Electronic Supplementary Material (ESI) for Molecular BioSystems

A comprehensive analysis of the influence of drug binding kinetics on drug action at molecular and systems levels

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Supplementary Material

The reactions for the arachidonic acid metabolic network, as well as the parameters, are listed below[1].

Table 1 Enzymatic reactions and competitive feedbacks in arachidonic acid metabolic network

Reactions	**Forward rate ($\mu M^{-1}min^{-1}$ or min^{-1})**	**Backward rate (min^{-1})**
PL + PLA2 ↔ PLPLA2	2	1600
PLPLA2 → AA + PLA2	3600	
AA+15LOX ↔ AA15LOX	20	400
AA15LOX → 15HPETE + 15LOX	1000	
AA + 12LOX ↔ AA12LOX	21	50
AA12LOX → 12HPETE + 12LOX	1000	
15HETE + 12LOX ↔ 15HETE12LOX	10	100
AA + 5LOX ↔ AA5LOX	1020	100
AA5LOX → 5HPETE + 5LOX	5000	
12HETE + 5LOX ↔ 12HETE5LOX	10	300
15HETE + 5LOX ↔ 15HETE5LOX	10	40
PGE2 + 5LOX ↔ PGE25LOX	10	150
5HETE + 5LOX ↔ 5HETE5LOX	10	63
AA + COX2 ↔ AACOX2	22	100
AACOX2 → PGH2 + COX2	1000	
PGE2 + COX2 ↔ PGE2COX2	10	300
15HPETE + PHGPx ↔ 15HPETEPHGPx	8	60
15HPETEPHGPx → 15HETE + PHGPx	500	
15HPETE → ∅	0.05	
15HETE → ∅	0.1	
12HPETE + PHGPx ↔ 12HPETEPHGPx	8	60
12HPETEPHGPx → 12HETE + PHGPx	500	
PGH2 + TXAS ↔ PGH2TXAS	405	20
PGH2TXAS → TXA2 + TXAS	1600	
PGH2 + PGES ↔ PGH2PGES	20	200
PGH2PGES → PGE2 + PGES	3000	
AA + PGES ↔ AAPGES	100	30

15HETE + PGES ↔ 15HETEPGES	10	300
TXA2 → ∅	0.8	
5HPETE + 5LOX ↔ 5HPETE5LOX	1020	100
5HPETE5LOX → LTA4 + 5LOX	5000	
5HPETE + PHGPx ↔ 5HPETEPHGPx	8	60
5HPETEPHGPx → 5HETE + PHGPx	500	
5HETE → ∅	0.001	
LTA4 + LTA4H ↔ LTA4LTA4H	7	15
LTA4LTA4H → LTB4 + LTA4H	125	
LTB4 + CYP4F3 ↔ LTB4CYP4F3	40	10
LTB4CYP4F3 → ωLTB4 + CYP4F3	150	
12HETE + CYP4F3 ↔ 12HETECYP4F3	100	20
5HETE + CYP4F3 ↔ 5HETECYP4F3	100	86
LTB4 → ∅	0.01	

The concentrations of the enzymes are subject to transcriptional regulation and feedbacks:

$$\frac{d[15LOX]}{dt} = \frac{k_1[PGE2]^2}{[PGE2]^2 + K_1}$$

$$\frac{d[12LOX]}{dt} = -k_2[15HPETE][12LOX]$$

$$\frac{d[TXAS]}{dt} = -(k_3[15HPETE] + k_4[PGH2])[TXAS]$$

$$\frac{d[5LOX]}{dt} = (k_5[LTB4] - k_6[LTA4] - k_7[5HPETE] - k_8[15HPETE])[5LOX]$$

$$\frac{d[LTA4H]}{dt} = -\frac{k_9[LTA4H][LTA4]}{129(K_2 + [LTA4])}$$

Table 2 Parameters for enzyme feedbacks and transcriptional regulations

$\mathbf{k_1}$ (min^{-1})	0.15	$\mathbf{k_7}$ ($\mu M^{-1}min^{-1}$)	0.01
$\mathbf{k_2}$ ($\mu M^{-1}min^{-1}$)	10	k_8 ($\mu M^{-1}min^{-1}$)	0.01
$\mathbf{k_3}$ ($\mu M^{-1}min^{-1}$)	0.6	k_9 ($\mu M^{-1}min^{-1}$)	125
$\mathbf{k_4}$ ($\mu M^{-1}min^{-1}$)	0.1	K_1 (μM)	0.000023
$\mathbf{k_5}$ ($\mu M^{-1}min^{-1}$)	0.053	K_2 (μM)	20
$\mathbf{k_6}$ ($\mu M^{-1}min^{-1}$)	0.175		

