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Prediction of novel virus–host interactions by integrating clinical symptoms and protein sequences

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Abstract

Motivation: Infectious diseases from novel viruses are becoming a major public health concern. Fast identification of virus–host interactions can reveal mechanistic insights of infectious diseases and shed light on potential treatments and drug discoveries. Current computational prediction methods for novel viruses are based only on protein sequences. Yet, it is not clear to what extent other important features, such as the symptoms caused by the viruses, could contribute to a predictor. Disease phenotypes (i.e., symptoms) are readily accessible from clinical diagnosis and we hypothesize that they may act as a potential proxy and an additional source of information for the underlying molecular interactions between the pathogens and hosts.
Results: We developed *DeepViral*, a deep learning method that predicts potential protein–protein interactions between human and viruses. First, human proteins and viruses were embedded in a shared space using their associated phenotypes, functions, taxonomic classification, as well as formalized background knowledge from biomedical ontologies. By extending a sequence learning model with phenotype features, our model can not only significantly improve over previous sequence-based approaches for inter-species interaction prediction, but also identify pathways of viral targets under a realistic experimental setup for novel viruses.
Availability: `https://github.com/bio-ontology-research-group/DeepViral`
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1 Introduction

Infectious diseases emerging unexpectedly from novel pathogens have been a major public health concern around the globe (Jones *et al.*, 2008). Pathogens disrupt host cell functions (Finlay and Cossart, 1997) and target immune pathways (Dyer *et al.*, 2010) through complex inter-species interactions of proteins (Dyer *et al.*, 2008), RNA (Fajardo *et al.*, 2015) and DNA (Weitzman *et al.*, 2004). The study of pathogen–host interactions (PHI) can therefore provide insights into the molecular mechanisms underlying infectious diseases and guide the discoveries of novel therapeutics or provide a basis for repurposing of available drugs. For example, a previous study of many PHIs showed that pathogens typically interact with the protein hubs (those with many interaction partners) and bottlenecks (those of central location to important pathways) in human protein–protein interaction (PPI) networks (Dyer *et al.*, 2008). However, due to cost and time constraints, experimentally validated pairs of interacting pathogen–host proteins are limited in number. Moreover, there exists a time delay for a validated PHI to be included in a database of PHIs, often requiring manual curation of the literature or text mining efforts (Thieu *et al.*, 2012). Therefore, the computational prediction of PHIs is a useful complementary approach in suggesting candidate interaction partners out of all the human proteins.

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Existing PHI prediction methods typically utilize features of the interacting proteins, such as PPI network topology, protein structures and sequences, or functional profiling such as Gene Ontology similarity and KEGG pathway analysis (Nourani *et al.*, 2015). While protein functions have been shown to predict intra-species (e.g., human) PPIs (Guzzi *et al.*, 2011; Jain and Bader, 2010; Pesquita *et al.*, 2009) and such protein specific features exist for some extensively studied pathogens, such as *Mycobacterium tuberculosis* (Huo *et al.*, 2015) and HIV (Mukhopadhyay *et al.*, 2014), for most of the novel pathogens, these features are rare and expensive to obtain. As new virus species are being discovered each year, with potentially many more to come (Woolhouse *et al.*, 2012), a method is needed to rapidly identify candidate interactions from information that can be obtained quickly – such as the signs and symptoms of the host, which may be utilized as a proxy for the underlying molecular interactions between host and pathogen proteins.

The phenotypes elicited by pathogens, i.e., the signs and symptoms observed in a patient, may provide information about molecular mechanisms (Gkoutos *et al.*, 2018). The information that phenotypes provide about molecular mechanisms is commonly exploited in computational studies of Mendelian disease mechanisms (Oellrich *et al.*, 2016; Schofield *et al.*, 2012), for example to suggest candidate genes (Hoehndorf *et al.*, 2011; Meehan *et al.*, 2017) or diagnose patients (Köhler *et al.*, 2009), but the information can also be used to identify drug targets (Hoehndorf *et al.*, 2013a) or gene functions (Hoehndorf *et al.*, 2013b). To the best of our knowledge, phenotypes and phenotype similarity have not yet been utilized for the prediction of PHIs.

We hypothesize that the phenotypes elicited by an infection with a pathogen are, among others, the result of molecular interactions, and that knowledge of the phenotypes in the host can be used to suggest the protein perturbations, from which these phenotypes arise. While a large number of phenotypes resulting from infections are a consequence of immune system processes that are shared across a wide range of different types of pathogens, certain hallmark phenotypes, such as decreased CD4 cell-count in infections with HIV (Ford *et al.*, 2017) or microcephaly resulting from Zika virus infections (Mlakar *et al.*, 2016), can be used to suggest interacting host proteins, through which these symptoms are elicited.

