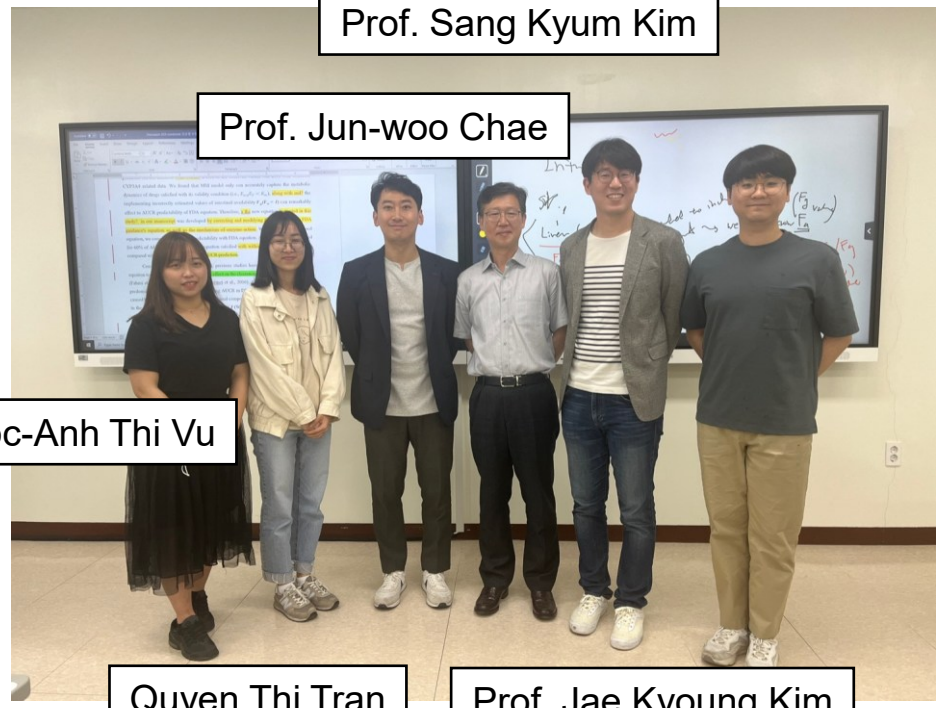
Beyond FDA Guidance: Enhancing Accuracy in Predicting Drug-Drug Interactions



Prof. Hwi-yeol Yun

Hyeong Jun Jang

PAGK Annual Meeting

24.12.18.

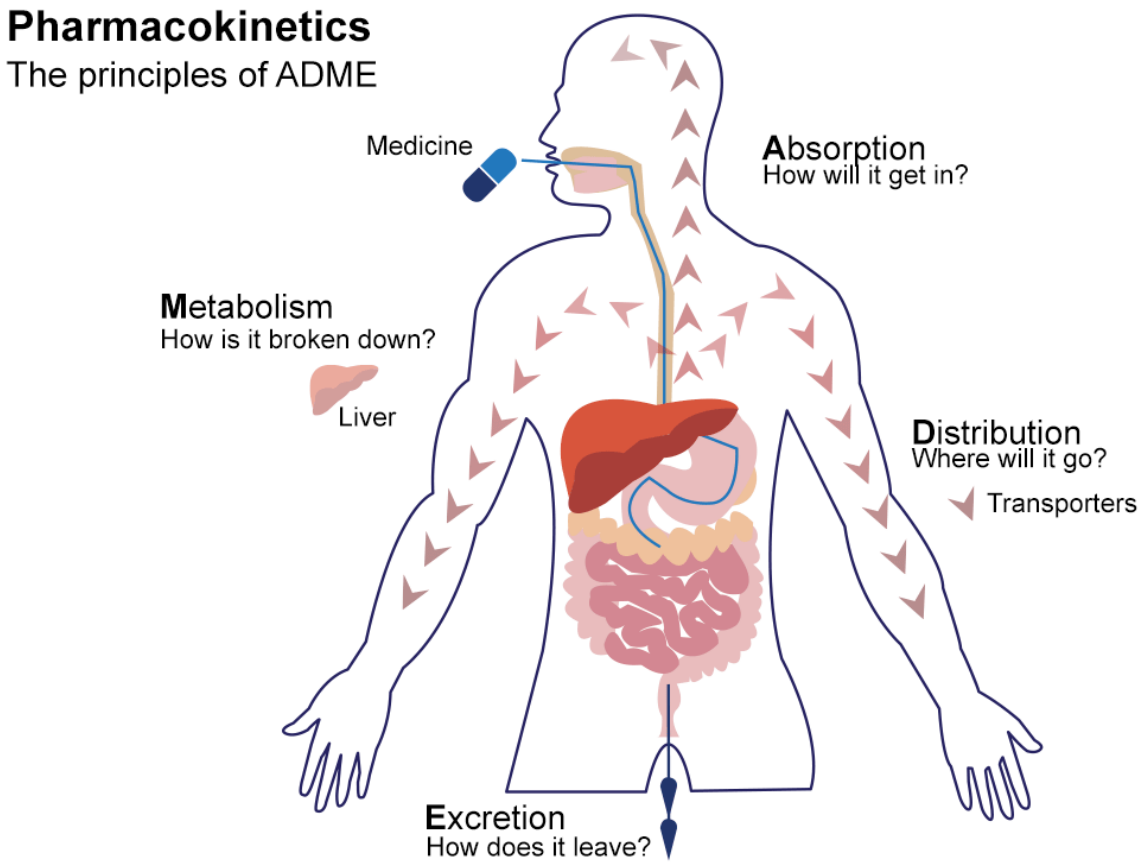
KAIST Korea Advanced Institute of Science and Technology

ibs Biomedical Mathematics Group 의생명수학그룹

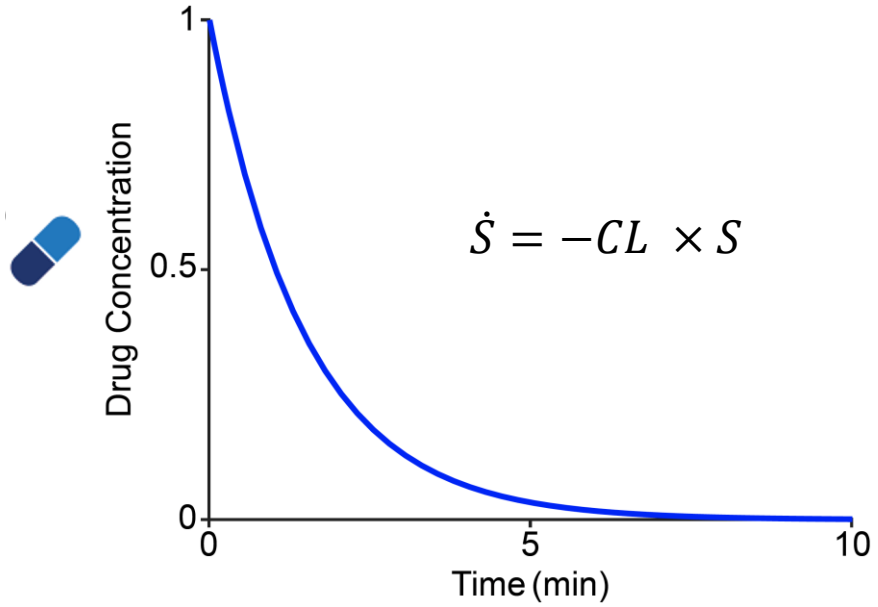
Yun Min Song

Ph.D.

Drug Clearance (CL) is the primary PK parameter for predicting drug disposition



https://toolbox.eupati.eu/glossary/pharmacokinetics/



More than 65,000 publications have appeared in the scientific literature addressing drug clearance as used in pharmacokinetics, with a significant number of these articles evaluating the appropriate model to be used to describe organ elimination of drugs. The great majority of these articles address hepatic elimination, utilizing predominantly what is called the well-stirred model.[1,2]

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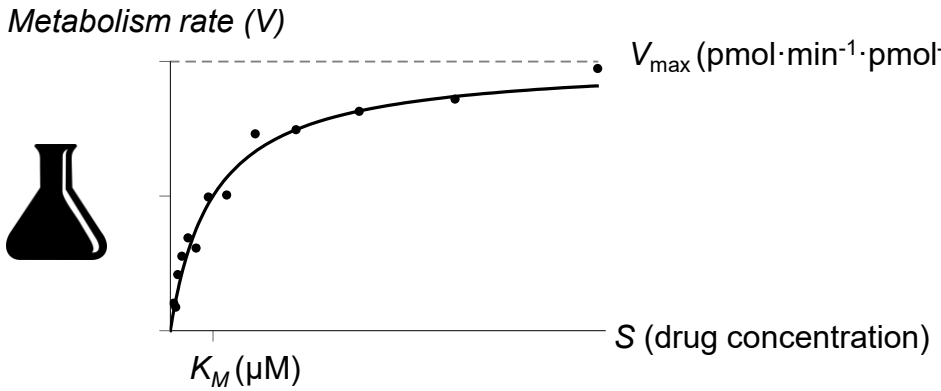
CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 103 NUMBER 3 | MARCH 2018

In-vivo hepatic CL (CL_h) is predicted by extrapolating in-vitro CL



Metabolism rate is described by
Michaelis-Menten (MM) Equation

$$V = \frac{V_{max} E_T S}{K_M + S} \approx \frac{V_{max} E_T S}{K_M} = CL_{int}^{vitro} E_T S$$

$$CL_{int}^{vitro} = \frac{V_{max}}{K_M}$$

Is MM equation always valid?

