The Importance of Health Informatics in Public Health during a Pandemic
J. Mantas et al. (Eds.)

doi:10.3233/SHTI200501

Visualization of Potential Drug Synergies

Jean-Baptiste LAMY [a,b,1]
[a] *Université Sorbonne Paris Nord, LIMICS, INSERM, UMR 1142, F-93000, Bobigny, France*
[b] *Laboratoire de Recherche en Informatique, CNRS/Université Paris-Sud/Université Paris-Saclay, Orsay, France*

Abstract. Drug synergy must be taken into account when prescribing several drugs for treating the same disorder. Synergies are sometimes known from clinical trials, but they are not systematically studied. In this paper, we present a visual approach for identifying and explaining the potential synergies between the 2-15 drugs available for a given disorder. It is based on the chaining of two bioinformatics databases, Drug Bank and Signor, and relies on set visualization with rainbow boxes. We apply this approach to antihypertensive drugs, and show that some European recommendations can be visually deduced and explained.

Keywords. Drug synergy, Hypertension, Visual analytics, Visualization, Non-verbal communication

1. Introduction

For many disorders, several drug treatments are available and can be prescribed. In patients with advanced forms of the disease, it is sometimes possible to associate several drugs or active principles (*i.e.* a bitherapy or tritherapy), in order to obtain a synergy in their beneficial effects. However, this synergy is not systematic and depends on the mechanisms of action of the drugs involved: in some cases, no benefit is obtained by combining several drugs. Moreover, when prescribing several drugs, the risk of adverse effects may be increased.

In clinical practice, the decision to prescribe a drug association is made on the basis of recommendations given in clinical practice guidelines. The guidelines themselves rely on clinical trial results and/or professional expertise when no medical evidence is available. Nevertheless, it would be of particular interest to be able to predict the potential synergy between the drugs available for a given disorder, especially when guidelines are not available, or in order to confirm and strengthen the existing guidelines. In the literature, several systems were proposed for predicting drug synergies [6-7]. However, these systems focused on automatic prediction, while a visual approach would be interesting for presenting the pharmacological data available to experts and clinicians, and for explaining why a synergy exists between two drugs.

In this paper, we present a preliminary study aimed at visualizing, identifying and explaining the potential synergies between the main antihypertensive drug classes, by

[1] Corresponding Author, Jean-Baptiste LAMY, Université Sorbonne Paris Nord, LIMICS, INSERM, UMR 1142, F-93000, Bobigny, France; E-mail: jibalamy@free.fr.

chaining two bioinformatics databases, Drug Bank and Signor, and applying a set visualization technique, rainbow boxes.

2. Methods

We used two bioinformatics databases. First, Drug Bank 5.0 [1] was used to extract the therapeutic and non-therapeutic targets of each drug. Since most targets are proteins, we also used Signor 2.0 [2], which describes up- and down-regulation between proteins in Human. Both data sources were integrated in an OWL ontology using ontology-oriented programming [3], and relations present in Signor were chained, in order to obtain, for each drug, the list of protein targets that the drug activates and inhibits, directly but also indirectly (using simple Boolean rules such as if drug D activates protein P1 that inhibits protein P2, then drug D indirectly inhibits protein P2).

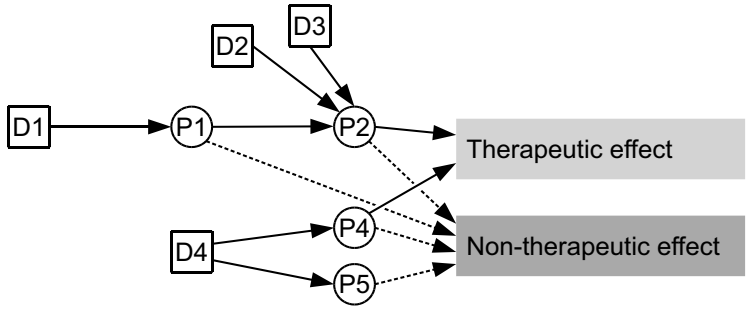

Figure 1. Simple example of drug and protein regulation pathway (D: drug, P: protein / target).

