Who Metabolizes Your Drug?

An Explainable Cross-Attention AI for Predicting Bacteria-Specific Drug Metabolism

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ABSTRACT

Problem: Gut bacteria turn the same drug on, off, or toxic – differently in each person – so predicting and explaining this is key to personalized medicine and mechanistic insight.

Model: Multimodal Bi-MHA: bidirectional cross-attention fusing drug atoms (MolE[1]) + bacterial proteins (ESM-C[2])

Performance: High ROC AUC (unseen drug: 0.690, unseen bacteria: 0.920, unseen interaction: 0.949); 60% accuracy on out-of-distribution pairs.

Explainable: Attention weights from the proposed model recover validated enzymes and exact reaction sites.

GitHub for usage

01 INTRODUCTION

Why bacteria-specific drug metabolism matters

Prodrug activation — switched on too early (e.g., misoprostol)[3].

Drug inactivation — loss of efficacy (digoxin by *E. lenta*)[3].

Toxic metabolites — adverse effects (irinotecan → SN-38)[3].

What's still missing

Experimental limit — Anaerobic culture is costly and technically unstable.

Computational limit — Existing models predict only at community-level and offer no atom/protein-level interpretability.

What we focus on

Novel in silico framework for bacteria-specific drug metabolism.

Protein-level and atom-level explainable model.

Systematic generalization evaluation under unseen-entity settings.

02 METHODS

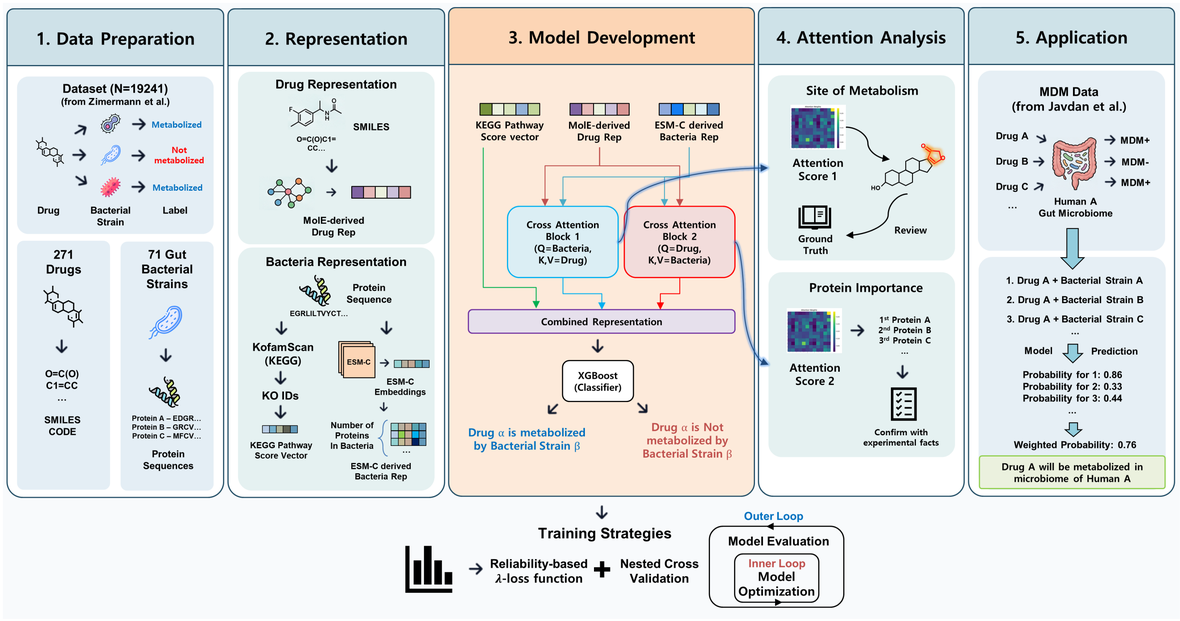


Figure 1. Development pipeline of the proposed model from data preparation to application with training strategies.

Main Dataset

- From Zimmermann et al.[4]
- 271 Drugs × 71 Strains (19,241 Interactions)

External Val. Dataset

- From curated literature
- 5 novel drug-bacteria pairs

Application Dataset

- From Javdan et al.[5]
- Independent fecal sample (community-level test)

Training Strategies

- high- and low reliability (q-value-stratified), leveraged via λ-scaled loss
- Nested Cross Validation

03 RESULT

A Rank Sum Metric was computed by ranking each model across all nine performance scores, where a lower value indicates more consistently top-performing results.