One common limitation of the PHI prediction problem is the lack of ground truth negative data. A recent method *DeNovo* (Eid *et al.*, 2015) adopted a "dissimilarity-based negative sampling": for each virus protein, the negatives are sampled from human proteins that do not have known interactions with other similar virus proteins (above a certain sequence similarity threshold). Another method based on protein sequences (Zhou *et al.*, 2018) samples negatives from only the set of host proteins that are less than 80% similar (in terms of sequence similarity) from the host proteins in the positive training data. By construction, these sampling schemes make the human proteins in the negative set different from the positive set; when used not only for training a model but also for evaluating the model's performance, this sampling scheme has the potential to over-estimate the actual performance for finding novel PHIs. In a more realistic evaluation for a novel virus species, a model would be evaluated on all the host proteins that it could potentially interact with, regardless of sequence similarity.

We developed a machine learning method, *DeepViral*, to predict potential interactions between viruses and all human proteins for which we can generate the relevant features. Firstly, the features of phenotypes, functions and taxonomic classifications are embedded in a shared space for human proteins and viruses. We then extend a sequence model by incorporating the phenotype features of viruses into the model. We show that the joint model trained on both the sequences and phenotypes can significantly improve over the state-of-the-art method and predict potential PHIs in a realistic experimental setup for novel viruses and predict human protein targets that are enriched for relevant pathways.

2 Materials and methods

2.1 Data sources of interactions, phenotypes, functions and ontologies

Interactions between hosts and pathogens were downloaded from the Host Pathogen Interaction Database (HPIDB) (Ammari *et al.*, 2016) The database contains 32,758 distinct pairs of protein-protein interaction between human and viruses, equipped with a corresponding MIscore (see Section 2.3) and the virus has a family taxon present in the NCBI taxonomy (Sayers *et al.*, 2009).

The phenotypes associated with pathogens were collected from the PathoPhenoDB (Kafkas *et al.*, 2018), a database of manually curated and text-mined associations of pathogens, diseases and phenotypes. We downloaded the PathoPhenoDB database version 1.2.1 (`http://patho.phenomebrowser.net/`).

The phenotypes associated with human genes were collected from the Human Phenotype Ontology (HPO) database (Köhler *et al.*, 2018), and the phenotypes associated with mouse genes and the orthologous gene mappings from mouse genes to human genes, originated from the Mouse Genome Informatics (MGI) database (Smith *et al.*, 2018). The Entrez gene IDs in HPO and MGI were mapped to reviewed Uniprot protein IDs using the Uniprot Retrieve/ID mapping tool (`https://www.uniprot.org/uploadlists`). The Gene Ontology annotations of human proteins (release date 2020-02-22) were downloaded from the Gene Ontology Consortium (Ashburner *et al.*, 2000; The Gene Ontology Consortium, 2017).

To add background knowledge from biomedical ontologies of phenotypes and GO classes, we downloaded the cross-species PhenomeNET Ontology (Hoehndorf *et al.*, 2011; Rodríguez-García *et al.*, 2017), which is built upon and includes the Gene Ontology (Ashburner *et al.*, 2000; The Gene Ontology Consortium, 2017), from the AberOWL ontology repository (Hoehndorf *et al.*, 2015a) on September 13, 2018. We obtained the NCBI Taxonomy classification (Sayers *et al.*, 2009) as an ontology in OWL format (version 2018-07-27) from EMBL-EBI ontology repository (`https://www.ebi.ac.uk/ols/ontologies/ncbitaxon`).

2.2 Learning feature embeddings

To generate feature embeddings, we use DL2Vec (Chen *et al.*, 2020), a recent method for learning features for entities (in our case, the human proteins and viruses) from their associations to ontology classes. DL2Vec first converts the ontologies and entity associations into a graph, with the classes and entities as the nodes and the associations and ontology axioms as the edges. Then several random walks are performed, starting from the entities over to the ontology graph and thereby generating a corpus of walks in the form of sentences capturing the graph neighborhoods and thereby the ontology axioms. Following the construction of such sentences, a Word2vec skipgram model (Mikolov *et al.*, 2013) is used to learn an embedding for each entity by learning from the corpus. The resulting embedding is a vector representation of an entity capturing its co-occurrence relations with other entities within the graph generated by DL2Vec. For an example, the embedding of a virus contains the feature information from its neighborhood on the graph, i.e., its phenotypes and its taxonomic relatives.

