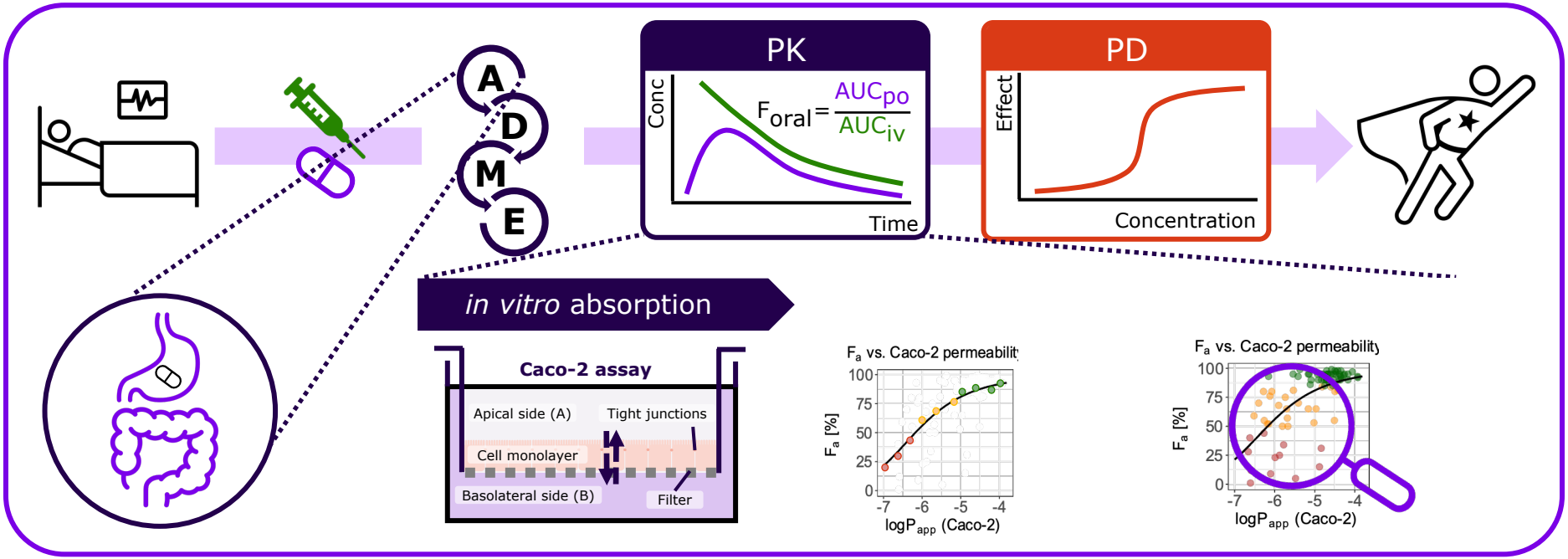
Prediction of human fraction absorbed from in vitro Caco-2 permeability – are we there yet?

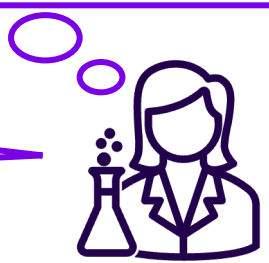
OSP Community Conference, Basel, Oct 7-8, 2024
Session II: In Vitro-In Vivo Extrapolation

Denise Feick, DMPK Modeling & Simulation, Sanofi, Frankfurt

From **compound** to **cure**



Let's take a closer look!

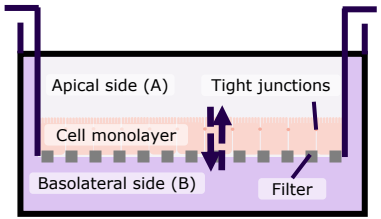


How can we inform intestinal absorption for MID3?

Examples for in vitro, in situ and in silico models

in vitro

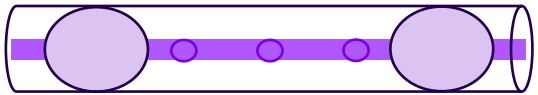
- Cell systems -



Caco-2 permeability assay[1,2]

in situ

- Intestinal perfusion studies -



Loc-I-Gut technique[3]

in silico

- Regression models -

Quantitative Structure Property Relationship (QSPR) models[4]

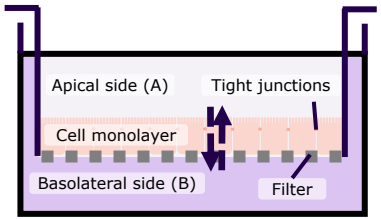
[1] Sun et al. Expert Opin Drug Metab Toxicol. 2008;4(4):395-411
[2] van Breemen and Li. Expert Opin. Drug Metab. Toxicol. 2005, 1, 175-185
[3] Lennernäs. Xenobiotica. 2007;37(10-11):1015-51.
[4] O'Shea et al. Eur. J. Pharm. Sci. 2022, 1:170:106098

How can we inform intestinal absorption for MID3?