$\tilde{E}_T$ = hepatic CYP abundance

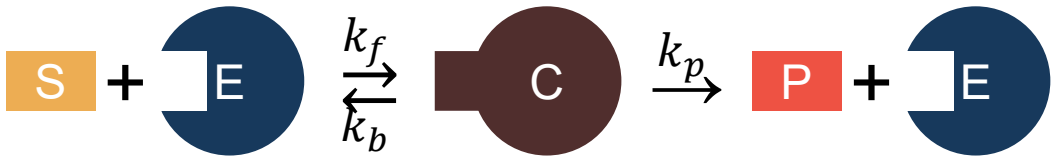
$$CL_{int}^{liver} = CL_{int}^{vitro} \tilde{E}_T$$

$$CL_h = f(CL_{int}^{liver})$$

f = liver model

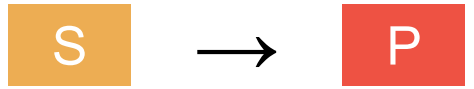
$$\frac{Q_h \cdot f_{u-blood} \cdot \frac{CL_{int}^{liver}}{f_{u-mic}}}{Q_h + f_{u-blood} \cdot \frac{CL_{int}^{liver}}{f_{u-mic}}}$$

MM equation can be inaccurate when enzyme concentration is high



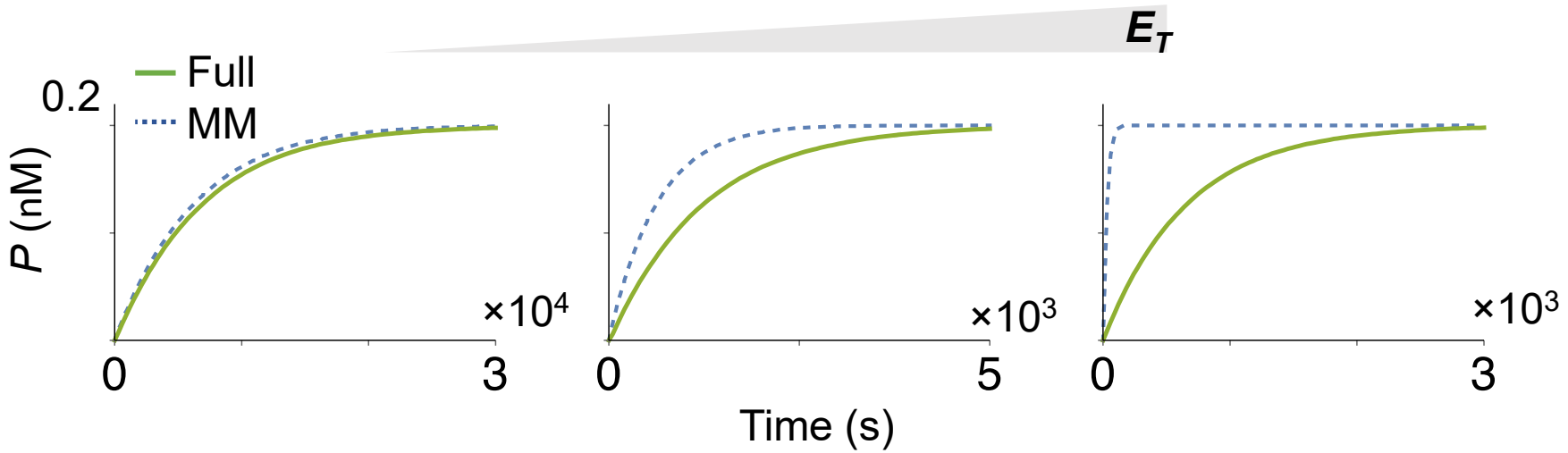
$$K_M = \frac{k_b + k_p}{k_f}$$

$$E_T = E + C$$



$$\dot{P} = \frac{k_p E_T S}{K_M + S}$$

Mathematically valid only when $E_T \ll K_m + S_0$ $\quad \frac{E_T}{K_M} < 0.1$



$pM \sim nM$ CYP < K_M is used.

$$\left(\frac{E_T}{K_M} < 0.1\right)$$

How about liver?

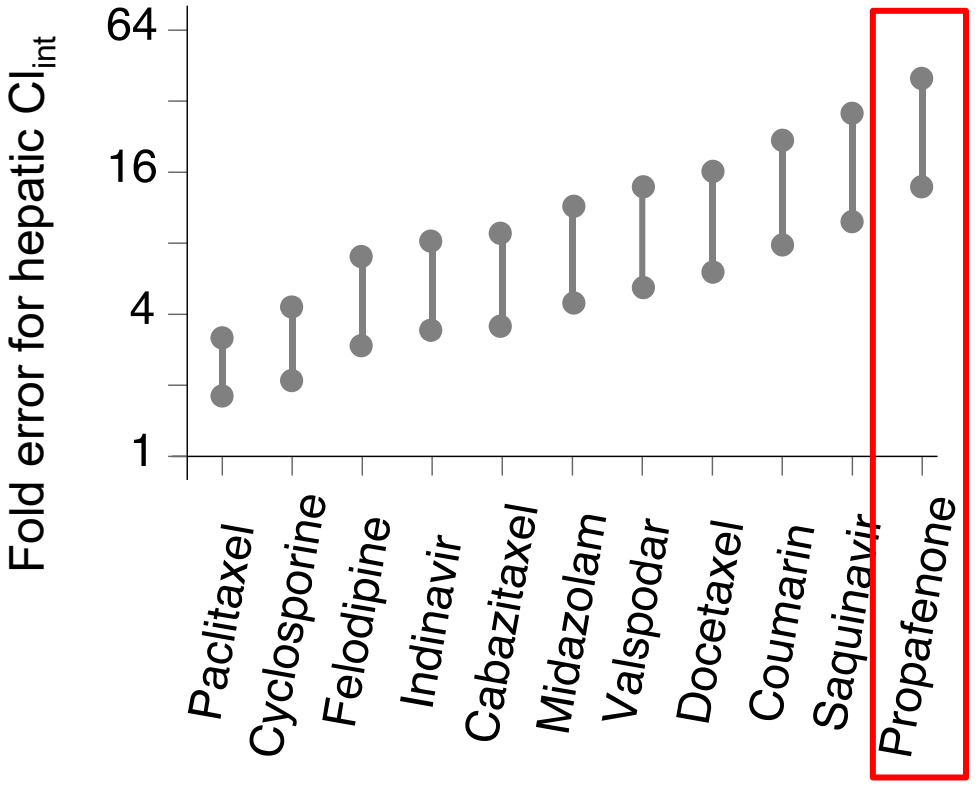
Choi BS, Rempala G, Kim JK, Beyond Michaels-Menten equations: unbiased estimation of enzyme kinetics, Scientific Report (2017)

Many drugs with low K_M does not satisfy the condition ($\frac{E_T}{K_M} < 0.1$)

[1]Drugs	[2]K_m (μM)	[3]E_T (μM)
Coumarin	0.75	1.03 ~ 3.10[a,b]
Paclitaxel	5.5	0.90 ~ 2.37[b,c]
Propafenone	0.12	0.31 ~ 0.95[a,c]
Midazolam	1.6	1.10 ~ 3.33[a,c]
Indinavir	2.3	
Cyclosporine	5	
Saquinavir	0.61	
Cabazitaxel	2.1	
Docetaxel	1.1	
Valspodar	1.3	
Felodipine	2.81	

$\frac{E_T}{K_M} \approx 2.5833 \sim 7.9167$

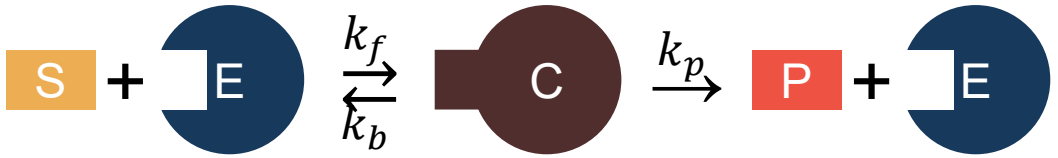
Considerable Error



We need a better equation!

Baik H, Yoon H, Kim S, Kim JK, Prediction of in vivo clearance for drug with low K_M , CTS (2020)

The new equation (tQSSA) is accurate for any condition



$$K_M = \frac{k_b + k_p}{k_f}$$

$$E_T = E + C$$

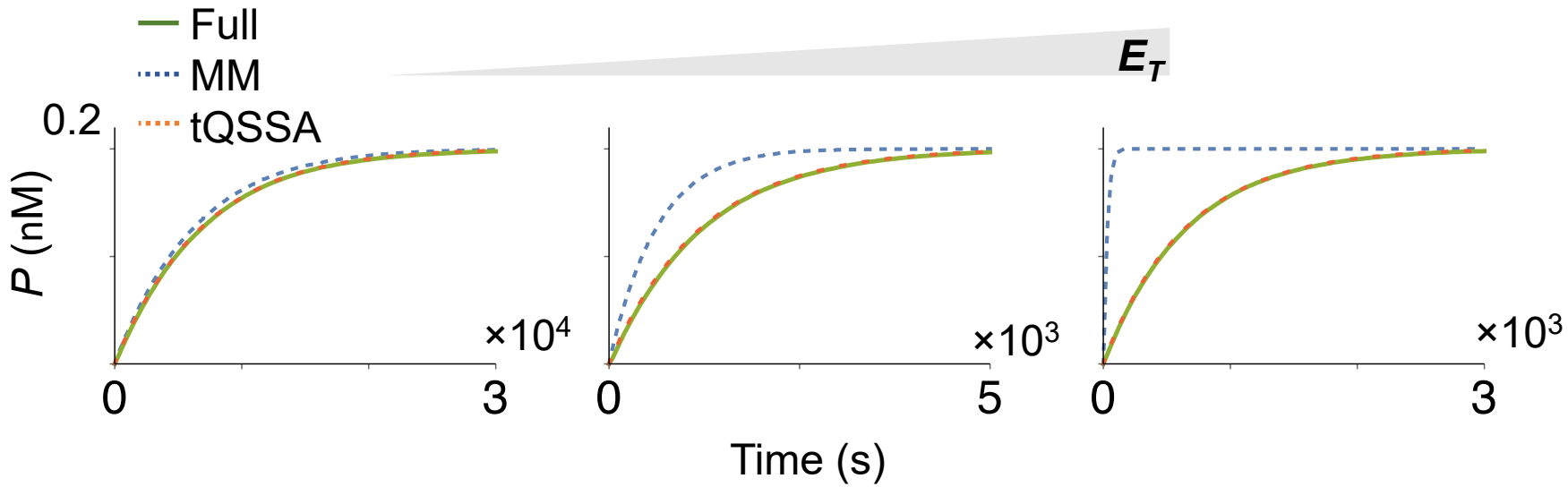
Conventional (MM)

$$\dot{P} = \frac{k_p E_T S}{K_M + S}$$

New (tQSSA)

