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1 Optimized therapeutic drug monitoring: the role of 2 machine learning model

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26 Abstract

27 Introduction: Traditional therapeutic drug monitoring (TDM) faces limitations in accuracy
28 and adaptability, often failing to optimize therapy for complex patients. Machine learning
29 (ML) is emerging as a powerful tool to overcome these challenges, offering a data-driven
30 paradigm to enhance therapeutic outcomes and minimize toxicity for drugs with narrow
31 therapeutic indices.

32 Areas covered: This review synthesizes the evolution of ML in TDM. We cover foundational
33 models that predict drug exposure from sparse data using either real-world or simulation-
34 based training. We then explore the extension of these techniques to proactive first-dose
35 optimization and the recent development of hybrid models, which integrate the physiological
36 interpretability of population pharmacokinetic frameworks with the corrective power of ML.

37 Expert Opinion: The future of TDM lies not in replacing mechanistic models, but in their
38 convergence with ML. While promising, clinical translation requires overcoming critical
39 barriers in data access, model interpretability, and workflow integration. The long-term
40 trajectory points toward dynamic Digital Twins capable of forecasting patient-specific benefit-
41 risk profiles. Ultimately, validated hybrid tools embedded in clinical decision support systems
42 could establish proactive, individualized dosing as the new standard of care in personalized
43 pharmacotherapy.

44

45

46 **Keywords:** Machine Learning; Therapeutic Drug Monitoring (TDM), Model Informed
47 Precision Dosing (MIPD), Artificial Intelligence; Population Pharmacokinetics; Hybrid
48 Models; Monte Carlo simulation; Digital Twin

49 1.Introduction

50 In clinical pharmacology, individualized dosing strategies are grounded in pharmacokinetic
51 (PK) and pharmacodynamic (PD) principles and aim to optimize the benefit–risk ratio by
52 tailoring doses to the patient’s profile. Fixed dosing may be sufficient for drugs with a wide
53 therapeutic window, but it is inadequate for agents with a narrow therapeutic index and high
54 inter- and mid to long term intra-individual variability. Inter-individual variability arises from
55 diverse patient-specific factors such as age, organ function, genetic polymorphisms,
56 comorbidities, and drug–drug interactions, whereas intra-individual variability may reflect
57 temporal changes in physiology, adherence, or disease state. These factors significantly
58 influence drug exposure and response [1–4]. Covariate-based dosing partially addresses this
59 challenge by adjusting doses according to demographic and physiological factors such as
60 body weight, age, renal or hepatic function, or concomitant therapies. However, this approach
61 remains limited in precision [5].

62 Therapeutic Drug Monitoring (TDM) is a central clinical tool for guiding dose adjustments
63 based on target plasma concentrations or therapeutic ranges [5–7]. This strategy is routinely
64 applied to immunosuppressants (e.g., tacrolimus, mycophenolate, everolimus), antibiotics
65 (e.g., beta-lactams, aminoglycosides, vancomycin, daptomycin), antiviral (e.g, ganciclovir),
66 antiepileptics (e.g., phenytoin, valproate), psychotropics (e.g., lithium), anticancer drugs (e.g.,
67 methotrexate, imatinib), and antituberculosis agents (e.g., rifampicin) [1,8–17]. However,
68 classical TDM strategies have limitations: they often rely on sparse sampling (commonly
69 trough levels), may assume steady-state conditions or linear pharmacokinetics that are not
70 always present, and do not consistently capture temporal variability (e.g., changes in
71 adherence or clinical status). Consequently, measured concentrations do not always reflect
72 total exposure (area under the curve; AUC) or predict clinical outcomes [18].

73 To overcome these limitations, precision dosing strategies increasingly rely on model-based
74 approaches (Model Informed Precision Dosing; MIPD). MIPD integrates mathematical and
75 statistical models, typically nonlinear mixed-effects models (NLME), that account for
76 population PK behavior, covariate effects, and residual variability. Through maximum a
77 posteriori Bayesian estimation (MAP-BE), individual PK parameters can be inferred from
78 sparse data (limited sampling strategies; LSS) and used to optimize individualized dosing
79 regimens. MIPD enables proactive and dynamic dose optimization across the treatment
80 course, including before the first dose [7–9,12,18,19].

81 Yet, this approach is not without limitations. The accuracy of MIPD critically depends on the
82 suitability of the selected population pharmacokinetic (popPK) model, the quality and
83 completeness of input data, and the robustness of the computational methods employed. A key
84 challenge lies in selecting an adequate model: multiple models may exist for the same drug,
85 each developed under different clinical contexts, in distinct populations, or using varying
86 sampling designs [20]. When there is a mismatch between the model's assumptions and the
87 characteristics of the target population, significant bias can be introduced into individualized
88 predictions [21]. Moreover, MAP-BE-based approaches depend on rigid, pre-specified model
89 structures and commonly assume that individual parameters follow a normal distribution.
90 These assumptions may inadequately reflect nonlinear pharmacokinetics or atypical patient
91 profiles. Additionally, the shrinkage effect inherent to MAP-BE, particularly in the context of
92 sparse or imprecisely timed data, can mask clinically relevant variability by pulling individual
93 estimates toward the population mean [22–27].

