

Hybrid modelling for improved prediction of intestinal solubility

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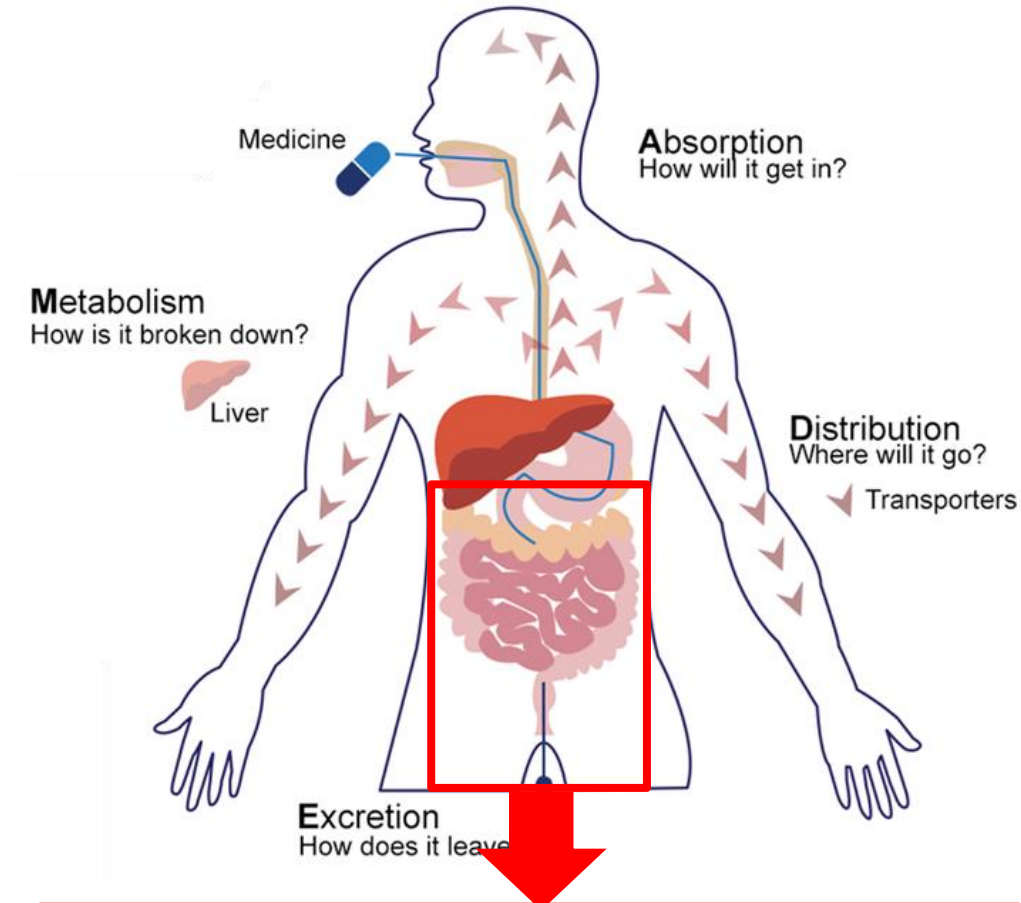
Interaction drug-human body for oral dosage drug

► Pharmacokinetics

- interaction drug-human body
- physiologically-based pharmacokinetics (**PBPK**)
 - Compartments are physiologically discrete entities

► **Drug** must enter in the **systemic circulation** to fulfill its function

- Drug compound must be **absorbed** before any medical effects



Absorption mainly occurs in the **gastrointestinal tract** and **intestinal solubility** is a **key factor**

Dataset available

- ▶ Industrial Active Pharmaceutical Ingredient (API) *
 - ▶ ampholyte drug
 - ▶ in-vitro intestinal fluids characterized by different intestinal composition
 - ▶ 153 experimental measurements of intestinal solubility with 3 replicates

