

## Drug Repurposing for COVID-19: A Knowledge Graph Approach 建立用於新冠肺炎藥物開發的知識圖譜平台

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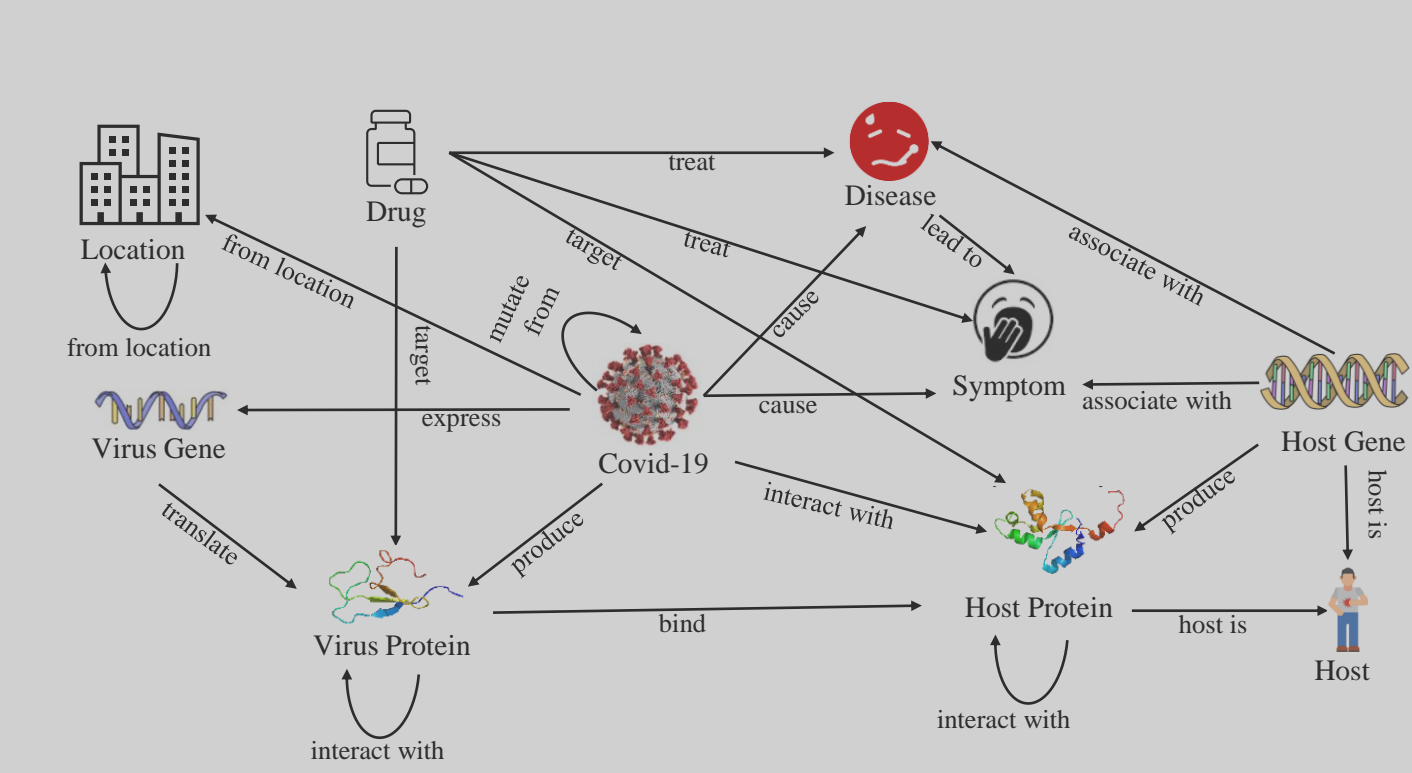
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### Motivations