94 To address some of the limitations of parametric approaches, researchers have increasingly
95 explored machine learning (ML), not as a universal replacement, but as a complementary tool.
96 As a subset of artificial intelligence, ML offers data-driven methods capable of capturing non-
97 linear relationships and complex interactions without an imposed mechanistic structure.

98 However, these data driven methods are themselves constrained by the quality,
99 representativeness, and labeling of the training data, and require rigorous validation before
100 clinical deployment [25–29].

101

102 This review explores how ML is transforming TDM—from model development to real-time
103 dose optimization—highlighting recent advances, implementation challenges, and future
104 perspectives toward data-driven precision pharmacotherapy.

105

106

107 2.Fundamentals of ML in clinical pharmacology

108 ML, historically applied in drug discovery, is now increasingly used across the drug
109 development continuum, including biomarker identification, clinical outcome prediction, and
110 clinical trial design. Within clinical pharmacology, ML offers the ability to capture nonlinear,
111 high-dimensional relationships that often elude traditional parametric approaches [30].

112

113 2.1 Learning paradigms

114 In pharmacology, supervised learning is the most common paradigm. It involves training a
115 model on labeled datasets, where both input variables (e.g., patient covariates, time points,
116 concentrations) and outputs (e.g., drug exposure metrics or therapeutic response) are known,
117 to learn predictive mappings. The algorithm minimizes a loss function (e.g., mean squared
118 error or cross-entropy) to optimize predictive accuracy. Common supervised models include
119 linear regression model combining Ridge and LASSO penalization (glmnet), multivariate
120 adaptive regression spline (MARS), random forests, support vector machines (SVM) and

121 gradient boosting (e.g., XGBoost) [31,32]. The glmnet algorithm applies both Ridge and
122 LASSO penalizations to linear regression, balancing feature selection and regularization [33].
123 MARS create piecewise linear models, adapting to nonlinear relationships by automatically
124 detecting changes in data patterns [34]. Random forests aggregate independent predictions
125 from multiple decision trees, reducing overfitting and enhancing model generalizability [35].
126 SVM for regression works by finding the optimal hyperplane that best fits the data while
127 minimizing prediction errors [36]. Finally, XGBoost is a gradient boosting algorithm that
128 builds an ensemble of weak decision trees applied in series to improve prediction accuracy
129 [37].

130 In contrast, unsupervised learning operates on unlabeled datasets to identify intrinsic
131 structures or groupings. In clinical pharmacology, this approach is useful for clustering
132 patients based on drug response, stratifying risk groups, or exploring hidden phenotypes in
133 high-dimensional datasets such as omics or longitudinal biomarker profiles [38].

134

135 2.2 Model development and validation

136 Standard ML workflows split data into training and testing sets. The training set is used to fit
137 the model and optimize hyperparameters such as learning rate, number of trees, or
138 regularization strength typically via k-fold cross-validation. The testing set, composed of
139 unseen data from the same distribution, provides an unbiased estimate of model performance
140 [39,40]. To evaluate true generalizability, a separate external validation set is usually used.
141 This multi-tiered evaluation strategy is particularly relevant in pharmacometrics, where
142 extrapolability to diverse patient profiles is essential [41].

143 One critical pitfall to avoid in ML is data leakage, which occurs when information that would
144 not be available at the time of prediction is inadvertently included during model training. This

145 can lead to artificially inflated performance metrics and poor generalizability [42]. A clear
146 example of data leakage in pharmacometrics is the use of post-hoc individual parameter
147 estimates, such as an individual CL obtained from a popPK model via the EBE method, as a
148 feature to predict that same individual's AUC. Since AUC is directly calculated from
149 clearance ($AUC = Dose / CL$), incorporating individual CL into the model introduces future
150 information, resulting in circular reasoning and an overly optimistic model that will fail in
151 practice. This is fundamentally different from the methodologically sound hybrid approach
152 discussed later, where ML is trained to predict the residual error of a popPK model initial
153 prediction which does not rely on EBE.

154

155 2.3 Challenges of ML in clinical pharmacology

156 Despite its promise, ML in pharmacology faces several domain-specific challenges that set it
157 apart from more mature applications such as image or speech recognition. Unlike these fields,
158 which benefit from large, well-structured datasets, pharmacological data are typically sparse,
159 noisy, and heterogeneous. Clinical drug data often includes repeated measurements with
160 irregular sampling intervals, missing data points, and a mix of continuous and categorical
161 covariates. A classic example of a data quality issue in TDM is an incorrectly recorded
162 sampling time: a blood sample drawn 30 minutes post-dose but logged as a pre-dose 'trough'
163 level can fundamentally corrupt the information provided to the model, leading it to learn
164 erroneous relationships. Moreover, real-world datasets are frequently imbalanced, with certain
165 subgroups, such as pediatric or geriatric patients, being underrepresented, which can result in
166 biased or non-generalizable ML models unless carefully mitigated. These limitations
167 necessitate rigorous data preprocessing, involving normalization, imputation, feature
168 engineering, and resampling to ensure model robustness and fairness [29,43]. A central
169 question is how much data is sufficient to train a robust ML model. Unlike traditional
170 statistics, there is no universal 'rule of thumb,' as the required sample size depends on the
171 complexity of the model, the number of features, and the signal-to-noise ratio in the data.

