# Prediction in silico of major clearance pathway of drugs in vivo

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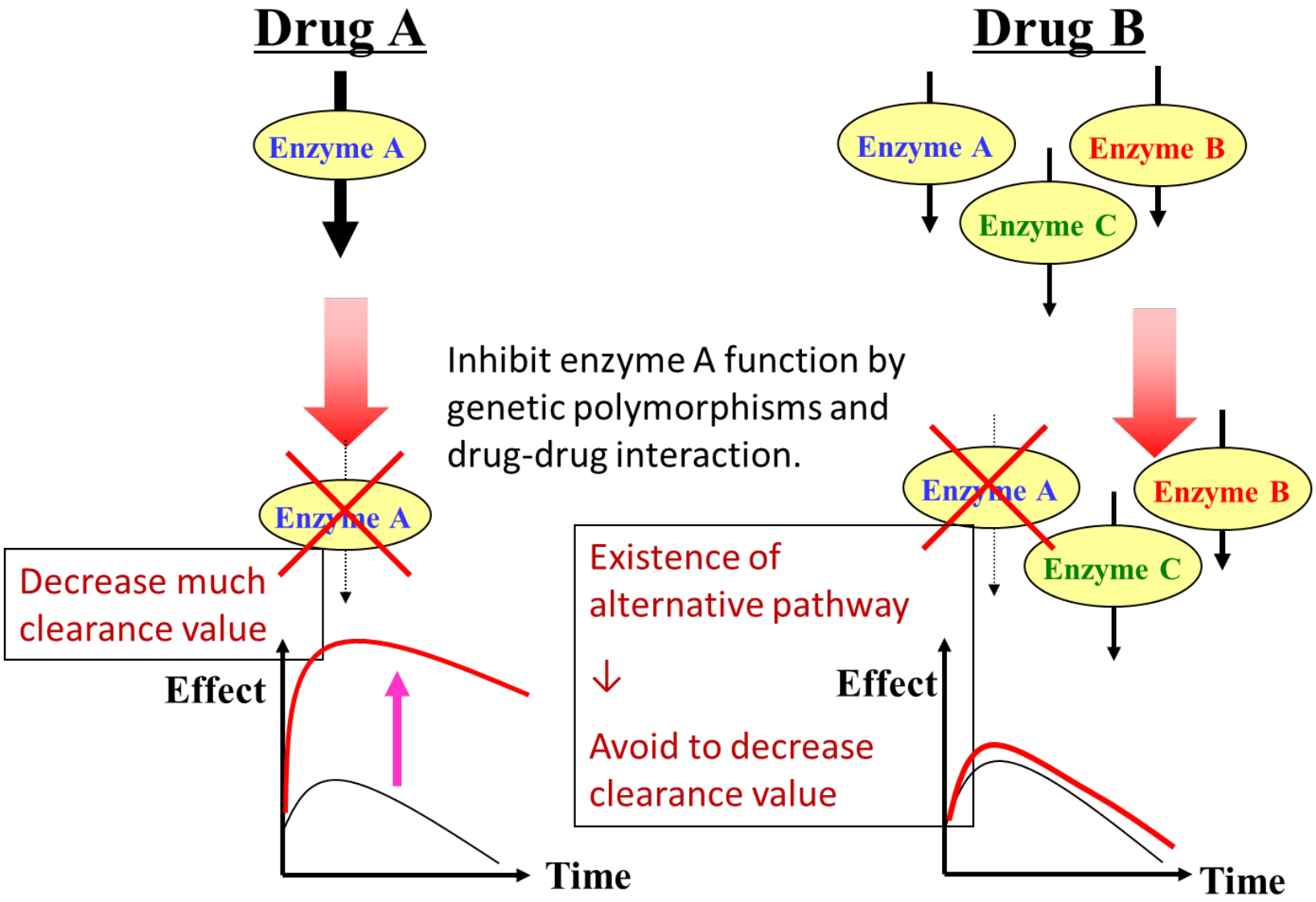
# Importance of predicting drug clearance pathways

Selection of multiple clearance pathways drug



# Problem for the prediction of drug clearance pathway

- Drug clearance pathway is not determined only by the information whether drug is a substrate for each enzyme and transporter!