2.3 Positive and negative sampling

For training *DeepViral*, curated virus–host interactions were obtained from HPIDB (Ammari *et al.*, 2016), a database of host–pathogen protein protein interactions. Next two positive sets were constructed by filtering using different confidence levels. HPIDB (Ammari *et al.*, 2016) provides MIscores (Villaveces *et al.*, 2015), a confidence score for molecular

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interactions, for the curated PHIs from two sources, IntAct (Kerrien *et al.*, 2011) and VirHostNet (Guirimand *et al.*, 2015). We filter HPIDB with a MIscore threshold at 0.4 to construct a high confidence positive set of PHIs, reducing the number of distinct interaction pairs to 3,600. Our threshold of 0.4 is chosen to ensure high confidence as it filters out the peak of the data between 0.3 and 0.4, as shown in Figure 1.

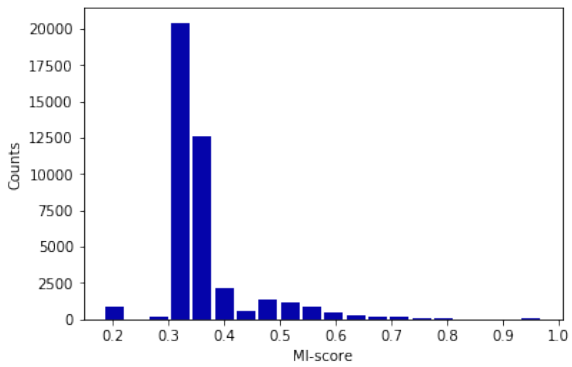

Fig. 1: The distribution of MIscores in HPIDB.

Since ground truth negatives are not available, we sample our negatives from all the possible pairwise combinations of human and viral proteins, as long as the pair does not occur in the positive set. Essentially, we treat all "unknown" interactions as negatives.

2.4 Supervised prediction models and parameter tuning

The neural network model of *DeepViral* consists of two components: a phenotype model based on the feature embeddings of viruses and human proteins and a sequence model based on the amino acid sequences of the human and viral proteins. The maximum length of protein sequences is set to 1000 amino acids and all sequences shorter than 1000 are repeated up to the maximum length.

To predict the likelihood of an interaction between a pair of proteins, we train the network as a binary classifier, to minimize the binary cross-entropy loss defined as below,

$$L = -\frac{1}{N}\sum_{i=1}^{N} y_t \cdot log(y_p) + (1 - y_t) \cdot log(1 - y_p)$$

where N is the total number of predictions, y_t and y_p is the true label and predicted likelihood of y.

We implemented our model using the Keras library (Chollet *et al.*, 2015) and performed training on Nvidia Tesla V100 GPUs. The phenotype model consists of a fully connected layer with the feature embeddings as input. The sequence model is a convolutional neural network (CNN) with the sequences as input and consists of 1-dimensional convolution, max pooling and fully connected layers. We tune the following hyperparameters of the model: the sizes and numbers of the convolution filters, the size of the max pool and the number of neurons in the fully connected layers. We fix these hyperparameters throughout all the experiments: 16 convolutional layers for each filter of 8, 16, ..., 64 in length, a pool size of 200 and 8 neurons for the dense layers. We also use dropouts (Srivastava *et al.*, 2014) for the convolutional and dense layers with a rate of 0.5 and LeakyReLU as the activation function for the dense layer with an alpha set to 0.1.

2.5 Experimental setup and evaluation metrics

A method to predict PHIs for a novel virus should have the capacity to predict for all human proteins that the novel virus could potentially interact with, and realistically simulate a scenario where a novel virus emerges, for which we have no known interactions and no knowledge about the molecular functions of the viral proteins.

To evaluate the model realistically for a novel virus, the predictive performance is evaluated in a leave-one-family-out (LOFO) cross validation manner, in which we leave out one virus family in our positive set for testing, 20% of the remaining families for validation, and the rest 80% for training. The objective of the LOFO cross-validation is to evaluate the model under a scenario where the novel virus emerges from a novel virus family in the situation where we have no knowledge about its protein interactions.

For each viral protein in the test family, we rank all the human proteins by the predicted likelihood of interaction and evaluate the model by aggregating the normalized ranks of the true positive interacting human proteins to compute the area under the receiver operating characteristic (ROC) curve (Fawcett, 2006). Due to the large number of negatives in relation to the positives, normalized ranks approximate the true negative rate (TNR) of the ROC curve. A high ROCAUC indicates the ability of the model to prioritize the true positive proteins among all the human proteins. We also evaluate by the hit rates at rank 10 and rank 100, denoted Hit@10/100, which are defined as the proportion of true positive human proteins ranked within the top 10 or 100 across all the human proteins.

