

A machine-built self-updating model of COVID-19 mechanisms

Benjamin M. Gyori, John A. Bachman, Diana Kulusheva
Laboratory of Systems Pharmacology, Harvard Medical School



INTRODUCTION

The Ecosystem of Machine-maintained Models with Automated Analysis (EMMAA, emmaa.indra.bio) is a framework for automatically building a set of disease-related models and keeping them up to date using the latest results from the scientific literature. EMMAA uses the INDRA system (indra.bio) to run multiple machine reading systems on literature relevant for a model, and extract molecular and higher-level causal mechanisms from these publications. During daily update cycles, extractions from newly published literature are aligned with the existing model and are used to corroborate existing relations or extend the model with new relations.

Using INDRA assembly, the **EMMAA COVID-19 model** combines mechanisms from structured sources with ones obtained from existing literature on coronaviruses, as well as the emerging body of new literature on COVID-19/SARS-CoV-2. The EMMAA dashboard allows exploring and curating the content of the COVID-19 model, with each mechanism shown in the context of the specific sentences from which it was derived, and linked back to the underlying literature.

1. Extract knowledge when it appears

300 new COVID-19 Papers in PubMed each day + preprints!

Ecosystem of Machine-maintained Models with Automated Analysis (EMMAA)

Scientists / Clinicians

Queries: Register scientific questions

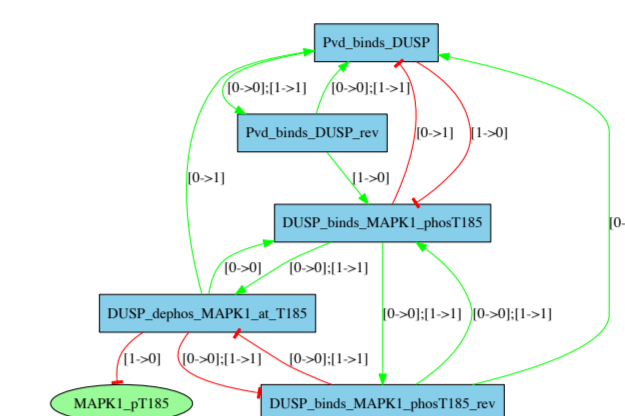
Notifications: novel hypotheses, analysis reports,

4. Notify users about novel hypotheses

2. Assemble new knowledge into model

EMMAA COVID-19 model @covid19_emmaa · 16h
Today I learned 465 new mechanisms. See emmaa.indra.bio/dashboard/covi... for more details.

3. Run relevant analysis



EMMAA COVID-19 model @covid19_emmaa · Oct 4
Today I explained 2 new observations in the MITRE drug-virus effect corpus with my Signed Graph model. See emmaa.indra.bio/dashboard/covi... for more details.

A self-updating model of the COVID-19 literature

Literature sources

- All COVID-19 papers, pulled daily from Kaggle
- All new COVID-19/SARS-CoV-2 papers from PubMed/PMC
- All new COVID-19/SARS-CoV-2 preprints from bioRxiv and medRxiv

Structured sources

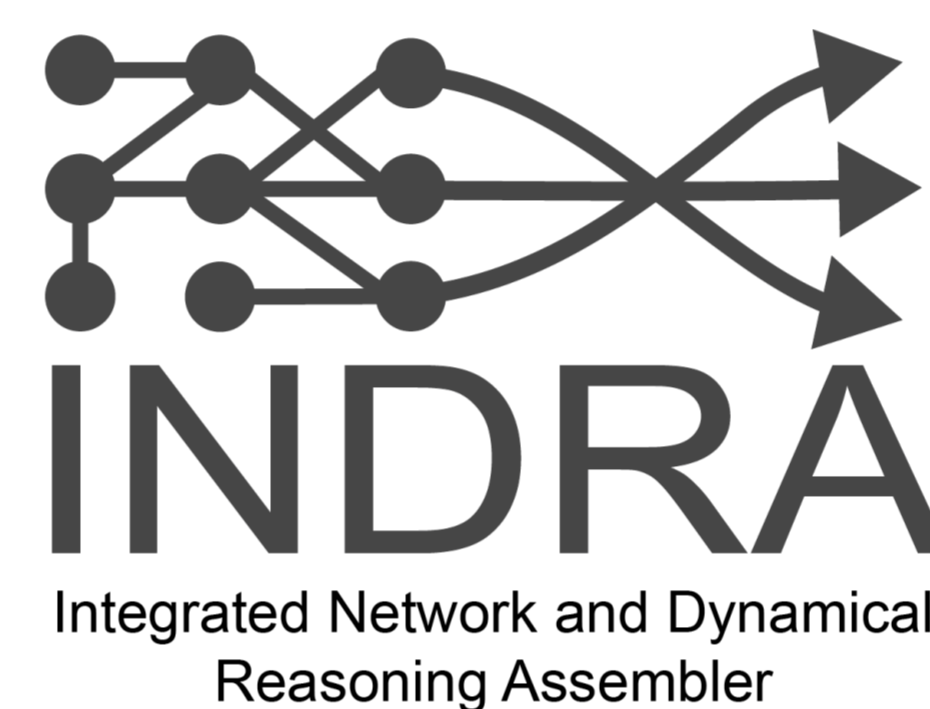
- Small molecule-protein interactions from DrugBank and Small Molecule Suite
- Small-molecule gene and gene-disease relationships from Comparative Toxicogenomics Database
- VirHostNet coronavirus/host interactions
- Gordon et al. SARS-CoV-2/host interactome



