, GERD)*.

Table 1 presents the testing results. Column *(A)* indicates categories of cases that have at least one multi-disease and the same number of all treated conditions. Column *(B)* shows the count of *EMR*s in each category. Column *(C)* displays the average number of considered drugs in each group, taken from the patient history, and column *(D)* the average *CADIs* of their optimal therapies for considered drugs *(OTCDs)*.

The next columns show the testing results for drugs prescribed for the patient's conditions in any *EMR*. The average count of these drugs is indicated in column *(E)*, and the average *CADI* of their *OTAD* in column *(F)*. In column *(H)*, we also calculated the average *CADI* for maximum drug and gene interaction therapies for all drugs (*MITAD)*. *MITAD* analysis illustrates the worst-case scenarios. Additionally, pair *OTAD* and *MITAD* show the *CADI* range for all possible treatments.

Finally, column *(G)* presents the *CADI* improvements between the *OTCD* and *OTAD*, which is, on average, about four times. Also, column *(I)* shows the ratio between the corresponding *OTAD* and *MITAD CADI*s, which come to 9 times on average.

These results suggest that various candidate multi-disease therapies show a rather large range of *CADI*s and that *CDSSs* can significantly support the physicians and clinical pharmacists to select proper treatments that minimize these interactions.

Table 1. Average *CADI* of optimal and least desirable therapies for common multi-diseases.

A	B	C	D	E	F	H	G	I
Total conditions	**Patients**	**Considered drugs (avg.)**	***OTCD - CADI* (avg.)**	**Appl. drugs (avg.)**	***OTAD - CADI* (avg.)**	***MITAD CADI* (avg.)**	**D/F *CADI***	**H/F *CADI***
3	7	3.57	2.14	19.29	1	5	2.14	5
4	4	5.25	4	29.5	0.5	7.25	8	14.5
5	7	6.43	4.86	27	1.57	15	3.09	9.55
6	2	7	9	32.5	3	14.5	3	4.83
7	3	8.33	14	38.33	4	18	3.5	4.5
8	2	11.5	17.5	47.5	1.5	34.5	11.67	23
>8	3	12.67	24.33	38	9	72	3.02	8
Avg.							**4.02**	**9.05**

4. *Discussion and Conclusions*

As an additional illustration, we discuss the case of a male, 62 years old patient. He suffers from a complex multi-disease (*Asthma, BPH, Diabetes Mellitus, GERD, Hypertension, Hypothyroidism, Hypercholesterolemia,* and *Keratosis*). His genome contains pharmaco-genetic genes *ABCC6, CYP2C9,* and *TPMT,* and pathogenic genes *AIP, APOA5, ELAC2, HFE, KRT5, MTRR, RNASEL, SLC4A1, SP110, TGIF1.*

PM-TOM returned *OTCD* as *Efudex (Fluorouracil)* for *Keratosis*, *Finasteride* for *BPH*, *Flovent (Fluticasone Propionate)* for *Asthma*, *Levothyroxine (Liothyronine)* for *Hypothyroidism*, *Metformin* for *Diabetes Mellitus*, *Micardis (Telmisartan)* for *Hypertension*, *Zocor (Simvastatin)* for *Hypercholesterolemia* and *Nexium (Esomeprazole)* for *GERD*. This therapy has 19 *DDIs* and 7 *DGIs* (*CADI* = 26). Examples of these interactions are *'The metabolism of Fluorouracil can be decreased when combined with Simvastatin'*, and *DGI 'Gene TPMT affects the response to Fluorouracil'*.

After considering all applicable drugs from the *PGP* database, *PM-TOM* returned the following *OTAD*: *Exenatide* for *Diabetes Mellitus*, *Famotidine* for *GERD*, *Imiquimod* for *Keratosis*, *Minoxidil* for *Hypertension*, *Niacin* for *Hypercholesterolemia*, *Omalizumab* for *Asthma*, *Terazosin* for *BPH* and *Thyroid Porcine* for *Hypothyroidism*. This therapy has only 2 *DDIs* and no *GDIs* (*CADI* = 2). The complete example and its *PTR* can be found at https://www.abs-info-age.com/precision-medicine-report-3.

The above results lead to the conclusion that finding effective polypharmacy therapies for multi-diseases with minimal adverse interactions is not a simple task and that *CDSSs* like *PM-TOM* can provide significant support to the physicians and clinical pharmacists in making decisions about these therapies.

PM-TOM is an efficient iterative heuristic algorithm. Its complexity is rather low as it evaluates a small subset of all possible candidate therapies. That leaves room for its further extension with additional knowledge about the patient, such as age, gender, race, lab tests, etc.

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