Real world application of the LIFE method to a model of cholesterol metabolism

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Use of QSP models in the pharmaceutical industry

- Our group at Sanofi is focused on creating quantitative systems pharmacology (QSP) models of drug and disease that can assist in the design of trials, approval of drugs, and marketing of drugs

- QSP models can add value in situations where:
  - A question of interest to the clinical team arises which cannot be tested experimentally, or which would be too costly to test experimentally
    - *In cases where data is available:* A biological context is needed to analyze the data in a way that would answer the question, pure statistical analysis is insufficient
    - *In cases where data is not available:* A prediction is needed, which takes into account both the biological context and the data available on a similar population or drug

Example cases when QSP models have been requested

- Extrapolate data from adult clinical trials and limited pediatric studies to predict the effect on all pediatric patients
- Explain why there is a difference in the response of patient populations to therapy, and what criteria should determine how well a patient will respond to drug
- Predict how well our drug will perform against a competitor drug or standard of care therapy, and what characteristics differentiate our drug from the others
- Predict whether a drug combination would provide additional benefit
- Design dosing for specific patient populations
- Anticipate whether different patient populations will be equally well treated by therapy and identify criteria for determining whether a patient will respond well to therapy
- Out of a panel of biomarkers suggested by the literature, predict which one will be most informative and correlated with patient outcomes
- Help to distinguish mechanism of action of a drug by simulating different hypotheses and comparing to data

Stage at which QSP models are requested

- QSP models are utilized at different stages of drug development:
  - After preclinical testing prior to testing in humans
  - After initial stage one clinical trials have shown success
  - After a drug is approved, to assist in marketing our drug versus a competitor
  - After a drug is approved in one population, or for one indication and there is interest in expanding this
- There needs to be some kind of data available to train the model
- There needs to be an understanding of the important pathways and mechanisms involved in the disease and in the action and effect of the drug

The LIFE method is valuable in differentiating patient populations and understanding mechanistic differences between them

