

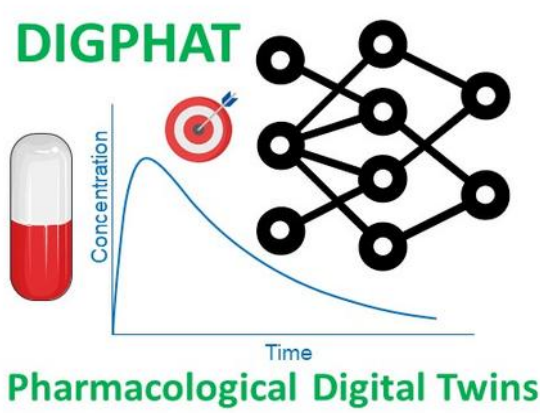
NETWORK-INFORMED PHARMACOKINETICS

NetPK: fusing published biological knowledge into pharmacokinetic models through network diffusion

A literature-augmented population PK framework — tacrolimus as proof of concept, built to generalize

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1 Background & aim

Decades of **independent** studies have quantified tacrolimus pharmacology: in-vitro drug–drug interactions, CYP3A fractional contributions, pharmacogenetics, hematocrit partitioning, corticosteroid induction, inflammation, food effects...

Yet population PK (PopPK) models encode only **2–4 empirically estimated covariates**: identifying more would require very large, covariate-complete cohorts that rarely exist.

- Three questions.
- Can published knowledge be fused into a PopPK model via network diffusion?
 - Does the model estimate AUC better from sparse monitoring?
 - Does it generate better virtual patients for machine-learning training?

NetPK is not a neural network. It is an ordinary nonlinear mixed-effects model — its novelty is that the covariate structure is selected and quantified by the literature, not estimated from the data.

2 The NetPK workflow

1 Formalize the literature as a network

STRING

Drug-centered interaction graph; published confidence scores as edge weights.

2 Prioritize mechanisms by diffusion

RWR

Random Walk with Restart from the proteins in physical contact with the drug ranks every candidate mechanism.

3 Encode literature-fixed modules

nlmixr2

Retained mechanisms become fixed covariate modules; only baseline PK parameters are estimated (study 1, n = 169), then locked.

4 Evaluate under sparse sampling

mapbayr

Bayesian AUC estimation from C0, C0+C1, C0+C1+C3 in an independent trial (study 2, n = 76 profiles), no refitting.

5 Reuse as a virtual-patient generator

XGBoost

5,000 biologically constrained virtual patients train ML AUC estimators, evaluated on the real external profiles.

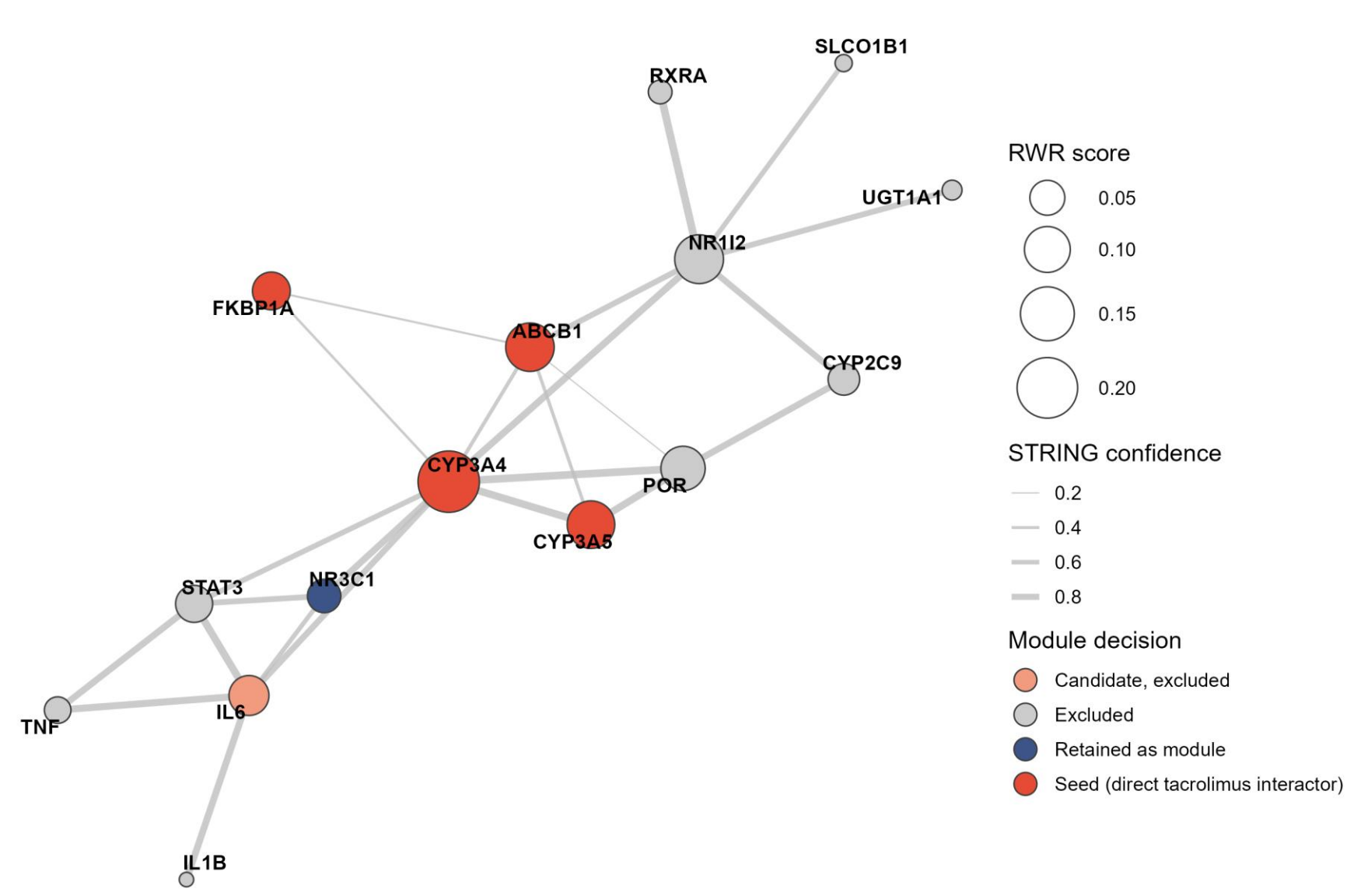
Design point: study 1 (PCCP) is the development dataset of both NetPK and the reference Woillard 2011 estimator — study 1 comparisons are internal for both models; all conclusions rest on the external study 2 (AADAPT).

