An Interpretable Machine Learning Framework for Adverse Drug Reaction Prediction from Drug-Target Interactions

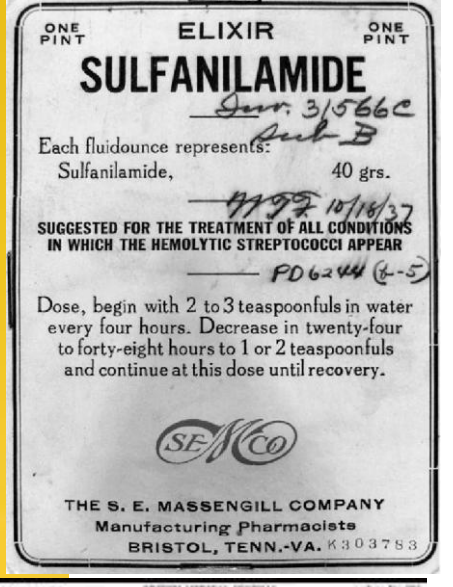
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XXXII Symposium on Bioinformatics and Computer-Aided Drug Discovery
BCADD 2026



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ONE PINT ELIXIR ONE PINT

SULFANILAMIDE

Each fluidounce represents:
Sulfanilamide, 40 grs.

SUGGESTED FOR THE TREATMENT OF ALL CONDITIONS IN WHICH THE HEMOLYTIC STREPTOCOCCI APPEAR

Dose, begin with 2 to 3 teaspoonfuls in water every four hours. Decrease in twenty-four to forty-eight hours to 1 or 2 teaspoonfuls and continue at this dose until recovery.

THE S. E. MASSENGILL COMPANY
Manufacturing Pharmacists
BRISTOL, TENN.-VA.





Pharmacovigilance

PHARMACEUTICAL PRESS
Essential Knowledge

What is a safety signal in pharmacovigilance?

In short, a safety signal in pharmacovigilance is information on a potential new or known adverse drug reaction that warrants further investigation.[1]



1 EMA. (n.d.). Signal management. Available at: https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/signal-management Last accessed: 8th April 2025.

Available through Medicines Complete

£2.21bn

The projected annual cost of ADR admissions to the NHS in England.[1]

464

Total number of medicinal products withdrawn from the pharmaceutical market worldwide due to safety reasons.[2]

References

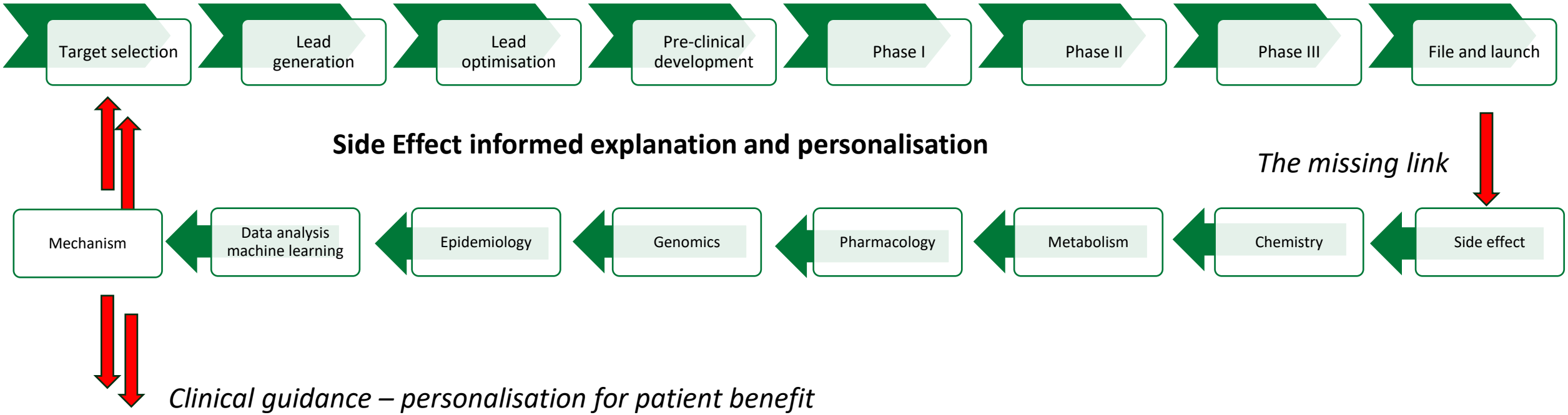
1. Guidance_on_adverse_drug_reactions.pdf (publishing.service.gov.uk) Osanlou, Rostam, et al. 'Adverse Drug Reactions, Multimorbidity and Polypharmacy: A Prospective Analysis of 1 Month of Medical Admissions'. BMJ Open, vol. 12, no. 7, July 2022, p. e055551. bmjopen.bmj.com, https://doi.org/10.1136/bmjopen-2021-055551

