

# Refining the mechanism of CETP mediated lipid transfer in a stochastic model of the Lipoprotein Metabolism and Kinetics (LMK model)

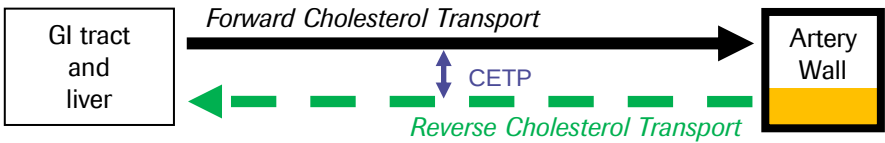


James Lu<sup>1</sup>, Katrin Hübner<sup>2</sup>, Norman Mazer<sup>1</sup>

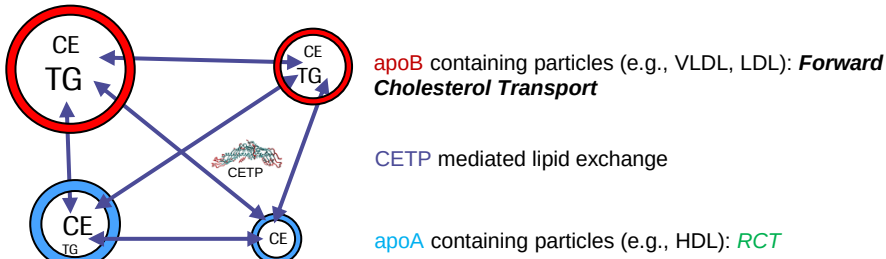
- (1) Modeling and Simulation, Translational Research Sciences, F. Hoffmann-La Roche Ltd, Basel, Switzerland  
(2) Modeling Biological Processes, BioQuant, University of Heidelberg, Heidelberg, Germany

## 1 – Introduction

The transport of cholesterol in the body occurs via two main pathways, the Forward Cholesterol Transport from the GI tract and liver to the peripheral tissues (e.g., artery wall) and the Reverse Cholesterol Transport (RCT) from the peripheral tissues to the liver.

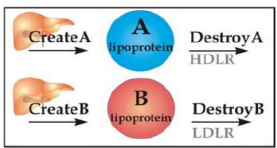


Lipoprotein particles contain apolipoproteins (apoA, apoB, ...) on their surfaces and neutral lipids cholesterol ester (CE) & triglycerides (TG) in their cores. Transfers of CE and TG between particles are mediated by the Cholesterol Ester Transfer Protein (CETP).



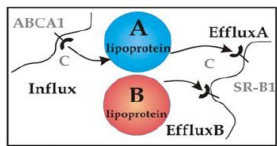
## 2 – Our starting point: the stochastic model by Hübner et al [1]

The model by Hübner et al [1] (KH model) describes the birth and destruction of A (apoA containing) and B (apoB containing) particles, as well as the lipid and protein transfer mechanisms that occur.



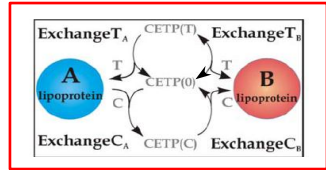
### Synthesis and degradation of A and B particles

System level reactions: zero-order rate for particle synthesis in the liver, first-order destruction rate via HDL- and LDL-Receptor respectively.



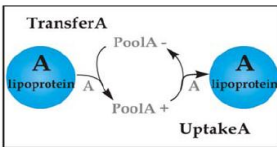
### ABCA1 mediated influx of cholesterol (=initiation of RCT) SR-B1 mediated efflux of cholesterol to the liver

Cholesterol input to each A particles at a constant rate, efflux of cholesterol from all particles occur at a rate proportional to C content.



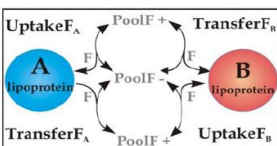
### CETP mediated exchange of triglycerides and cholesterol

Bimolecular reactions between CETP (in its 3 possible occupancy states: empty, with C or with T in it) and A or B particles. The rates of pickup of neutral lipids depend in a first-order manner on the particle content. Only uni-directional fluxes of C from A to B particles and of T from B to A particles are represented.