In vitro Caco-2 permeability assay

in vitro

- Cell systems -



Caco-2 permeability assay[1,2]

SETUP

- Human colon epithelial cell line
- Cell monolayer with tight junctions, transporters and enzymes
- Compound added to apical (A) or basolateral (B) compartment (donor) and determined in opposite compartment (receiver)

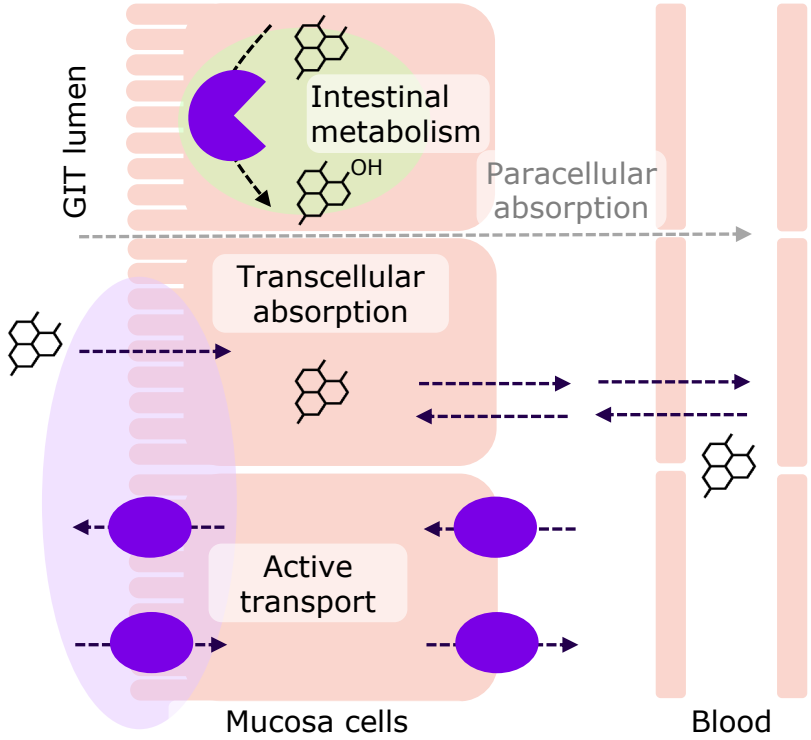
COMMON READOUTS

1. *Apparent permeability coefficient (P_{app})*
   Calculated from steady-state flux, surface area of the filter and initial compound concentration
2. *Efflux ratio (P_{app}B-A/ P_{app}A-B)*
3. *Absorptive or secretory quotient*
   Permeability in presence vs. in absence of specific inhibitor
4. *Recovery (mass balance)*
   Compound in donor and receiver at end of experiment

[1] Sun et al. Expert Opin Drug Metab Toxicol. 2008;4(4):395-411
[2] van Breemen and Li. Expert Opin. Drug Metab. Toxicol. 2005, 1, 175-185

Intestinal absorption

High physiological complexity



$$F_{oral} = F_a \times F_g \times F_h$$

F_a Fraction of a dose permeated from gut lumen into enteroctes

F_g Fraction of a dose that escaped intestinal metabolism

F_h Fraction of a dose that escaped hepatic metabolism

Key assumptions

1. Fraction absorbed ≠ oral bioavailability
2. Fraction absorbed is the sum of **passive** and **transporter-mediated** membrane permeation

Intestinal absorption

Affected by various conditions

How is this represented in OSP Suite?

Physiological properties

- pH in lumen
- Feeding state
- Location of intestinal segment
- Intestinal transit time
- …

Formulation properties

- Formulation dissolution
- Drug release
- Excipient effects
- …

Drug properties

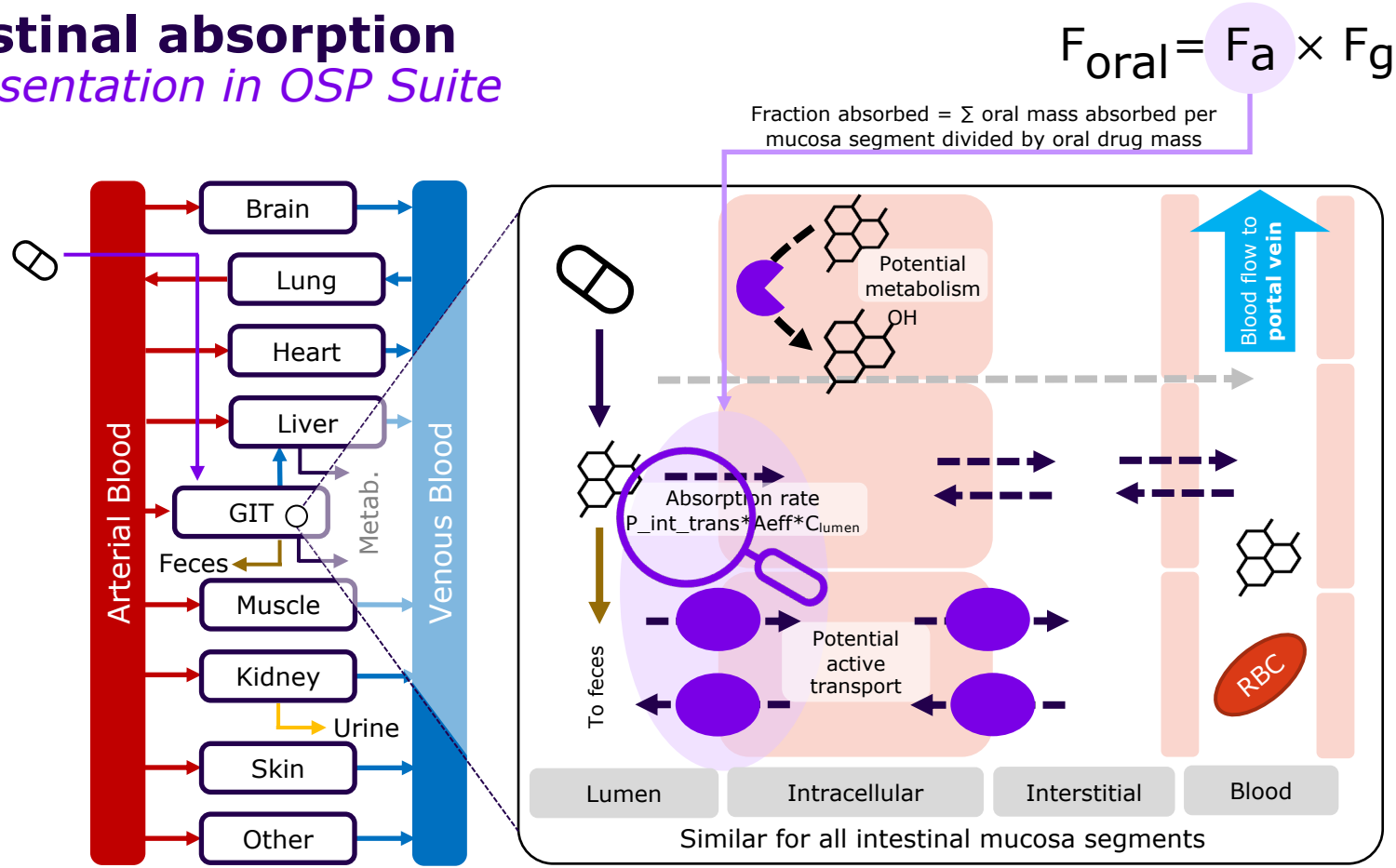
- Molecule size
- Solubility
- Lipophilicity
- Binding
- Metabolism
- Active transport
- …