**Drug X**

Substrate of metabolic enzyme A, B, and C by in vitro experiment.

**What is the in vivo major clearance pathway?**

Requirement of in silico prediction

- Contribution ratio (e.g. RAF method).
- Prediction of urinary excretion ratio.
- Involvement of hepatic uptake transporters

**- Prediction whether drug is metabolized for each enzyme.**

**- Quantitative estimation of intrinsic clearance for each enzyme.**

**- Quantitative estimation of renal clearance.**

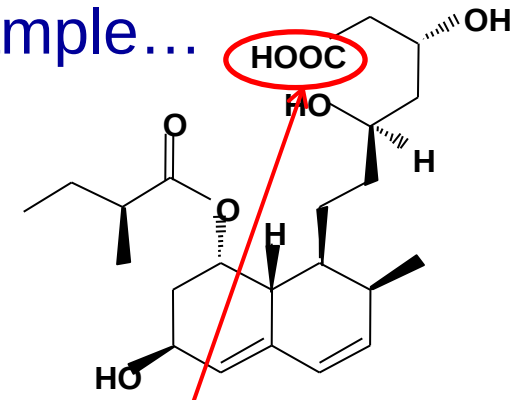
**- Prediction whether drug is substrate for each uptake transporter.**

**Too complex and difficult!!**

# Intuitive prediction of drug clearance pathway

Experts of pharmacokinetics can roughly predict the clearance pathways of drugs only by looking at their structures.

Example…



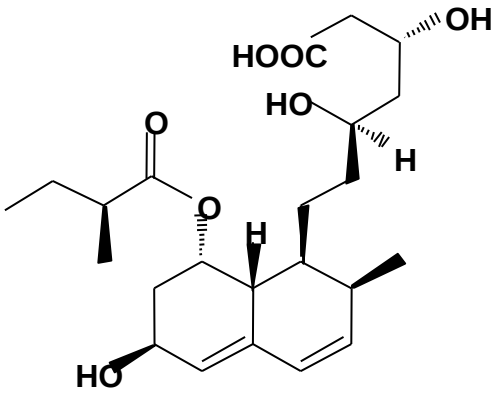

Substrate of OATPs…?

We suppose that experts predict the clearance pathways of drugs using a certain characteristic (feature) which represents drug chemical structure

Charge: anion → a substrate of OATPs?

Lipophilicity:
low → renal excretion?
high → high permeability?

# Strategy of drug clearance pathway prediction




Chemical Structure

Calculate 4 descriptors (default descriptors)

- MW (molecular weight; published data)
- log D (lipophilicity; SciFinder)
- fup (unbound fraction; ADME boxes)
- Charge at PH7.0 (ADMET predictor)