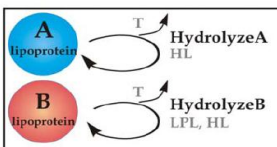
### Exchange of apolipoprotein A among A particles

Dissociation of apoA protein from the surface of A particles to the plasma pool and the association back onto A particles.



### Exchange of apolipoprotein F (i.e., other) among A and B particles

Dissociation of other apolipoproteins from the surface of A & B particles to the plasma pool as well as its reverse reaction.



### Hydrolysis of triglycerides from A and B particles

The enzymes Hepatic Lipase (HL) and Lipoprotein Lipase (LPL) remove triglycerides from the lipoprotein particles. For LPL, a first-order rate of hydrolysis is assumed, proportional to the number of TG molecules in each particle.

In the current work we revise the CETP module (see red box) of the KH model [1] to account for discrepancies in the model prediction compared to literature data.

[1] K. Hübner et al, "Computational lipidology: predicting lipoprotein density profiles in human blood plasma", PLoS Computational Biology, 23:4(5), May 2008.

## 3 – Revision of CETP module: competing hypotheses

In order to account for the known bidirectional exchange of neutral lipid between A and B particles, the symmetrization of the CE and TG transfer reactions is needed. We propose two candidate models: the **symmetrized exchange** and the **swap mechanism**, as schematized in Fig. 1 and 2.

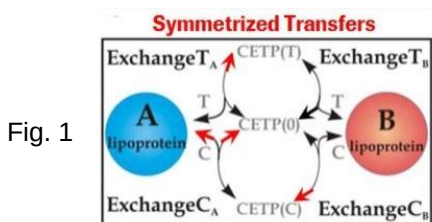


Fig. 1

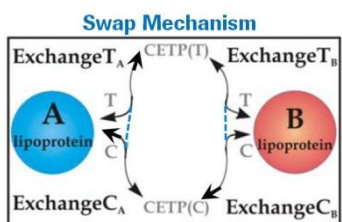
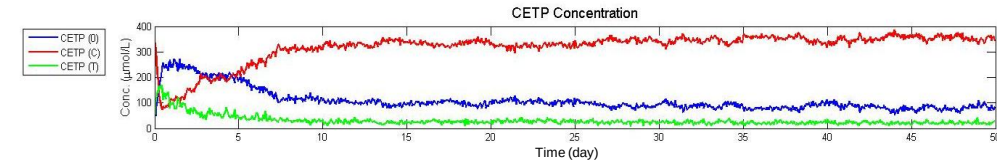


Fig. 2

The red arrows in Fig. 1 denote the added lipid transfers compared to KH model. In Fig. 2, we assume CETP does not simply take up and give up CE or TG in an arbitrary order; instead, CETP performs a swapping of CE for TG, or vice versa. The two hypotheses can be differentiated based on their predicted behavior.

## 4 – Computational simulation: choice of platform and algorithm

Through the appropriate combination of computational platform, algorithm implementation and parallel computing, ~4 orders of magnitude speedup has been gained in the simulation speed compared to our first implementation of the published model using Mathematica.



Algorithms and implementations

### Algorithms

- **SSA**: Stochastic Simulation Algorithm [2].
- **NRM**: Next Reaction Method [3]. A specialized data structure allows for an efficient sampling from the set of all reactions.
- **MQ NRM**: A novel, Multi-Queue variant of NRM. The use of multiple queues decouples the co-dependence of certain reactions on common species.

### Implementation

- **Mex**: Matlab interface to routines written in the C language.
- **Parallelization**: The utilization of 8 CPU cores on the desktop machine.

[2] D. Gillespie, J Phy Chem, 82(25), 1977.  
[3] M.A. Gibson et al, J Phy Chem, 104(9), 2000.

