Finding Optimum Solutions for Multiple Target Control in Disease Related Molecular Network

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Supplementary Protocol

The construction of arachidonic acid metabolic network

The arachidonic acid metabolic network (AAnetwork) with a multi-cellular ensemble of human polymorphonuclear leukocyte (PMN), endothelial cells (EC) and platelet (PLT) was constructed based on our previous work and published experiments (Claesson &Haeggstrom, 1988; Denzlinger, 1996; Husain &Abdel-Latif, 2001; Inoue *et al*, 2000; Kojima *et al*, 2005; Ohd *et al*, 2000; Tsubouchi *et al*, 2001; Weaver *et al*, 2001; Yang *et al*, 2007). A group of ordinary differential equations (ODE) were written for PMN, EC and PLT, respectively, to simulate the time-course metabolism of arachidonic acid (AA). The productions of metabolites in the network were calculated as the sum of the corresponding output in three types of cells. For example:

$$Output_{PGE2} = C_{PGE2,PMN} \cdot V_{PMN} \cdot n_{PMN} + C_{PGE2,EC} \cdot V_{EC} \cdot n_{EC} + C_{PGE2,PLT} \cdot V_{PLT} \cdot n_{PLT} \quad \text{--- (1)}$$

where $C_{PGE2,PMN}$ is the concentration of PGE2 in PMN, V_{PMN} is the volume of PMN and n_{PMN} is the number of PMN in the model. Parameters and initial concentrations in the model are list in Table SI. Results of MTOI for different parameter sets are summarized in Table SII. The ODEs for PMN are:

$$\frac{d[AA]}{dt} = \frac{K_{cat,PLA2}(1+\frac{[12-HPETE]}{K_{12-HPETE\to PLA2}}+\frac{[15-HPETE]}{K_{15-HPETE\to PLA2}}+\frac{[LTB4]}{K_{LTB4\to PLA2}}+\frac{[5-HETE]}{K_{5-HETE\to PLA2}})[PLA2][PL]}{K_{m,PLA2}(1+\frac{[AA]}{Ki})+[PL]}$$

$$-\frac{K_{cat,15-LOX}[15-LOX][AA]}{K_{m,15-LOX}(1+\frac{[15-HPETE]}{Ki})+[AA]}-\frac{K_{cat,12-LOX}[12-LOX][AA]}{K_{m,12-LOX}(1+\frac{[12-HPETE]}{Ki_{12-HPETE\to 12-LOX}}+\frac{[15-HETE]}{Ki_{15-HETE\to 12-LOX}})+[AA]}$$

$$-\frac{K_{cat,5-LOX}[5-LOX][AA]}{K_{m,5-LOX}(1+\frac{[5-HPETE]}{Ki}+\frac{[12-HETE]}{Ki_{12-HETE\to 5-LOX}}+\frac{[15-HETE]}{Ki_{15-HETE\to 5-LOX}}+\frac{[PGE2]}{Ki_{PGE2\to 5-LOX}}+\frac{[5-HETE]}{Ki_{5-HETE\to 5-LOX}})+[AA]}$$

$$-\frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1+\frac{[PGH2]}{Ki}+\frac{[PGE2]}{Ki_{PGE2\to COX2}})+[AA]}+Kd_{exoAA}[exoAA]-Kd_{AA}[AA]$$

$$\frac{d[15-HPETE]}{dt}=\frac{K_{cat,15-LOX}[15-LOX][AA]}{K_{m,15-LOX}(1+\frac{[15-HPETE]}{Ki})+[AA]}-\frac{K_{cat,PHGPx}[PHGPx][15-HPETE]}{K_{m,PHGPx}(1+\frac{[15-HETE]}{Ki})+[15-HPETE]}$$
$$-Kd_{15-HPETE}[15-HPETE]$$

$$\frac{d[15-HETE]}{dt}=\frac{K_{cat,PHGPx}[PHGPx][15-HPETE]}{K_{m,PHGPx}(1+\frac{[15-HETE]}{Ki})+[15-HPETE]}-Kd_{15-HETE}[15-HETE]$$

$$\frac{d[12-HPETE]}{dt}=\frac{K_{cat,12-LOX}[12-LOX][AA]}{K_{m,12-LOX}(1+\frac{[12-HPETE]}{Ki_{12-HPETE\to 12-LOX}}+\frac{[15-HETE]}{Ki_{15-HETE\to 12-LOX}})+[AA]}$$
$$-\frac{K_{cat,PHGPx}[PHGPx][12-HPETE]}{K_{m,PHGPx}(1+\frac{[12-HETE]}{Ki})+[12-HPETE]}$$

$$\frac{d[12-HETE]}{dt}=\frac{K_{cat,PHGPx}[PHGPx][12-HPETE]}{K_{m,PHGPx}(1+\frac{[12-HETE]}{Ki})+[12-HPETE]}$$

$$\frac{d[PGH2]}{dt}=\frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1+\frac{[PGH2]}{Ki}+\frac{[PGE2]}{Ki_{PGE2\to COX2}})+[AA]}-\frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXA2]}{Ki})+[PGH2]}$$
$$-\frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1+\frac{[PGE2]}{Ki}+\frac{[AA]}{Ki_{AA\to PGES}}+\frac{[15-HETE]}{Ki_{15-HETE\to PGES}})+[PGH2]}$$

$$\frac{d[PGE2]}{dt}=\frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1+\frac{[PGE2]}{Ki}+\frac{[AA]}{Ki_{AA\to PGES}}+\frac{[15-HETE]}{Ki_{15-HETE\to PGES}})+[PGH2]}$$

$$\frac{d[TXA2]}{dt}=\frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXA2]}{Ki})+[PGH2]}-Kd_{TXA2}[TXA2]$$

$$\frac{d[TXB2]}{dt}=Kd_{TXA2}[TXA2]-Kd_{TXB2}[TXB2]$$

$$\frac{d[5-HPETE]}{dt}=\frac{K_{cat,5-LOX}[5-LOX][AA]}{K_{m,5-LOX}(1+\frac{[5-HPETE]}{Ki}+\frac{[12-HETE]}{Ki_{12-HETE\to 5-LOX}}+\frac{[15-HETE]}{Ki_{15-HETE\to 5-LOX}}+\frac{[PGE2]}{Ki_{PGE2\to 5-LOX}}+\frac{[5-HETE]}{Ki_{5-HETE\to 5-LOX}})+[AA]}$$

$$-\frac{K_{cat,5-LOX}[5-LOX][5-HPETE]}{K_{m,5-LOX}(1+\frac{[LTA4]}{Ki}+\frac{[12-HETE]}{Ki_{12-HETE\to 5-LOX}}+\frac{[15-HETE]}{Ki_{15-HETE\to 5-LOX}}+\frac{[PGE2]}{Ki_{PGE2\to 5-LOX}}+\frac{[5-HETE]}{Ki_{5-HETE\to 5-LOX}})+[5-HPETE]}$$

$$-\frac{K_{cat,PHGPx}[PHGPx][5-HPETE]}{K_{m,PHGPx}(1+\frac{[5-HETE]}{Ki})+[5-HPETE]}$$

$$\frac{d[5-HETE]}{dt}=\frac{K_{cat,PHGPx}[PHGPx][5-HPETE]}{K_{m,PHGPx}(1+\frac{[5-HETE]}{Ki})+[5-HPETE]}-Kd_{5-HETE}[5-HETE]$$

$$\frac{d[LTA4]}{dt}=\frac{K_{cat,5-LOX}[5-LOX][5-HPETE]}{K_{m,5-LOX}(1+\frac{[LTA4]}{Ki}+\frac{[12-HETE]}{Ki_{12-HETE\to 5-LOX}}+\frac{[15-HETE]}{Ki_{15-HETE\to 5-LOX}}+\frac{[PGE2]}{Ki_{PGE2\to 5-LOX}}+\frac{[5-HETE]}{Ki_{5-HETE\to 5-LOX}})+[5-HPETE]}$$

$$-\frac{K_{cat,LTA4H}[LTA4H][LTA4]}{K_{m,LTA4H}(1+\frac{[LTB4]}{Ki})+[LTA4]}-Kd_{LTA4}[LTA4]$$

$$\frac{d[LTB4]}{dt}=\frac{K_{cat,LTA4H}[LTA4H][LTA4]}{K_{m,LTA4H}(1+\frac{[LTB4]}{Ki})+[LTA4]}-Kd_{LTB2}[LTB2]$$

$$-\frac{K_{cat,CYP4F3}[CYP4F3][LTB4]}{K_{m,CYP4F3}(1+\frac{[20-OH-LTB4]}{Ki}+\frac{[12-HETE]}{Ki_{12-HETE\to CYP4F3}}+\frac{[5-HETE]}{Ki_{5-HETE\to CYP4F3}})+[LTB4]}$$

$$-Kd_{LTB4}[LTB4]$$

$$\frac{d[20-OH-LTB4]}{dt}=\frac{K_{cat,CYP4F3}[CYP4F3][LTB4]}{K_{m,CYP4F3}(1+\frac{[20-OH-LTB4]}{Ki}+\frac{[12-HETE]}{Ki_{12-HETE\to CYP4F3}}+\frac{[5-HETE]}{Ki_{5-HETE\to CYP4F3}})+[LTB4]}$$

$$\frac{d[PLA2]}{dt}=0$$

$$\frac{d[15-LOX]}{dt}=\frac{k_{PGE2\to 15-LOX}[PGE2]^2}{[PGE2]^2+K_{PGE2\to 15-LOX}{}^2}-Kd_{15-LOX}[15-LOX]$$

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

$$\frac{d[COX-2]}{dt}=0$$

$$\frac{d[PGES]}{dt}=0$$

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

$$\frac{d[5-LOX]}{dt} = (K_{LTB4 \to 5-LOX}[LTB4] - Ki_{LTA4 \to 5-LOX}[LTA4] - Ki_{5-HPETE \to 5-LOX}[5-HPETE] - Ki_{15-HPETE \to 5-LOX}[15-HPETE])[5-LOX]$$

$$\frac{d[LTA4H]}{dt} = -\frac{K_{cat,LTA4H}[LTA4H][LTA4]}{129(K_{m,LTA4H} + [LTA4])}$$

$$\frac{d[CYP4F3]}{dt} = 0$$

$$\frac{d[PHGPx]}{dt} = 0$$

The ODEs for EC are:

$$\frac{d[AA]}{dt} = \frac{K_{cat,PLA2}(1 + \frac{[12-HPETE]}{K_{12-HPETE \to PLA2}} + \frac{[15-HPETE]}{K_{15-HPETE \to PLA2}} + \frac{[PGF2\alpha]}{K_{PGF2\alpha \to PLA2}})[PLA2][PL]}{K_{m,PLA2}(1 + \frac{[AA]}{Ki}) + [PL]}$$
$$- \frac{K_{cat,15-LOX}[15-LOX][AA]}{K_{m,15-LOX}(1 + \frac{[15-HPETE]}{Ki}) + [AA]} - \frac{K_{cat,12-LOX}[12-LOX][AA]}{K_{m,12-LOX}(1 + \frac{[12-HPETE]}{Ki_{12-HPETE \to 12-LOX}}) + [AA]}$$
$$- \frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1 + \frac{[PGH2]}{Ki} + \frac{[PGE2]}{Ki_{PGE2 \to COX2}}) + [AA]}$$

$$\frac{d[15-HPETE]}{dt} = \frac{K_{cat,15-LOX}[15-LOX][AA]}{K_{m,15-LOX}(1 + \frac{[15-HPETE]}{Ki}) + [AA]} - \frac{K_{cat,PHGPx}[PHGPx][15-HPETE]}{K_{m,PHGPx}(1 + \frac{[15-HETE]}{Ki}) + [15-HPETE]}$$
$$- Kd_{15-HPETE}[15-HPETE]$$

$$\frac{d[15-HETE]}{dt} = \frac{K_{cat,PHGPx}[PHGPx][15-HPETE]}{K_{m,PHGPx}(1 + \frac{[15-HETE]}{Ki}) + [15-HPETE]} - Kd_{15-HETE}[15-HETE]$$

$$\frac{d[12-HPETE]}{dt} = \frac{K_{cat,12-LOX}[12-LOX][AA]}{K_{m,12-LOX}(1 + \frac{[12-HPETE]}{Ki}) + [AA]} - \frac{K_{cat,PHGPx}[PHGPx][12-HPETE]}{K_{m,PHGPx}(1 + \frac{[12-HETE]}{Ki}) + [12-HPETE]}$$

$$\frac{d[12-HETE]}{dt} = \frac{K_{cat,PHGPx}[PHGPx][12-HPETE]}{K_{m,PHGPx}(1+\frac{[12-HETE]}{Ki})+[12-HPETE]} - Kd_{12-HETE}[12-HETE]$$