2. Kocadal, Kumsal, et al. 'Drug-Associated Cardiovascular Risks: A Retrospective Evaluation of Withdrawn Drugs'. Northern Clinics of Istanbul, vol. 6, no. 2, Sept. 2018, pp. 196–202. PubMed Central, https://doi.org/10.14744/nci.2018.44977

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Drug class by drug class examples

Open Access Article

Suspected Adverse Drug Reactions Associated with Leukotriene Receptor Antagonists Versus First-Line Asthma Medications: A National Registry–Pharmacology Approach

by Mohammed Khan, Christine Hirsch * and Alan M. Jones *

Observational suspected adverse drug reaction profiles of fluoro-pharmaceuticals and potential mimicry of per- and polyfluoroalkyl substances (PFAS) in the United Kingdom

Banurja Balasubramaniam, Alan M. Jones

Article | Open access | Published: 14 October 2025

Adverse drug reaction profiles of histone deacetylase inhibitors

Ruqayyah Begum, Jason L. Parsons & Alan M. Jones

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COMPUTER-AIDED DRUG DESIGN

The Prediction–Safety Paradox

WHAT WE PREDICT

Models are increasingly powerful

Binding
Docking, molecular dynamics, interaction fingerprints

Affinity
Free-energy perturbation, ML-based ΔG scoring

Selectivity
Multi-target profiling, off-target panel prediction

COMPUTATIONAL MATURITY

Advanced & expanding →

YET

GAP

WHAT REMAINS REACTIVE

Safety still lags behind

Safety assessment
Largely empirical — toxicity caught late in the pipeline

Post-market surveillance
Adverse events detected only after patient exposure

Model blind spots
Idiosyncratic toxicity, metabolite effects, immune-mediated ADRs

PREDICTIVE INTEGRATION

← Underserved & reactive

"So why doesn't our growing predictive power translate into safer drugs?"

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Data Sources - Inputs

Yellow Card

STITCH

EMBL

SIDER

EMBL

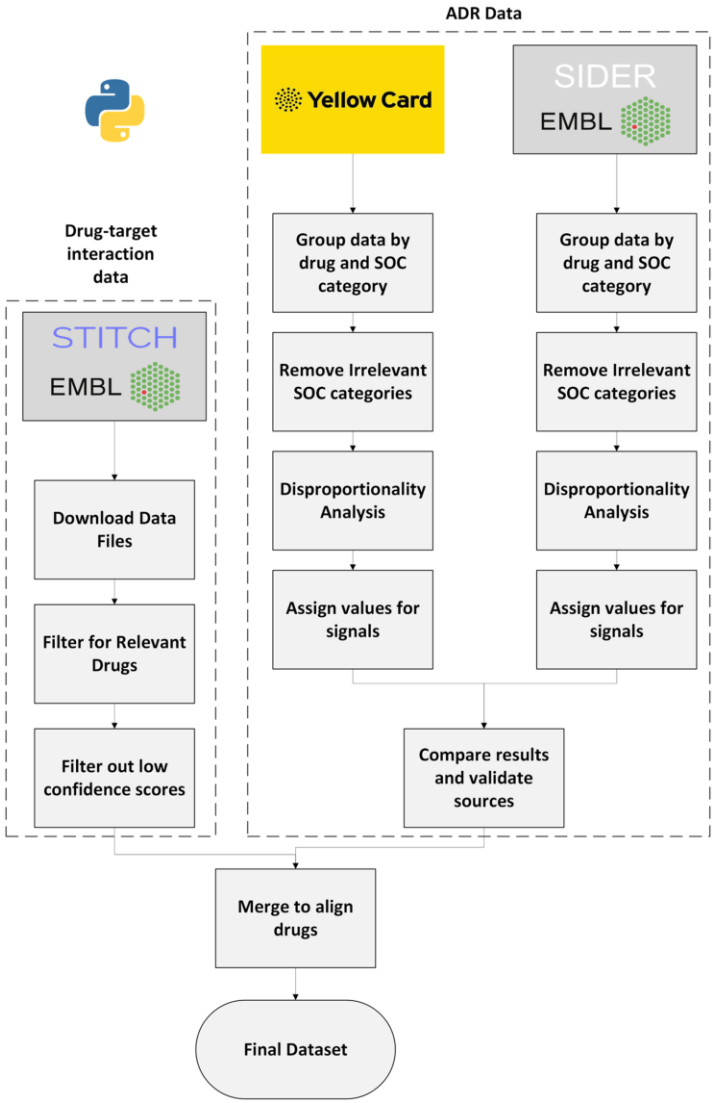
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Roberts-Nuttall J, Jones AM, Castellani M, Pham D (**2026**) An interpretable machine learning framework for adverse drug reaction prediction from drug-target interactions. PLoS One 21(1): e0340900

