

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

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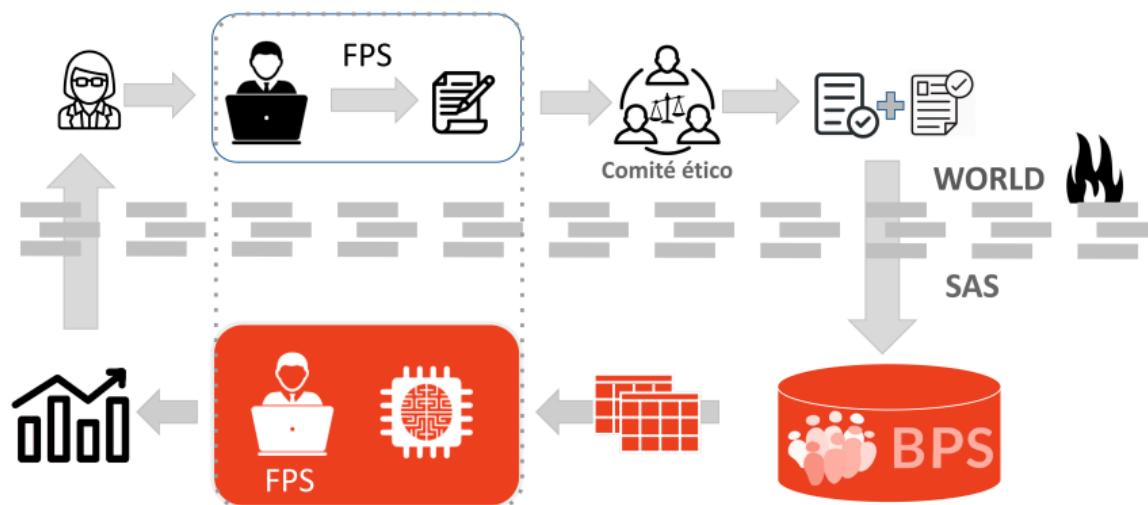
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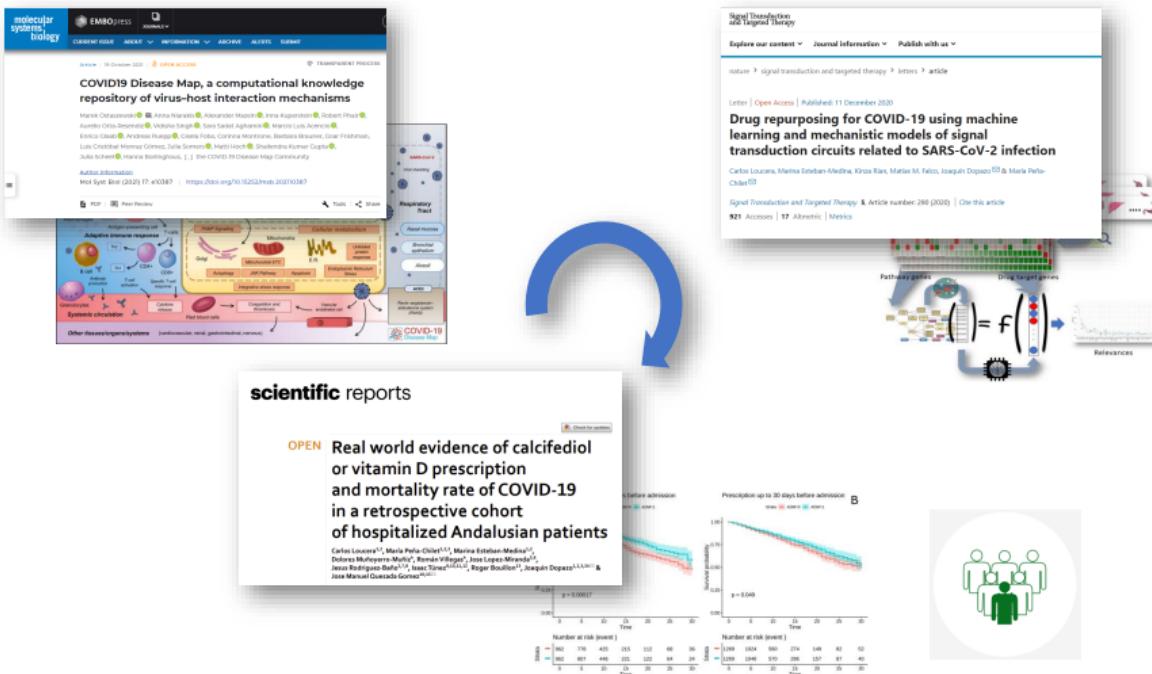
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Infrastructure for secure generation of Real World Evidence from Real World Data from the Andalusian Health Population Database