Regarding the underlying mechanism for drug synergy, our hypotheses are the following: (a) Non-therapeutic targets (*e.g.* P5) may cause undesired effects, including adverse effects. (b) No synergy is expected between two drugs that have the same target. In this case, it is probably better to prescribe only one drug, with an increased dose. For example, in Figure 1, no synergy is expected between D2 and D3. (c) No synergy is expected between two drugs when the target of one drug is located upstream the regulation flow of the target of the other drug (*e.g.* in Figure 1, between D1 and D2, or D1 and D3). In addition, drugs acting upstream are expected to have more adverse effects, e.g. here D1 may cause more adverse effects than D2 and D3 because P1 may have additional undesired effects. (d) On the contrary, a synergy is expected between drugs having distinct unrelated targets (*e.g.* in Figure 1, between D1 and D4, D2 and D4, or D3 and D4. (e) When drugs have more than one therapeutic target, we expect a higher synergy when their targets differ and are not located upstream one of each other.

To facilitate the identification of drugs having similar or different targets, we used visual analytics and set visualization with rainbow boxes [4]. Each drug can be considered as an element, and each protein can be modeled as the set of all drugs acting on that protein (directly or indirectly). The nature of the drug targets are indicated using colors, and we add hatches to indicate indirect targets.

3. Results

We applied our approach to antihypertensive drugs. Existing synergies between these drugs are well-known and described in guidelines. This allows the validation of our approach. Five main antihypertensive drug classes exist: Betablocking agents (*e.g.* acebutolol), Angiotensin-Converting Enzyme (ACE) inhibitors (*e.g.* captopril), Angiotensin II receptor blockers (ARB, *e.g.* irbesartan), Thiazide diuretics (*e.g.* hydrochlorothiazide) and Calcium channel blockers (CCB, *e.g.* diltiazem).

Figure 2 shows the resulting visualization with rainbow boxes. Drug classes are shown in columns, and target proteins in colored boxes. Boxes cover one or more column, corresponding to the drug that acts on this target, *e.g.* only Betablocking agents act on the "Beta-1 adrenergic receptor" target, while Betablocking agents, ARB and ACE inhibitors act on the "Beta-2 adrenergic receptor" target. Columns were ordered according to box similarity, as usually done with rainbow boxes.

Box color indicates the nature of the target: red for non-therapeutic targets, yellow for therapeutic targets located upstream another therapeutic target (*e.g.* P1 in Figure 1), green for other therapeutic targets (*e.g.* P2 and P4 in Figure 1). White hatches indicate indirect targets, *e.g.* for ACE inhibitors, their action on "Type-1 angiotensin II receptor" is indirect, and results from their action on "Angiotensin-converting enzyme". Drug synergy is expected to occur between columns having different green boxes.

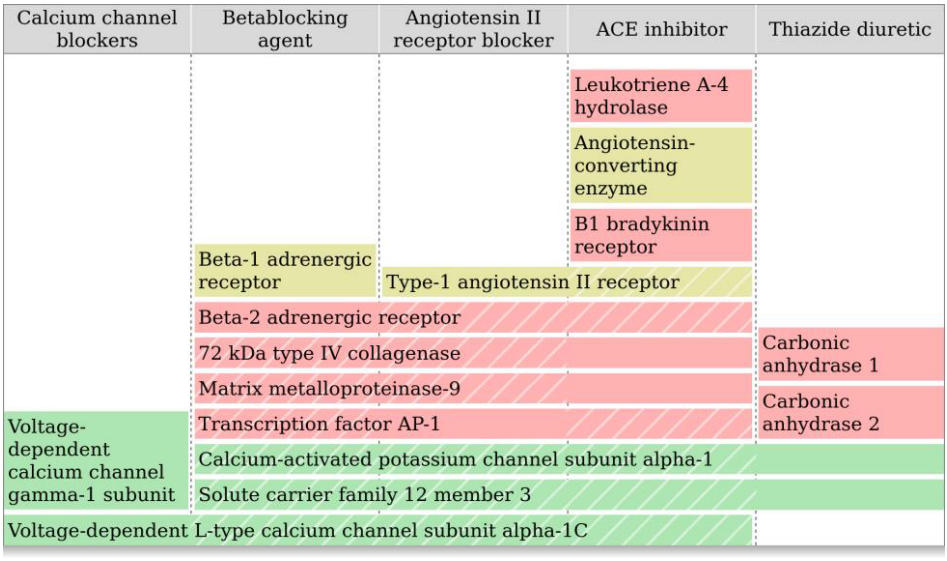

Figure 2. Rainbow boxes showing the direct and indirect targets of the five main antihypertensive classes.