172 While some tasks may require thousands of patient profiles for deep learning, effective
173 models have been built with a few hundred well-characterized patients. For the common
174 challenge of small or imbalanced datasets, several strategies can be employed. Data
175 augmentation can expand the training set. While this can be achieved by generating new data
176 points from established PK models by Monte Carlo simulations, more advanced generative
177 approaches are emerging [44]. Techniques such as CTGAN, Avatar, and Synthpop learn the
178 underlying distribution of a real dataset to create highly realistic, synthetic patient profiles that
179 preserve complex relationships while maintaining privacy [45]. Finally, techniques like
180 SMOTE (Synthetic Minority Over-sampling Technique) can address class imbalance,
181 ensuring that underrepresented groups, such as pediatric patients, are not overlooked by the
182 model [46]. On the other hand, when building larger datasets by pooling multicenter data, an
183 important prerequisite is the harmonization of data. This involves the fine process of
184 standardizing variable definitions (e.g., 'creatinine clearance' vs. 'eGFR'), units, and laboratory
185 assay methods to create a cohesive dataset. Failure to do so can introduce severe bias; for
186 instance, a model might incorrectly learn that a specific hospital is a predictor of drug
187 clearance, simply because its creatinine assay is calibrated differently. Beyond data-related
188 limitations, one of the most critical barriers to clinical adoption of ML in pharmacology is the
189 lack of model explainability and transparency. Unlike classical pharmacometrics models,
190 which are physiologically grounded and offer interpretable parameters such as clearance or
191 volume of distribution, ML models often function as “black boxes”. For instance, a model
192 might learn that prescriptions written by a specific physician are consistently associated with
193 better patient outcomes. A 'black box' model would simply treat 'prescriber ID' as an
194 important feature, which is clinically un-actionable. However, an explainability tool might
195 reveal that this physician is a senior specialist who systematically co-prescribes an adjuvant
196 therapy not captured in the dataset. The model has not learned a biological truth but rather has

197 identified a hidden confounding variable related to clinical practice. This opaqueness
198 undermines clinician trust and complicates the integration of ML tools into clinical decision-
199 making workflows. Additionally, many ML models fail to provide actionable or
200 mechanistically meaningful insights, limiting their added value beyond mere prediction [47].
201 In response, several methods have been proposed to enhance post hoc interpretability,
202 including SHAP (Shapley Additive Explanations) and LIME (Local Interpretable Model-
203 Agnostic Explanations). These tools attribute importance to input features and offer partial
204 transparency [48,49].

205 This stands in contrast to traditional NLME modeling, which relies on predefined biological
206 and statistical assumptions to describe the course of drug exposure and response time. NLME
207 models are not only interpretable and physiologically plausible, but also capable of
208 extrapolation, making them particularly useful for simulation-based applications such as trial
209 design or dose adjustment in special populations. However, their development is manual,
210 expert-driven, and iterative, requiring extensive pharmacological insight and careful model
211 refinement. While this process ensures rigor and physiological coherence, it also limits
212 scalability and can lead to variability in model structure across developers, even when based
213 on the same dataset [24].

214 In contrast, ML models are more scalable and automatable and can uncover latent patterns in
215 unstructured or high-dimensional data. Yet, this flexibility comes at the cost of interpretability
216 and poses risks of overfitting or poor generalizability if the training data are not representative
217 of the target population. Therefore, while ML offers a powerful complement to mechanistic
218 approaches, its clinical utility will depend on striking a balance between performance and
219 explainability, supported by rigorous validation and transparent reporting.

220

221

222 3.State of the art: evolution of ML in TDM

223 Before reviewing specific applications, it is important to address the selection of the
224 prediction target. Many studies aim to predict metrics such as AUC or clearance. However,
225 these values are rarely measured directly and are typically estimated from sparse data using a
226 popPK model. Using these model-derived estimates as 'ground truth' labels introduces a
227 significant risk: any biases or structural misspecifications from the original popPK model will
228 be learned and propagated by the ML algorithm. This can lead to a form of methodological
229 circularity, where the ML model's performance reflects its ability to replicate the assumptions
230 of the tool used to generate its labels, rather than a true underlying biological reality.

231 Alternatively, training a model to predict a directly measured concentration, such as a C_0 ,
232 avoids this circularity. However, this approach has its own limitations. Trough concentrations
233 are subject to significant variability from both analytical measurement error and imprecise
234 sample timing, introducing noise into the training label. Moreover, for some drugs (as MMF),
235 C_0 is a poor surrogate for the total drug exposure that correlates with clinical outcomes.
236 Therefore, the choice of the prediction target represents a fundamental trade-off between the
237 pharmacological relevance of a metric and the reliability of its measurement. This decision
238 has profound implications for a model's statistical performance, its generalizability, and its
239 clinical utility.