Knowledge paradigm



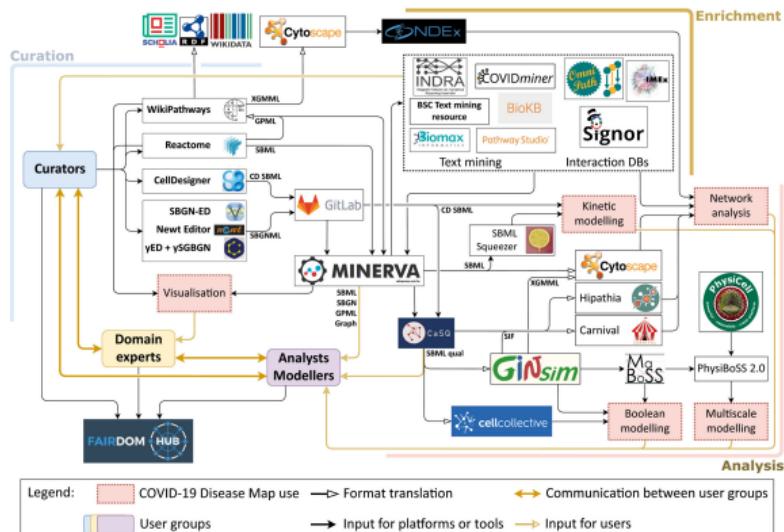
Knowledge discovery

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**

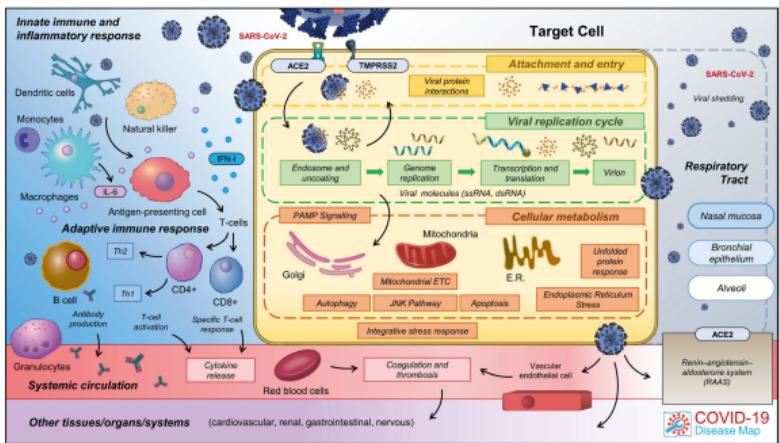
Building a COVID-19 Disease Map



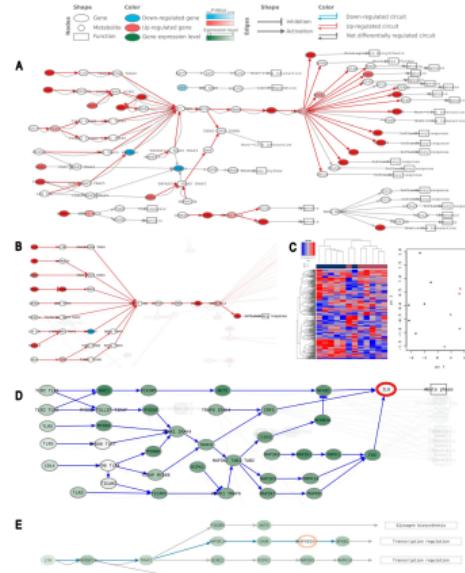
COVID-19 Disease Map¹

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

Building a COVID-19 Disease Map



COVID-19 Disease Map¹

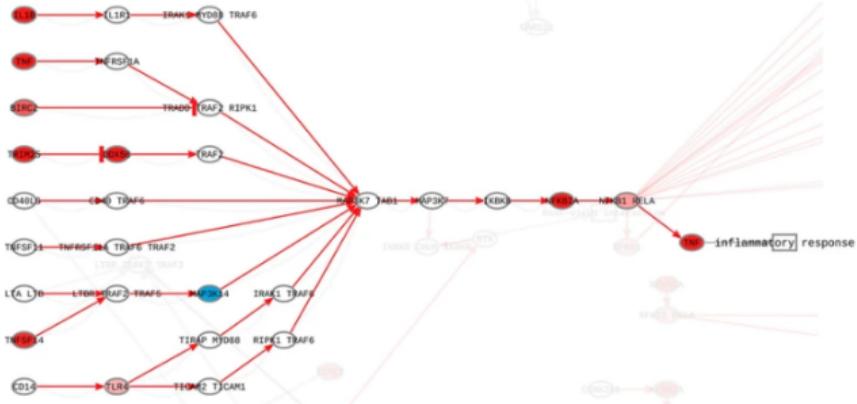


(Simplified) COVID-19 Disease Map²

