Supplementary Information

Control of Cholesterol homeostasis by Entero-hepatic bile transport – Role of feedback mechanisms

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The model details are presented below. The model equations for the network shown in Fig 1 (and Fig S1) are also presented below.

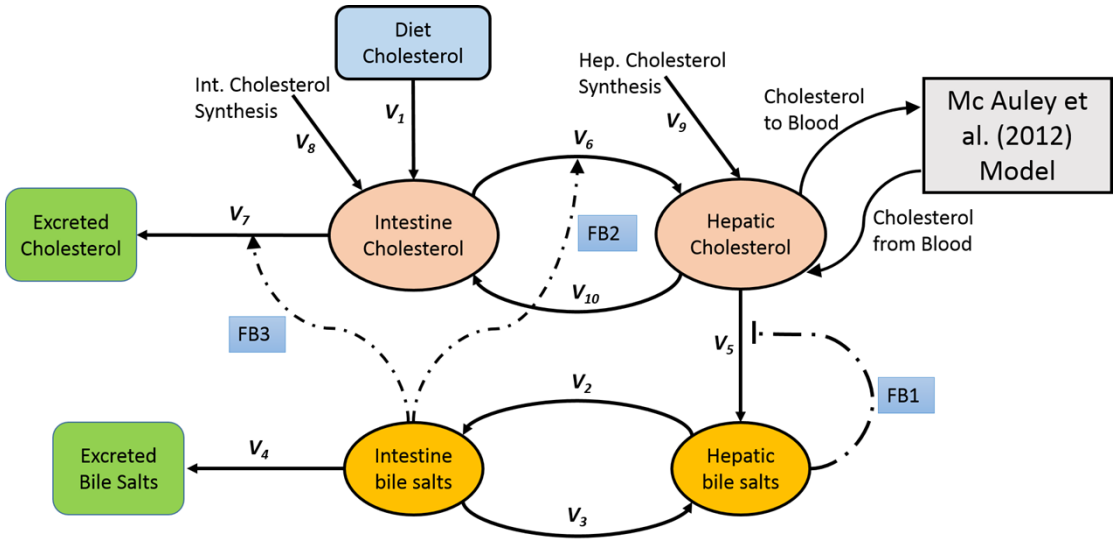

Figure S1

Parameters description for cholesterol model

$MW_{chol} = 386.65\ g/mol;$

$MW_{chol-est} = 386.65\ g/mol;$

$MW_{bile} = 430.6\ g/mol;$

$Vol_L = 1.5\ L;$

$Vol_I = 1.9\ L;$

$Vol_P = 25\ L;$

$VC = 10;$

$Time = 1440\ min;$

Parameters	Rate Description	Values	Units
k1	Diet absorption in to the intestine	$\frac{1}{Time}$	min^{-1}
k2	Transport of bile salts from liver to intestine	$\frac{6.0}{Time}$	min^{-1}
k3	Transport of bile salts from intestine to liver	$\frac{4.29}{Time}$	min^{-1}

k4	Excretion of bile salts from intestine	$\frac{0.856}{Time}$	min^{-1}
k5	Synthesis of hepatic bile salts from hepatic free cholesterol	$\frac{2.66}{MW_{bile} * Vol_L * Ti}$	mM/min
k6	Intestinal cholesterol absorption (from intestine to liver)	$(5.286 * 10^{-4}) * V$	$mM^{-1}min^{-1}$
k7	Intestinal cholesterol excretion	$(5.286 * 10^{-4}) * V$	$mM^{-1}min^{-1}$
Kdc	Km value for Diet absorption	$\frac{304}{MW_{chol} * Vol_I}$	mM
Kbs1	Km value for hepatic bile synthesis (substrate)	103.45	mM
Kbs2	Km value for hepatic bile synthesis (regulation)	0.62	mM
nbs	Cooperativity for regulation in hepatic bile synthesis	2	–
Kic1	Km value for intestinal cholesterol absorption (regulation)	$2 * 0.571$	mM
Kic2	Km value for intestinal cholesterol absorption (substrate)	$2 * 4.28$	mM
nic1	Cooperativity for regulation in intestinal cholesterol absorption	2.5	–
nic2	Cooperativity for substrate kinetics in intestinal cholesterol absorption	1	–
Kbe	Km value for intestinal bile excretion	0.571	mM
ICS_{max}	Vmax for intestinal cholesterol synthesis	$\frac{10^2}{MW_{chol} * Vol_I * Ti}$	mM/min
IC_t	Km for intestinal cholesterol synthesis	$\frac{3.12 * 10^3}{MW_{chol} * Vol_I}$	mM
IS	Cooperativity for intestinal cholesterol synthesis	5	–
HCS_{max}	Vmax for hepatic cholesterol synthesis	$\frac{5 * 10^2}{MW_{chol} * Vol_L * Ti}$	mM/min
HC_t	Km for hepatic cholesterol synthesis	$\frac{9.3925 * 10^4}{MW_{chol} * Vol_L}$	mM
HS	Cooperativity for hepatic cholesterol synthesis	5	–
BCR_{max}	Vmax for biliary cholesterol release	$\frac{2 * 10^3}{MW_{chol} * Vol_L * Ti}$	mM/min
BCR_t	Km for biliary cholesterol release	$\frac{5.5326 * 10^4}{MW_{chol} * Vol_L}$	mM
BS	Cooperativity for biliary cholesterol release	5	–
Diet chol	Dietary cholesterol	$\frac{304}{MW_{chol} * Vol_I}$	mM