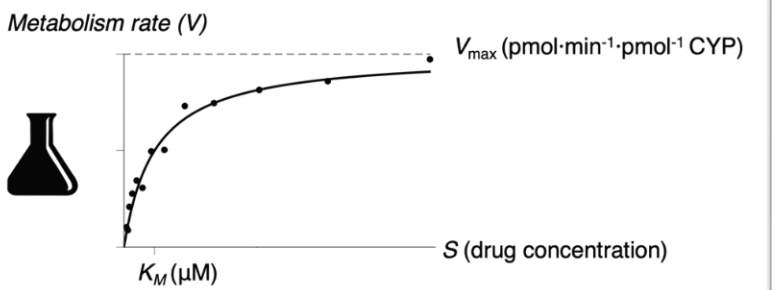
$$\dot{P} = \frac{k_p E_T S_T}{E_T + S_T + K_M}$$

$$S_T = S + C$$



Choi BS, Rempala G, Kim JK, Beyond Michaels-Menten equations: unbiased estimation of enzyme kinetics, Scientific Report (2017)

Does metabolism rate double as enzyme concentration doubles?



$$CL_{int}^{vitro} = V_{max}/K_m$$

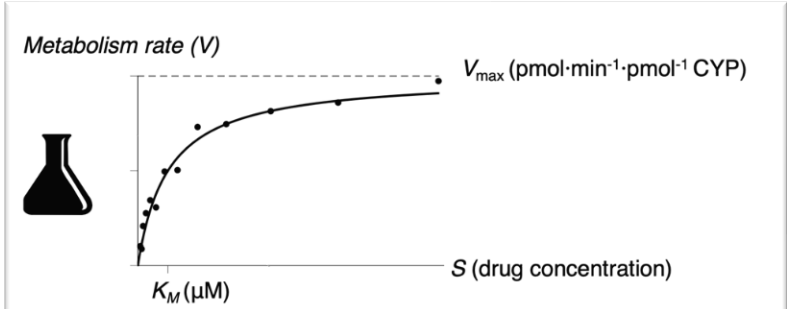
$$CL_{int}^{vitro} = \frac{V_{max}}{K_M}$$

$$V = \frac{V_{max} E_T S}{K_M + S} \approx CL_{int}^{vitro} E_T S$$

$\tilde{E}_T$ = hepatic CYP abundanc

$$CL_{int}^{liver} = CL_{int}^{vitro} \tilde{E}_T$$

Conventional Approach



$$CL_{int}^{vitro} = V_{max}/K_m$$

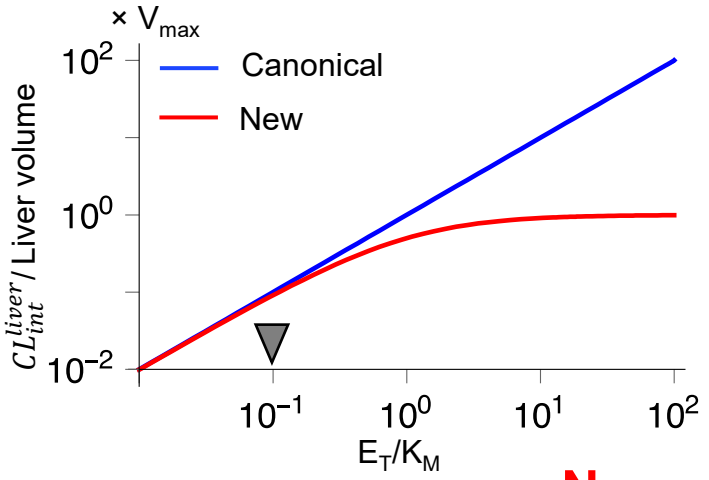
$$CL_{int}^{vitro} = \frac{V_{max}}{K_M}$$

$$V = \frac{V_{max} E_T S}{K_M + S + E_T} \approx CL_{int}^{vitro} \frac{K_M E_T}{K_M + E_T} S$$

$_T$ = hepatic CYP abundance

$$\frac{K_M}{\tilde{E}_T + K_M}$$

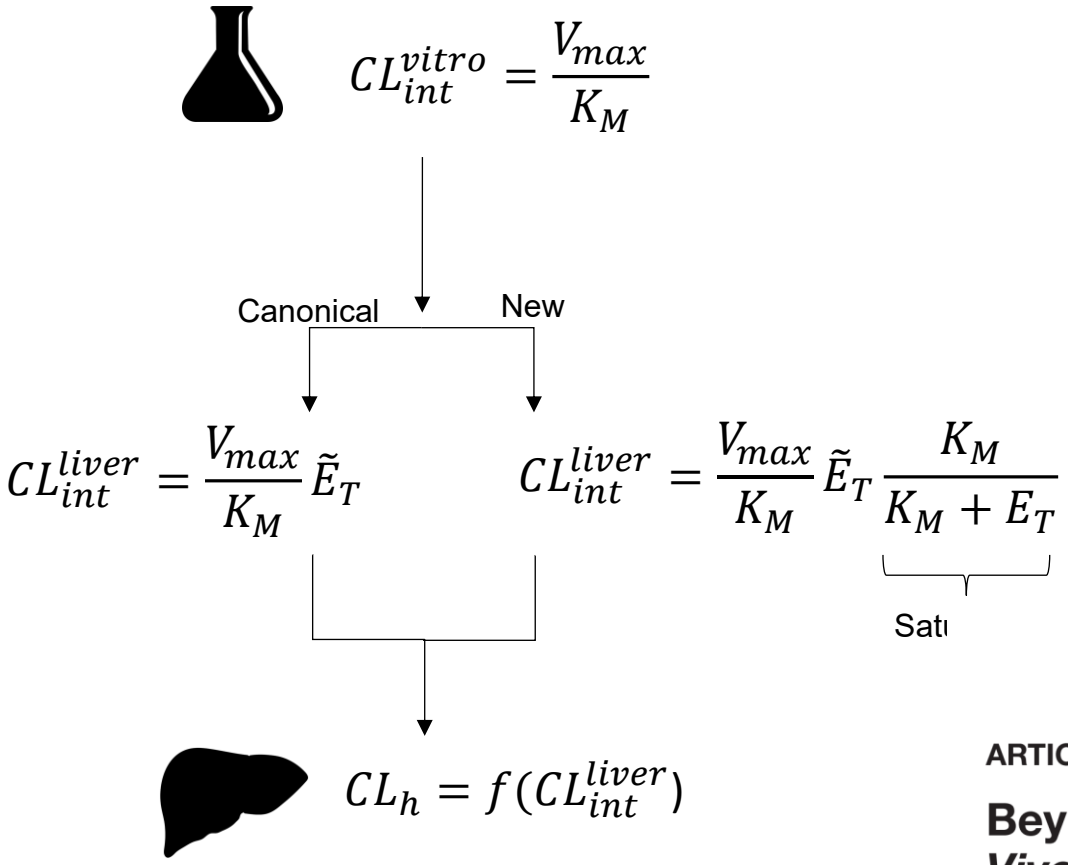
pproach

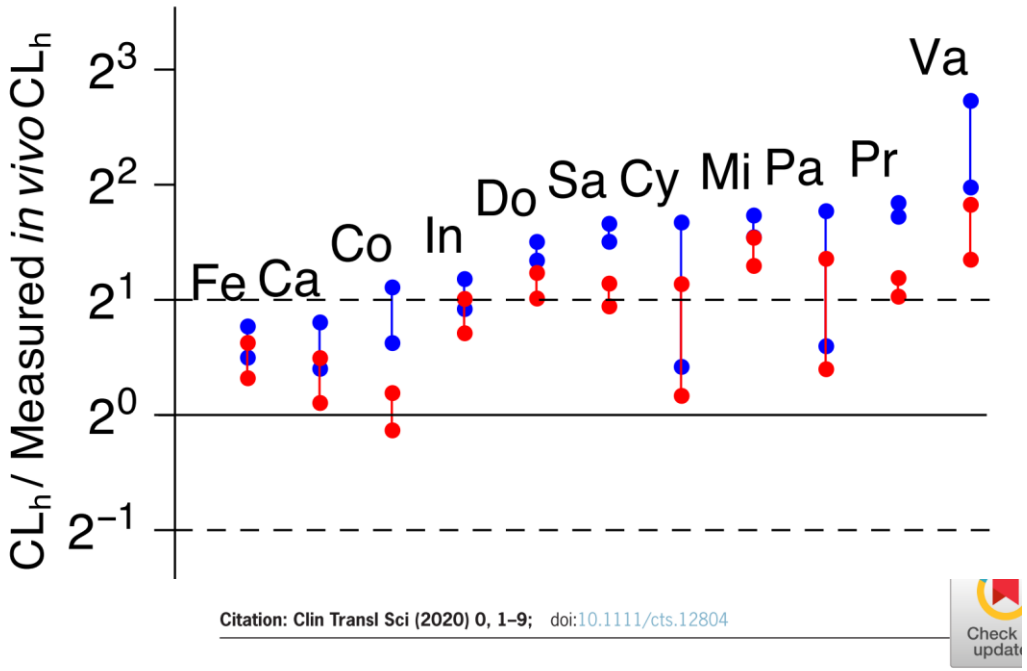


New approach seems more realistic

Baik H, Yoon H, Kim S, Kim JK, Prediction of in vivo clearance for drug with low K_M , CTS (2020)