$$\frac{d[PGH2]}{dt} = \frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1+\frac{[PGH2]}{Ki}+\frac{[PGE2]}{Ki_{PGE2\to COX2}})+[AA]} - \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXA2]}{Ki})+[PGH2]}$$
$$- \frac{K_{cat,PGIS}[PGIS][PGH2]}{K_{m,PGIS}(1+\frac{[PGI2]}{Ki}+\frac{[15-HPETE]}{Ki_{15-HPETE\to PGIS}})+[PGH2]} - \frac{K_{cat,PGDS}[PGDS][PGH2]}{K_{m,PGDS}(1+\frac{[PGD2]}{Ki})+[PGH2]}$$
$$- \frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1+\frac{[PGE2]}{Ki}+\frac{[AA]}{Ki_{AA\to PGES}}+\frac{[15-HETE]}{Ki_{15-HETE\to PGES}})+[PGH2]} - Kd_{PGH2}[PGH2]$$

$$\frac{d[TXA2]}{dt} = \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXA2]}{Ki})+[PGH2]} - Kd_{TXA2}[TXA2]$$

$$\frac{d[TXB2]}{dt} = Kd_{TXA2}[TXA2] - Kd_{TXB2}[TXB2]$$

$$\frac{d[PGI2]}{dt} = \frac{K_{cat,PGIS}[PGIS][PGH2]}{K_{m,PGIS}(1+\frac{[PGI2]}{Ki}+\frac{[15-HPETE]}{Ki_{15-HPETE\to PGIS}})+[PGH2]} - Kd_{PGI2}[PGI2]$$

$$\frac{d[6-keto-PGF1\alpha]}{dt} = Kd_{PGI2}[PGI2] - Kd_{6-keto-PGF1\alpha}[6-keto-PGF1\alpha]$$

$$\frac{d[PGD2]}{dt} = \frac{K_{cat,PGDS}[PGDS][PGH2]}{K_{m,PGDS}(1+\frac{[PGD2]}{Ki})+[PGH2]} - Kd_{PGD2}[PGD2]$$
$$- \frac{K_{cat,PGFS}[PGFS][PGD2]}{K_{m,PGFS}(1+\frac{[11-epi-PGF2\alpha]}{Ki})+[PGD2]}$$

$$\frac{d[PGJ2]}{dt} = Kd_{PGD2}[PGD2] - Kd_{PGJ2}[PGJ2]$$

$$\frac{d[15d-PGJ2]}{dt} = Kd_{PGJ2}[PGJ2]$$

$$\frac{d[PGE2]}{dt} = \frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1+\frac{[PGE2]}{Ki}+\frac{[AA]}{Ki_{AA\to PGES}}+\frac{[15-HETE]}{Ki_{15-HETE\to PGES}})+[PGH2]}$$

$$-\frac{K_{cat,CR}[CR][PGE2]}{K_{m,CR}(1+\frac{[PGF2\alpha]}{Ki})+[PGE2]}-\frac{K_{cat,9-KPR}[9-KPR][PGE2]}{K_{m,9-KPR}(1+\frac{[PGF2\alpha]}{Ki})+[PGE2]}$$

$$\frac{d[PGF2\alpha]}{dt}=\frac{K_{cat,CR}[CR][PGE2]}{K_{m,CR}(1+\frac{[PGF2\alpha]}{Ki})+[PGE2]}+\frac{K_{cat,9-KPR}[9-KPR][PGE2]}{K_{m,9-KPR}(1+\frac{[PGF2\alpha]}{Ki})+[PGE2]}+Kd_{PGH2}[PGH2]$$

$$-\frac{K_{cat,15-PGDH}[15-PGDH][PGF2\alpha]}{K_{m,15-PGDH}(1+\frac{[15-keto-PGF2\alpha]}{Ki})+[PGF2\alpha]}$$

$$\frac{d[15-keto-PGF2\alpha]}{dt}=\frac{K_{cat,15-PGDH}[15-PGDH][PGF2\alpha]}{K_{m,15-PGDH}(1+\frac{[15-keto-PGF2\alpha]}{Ki})+[PGF2\alpha]}$$

$$\frac{d[PLA2]}{dt}=-Ki_{15d-PGJ2\rightarrow PLA2}[15d-PGJ2][PLA2]$$

$$\frac{d[15-LOX]}{dt}=\frac{k_{PGE2\rightarrow 15-LOX}[PGE2]^2}{[PGE2]^2+K_{PGE2\rightarrow 15-LOX}{}^2}-Kd_{15-LOX}[15-LOX]$$

$$\frac{d[12-LOX]}{dt}=0$$

$$\frac{d[PHGPx]}{dt}=0$$

$$\frac{d[COX-2]}{dt}=0$$

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

$$\frac{d[PGIS]}{dt}=0$$

$$\frac{d[PGDS]}{dt}=0$$

$$\frac{d[PGFS]}{dt}=0$$

$$\frac{d[PGES]}{dt}=-Ki_{15d-PGJ2\rightarrow PGES}[15d-PGJ2][PGES]$$

$$\frac{d[CR]}{dt} = 0$$

$$\frac{d[9-KPR]}{dt} = 0$$

$$\frac{d[15-PGDH]}{dt} = 0$$

The ODEs for PLT are:

$$\frac{d[AA]}{dt} = \frac{K_{cat,PLA2}(1+\frac{[12-HPETE]}{K_{12-HPETE\rightarrow PLA2}})[PLA2][PL]}{K_{m,PLA2}(1+\frac{[AA]}{Ki})+[PL]} - \frac{K_{cat,12-LOX}[12-LOX][AA]}{K_{m,12-LOX}(1+\frac{[12-HPETE]}{Ki})+[AA]} - \frac{K_{cat,COX1}[COX-1][AA]}{K_{m,COX1}(1+\frac{[PGH2]}{Ki})+[AA]}$$

$$\frac{d[12-HPETE]}{dt} = \frac{K_{cat,12-LOX}[12-LOX][AA]}{K_{m,12-LOX}(1+\frac{[12-HPETE]}{Ki})+[AA]} - \frac{K_{cat,PHGPx}[PHGPx][12-HPETE]}{K_{m,PHGPx}(1+\frac{[12-HETE]}{Ki})+[12-HPETE]}$$

$$\frac{d[12-HETE]}{dt} = \frac{K_{cat,PHGPx}[PHGPx][12-HPETE]}{K_{m,PHGPx}(1+\frac{[12-HETE]}{Ki})+[12-HPETE]}$$

$$\frac{d[PGH2]}{dt} = \frac{K_{cat,COX1}[COX-1][AA]}{K_{m,COX1}(1+\frac{[PGH2]}{Ki})+[AA]} - \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXA2]}{Ki})+[PGH2]}$$

$$\frac{d[TXA2]}{dt} = \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXA2]}{Ki})+[PGH2]} - Kd_{TXA2}[TXA2]$$

$$\frac{d[TXB2]}{dt} = Kd_{TXA2}[TXA2] - Kd_{TXB2}[TXB2]$$

$$\frac{d[PLA2]}{dt} = 0$$

$$\frac{d[12-LOX]}{dt} = 0$$

$$\frac{d[COX\ -1]}{dt} = 0$$

$$\frac{d[TXAS]}{dt} = -Ki_{PGH2\to TXAS}[PGH2][TXAS]$$

$$\frac{d[PHGPx]}{dt} = 0$$

The construction of simplified AAnetwork model

The simplified AAnetwork model was set up to verify the practicability of MTOI in incomplete network. Only disease-related metabolites and enzymes were included. Like the full model, a group of ODEs were written for PMN, EC and PLT, respectively, to simulate the time-course metabolism of AA. The productions of metabolites in the network were calculated as equation 1. Unknown parameters and initial concentrations were evaluated by parameter fitting (Fig. S1, Table SIII). Results of MTOI are summarized in Table SIV. The ODEs for PMN are:

$$\frac{d[AA]}{dt} = \frac{K_{cat,PLA2}(1+\frac{[AA]}{K_{AA\to PLA2}}+)[PLA2][PL]}{K_{m,PLA2}(1+\frac{[AA]}{Ki})+[PL]} - \frac{K_{cat,E1}[E1][AA]}{K_{m,E1}(1+\frac{[HETEs]}{Ki})+[AA]}$$

$$- \frac{K_{cat,5-LOX}[5-LOX][AA]}{K_{m,5-LOX}(1+\frac{[LTA4]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to 5-LOX}})+[AA]} - \frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1+\frac{[PGH2]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to COX2}})+[AA]}$$

$$\frac{d[HETEs]}{dt} = \frac{K_{cat,E1}[E1][AA]}{K_{m,E1}(1+\frac{[HETEs]}{Ki})+[AA]} - Kd_{HETEs}[HETEs]$$

$$\frac{d[PGH2]}{dt} = \frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1+\frac{[PGH2]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to COX2}})+[AA]} - \frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1+\frac{[PGE2]}{Ki})+[PGH2]}$$

$$- \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXs]}{Ki})+[PGH2]}$$

$$\frac{d[PGE2]}{dt} = \frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1+\frac{[PGE2]}{Ki})+[PGH2]}$$

$$\frac{d[TXs]}{dt} = \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXs]}{Ki})+[PGH2]}$$

$$\frac{d[LTA4]}{dt} = \frac{K_{cat,5-LOX}[5-LOX][AA]}{K_{m,5-LOX}(1+\frac{[LTA4]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to 5-LOX}})+[AA]} - \frac{K_{cat,LTA4H}[LTA4H][LTA4]}{K_{m,LTA4H}(1+\frac{[LTB4]}{Ki})+[LTA4]}$$

$$\frac{d[LTB4]}{dt} = \frac{K_{cat,LTA4H}[LTA4H][LTA4]}{K_{m,LTA4H}(1+\frac{[LTB4]}{Ki})+[LTA4]} - Kd_{LTB4}[LTB4]$$

$$\frac{d[PLA2]}{dt} = 0$$

$$\frac{d[E1]}{dt} = 0$$

$$\frac{d[COX-2]}{dt} = 0$$

$$\frac{d[PGES]}{dt} = 0$$

$$\frac{d[TXAS]}{dt} = -Ki_{PGH2\to TXAS}[PGH2][TXAS]$$

$$\frac{d[5-LOX]}{dt} = -Ki_{LTA4\to 5-LOX}[LTA4][5-LOX]$$

$$\frac{d[LTA4H]}{dt} = -Ki_{LTA4\to LTA4H}[LTA4][LTA4H]$$

The ODEs for EC are:

$$\frac{d[AA]}{dt} = \frac{K_{cat,PLA2}(1+\frac{[AA]}{K_{AA\to PLA2}}+)[PLA2][PL]}{K_{m,PLA2}(1+\frac{[AA]}{Ki})+[PL]} - \frac{K_{cat,E1}[E1][AA]}{K_{m,E1}(1+\frac{[HETEs]}{Ki})+[AA]}$$

$$- \frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1+\frac{[PGH2]}{Ki})+[AA]}$$

$$\frac{d[HETEs]}{dt} = \frac{K_{cat,E1}[E1][AA]}{K_{m,E1}(1+\frac{[HETEs]}{Ki})+[AA]} - Kd_{HETEs}[HETEs]$$

$$\frac{d[PGH2]}{dt} = \frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1+\frac{[PGH2]}{Ki})+[AA]} - \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXs]}{Ki})+[PGH2]}$$

$$- \frac{K_{cat,PGIS}[PGIS][PGH2]}{K_{m,PGIS}(1+\frac{[PGI2]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to PGIS}})+[PGH2]}$$

$$- \frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1+\frac{[PGE2]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to PGES}})+[PGH2]} - Kd_{PGH2}[PGH2]$$

$$\frac{[PGE2]}{dt} = \frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1+\frac{[PGE2]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to PGES}})+[PGH2]} - Kd_{PGE2}[PGE2]$$

$$\frac{[PGI2]}{dt} = \frac{K_{cat,PGIS}[PGIS][PGH2]}{K_{m,PGIS}(1+\frac{[PGI2]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to PGIS}})+[PGH2]}$$

$$\frac{d[TXs]}{dt} = \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1+\frac{[TXs]}{Ki})+[PGH2]}$$

$$\frac{d[PLA2]}{dt} = 0$$

$$\frac{d[E1]}{dt} = 0$$

$$\frac{d[COX-2]}{dt} = 0$$

$$\frac{d[PGES]}{dt} = 0$$

$$\frac{d[PGIS]}{dt} = 0$$

$$\frac{d[TXAS]}{dt} = -Ki_{PGH2\to TXAS}[PGH2][TXAS]$$

The ODEs for PLT are:

$$\frac{d[AA]}{dt} = \frac{K_{cat,PLA2}(1+\frac{[AA]}{K_{AA\to PLA2}}+)[PLA2][PL]}{K_{m,PLA2}(1+\frac{[AA]}{Ki})+[PL]} - \frac{K_{cat,E1}[E1][AA]}{K_{m,E1}(1+\frac{[HETEs]}{Ki})+[AA]}$$

$$- \frac{K_{cat,COX1}[COX-1][AA]}{K_{m,COX1}(1+\frac{[PGH2]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to COX1}})+[AA]}$$

