

A unified Rodgers et al model for predicting tissue partitioning reveals the need for a theoretical derivation of the Lukacova et al (Simulations Plus) model

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Motivation

The *a priori* prediction of tissue-to-plasma / tissue-to-plasma water partition coefficients (K_p / K_{pu}) is a core element of PBPK modelling.

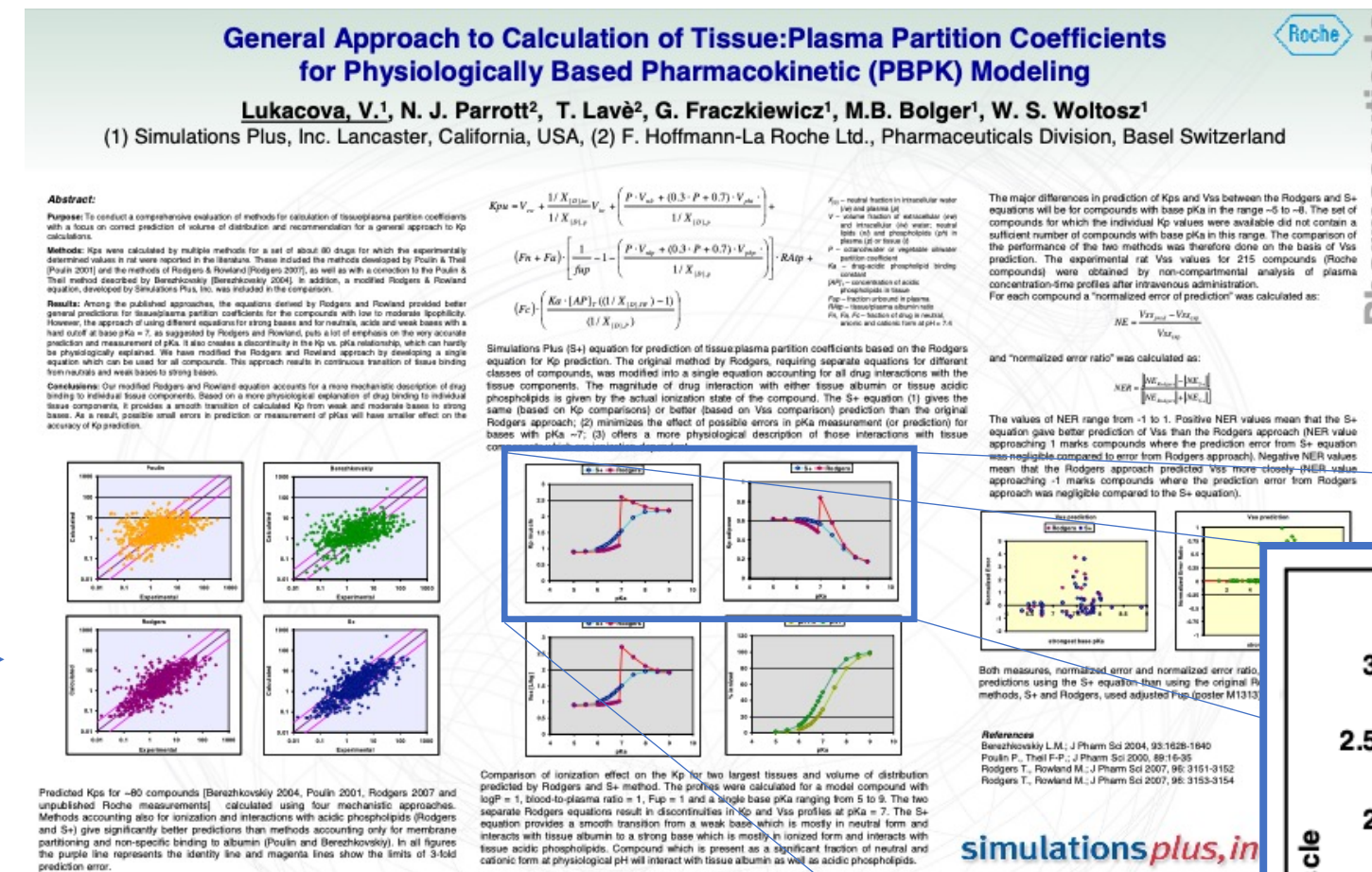
Approaches

Rodgers et al. [1]: moderate-to-strong bases (basic $pK_a > 7$)