240 The evolution of ML in TDM has progressed through several distinct stages, each with its
241 own goals, methodologies, and limitations (Table 1). In response to the limitations of
242 parametric approaches, the earliest applications of ML in TDM logically focused on drugs
243 posing the greatest clinical challenges: those with a narrow therapeutic index and high inter-
244 individual variability. A systematic review by Li et al. (2024) confirms this orientation,

245 showing that up to 2023, nearly 70% of published studies concerned immunosuppressants
246 (35.9%) and anti-infectives (32.8%), two classes where clinical relevance and the availability
247 of routine data are maximal.[50]

248 While applications are emerging across many pharmacological fields, this article will focus
249 primarily on these two areas, as they not only represent the most mature fields of research but
250 also align with our group's expertise, enabling a more critical and in-depth analysis. These
251 foundational efforts primarily involved training supervised learning algorithms, most often
252 XGBoost and artificial neural networks (ANN), on real-world clinical datasets. The objective
253 was to predict key exposure metrics, such as trough concentration (C_0) or AUC, from the
254 sparse sampling strategies typical of clinical practice.

255

256 3.1 Foundational applications on real-world data: the proof of concept

257 *3.1.1 Immunosuppressants*

258 Among immunosuppressants, tacrolimus (TAC) and mycophenolic acid (MPA) served as
259 forerunner models. In a landmark study, Woillard et al. (2021) developed XGBoost models
260 capable of predicting TAC AUC with high accuracy (RMSE 7–11%) in over 2,800 transplant
261 patients, using only two to three concentrations and standard covariates. Notably, these
262 models outperformed MAP-BE in multiple external validation cohorts [51]. Similar methods
263 applied to 6,884 MPA profiles yielded higher predictive accuracy and lower bias than
264 conventional approaches.[52] Other works, such as Shao et al. (2022) using neural networks,
265 confirmed ML's ability to rival, and sometimes surpass, classical pharmacometrics methods
266 for estimating individual exposure from routine data [53].

267 3.1.2 Anti-Infectives

268 Parallel efforts quickly emerged for anti-infectives, with vancomycin being the most studied
269 agent. Huang et al. (2021), for instance, designed an ensemble model that outperformed
270 popPK models for predicting trough concentrations [54]. Nigo et al. (2022) used a recurrent
271 neural networks (RNNs) on longitudinal data to improve prediction accuracy relative to
272 Bayesian estimation [55]. Moving beyond simple exposure prediction, Wang et al. (2022)
273 employed a LightGBM model to directly predict the vancomycin dose required to reach
274 therapeutic targets, achieving a significantly higher success rate than standard dosing methods
275 [56]. Although less frequent, studies on other antibiotics confirmed the versatility of these
276 approaches.

277 However, this first wave of real-world data research highlighted a major bottleneck mentioned
278 earlier: the scarcity of rich and complete PK profiles in clinical practice. The reliance on
279 sparse, noisy, and heterogeneous data limits the robustness and generalizability of the models,
280 particularly for underrepresented populations. To overcome this structural challenge, a
281 methodological pivot was necessary: training ML models on synthetic datasets, an approach
282 explored in the next section.

283

284 3.2 Simulation-based training: a methodological pivot

285 To overcome the bottleneck posed by the scarcity of rich clinical data, a strategic approach
286 has emerged: training ML models on synthetic datasets. This method involves generating
287 thousands of virtual PK profiles from validated popPK models. It offers complete control over
288 dosing regimens, sampling schedules, and patient characteristics, while providing a scalable
289 and customizable solution where clinical data are lacking.

290 The seminal study by Woillard et al. (2021) on TAC served as proof of concept. By simulating
291 over 9,000 PK profiles that incorporated relevant covariates and realistic variability, they
292 demonstrated that an XGBoost model trained on just two or three concentrations could
293 achieve excellent internal accuracy (RMSE <10%) and generalize effectively to clinical
294 cohorts [44]. Building on this success, Labriffe et al. (2022) not only applied the method to
295 everolimus but also systematically compared the performance of models trained on simulated,
296 real-world, or hybrid data. Their findings suggested that purely simulated datasets, if well-
297 designed, can perform as well as, or even better than, other approaches [57].

298 This approach quickly demonstrated its versatility beyond immunosuppressants. In the field
299 of anti-infectives, Bououda et al. (2022) used vancomycin profiles simulated from six distinct
300 popPK models to cover complex subpopulations (e.g., obese, septic patients), achieving
301 performance comparable to MAP-BE in external validation [58]. Its utility has been
302 particularly evident in pediatrics, where sampling constraints are significant. Ponthier et al.
303 (2024) showed for ganciclovir (GCV) and valganciclovir (VGCV) that models trained on over
304 10,000 simulated profiles outperformed MAP-BE on real-world data, even with very limited
305 sampling [59]. Subsequent work on daptomycin (Codde et al., 2024) and VGCV in adults
306 (Sayadi et al., 2025) has confirmed the robustness of this method, with the latter study even
307 showing superior performance over MAP-BE when benchmarked against an independent
308 validation PK model [60,61].