The new approach can accurately predict hepatic CL





Citation: Clin Transl Sci (2020) 0, 1–9; doi:10.1111/cts.12804

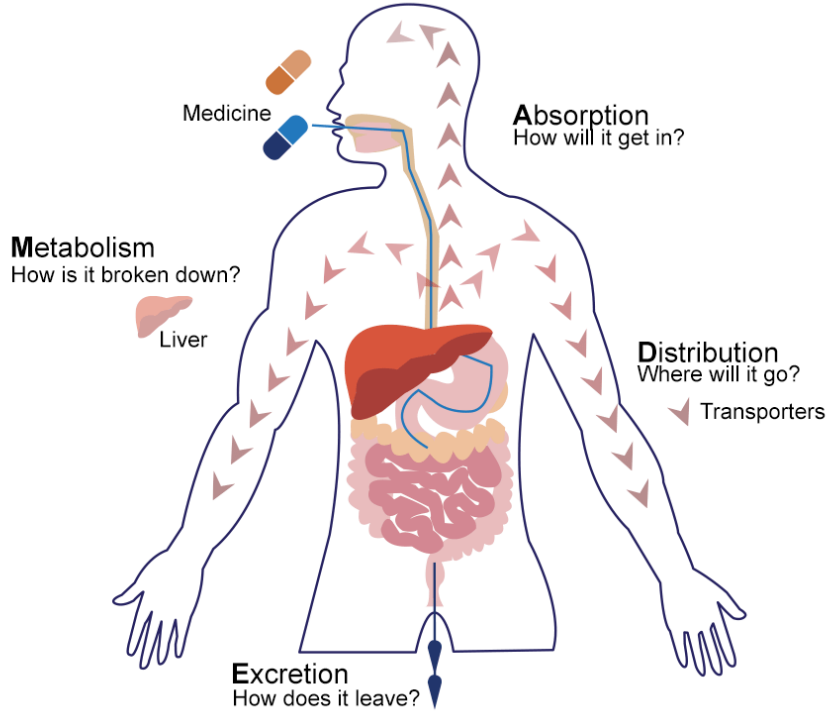
ARTICLE

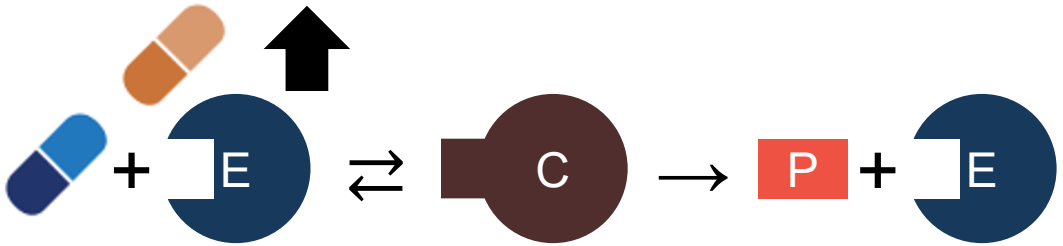
Beyond the Michaelis-Menten: Accurate Prediction of *In Vivo* Hepatic Clearance for Drugs With Low K_M

Hyun-moon Back[1,†], Hwi-yeol Yun[2,†], Sang Kyum Kim[2,*] and Jae Kyoung Kim[3,*]

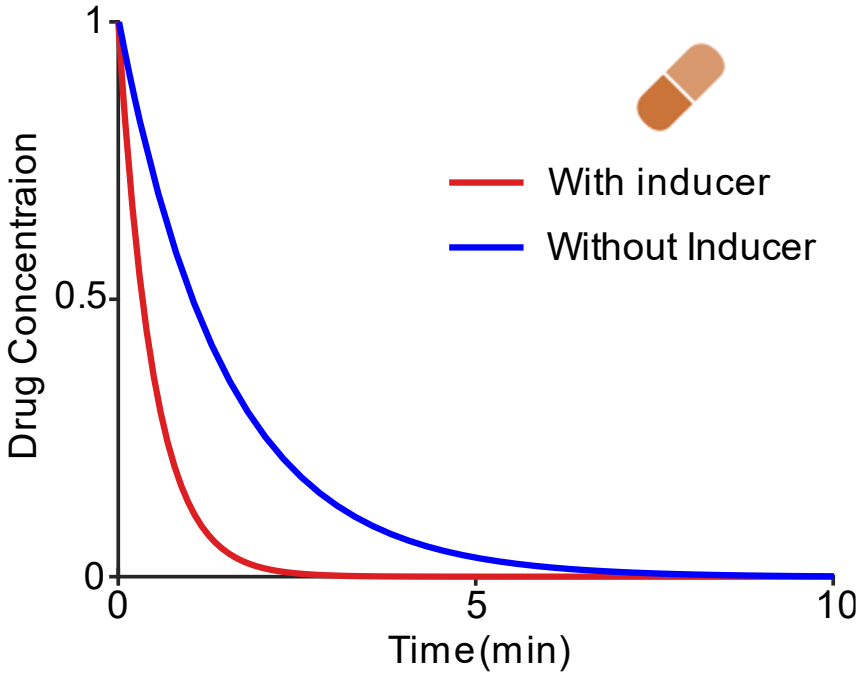
Baik H, Yoon H, Kim S, Kim JK, Prediction of in vivo clearance for drug with low K_M, CTS (2020)

Some drugs interact each other by increasing enzyme concentration





Induction

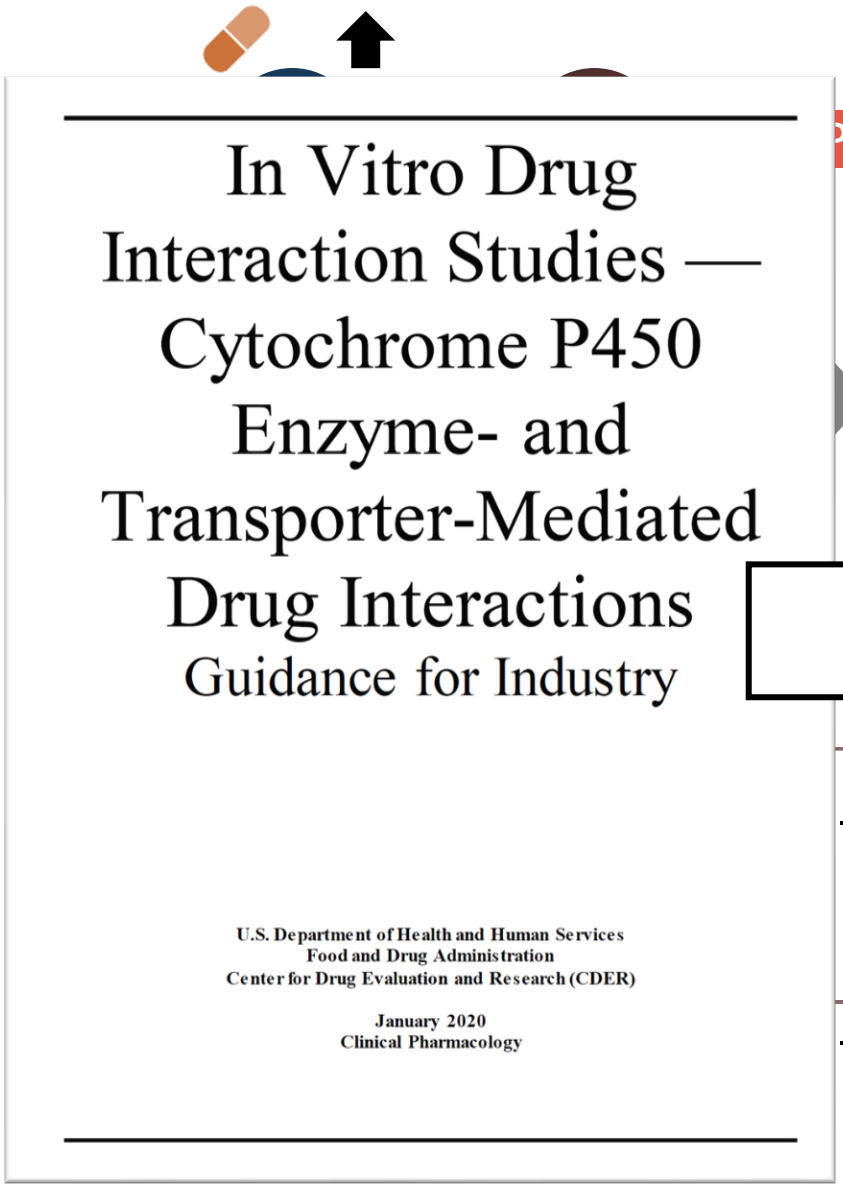


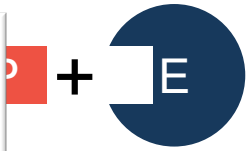
$$AUCR = \frac{\text{Area under}\ \text{—}}{\text{Area under}\ \text{—}}$$