Table 3 Initial conditions for the species in AA metabolic network

Species	Description	Initial concentration (μM)
PL	Phospholipids	12
PLA2	Phospholipase A2	1.5
PLPLA2	Complex of PL & PLA2	0
AA	Arachidonic acid	0
15LOX	15-Lipoxygenase	1.5

AA15LOX	Complex of AA & 15LOX	0
15HPETE	15-Hydroperoxyeicosatetraenoic acid	0.001
12LOX	12-Lipoxygenase	0.5
12HPETE	12-hydroperoxyeicosatetraenoic acid	0.001
AA12LOX	Complex of AA & 12LOX	0
5LOX	5-Lipoxygenase	5
AA5LOX	Complex of AA & 5LOX	0
5HPETE	5-Hydroperoxyeicosatetraenoic acid	0
12HETE5LOX	Complex of 12HETE & 5LOX	0
15HETE5LOX	Complex of 15HETE & 5LOX	0
PGE25LOX	Complex of PGE2 & 5LOX	0
5HETE5LOX	Complex of 5HETE & 5LOX	0
COX2	Cyclooxygenase-2	0.8
AACOX2	Complex of AA & COX2	0
PGH2	Prostaglandin H2	0.001
PGE2COX2	Complex of PGE2 & COX2	0
PHGPx	Phospholipid-hydroperoxide glutathione peroxidase	0.8
15HPETEPHGPx	Complex of 15HPETE & PHGPx	0
15HETE	15-Hydroxyeicosatetraenoic acid	0.001
12HPETEPHGPx	Complex of 12HPETE & PHGPx	0
12HETE	12-Hydroxyeicosatetraenoic acid	0.001
TXAS	TxA2 synthase	0.1
PGH2TXAS	Complex of PGH2 & TXAS	0
TXA2	Thromboxane A2	0.001
PGES	Prostaglandin E2 synthase	0.5
PGE2	Prostaglandin E2	0.001
PGH2PGES	Complex of PGH2 & PGES	0
AAPGES	Complex of AA & PGES	0
15HETEPGES	Complex of 15HETE & PGES	0
5HPETE5LOX	Complex of 5HPETE & 5LOX	0
LTA4	Leukotriene A4	0.001
5HPETEPHGPx	Complex of 5HPETE & PHGPx	0
5HETE	5-Hydroxyeicosatetraenoic acid	0.001
LTA4H	Leukotriene A4 hydrolase	0.76
LTA4LTA4H	Complex of LTA4 & LTA4H	0
LTB4	Leukotriene B4	0.001
LTB4CYP4F3	Complex of LTB4 & CYP4F3	0
CYP4F3	Leukotriene-B(4)	0.07

	omega-hydrolase 2	
ωLTB4	20-hydroxy leukotriene B4	0.001
15HETE12LOX	Complex of 15HETE & 12LOX	0
12HETECYP4F3	Complex of 12HETE & CYP4F3	0
5HETECYP4F3	Complex of 5HETE & CYP4F3	0