$$\frac{d[HETEs]}{dt} = \frac{K_{cat,E1}[E1][AA]}{K_{m,E1}(1+\frac{[HETEs]}{Ki})+[AA]} - Kd_{HETEs}[HETEs]$$

$$\frac{d[TXs]}{dt} = \frac{K_{cat,COX1}[COX-1][AA]}{K_{m,COX1}(1+\frac{[PGH2]}{Ki}+\frac{[HETEs]}{Ki_{HETEs\to COX1}})+[AA]}$$

$$\frac{d[PLA2]}{dt} = 0$$

$$\frac{d[E1]}{dt} = 0$$

$$\frac{d[COX-1]}{dt} = -Ki_{TXs \to COX1}[TXs][COX-1]$$

Single parameter sensitivity analysis

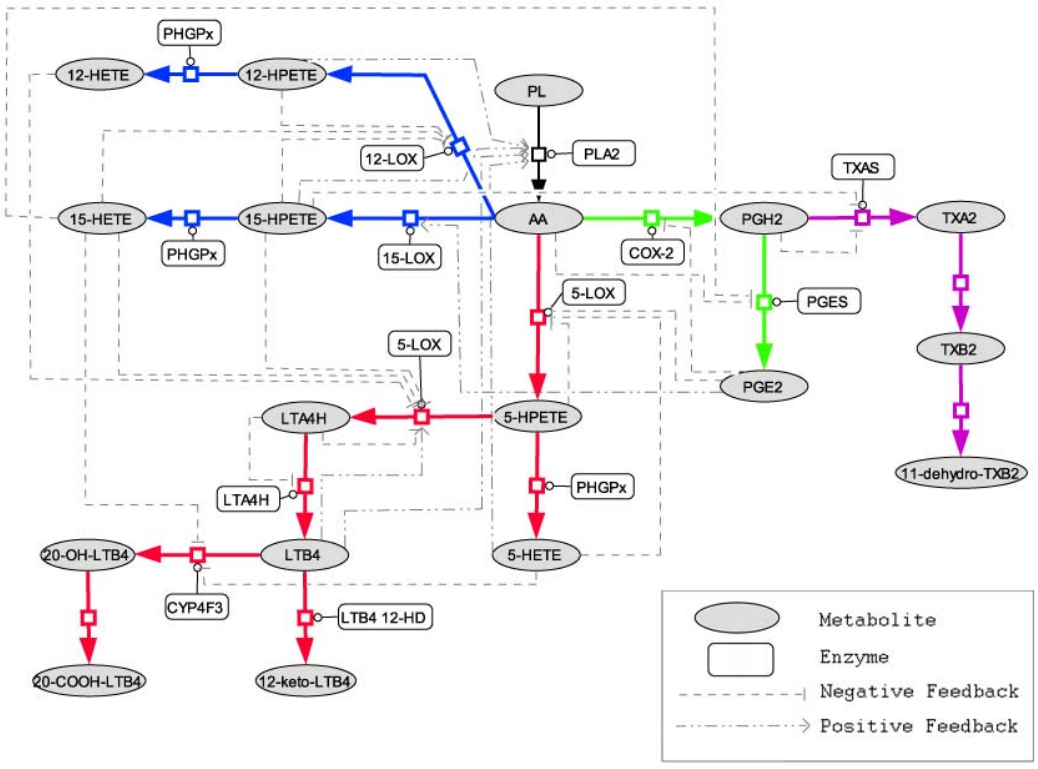
Single parameter sensitivity analysis was performed using the reported method (Pant &Ghosh, 2005). The sensitivity coefficient is calculated as:

$$C = \frac{\Delta F_{obj} / F_{obj}}{\Delta K / K}$$

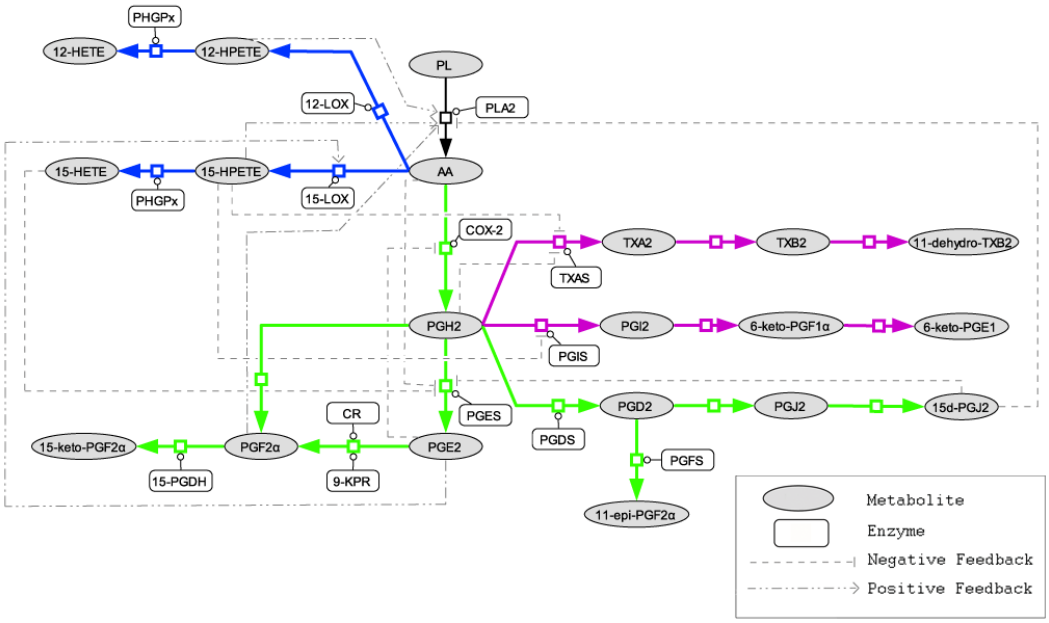
The result of AAnetwork is summarized in Table SV

Supplementary Figures

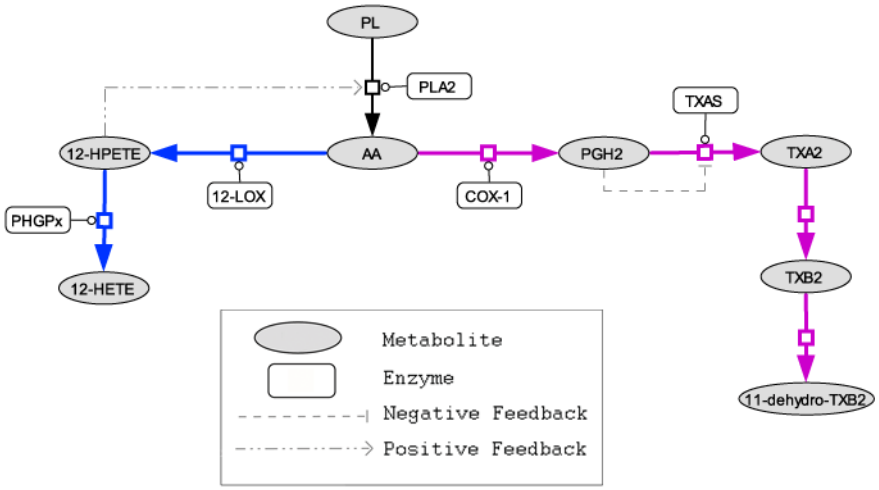
Figure S1. The AAnetwork in human PMN (**A**), EC (**B**) and PLT (**C**). Two pathways are responsible to the production of inflammatory mediators: COX-2 pathway (green) and 5-LOX pathway (red). LTB4 and PGE2 are major inflammatory mediators produced in the AAnetwork. The HETEs pathway is in blue, while the pathways of PGI2 and TXA2 production are in purple.



(**A**)

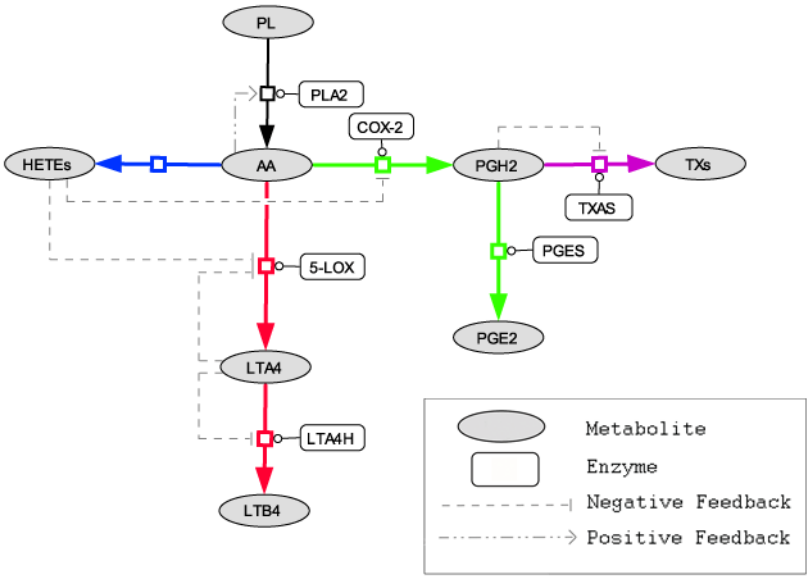


(**B**)

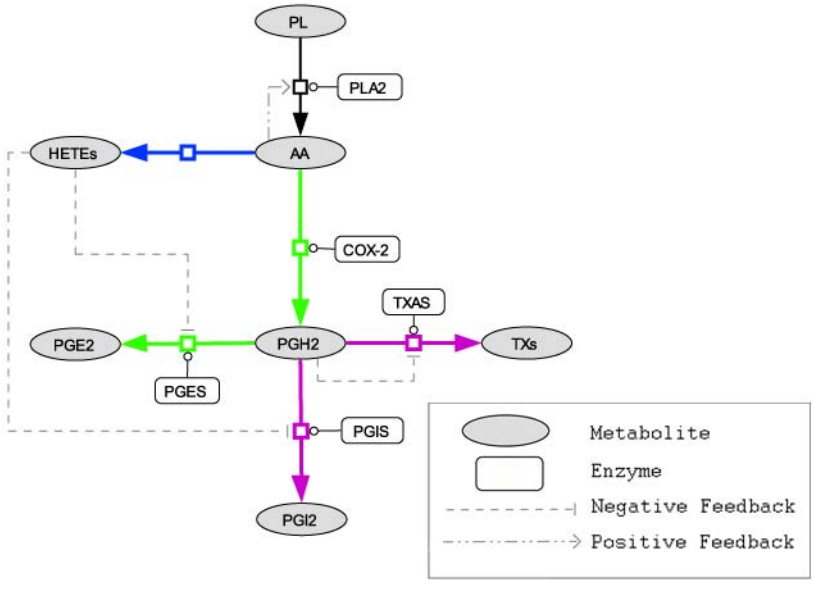


(**C**)

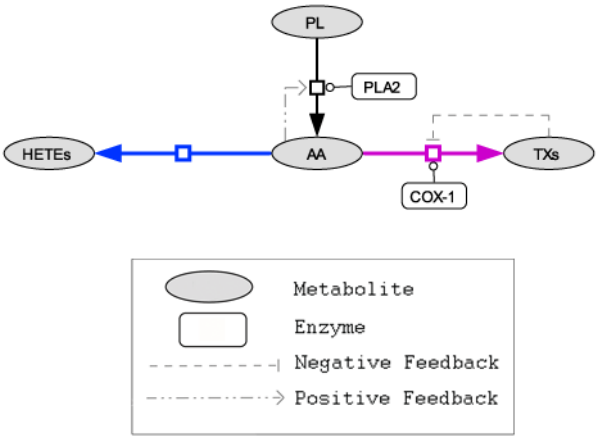
Figure S2. The simplified AAnetwork in human PMN (A), EC (B) and PLT (C). The COX-2 pathway is in green, the 5-LOX pathway is in red, the HETEs pathway is in blue, and the pathways of PGI2 and TXA2 production are in purple.


