Combining machine learning and mechanistic modeling approaches to solve real life problems – assessment of the local tissue binding and its influence on the systemic exposure after topical application of drugs

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Introduction

Dermal drug administration can be a preferred route for the delivery of drugs for local or systemic action, with numerous advantages over oral administration. Physiologically Based Pharmacokinetic (PBPK) models have recently gained significant attention in regulatory submissions to quantitatively predict drug-drug interactions (DDIs) and absorption/bioavailability processes [1]. A PBPK approach has a strong potential to help bridge the gap in clinical knowledge in a situation where clinical studies are either difficult or practically infeasible.

Drug binding in the human tissues is one of the crucial parameters needed for the proper prediction of the drug exposure. Assuming that only unionized and unbound molecule can diffuse through the skin and subcutis tissues, and that the experimental measurement of this parameter is not routinely done, its prediction becomes crucial. In the current study we applied machine learning approach to develop empirical model for the stratum corneum binding. In the next step we utilized the predicted values to assess their influence on the dermally applied model drug (ketoprofen) local and systemic exposure predicted with the use of mechanistic PBPK model (Simcyp MPML MechDermA model) [1].

Methods

Binding coefficients to different keratins, namely, bovine hoof and horn, human delipidized callus, human delipidized stratum corneum (SC), human nail, human hair, and sheep wool collected by Hansen and colleagues from the literature, were utilized for the modeling purposes [4]. The modelled endpoint was Nernst binding coefficient K_{Nernst} (log K_{Nernst}). The model was developed using data-driven approach based on the gathered data set and bioinspired heuristic algorithm so-called genetic programming (GP), based on simple physico-chemical parameters (logP, HBA).

GP is a machine learning system belonging to the evolutionary computation (EC) systems, where solution is represented as an artificial chromosome and based on available data developed iteratively by means of genetic operators (mutation, crossing-over, etc.) performed on the population of chromosomes towards the optimum state. In this work we used a variant of GP called symbolic regression where the artificial chromosome represents mathematical equation, both its structure and coefficients.

R statistical environment [6] was used to perform all calculations with GP implementation in rgp module [7] extended by Pacławski et al. [8]. The model quality was assessed with the use of root mean squared error (RMSE) and normalized RMSE (NRMSE). The predicted fusc value for ketoprofen (0.093) was further applied to the MPML MechDermA model, and the systemic concentration predictions for fusc = 1, and the predicted value were compared.

Table 1a, b. Ketoprofen ADME / skin permeation parameters.

a

Group	Parameter	Value [unit]	Source
Phys-chem	MW	254.285	[2]
	logP	3.12	[3]
	Type	monoprotic acid	[2]
	pKa	4.45	[2]
Binding	B/P partition ratio	1.1	[4]
	fu_{plasma}	0.01	[3]
Distribution	Vss	0.132 [L/kg]; CV=17.2%	[5]
Elimination	CLIV	5.16 [L/h]; CV=17.4%	[5]

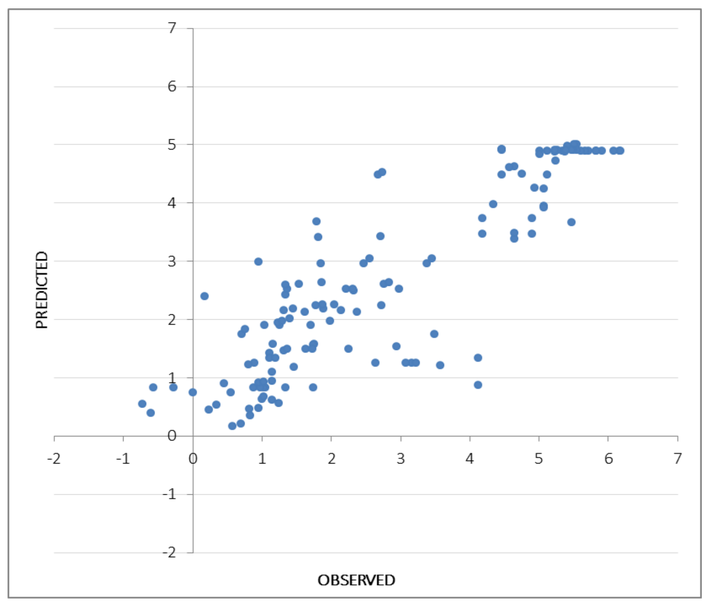
b

Group	Parameter	Value [unit]	Source
Absorption	$Kp_{sc\_lip:vehicle}$	162.5451	predicted – Hansen 2013
	$Kp_{sc:ve}$	6.9144	predicted – Kretsos 2008
	$Kp_{dermis:ve}$	1	assumed
	$Kp_{sebum:vehicle}$	1643.341	predicted – Valiveti et al. 2008
	$Kp_{skin:blood}$	2.67544	predicted – Shatkin&Brown 1991
	$Kp_{sebum:ve}$	0.0989	calculated – $Kp_{lip:vehicle}/Kp_{sebum:vehicle}$
	D_{sc_lip}	3.392E-06 [cm^2/h]	predicted – Mitragotri et al. 2003
	D_{ve}	0.000311 [cm^2/h]	predicted –Bunge&Cleek
	D_{dermis}	0.000311 [cm^2/h]	predicted –Kretsos et al. 2008
	D_{sebum}	0.000653 [cm^2/h]	predicted – Johnson et al. 1996
	fu sc	0.0934	predicted – Polak et al. 2016
	$f_{ni,\ corneocytes}$	1	assumed

Ballerini et al. reported plasma and synovial fluid concentration after topical application of ketoprofen gel [9]. 10cm long strip containing 70-80 mg of ketoprofen was applied on the knee (assumed area 400 cm^2). Plasma and synovial fluid concentrations were measured.

