

# Drug repurposing for COVID-19 using explainable machine learning and mechanistic models of signal transduction circuits related to SARS-CoV-2 infection with real world data validation

Carlos Loucera

Bioinformatics Area, Andalusian Public Foundation Progress and Health-FPS, 41013 Sevilla, Spain  
Institute of Biomedicine of Seville, IBiS, University Hospital Virgen del Rocío/CSIC/University of Seville,  
41013 Sevilla, Spain

MAQC 2022  
2022 September 26



Consejería de Salud  
y Consumo

Fundación  
Progreso y Salud



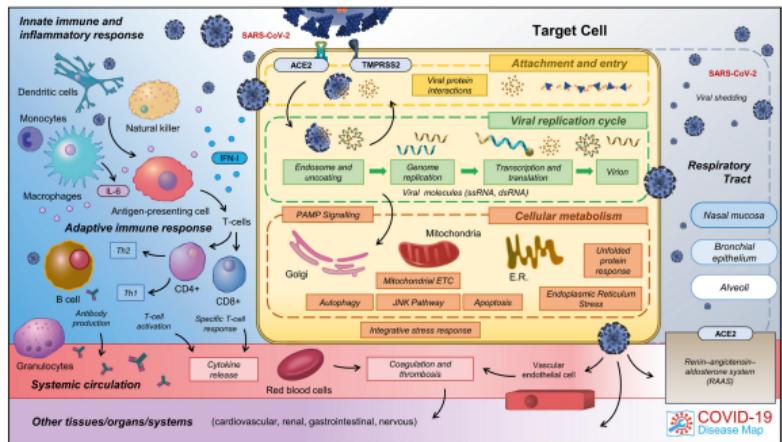
# Knowledge discovery

**Living Contradiction** is a fascinating, honest examination of that genuine contradiction faced by teachers in reconciling the effort made to encourage young people towards independent critical thinking, with the simultaneous sense of responsibility to instruct and insist on a particular behavior.

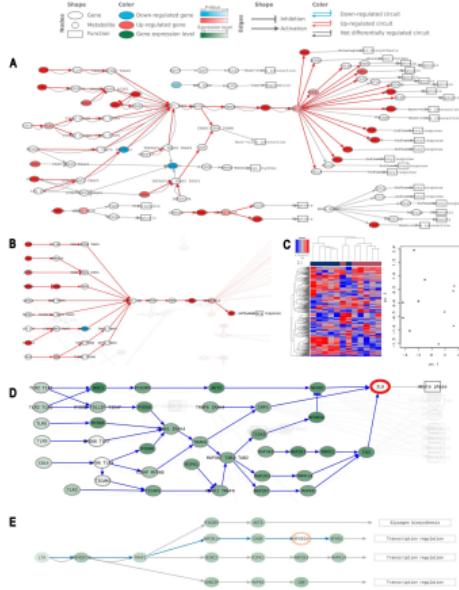
## Trustworthiness

The **WHY** is as important as the **WHAT**

# Building a COVID-19 Disease Map



COVID-19 Disease Map<sup>1</sup>

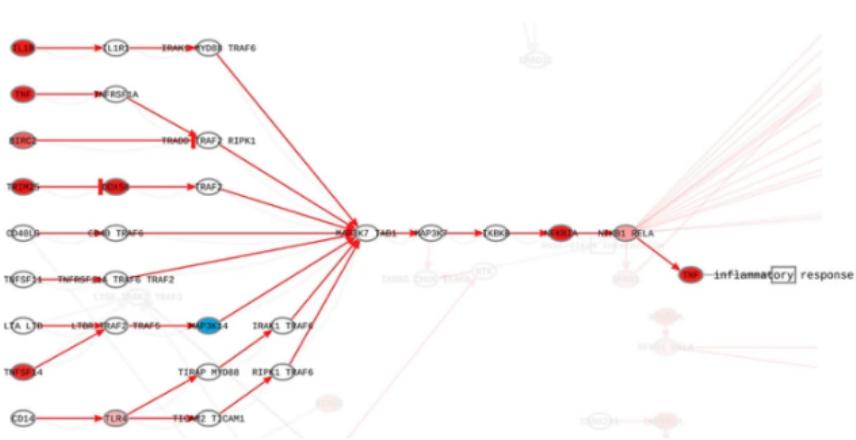


(Simplified) COVID-19 Disease Map<sup>2</sup>

<sup>1</sup> Marek Ostaszewski et al. (2021). "COVID19 Disease Map, a computational knowledge repository of virus–host interaction mechanisms." In: *Molecular systems biology* 17.10, e10387