AUCR ↑ => Induction effect ↓

AUCR ↓ => Induction effect ↑

AUCR has been predicted based on MM equation





cf) MM Equation

$$\frac{V_{max}E_T S}{K_M + S} \approx \frac{V_{max}E_T S}{K_M} = CL_{int} S$$

$$\frac{CL'_{int}}{CL_{int}} = \frac{\frac{V_{max}E_T E_{ind}}{K_M}}{\frac{V_{max}E_T}{K_M}} = E_{ind}$$

This equation has been recommended by FDA

$$\frac{1}{(1 - F_g)\frac{CL'_{int,G}}{CL_{int,G}}} \times \frac{1}{f_{m,C}}$$

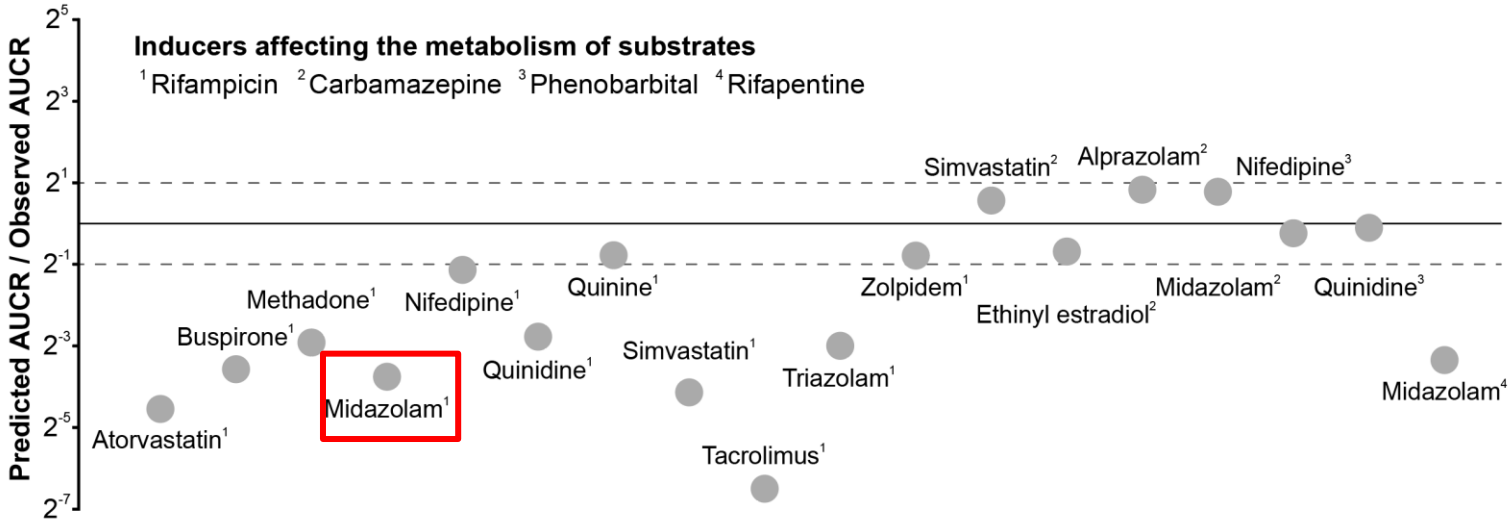
However…

$$\frac{1}{(1 - F_g)E_{ind,G}} \times \frac{1}{f_{m,CYP3A4}E_{ind,H} + (1 - f_{m,CYP3A4})}$$

Vu et al., Beyond the Michaelis-Menten: Accurate Prediction of Drug Interactions through Cytochrome P450 3A4 Induction, CPT (2023)

The increased enzyme concentration can violate the MM validity condition ($\frac{E_T}{K_M} < 0.1$)

Inducer	Dose regimen[a]	Substrate	$\frac{E_{ind,G}E_{T,G}}{K_m}$[e]	$\frac{E_{ind,H}E_{T,H}}{K_m}$[e]
Rifampicin	600 mg q.d.	Atorvastatin	0.266	1.346
		Buspirone	0.676	3.427
		Methadone	0.050	0.252
		Midazolam	1.746	8.855
		Nifedipine	0.357	1.809
		Quinidine	0.232	1.174
		Quinine	0.066	0.334
		Simvastatin	0.294	1.491
		Tacrolimus	1.456	7.384
		Triazolam	0.050	0.254
		Zolpidem	0.079	0.402

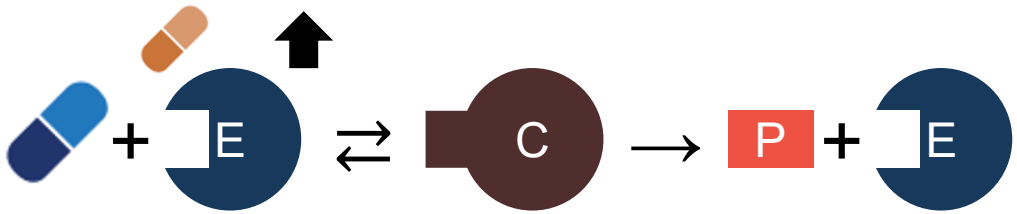


FDA equation significantly underpredicts AUCR

We need a better equation!

Vu et al., Beyond the Michaelis-Menten: Accurate Prediction of Drug Interactions through Cytochrome P450 3A4 Induction, CPT (2023)

We derived a new equation for AUCR using the tQSSA



cf) New Equation (tQSSA)

$$\frac{V_{max}E_T S}{K_M + E_T + S} \approx \frac{V_{max}E_T S}{K_M + E_T} = CL_{int}S$$

$$E_T \rightarrow E_T E_{ind}$$

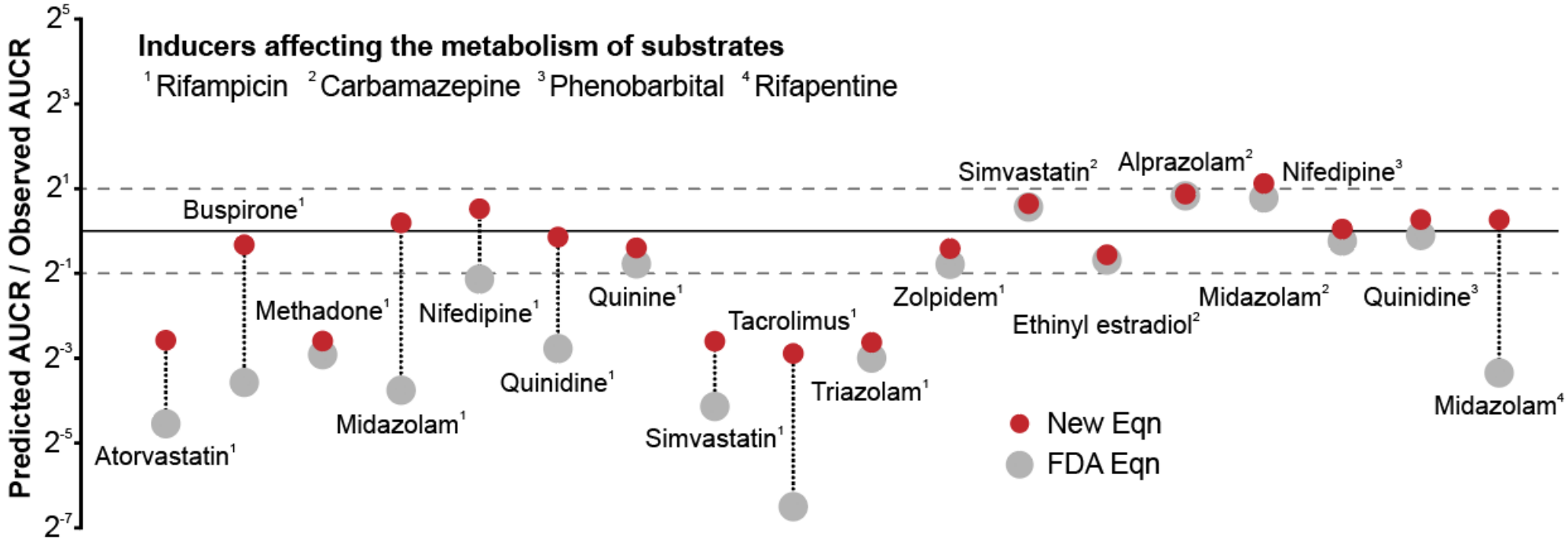
$$\frac{CL'_{int}}{CL_{int}} = \frac{\frac{V_{max}E_T E_{ind}}{K_M + E_T E_{ind}}}{\frac{V_{max}E_T}{K_M + E_T}} = E_{ind}\frac{K_M + E_T}{K_M + E_T E_{ind}}$$

$$\text{AUCR} = \frac{1}{F_g + (1 - F_g)\frac{CL'_{int,G}}{CL_{int,G}}} \times \frac{1}{f_{m,CYP3A4}\frac{CL'_{int,H}}{CL_{int,H}} + (1 - f_{m,CYP3A4})}$$

$$= \frac{1}{F_g + (1 - F_g)E_{ind}\frac{K_M + E_T}{K_M + E_T E_{ind}}} \times \frac{1}{f_{m,CYP3A4}E_{ind}\frac{K_M + E_T}{K_M + E_T E_{ind}} + (1 - f_{m,CYP3A4})}$$

Vu et al., Beyond the Michaelis-Menten: Accurate Prediction of Drug Interactions through Cytochrome P450 3A4 Induction, CPT (2023)