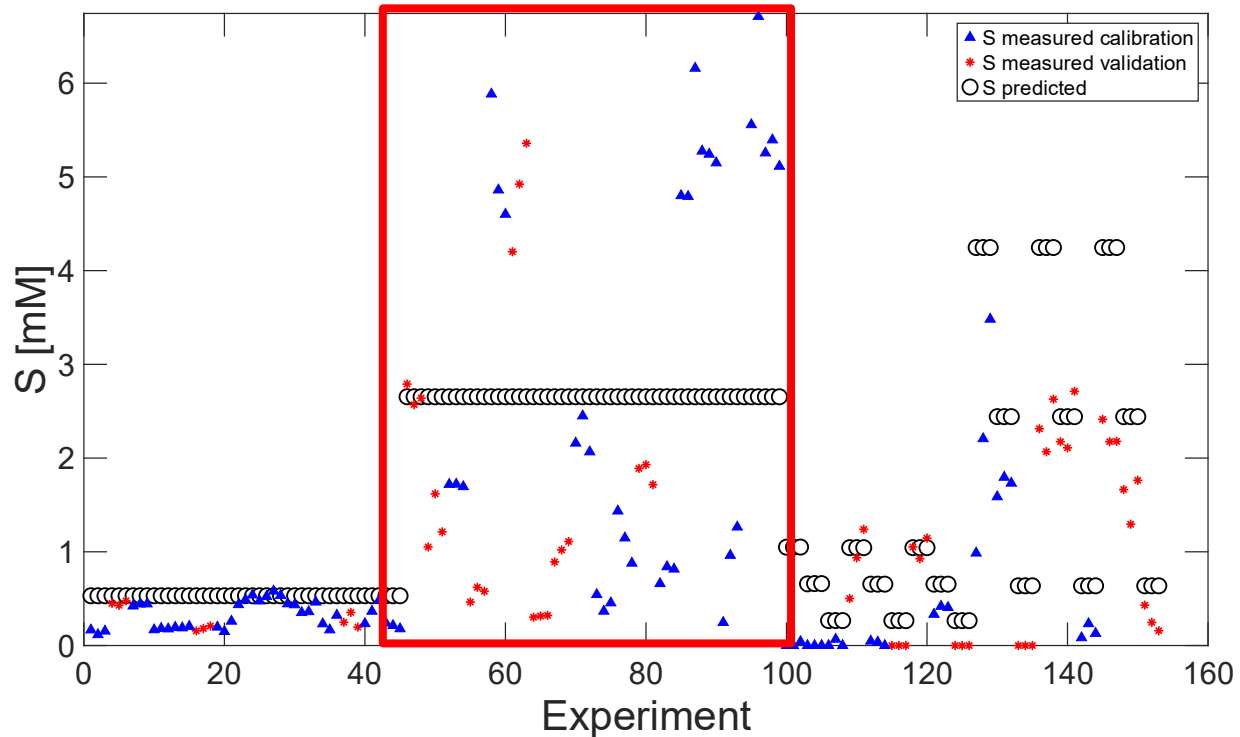
Solution	Total BS (mM)	LE (mM)	OA (mM)	CH (mM)	MG (mM)
I	5.9	1	10	0.26	2.8
⋮	⋮	⋮	⋮	⋮	⋮
n	3.6	0.5	0.8	0.13	1

- ▶ Bile salts (BS)
- ▶ Lecithin (LE)
- ▶ Oleic acid (OA)
- ▶ Cholesterol (CH)
- ▶ Monoglyceride (MG)



State-of-the-art in modelling intestinal solubility

Literature model



$$*S = S_0 \left(1 + \frac{[BS](t)}{C_{H_2O}} K_{m:w,u} \right) + S_i(t) \left(1 + \frac{[BS](t)}{C_{H_2O}} K_{m:w,i} \right)$$

- ▶ Two **partition coefficients** based on experimental measurements
 - ▶ $K_{m:w,u}$ and $K_{m:w,i}$ regulate drug distribution in aqueous and micelle phase
- ▶ Dependence on **Bile Salts (BS)** and **pH** ($S_i(t)$ depends on pH)

▶ Inaccurate predictions for **moderate-fat meal compositions**

Gaussian Process Regression (GPR)*

$K'_{m:w,u} = \mathbf{f}(\mathbf{X}) + \varepsilon$
 $\mathbf{f}(\mathbf{X})$ is described as a
Gaussian distribution

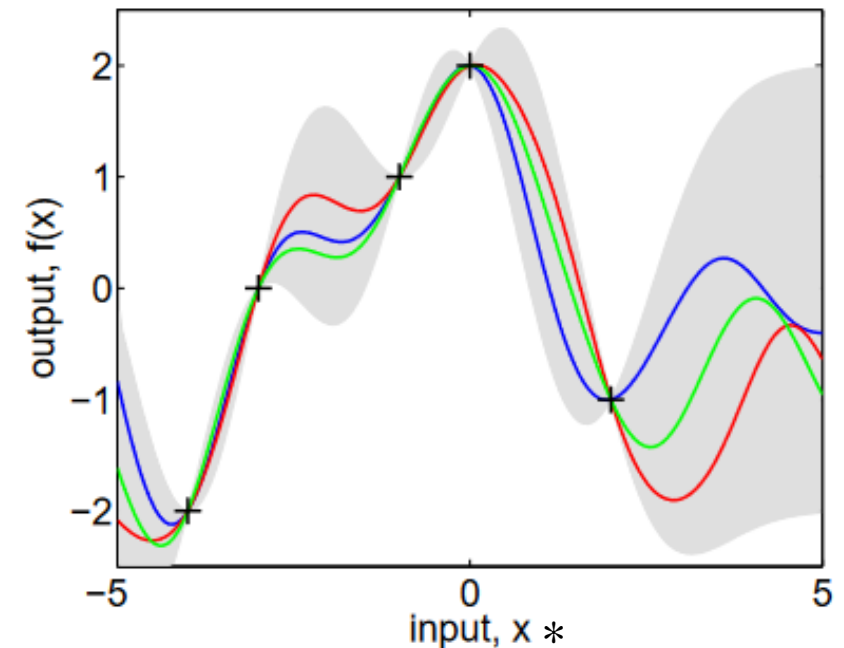
$\mathbf{X}$ are the **intestinal components**
(pH, [BS], etc.)

