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Scientific Tracks & Abstracts

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Development of a novel filtered-based pharmacophore for the identification of human equilibrative nucleoside transporter 1 inhibitors

Azza Ramadan
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Statement of the Problem: The human equilibrative nucleoside transporters (hENTs) are important transporters that allow nucleosides and nucleobases permeation into the cell. hENT 1 is a promising target against heart and Huntington's diseases as its inhibition mediates cardiac- and neural protection effects, respectively. However, the current hENT1 inhibitors have significant off-target effects and poor pharmacological profile. Hence there is a need for new novel inhibitors.

Methodology: Therefore, we developed a computational protocol for developing ligand-based pharmacophores that identify and select inhibitors of hENT1 in an efficient and specific manner. To examine the efficacy of the pharmacophore and its application later on in the drug discovery of new hENT1 inhibitors, we used this pharmacophore as a filter prior to a small-scale virtual screening (VS) of a drug-like ligand library. The library consisted of 5000 compounds; 56 of which were known hENT1 inhibitors.

Findings: First, several pharmacophores were created using a set of known inhibitors. Among the several created pharmacophores, the best inhibitor pharmacophore exhibited high selectivity and specificity rates of 92% and 88%, respectively. Furthermore, another pharmacophore was validated for the oppositely acting type of the hENT1 molecules (i.e. permeants) to act as an extra refinement step in our search for hENT1 inhibitors. Interestingly, employing the inhibitor pharmacophore as a filter-in along with the permeant pharmacophore as a filter-out resulted in up to twofold enhancement of docking-based virtual screening results (see Table 1).

Conclusion & Significance: This in silico approach can prove very useful in the discovery of new cardio- and neuroprotective hENT1 inhibitors.

Table 1. Retrieved rate of hENT1 inhibitors at various portions of the sorted docked ligands from filter-based and non-filtered-based virtual screening

Output percentage of the top-ranked docked 5000-ligand library	The rate of retrieved inhibitors		
	No-filter	One filter	Two filters
1	12.5	19.6	21.27
3	17.8	35.29	34.04
5	26.78	49.02	48.93
10	42.85	80.39	80.85
20	57.14	98.04	100

Biography

Azza Ramadan is a molecular biologist and currently an Assistant Professor at Al Ain University in the United Arab Emirates. She obtained her PhD from the University of Toronto in Canada with a specialization in biomedical sciences. Among her areas of research, is investigating the role of the human equilibration nucleoside membrane transporter hENT1 in cardio and neuroprotection. Her research interest stems from her work during her graduate studies that shed light on ENT1 central role in purinergic s signalling in the cardiovascular system. Her research was supervised by the internationally renowned expert in membrane transport proteins, Prof Imogen Coe.

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COVID-19 detection on chest x-ray using an enhanced neural network model: Impact of data network complexity, data augmentation, and transfer learning

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Statement of the Problem: Machine learning (ML) algorithms have potential to rapidly screen COVID-19 from chest x-ray (CXR). Current deep convolutional neural network (DCNN) models for COVID-19 detection are limited by small datasets and are prone to over fitting. To optimize such a model, we assessed the performance impact of network complexity, data augmentation, and transfer learning on model performance.

Methodology & Theoretical Orientation: A DCNN model was developed using the COVID open access dataset of 16,352 CXR images associated with known COVID-19 status by RT-PCR. Performance characteristics of pre-trained CNNs, 24 models in all, with various enhancement features were compared.

Findings: Among 5 pertained DCNNs, low complexity ResNet18 architecture performed best. Increasing complexity correlated with validation loss. Adding data augmentation using horizontal flip (HF), Gaussian blurs (GB), and cut out (CO) improved ResNet18 performance—with the ResNet18-CO/GB model performing best at 1,000 iterations. Transfer learning using a tuberculosis (TB) detection model enhanced the performance of ResNet18-HF and ResNet18-CO/HF/GB models, while transfer learning using a pneumonia dataset for pertaining did not improve model performance. At 10,000 iterations, the best model for COVID-19 detection was ResNet18-GB/CO, with a sensitivity of 82.0%, specificity 96.5%, positive predictive value 81.8%, negative predictive value 95.0%, F-score 81.5%, and accuracy 94.5%. Validation loss was low overall at 0.18, but mild over fitting was observed with validation-training loss difference of 0.06. This robust final COVID-19 CXR detection model meets the World Health Organization standards for COVID-19 antigen tests (sensitivity>80%, specificity>97% and exceeds the <50% sensitivity and <80% specificity achieved by unassisted radiologists. Transfer learning models did not perform as well as the data augmented DCNNs.

Conclusion & Significance: Our findings suggest there is clinical utility for automated COVID-19 detection by CXR, particularly if data augmentation is heavily incorporated into such models.

Biography

Himal Bamzai-Wokhlu is a student at Buchholz High School in Gainesville, FL. She developed this model under the mentorship of Dr. Parsa Akbari at University of Oxford at Cambridge.

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