PL
PLA2
COX-2
HETEs
AA
PGH2
TXs
TXAS
PGES
5-LOX
PGE2
LTA4
LTA4H
LTB4
Metabolite
Enzyme
Negative Feedback
Positive Feedback

(**A**)

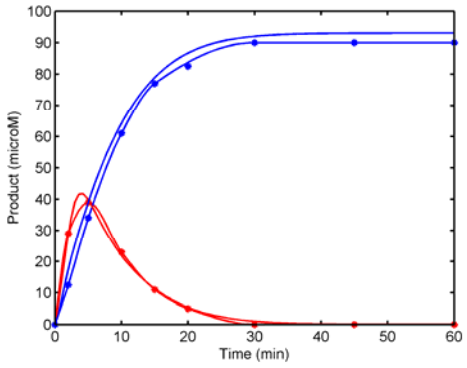

PL
PLA2
HETEs
AA
COX-2
TXAS
PGE2
PGH2
TXs
PGES
PGIS
PGI2
Metabolite
Enzyme
Negative Feedback
Positive Feedback

(**B**)

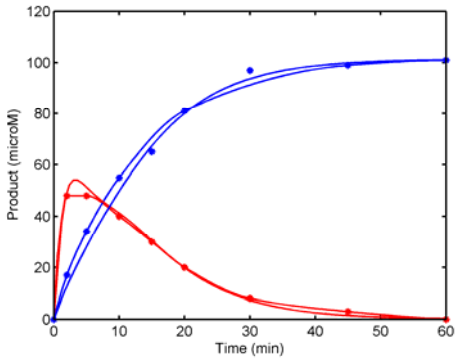


(**C**)

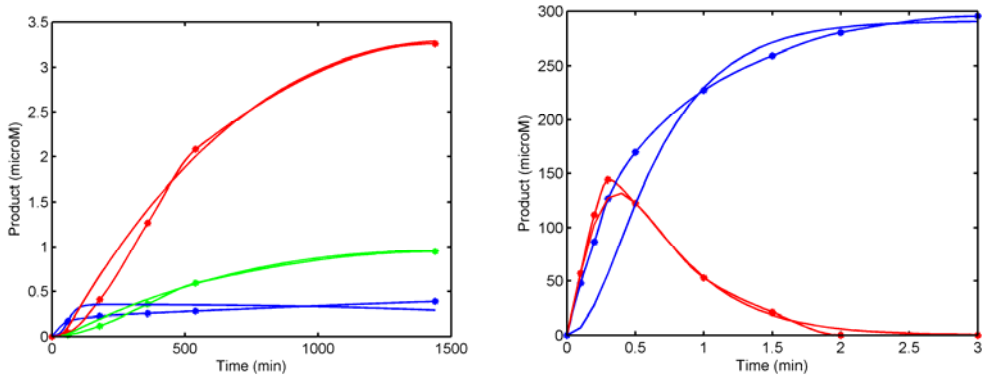
Figure S3. Experimental data and Parameter fitting results. Lines with star are experimental curves while the ones without star are model calculations with fitted parameters. (**A**) The production curve of LTB4 (red) and ω-LTB4 (blue) in PMN. In the experiment (Shak &Goldstein, 1984), PMN were incubated at 37℃ with 10 microM A23187 (a calcium ionophore) added at time zero. (**B**) The same as in (**A**), but with 10 microM A23187 + 30microM arachidonic acid added at time zero. (**C**) The production curve of PGF2α (red), PGE2 (green) and 6-keto-PGF1α (blue) in EC where 10U/mL 1L-1β was added at time zero (Camacho *et al*, 1998). (**D**) The production curve of TXA2 (red) and TXB2 (blue) in PLT, where 160 μM exogenous AA was added at time zero (Anderson *et al*, 1978).



(**A**)

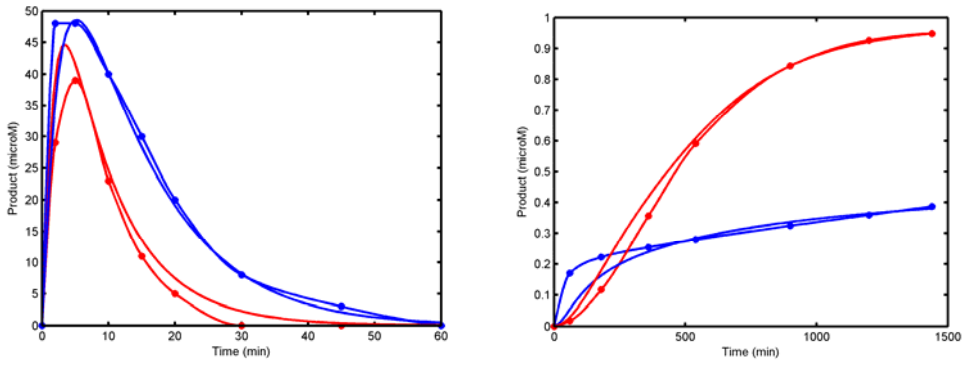


(**B**)

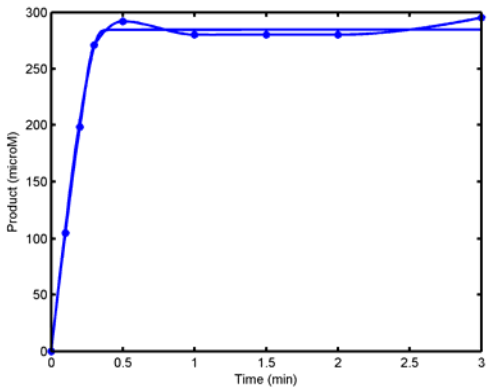


(**C**) (**D**)

Figure S4. Parameter fitting results of the simplified AAnetwork model. Lines with star are experimental curves while the ones without star are model calculations with fitted parameters. (**A**) The production curve of LTB4 in PMN. In the experiment (Shak *et al*, 1984), PMN were incubated at 37℃ with 10 microM A23187 (red) or with 10 microM A23187 + 30microM arachidonic acid (blue) added at time zero. (**B**) The production curve PGE2 (red) and PGI2 (blue) in EC where 10U/mL 1L-1β was added at time zero (Camacho *et al*, 1998). (**C**) The total production curve of TXA2 and TXB2 in PLT, where 160 μM exogenous AA was added at time zero (Anderson *et al*, 1978).

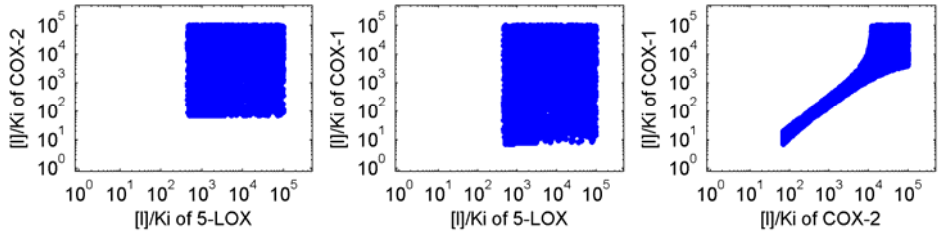


(**A**) (**B**)

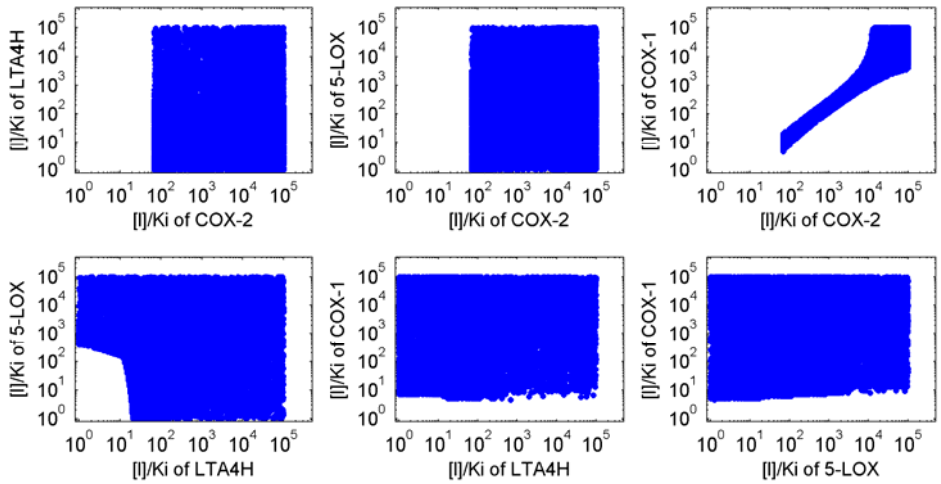


(**C**)

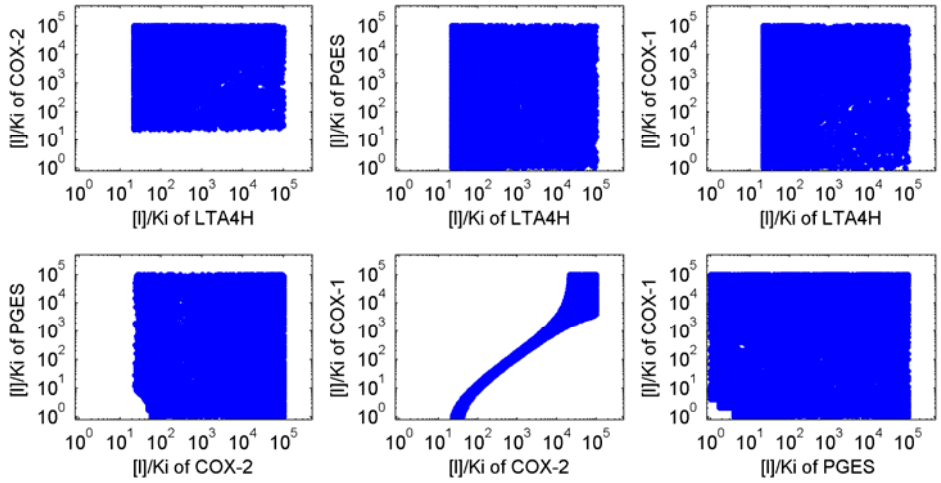
Figure S5. The distribution of [I]/Ki of MTOI solutions: the inhibitor against COX1/2 and 5-LOX (A), the inhibitor against COX1/2, 5-LOX and LTA4H (B), the inhibitor against COX1/2, PGES and LTA4H (C), the inhibitor against COX1/2, PGES and 5-LOX (D), the inhibitor against COX1/2, PGES, 5-LOX and LTA4H (E), the inhibitor against PLA2 and COX1/2 (F), the inhibitor against PLA2, COX1/2 and 5-LOX (G), the inhibitor against PLA2, COX1/2, 5-LOX and LTA4H (H), the inhibitor against PLA2, COX1/2 and PGES (I), the inhibitor against PGES and LTAH4 (J), the inhibitor against PLA2, COX1/2, PGES and LAT4H (K), the inhibitor against PLA2, COX1/2, PGES and 5-LOX (L), the inhibitor against PLA2, COX-1/2, PGES, 5-LOX and LTA4H (M).



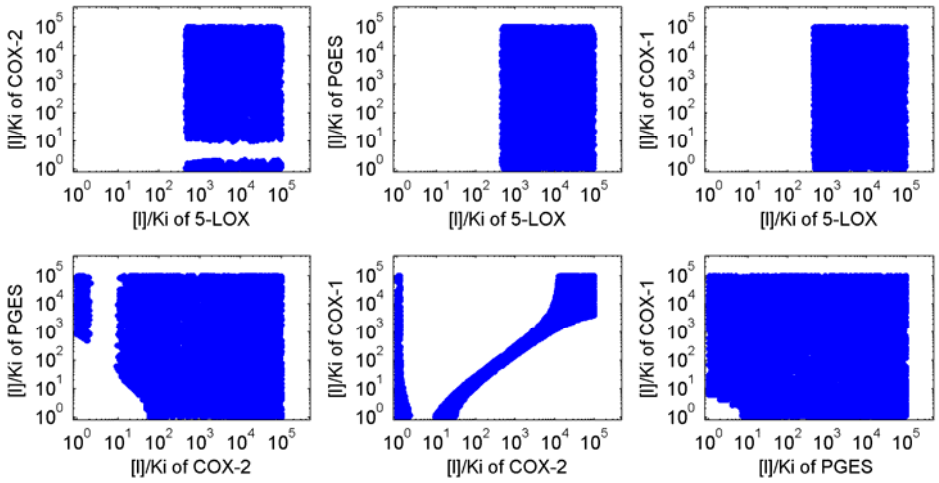
(**A**)


[I]/Ki of LTA4H
[I]/Ki of 5-LOX
[I]/Ki of COX-1
[I]/Ki of COX-2
[I]/Ki of 5-LOX
[I]/Ki of COX-1
[I]/Ki of LTA4H
[I]/Ki of 5-LOX

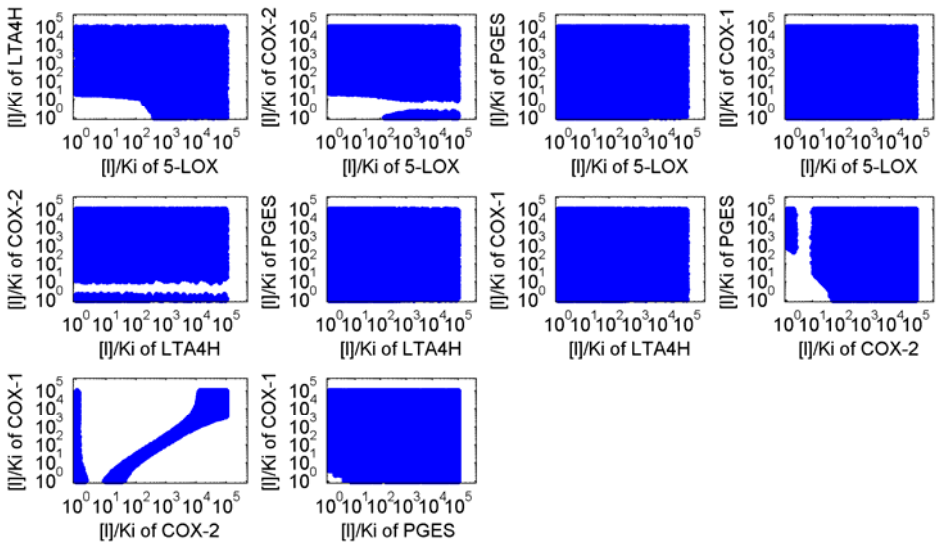
(**B**)