GPR input

- ▶ $\kappa(\mathbf{x}, \mathbf{x}') = \sigma_{SE}^2 \exp\left(\frac{-\|\mathbf{x} - \mathbf{x}'\|^2}{\ell^2}\right)$
- ▶ Prior mean as linear combination of intestinal components

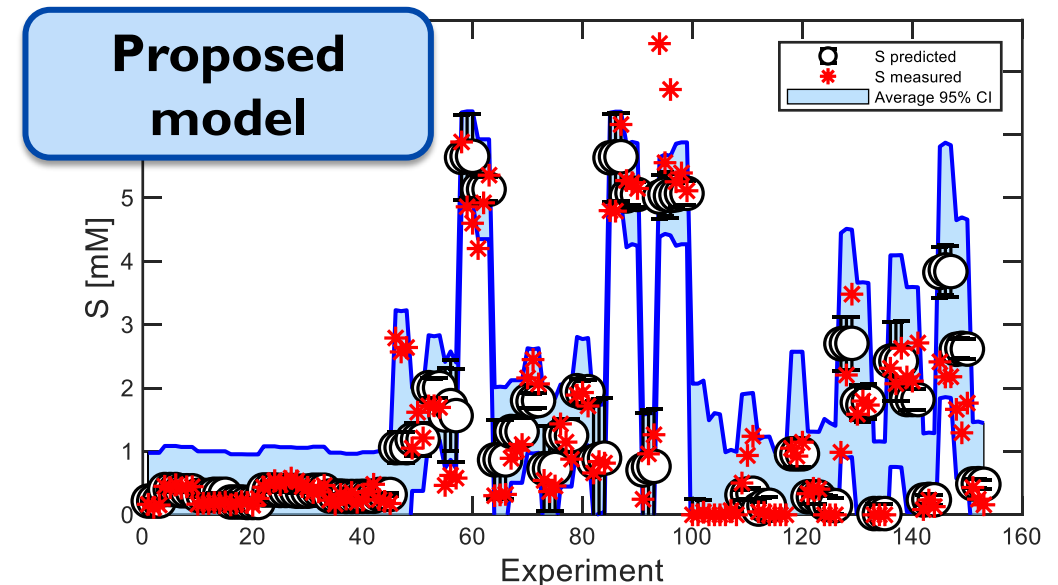
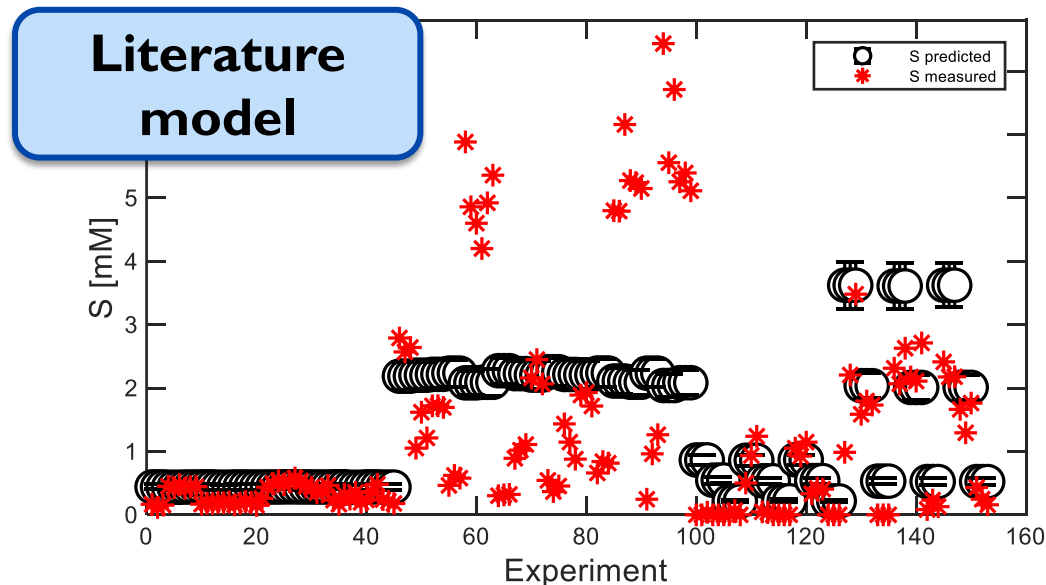
GPR output