<sup>2</sup> Kinza Rian et al. (2021). "Mechanistic modeling of the SARS-CoV-2 disease map." In: *BioData Mining* 14.1, pp. 1–8

# Mechanistic modeling



High throughput estimation of functional cell activities reveals disease mechanisms and relevant clinical outcomes

[PDF](#) | [HTML](#) | [Supplementary Files](#) | [How to cite](#) | [Order a Reprint](#)  
Oncotarget, 2017; 8:5160-5178. <https://doi.org/10.18637/oncotarget.14107>

Metrics: PDF 1955 views | HTML 4565 views

Marta R. Hidalgo<sup>1</sup>, Cankut Cubuk<sup>1</sup>, Alicia Amadoz<sup>1,2</sup>, Francisco Salavert<sup>1,3</sup>, José Carbonell-Caballero<sup>1</sup>, Joaquín Dopazo<sup>1,2</sup>

<sup>1</sup>Computational Genomics Department, Centro de Investigación Príncipe Felipe (CIPF), Valencia, 46012, Spain

<sup>2</sup>Functional Genomics Node (INB-ELIXIR-es), Valencia, 46012, Spain

<sup>3</sup>Bioinformatics in Rare Diseases (BIER), Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Valencia, 46012, Spain

Correspondence to:

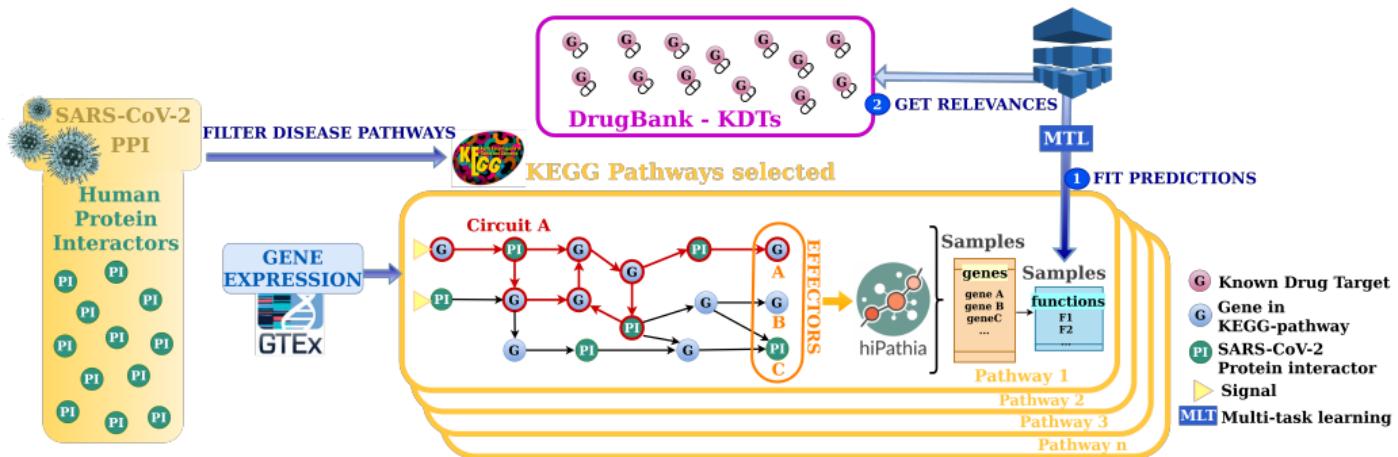
Joaquín Dopazo, email: [jdopazo@cinf.es](mailto:jdopazo@cinf.es)

Keywords: signaling pathway, disease mechanism, prognostic, survival, biomarker

Received: September 01, 2016 Accepted: November 21, 2016 Published: December 22, 2016

$$S_n = v_n \left( 1 - \prod_{s_a \in \mathcal{A}} (1 - s_a) \right) \prod_{s_i \in \mathcal{I}} (1 - s_i)$$