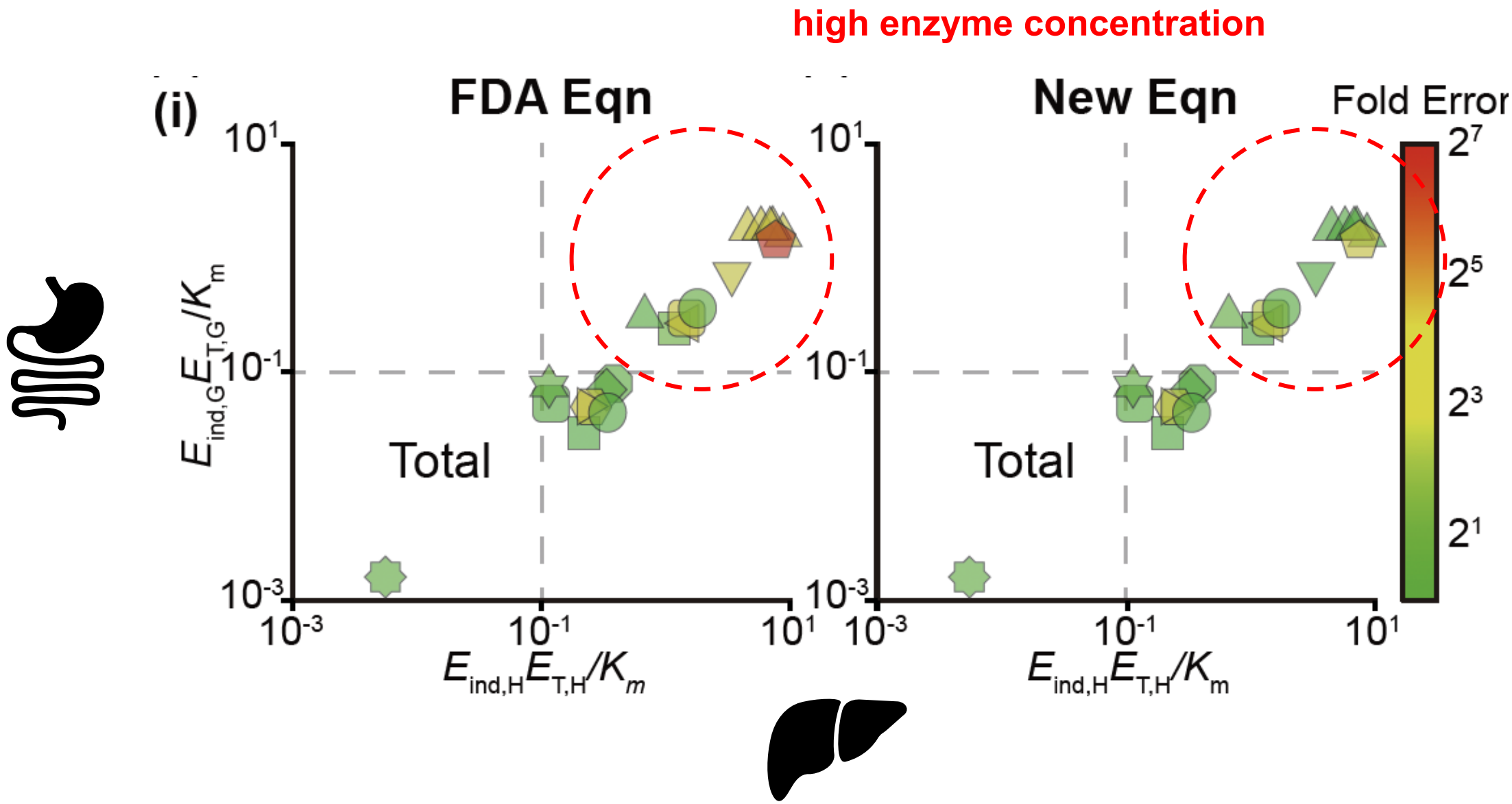
The new equation is better than the FDA equation



	FDA Eqn	New Eqn
AFE	0.222	0.686
AAFE	5.035	1.902
RMSE	0.876	0.411
% of 2-fold error	38%	76%

Vu et al., Beyond the Michaelis-Menten: Accurate Prediction of Drug Interactions through Cytochrome P450 3A4 Induction, CPT (2023)

The new equation is better than the FDA equation



Vu et al., Beyond the Michaelis-Menten: Accurate Prediction of Drug Interactions through Cytochrome P450 3A4 Induction, CPT (2023)

We suggest a new guidance for accurately predicting DDI

Clinical Pharmacology & Therapeutics

Article | Open Access

Beyond the Michaelis-Menten: Accurate Prediction of Drug Interactions through Cytochrome P450 3A4 Induction

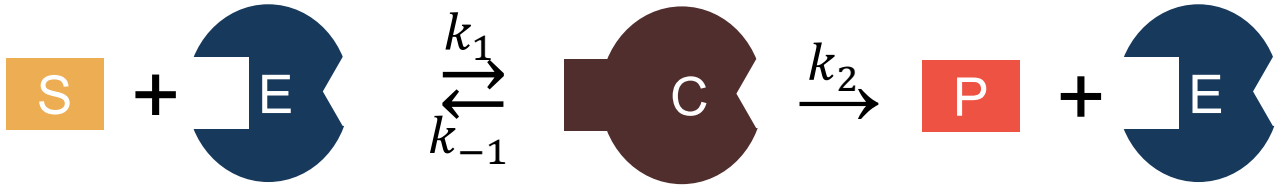
Ngoc-Anh Thi Vu, Yun Min Song, Quyen Thi Tran, Hwi-yeol Yun, Sang Kyum Kim, Jung-woo Chae, Jae Kyoung Kim

First published: 15 December 2022 | https://doi.org/10.1002/cpt.2824

$$E_{ind} \qquad E_{ind}\frac{\quad}{E_{ind}E_T+K_m}$$

Vu et al., Beyond the Michaelis-Menten: Accurate Prediction of Drug Interactions through Cytochrome P450 3A4 Induction, CPT (2023)

Inhibition constants represent the mechanism of enzyme inhibition



Inhibition parameters

$$K_{ic} := \frac{k_{-3}}{k_3}$$

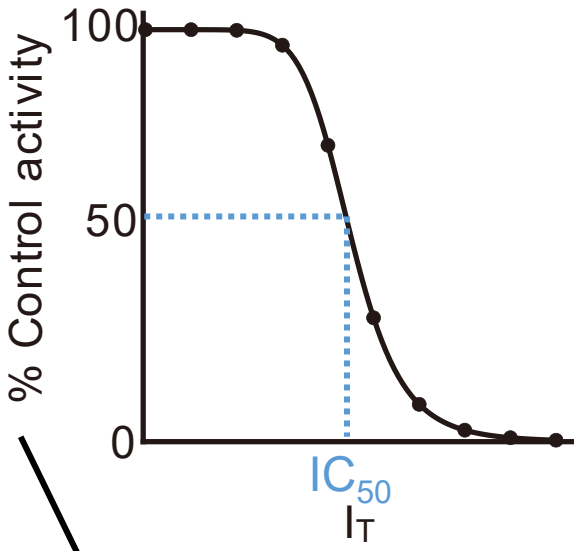
: How strong inhibition occurs in ①

$$K_{iu} = \frac{k_{-4}}{k_4}$$

: How strong inhibition occurs in ②

Inhibition constants are estimated from in vitro data generated by following three steps

1. Estimate IC_{50}



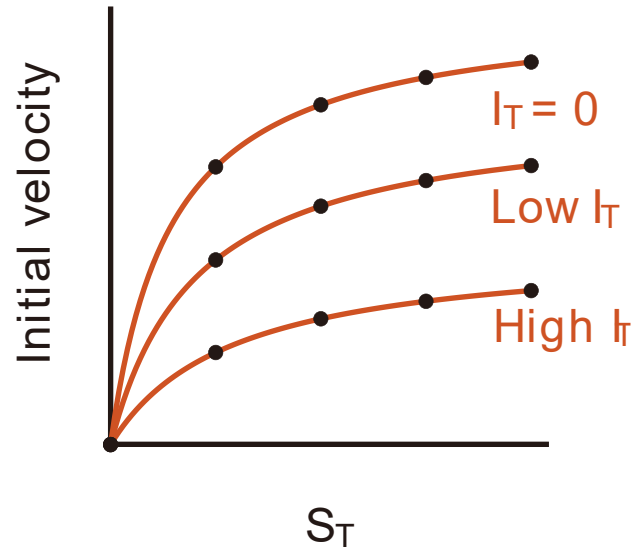
$$\frac{\text{Reaction velocity with } I}{\text{Reaction velocity without } I}$$

2. Set up S_T, I_T

S_T: $0.2K_M \sim 5K_M$

I_T: $\frac{1}{3}IC_{50} \sim 3IC_{50}$

3. Estimate K_{ic}, K_{iu}



Y-variables V_0: initial reaction velocity forming P

X-variables $S_T = S + C + Y$: substrate concentration

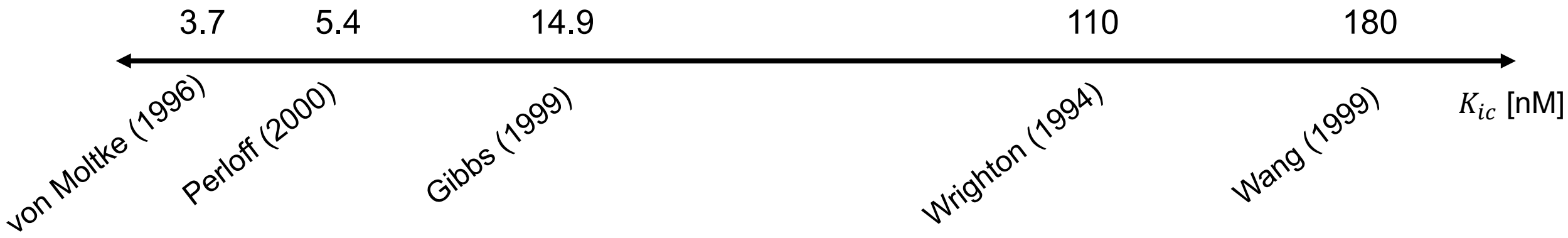
$I_T = I + B + Y$: inhibitor concentration

$$V_0 = \frac{V_{max} S_T}{K_M\left(1 + \frac{I_T}{K_{ic}}\right) + S_T\left(1 + \frac{I_T}{K_{iu}}\right)}$$