Database collection methods

The classification task

- Framework trains individual binary classifiers for 21/27 MedDRA SOCs
- Ground truth – use of DA (ROR/PRR >2)



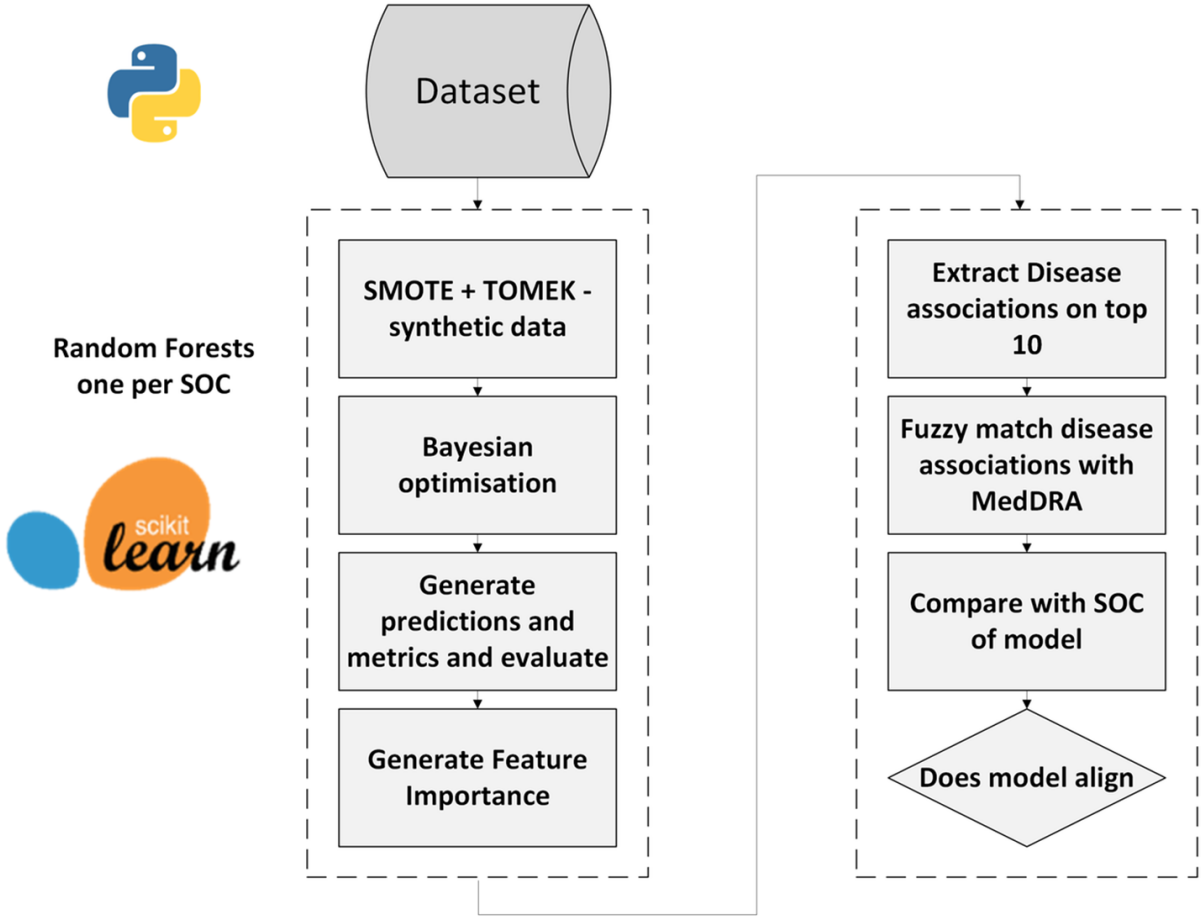
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Machine Learning methods

Mitigation Strategy

- *Medical datasets (e.g. MHRA) are heavily skewed/underreporting*
- Hybrid resampling technique
- SMOTE – synthetically over-sample the minority class (significant ADRs)
- TOMEK - under-sample noisy borderline examples in the majority class