Model	Rank Sum	Unseen Drug		Unseen Bacteria		Unseen interaction	
		ROC AUC	BAL ACC	ROC AUC	BAL ACC	ROC AUC	BAL ACC
Multimodal Bi-MHA	**1.78**	0.690 ± 0.016	0.638 ± 0.012	0.920 ± 0.005	**0.839 ± 0.017**	0.949 ± 0.010	**0.869 ± 0.014**
Multimodal Single-MHA	2.17	**0.703 ± 0.013**	**0.644 ± 0.007**	0.917 ± 0.008	**0.839 ± 0.014**	0.946 ± 0.008	0.868 ± 0.012
XGBoost	2.83	0.675 ± 0.014	0.626 ± 0.013	**0.922 ± 0.007**	0.836 ± 0.019	**0.953 ± 0.005**	**0.869 ± 0.015**
Bi-MHA	4.56	0.656 ± 0.021	0.607 ± 0.026	0.916 ± 0.007	0.835 ± 0.016	0.947 ± 0.012	0.867 ± 0.017
Single-MHA	4.56	0.688 ± 0.023	0.628 ± 0.015	0.912 ± 0.005	0.834 ± 0.017	0.945 ± 0.006	0.863 ± 0.010
MLP	5.11	0.680 ± 0.054	0.634 ± 0.040	0.904 ± 0.012	0.819 ± 0.018	0.939 ± 0.009	0.855 ± 0.013
LR	7.00	0.637 ± 0.044	0.600 ± 0.032	0.873 ± 0.049	0.787 ± 0.046	0.932 ± 0.015	0.850 ± 0.017

Table 1. Model evaluation table, comparing with other machine learning models.

Our proposed Multimodal Bi-MHA model (highlighted in red) recorded **the highest Rank Sum Metric** by ranking consistently at the high performance score across all tasks.

Model Inputs

Attention models — token-level MolE (drug) + ESM-C (bacteria) embeddings, which enable atom/protein attention (see Fig. 1).

Traditional ML / MLP — fixed-length vectors: drug = RDKit descriptors / ECFP4, bacteria = one-hot taxonomy / CTD descriptors.

All models additionally share a KEGG pathway score.

04 EXTERNAL VALIDATION

Generalizes to Out-of-Distribution drug-bacteria pairs

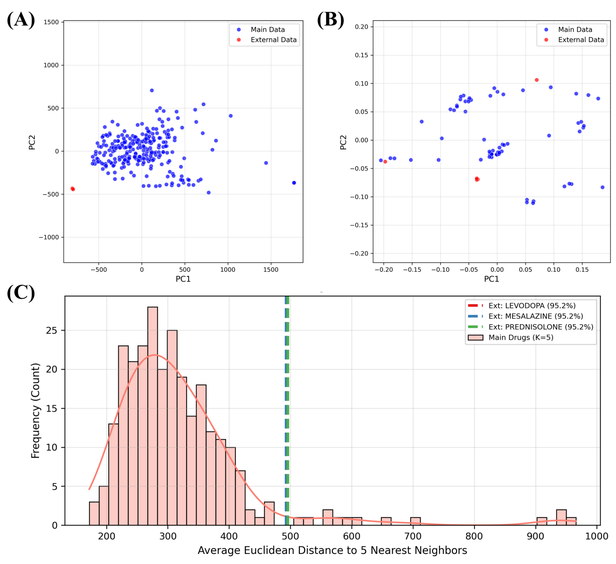


Figure 2. (A,B) External data occupy distinct space in PCA (principal component analysis); (C) distances exceed the 95th percentile of the main set.

We tested three drugs and their strains **completely absent from training** (Levodopa, Mesalazine, Prednisolone) — a true out-of-distribution (OOD) test. PCA and nearest-neighbor distances confirm they sit far outside the training space (Fig 2).

Drug	Strain	Actual	Model	KNN
Levodopa	*E. faecalis MMH594*	True	True (0.51)	False
Levodopa	*E. faecalis OG1RF*	True	True (0.51)	False
Levodopa	*E. faecalis TX0104*	True	False (0.49)	False
Mesalazine	*F. prausnitzii DSM-17677*	True	True (0.58)	False
Prednisolone	*C. steroidoreducens HCS.1*	True	False (0.22)	False

Table 2. External validation table of the proposed model.

Our model: 3 / 5 correct (60%) vs **KNN: 0 / 5 (0%)**
It learns generalizable rules — not memorized drug–bacteria pairs.