O'Shea et al. Eur. J. Pharm. Sci. 2022, 1:170:106098

Intestinal absorption

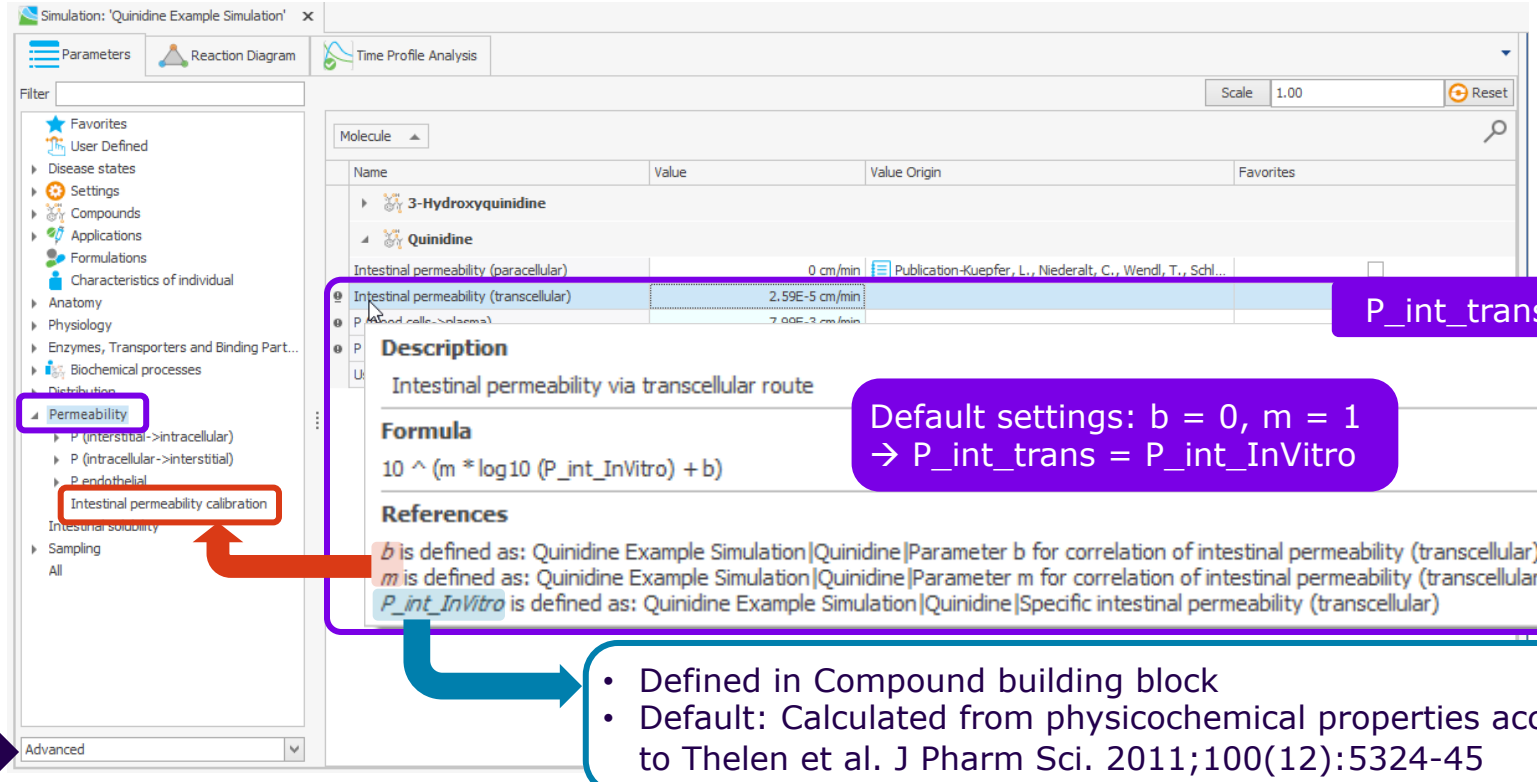
Representation in OSP Suite

$$F_{oral} = F_a \times F_g \times F_h$$



Intestinal absorption
Representation in OSP Suite

PK-Sim
Simulation



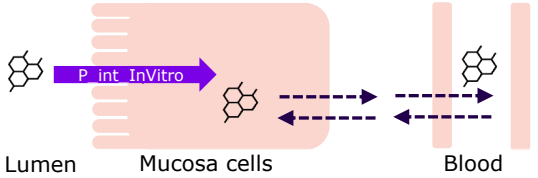
- Defined in Compound building block
- Default: Calculated from physicochemical properties according to Thelen et al. J Pharm Sci. 2011;100(12):5324-45

Intestinal absorption
Representation in OSP Suite

Can we inform P_int_trans with *in vitro* permeability from Caco-2?