309 Collectively, these studies establish simulation-based training as a key methodological
310 advance. By providing standardized, diverse, and rich training datasets, this strategy
311 significantly broadens the applicability of ML models for TDM, particularly when real-world
312 data are sparse, biased, or poorly structured.

313 While the overall strategy is consistent, the design of the simulation plan itself can differ
314 significantly across studies, impacting model robustness. A typical workflow involves: (1)
315 selecting one or more validated popPK models as the generative engine; (2) defining a virtual
316 population by creating realistic distributions for key patient covariates, often mirroring the
317 distributions from the original model's publication to prevent extrapolation; (3) simulating
318 thousands of individual concentration-time profiles under various dosing regimens; and (4)
319 adding plausible sources of variability, including inter-individual variability, imprecision in
320 sampling times, and residual error, to mimic real-world conditions. However, specific design
321 choices within this framework vary. A key difference lies in the handling of model
322 uncertainty: some studies use a single popPK model, while more robust approaches use an
323 ensemble of different popPK models for the same drug to ensure the final ML model is not
324 overfitted to one particular set of structural assumptions. Another source of variation is the
325 complexity of the virtual population: some plans sample covariates independently, while more
326 sophisticated designs model the correlations between them (e.g., age and renal function).
327 Finally, the handling of residual unexplained variability (RUV) is of particular importance.
328 Some studies remove RUV from the simulated concentrations, which can improve the
329 apparent performance of the ML model by providing 'cleaner' training data, though this may
330 not reflect the noise inherent in real-world TDM [44,57].

331 Nevertheless, a critical analysis warrants caution regarding several limitations. The quality
332 and generalizability of the ML model are intrinsically linked to the validity of the underlying
333 popPK model. Any bias, structural misspecification, or lack of representativeness in the
334 popPK model will not only be learned but potentially amplified by the ML algorithm at scale.
335 This creates a significant risk of developing a model that is precise but fundamentally
336 inaccurate, giving a false sense of confidence in its predictions. Therefore, rigorous validation
337 of the source popPK model in the target population is a fundamental prerequisite.

338 Furthermore, clinical complexity including non-adherence, drug interactions, and analytical
339 variability is often underrepresented in synthetic datasets. Perhaps most critically, validation
340 remains almost exclusively retrospective, with no interventional or prospective studies to date
341 having confirmed the clinical benefit of these tools.

342 In summary, while simulation-based training represents a critical step forward for
343 pharmacometric ML modeling, its successful translation into clinical practice will depend on
344 rigorous simulation design, robust external validation, and, ultimately, proof of its efficacy in
345 real-world settings via prospective trials.

346

347 3.3ML for initial dose optimization: towards proactive TDM

348 Building on the success of exposure prediction, a logical and impactful extension of ML in
349 TDM has been the optimization of the initial dose. This marks a critical shift from reactive
350 monitoring to proactive dose individualization, a particularly valuable approach for drugs
351 with high PK variability where achieving therapeutic targets from the outset is paramount.
352 Using patient characteristics available before treatment initiation, these models aim to predict
353 the dose most likely to achieve a desired therapeutic endpoint.

354 This proactive paradigm is well-exemplified by simulation-based models. For instance, Rivals
355 et al. (2024) used thousands of simulated PK profiles to train an XGBoost model for
356 daptomycin that improved the achievement of dual efficacy and safety targets in a real-world
357 validation cohort compared to conventional weight-based dosing [62]. Similarly, Tang et al.
358 (2024) developed a simulation-trained model to individualize isoniazid dosing, demonstrating
359 the potential for early therapeutic optimization based on patient covariates alone, which is
360 especially relevant in settings where TDM is not readily available [63].

361 The approach is not limited to simulated data. Imai et al. (2020) constructed a decision tree
362 model from real-world clinical data to optimize vancomycin loading doses, significantly
363 improving the attainment of target trough concentrations over guideline-based methods.[64]
364 The value of this strategy has been further underscored in challenging populations such as
365 pediatrics. Ponthier et al. demonstrated that ML models trained on simulated neonatal profiles
366 could select vancomycin doses more effectively than reference equations, improving target
367 attainment while reducing the risk of toxicity. In a similar framework for GCV and VGCV,
368 their work showed that ML could guide dose selection to achieve target AUCs with greater
369 accuracy than traditional approaches [65,66].

370 Collectively, these studies illustrate that ML-driven dose optimization represents a significant
371 advance over traditional weight- or creatinine-based nomograms. By integrating
372 multidimensional patient information, these models, whether trained on simulated or clinical
373 data, offer a powerful tool for personalized, proactive dosing. However, their successful
374 translation into routine clinical practice hinges on prospective validation, transparent and
375 interpretable algorithms, and their seamless integration into clinical decision-support systems.

376

377 3.4 Hybrid ML-popPK models: a converging paradigm

378 As the respective strengths and limitations of ML and mechanistic models have become clear,
379 a converging paradigm has emerged: hybridizing ML with popPK frameworks (Figure 1).
380 This approach seeks to create a synergistic tool that preserves the physiological
381 interpretability of popPK models while leveraging ML's power to enhance predictive
382 accuracy by correcting for systematic error.