Results

The best obtained model for the protein binding in stratum corneum had RMSE = 0.92 and NRMSE = 13.31%. The final equation is presented below (Equation 1).



fu_{sc} = $1 - (EXP(logK_{Nernst})/(1+EXP(logK_{Nernst}))$

where:
$logK_{Nernst} = (ln(HBA+4.824))^{\wedge(ln(abs(logP)))}$

The observed vs predicted $LogK_{Nernts}$ values are presented on Figure 1.

Figure 1. Observed and Predicted $logK_{Nernst}$ values.

MechDermA model simulation results for the Ballerini study for two scenarios: A) fu_{SC} = 1 (lack of binding assumed), B) fu_{SC} = 0.093 (predicted with the Equation 1) are presented below on Figure 2.

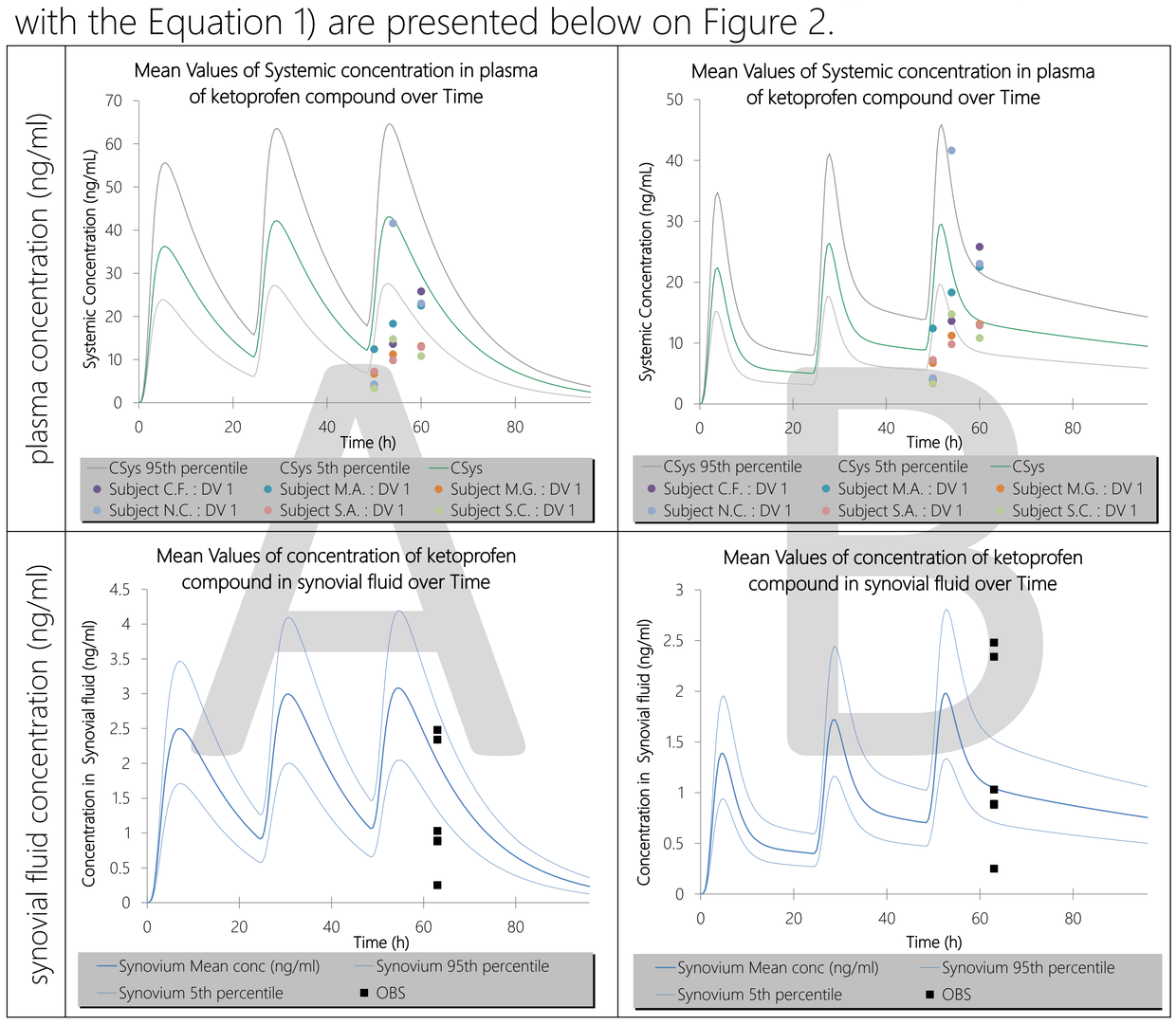


Figure 2. MechDermA model simulation results for two tested scenarios.

Discussion and Conclusions

The current study presents the problem solving approach based on combining machine learning and mechanistic modeling. Drug absorption after dermal application was used as an exemplary problem. As only the free, unbound drug can permeate and partition between skin layers, the knowledge about binding to the SC structures allows proper parametrization of the model. This value is although not commonly measured, and the QSAR model utilizing simple physico-chemical data.

Ketoprofen plasma exposure after topical application was simulated with the assumption that the binding in SC is negligible (fu_{SC}=1). The model overpredicted the plasma concentration. Based on the ketoprofen specific phys-chem data the fu_{SC} value was calculated (fu_{SC}=0.093) and applied to the MechDermA model. The simulated exposure closely mimicked the clinically observed plasma concentrations.

References

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