# Drug repurposing schema



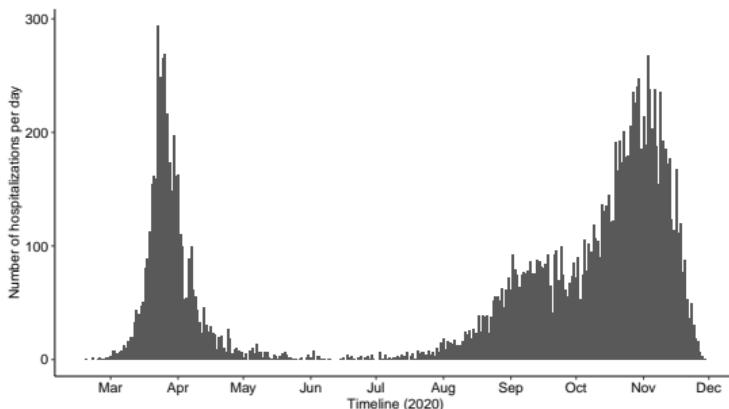
# Data facts

Andalusian public health system

Year 2020, no COVID-vaccine

15968 COVID-19 hospitalized patients

End point: COVID-19 certified death (28 days)



covariate	survival	death	p-value
Total N	13116	2678	
Sex (female)	6024 (45.9)	1129 (42.2)	<0.001
Flu vaccine	5465 (41.7)	1746 (65.2)	<0.001
Pneumococcal vaccine	3441 (26.2)	1111 (41.5)	<0.001
Diabetes	3856 (29.4)	1167 (43.6)	<0.001
Circulatory diseases	8111 (61.8)	2261 (84.4)	<0.001
Cancer	1550 (11.8)	545 (20.4)	<0.001
Respiratory diseases	2896 (22.1)	828 (30.9)	<0.001
Dementia	964 (7.3)	536 (20.0)	<0.001
Other mental diseases	1764 (13.4)	407 (15.2)	0.018
Anxiety and mood disorders	3382 (25.8)	784 (29.3)	<0.001
Age			<0.001
18_41	1399 (10.7)	20 (0.7)	
41_68	5971 (45.5)	380 (14.2)	
68_99	5746 (43.8)	2278 (85.1)	

# Methods Facts

We Only include properly balanced treatments<sup>1</sup>

964 treatments found

122 were eligible

HR Closed-form variance estimator for Weighted Propensity Scores<sup>2</sup>

Lymphocyte count registered up to 14 days since hospitalization begins

Covariate-adjusted linear mixed effect model to test Lymphocyte progression trends