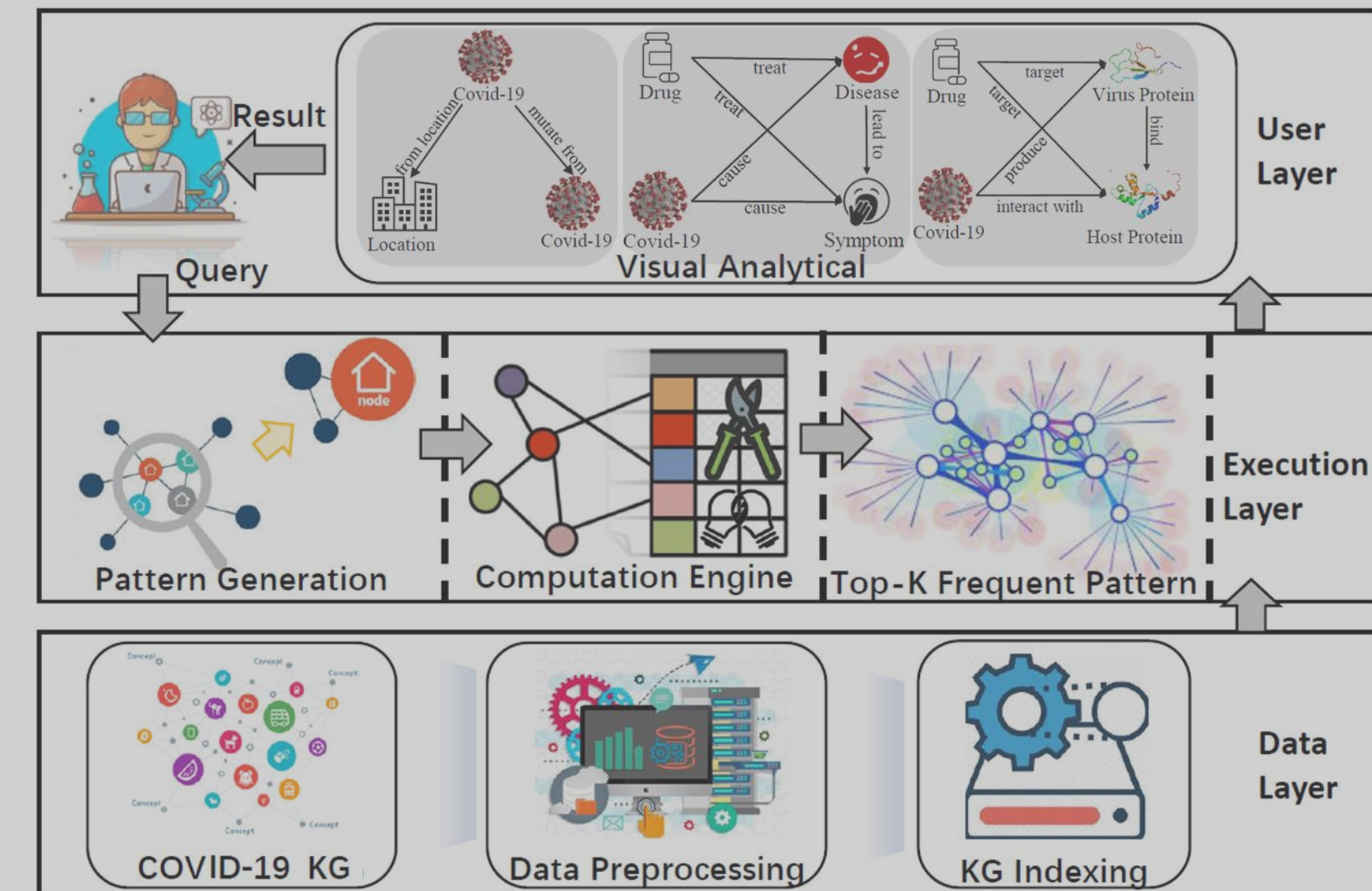
- SARS-CoV-2 outbreak (Covid-19) has become a global pandemic.
- No known effective Covid-19 drug treatment.
- Discovery of new drugs is time consuming + expensive.
- Traditional drug-repurposing methods (e.g., protein docking) does not consider complex interrelationship of drugs, proteins, genes, symptoms, diseases, etc.
- Therefore, we repurpose **existing drugs** using **network-based strategies**.