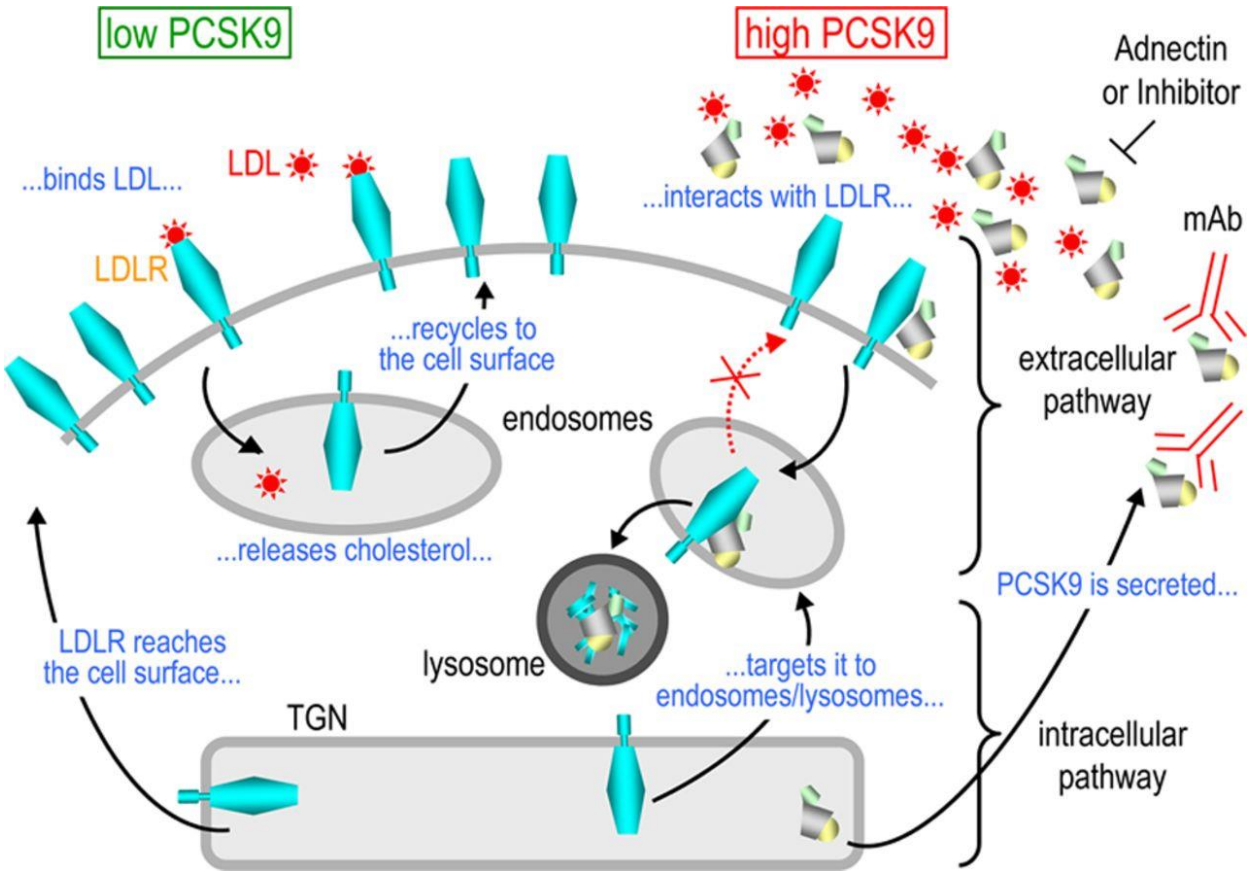
- Typically, one must run separate optimizations for each patient population
  - Because correlations between parameters are not taken into account, variability in response of each population can be overestimated
  - Insights on mechanistic differences between populations come from observing optimized distributions of parameters selected for inclusion in optimization
- LIFE can give useful insight into patient populations in several ways:
  - LIFE takes into account parameter correlations and puts constraints on parameters which limits the variability in patient populations and better differentiates response
  - Once baseline parameters are fit for each population, LIFE can analytically show what parameter combinations would fit the same baseline but lead to different therapeutic responses to make fitting more efficient

PCSK9 inhibitor therapy aims to reduce LDL cholesterol levels

- Gain and loss of function mutations have been found in the PCSK9 of different patients
  (Dadu, R.T. and Ballantyne, C.M. Nat. Rev. Cardiol 2014)
  - Gain of function mutations can lead to familial hypercholesterolaemia and increased risk of premature cardiovascular disease
  - Loss of function mutations cause very low levels of LDL-cholesterol and apoB and have been associated with a reduction in coronary events in several epidemiological studies
- These findings pointed to the important role of PCSK9 in determining cholesterol levels and raised interest in PCSK9 as a target for cholesterol-lowering therapies

Our cholesterol metabolism model was developed around the Sanofi PCSK9 inhibitor therapy Praluent

- Loss of PSK9 functionality in patients is associated with lower LDL-cholesterol (Dadu, R.T. and Ballantyne, C.M. *Nat. Rev. Cardiol.* 2014)
- Plasma PCSK9 binds the LDL-receptor on the surface of hepatic and peripheral cells
- The PCSK9-LDLR complex is internalized and degraded, leaving fewer LDLRs at the cell surface to remove LDL-cholesterol from plasma
- *By inhibiting PCSK9, current therapies aim to increase the number of LDL receptors and reduce LDL cholesterol*



Nabil G. Seidah et al. Circ Res. 2014;114:1022-1036

Motivation for development of cholesterol metabolism model

- Many people with high cholesterol take statins
- Statins have been shown to cause elevated levels of PCSK9
- Our first goal was to develop model parameterizations for statin responders and non-responders and determine whether the statin-responders have a better outcome on PCSK9 therapy than statin-non-responders

