**Exploiting hybrid modelling strategies for predicting intestinal solubility**

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This study addresses the challenge of identifying poorly soluble drug compounds during the early stages of pharmaceutical development by introducing a hybrid modelling approach aimed at enhancing both predictive accuracy and mechanistic understanding. Equilibrium solubility within gastrointestinal fluids is a critical parameter of oral drug bioavailability. Its in-vivo experimental assessment is difficult because of the complexity related to the collection of human intestinal fluids. Consequently, in-vitro evaluations using Simulated Intestinal Fluids (SIFs) have become extremely important for assessing drug solubility. Furthermore, pharmacokinetics physiologically based are typically used to predict intestinal solubility. Nevertheless, the state-of-the-art models [1] often neglect complex physiological effects such as the effect of food intake, which results in limited predictive reliability.

This work proposes a hybrid model that integrates Gaussian Process Regression, a supervised machine learning technique, to improve both the quantitative accuracy and the physiological interpretability of state-of-the-art models. This hybrid methodology was applied to a real industrial Active Pharmaceutical Ingredient, which is characterized by low aqueous solubility [2]. The results demonstrate that the proposed model significantly outperforms existing approaches in the literature, capturing both inter-subject and intra-subject variability in gastrointestinal solubility with a high degree of accuracy. The proposed model facilitates an in-depth understanding of the interactions between drug compounds and intestinal components under various physiological states, determining also important implications, such as a streamlined drug development process, a reduced reliance on resource-intensive experimentation, ultimately improving the efficiency of oral drug formulation strategies.

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

**References**

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