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

² 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 p relevant clinical outcomes

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Oncotarget. 2017; 8:5160-5178. <https://doi.org/10.18632/oncotarget.14107>

Metrics: PDF 1955 views | HTML 4565 views

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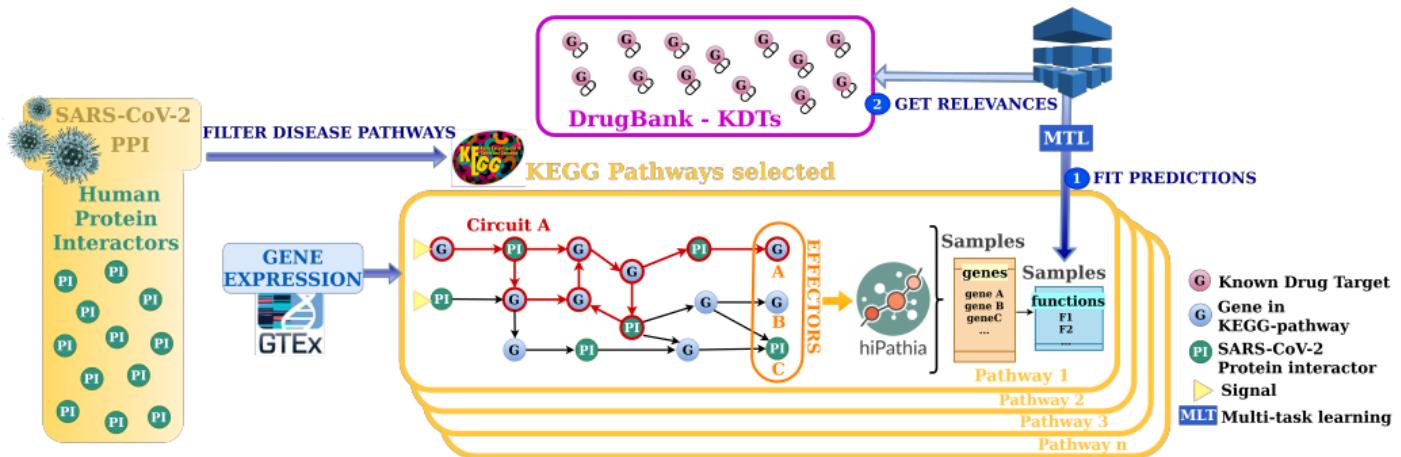
Keywords: signaling pathway, disease mechanism, prognostic, survival, biomarker