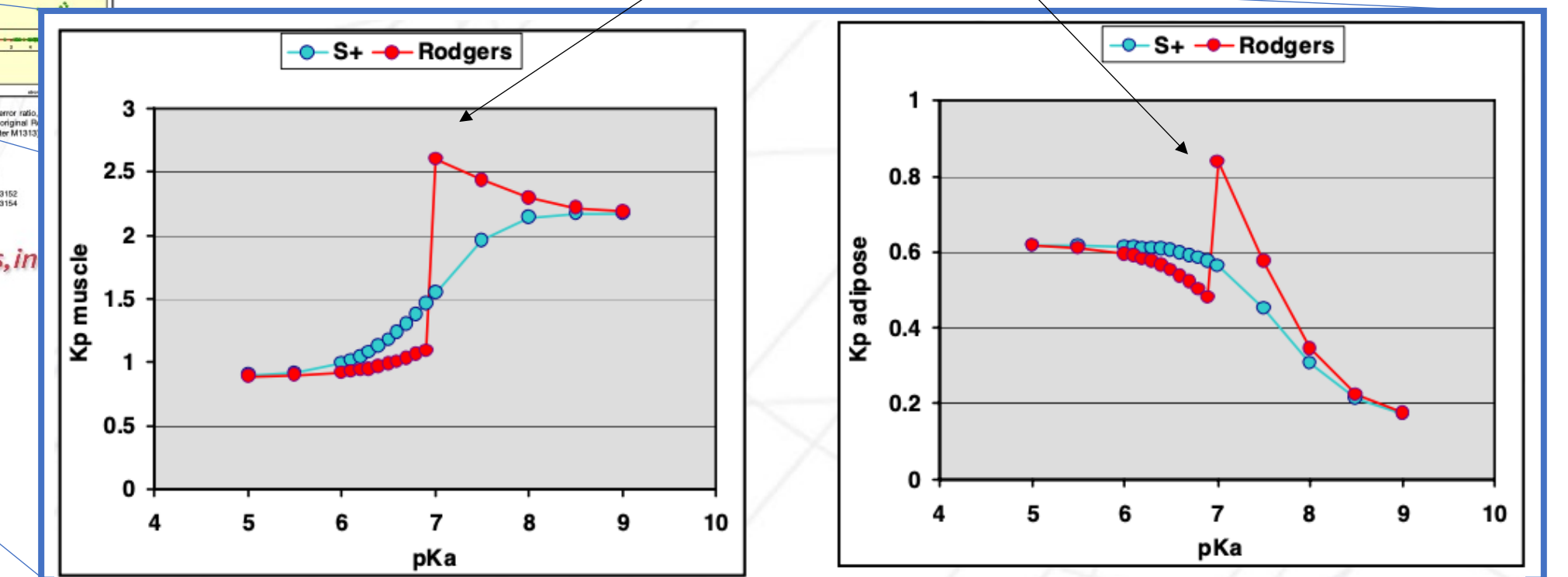
Rodgers/Rowland [2]: weak bases /other classes (no basic $pK_a > 7$)

Lukacova et al. [3]: all substance classes, but no theoretical justification
claim: mechanistic unification of Rodgers et al. models

Aim: derive a unified Rodgers et al. model based on solid theory



Seemingly undesirable discontinuity (Rodgers et al.) & desirable smoothing (S+, i.e. Lukacova et al.) at pK_a 7



Unified Rodgers et al. model

Assumptions: a potentially ionizable drug:

- is dissolved in extracellular (ew) and intracellular water (iw);
- distributes into neutral lipids (nl) and neutral phospholipids (np);
- binds to interstitial binding proteins (pr) in its neutral & anionic form (same association constant in plasma and interstitial space);
- binds to cellular acidic phospholipids (ap) in its cationic form (same association constant in red blood cells and cellular space)
- Plasma water volume equals total plasma volume