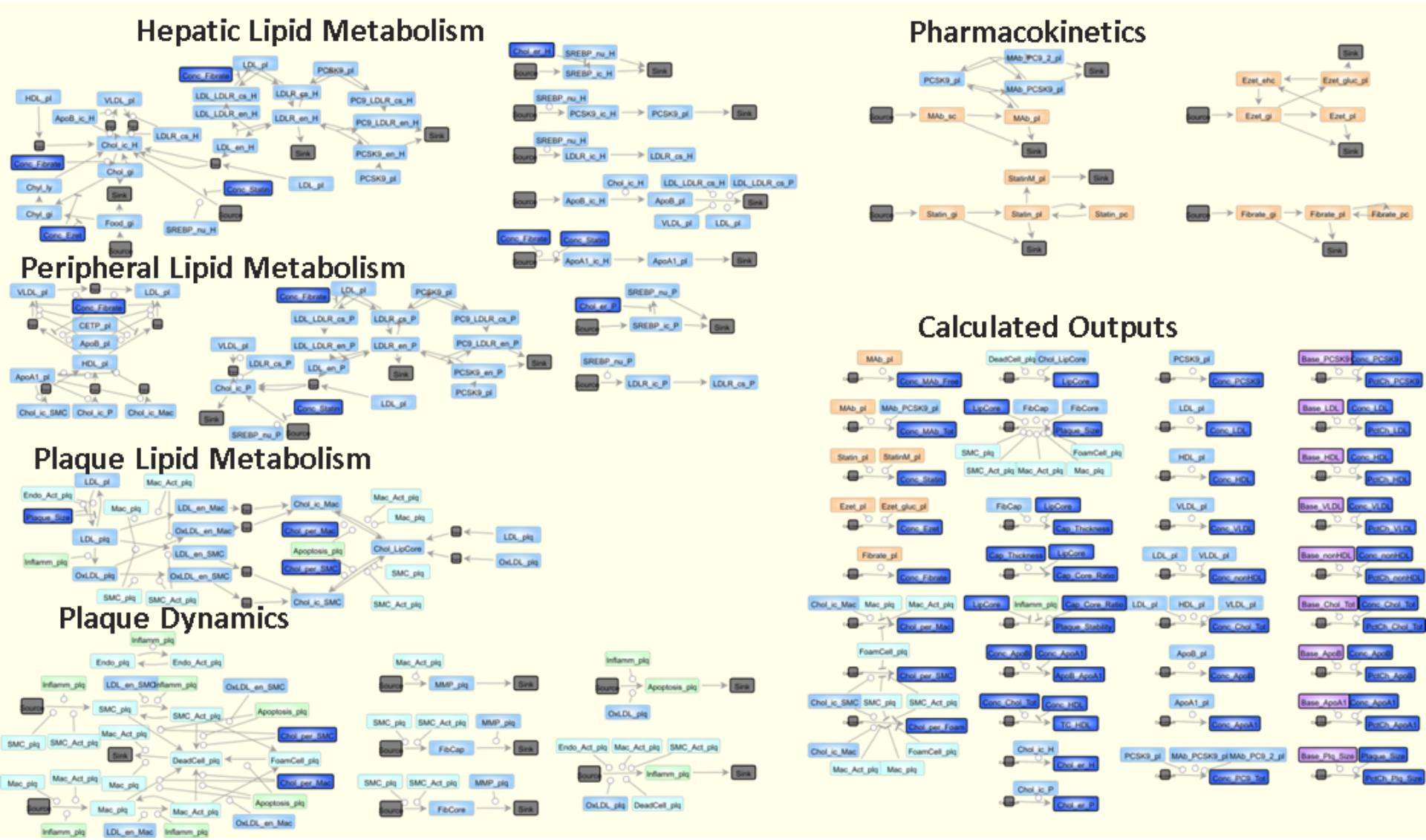
Additional uses of the cholesterol QSP model

- Prediction of how LDL lowering would effect long term plaque build up (effecting cardiac outcomes)
- Use of a revised version of the model to explain differences found in two patient populations (*Paper in development on this work*)