Ramsay RR, Tipton KF. Assessment of Enzyme Inhibition: A Review with Examples from the Development of Monoamine Oxidase and Cholinesterase Inhibitory Drugs. Molecules (2017)

Imprecise results have been occurred in estimations

Substrate: Midazolam Inhibitor: Ketoconazole



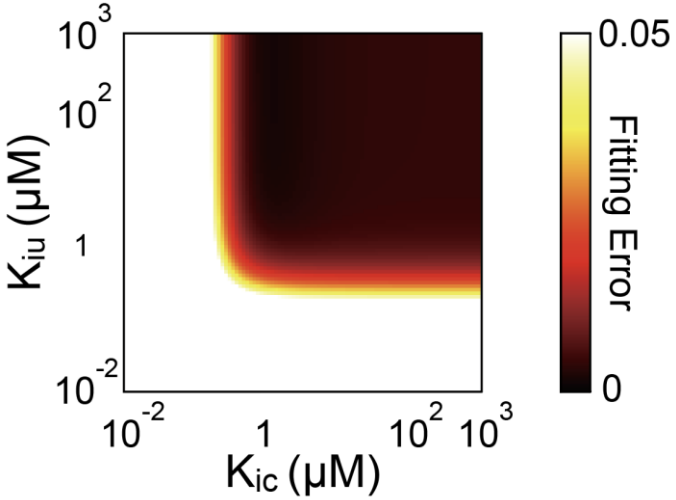
Ranged 1 to 100!

How can we achieve precise estimation?

Quinney, Sara K et al., *CPT: pharmacometrics & systems pharmacology* (2013)

Inhibitor concentration higher than K_{ic}, K_{iu} only contributes to the precise estimation

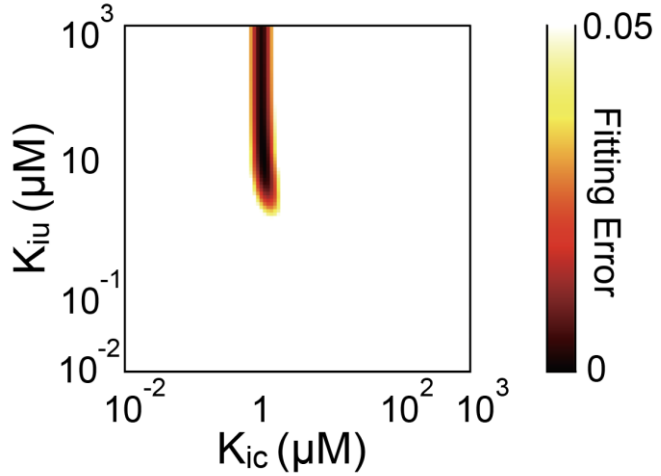
$I_T \ll K_{ic}, K_{iu}$



→ Imprecise

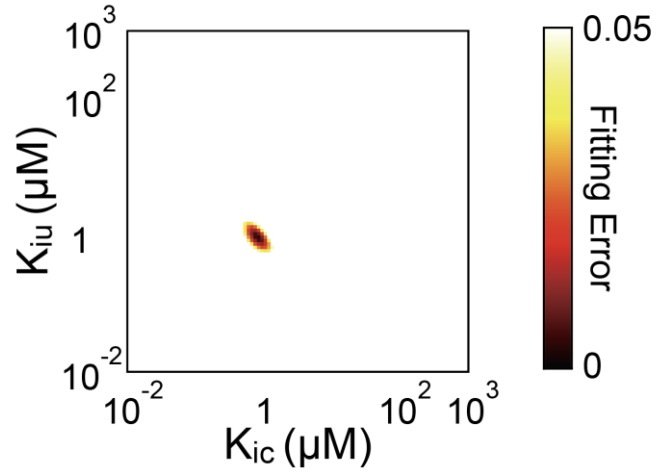
I_T ↑

$K_{ic} \leq I_T \ll K_{iu}$ (or $K_{iu} \leq I_T \ll K_{ic}$)



I_T ↑

$I_T \geq K_{ic}, K_{iu}$



→ Precise

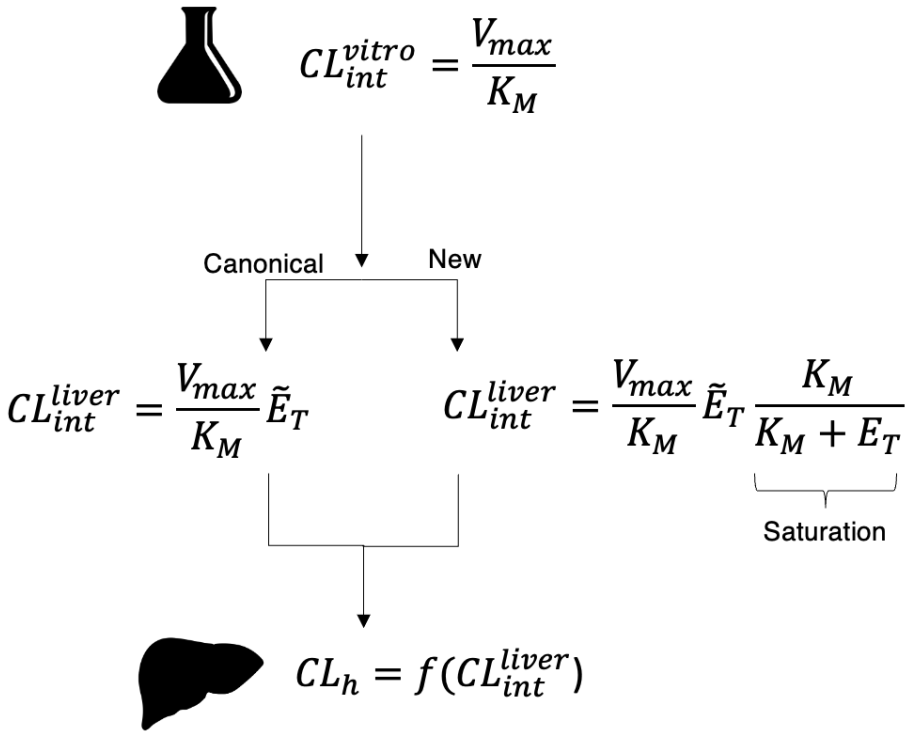
We have solved this issue

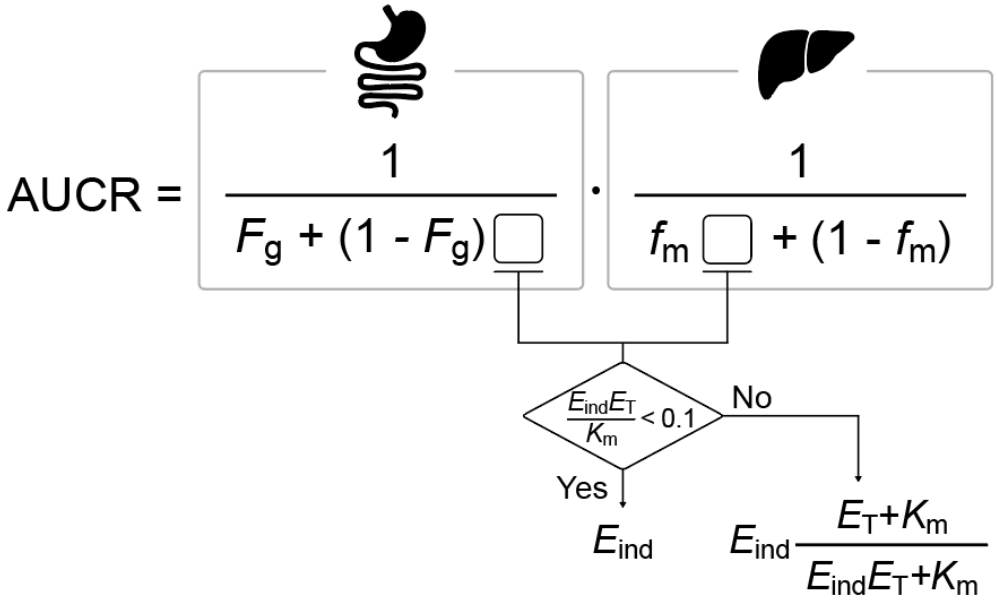
Now we can precisely estimate the inhibition constants in a more efficient way

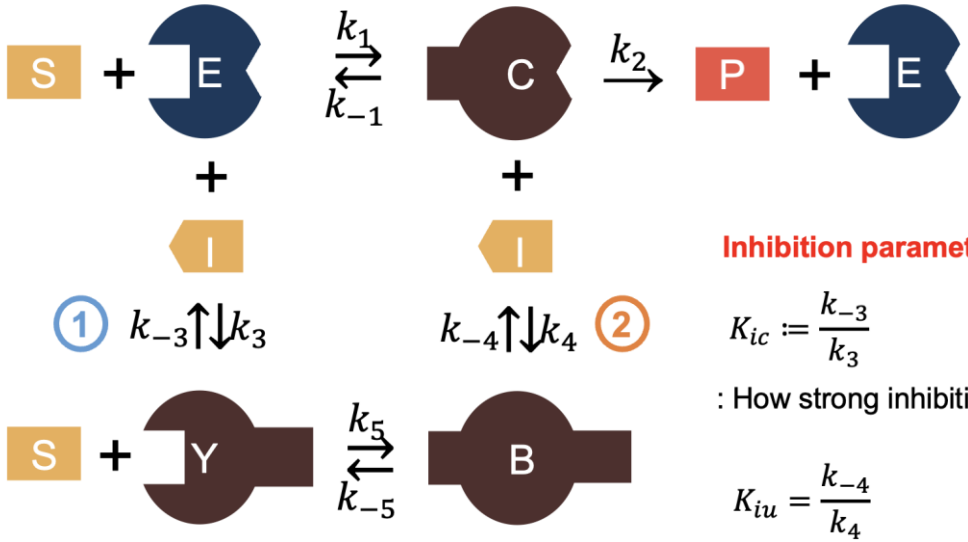
Unknown values… how can we set appropriate I_T?