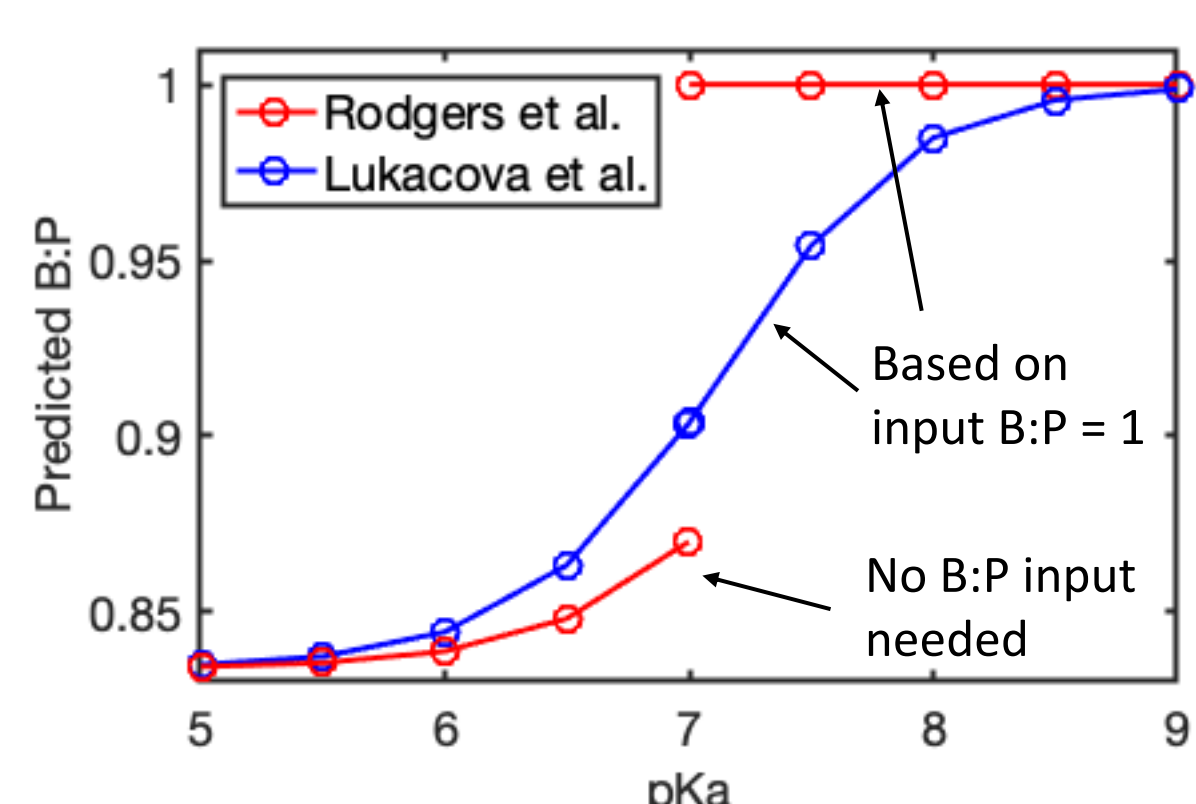
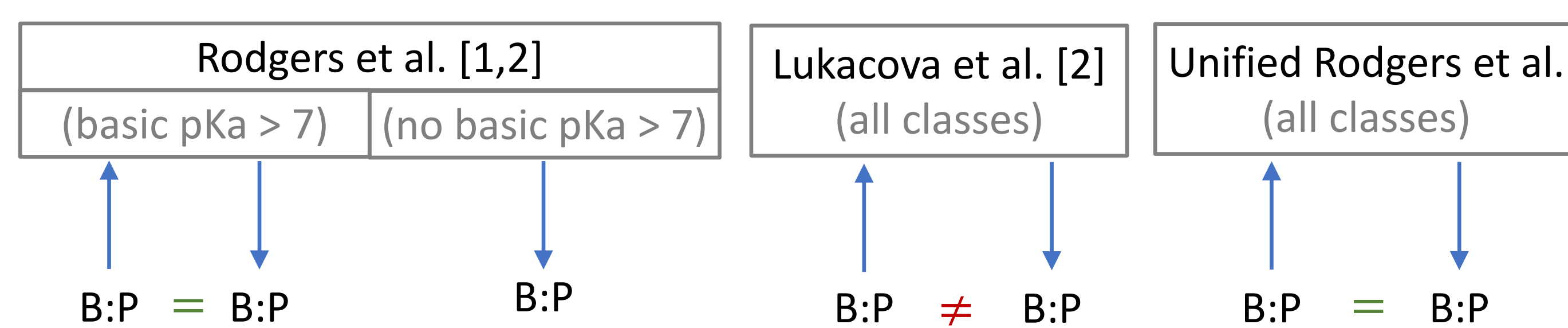
Unified Rodgers et al. and Lukacova et al. model equations differ