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



ML pipeline

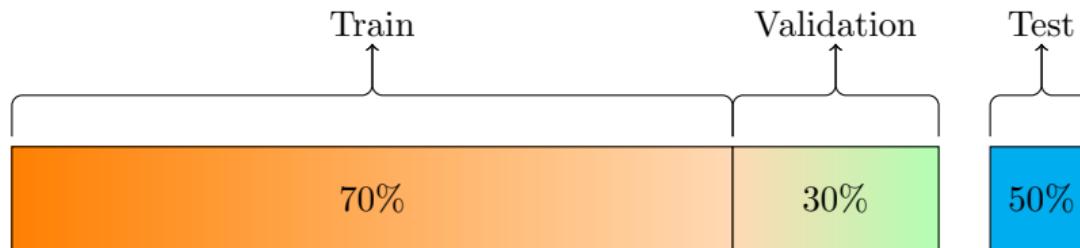
Our **FS** model makes decisions based on the **SHAP** ranks

We want to be **true to the data**

- Avoid overconfidence

- Draw from a background distribution

- Compute the explanations using a different subset



(Nogueira) Build a population (repeat the whole procedure **100 times**)
Make it faster: **GPU-CUDA**

Data-driven Validation (Performance + Explanations)

Explanation stability

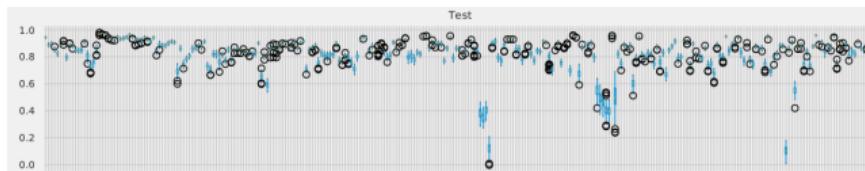
Robustness Vs Stochastic, Noise, Sampling

100 Holdout splits of half the sample size

Split *training* into *learning* and *validation*

Check unbiased performance over *test*

Compute Nogueiras¹ statistic test and CI



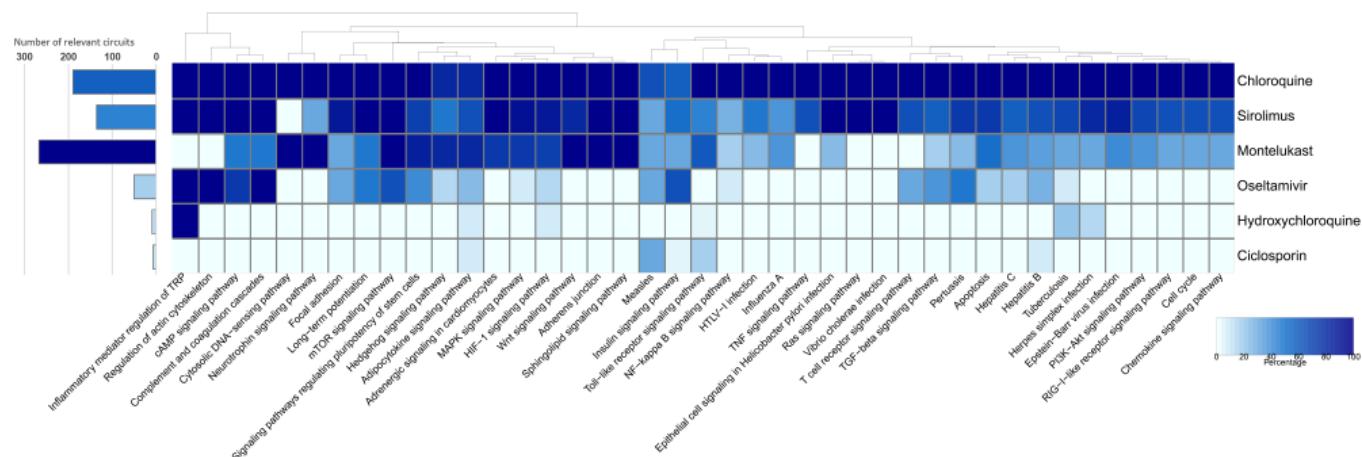
R^2 score distribution over the test splits