3 Results

DeepViral is a model that predicts potential protein interactions between viruses and human from the protein sequences and feature embeddings of phenotypes, functions and taxonomies. To enable predictions based on such different types of features we embed them in a shared representation space. Then we incorporate these feature embeddings with a protein sequence model to predict for potential PHIs of novel viruses. The workflow of *DeepViral* is illustrated in Figure 2.

3.1 Embedding features of viruses and human proteins from phenotypes, functions and taxonomies

We start with the biological hypothesis that phenotypes (i.e., symptoms) elicited by viruses in their hosts can act as a proxy for the underlying molecular mechanisms of the infection, and therefore may provide additional information to the prediction of potential PHIs for novel viruses.

To generate feature embeddings for human proteins and virus taxa, we apply a recent representation learning method DL2Vec (Chen *et al.*, 2020), which learns feature embeddings for entities based on their annotations to ontology classes (see Section 2.2). DL2Vec takes two types of inputs: the associations of the entities with ontology classes (e.g., human proteins and their functions), and the ontologies themselves. DL2Vec exploits the underlying semantic information to provide formalized background knowledge through connecting different ontologies of phenotypes, functions and virus taxonomy.

For representing virus taxa through the phenotypes they elicit in their hosts, we use the phenotype associations for viruses from PathoPhenoDB (Kafkas *et al.*, 2018), a database of pathogen to host phenotype (signs and symptoms) associations. To increase the coverage of phenotypes beyond PathoPhenoDB, the taxonomic relations of the viruses were added from the NCBI Taxonomy (Sayers *et al.*, 2009). By adding these taxonomic relations (as annotations of viruses to DL2Vec), we propagate the known phenotypes along the taxonomic hierarchies and learn a generalized embedding for viruses that do not have any phenotype annotations in PathoPhenoDB but have close relatives that do.

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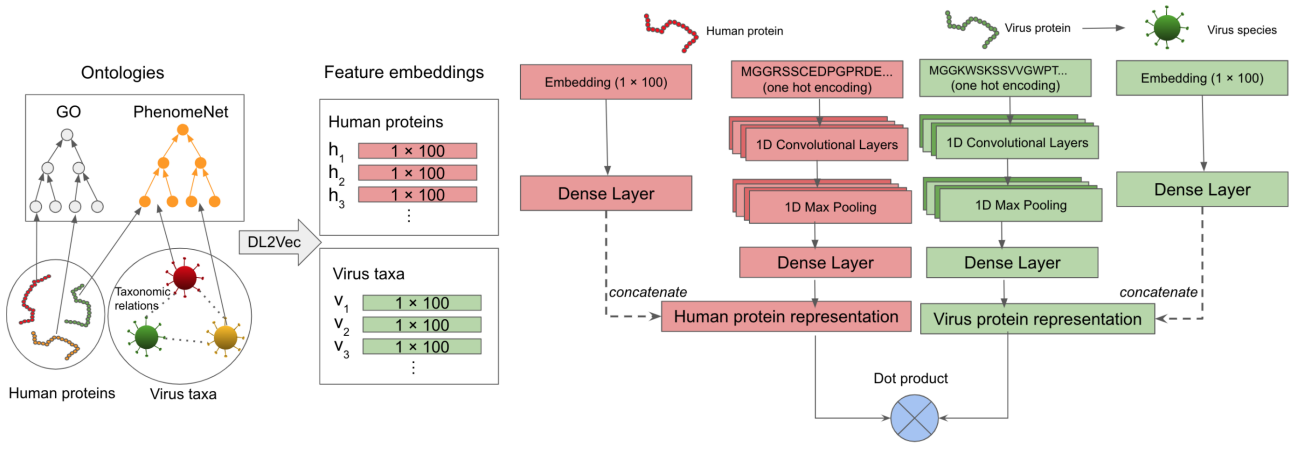

(a) Generation of feature embeddings (b) Joint prediction model from embeddings and sequences

Fig. 2: The workflow of *DeepViral*. (a) Generation of an embedding: the arrows of human proteins and virus taxa represent their annotations to the ontology classes. The dashed lines between viruses represent their taxonomic relations. The annotations, taxonomy relations and ontologies are inputs to DL2Vec to generate feature embeddings of dimension 100 for each human protein and virus taxa. (b) Joint prediction model: latent representation learned from feature embeddings and protein sequences are concatenated into a joint representation, for human protein and virus protein respectively, on which a dot product is performed to predict interactions.