$$K_{pu} = \frac{V_{iw}}{V_{tis}} + \frac{V_{cw}}{V_{tis}} \cdot \frac{f_{nP}}{f_{nC}} + \frac{V_{nl,C}}{V_{tis}} P_{(v)o:w} \cdot f_{nC} + \frac{V_{np,C}}{V_{tis}} (0.3 P_{(v)o:w} + 0.7) \cdot f_{nC} + (f_{nP} + f_{aniP}) \left[\frac{1}{f_{uP}} - 1 - \frac{V_{nl,P}}{V_{pla}} P_{o:w} \cdot f_{nP} - \frac{V_{np,P}}{V_{pla}} (0.3 P_{o:w} + 0.7) \cdot f_{nP} \right] \cdot \frac{PR_{tis}}{PR_{pla}} + f_{catP} \cdot K_{A,AP} \cdot AP_{tis}^- \cdot \frac{(f_{aniC} + f_{catC}) \cdot f_{nP}}{f_{nC}}$$

In Lukacova et al., but not in unified Rodgers et al. model

V: volume
P/C: plasma/cellular space
fu/fn/fani/fcat: fraction unbound/neutral/anionic/cationic
P_{o:w}/P_{v:o:w}: octanol/vegetable oil:water partition coefficient
PR_{tis}/PR_{pla}: protein concentration in tissue/plasma
AP_{tis}/K_{A,AP}: concentration of/association constant to acidic phospholipids