- ▶ $\bar{\mathbf{f}}_* = \mathbf{m}(\mathbf{X}_*) + \mathbf{K}(\mathbf{X}_*, \mathbf{X})[\mathbf{K}(\mathbf{X}, \mathbf{X}) + \sigma_n^2 \mathbf{I}]^{-1} (K'_{m:w,u} - \mathbf{m}(\mathbf{X}_*))$
- ▶ $cov(\mathbf{f}_*) = \mathbf{K}(\mathbf{X}_*, \mathbf{X}_*) - \mathbf{K}(\mathbf{X}_*, \mathbf{X})[\mathbf{K}(\mathbf{X}, \mathbf{X}) + \sigma_n^2 \mathbf{I}]^{-1} \mathbf{K}(\mathbf{X}, \mathbf{X}_*)$

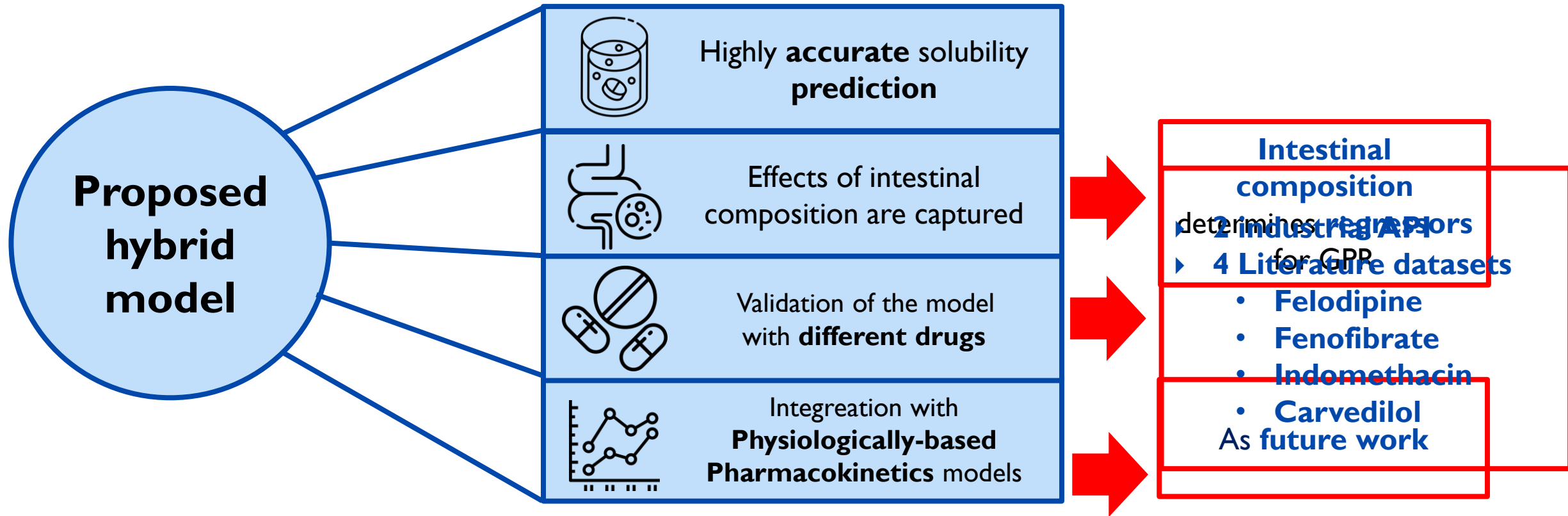


Prediction of intestinal solubility

- ▶ **Fasted-state conditions** are accurately described for the proposed model
 - ▶ **RMSE** of **0.095** mM vs **0.145** mM (reduction of 34%)
 - ▶ **R²** of **0.53** vs **-0.09**
- ▶ **Moderate-fat meal conditions** are accurately predicted for the proposed model
 - ▶ **RMSE** of **0.57** mM vs **2.19** mM
 - ▶ **R²** of **0.92** vs **-0.11**



Conclusion and future work





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<https://research.dii.unipd.it/capelab>



>_ Boosting innovation!



Architecture of the proposed model