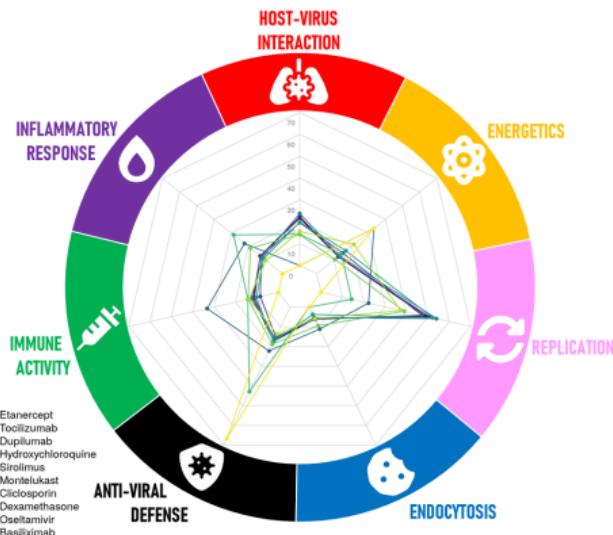
Mean R^2 : 0.82 ± 0.02
N-Stat CI: $(0.729, 0.735)$

¹Sarah Nogueira et al. (2017). "On the stability of feature selection algorithms." In: The Journal of Machine Learning Research 18.1, pp. 6345–6398

SHapley Additive exPlanations

Fair feature responsibility attribution.
Dis-aggregated by circuit by construction
Additive (use biologically-relevant groups)





380 KDTs (targeted by 679 drugs) have direct influence over the whole or partial parts of the map

The GO biological processes enriched are mostly related to immune activity (T-cell, inflammatory response)