3 At the bedside

Used exactly like any Bayesian estimator: enter the dosing history, the available concentrations (a single trough suffices) and routine covariates; the model returns the interdose AUC and the dose reaching the target.

No extra sampling, no covariates beyond routine transplant care — and a lower risk of overestimating exposure in prolonged-release patients monitored by trough only.

4 What the network retains



Tacrolimus-centered network: node size = RWR score, edge width = STRING confidence, color = module decision.

Three pre-specified selection criteria

(i) a quantitative, literature-supported effect size exists; (ii) a routinely measurable clinical covariate carries the mechanism; (iii) that covariate is available and non-redundant in the target datasets.

Topology alone decides nothing: **NR1I2** ranks #2 but has no targeted routine covariate (excluded); **IL-6** is credible but unharmonized here (future module via CRP); **ABCB1** is redundant with CYP3A in vivo (excluded); **NR3C1** enters through the corticosteroid dose (encoded).

5 Six literature-fixed modules

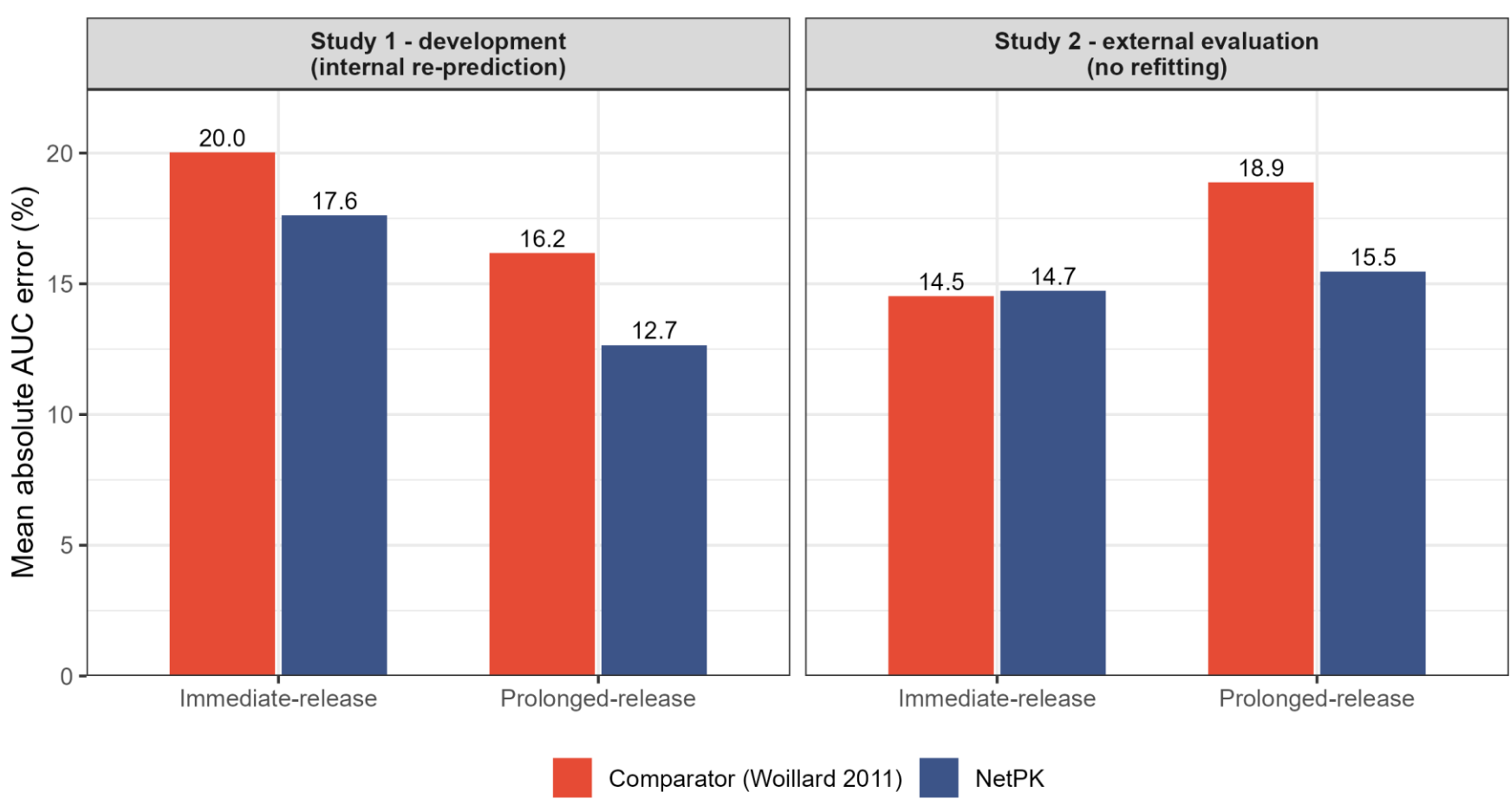
Mechanism	Literature-fixed encoding
CYP3A5 genotype	CL × (0.95 + 0.275·CYP) — fractional metabolism
Hematocrit	exp(±1.5·(HCT – 0.33)) on CL and V1 — partitioning
Corticosteroids	CL × 1.575 above 25 mg/day prednisone
Age	CL × (age/50) ^{–0.10}
Formulation	Separate transit constants; F = 0.825 (prolonged release)
Body composition	V2 = V2,lean + fat mass × 16.5 (Janmahasatian)

None of these coefficients is estimated from the study data. Magnitudes converge with the comparator for hematocrit but diverge for CYP3A5 (×1.29 literature vs ×2.0 estimated) — quantifying how much of an empirical covariate effect is mechanism vs absorbed correlation.

Key messages

- Published knowledge can be transferred into standard, fully interpretable PopPK models through a reproducible network recipe.