05 CASE STUDY

The model's attention matches real biochemistry

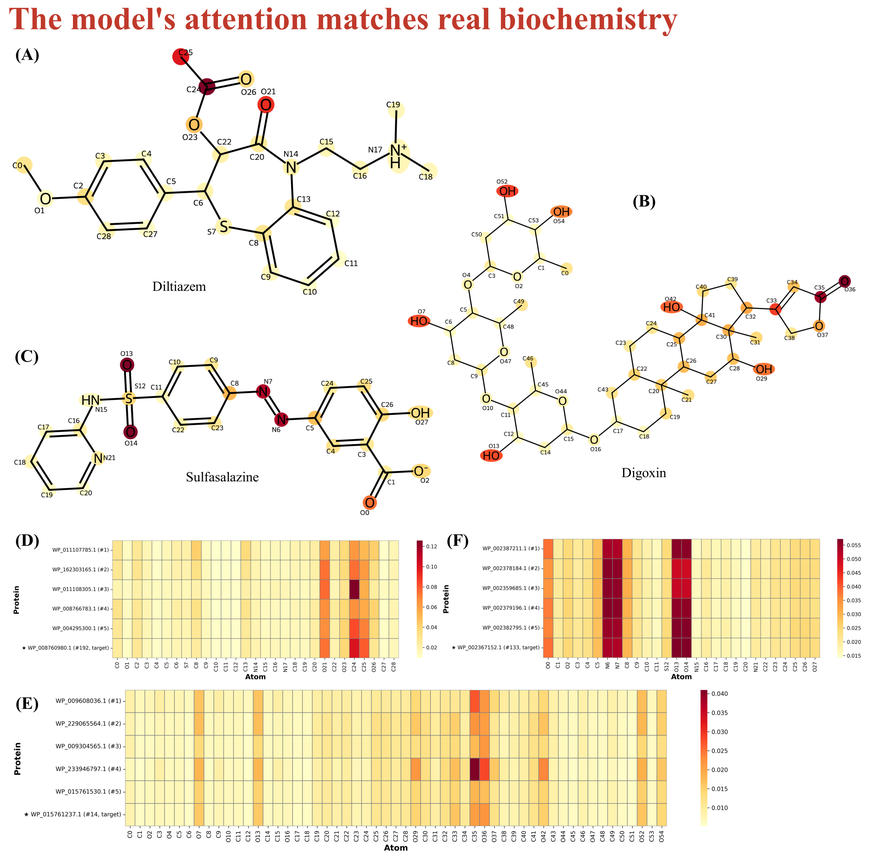


Figure 3. (A–C) atom-level attention on the true reaction sites; (D–F) protein-level attention peaks at the target enzymes.

Without being told any chemistry, the attention weights of the target protein precisely pinpointed **the corrected metabolic site** (Fig 3).

Digoxin[6]
Bacterium: *Eggerthella lenta*
Target: Cgr2
Rank: 14 / 454 (top 3.1%)
Reaction: α,β-unsaturated lactone ring reduction
Attn peak: C33, C34

Diltiazem[4]
Bacterium: *Bacteroides thetaiotaomicron*
Target: BT_4096
Rank: 192 / 672 (top 28.6%)
Reaction: Deacetylation (ester cleavage)
Attn peak: C24, C25 (acetyloxy)

Sulfasalazine[7]
Bacterium: *Enterococcus faecalis*
Target: AzoA
Rank: 133 / 540 (top 24.6%)
Reaction: Azo-bond cleavage
Attn peak: N6, N7 (azo linkage)

06 APPLICATION

Weighted Abundance Pipeline

Map donor bacteria to reference strains (family-level) → Compute metabolism probability per matched strain → Aggregate by abundance-weighted average → Classify MDM+ / MDM− from weighted probability

Community-level result

ROC AUC	BAL ACC
0.749	**0.663**

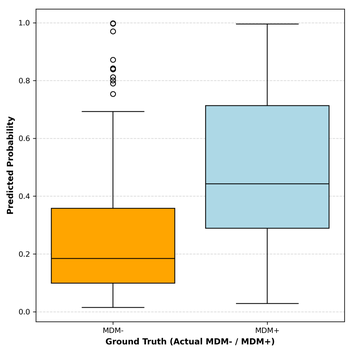
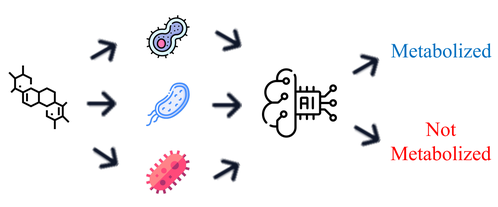


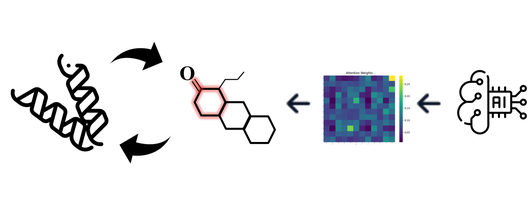
Figure 4. Predicted probability distribution by ground truth (MDM-/MDM+)

Covered 98% Bacterial Strains
Tested 438 Drugs

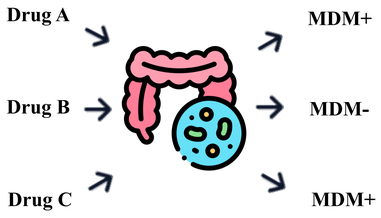
07 CONCLUSION



✓ Robust prediction
Multimodal Bi-MHA achieves robust prediction across unseen drugs, bacteria, and interactions with strong generalization to out-of-distribution scenarios



✓ Mechanistic explainability
attention analysis accurately localizes experimentally validated reaction sites and responsible enzymes.



✓ Community-level application
from individual bacterial strains to complex microbial communities

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