**Classification system**

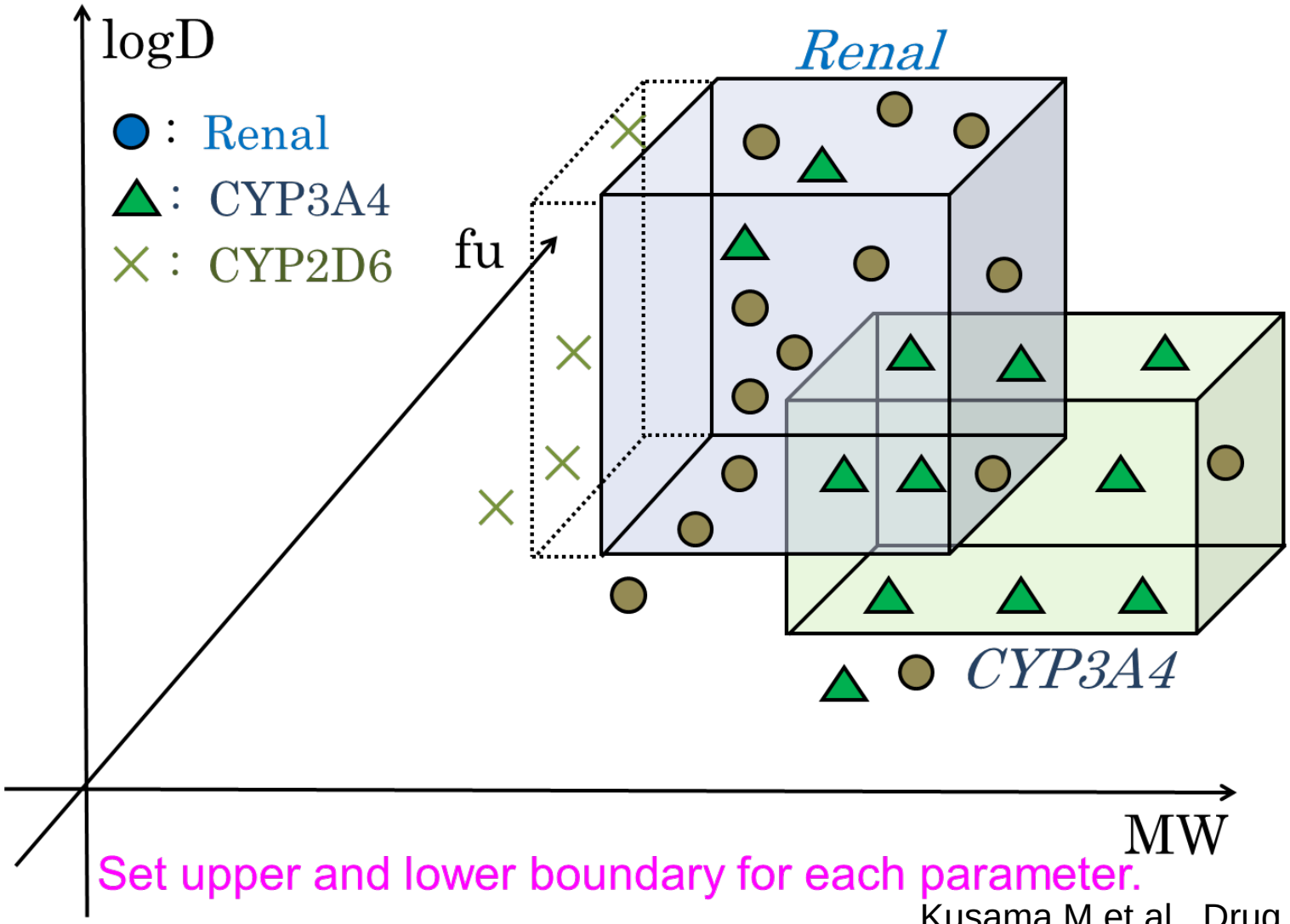
? ?