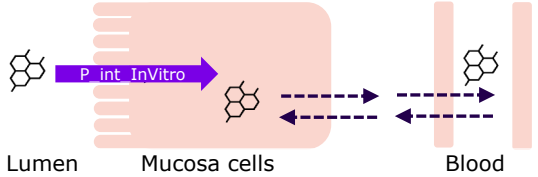
Scenario I: Default
P_int_InVitro calculated from physico-chemical properties

Intestinal permeability based on physico-chemical properties equals *in vivo* permeability
→ Unsaturable
→ *Only passive absorption considered*



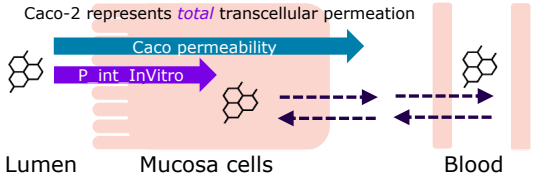
Scenario II: Common practice
User defined input for P_int_InVitro → fitted

Intestinal permeability fitted, leaving out physico-chemical properties and active processes
→ Unsaturable
→ *Does not support bottom-up approach*



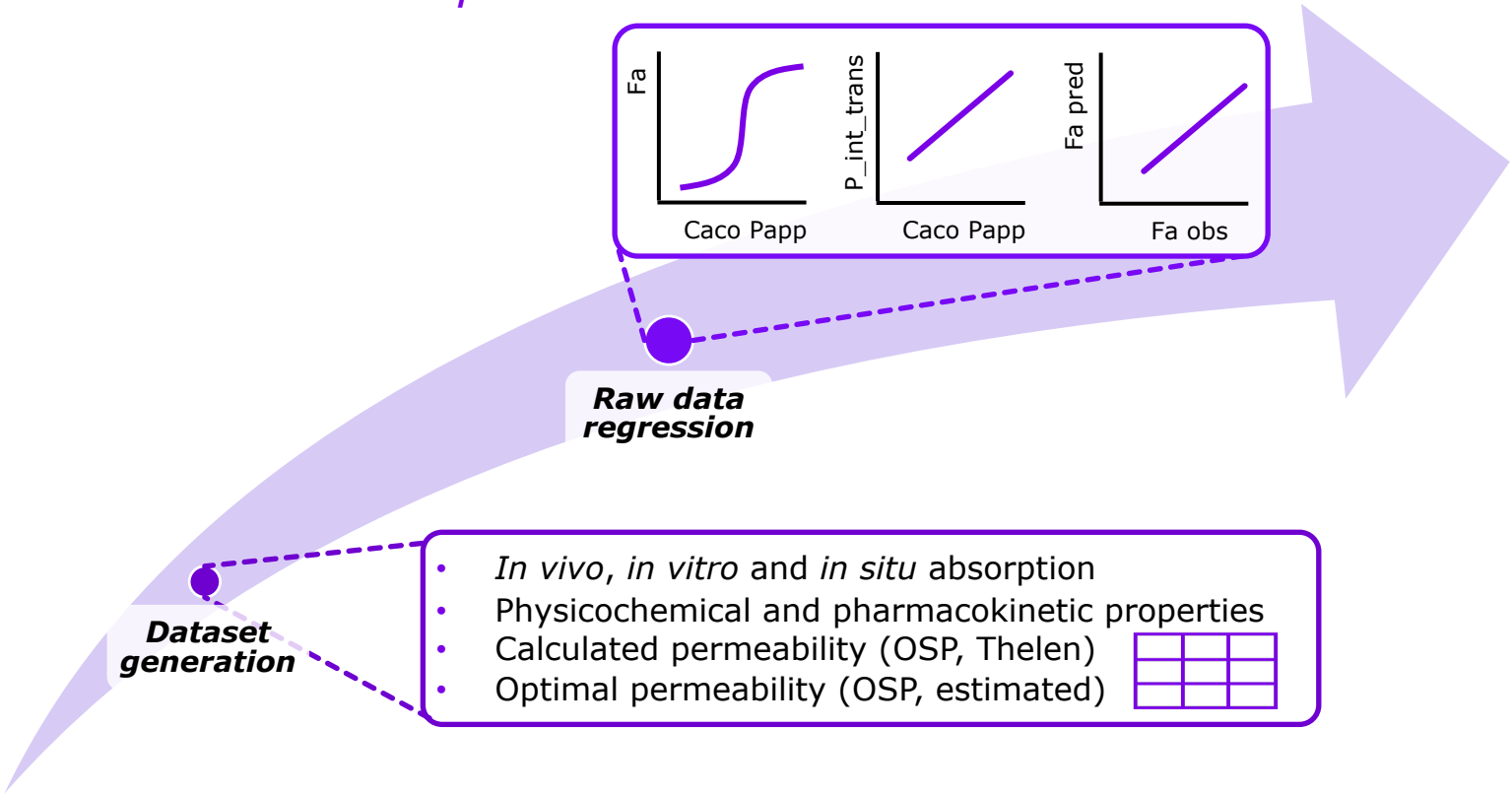
Scenario III: IVIVE
User defined input for P_int_InVitro → Caco-2 based

Linear correlation *in vitro* permeability and *in vivo* permeability
→ Unsaturable
→ *Postulates that Caco-2 is representative for F_a*