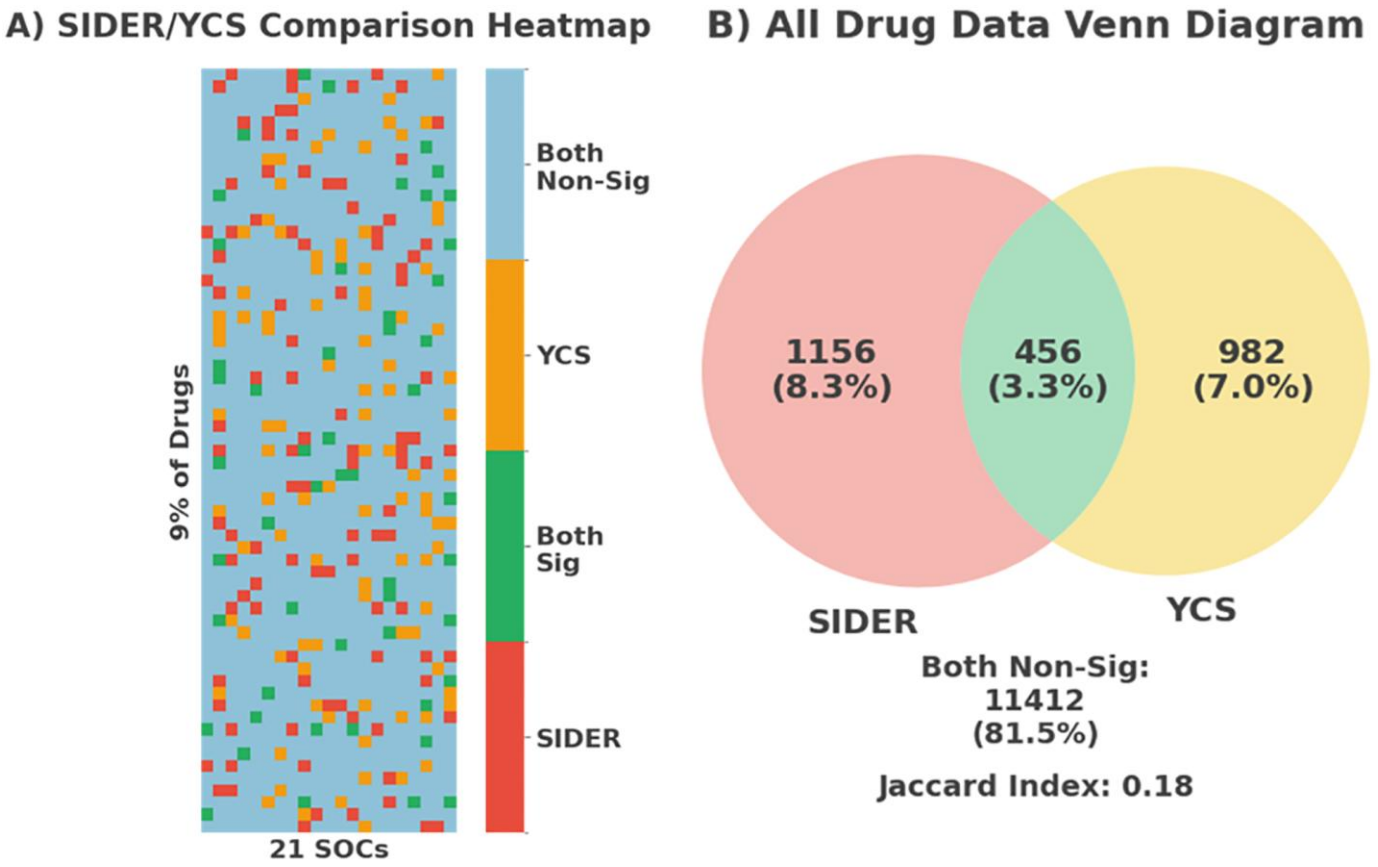
Random Forests one per SOC



Validation of Interpretability

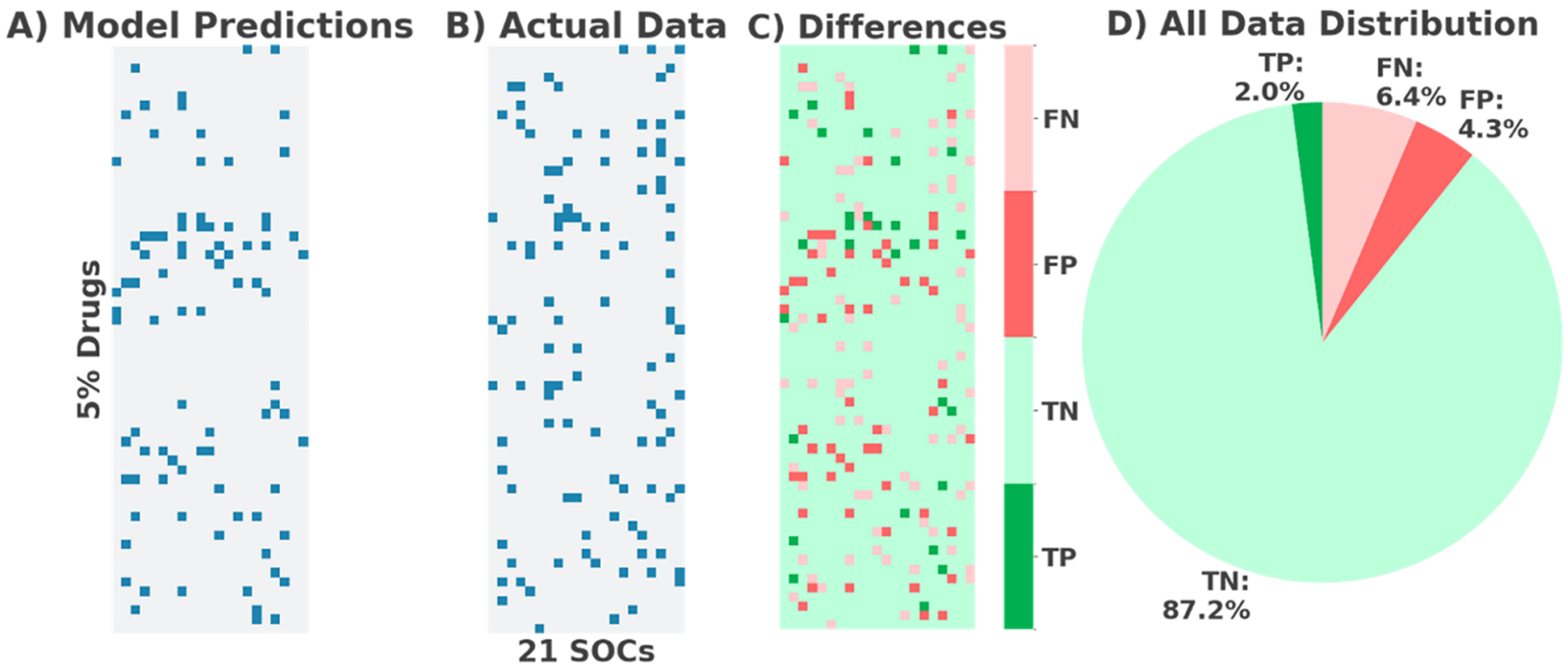
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Heatmap comparison of Drug-ADR associations between the SIDER and the YCS databases



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Heatmaps of model predictions versus actual data