CYP3A4 | CYP2D6 | CYP2C9 | OATPs | Renal

**Establishment of in silico prediction system of major drug clearance pathway using 4 chemical descriptors.**

# CPathPred ver. 1 (Empirical approach)

## Rectangular Method

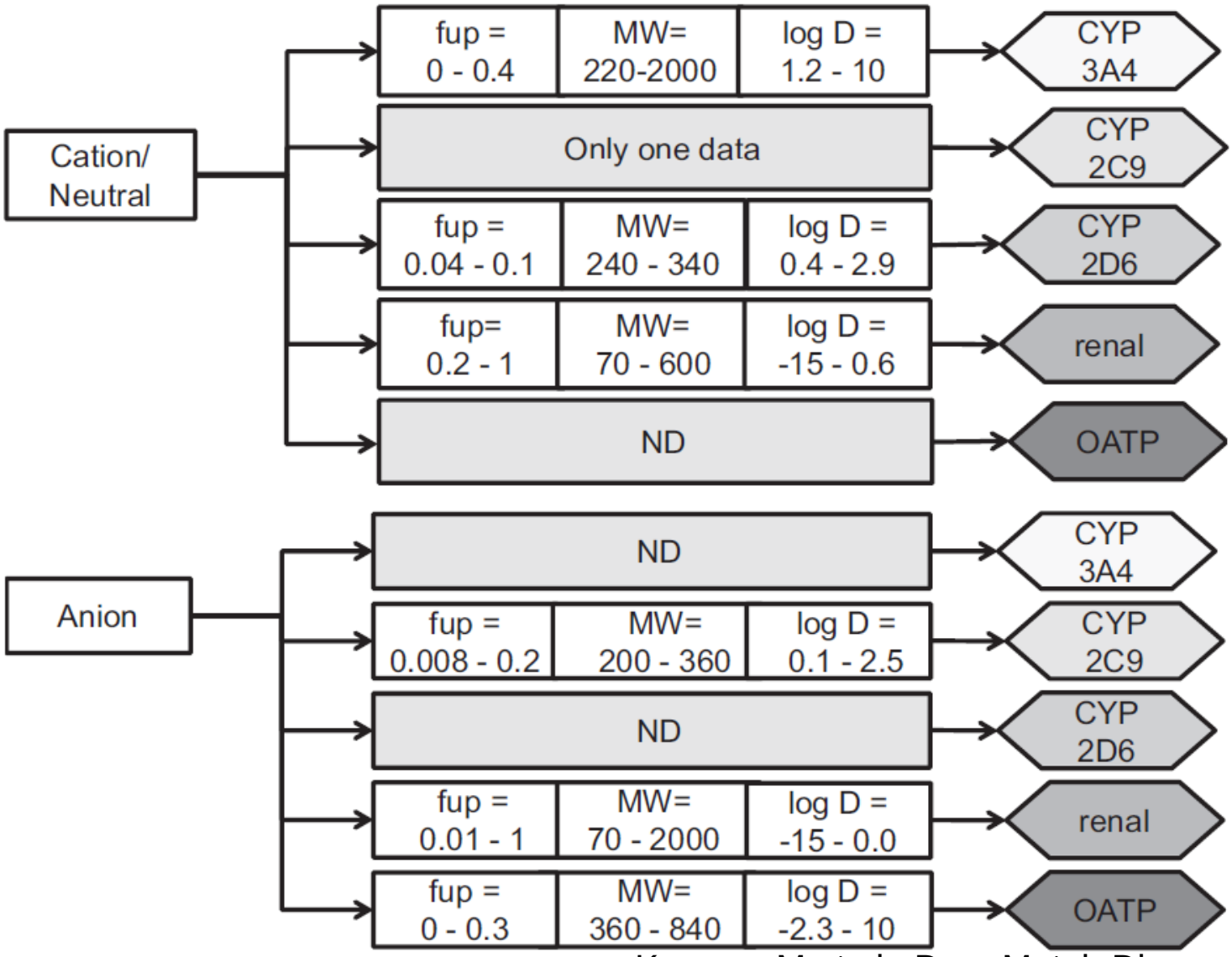



Set upper and lower boundary for each parameter.

Kusama M et al., Drug Metab Dispos, 38, 1362-70 (2010)