Intestinal absorption

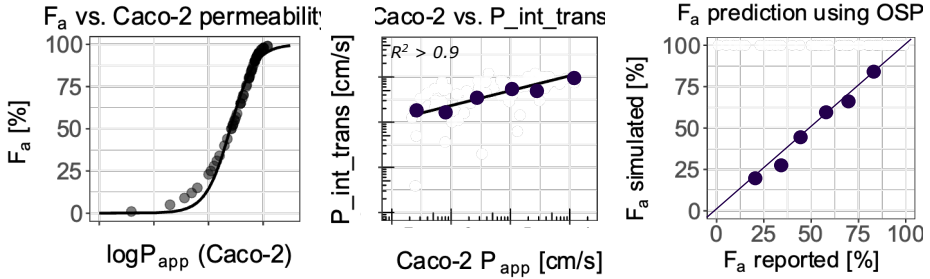
In Vitro-In Vivo Extrapolation



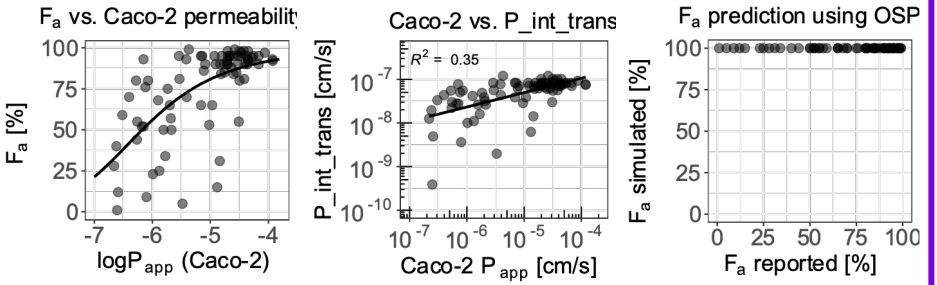
Correlation of Caco-2 permeability and fraction absorbed

Expectation vs. Reality

Expectation



Reality

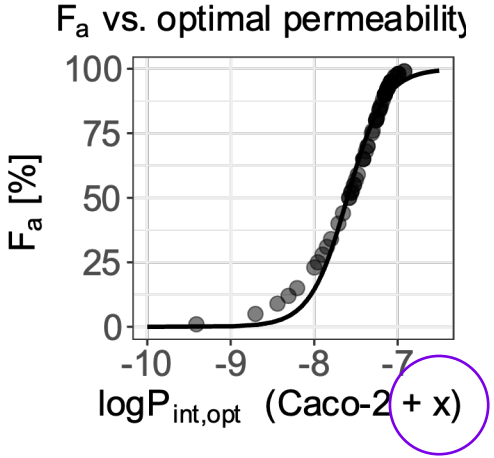


Be careful with literature statements about "perfect" correlation of Caco-2 permeability and fraction absorbed

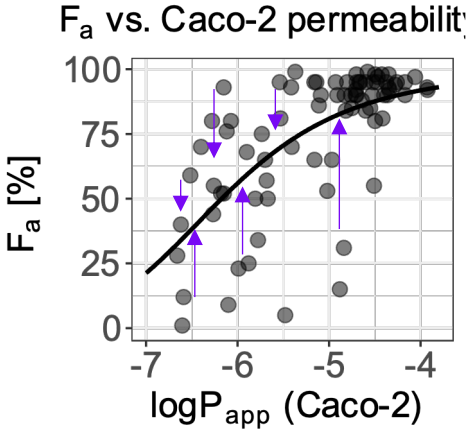
Correlation of Caco-2 permeability and fraction absorbed