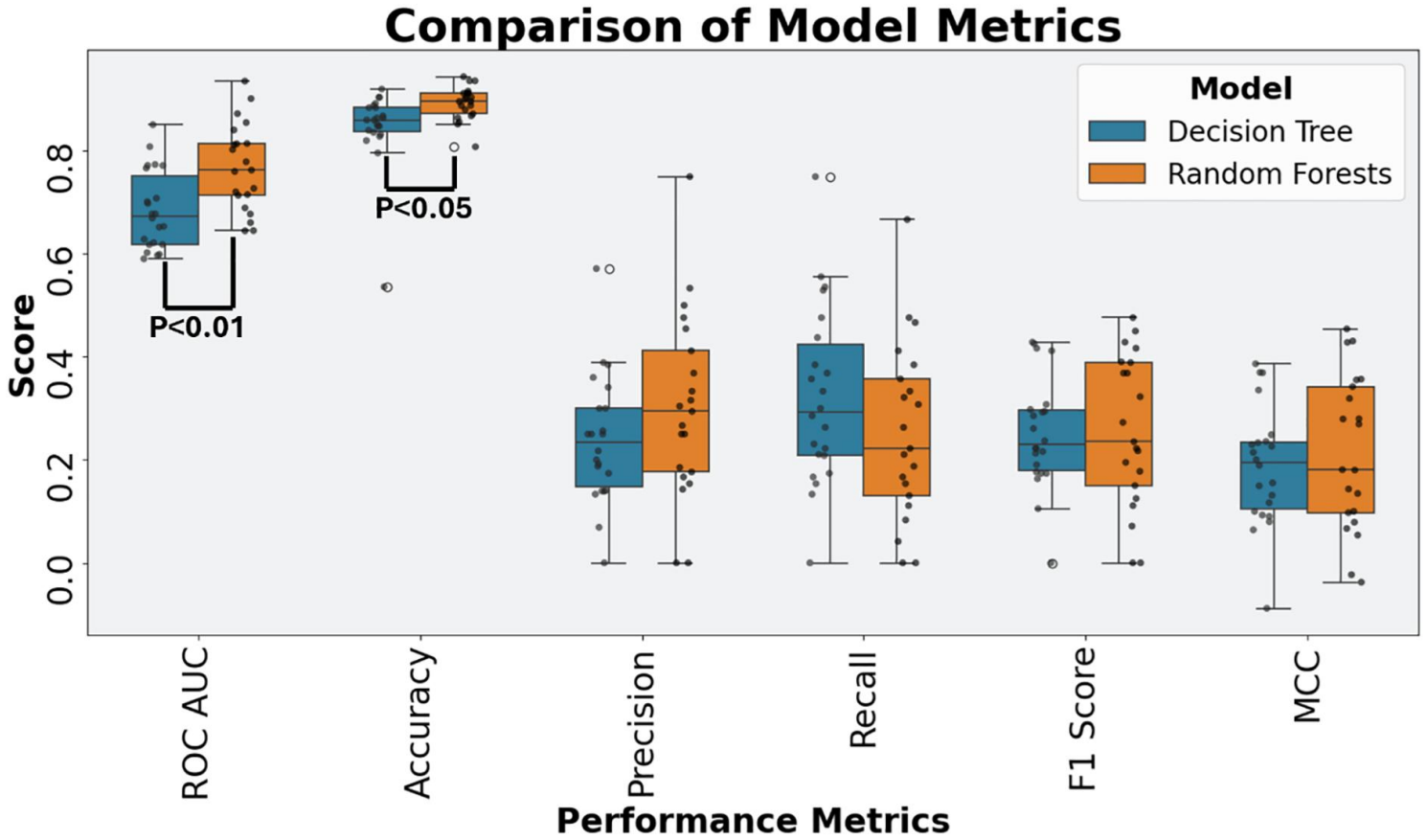


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Performance metrics of the 21 SOC models for Decision Trees and Random Forests

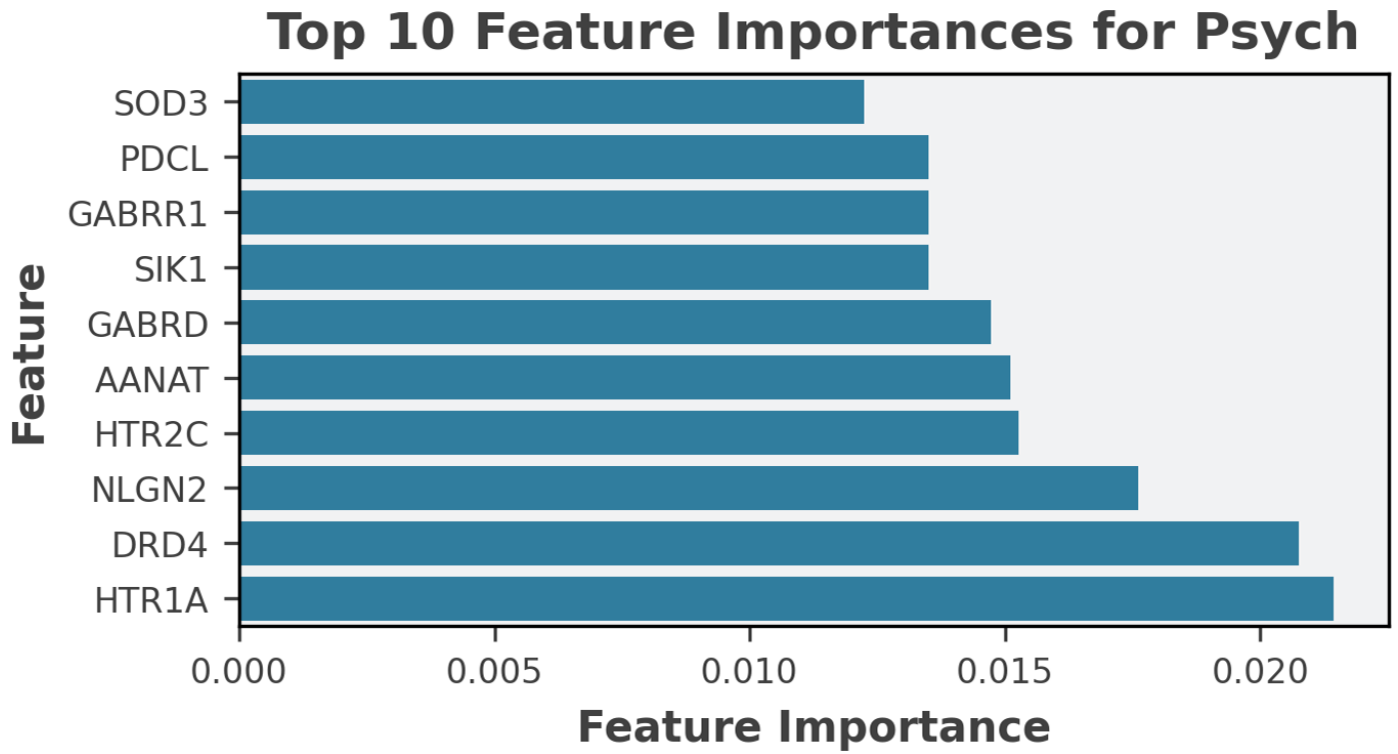
Why select Random Forests?