[I]/Ki of COX-2
[I]/Ki of PGES
[I]/Ki of COX-1
[I]/Ki of LTA4H
[I]/Ki of PGES
[I]/Ki of COX-1
[I]/Ki of COX-2
[I]/Ki of PGES

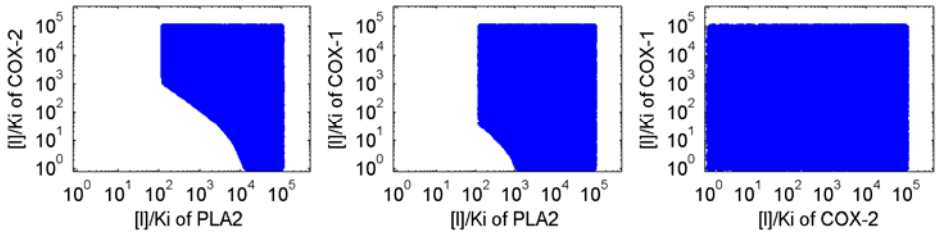
(**C**)


[I]/Ki of COX-2
[I]/Ki of 5-LOX
[I]/Ki of PGES
[I]/Ki of 5-LOX
[I]/Ki of COX-1
[I]/Ki of 5-LOX
[I]/Ki of PGES
[I]/Ki of COX-2
[I]/Ki of COX-1
[I]/Ki of COX-2
[I]/Ki of COX-1
[I]/Ki of PGES

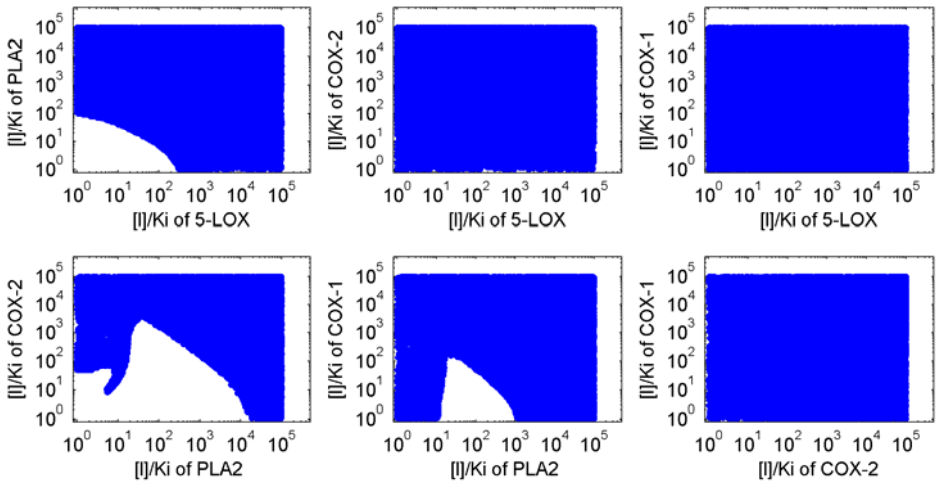
(**D**)


[I]/Ki of LTA4H
[I]/Ki of 5-LOX
[I]/Ki of COX-2
[I]/Ki of 5-LOX
[I]/Ki of PGES
[I]/Ki of 5-LOX
[I]/Ki of COX-1
[I]/Ki of 5-LOX
[I]/Ki of COX-2
[I]/Ki of LTA4H
[I]/Ki of PGES
[I]/Ki of LTA4H
[I]/Ki of COX-1
[I]/Ki of LTA4H
[I]/Ki of PGES
[I]/Ki of COX-2
[I]/Ki of COX-1
[I]/Ki of COX-2
[I]/Ki of COX-1
[I]/Ki of PGES

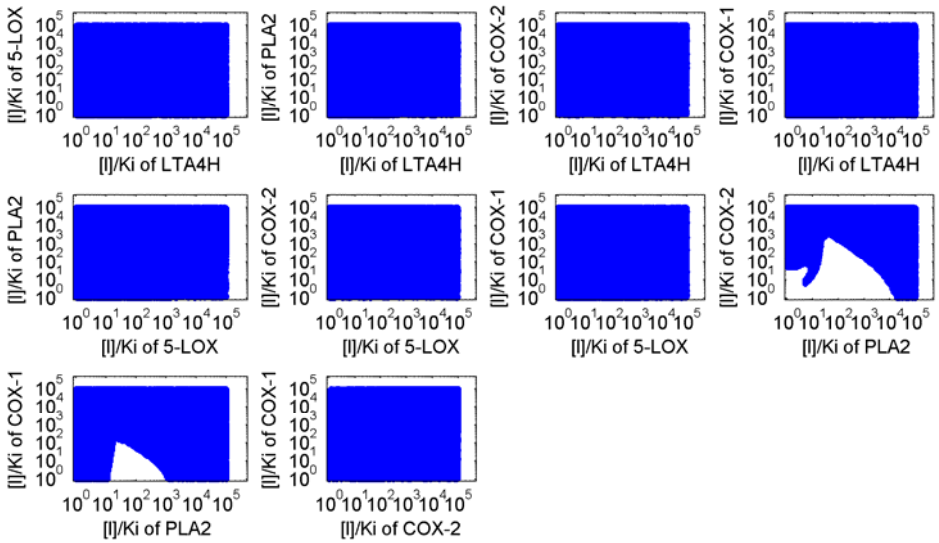
(**E**)


[I]/Ki of COX-2
[I]/Ki of PLA2
[I]/Ki of COX-1
[I]/Ki of PLA2
[I]/Ki of COX-1
[I]/Ki of COX-2

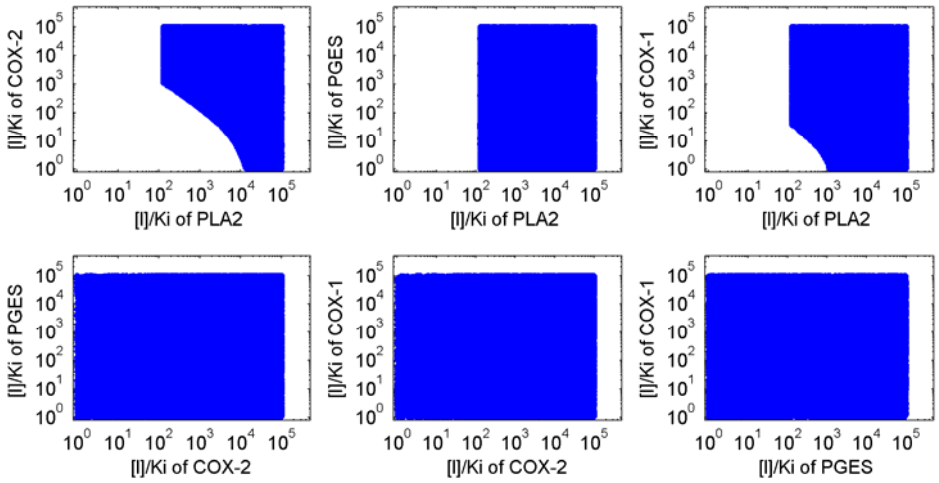
(**F**)


[I]/Ki of PLA2
[I]/Ki of 5-LOX
[I]/Ki of COX-2
[I]/Ki of 5-LOX
[I]/Ki of COX-1
[I]/Ki of 5-LOX
[I]/Ki of COX-2
[I]/Ki of PLA2
[I]/Ki of COX-1
[I]/Ki of PLA2
[I]/Ki of COX-1
[I]/Ki of COX-2

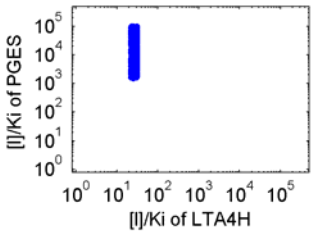
(**G**)


[I]/Ki of 5-LOX
[I]/Ki of LTA4H
[I]/Ki of PLA2
[I]/Ki of LTA4H
[I]/Ki of COX-2
[I]/Ki of LTA4H
[I]/Ki of COX-1
[I]/Ki of LTA4H
[I]/Ki of PLA2
[I]/Ki of 5-LOX
[I]/Ki of COX-2
[I]/Ki of 5-LOX
[I]/Ki of COX-1
[I]/Ki of 5-LOX
[I]/Ki of COX-2
[I]/Ki of PLA2
[I]/Ki of COX-1
[I]/Ki of PLA2
[I]/Ki of COX-1
[I]/Ki of COX-2

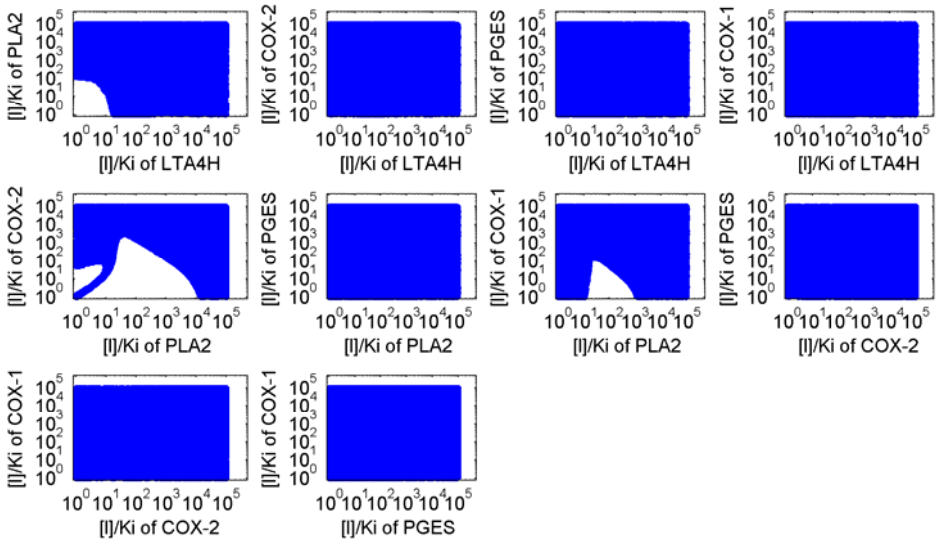
(**H**)


[I]/Ki of COX-2
[I]/Ki of PLA2
[I]/Ki of PGES
[I]/Ki of PLA2
[I]/Ki of COX-1
[I]/Ki of PLA2
[I]/Ki of PGES
[I]/Ki of COX-2
[I]/Ki of COX-1
[I]/Ki of COX-2
[I]/Ki of COX-1
[I]/Ki of PGES

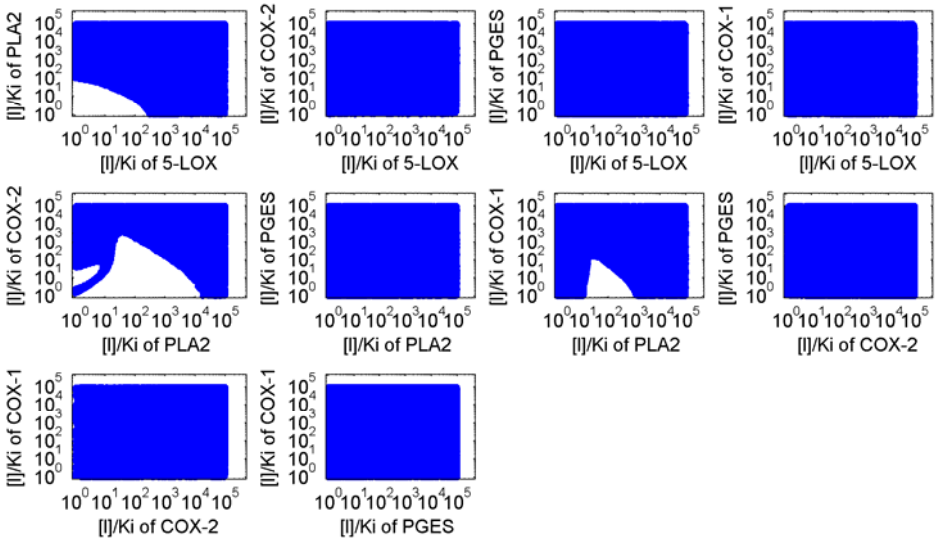
(**I**)