Similarly, for representing human proteins, we use the annotations of their associated phenotypes from the Human Phenotype Ontology (HPO) database (Köhler *et al.*, 2018), the phenotypes associated with their mouse orthologs from the Mouse Genome Informatics (MGI) database (Smith *et al.*, 2018), and their protein functions from the Gene Ontology (GO) database (Ashburner *et al.*, 2000; The Gene Ontology Consortium, 2017).

To provide DL2Vec with structured background knowledge through ontologies, we use the cross-species phenotype ontology PhenomeNET (Hoehndorf *et al.*, 2011; Rodríguez-García *et al.*, 2017) to associate human and mouse phenotypes, the Gene Ontology (Ashburner *et al.*, 2000; The Gene Ontology Consortium, 2017) to incorporate knowledge of protein functions and the NCBI Taxonomy ontology (Sayers *et al.*, 2009) for the taxonomic relations between viruses. These ontologies contain formalized biological background knowledge (Hoehndorf *et al.*, 2015b), which has the potential to significantly improve the performance of these features in machine learning and predictive analyses (Smaili *et al.*, 2019).

3.2 The joint prediction model from phenotypes and sequences

DeepViral consists of a phenotype model trained on phenotypes caused by a viral infection and a sequence model trained on protein sequences, as shown in Figure 2 (b). The models takes a pair of virus and human proteins as input and predicts the likelihood of their interaction. The inputs for a human protein are its feature embedding and sequence, and the features for a viral protein is its sequence and the feature embedding of the virus species it belongs to. The sequence model projects the protein sequence into a low dimension vector representation, which is concatenated with the vector projected from the embedding by the phenotype model to form a joint representation of the proteins. A dot product is performed over the two vector representations of the pair of proteins to compute their similarity, which then is used as input to a sigmoid activation function to compute their predicted probability of interaction.

To compare with the state-of-the-art method for PHI prediction of novel viruses, we train our model on the four datasets provided by a recent machine learning method (Zhou *et al.*, 2018) for predicting PHIs of Ebola and H1N1. *DeepViral* is able to improve over the previous method in all the evaluation metrics across these datasets, as summarized in Table 1. Notably, integrating the embeddings of protein functions (based on GO) with the sequences performs better in almost all the metrics as compared to the sequence only model.

3.3 Joint prediction for novel viruses from novel families

We then apply *DeepViral* following the experimental setup described in Section 2.5, to evaluate the prediction performance of the model under the scenario where a novel virus (from a novel family) emerges and no previous knowledge (except about its protein sequences and phenotypes) is known. Under this setting, we evaluated the performances of *DeepViral* with different combinations of features of virus and human proteins, as summarized in Table 2. The evaluation was performed on the full and the high confidence dataset respectively, and only on the viral families that have more positives than a threshold (set to be 1% of the total number of positives) in order to reduce the amount of runtime for model evaluation. The models are run 5 times for each set of features to compute the confidence interval of the ROCAUC. For the models using only the phenotype embeddings of viruses as input (i.e. the first six models in Table 2), a potential interaction is predicted between a human protein and a virus species, instead of a protein–protein interaction. In an evaluation where the inputs are not symmetric, e.g., only using the sequences of human proteins but not viruses, an additional dense layer is added to project the longer representation to the same dimension as the other so that the dot product can be performed.

Overall, among the features of human proteins, the protein function annotations based on GO perform better than phenotypes. Sequences from human and viral proteins almost always improve the performances, with the combination of GO, virus phenotypes and protein sequences performing the best. The dataset without filtering the positives tend to give higher ROCAUCs across most features, likely due to the larger set of training data. However, the models trained on the high confidence dataset perform consistently higher in the hit rates at rank 10 and 100, potentially a result of smaller but more distinctive set of proteins.

Remarkably, the predicted human proteins for the viruses are enriched in pathways of viral targets. We aggregate the top 100 predicted