Differences in B:P handling explain the Lukacova et al. poster figure

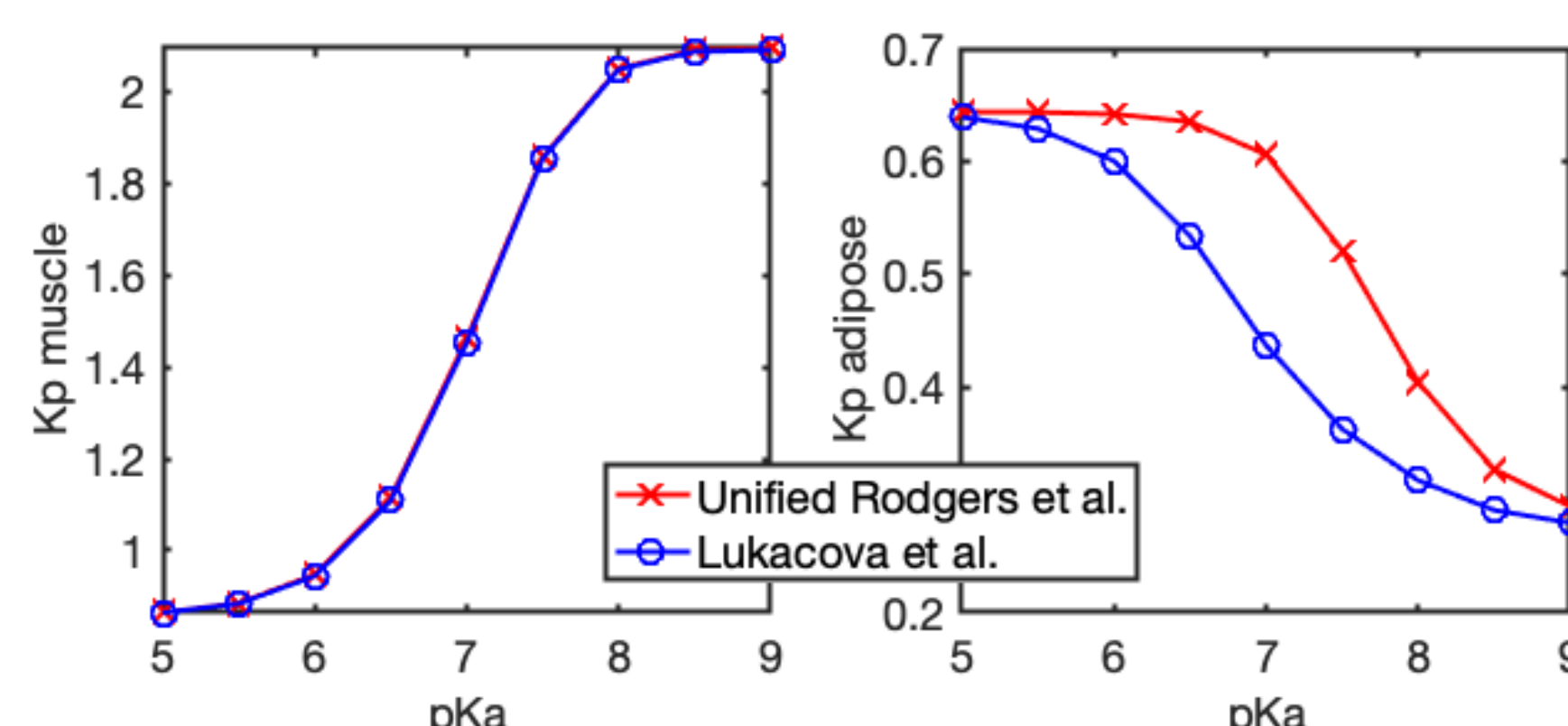


B:P inconsistency due to unphysiological interaction with acidic phospholipids

Jump in K_p for Rodgers et al. model is **expected** (assumptions on B:P differ on either side of $pK_a = 7$).

Rather than by introducing unphysiological terms, the jump is **resolved** by changing assumptions on B:P

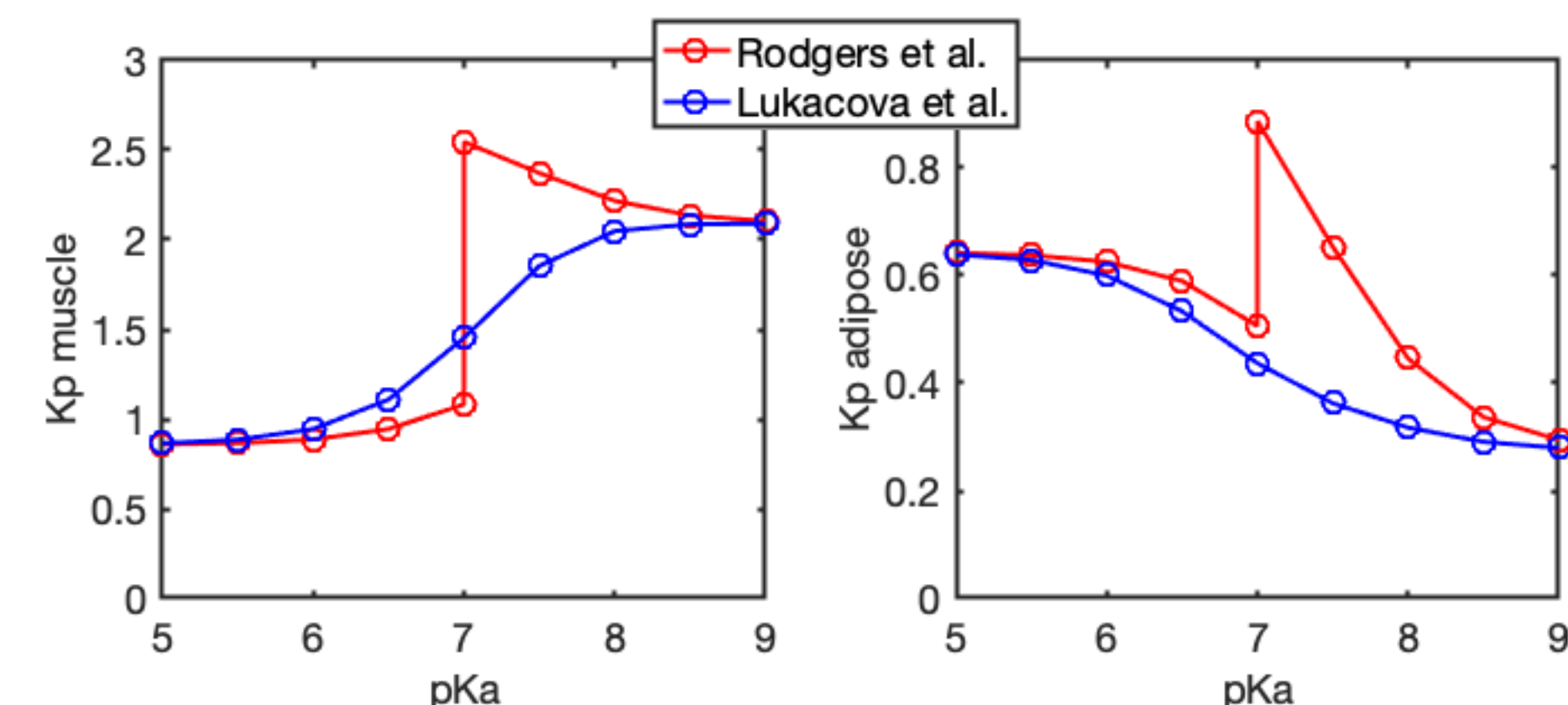
Using Lukacova et al. model-predicted B:P as input B:P in unified Rodgers et al. model



Reproducing results by Lukacova et al.

