

Integrated Modeling for Individualized Reverse Cholesterol Transport (RCT) Measurement and Management

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INTRODUCTION

REVERSE Cholesterol Transport (RCT) is a series of very complex biological pathways by which accumulated cholesterol is transported from the vessel wall macrophages and foam cells to the liver for excretion, thus preventing atherosclerosis, a build-up of plaque in the arteries often referred as ‘hardening of arteries.’ Major constituents of RCT include acceptors such as high density lipoprotein (HDL) and apolipoprotein A-I (ApoA-I), and enzymes such as lecithin:cholesterol acyltransferase (LCAT), Phospholipid transfer protein (PLTP), hepatic lipase (HL), and cholesterol ester transfer protein (CETP). In addition to traditionally recognized transport pathways, RCT also takes place through passive diffusion, protein-facilitated diffusion, and complex mechanisms involving membrane micro-solubilization. On top of that, RCT is facilitated by other apolipoproteins such as ApoE, and ApoM. They are required for HDL formation, maturation, and consequent enhancement of RCT performance. RCT has emerged in recent days as one of the most desirable methods of medical interventions to reverse the atherosclerotic lesions. Optimized dynamic RCT modeling helps in individualized therapeutic targeting of High Density Lipoproteins (HDL) with the help of ApoA-I Mimetic Peptides, and other oral small molecules.

MATERIALS AND METHODS

We have considered many known and clinically verified RCT pathways. Each individual quantitative model, with dynamic parameters, boundary conditions, and other variables has become part of a RCT quantitative model database accessible to the software configurator. Some of these models are kinetic models. In many cases, we had to adopt appropriate mathematical models using analytical and numerical methods.

The net RCT pathway is quantified with multiple parameters that can change depending on clinical in-vivo or in-vitro conditions. A standard relational database model holds all the objects of the quantitative model. An optimization algorithm matches the aggregate model with

the clinical RCT datasets. It automatically adjusts all the parameters till it can find the best solution. Multivariate analysis (MVA) aims to create a derived aggregate model reducing the complexity of multi-dimensional data to a few latent variables that express the majority of the variance of the data set. MVA is also utilized to perform nonlinear multiple regression analysis between large data sets. Our dynamic model interfaces with external data sets and other models using Systems Biology Markup Language (SBML). It is a computer-readable format for representing models of biochemical reaction network in software.

RESULTS

The software configurator based RCT model predicts the individualized effects of increased ApoA-I transcription and subsequent protein synthesis on RCT and cholesterol efflux. Results from our model can be used to predict, and manage RCT at individual level with the help of ApoA-I Mimetic Peptides, and other oral small molecules. For example, under a set of specific clinical parameters, a 13% increase in ApoA-I results in 15% predicted increase in net RCT from various pathways. The model provides dynamic RCT performance measure with varying pathway parameters. The database driven, configurator based optimized algorithm forms the basis of refining the aggregate dynamic quantitative RCT model with more clinical data in future.

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