### Knowledge Graph Schema

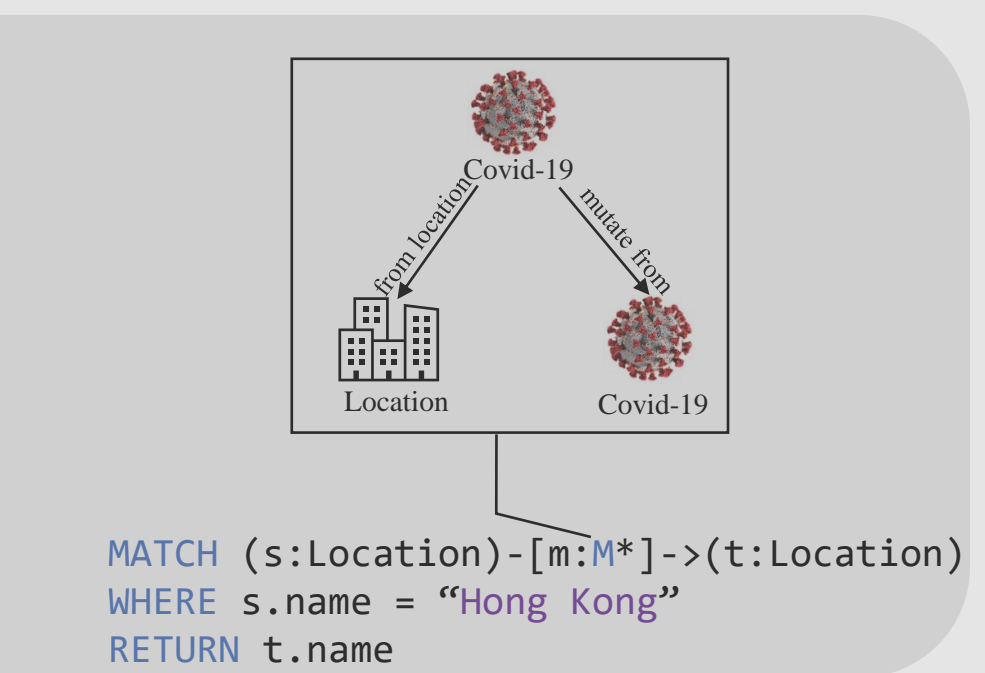