Assumptions for filling missing details of the Lukacova et al. equation:

- $K_{A,AP}$ was calculated as in the original Rodgers et al. model [1];
- $hct = 0.45$; $\log P_{v:o:w} = 1.115 \cdot \log P_{o:w} - 1.35$ (both taken from [4])



Input:

- $f_{uP} = 1$
- $B:P = 1$
- $\log P = 1$
- single basic pK_a

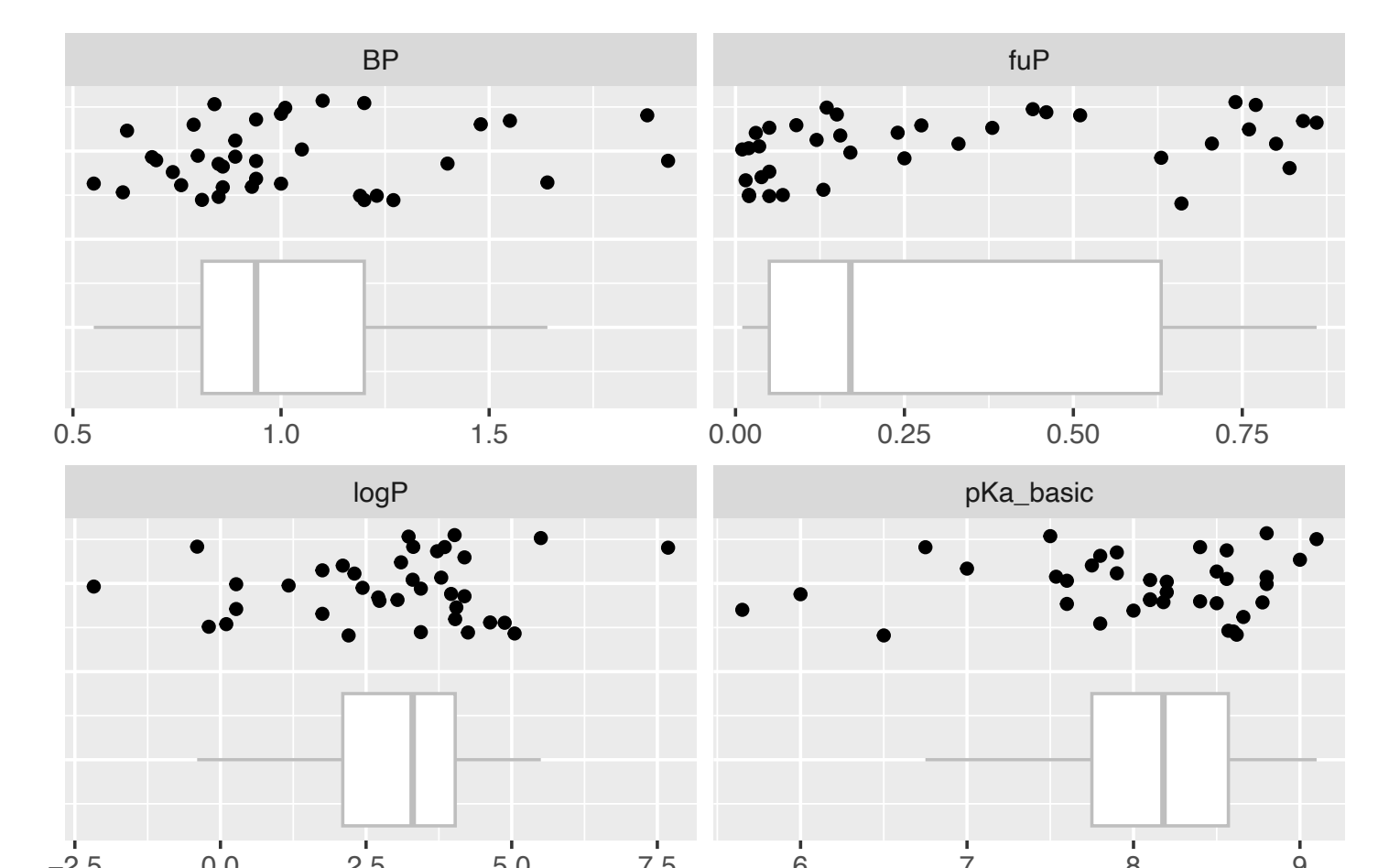
→ good agreement with Lukacova et al. poster in muscle, slight discrepancy for adipose

Data analysis

K_p predictions by Lukacova et al. were not thoroughly evaluated in the critical region (basic pK_a between 5 and 9). We fill this gap through a literature-based data analysis.