Reaction Rate	Description	Rate Expression

$V_1 : Diet\_absp$	Rate of absorption of cholesterol from diet	$k1 * DC$
$V_2 : BS\_release$	Rate of bile salt release from liver to intestine	$k2 * HBS$
$V_3 : HBS\_return$	Rate of bile salt transport from intestine to liver	$k3 * IBS$
$V_4 : BS\_excr$	Rate of bile salt excretion from the intestine	$(k4 * 0.571 * 2) * \left(\frac{IBS}{Kbe + IBS}\right) * Eff$
$V_5 : BS\_synth$		$\left(k5 * 2 * \frac{103.45}{0.62} * \left(\frac{0.62^{nbs} + Kbs2^{nbs}}{Kbs2^{nbs}}\right)\right.$
$V_6 : Int\_chol\_absp$	Rate of cholesterol absorption from intestine into liver	$(k6 * 0.571 * 4.28) * \left(\frac{0.571^{nic1} + Kic}{0.571^{nic1}}\right.$ $* \left(\frac{IBS^{nic1}}{IBS^{nic1} + Kic1^{nic1}}\right) * \left(\frac{}{IC^{n}}\right.$
$V_7 : Int\_chol\_excr$	Rate of excretion of cholesterol from the intestine	$(k7 * 0.571 * 2) * \left(\frac{IBS}{IBS + Kie}\right) * IC *$
$V_8 : IC\_synth$	Rate of cholesterol biosynthesis in the intestine	$\frac{ICS_{max}}{1 + \left(\frac{IC}{IC_t}\right)^{IS}}$
$V_9 : HC\_synth$	Rate of cholesterol biosynthesis in the liver	$\frac{HCS_{max}}{1 + \left(\frac{HFC}{HC_t}\right)^{HS}}$
$V_{10} : BC\_release$	Rate of cholesterol release from the liver into the bile	$\frac{BCR_{max}}{1 + \left(\frac{BCR_t}{HFC}\right)^{BS}}$
$HDLC\_synth$	Synthesis of HDLC from nascent HDL and peripheral cholesterol	Referred from Mc Auley et al.
Hep_VLDLC_synth	Rate of synthesis of VLDLC in the liver and secretion into the blood stream	Referred from Mc Auley et al.
HCE_to_HFC	Rate of hydrolysis of cholesterol ester in liver	Referred from Mc Auley et al.
HFC_to_HCE	Rate of esterification of cholesterol in liver	Referred from Mc Auley et al.
$Hep\_IDLC\_removal$	Rate of IDLC uptake by the liver	Referred from Mc Auley et al.
$Hep\_VLDLC\_removal$	Rate of VLDLC uptake by the liver	Referred from Mc Auley et al.
Hep_up_LDLC	Rate of LDLC uptake by liver through receptors	Referred from Mc Auley et al.
$Hep\_up\_LDLC\_indep$	Rate of receptor-independent LDLC uptake by liver	Referred from Mc Auley et al.
Hep_up_HDLC	Rate of uptake of HDLC particles by the liver	Referred from Mc Auley et al.

Ordinary Differential Equations for Cholesterol Metabolism

------ Total Cholesterol -----

$$\frac{d(TC)}{dt} = HDLC\_synth + VLDLC\_synth - Hepatic\_uptake - Peripheral\_uptake;$$

------ Hepatic Free Cholesterol -----

$$\frac{d(HFC)}{dt} = HCE\_to\_HFC - HFC\_to\_HCE - Hep\_VLDLC\_synth - BS\_synth + \left(\frac{Vol_I}{Vol_L}\right) + HC\_synth - BC\_release + (1/(VC * Vol_L)) * (Hep\_IDLC\_removal + Hep\_VLDLC\_removal + Hep\_up\_LDLC + Hep\_up\_LDLC\_indep + Hep\_up\_H$$

------ Hepatic Cholesterol Ester -----

$$\frac{d(HCE)}{dt} = HFC\_to\_HCE - HCE\_to\_HFC;$$

------ Hepatic LDL Receptors -----

$$\frac{d(HLDLR)}{dt} = Hep\_LDLR\_synth - Hep\_LDLR\_death;$$

------ Hepatic Bile Salts -----

$$\frac{d(HBS)}{dt} = BS\_synth + \left(\frac{Vol_I}{Vol_L}\right) * HBS\_return - BS\_release;$$

------ Intestinal Bile Salts -----

$$\frac{d(IBS)}{dt} = \left(\frac{Vol_L}{Vol_I}\right) * BS\_release - HBS\_return - BS\_excr;$$

------ Intestinal Cholesterol -----

$$\frac{d(IC)}{dt} = Diet\_absp + IC\_synth + \left(\frac{Vol_L}{Vol_I}\right) * BC\_release - Int\_chol\_absp - Int\_chol\_excr;$$

------ Excreted Cholesterol -----

$$\frac{d(EC)}{dt} = Int\_chol\_excr;$$

------ Excreted Bile Salts -----

$$\frac{d(EBS)}{dt} = BS\_excr;$$

References

Mc Auley, M. T., Wilkinson, D. J., Jones, J. J. L. & Kirkwood, T. B. L. A whole-body mathematical model of cholesterol metabolism and its age-associated dysregulation. *BMC Syst. Biol.***6,** 130 (2012).