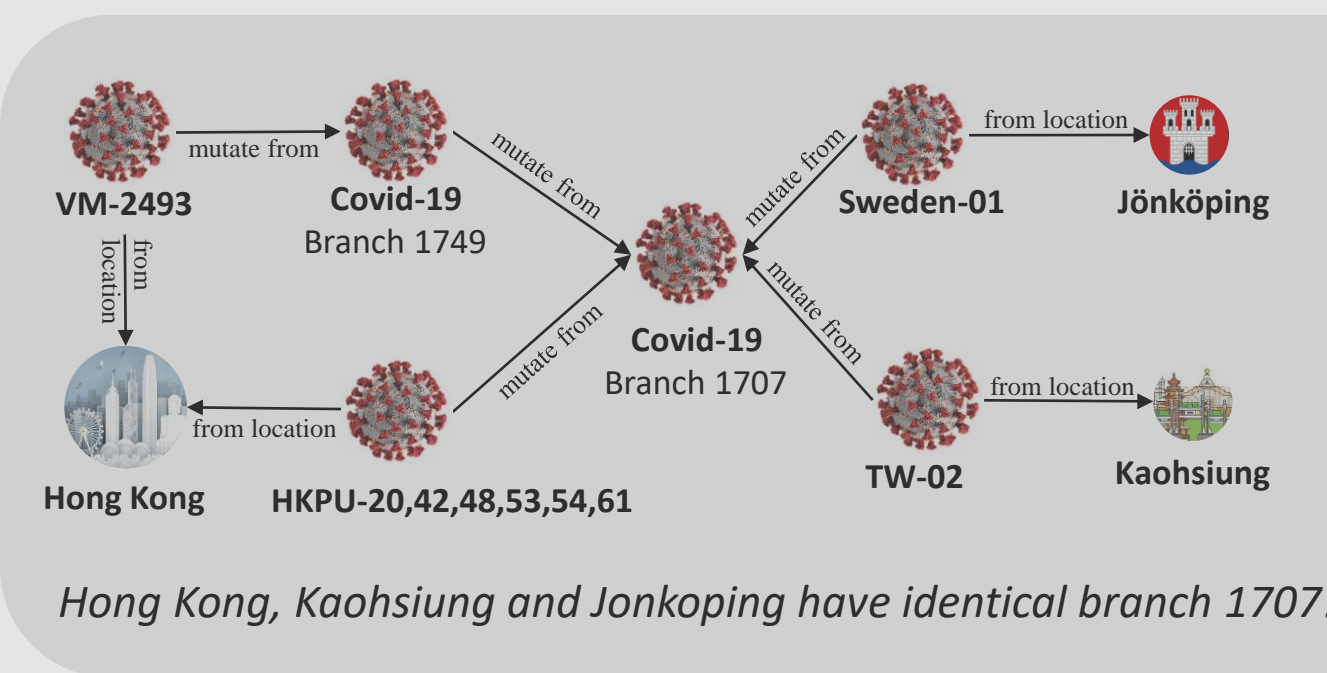