# CPathPred ver. 1 (Empirical approach)

## Classification boundaries

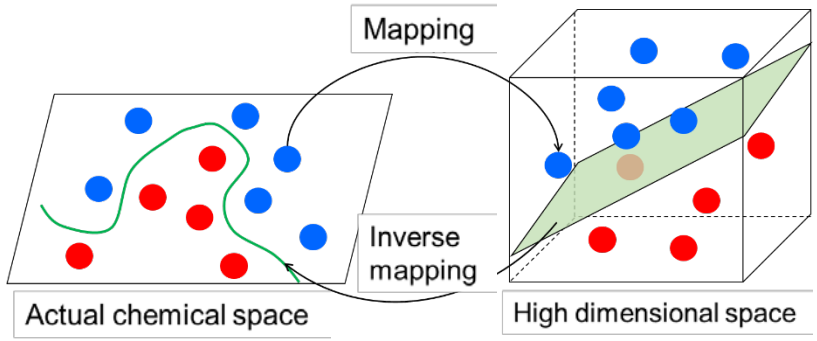


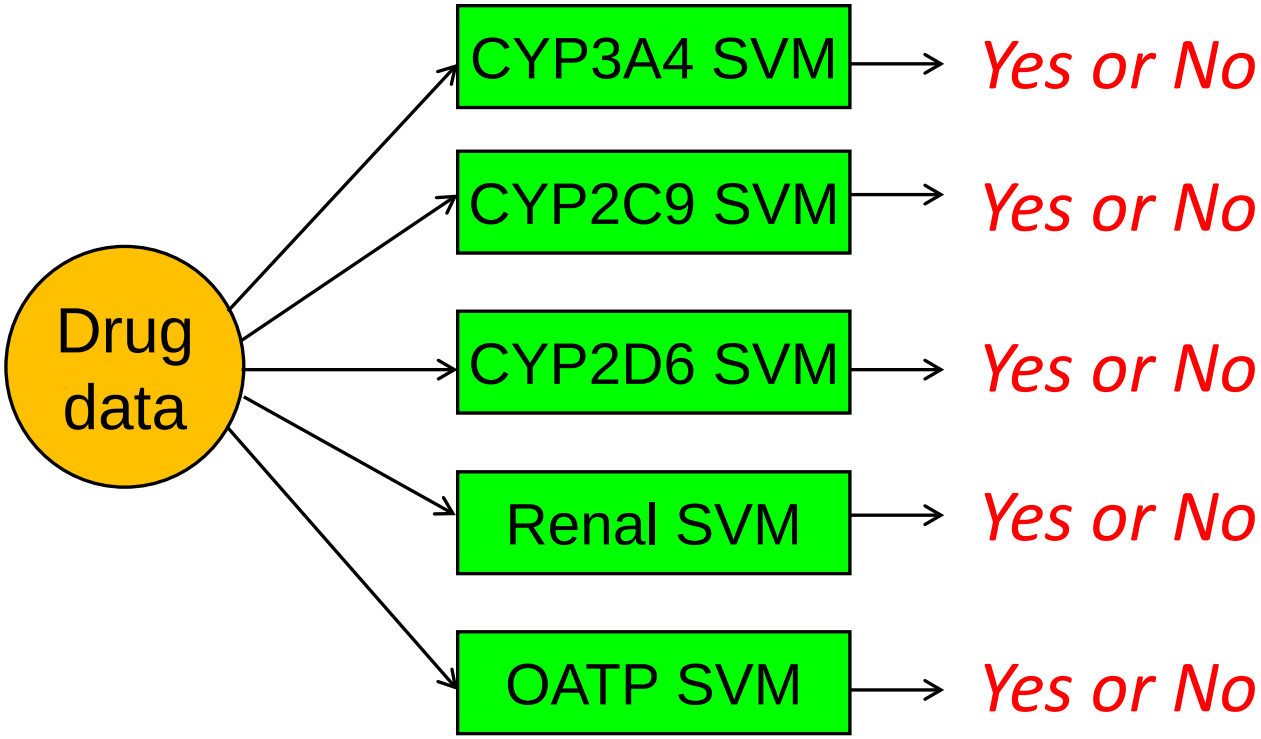

Kusama M et al., Drug Metab Dispos, 38, 1362-70 (2010)

# CPathPred ver. 2 (Machine learning technique)

## Support Vector Machine (SVM)

The major shallow machine learning technique.
Create the complex classification boundaries.




**Each SVM perform the prediction independently.**

Toshimoto K et al., Drug Metab Dispos, 42, 1811-9 (2014)