Continuous monitoring and processing on AWS

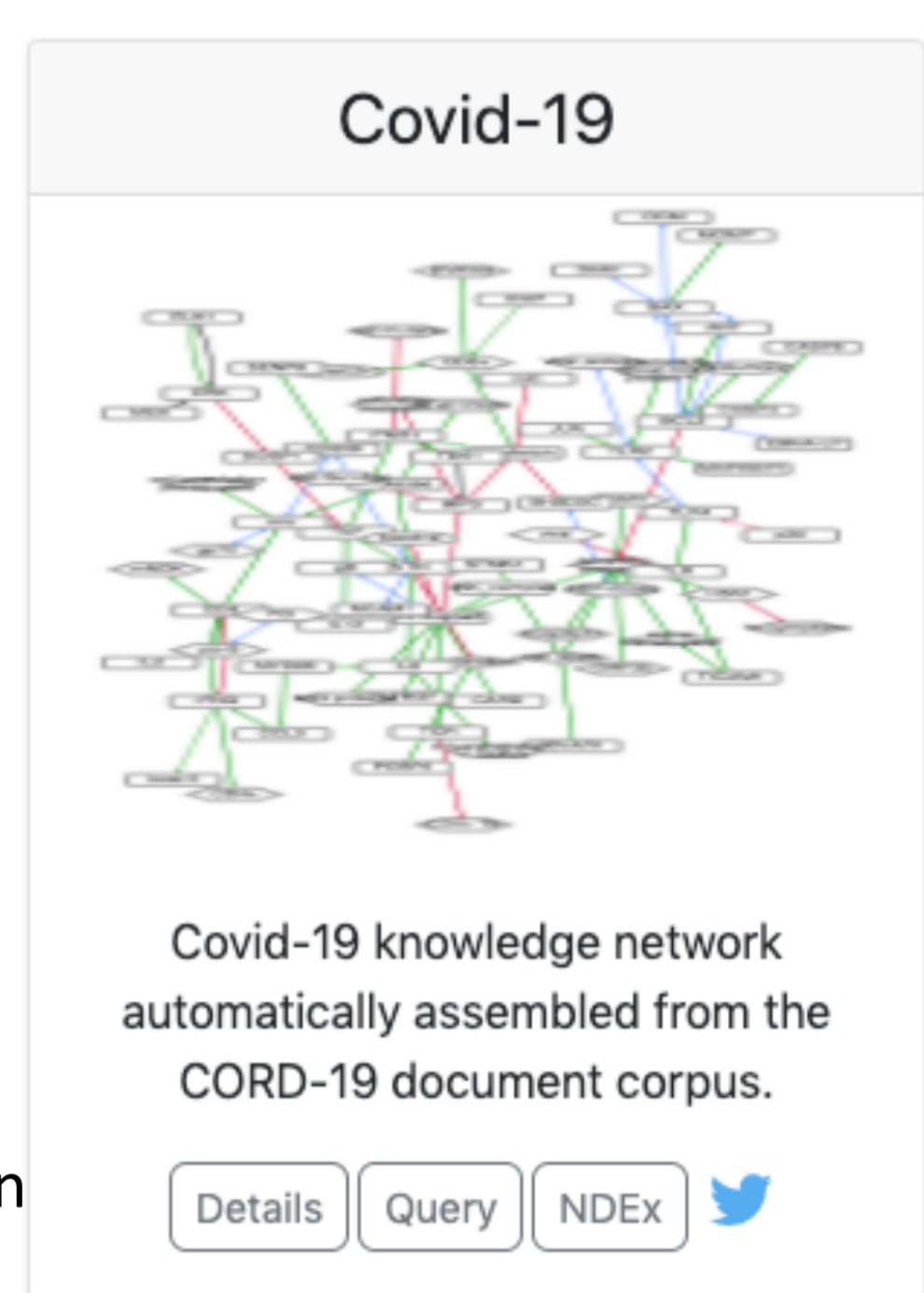
- NLP systems
- Reach (U. Arizona)
 - Eidos (U. Arizona)
 - Sparser (SIFT LLC)
 - RLIMS-P (U. Delaware)
 - TRIPS (IHMC)
 - ISI/AMR (ISI)

Continuous model assembly on AWS



How to integrate novel information with existing model?