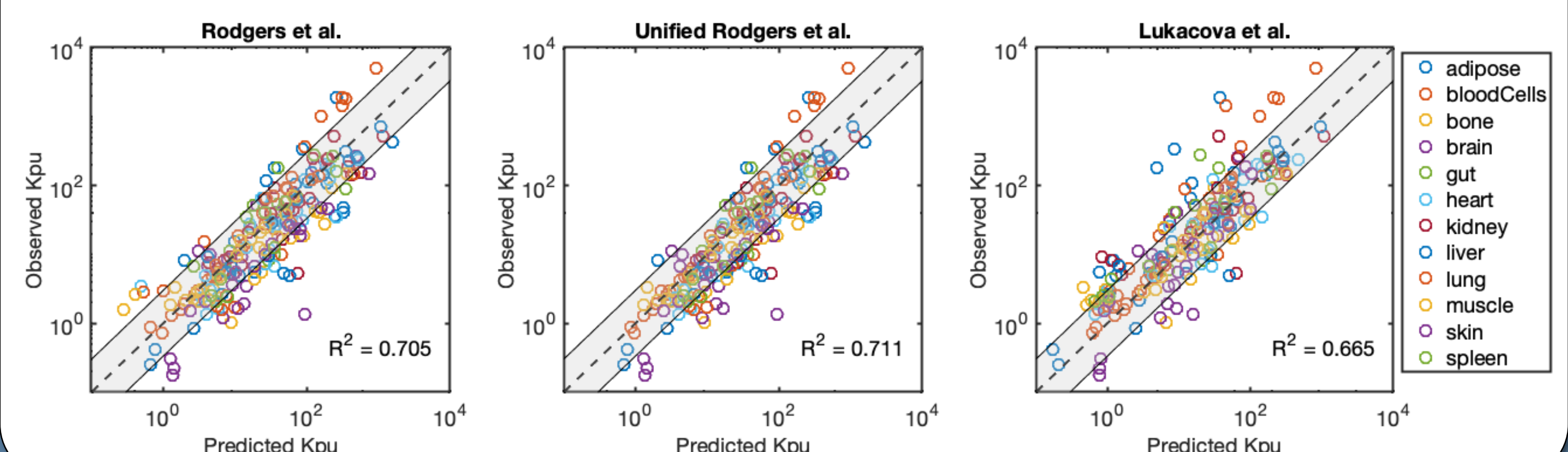
Dataset compilation [1,2,5-8]

- 37 compounds with most basic pK_a between 5 and 9
- f_{uP} , B:P measurements in rats available
- (K_p converted to $K_{pu} = K_p/f_{uP}$)
- 260 K_{pu} values in 12 tissues



Model comparison

- Successful predictions for 29/37 compounds



Conclusion

- A **theoretically sound** unified Rodgers et al. model was derived
- **Inconsistencies** in the Lukacova et al. model were detected
- The unified Rodgers et al. model showed a **better data fit** for a test set of 37 moderately-to-strong bases than the Lukacova et al. model

References

- [1] Rodgers et al., J Pharm Sci (2005) 94: 1259–1276
- [2] Rodgers & Rowland, J Pharm Sci (2006) 95: 1238–1257
- [3] Lukacova et al., AAPS conference poster (2008), https://www.simulations-plus.com/wp-content/uploads/Lukacova-General_Approach_Calc_Tissue_Plasma_Partition_Coefficients_PBPK_Modeling-AAPS-2008-1.pdf

- [4] Poulin & Theil, J Pharm Sci (2002) 91:129–156
- [5] Uchimura et al., Biopharm Drug Dispos (2010) 31: 286–297
- [6] Graham et al., J Pharm Pharmacol (2016) 64: 383–396
- [7] Chan et al., Pharm Res (2018) 35: 87
- [8] Pearce et al., J Pharmacokinet Pharmacodyn (2017) 44:549–565

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