- Balance predictive power/interpretability
- Resist overfitting of noisy, high dimensional healthcare data
- Bayesian optimisation >100 trials to maximise ROC AUC metric



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Random Forest feature importance results of the top 10 targets for the Psychiatric Disorder model

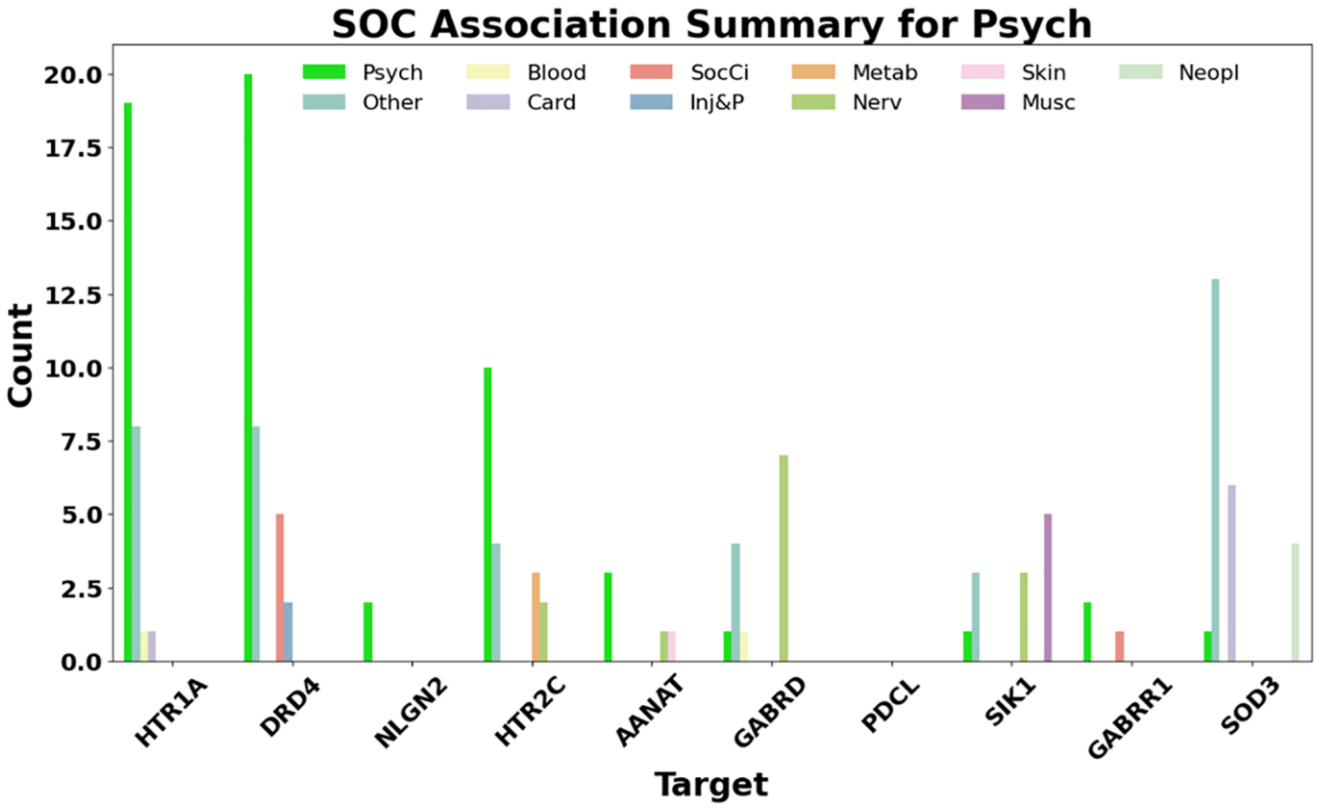


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Summary of SOC category associations for the top 10 targets based on feature importance

Is the model learning genuine pharmacology or just statistical noise?

- External validation step:
- Model's top-10 most influential targets (derived from feature importance)
- Cross-referenced against independent DisGeNET database
- 9 out of 10 had established biological association.