- **Redundancy:** new evidence, corroboration of existing knowledge
- **Refinement:** existing knowledge in more detail or in a specific context
- **Generalization:** existing knowledge generalized to broader context
- **Conflict:** contradicts existing knowledge
- **Novelty:** completely new information



Covid-19 knowledge network automatically assembled from the COVID-19 document corpus.

Details Query NDEX

Registering user queries and email notifications

Query: "What small molecules are known to lead to the inhibition of COVID-19 [in the EMMAA COVID-19 model]?"

Subscription to query: daily email updates pointing to new analysis results

Daily, user-specific notification email

Updates to your open queries

- "What inhibits COVID-19? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Unsigned Graph model type. For details click [here](#).
- "What inhibits TMPRSS2? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What inhibits TMPRSS2? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What inhibits COVID-19? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What inhibits ACE2? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What inhibits ACE2? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What inhibits Middle East Respiratory Syndrome Coronavirus? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What inhibits Middle East Respiratory Syndrome Coronavirus? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What does leupeptin inhibit? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What does leupeptin inhibit? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What inhibits CTSB? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).

Can pioglitazone be potentially useful therapeutically in treating patients with COVID-19?

Elena Carboni¹, Anna R. Carta² and Ezio Carboni^{1*}

losartan → ACE2 → COVID-19

- Losartan activates ACE2.
- Losartan increases the amount of ACE2.
- Losartan deubiquitinates ACE2.

ACE2 → COVID-19

- ACE2 inhibits COVID-19.
- ACE2 binds COVID-19.
- ACE2 increases the amount of COVID-19.
- ACE2 activates COVID-19.
- COVID-19 binds ACE2.

pioglitazone → ACE2 → COVID-19

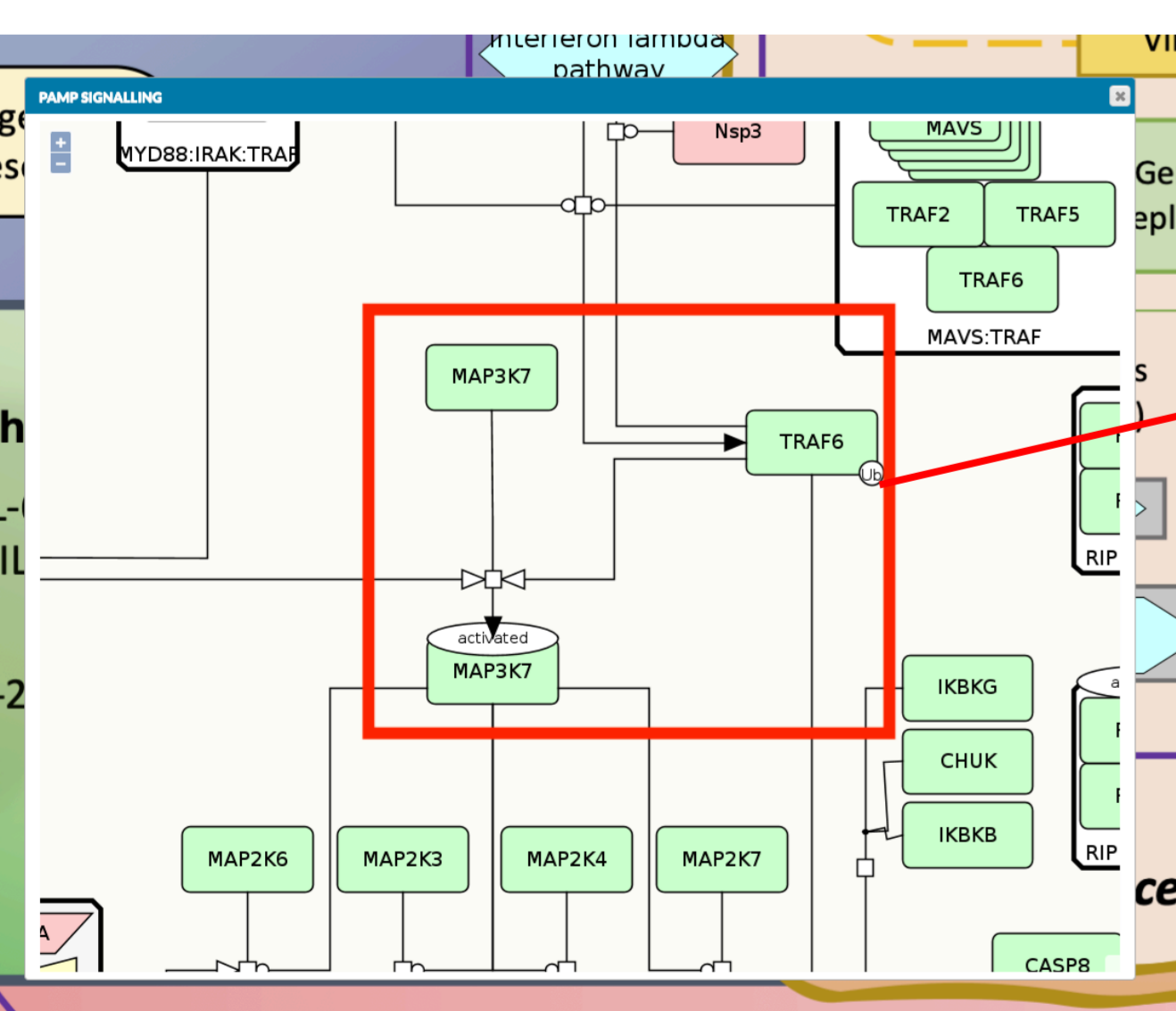
- Pioglitazone activates ACE2.
- Pioglitazone increases the amount of ACE2.
- Pioglitazone decreases the amount of ACE2.
- Pioglitazone inhibits ACE2.