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Datasets	Zhou *et al.* 2018				DeepViral																			
					Seq				Seq + Pheno				Seq + Pheno + HP				Seq + Pheno + MP				Seq + Pheno + GO			
	ACC	PPV	SN	AUC	ACC	PPV	SN	AUC	ACC	PPV	SN	AUC	ACC	PPV	SN	AUC	ACC	PPV	SN	AUC	ACC	PPV	SN	AUC
TR1–TS1	78.0	72.6	89.8	0.886	87.6	86.7	88.8	0.934	79.8	72.7	95.6	0.936	85.5	81.8	**98.8**	0.949	87.4	86.9	91.2	**0.951**	**89.1**	**87.8**	92.2	0.907
TR2–TS2	78.0	72.3	90.7	0.867	79.2	71.2	99.2	0.959	84.0	77.0	97.6	0.972	81.1	76.7	**100**	0.941	71.7	66.3	93.7	0.726	**90.3**	**87.1**	96.1	**0.973**
TR3–TS1	77.4	72.3	89.0	0.884	**79.5**	**73.1**	**92.9**	**0.904**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
TR4–TS2	81.7	75.1	94.7	0.890	**82.4**	**75.2**	**97.6**	**0.966**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 1. Comparison with the state-of-the-art method on the datasets of Ebola and H1N1 (Zhou et al., 2018) (the performances of the previous method are from Table 5 of the original paper). All evaluation metrics are computed following the original paper: ACC - accuracy, PPV - positive prediction value (precision), SN - sensitivity, AUC - area under the ROC curve. Different combinations of the features are used for training DeepViral: Seq - the protein sequences, Pheno - the virus phenotype embeddings, HP, MP and GO - the embeddings of human proteins from HPO, MGI and GO, respectively. The bold numbers represent the better metric for a dataset. The dash lines (–) mean that the datasets are not applicable: the training sets TR3 and TR4 contain host and viral proteins of other species (for transfer learning), but currently our set of feature embeddings only contain human proteins as host and human viruses as pathogens.

		PHIs without filtering					**High confidence PHIs**				
Features of viruses	**Features of human proteins**	**Positives**	**Proteins (H/V)**	**Families/ Species**	**ROCAUC**	**Hit@10/100**	**Positives**	**Proteins (H/V)**	**Families/ Species**	**ROCAUC**	**Hit@10/100**
Phenotypes	HP	6962	4262/-	14/278	0.524 [0.499-0.548]	0.006/0.032	1025	4262/-	12/198	0.603 [0.590-0.616]	0.028/0.087
	MP	14487	10827/-	13/309	0.555 [0.524-0.586]	0.002/0.012	2250	10827/-	11/234	0.621 [0.610-0.633]	0.006/0.031
	GO	21837	17992/-	13/320	0.675 [0.649-0.700]	0.002/0.025	2872	17992/-	11/244	0.742 [0.719-0.765]	0.005/0.051
	HP + Sequences	5495	3401/-	14/244	0.701 [0.664-0.738]	0.010/0.104	804	3401/-	13/171	0.693 [0.684-0.701]	0.030/0.196
	MP + Sequences	11908	9123/-	14/284	0.647 [0.601-0.694]	0.004/0.039	1841	9123/-	12/210	0.683 [0.670-0.695]	0.008/0.077
	GO + Sequences	18393	15758/-	13/294	0.751 [0.734-0.769]	0.003/0.028	2380	15758/-	11/217	0.733 [0.719-0.747]	0.004/0.058
Sequences	Sequences	24042	17948/1025	10/271	0.788 [0.781-0.795]	0.004/0.032	2515	17948/610	12/218	0.724 [0.714-0.734]	0.007/0.059
	HP + Sequences	7194	3401/753	11/218	0.751 [0.741-0.761]	0.012/0.098	846	3401/364	12/159	0.693 [0.683-0.703]	0.022/0.210
	MP + Sequences	15052	9123/954	9/251	0.737 [0.728-0.746]	0.004/0.044	1904	9123/547	12/201	0.703 [0.686-0.719]	0.008/0.090
	GO + Sequences	23779	15758/1025	10/271	0.763 [0.755-0.771]	0.002/0.024	2501	15758/609	12/218	0.780 [0.776-0.784]	0.004/0.056
Phenotypes + Sequences	HP + Sequences	7183	3401/746	11/217	0.774 [0.770-0.778]	0.015/0.106	834	3401/358	12/157	0.720 [0.714-0.727]	**0.040/0.255**
	MP + Sequences	15017	9123/942	9/249	0.773 [0.769-0.777]	0.005/0.047	1868	9123/535	12/199	0.702 [0.692-0.713]	0.009/0.080
	GO + Sequences	23732	15758/1012	10/269	**0.807 [0.802-0.812]**	0.003/0.027	2431	15758/584	11/208	0.779 [0.763-0.796]	0.007/0.061

Table 2. Evaluation results of DeepViral for predicting PHIs under a realistic setting for novel viruses. HP, MP and GO denote the source of the human protein embeddings, i.e. HPO, MGI and GO, respectively. For the models using only the phenotypes of the viruses, i.e., without sequences, the predicted interaction is between a human protein and a virus species (the dash line indicates the absence of viral proteins). The mean and confidence interval of ROCAUCs are provided as well as the mean of the hit rates at rank 10 and 100, i.e., Hit@10/100. The best performing combination of features across all datasets are bolded.