1. K. Yang, W. Ma, H. Liang, Q. Ouyang, C. Tang and L. Lai, *PLoS Comput Biol*, 2007, **3**, e55.

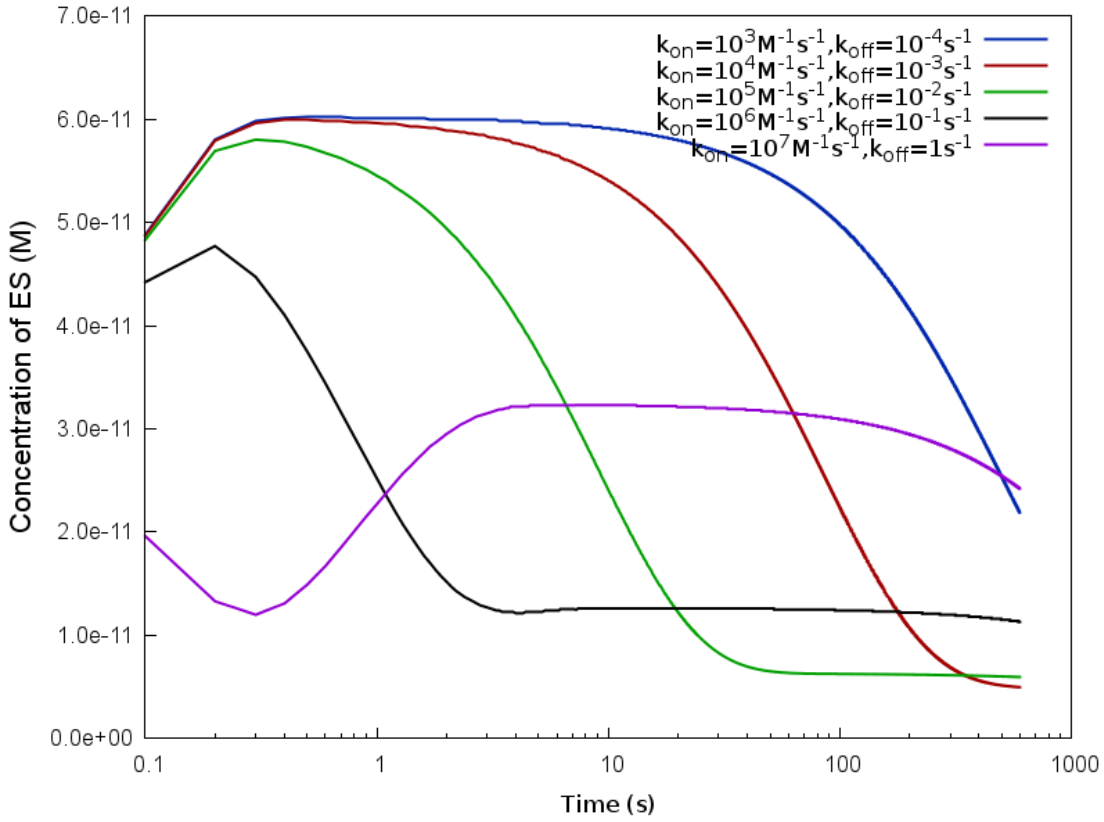

Fig. S1 Concentration of the catalytic active enzyme-substrate complex over time, under different inhibitors. When k_{off} of the inhibitor is larger than that of the substrate ($0.5s^{-1}$), [ES] rises after an initial drop, producing more products.

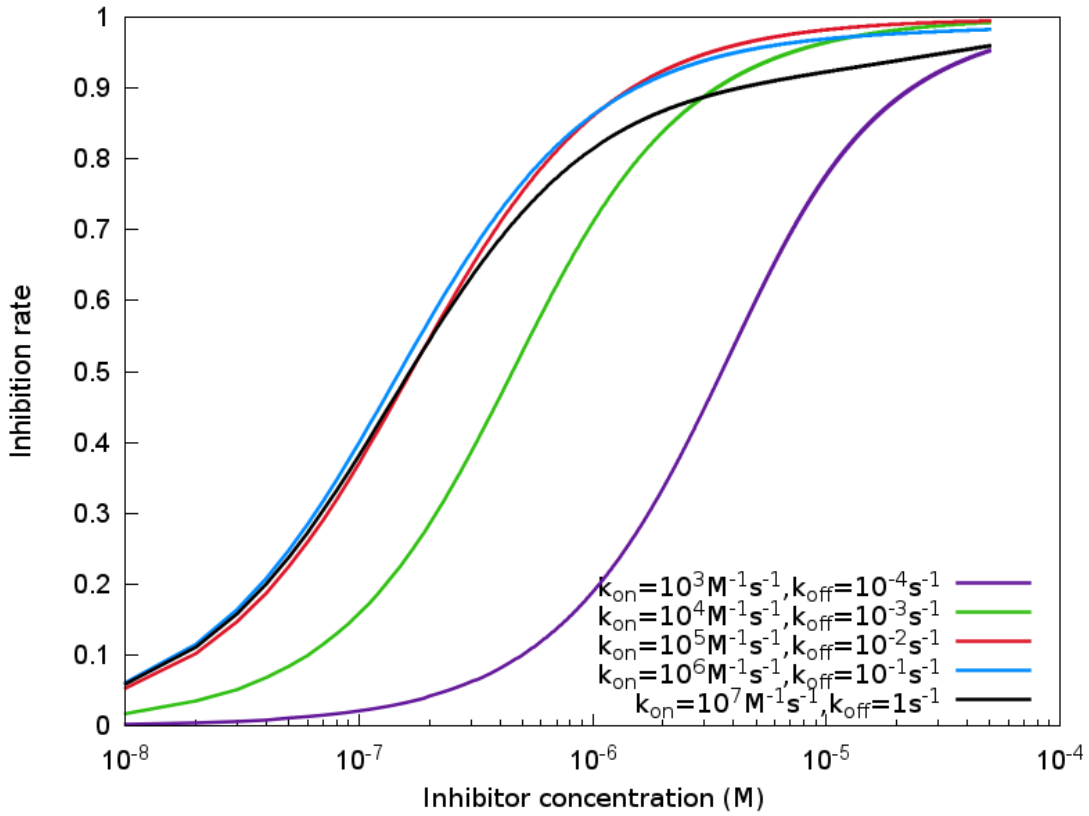

Fig S2 An example calculation of the influence of kinetics on enzyme inhibitory effect for mixed-type inhibition. All parameters were identical to Fig. 2, except that the binding of either substrate or inhibitor would slow the association rate of the other by tenfold. The graph shows features both from Fig. 1 (low concentration end) and Fig. 2 (high concentration end).