Path to an ideal correlation using OSP Suite

Goal



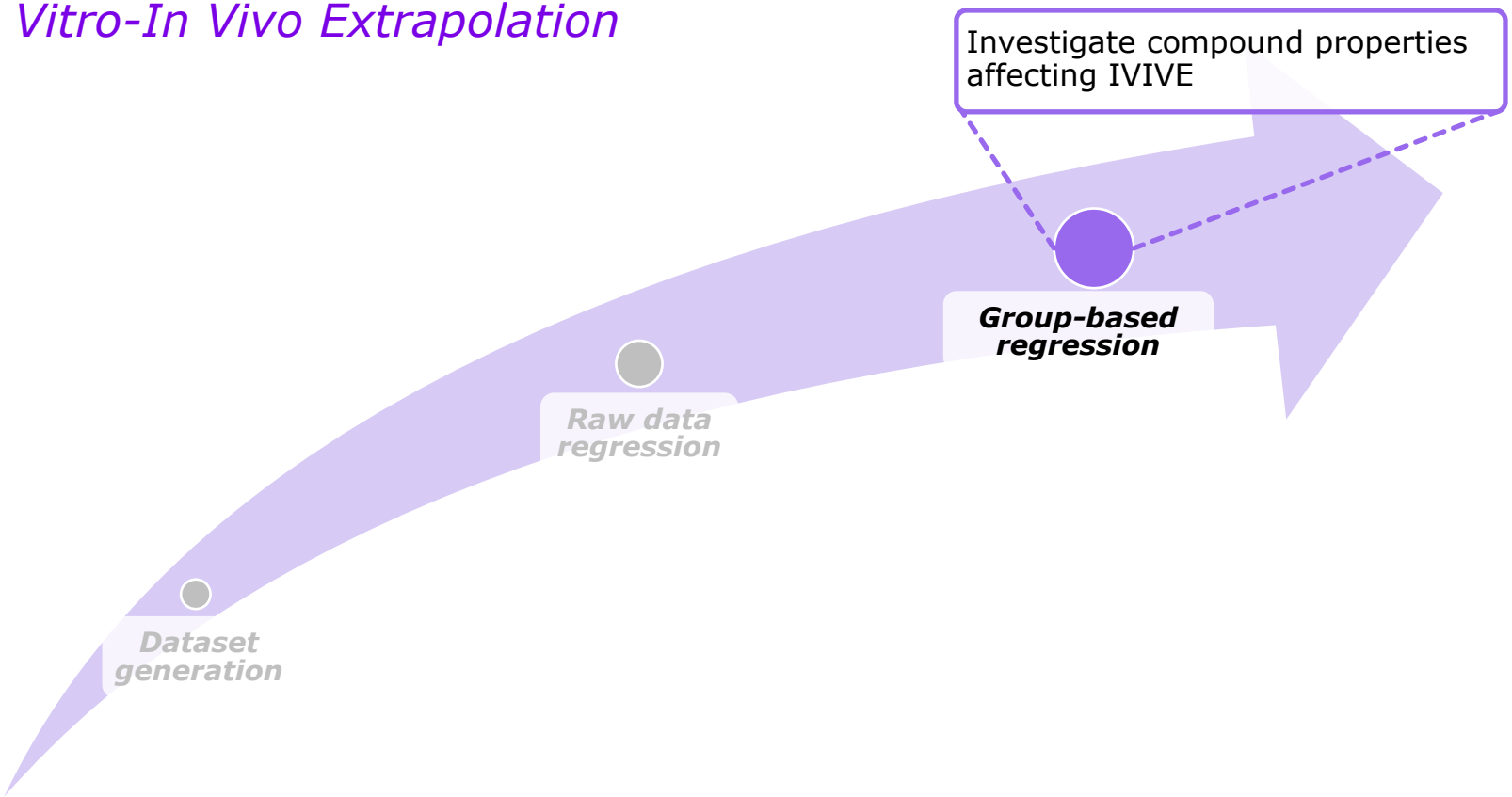
Status quo



Can we systematically assess "X"?

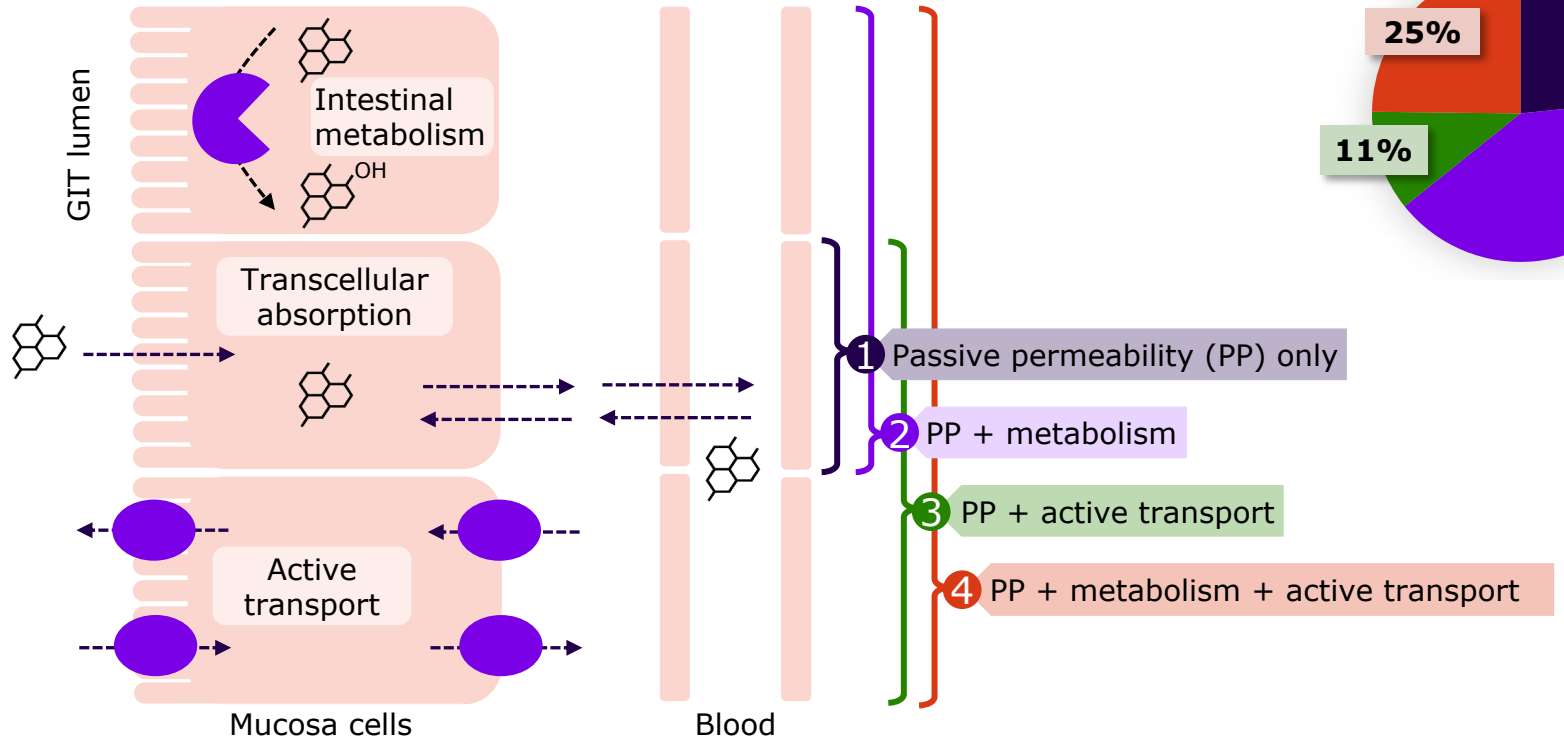
Intestinal absorption

In Vitro-In Vivo Extrapolation



Benchmark dataset

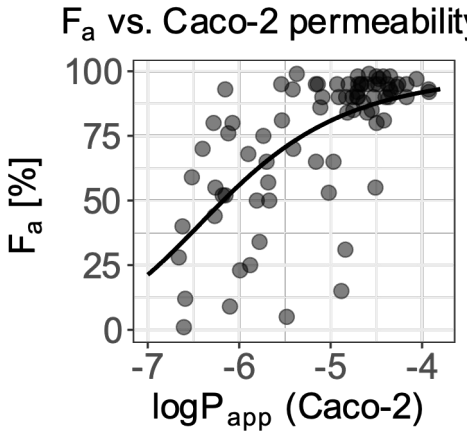
Compound assignment to four ADME-related groups