human proteins across the proteins of HIV 1 (`NCBITaxon:11676`) and Hepatitis C (`NCBITaxon:11103`), respectively. We then used the pathway enrichment analysis tool (`https://biit.cs.ut.ee/gprofiler/gost`) provided by g:Profiler (Raudvere *et al.*, 2019) to find enriched pathways based on three databases, KEGG (Kanehisa and Goto, 2000), Reactome (Jassal *et al.*, 2020) and WikiPathways (Slenter *et al.*, 2018). As shown in Figure 3, the predicted proteins for HIV 1 and Hepatitis C are enriched for not only pathways that are general to host immuno-responses, but also specific pathways related to the pathogenesis of these viruses, e.g., "`Dual hijack model of Vif in HIV infection`" in WikiPathways and "`Hepatitis C`" in KEGG. This suggests that despite not being trained on the interactions of these viruses, the joint prediction model is able to capture the relevant features specific to the interacting proteins involved in the pathways of pathogenesis of these viruses.

4 Discussion

We developed *DeepViral*, a machine learning method for predicting PHIs between viruses and human. *DeepViral* is, to the best of our knowledge, the first predictor using clinical phenotypes as an additional feature in PHI prediction and it turned out to provide a significant improvement over purely sequence based methods. Phenotype-based approaches have been successful in predicting disease-gene associations for Mendelian diseases (Hoehndorf *et al.*, 2011) and intra-species PPIs (Alshahrani *et al.*, 2017), but have not yet been used for the prediction of (inter-species) PHIs in infectious diseases. Our model avoids the bottleneck of identifying the molecular functions of pathogen proteins, by instead introducing a novel and – in the context of infectious diseases – rarely explored type of feature, the phenotypes elicited by pathogens in their hosts, as a "proxy" for the molecular mechanisms, which in turn eventually produce the observed clinical phenotypes.

By challenging *DeepViral* with novel viruses, we could extract specific pathways being attacked by the viruses, as indicated by the predicted interactions in the human proteome. The focus of our method on utilizing features generated based on endo-phenotypes observed in humans and mice (Schofield *et al.*, 2016) has therefore the crucial advantage that we can identify host-pathogen interactions that may contribute to particular signs and symptoms. For example, our model consistently prioritizes the interaction between the proteins of Zika virus (`NCBITaxon:64320`) and DDX3X (`UniProt:O00571`) in humans. Infections with Zika virus have the potential to result in abnormal embryogenesis and, specifically, microcephaly (Wang *et al.*, 2017). Phenotypes associated with DDX3X in the mouse ortholog include abnormal embryogenesis, microcephaly, and

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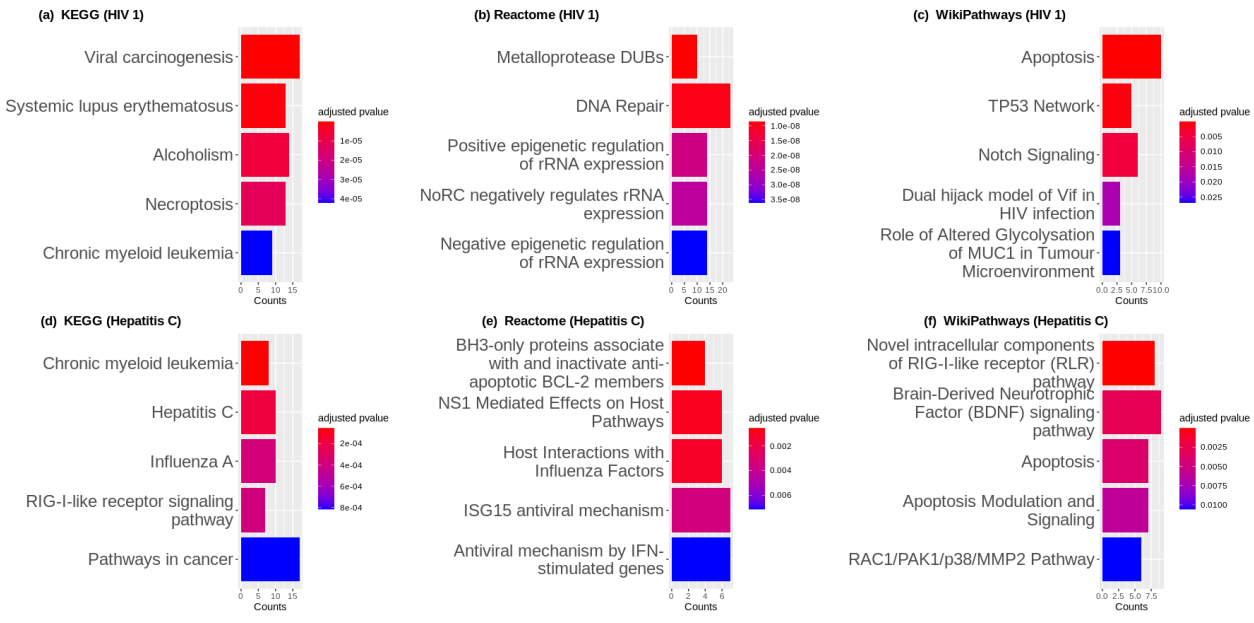