(Under Review in Nature Communications)

Summary







Inhibition parameters

$K_{ic} := \frac{k_{-3}}{k_3}$

: How strong inhibition occurs in ①

$K_{iu} = \frac{k_{-4}}{k_4}$

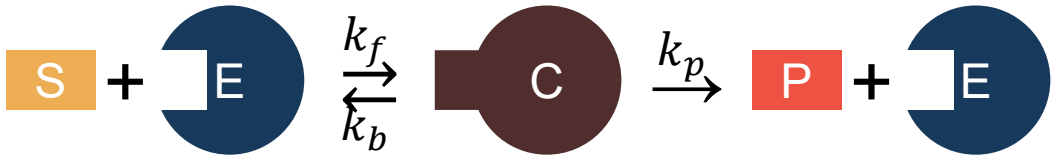
: How strong inhibition occurs in ②

Thank you!

KAIST Korea Advanced Institute of Science and Technology

ibs Biomedical Mathematics Group 의생명수학그룹

MM equation was derived using QSSA



Full system

$$\dot{S} = -k_f S(E_T - C) + k_b C$$

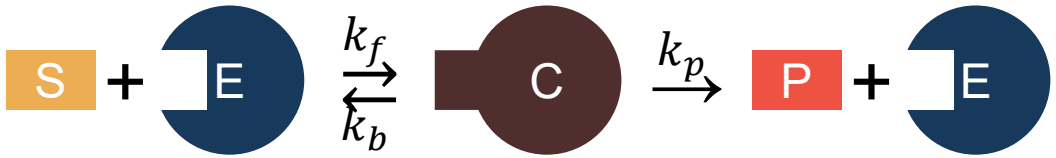
Fast → 0

$$\dot{C} = k_f S(E_T - C) - k_b C - k_p C$$

$$\dot{P} = k_p C$$

$$E_T = C + E$$

MM equation was derived using QSSA



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$$E_T = C + E$$

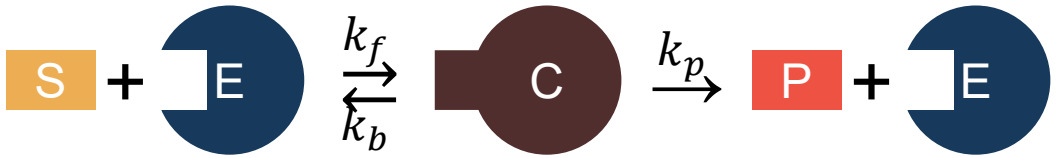
Quasi-Steady State Approximation

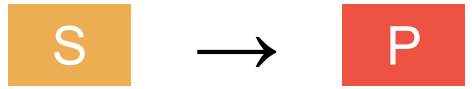
$$0 = k_f S(E_T - C) - k_b C - k_p C$$

$$C(S) = \frac{E_T S}{K_M + S}$$

$$K_M = \frac{k_b + k_p}{k_f}$$

MM equation was derived using QSSA





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$$C(S) = \frac{E_T S}{K_M + S}$$

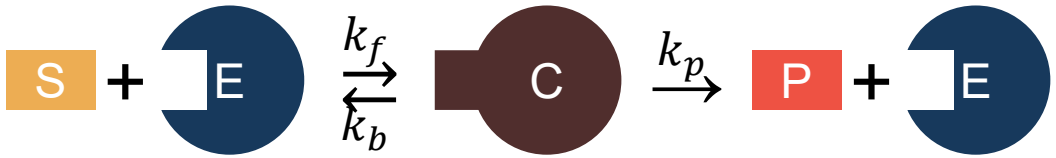
$$K_M = \frac{k_b + k_p}{k_f}$$

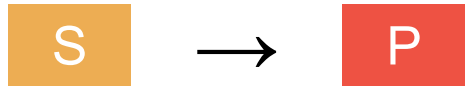
Reduced system

$$\dot{S} = -k_p \frac{E_T S}{K_M + S}$$

$$\dot{P} = k_p \frac{E_T S}{K_M + S}$$

MM equation was derived using QSSA





Full system

$$\dot{S} = -k_f S(E_T - C) + k_b C$$

Fast → $\dot{C} \approx 0$: $\dot{C} = k_f S(E_T - C) - k_b C - k_p C$

$$\dot{P} = k_p C$$

$$E_T = C + E$$

Quasi-Steady State Approximation

$$K_M = \frac{k_b + k_p}{k_f}$$

Reduced system

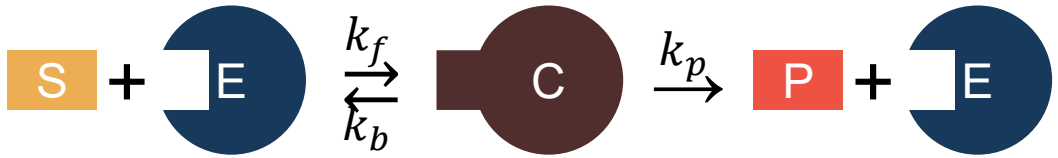
$$\dot{S} = -k_p \frac{E_T S}{K_M + S}$$

$$\dot{P} = k_p \frac{E_T S}{K_M + S}$$

$$\frac{E_T}{S + K_M} \ll 1 \qquad \frac{E_T}{K_M} < 0.1$$

Q: Always Valid? **A: No! C is fast only when enzyme concentration is low.**

New equation can be derived using the change of variable



Full system

$$\dot{S} = -k_f S(E_T - C) + k_b C$$

Fast → $\dot{C} \approx 0$

$$\dot{C} = k_f(S_T - C)(E_T - C) - k_b C - k_p C$$

$$\dot{P} = k_p C$$

$$E_T = C + E$$

Change of variable

$$S_T = S + C$$

$$\dot{S_T} = -k_p C$$

Fast → $\dot{C} \approx 0$

$$\dot{C} = k_f(S_T - C)(E_T - C) - k_b C - k_p C$$

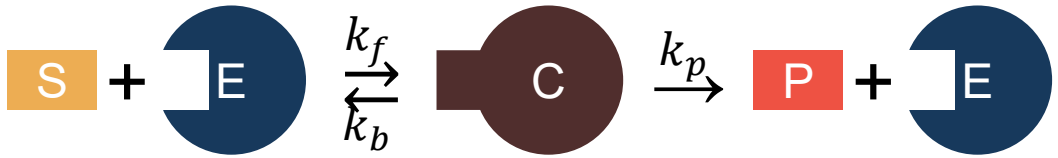
$$\dot{P} = k_p C$$

$$E_T = C + E$$

Valid only when E_T is low enough

More plausible assumption

New equation can be derived using the change of variable



Full system

$$\dot{S_T} = -k_p C \qquad (S_T = S + C)$$

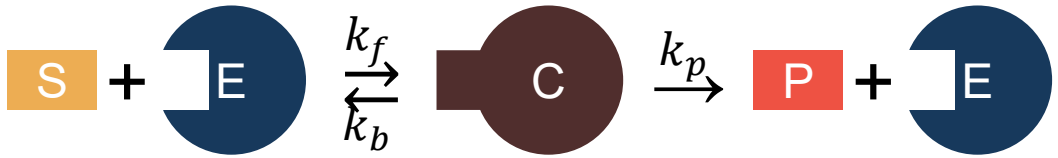
Fast → 0

$$\dot{C} = k_f(S_T - C)(E_T - C) - k_b C - k_p C$$

$$\dot{P} = k_p C$$

$$E_T = C + E$$

New equation can be derived using the change of variable



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$$\dot{P} = k_p C$$

$$E_T = C + E$$

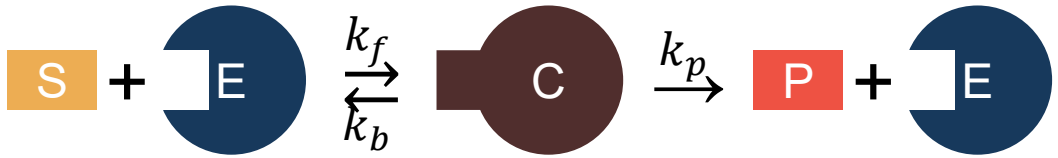
Quasi-Steady State Approximation

$$0 = k_f(S_T - C)(E_T - C) - k_b C - k_p C$$

$$C(S_T) = \frac{1}{2}\left(E_T + S_T + K_M + \sqrt{(E_T + S_T + K_M)^2 - 4E_T S_T}\right) \approx \frac{E_T S_T}{E_T + S_T + K_M}$$

$$K_M = \frac{k_b + k_p}{k_f}$$

New equation can be derived using the change of variable



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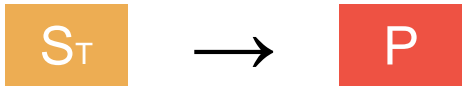

Reduced system

$$\dot{S_T} = -k_p \frac{E_T S_T}{E_T + S_T + K_M}$$

$$\dot{P} = k_p \frac{E_T S_T}{E_T + S_T + K_M}$$

total QSSA (tQSSA)