[I]/Ki of PGES
[I]/Ki of LTA4H

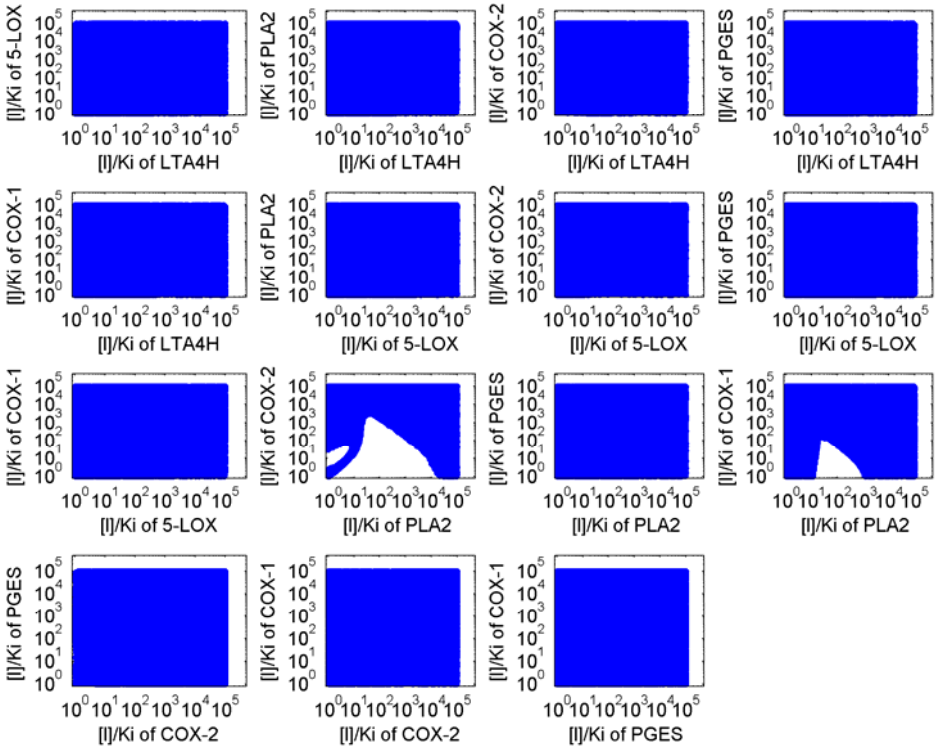
(**J**)


[I]/Ki of PLA2
[I]/Ki of LTA4H
[I]/Ki of COX-2
[I]/Ki of LTA4H
[I]/Ki of PGES
[I]/Ki of LTA4H
[I]/Ki of COX-1
[I]/Ki of LTA4H
[I]/Ki of COX-2
[I]/Ki of PLA2
[I]/Ki of PGES
[I]/Ki of PLA2
[I]/Ki of COX-1
[I]/Ki of PLA2
[I]/Ki of PGES
[I]/Ki of COX-2
[I]/Ki of COX-1
[I]/Ki of COX-2
[I]/Ki of COX-1
[I]/Ki of PGES

(**K**)



(**L**)



(**M**)

Reference

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Table SI-I. The feedback parameters used in the ODEs. Italics means the corresponding parameter has no direct value from experiments and is derived from parameter fitting. The parameter set used in the main manuscript is referred as set 1.

PMN:						
Feedbacks	Parameters	Set 1	Set 2	Set 3	Set 4	Set 5
AA→PGES (Quraishi O., et al., 2002)	$Ki_{AA\rightarrow PGES}$	0.3μM	0.3μM	0.3μM	0.3μM	0.3μM
15-HETE→PGES (Quraishi O., et al., 2002)	$Ki_{15\text{-}HETE\rightarrow PGES}$	*0.53μM*	*30μM*	*1.4μM*	*0.29μM*	*1.4μM*
PGE2→COX2 (Nathan C., 2002)	$Ki_{PGE2\rightarrow COX2}$	*2.8μM*	*30μM*	*0.13μM*	*5.2μM*	*0.13μM*
15-HPETE→TXAS (Jones D. A.&Fitzpatrick F. A., 1991)	$Ki_{15\text{-}HPETE\rightarrow TXAS}$	*0.52(μM*min)$^{-1}$*	*0.6(μM*min)-1*	*0.73(μM*min)-1*	*0.031(μM*min)-1*	*0.73(μM*min)-1*
PGH2→TXAS (Jones D. A.&Fitzpatrick F. A., 1990)	$Ki_{PGH2\rightarrow TXAS}$	*0.029(μM*min)$^{-1}$*	*0.1(μM*min)-1*	*0.018(μM*min)-1*	*3.4(μM*min)-1*	*0.018(μM*min)-1*
15-HPETE→5-LOX (Cashman J. R., et al., 1988)	$Ki_{15\text{-}HPETE\rightarrow 5\text{-}LOX}$	0.01(μM*min)$^{-1}$	0.01(μM*min)-1	0.01(μM*min)-1	0.01(μM*min)-1	0.01(μM*min)-1
12-HETE→5-LOX (Vanderhoek J. Y., et al., 1985)	$Ki_{12\text{-}HETE\rightarrow 5\text{-}LOX}$	30 μM	30 μM	30 μM	30 μM	30 μM
15-HETE→5-LOX (Vanderhoek J. Y., et al., 1985)	$Ki_{15\text{-}HETE\rightarrow 5\text{-}LOX}$	4 μM	4 μM	4 μM	4 μM	4 μM
LTA4→5-LOX (Lepley R. A.&Fitzpatrick F. A., 1994)	$Ki_{LTA4\rightarrow 5\text{-}LOX}$	0.175(μM*min)$^{-1}$	0.175(μM*min)-1	0.175(μM*min)-1	0.175(μM*min)-1	0.175(μM*min)-1
5-HPETE→5-LOX (Aharony D., et al., 1987)	$Ki_{5\text{-}HPETE\rightarrow 5\text{-}LOX}$	*0.26(μM*min)$^{-1}$*	*0.01(μM*min)-1*	*5.8(μM*min)-1*	*0.019(μM*min)-1*	*5.8(μM*min)-1*
PGE2→5-LOX (Levy B. D., et al., 2001)	$Ki_{PGE2\rightarrow 5\text{-}LOX}$	*72μM*	*15μM*	*88μM*	*25μM*	*88μM*
5-HETE→5-LOX (Aharony D., et al., 1987)	$Ki_{5\text{-}HETE\rightarrow 5\text{-}LOX}$	6.3μM	6.3μM	6.3μM	6.3μM	6.3μM
LTA4→LTA4H (Orning L., et al., 1992)	$Ki_{LTA4\rightarrow LTA4H}$	129（turnover/inactivition）	129（turnover/inactivition）	129（turnover/inactivition）	129（turnover/inactivition）	129（turnover/inactivition）
12-HETE→CYP4F3 (Soberman R. J., et al., 1987)	$Ki_{12\text{-}HETE\rightarrow CYP4F3}$	*0.29μM*	*0.2μM*	*0.46μM*	*0.12μM*	*0.46μM*
5-HETE→CYP4F3 (Soberman R. J., et al., 1987)	$Ki_{5\text{-}HETE\rightarrow CYP4F3}$	*0.8μM*	*0.86μM*	*2μM*	*2μM*	*2μM*
15-HETE→12-LOX (Kishimoto K., et al., 1996)	$Ki_{15\text{-}HETE\rightarrow 12\text{-}LOX}$	*1.5μM*	*10μM*	*0.8μM*	*58μM*	*0.8μM*
15-HPETE→12-LOX (Kishimoto K., et al., 1996)	$Ki_{15\text{-}HPETE\rightarrow 12\text{-}LOX}$	*0.23(μM*min)-1*	*10(μM*min)-1*	*2.2(μM*min)-1*	*3.4(μM*min)-1*	*2.2(μM*min)-1*
12-HPETE→12-LOX (Kishimoto K., et al., 1996)	$Ki_{12\text{-}HPETE\rightarrow 12\text{-}LOX}$	*1.6μM*	*10μM*	*16μM*	*1.1μM*	*16μM*
12-HPETE→PLA2 (Balboa M. A., et al., 2003)	$K_{12\text{-}HPETE\rightarrow PLA2}$	*260μM*	*500μM*	*150μM*	*530μM*	*150μM*
15-HPETE→PLA2 (Balboa M. A., et al., 2003)	$K_{15\text{-}HPETE\rightarrow PLA2}$	*430μM*	*200μM*	*920μM*	*210μM*	*920μM*
LTB4→PLA2 (Wijkander J., et al., 1995)	$K_{LTB4\rightarrow PLA2}$	*180μM*	*500μM*	*320μM*	*480μM*	*320μM*
5-HETE→PLA2 (Wijkander J., et al., 1995)	$K_{5\text{-}HETE\rightarrow PLA2}$	*240μM*	*500μM*	*970μM*	*990μM*	*970μM*
LTB4→5-LOX (Serio K. J., et al., 1997)	$K_{LTB4\rightarrow 5\text{-}LOX}$	*0.022(μM*min)-1*	*0.053(μM*min)-1*	*0.0153(μM*min)-1*	*0.013(μM*min)-1*	*0.0153(μM*min)-1*
PGE2→15-LOX (Levy B. D., et al., 2001)	$K_{PGE2\rightarrow 15\text{-}LOX}$	0.15	0.15	0.15	0.15	0.15
	$k_{PGE2\rightarrow 15\text{-}LOX}$	0.000023μM	0.000023μM	0.000023μM	0.000023μM	0.000023μM
Product inhibition	Ki	*500 μM*	*500 μM*	*500 μM*	*500 μM*	*500 μM*
EC:						
PGE2→COX2 (Akarasereenont P., et al., 2001)	$Ki_{PGE2\rightarrow COX2}$	30μM	30μM	30μM	30μM	30μM
15-HPETE→TXAS (Jones D. A.&Fitzpatrick F. A., 1991)	$Ki_{15\text{-}HPETE\rightarrow TXAS}$	*0.9(μM*min)-1*	*0.15(μM*min)-1*	*0.9(μM*min)-1*	*1.2(μM*min)-1*	*0.9(μM*min)-1*
PGH2→TXAS (Jones D. A.&Fitzpatrick F. A., 1990)	$Ki_{PGH2\rightarrow TXAS}$	*0.18(μM*min)-1*	*0.35(μM*min)-1*	*0.18(μM*min)-1*	*0.033(μM*min)-1*	*0.18(μM*min)-1*
15-HPETE→PGIS (Weaver J. A., et al., 2001)	$Ki_{15\text{-}HPETE\rightarrow PGIS}$	*0.18μM*	*0.01μM*	*0.18μM*	*0.46μM*	*0.18μM*
AA→PGES (Quraishi O., et al., 2002)	$Ki_{AA\rightarrow PGES}$	0.3μM	0.3μM	0.3μM	0.3μM	0.3μM
15-HETE→PGES (Quraishi O., et al., 2002)	$Ki_{15\text{-}HETE\rightarrow PGES}$	*0.91μM*	*500μM*	*0.91μM*	*5.9μM*	*0.91μM*
15d-PGJ2→PGES (Kojima F., et al., 2005)	$Ki_{15d\text{-}PGJ2\rightarrow PGES}$	*0.018(μM*min)-1*	*0.01(μM*min)-1*	*0.018(μM*min)-1*	*0.01(μM*min)-1*	*0.018(μM*min)-1*
15d-PGJ2→PLA2 (Tsubouchi Y., et al., 2001)	$Ki_{15d\text{-}PGJ2\rightarrow PLA2}$	*0.018(μM*min)-1*	*0.015(μM*min)-1*	*0.018(μM*min)-1*	*0.28(μM*min)-1*	*0.018(μM*min)-1*
12-HPETE→PLA2 (Balboa M. A., et al., 2003)	$K_{12\text{-}HPETE\rightarrow PLA2}$	*140μM*	*500μM*	*140μM*	*730μM*	*140μM*
15-HPETE→PLA2 (Balboa M. A., et al., 2003)	$K_{15\text{-}HPETE\rightarrow PLA2}$	*120μM*	*200μM*	*120μM*	*510μM*	*120μM*
PGF2→PLA2 (Husain S.&Abdel-Latif A. A., 2001)	$K_{PGF2\rightarrow PLA2}$	*210μM*	*500μM*	*210μM*	*200μM*	*210μM*
PGE2→15-LOX (Levy B. D., et al., 2001)	$K_{PGE2\rightarrow 15\text{-}LOX}$	0.15	0.15	0.15	0.15	0.15
	$k_{PGE2\rightarrow 15\text{-}LOX}$	0.000023μM	0.000023μM	0.000023μM	0.000023μM	0.000023μM
Product inhibition	Ki	*500 μM*	*500 μM*	*500 μM*	*500 μM*	*500 μM*
PLT:						
PGH2→TXAS (Jones D. A.&Fitzpatrick F. A., 1990)	$Ki_{PGH2\rightarrow TXAS}$	*0.025 (μM*min)-1*	*0.08 (μM*min)-1*	*0.025 (μM*min)-1*	*0.035 (μM*min)-1*	*0.031 (μM*min)-1*
12-HPETE→PLA2 (Balboa M. A., et al., 2003)	$K_{12\text{-}HPETE\rightarrow PLA2}$	*310μM*	*500μM*	*230μM*	*610μM*	*150μM*
Product inhibition	Ki	*500μM*	*500μM*	*500μM*	*500μM*	*500μM*

Table SI-II. The Km and Kcat of enzymes used in the ODEs. Italics means the corresponding parameter has no direct value from experiments and is derived from parameter fitting.