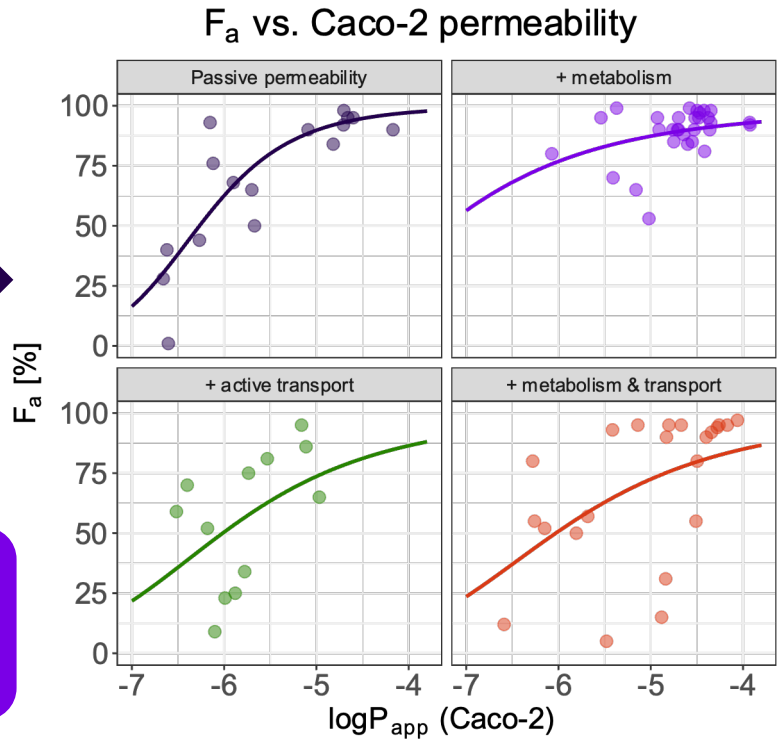


Distribution of ADME groups in dataset

Benchmark dataset

Compound assignment to four ADME-related groups





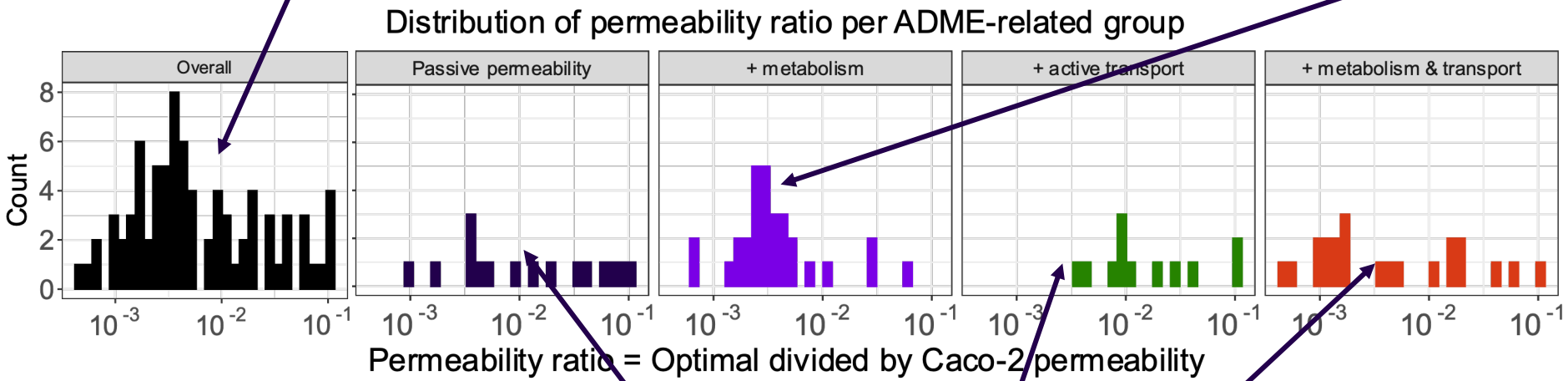
Knowledge about compound properties with respect to metabolism and active transport can help to improve prediction of fraction absorbed