Fig. 3: Pathway enrichment analysis for the predicted interacting proteins for HIV 1 and Hepatitis C, based on KEGG, Reactome and WikiPathways. The top 5 enriched pathways from each database are used for the barplot, ranked by adjusted p-value.

abnormal neural tube closure (Chen *et al.*, 2016). DDX3X mutations in humans have been found to result in intellectual disability, specifically in females and affecting individuals in dose-dependent manner (Blok *et al.*, 2015). While DDX3X has previously been linked to the infectivity of Zika virus (Doñate-Macián *et al.*, 2018), our model further suggests a role of DDX3X in the development of the embryogenesis phenotypes resulting from Zika virus infections.

While improving over a previous model on Ebola and H1N1 (Zhou *et al.*, 2018), we argue that the performance of *DeepViral* on these datasets may have been over-estimated due to the negative sampling scheme based on sequence similarity that is used not only for training but also for evaluation of the model. Under a more realistic evaluation procedure that considers all host proteins as potential interaction partners for novel viruses, the achieved predictive performances are considerably lower. This calls for future efforts in the direction of PHI prediction of novel viruses, an issue today of increasing relevance to global public health. Accurate predictions of potential PHIs for novel pathogens with rapidly obtainable features would be an important aid for the understanding of infectious disease mechanisms and the repurposing of existing drugs.

An example of such a novel virus is the novel coronavirus SARS-CoV-2, which as of 21st April 2020 reached more than 2.5 million infected cases and 170 thousand fatalities globally (Dong *et al.*, 2020) in a timespan of 5 months. Based on a recently released dataset of 332 PHIs from 26 viral proteins of SARS-CoV-2 (Gordon *et al.*, 2020), we applied *DeepViral* by treating it as a novel family (with no other Coronaviridae viruses in the dataset) and achieved a ROCAUC of 0.738 (0.730–0.747), which is within the observed variability in predicting for different virus families, as shown in Figure 4. This family-wise variability suggests that the learned features to predict for PHIs may have different generalization power across families, possibly a result of varying degrees of (dis)similarity between the virus families. Nevertheless, optimizing the predictive power for a single virus, e.g., SARS-CoV-2, requires a case-by-case experimental setup. Specifically in the case of SARS-CoV-2, one can potentially relax the leave-one-family-out evaluation, as we have prior knowledge about other species in its family, e.g., SARS and MERS, such as their interactions with hosts and protein functions (Thiel *et al.*, 2003). This is indeed a topic for further investigation.

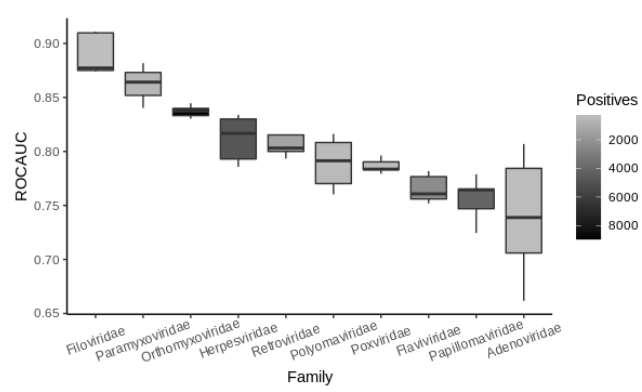

Fig. 4: Evaluation results for 10 virus families in the joint model with the "GO + Sequence" features of human proteins.

There are several limitations that can be addressed by future efforts. One is the scarcity of training data for inter-species PPIs and this may be leveraged by transfer learning on the much larger intra-species PPI data available for humans and other model organisms. We also ignored other types of PHIs outside virus–human interactions in our current study, such as those of other hosts, e.g., plants and fishes, and other pathogens, e.g., bacteria and fungi, which have been shown to improve the prediction performance for Ebola (but not H1N1) in a previous method (Zhou *et al.*, 2018) (see Table 1; the training sets TR3 and TR4 contain host proteins from species other than human). Additionally, predicting tissue-specific PHIs would also provide additional insights, as proteins of both human (Fagerberg *et al.*, 2014) and viruses (Jarosinski *et al.*, 2012) often have tissue-specific expressions and functions.

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