PMN:											
Enzyme Name	EC number	Set 1		Set 2		Set 3		Set 4		Set 5	
		K_{cat}（1/min）	K_m（μM）	K_{cat}（1/min）	K_m（μM）	K_{cat}（1/min）	K_m（μM）	K_{cat}（1/min）	K_m（μM）	K_{cat}（1/min）	K_m（μM）
15-LOX (Schomburg I., et al., 2004)	1.13.11.33	*5000*	*13*	*1000*	*70*	*4200*	*11*	*460*	*0.69*	*4200*	*11*
5-LOX (Schomburg I., et al., 2004)	1.13.11.34	*6000*	*1.4*	*5000*	*5*	*3500*	*3.3*	*520*	*2.3*	*3500*	*3.3*
LTA4H (Schomburg I., et al., 2004)	3.3.2.6	*150*	20	*125*	20	*7600*	20	*210*	20	*7600*	20
CYP4F3A (Christmas P., et al., 1999)	1.14.13.30	150	3.9	150	3.9	150	3.9	150	3.9	150	3.9
PHGPx (Schomburg I., et al., 2004)	1.11.1.12	*2000*	*58*	*500*	*70*	*600*	*0.14*	*290*	*0.12*	*600*	*0.14*
COX-2 (Schomburg I., et al., 2004)	1.14.99.1	1000	*33*	1000	*50*	1000	*0.52*	1000	*4*	1000	*0.52*
PGES (Schomburg I., et al., 2004)	5.3.99.3	3000	160	3000	160	3000	160	3000	160	3000	160
TXAS (Schomburg I., et al., 2004)	5.3.99.5	1599	4	1599	4	1599	4	1599	4	1599	4
PLA2 (Schomburg I., et al., 2004)	3.1.1.4	3600	2600	3600	2600	3600	2600	3600	2600	3600	2600
12-LOX (Schomburg I., et al., 2004)	1.13.11.31	*9500*	*160*	*1000*	*50*	*1800*	*36*	*580*	*14*	*1800*	*36*
EC:											
15-LOX (Schomburg I., et al., 2004)	1.13.11.33	*360*	*91*	*1000*	*70*	*360*	*91*	*160*	*120*	*360*	*91*
PHGPx (Schomburg I., et al., 2004)	1.11.1.12	*160*	*250*	*500*	*50*	*160*	*250*	*6900*	*1*	*160*	*250*
COX-2 (Schomburg I., et al., 2004)	1.14.99.1	*250*	5	*9000*	5	*250*	5	*100*	5	*250*	5
PGES (Schomburg I., et al., 2004)	5.3.99.3	3000	160	3000	160	3000	160	3000	160	3000	160
TXAS (Schomburg I., et al., 2004)	5.3.99.5	1599	4	1599	4	1599	4	1599	4	1599	4
PLA2 (Schomburg I., et al., 2004)	3.1.1.4	3600	2600	3600	2600	3600	2600	3600	2600	3600	2600

PGIS (Schomburg I., et al., 2004)	5.3.99.4	147	9	147	9	147	9	147	9	147	9
PGDS (Schomburg I., et al., 2004)	5.3.99.2	*6900*	4	*200*	4	*6900*	4	*240*	4	*6900*	4
PGFS (Schomburg I., et al., 2004)	1.1.1.188	*6000*	3.4	*6000*	3.4	*6000*	3.4	*1100*	3.4	*6000*	3.4
CR (Schomburg I., et al., 2004)	1.1.1.184	*110*	100	*100*	100	*110*	100	*130*	100	*110*	100
9-KPR (Schomburg I., et al., 2004)	1.1.1.189	*120*	90	*100*	90	*120*	90	*130*	90	*120*	90
15-PGDH (Schomburg I., et al., 2004)	1.1.1.196	*1700*	400	*1000*	400	*1700*	400	*950*	400	*1700*	400
12-LOX (Schomburg I., et al., 2004)	1.13.11.31	840	8	840	8	840	8	840	8	840	8
PLT:											
PHGPx (Schomburg I., et al., 2004)	1.11.1.12	*550*	*0.83*	*1000*	*5*	*120*	*4.4*	*5200*	*0.16*	*6900*	*1.4*
COX-1 (Schomburg I., et al., 2004)	1.14.99.1	*6000*	4.5	*1000*	4.5	*9500*	4.5	*1100*	4.5	*9500*	4.5
TXAS (Schomburg I., et al., 2004)	5.3.99.5	1599	4	1599	4	1599	4	1599	4	1599	4
PLA2 (Schomburg I., et al., 2004)	3.1.1.4	3600	2600	3600	2600	3600	2600	3600	2600	3600	2600
12-LOX (Schomburg I., et al., 2004)	1.13.11.31	840	8	840	8	840	8	840	8	840	8

Table SI-III. The decay rate of molecules used in ODEs. All the decay rate has no direct value from experiments and is derived from parameter fitting

PMN:					
Decay rate	Set 1（1/min）	Set 2（1/min）	Set 3（1/min）	Set 4（1/min）	Set 5（1/min）
$Kd_{15\text{-}HPETE}$	0.36	0.05	0.1	8.7	0.1
$Kd_{15\text{-}HETE}$	0.1	0.1	6.00E-05	0.1	6.00E-05
Kd_{TXA}	1.00E-04	0.8	0.55	2	0.55
Kd_{TXB}	1.30E-03	0.5	2.80E-04	2	2.80E-04
$Kd_{5\text{-}HETE}$	4.20E-04	0.001	3.50E-05	1.80E-04	3.50E-05
Kd_{LTA4}	1.70E-03	0.07	0.02	8.30E-04	0.02
Kd_{LTB4}	6.30E-04	0.01	5.50E-04	6.00E-05	5.50E-04
$Kd_{15\text{-}LOX}$	8.30E-04	0	5.50E-04	1.1	5.50E-04
Kd_{exoAA}	0.017	0.5	1.30E-03	2.5	1.30E-03
Kd_{AA}	0.14	0.1	0.16	2.5	0.16
EC:					
$Kd_{15\text{-}HPETE}$	1.10E-03	0.5	1.10E-03	0.01	1.10E-03
$Kd_{15\text{-}HETE}$	0.55	0.1	0.55	0.03	0.55
$Kd_{12\text{-}HETE}$	2.10E-04	0.1	2.10E-04	2.90E-03	2.10E-04
Kd_{PGH2}	1.2	0.25	1.2	6.40E-03	1.2
Kd_{TXA}	3	3.2	3	5	3
Kd_{TXB}	3	3.2	3	5	3
Kd_{PGI2}	3.8	0.003	3.8	1.90E-03	3.8
Kd_{PGF2}	0.048	0.04	0.048	0.011	0.048
Kd_{PGD2}	9.50E-04	0.025	9.50E-04	7.90E-05	9.50E-04
Kd_{PGJ2}	2.40E-04	0.04	2.40E-04	0.18	2.40E-04
$Kd_{15\text{-}LOX}$	1.7	0.01	1.7	5.80E-03	1.7
PLT:					
Kd_{TXA}	2.5	2.3	2.5	2.5	2.5
Kd_{TXB}	6.90E-05	1.00E-04	0.01	4.40E-03	0.02

Table SI-IV. Initial concentrations used in ODEs. All the initial concentration has no direct value from experiments and is derived from parameter fitting

PMN:					
Initial concentrations	Set 1（μM）	Set 2（μM）	Set 3（μM）	Set 4（μM）	Set 5（μM）
$[AA]_0$	0.001	0.001	0.001	0.001	0.001
$[15\text{-}HPETE]_0$	0.001	0.001	0.001	0.001	0.001
$[15\text{-}HETE]_0$	0.001	0.001	0.001	0.001	0.001
$[12\text{-}HPETE]_0$	0.001	0.001	0.001	0.001	0.001
$[12\text{-}HETE]_0$	0.001	0.001	0.001	0.001	0.001
$[PGH2]_0$	0.001	0.001	0.001	0.001	0.001
$[PGE2]_0$	0.001	0.001	0.001	0.001	0.001
$[TXA2]_0$	0.001	0.001	0.001	0.001	0.001
$[TXB2]_0$	0.001	0.001	0.001	0.001	0.001
$[5\text{-}HPETE]_0$	0.001	0.001	0.001	0.001	0.001
$[5\text{-}HETE]_0$	0.001	0.001	0.001	0.001	0.001
$[LTA4]_0$	0.001	0.001	0.001	0.001	0.001
$[LTB4]_0$	0.001	0.001	0.001	0.001	0.001
$[20\text{-}OH\text{-}LTB4]_0$	0.001	0.001	0.001	0.001	0.001
$[15\text{-}LOX]_0$	6.30E-03	1.5	4.00E-03	0.11	4.00E-03
$[12\text{-}LOX]_0$	2.5	0.5	6.9	0.69	6.9
$[TXAS]_0$	0.083	0.1	0.13	2.10E-03	0.13
$[5\text{-}LOX]_0$	1.1	5	0.69	0.58	0.69
$[LTA4H]_0$	0.83	0.76	1.1	0.76	1.1
$[lin\_PMN]_0$	4.4	12	2.2	17	2.2
$[PLA2]_0$	4.8	1.5	9.1	2.5	9.1
$[COX\text{-}2]_0$	0.63	0.8	0.012	1	0.012
$[PGES]_0$	5.20E-03	0.5	1.9	4.00E-03	1.9
$[CYP4F3]_0$	0.13	0.07	0.14	0.12	0.14
$[PHGPx]_0$	0.069	0.8	5.20E-03	3.30E-03	5.20E-03
$[exoAA]_0$	0	0	0	0	0
	30	30	30	30	30

EC:					
$[AA]_0$	0.001	0.001	0.001	0.001	0.001
$[15\text{-HPETE}]_0$	0.001	0.001	0.001	0.001	0.001
$[15\text{-HETE}]_0$	0.001	0.001	0.001	0.001	0.001
$[12\text{-HPETE}]_0$	0.001	0.001	0.001	0.001	0.001
$[12\text{-HETE}]_0$	0.001	0.001	0.001	0.001	0.001
$[PGH2]_0$	0.001	0.001	0.001	0.001	0.001
$[TXA2]_0$	0.001	0.001	0.001	0.001	0.001
$[TXB2]_0$	0.001	0.001	0.001	0.001	0.001
$[PGI2]_0$	0.001	0.001	0.001	0.001	0.001
$[6\text{-Keto-PGF1}\alpha]_0$	0.001	0.001	0.001	0.001	0.001
$[PGD2]_0$	0.001	0.001	0.001	0.001	0.001
$[PGJ2]_0$	0.001	0.001	0.001	0.001	0.001
$[15\text{d-PGJ2}]_0$	0.001	0.001	0.001	0.001	0.001
$[PGE2]_0$	0.001	0.001	0.001	0.001	0.001
$[PGF2\alpha]_0$	0.001	0.001	0.001	0.001	0.001
$[15\text{-Keto-PGF2}\alpha]_0$	0.001	0.001	0.001	0.001	0.001
$[PLA2]_0$	0.08	0.5	0.08	0.16	0.08
$[15\text{-LOX}]_0$	5.70E-03	1.5	5.70E-03	8	5.70E-03
$[TXAS]_0$	7.2	0.7	7.2	0.01	7.2
$[PGES]_0$	0.025	0.0034	0.025	3.10E-04	0.025
$[lin\_EC]_0$	5	5	5	16	5
$[12\text{-LOX}]_0$	3.20E-04	1.5	3.20E-04	2.3	3.20E-04
$[COX\text{-}2]_0$	0.11	3	0.11	1.4	0.11
$[PGIS]_0$	0.35	0.5	0.35	6.00E-04	0.35
$[PGDS]_0$	0.064	2.5	0.064	6.40E-03	0.064
$[PGFS]_0$	1.80E-03	5	1.80E-03	0.025	1.80E-03
$[CR]_0$	3.00E-04	6.00E-04	3.00E-04	2.00E-04	3.00E-04
$[9\text{-KPR}]_0$	5.00E-04	6.50E-04	5.00E-04	4.00E-04	5.00E-04
$[15\text{-PGDH}]_0$	3.50E-04	8.00E-04	3.50E-04	2.50E-04	3.50E-04
$[PHGPx]_0$	0.57	0.05	0.57	3.20E-03	0.57
PLT:					
$[AA]_0$	0.001	0.001	0.001	0.001	0.001
$[12\text{-HPETE}]_0$	0.001	0.001	0.001	0.001	0.001
$[12\text{-HETE}]_0$	0.001	0.001	0.001	0.001	0.001
$[PGH2]_0$	0.001	0.001	0.001	0.001	0.001
$[TXA2]_0$	0.001	0.001	0.001	0.001	0.001
$[TXB2]_0$	0.001	0.001	0.001	0.001	0.001
$[TXAS]_0$	0.51	0.635	0.58	0.54	0.62
$[lin\_PLT]_0$	1	12	20	0.5	16.5
$[PLA2]_0$	0.19	0.1	3.10E-03	0.15	7.50E-03
$[12\text{-LOX}]_0$	0.82	0.5	0.039	0.44	0.084
$[PHGPx]_0$	2.20E-03	0.5	9.20E-03	0.17	6.10E-03
$[COX\text{-}1]_0$	0.19	0.85	0.15	0.94	0.15