- External gains are modest but real: better prolonged-release trough-only estimation, corrected bias, stronger sparse-sampling ML training.
- May be applicable for the extrapolation to special populations

6 External results (study 2)



Prolonged release, trough only — absolute AUC error

18.9% → 15.5%

(% within ±20%: 64.3 → 83.3)

Systematic bias corrected (mean relative error)

+9.6% → –2.5%

% within ±20% of observed AUC (n = 73)	C0	C0+C1	C0+C1+C3
MAP-BE / comparator	71.2	76.7	87.7
MAP-BE / NetPK	78.1	74.0	90.4
XGB / comparator-gen.	71.2	75.3	89.0
XGB / NetPK-gen.	74.0	82.2	90.4

Same 73 daytime external profiles, same metrics; the reference AUC only scores predictions. Simulation-trained XGBoost matches or beats Bayesian estimation at every strategy; the NetPK generator adds most under sparse two-sample monitoring.

7 NetPK as a foundation

- Next drugs, same recipe.** Mycophenolate, everolimus, voriconazole — any drug with a documented ADME network.
- New modules.** Inflammation (CRP), assay-error layer, chronopharmacology of night dosing.
- Calibrated uncertainty.** Propagating literature coefficient uncertainty into individual AUC intervals.
- Stronger evidence.** Module ablation, weaker baseline models, prospective validation of dose adjustment.
- AI-ready virtual populations.** Biologically constrained synthetic cohorts for digital-health and ML pipelines.

Funding & reproducibility

Supported by the French government through the France 2030 program (PEPR Santé Numérique, DIGPHAT project), managed by the Agence Nationale de la Recherche, grant ANR-22-PESN-0017.

The full annotated R pipeline — network construction and RWR, executable model codes, Bayesian evaluation, virtual-patient generation, machine learning, SHAP — reproduces every number on this poster.

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