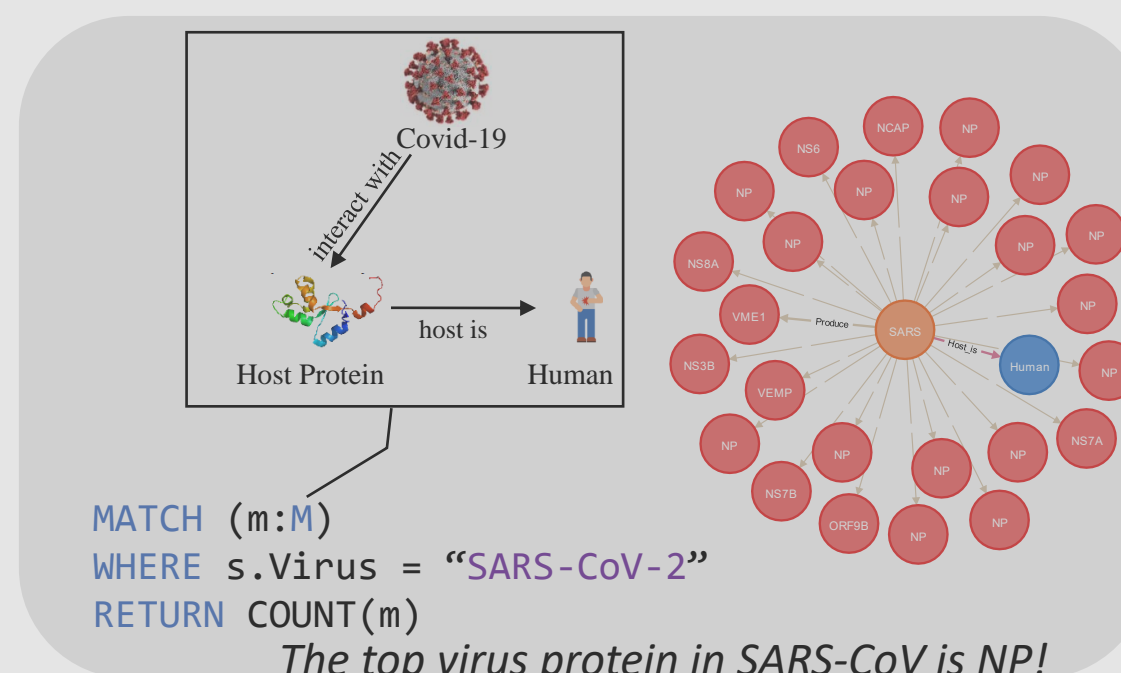
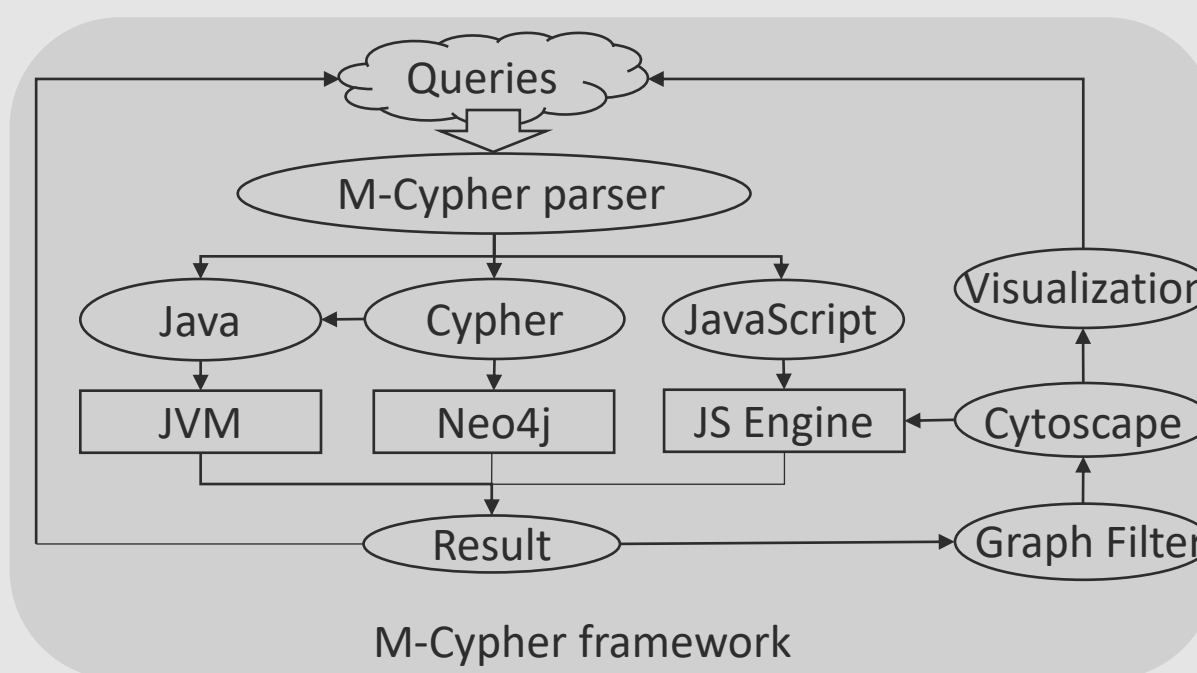