383 One of the earliest demonstrations of this hybrid strategy was proposed by Tang et al. (2021),
384 who sought to improve clearance predictions for renally eliminated drugs in neonates. By

385 training an ML model on the residuals of the popPK model's predicted PK parameters
386 (clearance), they showed a substantial reduction in prediction error [67].

387 Building on this foundational principle, the work by Destère et al. provides a clear illustration
388 of its power. In their study on iohexol, an initial clearance estimation via MAP-BE was
389 followed by an ML model trained on the remaining error. This second-stage correction
390 significantly reduced prediction error and, notably, mitigated the shrinkage effect often seen
391 with sparse data, all without discarding the underlying pharmacological structure [68]. They
392 validate this approach in a second example with isavuconazole [69]. This powerful concept
393 has since been rapidly adopted and extended. It has been used to enhance infliximab exposure
394 predictions in pediatric Crohn's disease, to refine TAC dosing by integrating complex clinical
395 and pharmacogenetic features [70,71]. This hybrid principle has also been extended into the
396 PK/PD space, where ML was used to correct a mechanistic model's predictions, significantly
397 improving the description of the dynamic time course of chemotherapy-induced neutropenia
398 [72].

399 Collectively, these studies position hybrid models as a compelling solution, offering a
400 pragmatic balance between data-driven adaptability and mechanistic robustness. While the
401 evidence remains largely retrospective, this approach represents a significant step towards
402 developing tools that are not only accurate but also transparent and trustworthy enough for
403 clinical adoption, pending essential prospective validation.

404

405

406 4.Conclusion

407 ML has emerged as a compelling answer to the inherent limitations of traditional
408 pharmacometrics approaches in TDM. Early studies established that ML could accurately
409 predict drug exposure from sparse clinical data, often outperforming conventional methods.
410 This data-driven approach, however, was constrained by the scarcity of rich clinical datasets,
411 a bottleneck that was effectively addressed by a strategic pivot to simulation-based training.
412 This methodological advance unlocked the potential for more robust and generalizable
413 algorithms, expanding ML's utility across diverse therapeutic areas and enabling a critical
414 shift towards proactive first-dose optimization.

415 More recently, the field has moved towards a synthesis of paradigms, with hybrid models that
416 couple the mechanistic interpretability of popPK frameworks with the corrective power of
417 ML. Collectively, the evidence paints a clear picture of ML's transformative potential. From
418 enhancing exposure prediction to enabling proactive dosing and refining mechanistic models,
419 these approaches represent a significant methodological advance. While the promise of a
420 paradigm shift in personalized pharmacotherapy is tangible, its clinical translation is
421 contingent upon rigorous validation in prospective clinical settings.

422

423

424 5.Expert Opinion

425 The integration of ML into TDM is poised to be more than an incremental improvement; it
426 represents a fundamental shift in how we approach personalized pharmacotherapy. While
427 accurately predicting PK surrogates is a critical first step, the clinical utility of ML will be
428 unlocked when models can move beyond exposure to directly forecast outcomes of clinical

429 relevance. This involves predicting not just the AUC of an immunosuppressant, but the
430 probability of graft rejection, not just the concentration of an antibiotic, but the likelihood of
431 clinical cure or the onset of nephrotoxicity. While the current evidence focuses on the former,
432 achieving the latter is the true promise of this technology. If implemented at scale, this
433 capability would translate into more precise therapeutic targeting, reduced toxicity, and
434 improved patient outcomes with significant clinical and economic value.

435 However, these promising results must be approached with scientific skepticism. The
436 published literature is inevitably subject to a positive publication bias, making it difficult to
437 find studies detailing failures of ML. Nevertheless, even within successful publications, there
438 are cases where ML models perform comparably to, but not better than, pharmacometric
439 approaches. For example, in the prediction of vancomycin exposure, an XGBoost model
440 showed similar performance to a model averaging approach using MAP-Bayesian estimation
441 [58]. Similarly, for the initial dose selection of daptomycin, an ML model was slightly
442 outperformed by a popPK-based approach in external validation [62].

443 These examples underscore that ML is not a panacea. When the underlying data is sparse or
444 the relationships are already well-captured by mechanistic models, the added complexity of
445 ML may not offer a significant advantage. A transparent assessment of both successes and
446 limitations is necessary for the field to mature and to delineate the specific contexts where ML
447 provides a genuine benefit. From a practical standpoint, translating this potential into routine
448 care requires overcoming three major hurdles. The first is data fragmentation and quality.
449 Current research is often constrained by single-center, demographically limited datasets,
450 which can lead to poorly generalizable models. Overcoming this will require fostering
451 multicenter collaborations and creating secure, federated learning frameworks. The second is
452 clinician trust and interpretability. The "black box" nature of some algorithms impedes
453 acceptance. This can be mitigated by systematically integrating explainable AI tools and,

454 more importantly, by prioritizing hybrid models where ML enhances, rather than replaces,
455 interpretable physiological frameworks. Finally, there is the barrier of clinical integration.
456 Without seamless EMR integration, clear regulatory pathways, and defined reimbursement
457 models, even the best algorithms will remain research curiosities.

