# A NETWORK-BASED APPROACH FOR THE PREDICTION OF SIDE EFFECTS OF REPURPOSED DRUGS DUE TO OFF-TARGET AND DRUG-DRUG INTERACTIONS

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Biological systems are made of heterogenous elements that form interaction networks at different levels of organization. Network medicine, as an extension of network biology, is based on the representation of biological components as nodes that are connected by edges in a graph with the purpose of understanding disease etiology, identifying potential biomarkers and drug targets, uncovering molecular interactions, and designing therapeutic interventions. Research on this field aims to understand the larger picture by treating biological systems holistically, instead of focusing solely on a set of genes, proteins, or interactions. Networks are thus the “heart” of biomedical data revolution and personalized medicine, while

providing the framework for creating innovative models and obtaining significant results.

It has been suggested that the proteins that directly interact with a drug's protein target (first neighbors) could act as off-targets for the specific drug in question, other drugs that share the same drug target with the drug in question and the drugs that target the drug's first neighbors in the network [1]. It has also been proposed that the drugs that share a drug target or target neighbor proteins in the human interactome could also participate in drug-drug interactions. Based on the above, we propose a network-based methodology as an initial prediction of the potential for side effects resulting from drug-drug or off-target interactions that could occur when a drug is repurposed [2].

In this work, a network-based methodology is applied for the prediction of possible side effects resulting from drug-drug or off-target interactions that could occur when known Food and Drug Administration (FDA) approved antihypertensive drugs sartans are repurposed as a treatment strategy for COVID-19. This methodology was also used for Paxlovid, an antiviral drug that is currently approved by the FDA for emergency use against COVID-19 as baseline.

The use of drugs that affect the Renin-Angiotensin-Aldosterone system (RAAS) in the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently being under investigation, as they are considered an efficient and promising treatment plan for the Coronavirus disease 19 (COVID-19). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are first-line treatments for hypertension, heart failure (CHF) and diabetic kidney disease (DKD). Recently, there has been research into the repurposing of ARBs for the treatment of COVID-19, due to their ability to bind to angiotensin-converting enzyme 2 (ACE2), the protein which interacts with SARS-CoV-2 spike (S-) protein. Though, so far no *in silico* study has been performed to predict their toxicity risks in the case that they target ACE2 and are repurposed to treat COVID-19. With the implementation of the methodology mentioned above, the undesirable involvement in numerous biological processes, and possible off-drug and drug-drug interactions of sartans are predicted. To do so, the human proteins targeted by sartans, their first neighbors, and any drugs that bind to them were identified and subsequently all that information was used for the construction of protein-drug networks.

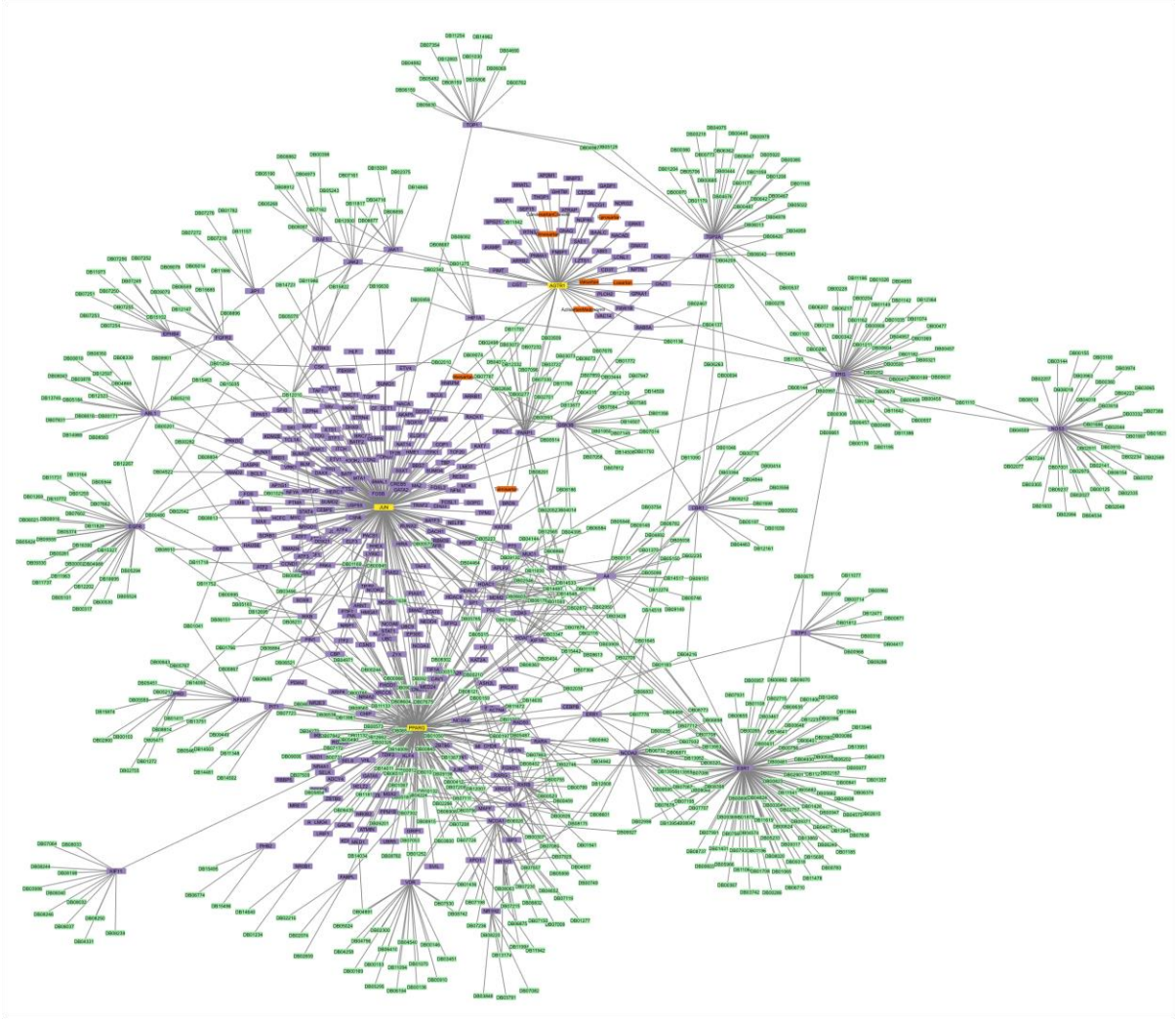

**Figure 1:** The protein-drug interaction network of sartans (orange), AT1R/c-JUN/PPAR-γ (yellow), the 3 targets' first neighbors (purple), and the drugs that target AT1R/c-JUN/PPAR-γ and their first neighbors (green).

## References:


1. Lin, S.F.; Xiao, K.T.; Huang, Y.T.; Chiu, C.C.; Soo, V.W. Analysis of adverse drug reactions using drug and drug target interactions and graph-based methods. *Artif Intell Med* **2010**, *48*, 161-166, doi:10.1016/j.artmed.2009.11.002.
2. Zhou, H.; Gao, M.; Skolnick, J. Comprehensive prediction of drug-protein interactions and side effects for the human proteome. *Scientific Reports* **2015**, *5*, 11090, doi:10.1038/srep11090.