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Table SII-I. Drug target search result by MTOI. The desired state was defined as a state where the cumulative output of LTB4 and PGE2 should be smaller than 10% of that in the disease state, respectively

Set 2:	Rank	Enzyme	abs(MD/SD)	MD	Set 3:	Enzyme	abs(MD/SD)	MD	Set 4:	Enzyme	abs(MD/SD)	MD	Set 5:	Enzyme	abs(MD/SD)	MD
	1	PLA2	1.1092	-1.04		COX-2	1.2919	-1.08		PGES	0.7292	-0.76		COX-2	1.1868	-1.08
	2	LTA4H	0.9709	-0.92		PLA2	0.9308	-1.16		LTA4H	0.7206	-0.76		PLA2	0.7961	-1
	3	COX-2	0.3992	-0.44		5-LOX	0.577	-0.56		PLA2	0.6673	-0.76		PGES	0.6302	-0.68
	4	5-LOX	0.3636	-0.44		PGES	0.541	-0.6		5-LOX	0.5284	-0.56		5-LOX	0.5163	-0.52
	5	15-LOX	0.2394	0.28		LTA4H	0.428	-0.48		COX-2	0.4202	-0.44		PHGPx	0.4223	0.48
	6	TXAS	0.2082	0.24		PHGPx	0.3431	0.4		PHGPx	0.3091	0.36		LTA4H	0.3968	-0.44
	7	CYP4F3	0.1715	0.2		PGDS	0.1404	0.16		TXAS	0.1029	0.12		PGDS	0.1032	0.12
	8	PGES	0.171	-0.2		TXAS	0.1058	0.12		15-LOX	0.1024	0.12		15-LOX	0.1024	0.12
	9	PGDS	0.1052	0.12		15-LOX	0.1025	-0.12		CYP4F3	0.0692	0.08		CYP4F3	0.1014	0.12
	10	PHGPx	0.0678	0.08		9-KPR	0.0696	0.08		PGIS	0.0349	0.04		TXAS	0.0696	0.08
	11	9-KPR	0.0345	0.04		PGIS	0.0348	0.04		PGDS	0.0347	0.04		PGFS	0.0346	-0.04
	12	PGIS	0.0343	-0.04		CR	0.0346	-0.04		9-KPR	0.0347	-0.04		CR	0.0346	0.04
	13	12-LOX	0.0342	0.04		12-LOX	0.0345	0.04		CR	0.0346	0.04		12-LOX	0.0343	0.04
	14	PGFS	0	0		COX-1	0	0		12-LOX	0.0346	-0.04		COX-1	0	0
	15	COX-1	0	0		CYP4F3	0	0		COX-1	0	0		15-PGDH	0	0
	16	12-PGDH	0	0		15-PGDH	0	0		15-PGDH	0	0		9-KPR	0	0
	17	CR	0	0		PGFS	0	0		PGFS	0	0		PGIS	0	0

Table SII-II. Drug target search result by MTOI. The desired state was defined as a state where the cumulative output of LTB4 and PGE2 should be smaller than 20% of that in the disease state, respectively

Set 1:	Rank	Enzyme	abs(MD/SD)	MD	Set 2:	Enzyme	abs(MD/SD)	MD	Set 3:	Enzyme	abs(MD/SD)	MD	Set 4:	Enzyme	abs(MD/SD)	MD	Set 5:	Enzyme	abs(MD/SD)	MD
	1	PLA2	0.7123	-0.8		PLA2	0.8923	-0.96		COX-2	0.9421	-0.88		PGES	0.6489	-0.68		COX-2	1.0209	-0.92
	2	PGES	0.6948	-0.72		LTA4H	0.7178	-0.68		PLA2	0.8185	-1		LTA4H	0.5744	-0.6		PLA2	0.6993	-0.88
	3	LTA4H	0.6244	-0.64		COX-2	0.3739	-0.4		PGES	0.5058	-0.56		PLA2	0.5576	-0.64		PGES	0.4687	-0.52
	4	COX-2	0.5711	-0.6		PGES	0.2408	-0.28		PHGPx	0.3432	0.4		5-LOX	0.41	-0.44		LTA4H	0.3164	-0.36
	5	5-LOX	0.4513	-0.52		5-LOX	0.2376	-0.28		5-LOX	0.3323	-0.32		COX-2	0.3226	-0.36		5-LOX	0.2864	-0.28
	6	CYP4F3	0.3482	0.4		12-LOX	0.2035	0.24		LTA4H	0.212	-0.24		PHGPx	0.2059	0.24		PHGPx	0.2748	0.32
	7	PHGPx	0.3191	0.36		CYP4F3	0.1723	0.2		TXAS	0.1762	0.2		15-LOX	0.1379	0.16		TXAS	0.1398	0.16
	8	TXAS	0.1431	0.16		PGDS	0.1048	0.12		PGDS	0.105	0.12		CYP4F3	0.0694	0.08		CYP4F3	0.1033	0.12
	9	PGDS	0.1035	0.12		PHGPx	0.0683	0.08		15-LOX	0.07	-0.08		TXAS	0.0348	0.04		9-KPR	0.0699	0.08
	10	9-KPR	0.0348	-0.04		COX-1	0	0		CYP4F3	0.0697	0.08		PGDS	0.0347	0.04		15-LOX	0.0353	-0.04
	11	PGIS	0.034	0.04		15-PGDH	0	0		12-LOX	0.068	0.08		12-LOX	0.0341	0.04		PGDS	0.0348	0.04
	12	15-LOX	0	0		9-KPR	0	0		9-KPR	0.0348	0.04		COX-1	0	0		12-LOX	0.0341	-0.04
	13	COX-1	0	0		CR	0	0		PGIS	0	0		15-PGDH	0	0		PGFS	0	0
	14	15-PGDH	0	0		PGFS	0	0		COX-1	0	0		9-KPR	0	0		COX-1	0	0
	15	CR	0	0		PGIS	0	0		15-PGDH	0	0		CR	0	0		15-PGDH	0	0
	16	PGFS	0	0		TXAS	0	0		CR	0	0		PGFS	0	0		CR	0	0
	17	12-LOX	0	0		12-LOX	0	0		PGFS	0	0		PGIS	0	0		PGIS	0	0

Table SIII-I. The feedback parameters used in the ODEs. Italics means the corresponding parameter has no direct value from experiments and is derived from parameter fitting.

PMN:		
Feedbacks	Parameters	value
HETEs→COX2	$Ki_{HETEs→COX2}$	*0.61μM*
HETEs→5-LOX	$Ki_{HETEs→5\text{-}LOX}$	*0.78μM*
LTA4→5-LOX	$Ki_{LTA4→5\text{-}LOX}$	*0.012(μM*min)* $^{-1}$
LTA4→LTA4H	$Ki_{LTA4→LTA4H}$	*0.016(μM*min)* $^{-1}$
PGH2→TXAS	$Ki_{PGH2→TXAS}$	*8.8(μM*min)* $^{-1}$
AA→PLA2	$Ki_{AA→PLA2}$	*480μM*
Product inhibition	Ki	*500 μM*
EC:		
HETEs→PGES	$Ki_{HETEs→PGES}$	*500μM*
HETEs→PGIS	$Ki_{HETEs→PGIS}$	*0.12μM*
PGH2→TXAS	$Ki_{PGH2→TXAS}$	*1.2(μM*min)-1*
AA→PLA2	$Ki_{AA→PLA2}$	*900μM*
Product inhibition	Ki	*500 μM*
PLT:		
PGH2→COX1	$Ki_{PGH2→COX1}$	*0.013 (μM*min)-1*
AA→PLA2	$K_{AA→PLA2}$	*220μM*
Product inhibition	Ki	*500μM*

Table SIII-II. The Km and Kcat of enzymes used in the ODEs. Italics means the corresponding parameter has no direct value from experiments and is derived from parameter fitting.

PMN:			
Enzyme Name	EC Number	K_{cat}（1/min）	K_m（μM）
E1	---	*290*	*28*
5-LOX	1.13.11.34	*2900*	*0.11*
LTA4H	3.3.2.6	*4200*	20

COX-2	1.14.99.1	1000	*76*
PGES	5.3.99.3	3000	160
TXAS	5.3.99.5	1599	4
PLA2	3.1.1.4	3600	2600
EC:			
E1	---	*600*	*58*
COX-2	1.14.99.1	*220*	5
PGES	5.3.99.3	3000	160
TXAS	5.3.99.5	1599	4
PLA2	3.1.1.4	3600	2600
PGIS	5.3.99.4	147	9
PLT:			
COX-1	1.14.99.1	*1300*	4.5
PLA2	3.1.1.4	3600	2600
E1	---	*910*	*69*

Table SIII-III. The decay rate of molecules used in ODEs. All the decay rate has no direct value from experiments and is derived from parameter fitting

PMN:	
Decay rate	value（1/min）
Kd_{HETEs}	0.01
Kd_{LTB4}	0.12
EC:	
Kd_{HETEs}	1.00E-04
Kd_{PGH2}	1.00E-04
Kd_{PGE2}	0.0066
PLT:	
Kd_{HETEs}	2.00E-05

Table SIII-IV. Initial concentrations used in ODEs. All the initial concentration has no direct value from experiments and is derived from parameter fitting

PMN:	
Initial concentrations	value（μM）
$[HETEs]_0$	0.001
$[PGH2]_0$	0.001
$[PGE2]_0$	0.001
$[TXs]_0$	0.001
$[LTA4]_0$	0.001
$[LTB4]_0$	0.001
$[5\text{-}LOX]_0$	0.083
$[LTA4H]_0$	0.014
$[TXAS]_0$	2.1
$[lin\_PMN]_0$	5.5
$[PLA2]_0$	10
$[COX\text{-}2]_0$	0.0044
$[PGES]_0$	0.025
$[E1]_0$	5.2
$[AA]_0$	0.001
	30
EC:	
$[AA]_0$	0.001
$[HETEs]_0$	0.001
$[PGH2]_0$	0.001
$[TXs]_0$	0.001
$[PGI2]_0$	0.001
$[PGE2]_0$	0.001
$[PLA2]_0$	0.022
$[E1]_0$	1.30E-04

$[TXAS]_0$	0.0023
$[PGES]_0$	0.067
$[lin\_EC]_0$	2.2
$[COX\text{-}2]_0$	3.20E-06
$[PGIS]_0$	0.195
PLT:	
$[AA]_0$	0.001
$[HETEs]_0$	0.001
$[TXs]_0$	0.001
$[lin\_PLT]_0$	340
$[PLA2]_0$	0.0011
$[E1]_0$	0.72
$[COX\text{-}1]_0$	0.88

Table SIV Multi-target intervention solutions found by MTOI for the simplified AAnetwork model. “---” denotes no regulation and “√” denotes that the corresponding enzyme is inhibited.

	PLA2	COX-2	PGES	5-LOX	LTA4H	COX-1
No.1	√	---	---	---	√	---
No.2	√	√	√	√	---	√
No.3	---	√	√	---	√	√
No.4	√	√	√	---	√	√
No.5	---	√	---	√	√	√
No.6	√	---	---	√	√	---
No.7	√	√	---	---	√	√
No.8	---	√	√	√	√	√
No.9	√	---	√	√	√	---
No.10	√	---	√	---	√	---
No.11	√	√	---	√	---	√
No.12	---	√	---	---	√	√
No.13	√	√	√	√	√	√
No.14	√	√	---	√	√	√

Table SV. The result of single parameter sensitivity analysis. Top 30 parameters are listed in the table. Kcat is turnover number, Km is Michaelis-Menten constant, con is concentration. “K(PGE2→15-LOX)” denotes the feedback constant of PGE2 to 15-LOX.

Rank	Parameter	Sensitivity
1	Km(PLA2)	0.7393
2	Kcat(PLA2)	0.7369
3	con(PLA2)	0.7014
4	Km(PGES)	0.5656
5	Kcat(PGES)	0.552
6	con(PGES)	0.4593
7	Kcat(15-LOX)	0.3875
8	K(PGE2→15-LOX)	0.3869
9	Km(15-LOX)	0.3831
10	K(LTA4→LTA4H)	0.359
11	con(LTA4H)	0.2838
12	con(COX-2)	0.268
13	K(15-HETE→PGES)	0.2672
14	Kcat(COX)	0.261
15	Km(COX)	0.2337
16	con(PHGPx)	0.232
17	Km(PHGPx)	0.2264
18	Kcat(PHGPx)	0.2257
19	K(LTB4→PLA2)	0.1674
20	K(15HPETE→TXAS)	0.112
21	con(TXAS)	0.0843
22	K(15HPETE→PLA2)	0.0819
23	Kcat(TXAS)	0.0723
24	Km(TXAS)	0.0715
25	Kcat(PGDS)	0.0699
26	con(PGDS)	0.0693
27	Km(PGDS)	0.0693
28	Kcat(5-LOX)	0.069
29	con(5-LOX)	0.069
30	Kcat(LTA4H)	0.0657