The COVID-19 Hallmarks are represented

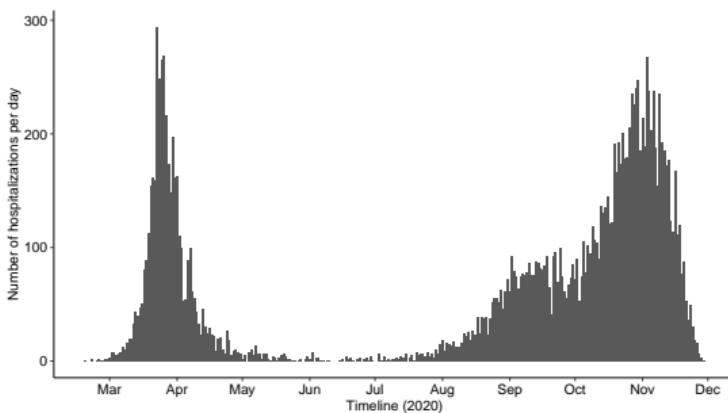
Data facts

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 treatments¹

964 treatments found

122 were eligible

HR Closed-form variance estimator for Weighted Propensity Scores²

Lymphocyte count registered up to 14 days since hospitalization begins

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

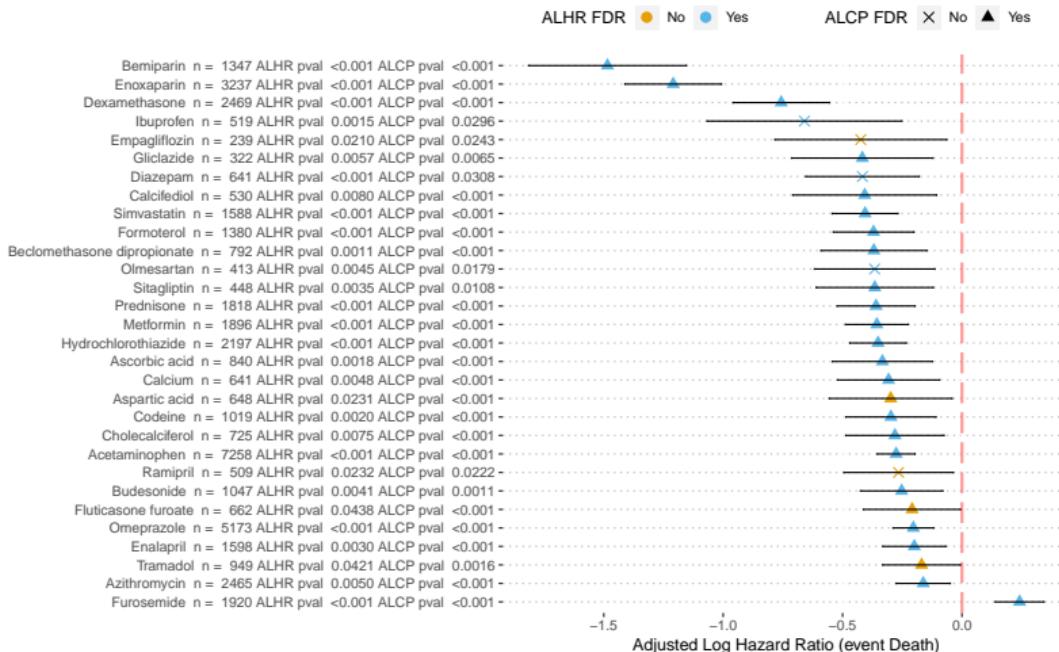
30 treatments are significant for both tests

22 after FDR adjustment

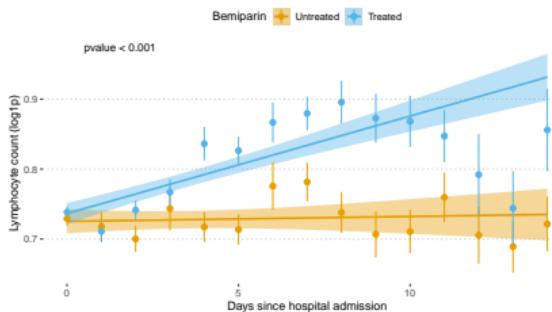
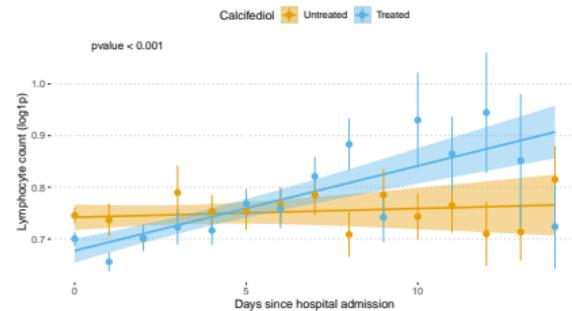
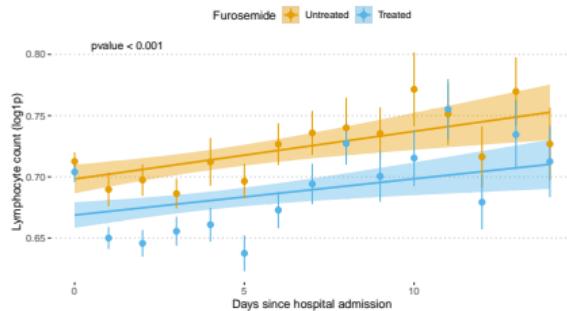
¹Elizabeth A Stuart et al. (2013). "Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research." In: Journal of clinical epidemiology 66.8, S84–S90

²David Hajage et al. (2018). "Closed-form variance estimator for weighted propensity score estimators with survival outcome." In: Biometrical Journal 60.6, pp. 1151–1163