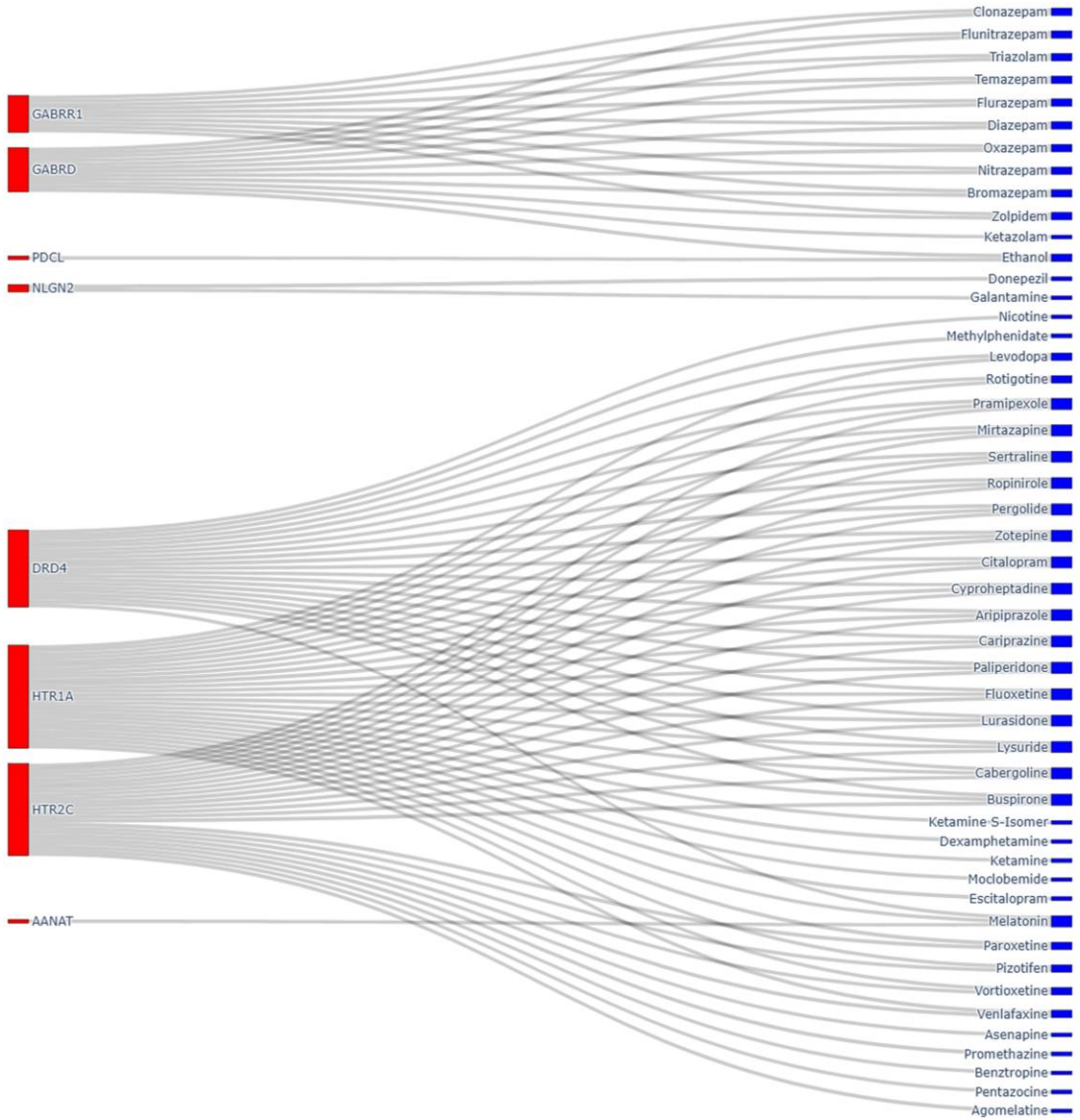


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Target Drug Relations linked to the top 10 targets based on feature importance

The ML results demonstrate how the algorithm translates back to practical pharmacology

- Mapping of influential targets to Anatomical Therapeutic Chemical (ATC) classifications → strong correlation with Nervous System drugs.
- Novel findings e.g. the 'PDCL' target lacked prior DisGeNET documentation for psychiatric conditions, the model flagged it based on its modulation of ethanol response.
- This helps prove the framework can propose novel targets for future laboratory research



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Conclusions

- High-confidence drug-target interaction data from the STITCH database with **nearly 3 million real-world ADR reports**
- This ML approach explicitly connects adverse side effects back to the precise biological targets and proteins that a drug interacts
- ML outputs generated new biological / clinical insight beyond feature rankings
- This framework could allow the pharmaceutical industry to anticipate side effects early in development, leading to safer drug design and fewer patient complications

Future Directions

Data Quality/Richness

- Use of causality data rather than correlation
- CPRD/THIN datasets with individual identifiable characteristics
- Comparison with other SRS databases

ML approaches drug–target–ADR

- attention mechanisms
- integrated gradients
- SHAP-compatible neural architectures
- graph-based / multimodal models



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