## 5 – Analysis and comparison of models

The bidirectional cholesterol ester flux values obtained from tracer kinetics analysis in normal subjects [4] were used to constrain the **symmetrized transfer** and **swap mechanism** models. For each model, parameters were found that allowed the computed fluxes to match the data.

In order to further differentiate the models, we used literature data on HDL cholesterol (HDL-C) levels in homozygotes and heterozygotes with genetic CETP deficiency, having 0% and 50% CETP mass compared to controls [5]; see Fig. 3.

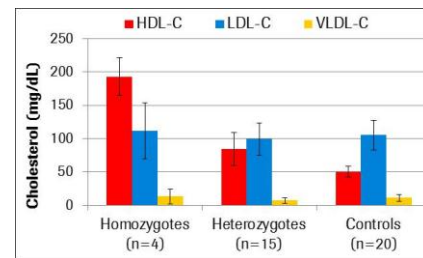


Fig. 3

In Fig. 4 the dependence of HDL-C on CETP mass is simulated for the KH and **symmetrized transfer model** and compared to the data in CETP deficiency. While a reasonably good match for the latter model is obtained at 50% CETP mass, both models over-predict the data point for homozygotes at 0% CETP mass.

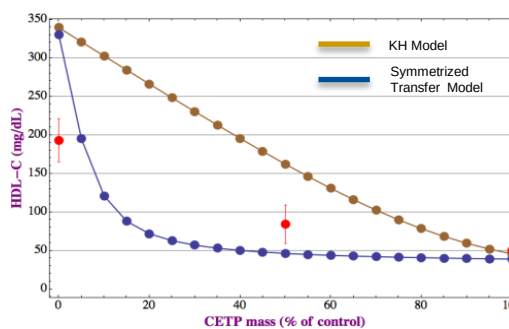


Fig. 4

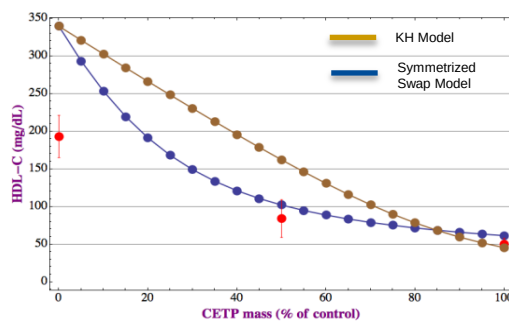


Fig. 5

As shown in Fig. 5, the **symmetrized swap model** shows better agreement with heterozygous CETP mutation than the previous models.

An additional prediction favoring the **swap model** is that it captures the known inverse relationship between HDL-C and TG level [6] (Fig. 6). This result suggests that some degree of CE-TG swapping is mediated by CETP.

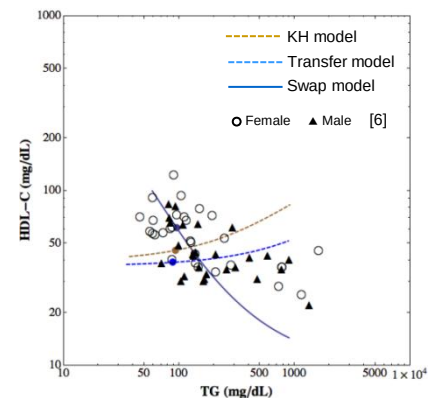


Fig. 6

[4] K. Ougerram et al, Metab, pp. 5-11, 51(1), 2002.  
[5] K. Yamashita et al, Metab, pp. 756-763, 50(7), 1991.  
[6] E. Brinton et al, Arterio Thromb Vasc Biol, pp. 707-720, 14, 1994.

## 6 – Conclusions

- In order to capture the complex dynamics of lipoprotein metabolism, a particle-centric view has been adopted and the model is simulated using a stochastic approach.
- We have focused on the CETP module and used a variety of literature data to differentiate between competing lipid transfer mechanisms. The results suggest that CETP swaps CE for TG (and vice versa) as it interacts with lipoprotein particles.
- Our future work will investigate other mechanisms of HDL remodeling and their effects on the RCT rate, allowing us to better understand and predict the effects of drugs that are designed to increase HDL-C.