458 Despite these barriers, tangible examples of integrated clinical decision support systems are
459 used, illustrating a viable path from research to routine care. A notable example is the ISBA
460 interface (<https://abis.chu-limoges.fr/login>), developed and deployed at the University
461 Hospital of Limoges for the TDM of immunosuppressants. This web-based platform provides
462 clinicians with a unified workflow for MIPD. Upon entering patient data and sparse drug
463 concentrations, the system estimates the drug's AUC and recommends a dose adjustment to
464 reach a specific therapeutic target. Critically, the platform provides AUC estimations and dose
465 recommendations from both MAP-Bayesian estimation and a parallel ML model, allowing the
466 clinician to gain confidence when the two independent approaches provide concordant results.
467 Such platforms represent an important step in translating advanced algorithms into actionable
468 clinical tools, demonstrating that the integration of ML into the daily TDM workflow is not
469 just a future possibility, but an emerging reality.

470 Critically, the future of TDM is unlikely to be a contest between ML and mechanistic
471 modeling, but rather their convergence. Hybrid models that couple the interpretability of
472 popPK with the pattern-recognition capacity of ML are the most promising path forward.
473 Looking ahead, the next frontier will be to move beyond static prediction towards a truly
474 dynamic and adaptive personalization engine.

475 The ultimate expression of this vision is the development of Digital Twins. In the context of
476 TDM, the potential role of a digital twin extends beyond static prediction. It would function
477 as an in-silico counterpart of the patient, allowing clinicians to simulate 'what-if' scenarios in

478 advance: What is the likely trajectory of both efficacy and toxicity if we increase the dose by
479 20%? How would a decline in renal function next week impact exposure? This would enable
480 truly proactive and dynamic treatment optimization over the entire course of therapy.

481 Realizing this vision requires integrating several key components: (1) a modular mechanistic
482 core that incorporates a suite of models ranging from traditional PK models to more complex
483 systems pharmacology frameworks to describe biological processes at different scales; (2) a
484 personalization layer where ML algorithms continuously update and connect these models
485 using patient-specific data (e.g., genomics, lab results, TDM); and (3) a dynamic integration
486 engine, likely leveraging advanced methods like Neural Ordinary Differential Equations
487 (NeuralODEs). This engine would serve as a data pipeline from sources like electronic health
488 records or wearable sensors but also dynamically fuse the outputs of the various sub-models
489 to predict their longitudinal evolution and interactions.

490 However, the current challenges are important. They include the technical requirements for
491 acquiring and processing continuous multimodal data streams, the high computational cost,
492 and the development of robust validation frameworks to ensure that a twin's predictions are
493 reliable enough for clinical decision-making. While still largely conceptual, they represent the
494 long-term ambition for the field.

495 Within the next 5 to 10 years, this convergence appears inevitable. Widespread adoption will
496 likely take the form of validated, hybrid dosing tools integrated directly into clinical
497 workflows, providing actionable recommendations at the point of care. As these systems
498 mature, trained on diverse, multicenter data and governed by clear regulatory frameworks, the
499 standard of care may finally shift from reactive dose adjustments to proactive, pre-dose
500 optimization as a default clinical strategy.

501

502

503 Article Highlights

- 504 • Machine learning (ML) offers a powerful data-driven approach to overcome the
505 limitations of traditional pharmacometric models in Therapeutic Drug Monitoring
506 (TDM).
- 507 • Simulation-based training has emerged as a key methodological pivot to overcome the
508 scarcity of rich clinical data, enabling the development of robust and generalizable ML
509 models.
- 510 • Hybrid models, which combine the physiological interpretability of popPK
511 frameworks with the predictive power of ML, represent a promising and pragmatic
512 path toward clinical adoption.
- 513 • The ultimate utility of ML lies in moving beyond predicting pharmacokinetic
514 surrogates to forecasting clinically meaningful outcomes like efficacy and toxicity.
- 515 • While formidable barriers to implementation remain (data access, interpretability,
516 workflow integration), the future of TDM points toward a convergence of
517 methodologies, culminating in dynamic tools like Digital Twins.

518

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536 HS and JBW conceptualized the review. HS wrote the first draft of the manuscript. YF, ML,
537 CC, LP, CM, PM and JBW critically reviewed and revised the manuscript for intellectual
538 content. JBW supervised the work. All authors reviewed and approved the final version of the
539 manuscript.

540

541

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543 During the preparation of this manuscript, the authors used the large language model 'Gemini'
544 (Google, version 1.5 Pro) to assist with language editing and rephrasing of sentences for

545 clarity and conciseness. The AI was used as a writing assistant; all content, scientific
546 assertions, and final decisions were made by the authors, who take full responsibility for the
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784 A key study demonstrating the extension of the hybrid paradigm beyond
785 pharmacokinetics and into the PK/PD space. It shows how ML can correct a
786 mechanistic model's predictions to better describe the dynamic time course of a
787 clinically relevant outcome, chemotherapy-induced neutropenia.