In Vitro-In Vivo Extrapolation

Determination of an ADME-group specific correction factor

Same correction factor not appropriate for all compounds

Narrow distribution could indicate one correction value per group



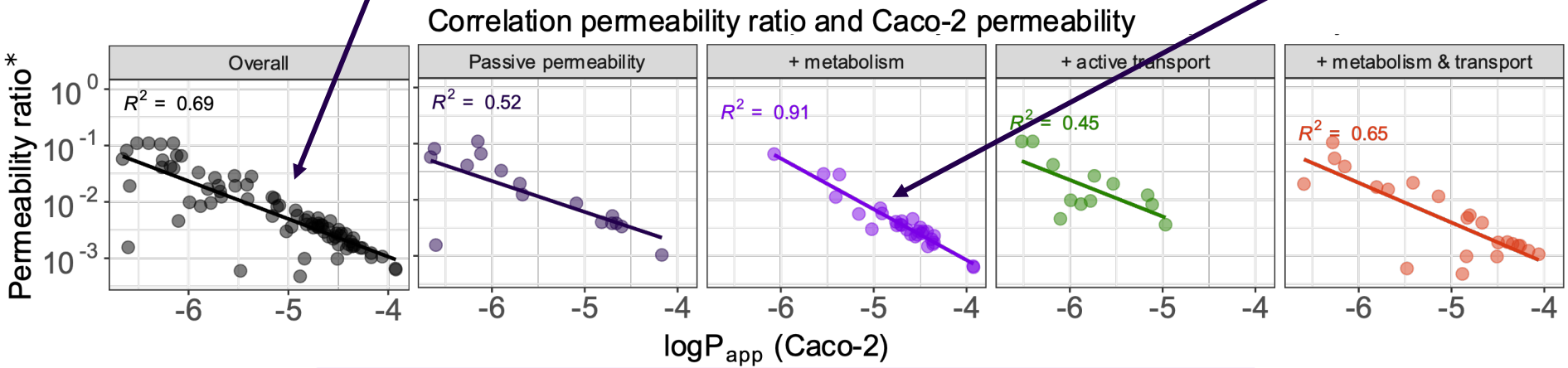
Flat distribution could indicate that rather a correction function than a correction value is appropriate

In Vitro-In Vivo Extrapolation

Determination of an ADME-group specific correction function

Overall larger gap between $P_{int,opt}$ and Caco-2 P_{app} identified for higher permeabile compounds

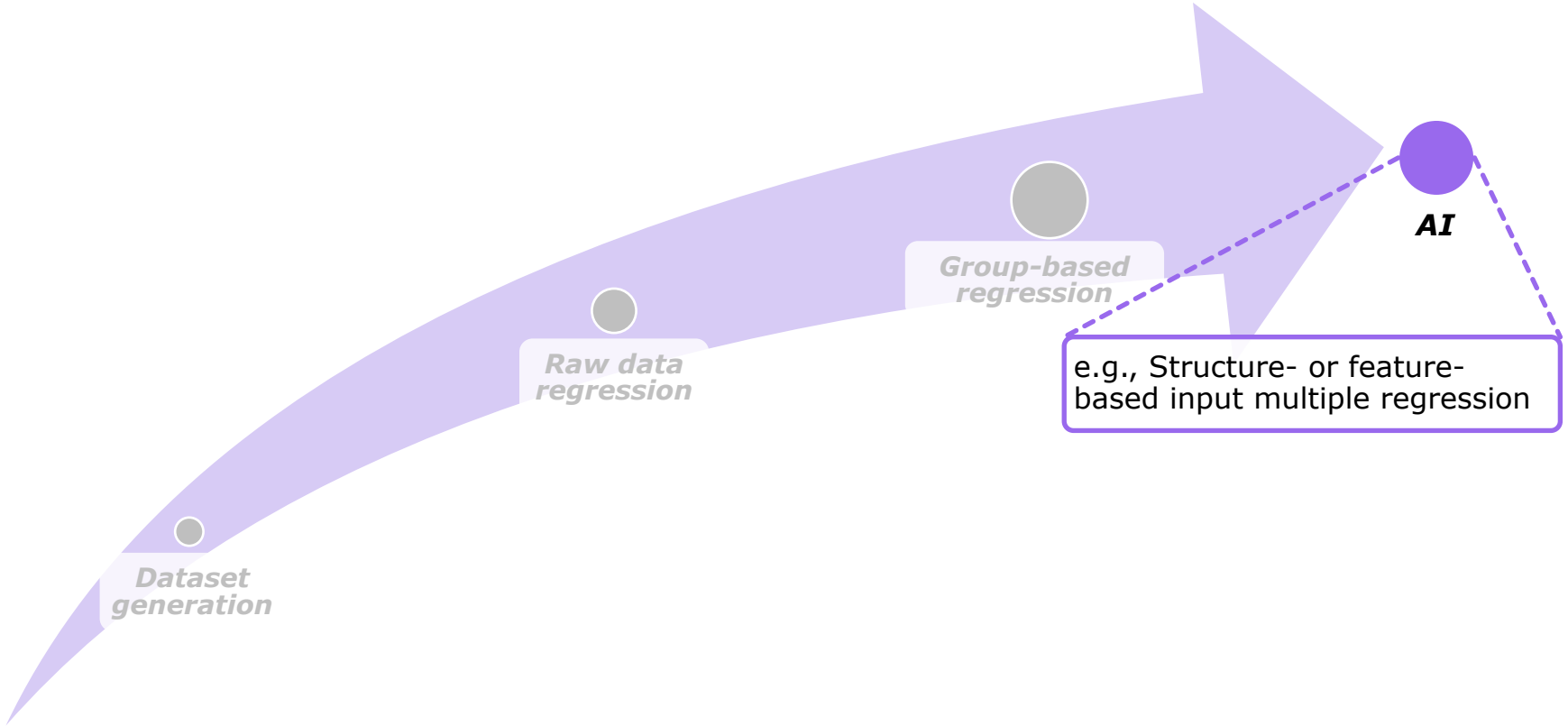
Best correlation for metabolized compounds



Improved P_int_trans and Caco-2 P_{app} correlation by incorporating function!

* Optimal divided by Caco-2 permeability

What comes next?



Prediction of human fraction absorbed from in vitro Caco-2 permeability – are we there yet?

Our analysis shows that **correction factors** and **functions** based on **active processes information** can **improve utilization of Caco-2 permeability** for IVIVE

How can we determine compound individual correction factors/functions?
- Can we integrate other DMPK assays to be more predictive?
- Can we systematically integrate non-linear ADME processes?
- Can we generate an optimal permeability with AI?

What does the OSP-Community think?

Acknowledgements

OSP Focus Group IVIVE

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sanofi

Thank you for your attention!