- Integrated from OpenKG, HPO, NCBI, and DrugBank.
- Over 48K nodes and 815K edges!

### System Architecture



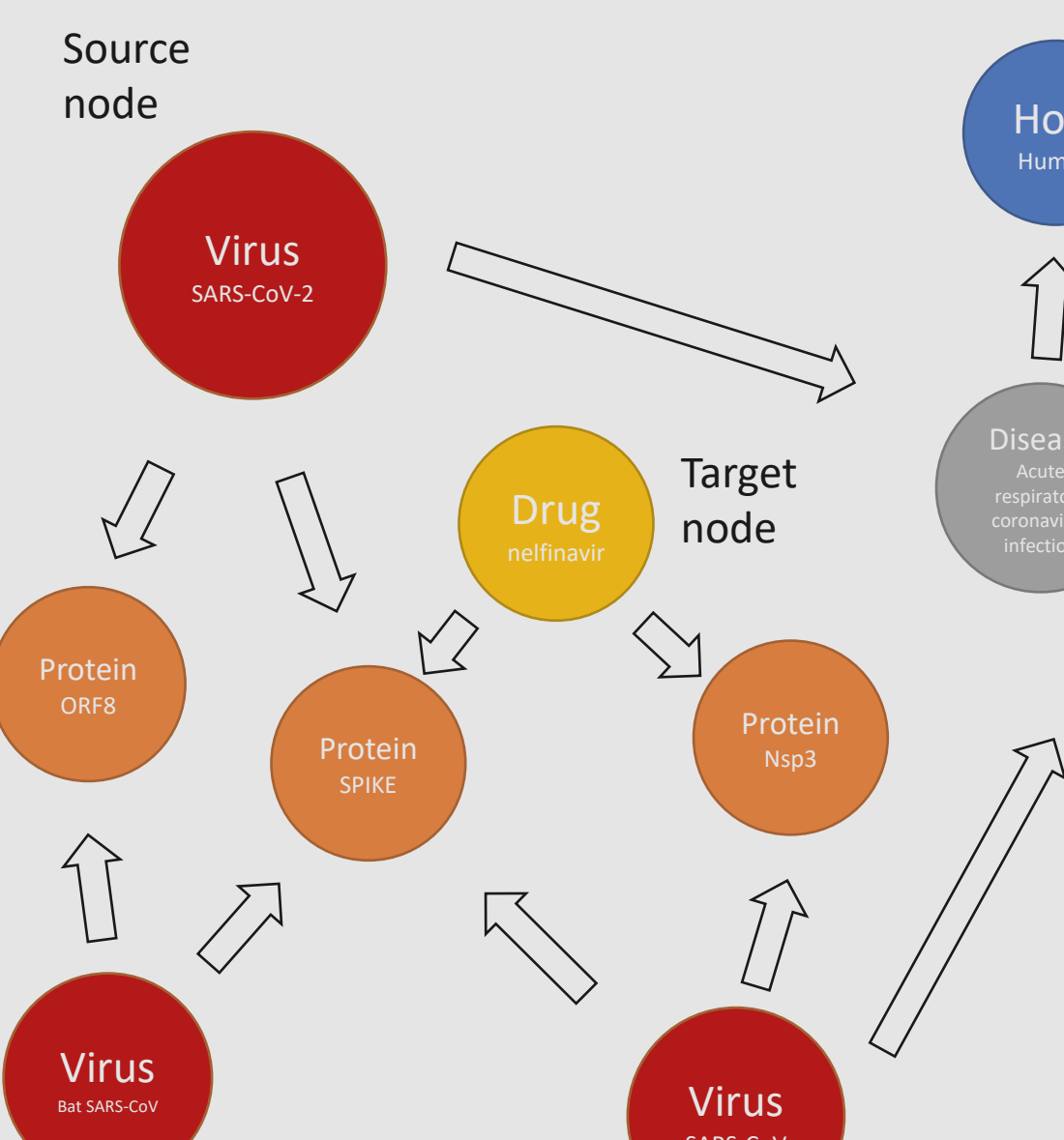
### M-Cypher: powerful tool to analyze knowledge graph