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789

790 **Table list:**

791 Summary of machine learning paradigms for therapeutic drug monitoring

792

793

794 **Figure list:**

795 The convergence of mechanistic and machine learning approaches for personalized
796 pharmacotherapy.

797 Table 1: Summary of machine learning paradigms for therapeutic drug monitoring

Paradigm / Application	Primary Goal	Key Methodologies	Primary Training Data Source	Key Strengths	Key Limitations & Challenges
1. Exposure Prediction (AUC, Cmin)	To estimate drug exposure (e.g., AUC) from sparse TDM samples.	XGBoost, Artificial Neural Networks (ANN), Random Forest.	1. Real-World Data: Rich but often scarce and heterogeneous. 2. Simulated Data: PK profiles generated from popPK models.	<ul style="list-style-type: none"> - Often more accurate than MAP-Bayesian estimation. - Simulation-based training is scalable and compensates for a lack of real-world data. 	<ul style="list-style-type: none"> - Real-world data is difficult to collect. - Performance on simulated data is entirely dependent on the validity of the underlying popPK model.
2. Initial Dose Optimization	To predict the optimal starting dose based solely on patient covariates (pre-TDM).	XGBoost, Decision Trees, GLMNET.	Real-world clinical data or simulated PK profiles.	<ul style="list-style-type: none"> - Enables proactive rather than reactive TDM. - Improves therapeutic target attainment from the first dose. - Outperforms simple 	<ul style="list-style-type: none"> - Requires comprehensive and high-quality baseline data. - Prospective validation is essential before clinical implementation.

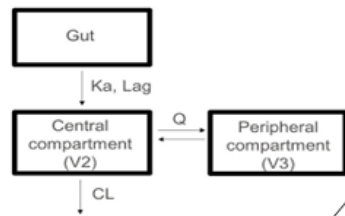
				weight- or renal function-based nomograms.	
3. Hybrid Models (ML + popPK)	To use ML to correct the residual error of a mechanistic popPK model.	PopPK model (1st stage) + ML (XGBoost, etc.) trained on the residuals (2nd stage).	The difference between the popPK model's prediction and the reference standard (measured or full profile).	<ul style="list-style-type: none"> - Preserves the physiological interpretability of the popPK model. - Improves accuracy and reduces bias and shrinkage. - "Best of both worlds" approach. 	<ul style="list-style-type: none"> - More complex to develop and validate. - Evidence remains mostly retrospective.
4. Digital Twins	To create a dynamic virtual model of the patient to forecast the trajectory of both benefit and risk as a function of exposure.	NeuralODEs, Deep Learning architectures.	Multimodal and longitudinal data (genomics, wearables, EMRs).	<ul style="list-style-type: none"> - Potential for ultimate, dynamic personalization. - Ability to integrate complex, real-time data streams. 	<ul style="list-style-type: none"> - High algorithmic complexity. - Massive data requirements. - Still in the fundamental research stage.

798 AUC, area under the concentration–time curve; C_{min}, minimum plasma concentration; popPK, population pharmacokinetics; ML, machine
799 learning; TMD, therapeutic drug monitoring; EMRs, electronic medical records.

800 Figure 1: The convergence of mechanistic and machine learning approaches for personalized pharmacotherapy.

Mechanistic Approach (Population Pharmacokinetics)

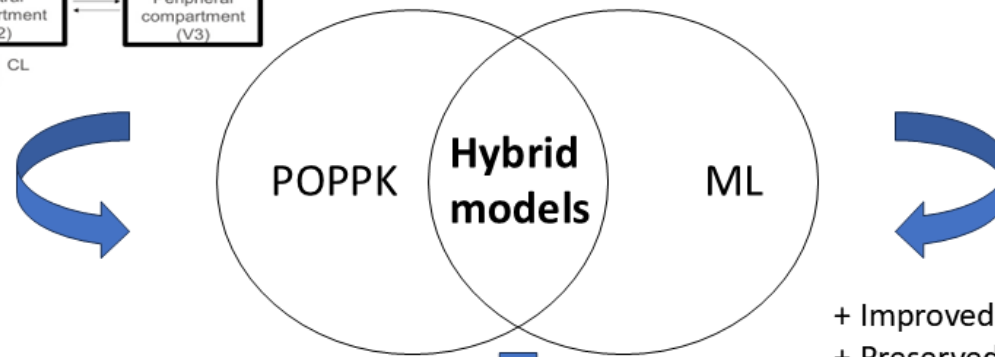
- + Interpretable
- + Physiology-based
- Dependent on a priori model assumptions



Machine Learning Approach

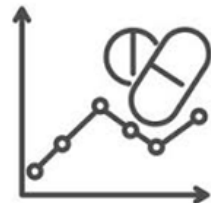


- + Flexible
- + Captures complex relationships
- "Black box" nature
- Data-hungry



- + Improved accuracy
- + Preserved interpretability

Digital Twin



- + dynamic and integrative patient model
- + Prediction of the benefit-risk balance