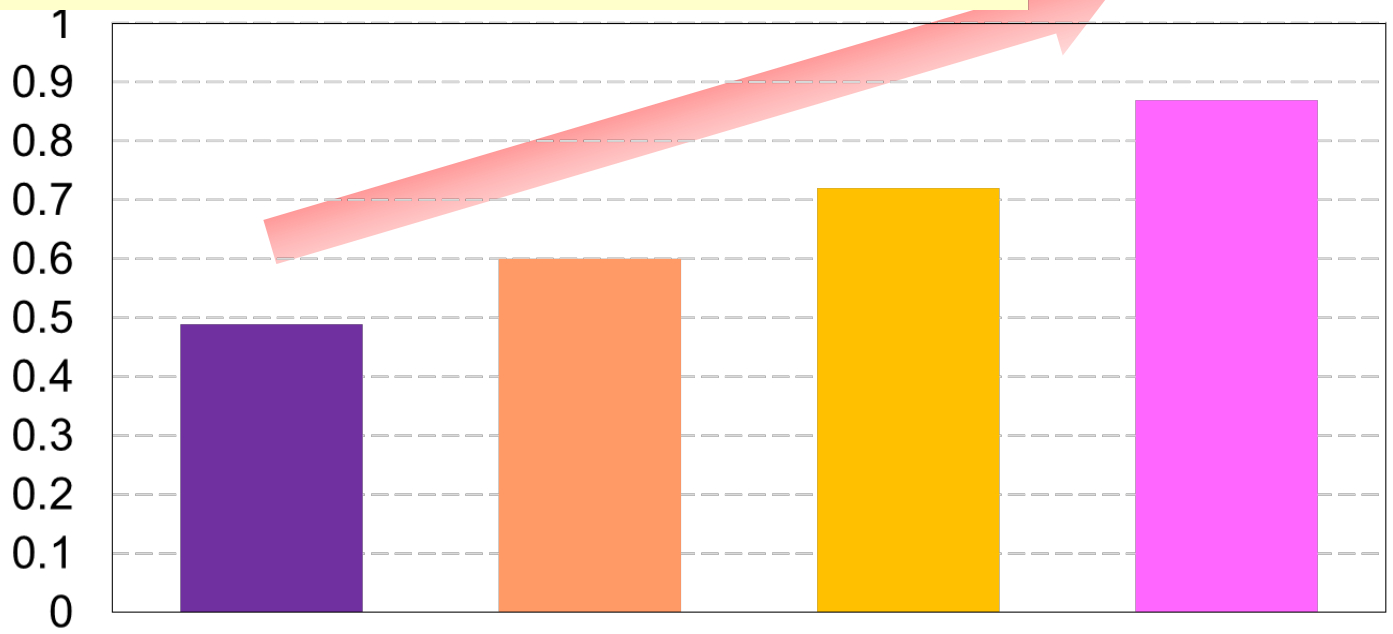
# Prediction performance

## f-measure

TP: true positive, FP: false positive
FN: false negative

$$\text{Recall} = \frac{\text{TP}}{\text{TP} + \text{FN}} \qquad \text{Precision} = \frac{\text{TP}}{\text{TP} + \text{FP}}$$

$$f - measure = \frac{2 * recall * precision}{recall + precision}$$

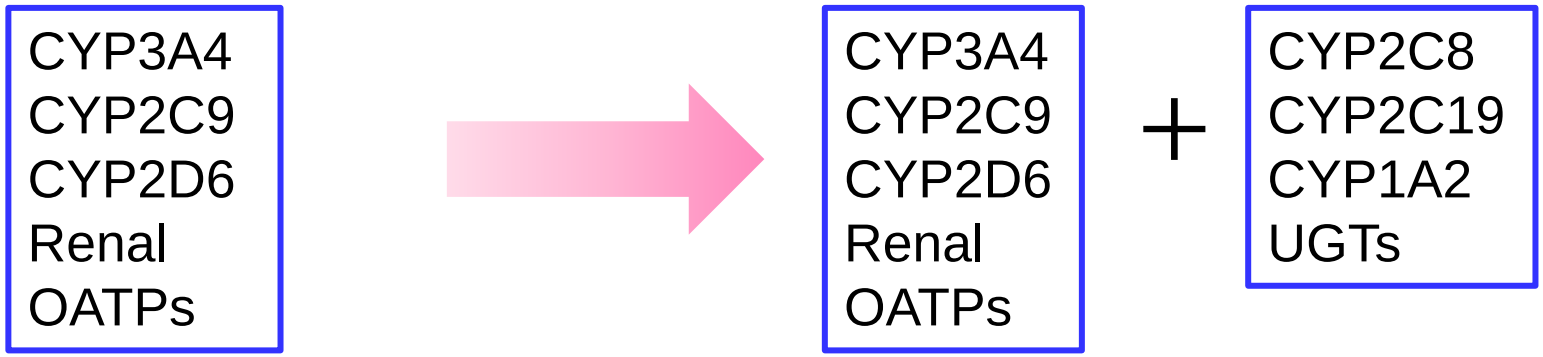



**No. additional descriptor**

CYP3A4: 4
CYP2D6: 3
CYP2C9: 2
Renal: 4
OATP: 2

# Our project (CPathPred 3)

## (1) Expansion of clearance pathway (5→9).




## (2) Multiple clearance pathways prediction.

Predict the most major clearance pathway (avoid the drugs which have multiple clearance pathway in the training dataset).