Several information regarding drug synergy can be obtained from Figure 2: (1) Betablocking agents, ARB and ACE inhibitors have the same "downstream" therapeutic targets. Consequently, there is no expected synergy between these drugs (hypothesis c above). (2) In addition, ACE inhibitors have more non-therapeutic targets that ARB. Thus they are expected to cause more adverse drug events. (3) Drug synergy is expected between CCB and one of Betablocking agents, ARB, ACE inhibitors or Thiazide diuretics. The European Society of Cardiology (ESC) and the European

Society of Hypertension (ESH) guidelines [5] recommend for uncomplicated hypertension one of the following four associations: ACE inhibitor + CCB, ACE inhibitor + diuretic, ARB + CCB, ARB + diuretic. This recommendation is partly concordant with the synergy expected from Figure 2, however, our approach allows explaining why a synergy is expected or not between some drugs. In addition, the same guidelines explicitly mention the absence of synergy between ACE inhibitors, and also mention that ARB cause fewer adverse drug events. On the contrary, our approach found no synergy between diuretics and ACE, ARB or Betablocking agents.

4. Discussion and Conclusions

In this paper, we proposed a visual approach for identifying and explaining the potential synergies between the drugs available in a given indication, on the basis of the data present in bioinformatics databases. We tested this approach in hypertension, a domain in which drug synergies are known from clinical trials, and detailed in guidelines. Our approach allowed identifying some already known synergies in this context. In the literature, few works focused on drug synergy. Protein-protein interaction networks are classically used for identifying synergies [6], as we did here. D. Chen *et al.* [7] used pathway-pathway interactions in addition to drug targets and showed that pathway-pathway interactions increased predicting performances. However, existing approaches do not propose a visual overview of the drug targets, as we did here with rainbow boxes. The perspective of this work are: (1) To improve the proposed approach by considering additional bioinformatics databases and by using more sophisticated rules for chaining regulation interactions between proteins, for example considering weighted interactions between proteins. (2) To apply the proposed approach to more complex domains, such as oncology, in which drug treatments are complex and often associated. In addition, new oncologic treatments are regularly marketed, and their synergy with previous treatments remain unknown at the beginning. (3) To extend our approach for supporting personalized medicine. For example, if the patient does not express a given receptor, the corresponding box can be hidden in rainbow boxes, adapting the visualization to the patient.

References

[1] Wishart DS et al., DrugBank 5.0: a major update to the DrugBank database for 2018, Nucleic acids research 46 (2018), D1074-D1082.
[2] Licata L et al., SIGNOR 2.0, the SIGnaling Network Open Resource 2.0: 2019 update, Nucleic acids research 48 (2020), D504-D510.
[3] Lamy JB, Ontology-Oriented Programming for Biomedical Informatics, Stud Health Technol Inform 221 (2016), 64-68.
[4] Lamy JB, H. Berthelot, C. Capron, M. Favre, Rainbow boxes: a new technique for overlapping set visualization and two applications in the biomedical domain, Journal of Visual Language and Computing, 43 (2017), 71-82.
[5] Williams B et al., 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH), European Heart Journal 39 (2018), 3021-3104.
[6] Jia J, Zhu F, Ma X, Cao ZW, Li YX, Chen YZ, Mechanisms of drug combinations: interaction and network perspectives, Nature Reviews Drug Discovery 8 (2009), 111-128.
[7] Chen D, Zhang H, Lu P, Liu X, Cao H, Synergy evaluation by a pathway–pathway interaction network: a new way to predict drug combination, Molecular BioSystems 12 (2016), 614-623.