30 treatments are significant for both tests

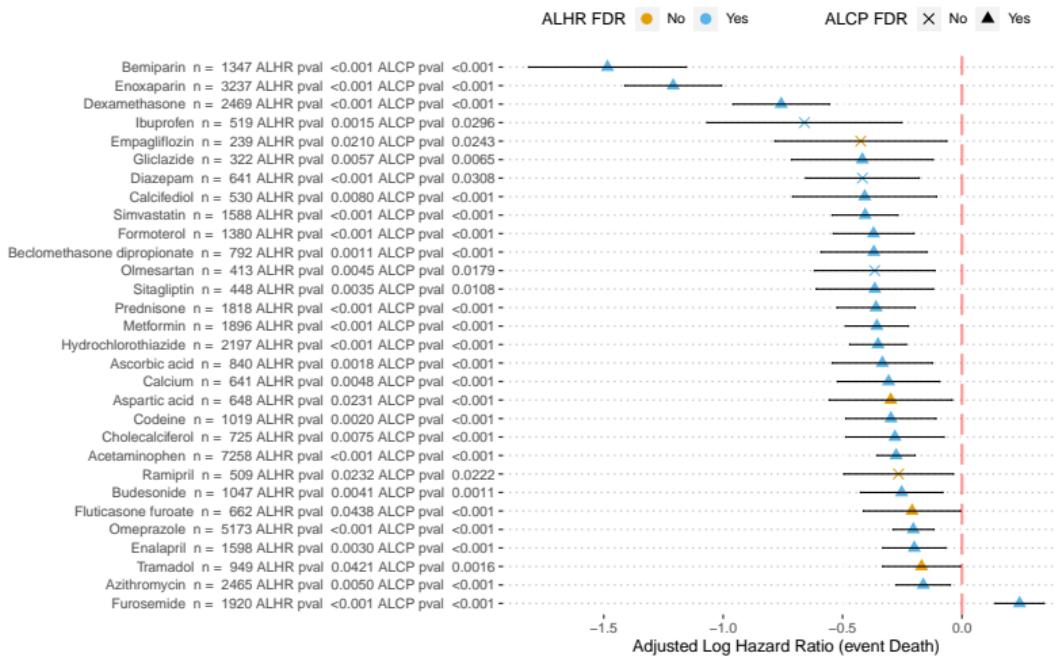
22 after FDR adjustment

---

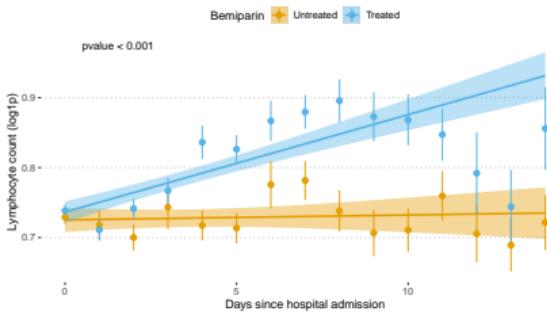
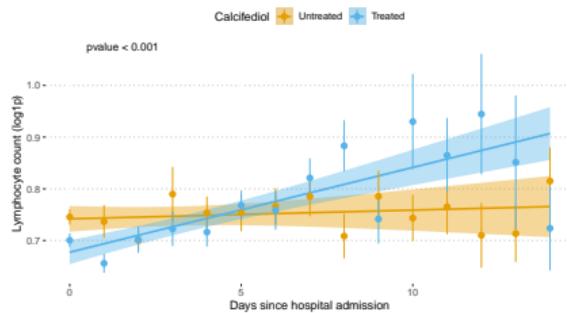
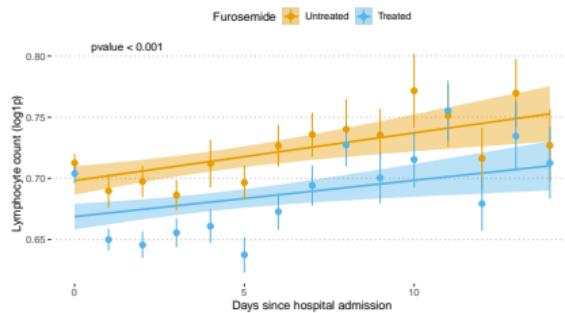
<sup>1</sup>David Hajage et al. (2018). "Closed-form variance estimator for weighted propensity score estimators with survival outcome." In: Biometrical Journal 60.6, pp. 1151–1163

<sup>2</sup>Elizabeth A Stuart et al. (2013). "Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research." In: Journal of clinical epidemiology 66.8, S84–S90

# Covariate-Adjusted LHR by Treatment



# Covariate-Adjusted Lymphocyte trend



# Conclusions

**Bemiparin and Enoxaparin** → Highest survival

prevent thrombotic and thromboembolic complications

enoxaparin has been previously reported as protective

the protective effect is not shared by other anticoagulants

**Calcifediol and Cholecalciferol** have a protective effect

probably due to vitamin D and its pro-immune and anti-inflammatory properties.

There is a **significative intersection** between **ML predicted drugs** and **RWE**

$$\chi^2 = 6.674, p - \text{value} = 0.009785$$

# Closing remarks

It is not a competition between paradigms and methods

We aim to gain evidences from as many sources as possible

Our xML tools aim to help users prioritize in order to *look for a needle in a haystack*

# Thank You!

Personal funding. Contact: [carlos.loucera@juntadeandalucia.es](mailto:carlos.loucera@juntadeandalucia.es)



**Junta de Andalucía**

Consejería de Transformación Económica,  
Industria, Conocimiento y Universidades



**UNIÓN EUROPEA**

Fondo Social Europeo

Carlos Loucera postdoctoral contract PAIDI2020-DOC\_00350 is funded by Junta de Andalucía and co-funded by the European Social Fund (FSE) 2014-2020





Fundación Progreso y Salud  
CONSEJERÍA DE SALUD Y FAMILIAS

## Clinical Bioinformatics Area Fundación Progreso y Salud, Sevilla, Spain, and...

...the INB-ELIXIR-ES, National Institute of Bioinformatics  
and the BiER (CIBERER Network of Centers for Research in Rare Diseases)



<https://www.slideshare.net/xdopazo/>

Follow us on  
twitter  
@xdopazo

@ClinicalBioinfo  
@loucerac  
@CSoriguer



Fundación BBVA