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

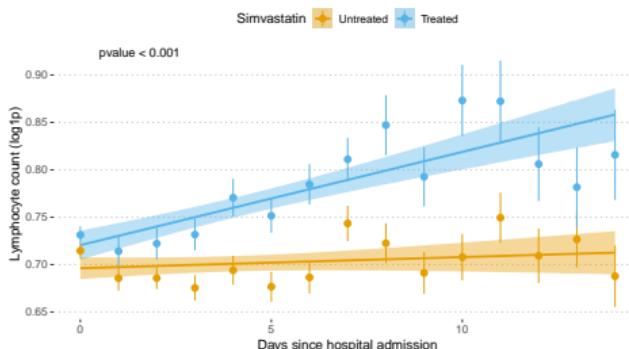
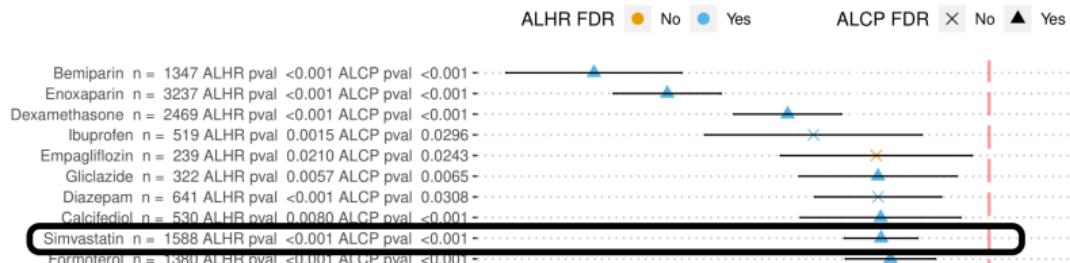
Calcifediol and **Cholecalciferol** have a protective effect

probably due to vitamin D and its pro-immune and anti-inflammatory properties²

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

$$\chi^2 = 6.674, \text{ pvalue} = 0.009785$$

Simvastatin summary



Pleiotropic effect
antiinflammatory and antithrombotic
inhibiting the NF-K β pathway
directly reduces inflammatory cytokines
(IL1, IL6, TNF- α), CRP, and neutrophils
Under heavy study

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** their work:

if they *look for a needle in a haystack*

help them by

(**filter**) removing stacks of hay

prioritize what remains

with **biology-driven constraints** and **explanations**

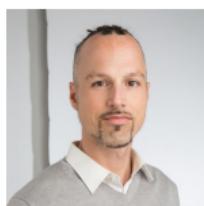
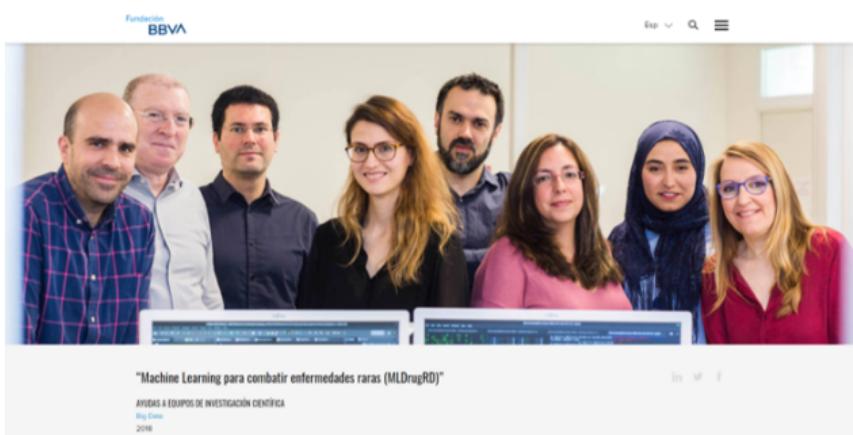
Explainability and interpretability should be **central** to ML solutions

If we include explanations we need to add a **new evaluation axis**:

predictive performance is not enough

BPS, the database for secondary use of clinical data of the Andalusian Public Health System, constitutes a unique resource for large-scale RWE studies

The team



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Personal funding. Contact: carlos.loucera@juntadeandalucia.es



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Introduction
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Methods
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Results
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Thanks
ooo●

Thank You!