In silico modelling of human lipoprotein metabolism

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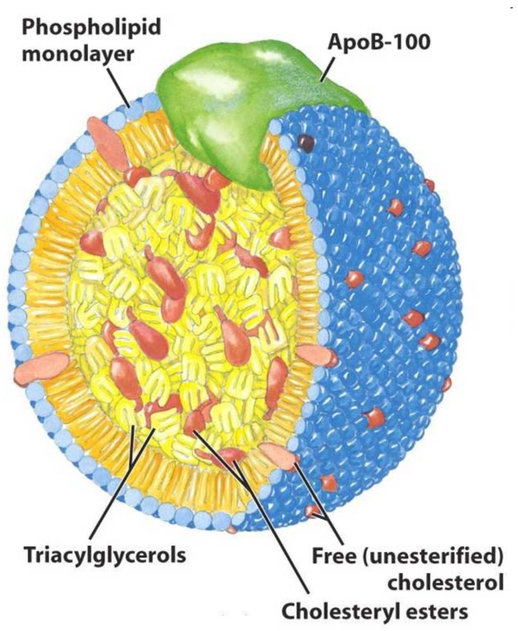
Introduction

Cholesterol and other lipids play an important role in the genesis of atherosclerosis and cardiovascular diseases. Lipids are transported in the bloodstream by lipoproteins. These lipoproteins are principally spherical and have a hydrophobic core consisting of triglycerides and cholesteryl esters. This core is covered by a phospholipid monolayer, in which free cholesterol and so called apolipoproteins are located. The most common and referenced method to classify lipoproteins is by density. High density lipoproteins (HDL) and low density lipoproteins (LDL) are of great interest in lipid research.

An important regulator of the lipid metabolism in the human blood plasma is the cholesteryl ester transfer protein (CETP), which mediates the exchange of lipids from one lipoprotein to another.

However, lipoprotein analysis is elaborate and expensive. A model predicting the risk of cardiovascular disease depending on the lipid metabolism may be of great benefit.



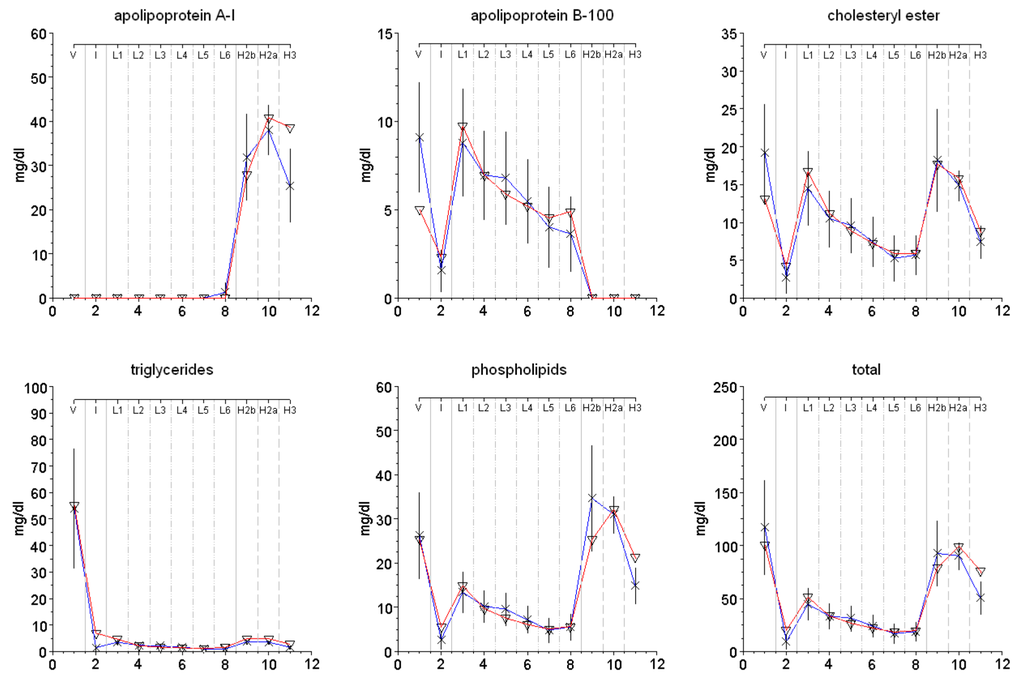
Structure of a triglycerid-rich lipoprotein with apolipoprotein B-100
(Nelson and Cox, 2006)

Methods

Here, we present a refined version of a previously described model of the human lipoprotein metabolism.[1]
The model describes the behaviour of particular lipoproteins dependent on a set of reaction rates. Due to the large number of possible lipoprotein compositions, the computation is done by the stochastic Gillespie algorithm.
The now presented model is based on a comprehensive dataset of lipoprotein measurements in healthy and pathologic patients (n=1764) and contains several changes and refinements to the prior approach. So, based on this dataset, we are able to improve the phospholipid and free cholesterol computation.
Our model takes into account, that the different reaction rates of lipoproteins with very low density (VLDL) and LDL lipoproteins are not only caused by simple mass action kinetics, but are also regulated by the different compositions of apolipoproteins. The immense size varieties of the particles (range of radius: 5 – 40 nm) are also taken into account in the reaction rate determination.
The bigger dataset provides us with more qualitative standard values for healthy and pathologic lipid and lipoprotein profiles.
Due to the work of Qiu et al.[2] we are able to refine the CETP exchange reactions by modelling the described ping pong bi-bi shuttle transport of lipids.[3]
The model is implemented in c++ and simulates the dynamics of lipoproteins in a 10^{-16} litre plasma, starting in a lipoprotein free situation.

Results

Our model is able to reproduce measured lipid data of humans with normal lipoprotein values. Furthermore, certain lipoprotein-associated diseases like hypercholesterolemia may be simulated by modifying the associated parameters of the metabolism.
As particular lipoproteins are simulated, we are able to get information about the distribution and metabolic rates of lipoproteins in any definable density classes.
We are also able to get insights in the metabolic fate of specific lipoproteins by tracing them in the simulation.



Clinical measured values of n=143 normolipidemic patients (red) versus calculated profiles with error bars (blue) in 11 established density (sub-)fractions V=VLDL,I=IDL, L1-L6 (LDL subfractions 1-6) and HDL subfractions H2b=HDL2b, H2a=HDL2a, H3=HDL3

Discussion

The model is capable to investigate associated diseases of lipid metabolism and to provide a powerful tool for possible therapeutic approaches.
However, as human lipoprotein metabolism is highly complex and not fully understood, there is a vast amount of possible improvements. So several reactions and apolipoprotein interactions are missing in the current model.
As (due to the model complexity) the simulation is only realizable in a relative small volume, stochastic influences may play a undesirable big role. Furthermore there are huge differences in the speed of the various reactions and number of lipoproteins in important subpopulations.
Taking these issues into account a refined version of the computation may be beneficial.

References

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2. Qiu, X. et al. , Crystal structure of cholesteryl ester transfer protein reveals a long tunnel and four bound lipid molecules. *Nat Struct Mol Biol, 14(2):106–113, Feb 2007*
3. Potter, L.K. et al. , Mechanism of inhibition defines CETP activity: a mathematical model for CETP in vitro. *J Lipid Res. 2009 Nov;50(11):2222-34.*

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