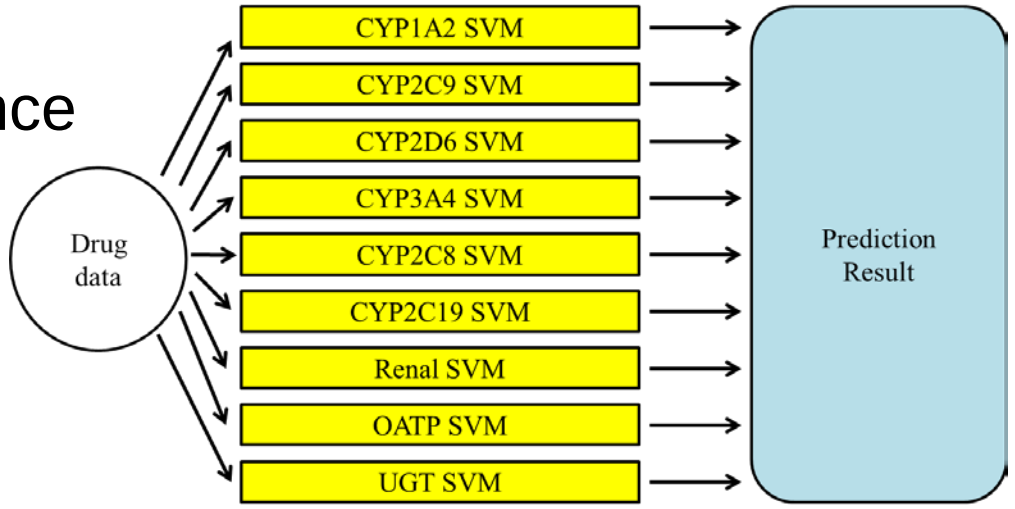
→

Predict multiple clearance pathways (>25% of systemic clearance).

# Two-step SVM approach

## Single-step SVM

Use one SVM per one clearance pathway



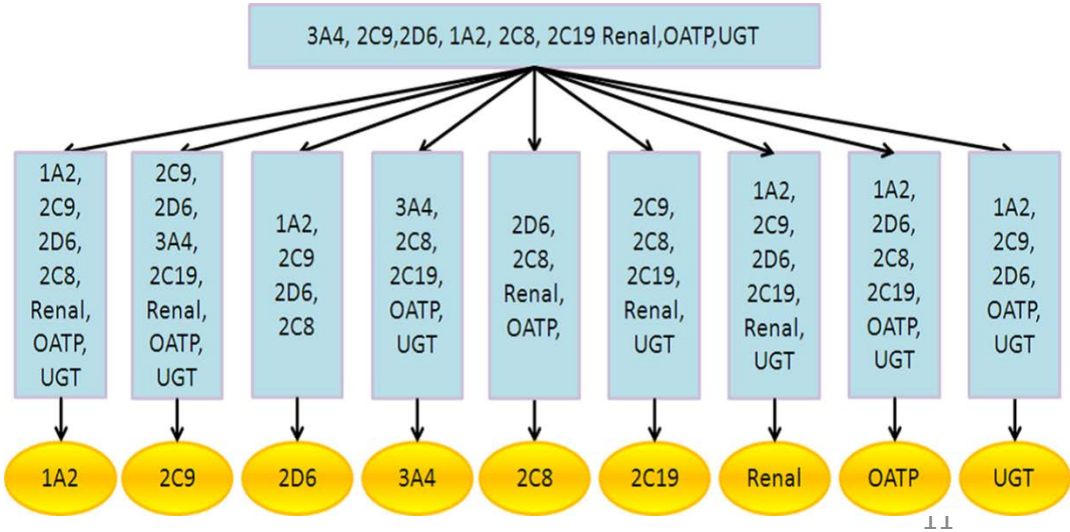

*Better predictability*

## Two-step SVM

Use two SVMs per one clearance pathway

1st SVM: predict clearance pathway roughly.

2nd SVM: predict a single target clearance pathway.



# Short summary

- The purpose of this research is to expand the number of clearance pathways (from 5 to 9, with metabolism by CYP1A2, CYP2C8, CYP2C19, or UGTs newly added) and to evaluate the prediction performance of this system.

<u>Plan and methods</u>

1. Establishment of a prediction system for 9 major clearance pathways
2. Evaluation of the prediction performance