### Drug Repurposing Algorithms

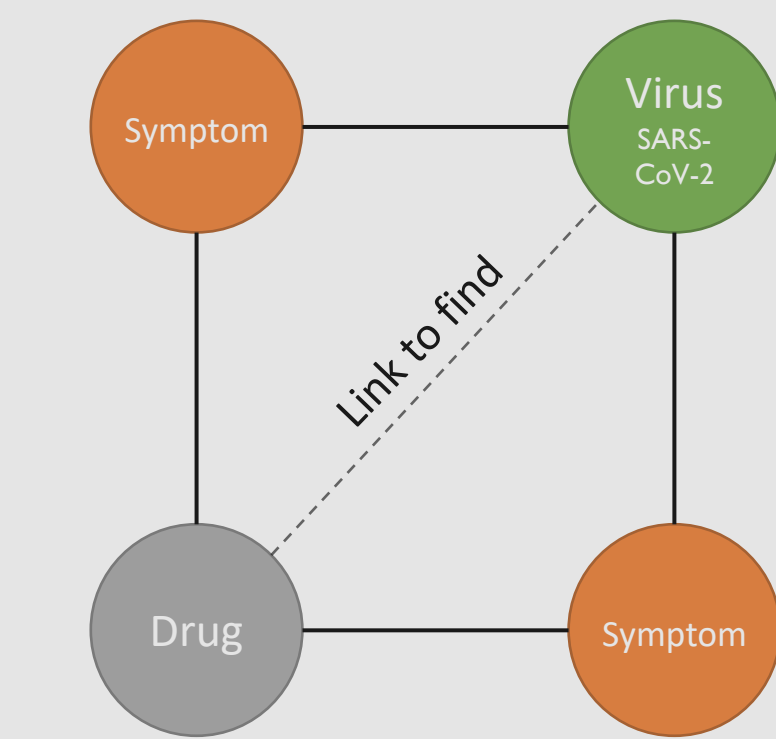
#### Alg.1 Knowledge graph Personalized Page Rank

- Personalized Page Rank (PPR) is used by Twitter to present users with recommendations of other accounts that they may wish to follow.
- We adapt PPR into a knowledge graph version.
- Source node (SARS-CoV-2), target node (Each drug), with parameters: damping factor 0.85, iteration 2M.