ACE2 → COVID-19

- ACE2 inhibits COVID-19.
- ACE2 binds COVID-19.
- ACE2 increases the amount of COVID-19.
- ACE2 activates COVID-19.
- COVID-19 binds ACE2.

New mechanistic discoveries highlight new therapeutic opportunities

Alignment with the COVID-19 Disease Map



251 evidences found for this reaction by INDRA

Source	Text	Count
reach	It was also shown that ubiquitinated TRAF6 activates the TAK1 complex to phosphorylate the IKK complex directly.	12106781
reach	Shortly, TLR4 homodimerization recruits MYD88 and the IRAK complex including TRAF6 that activates TAK1.	29438282
reach	The activated IRAK family proteins associate with TRAF6 (TNF receptor-associated factor 6), and TRAF6 activates TAK1, which in turn activates the IKK complex composed of NEMO, IKKα and IKKβ.	26309029
reach	It was previously shown that TRAF6 and RIP1 can activate TAK1 and lead to IKK phosphorylation and activation (xref , xref).	21911455
reach	The IRAK1-TRAF6 complex then activates TAK1 through a process involving cytosol translocation of TAK1 and two regulatory components TAK-binding protein 2 (TAB2) and TAB3 and the ubiquitination of TRAF6.	21977329

Full alignment (available through covid19.indra.bio):

- 656,418 INDRA Statements that contain at least one of the COVID-19 Disease Map entities
- 40,361 INDRA Statements whose entities are all in the COVID-19 Disease Map

Availability

- EMMAA: emmaa.indra.bio
- All COVID-19-related results: covid19.indra.bio
- INDRA: indra.bio
- Human-machine dialogue system: dialogue.bio
- INDRA Database: db.indra.bio
- INDRA Network Search: network.indra.bio

Funding

The development of EMMAA is funded under the DARPA Automating Scientific Knowledge Extraction (ASKE) program under award HR00111990009.

References

- [1] Gyori B., Bachman J., Subramanian K., Muhlich J., Galescu L., Sorger P. From word models to executable models of signaling networks using automated assembly (2017), Molecular Systems Biology 13, 954
- [2] Ostaszewski M., Niarakis A., et al. COVID-19 Disease Map, a computational knowledge repository of SARS-CoV-2 virus-host interaction mechanisms, bioRxiv 2020.10.26.356014 (2020)

Model updates on social media

Follow [@covid19_emmaa](https://twitter.com/covid19_emmaa) on Twitter for daily updates from the EMMAA COVID-19 model

Updates on new statements added to the model from the newly appearing literature

EMMAA COVID-19 model @covid19_emmaa · 16h
Today I learned 465 new mechanisms. See emmaa.indra.bio/dashboard/covi... for more details.

Updates on finding new explanations for ~3,000 drug-virus effects observed experimentally or tested clinically

EMMAA COVID-19 model @covid19_emmaa · Oct 4
Today I explained 2 new observations in the MITRE drug-virus effect corpus with my Signed Graph model. See emmaa.indra.bio/dashboard/covi... for more details.