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TITLE: Hybrid modelling for improved prediction of intestinal solubility

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ABSTRACT: This work addresses the challenge of identifying poorly soluble drugs during the early stages of pharmaceutical development by combining mechanistic knowledge with data-driven methodologies within a hybrid modelling framework. The assessment of equilibrium solubility in gastrointestinal fluids is pivotal for determining oral drug bioavailability. However, the complexity associated with handling in vivo gastrointestinal fluids has promoted the development of in vitro Simulated Intestinal Fluids (SIFs). Traditional mechanistic models, while widely used, are often unable to account for complex physiological factors such as food intake, and their predictive reliability remains limited1,2. To overcome these limitations, we propose a hybrid modelling framework that integrates Gaussian Process Regression with mechanistic modelling, aiming at improving both the quantitative accuracy and the physiological interpretability of conventional approaches. The model is validated using several drugs, including fenofibrate, used to treat hypercholesterolemia, and felodipine, used to treat hypertension. The results demonstrate that the proposed approach significantly outperforms traditional mechanistic models, capturing both inter- and intra-subject variability in in-vitro SIF systems and enabling a better understanding of drug-dependent food effects on oral drug bioavailability. Overall, this approach has important implications for streamlining the drug development process by reducing reliance on resource-intensive experimentation and improving the efficiency of oral drug formulation strategies.

Keywords: *hybrid model, drug intestinal solubility, physiological model, Gaussian Process*

References

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BRIEF SPEAKER BIO: Marco Brendolan is a second-year PhD student whose research explores the use of Artificial Intelligence methodologies to support and optimize product formulation