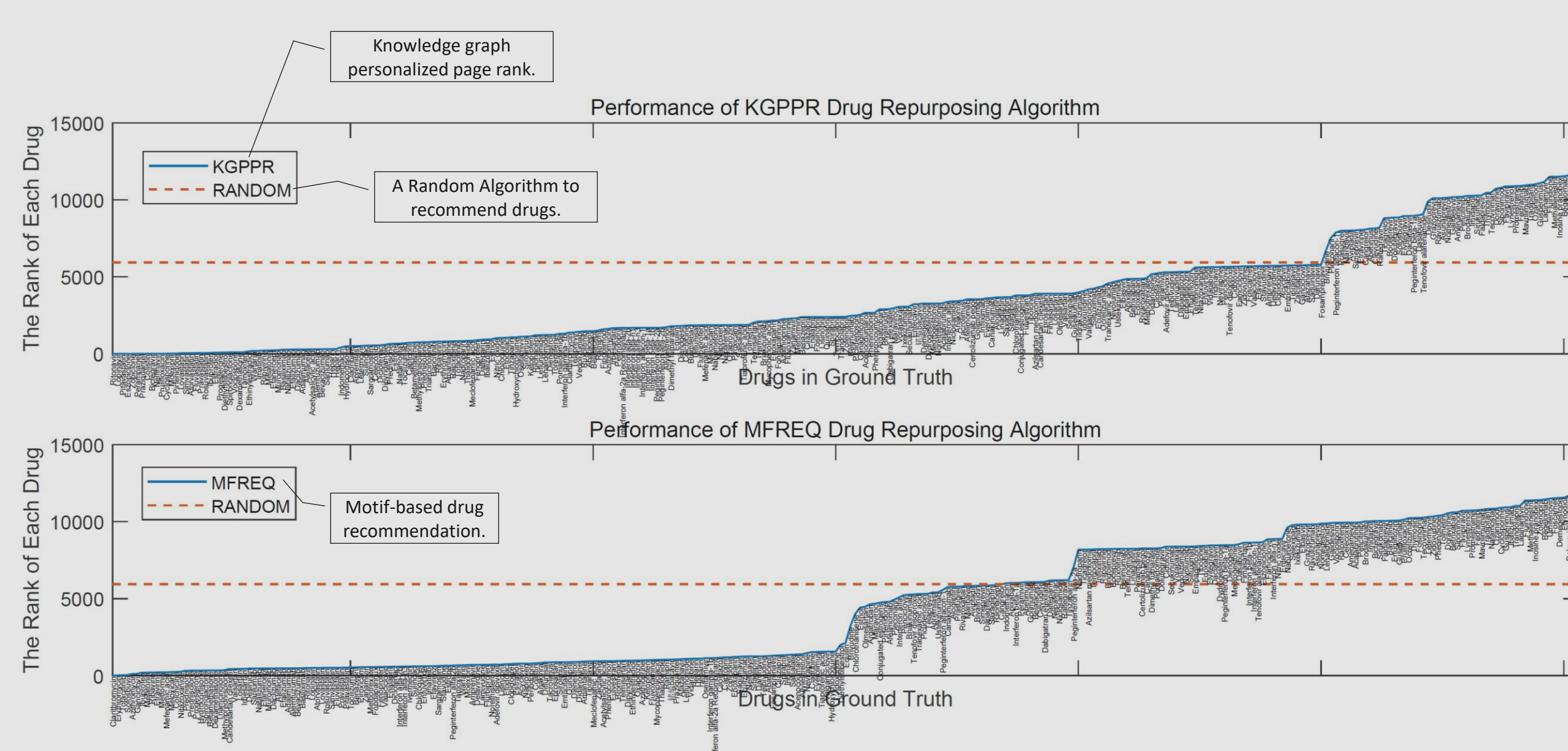


#### Alg.2 Motif based Link Prediction

- Knowledge Graph too complex & large (hundreds of thousands of edges).
- Motifs: small & frequent graphlets of size k nodes, k = 1, 2, 3, 4, 5.
- Use "interesting" motifs M to generate Motif Feature Vector (MFV). For each drug D, MFV describes the frequency of M that contains s and SARS-CoV-2. Train a classifier with input (MFVs) to predict if the link (D, SARS-CoV-2) exists.
- Greater chance of D to serve in covid-19 treatment if the link has higher existential probability.



### Drug Repurposing Results



#### Highlighted Drug Candidates for Repurposing

Drug name	Clinical trial	Drug type	Rank
Ritonavir	Y	Antiviral agents	0.01%
Loxapine	Y	Antipsychotics	0.02%
Pravastatin	N	Statins	0.03%
Moexipril	N	ACEIs	0.12%
Losartan	N	Statins	0.35%
Simvastatin	N	Statins	0.36%
Atorvastatin	N	Statins	0.37%
Fluvastatin	N	Statins	0.44%
Pravastatin	N	Statins	0.46%
Rosuvastatin	N	Statins	0.47%
Dexamethasone	Y	Corticosteroids	0.84%
Sarilumab	Y	Immunosuppressants	2.60%
Hydrocortisone	Y	Corticosteroids	4.10%
Prednisone	N	Corticosteroids	5.42%
Tocilizumab	Y	Immunosuppressants	5.81%

- Almost all drugs currently in clinical trial are recommended by our algorithms in top 10% from 11865 candidates in DrugBank!
- Potential drugs for covid-19 treatment but not currently considered in trial are also discovered: **statins**, **ACEIs** and **corticosteroids**, with literature support!
- Gheblawi, Mahmoud, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circulation research* 126.10 2020: 1456-1474.
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- Zhang F, Zhu L, Cai L, et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19 [published correction appears in *Circ Res*. 2020 Aug 28;127(6):e147. Rohit, Loomba [corrected to Loomba, Rohit]. *Circ Res*. 2020;126(12):1671-1681.
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- UK Government press release. World first coronavirus treatment approved for NHS use by government. (Accessed on June 16, 2020).