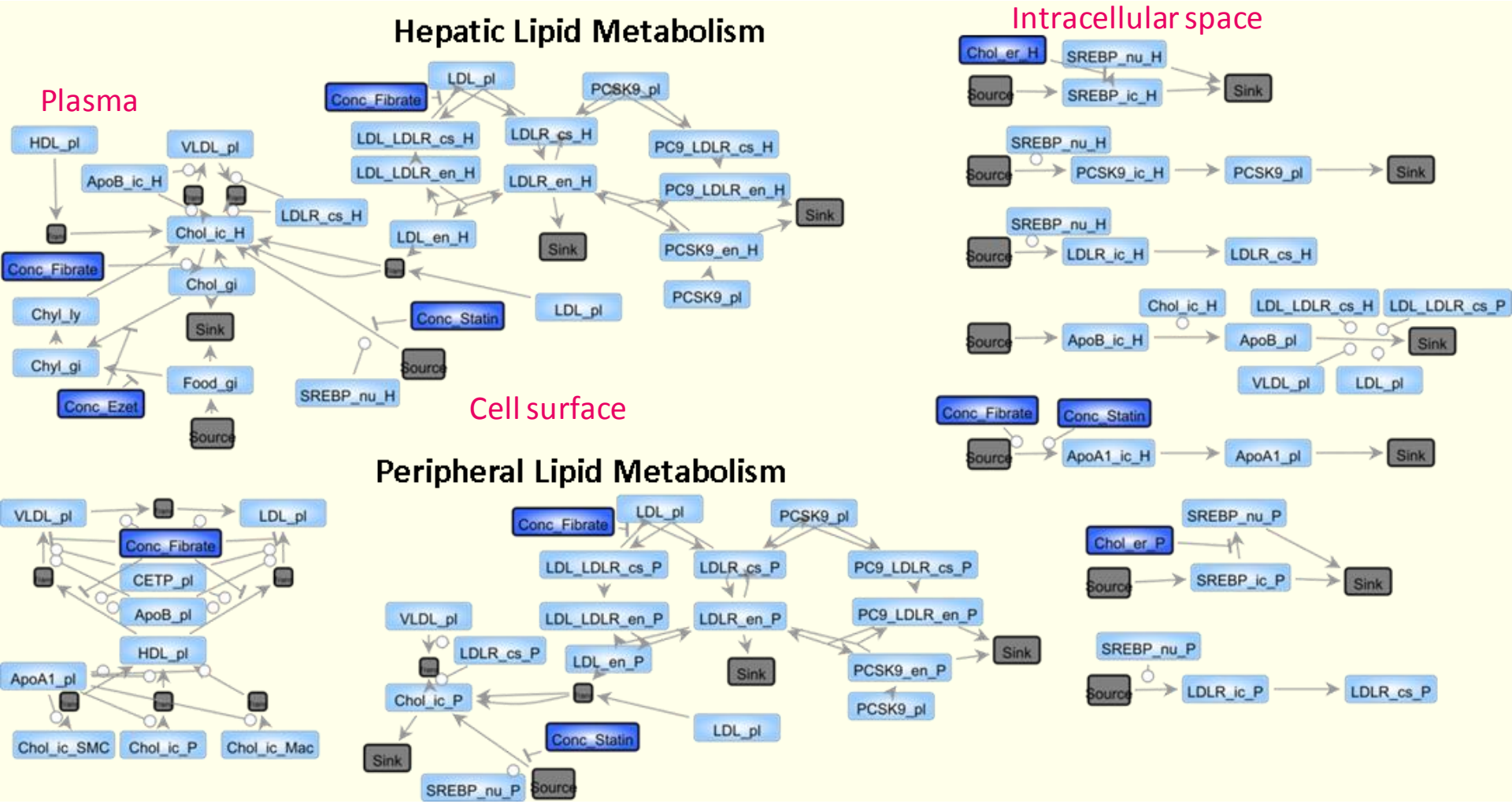
Cholesterol biology

- Cholesterol in the body originates from:
  - Cholesterol and saturated fats in the diet
  - Cholesterol produced within human cells
- Most cholesterol in the body is located in cell membranes and helps to maintain their structural integrity
- Excess cholesterol leads to build up of plaque in the arteries and negative cardiac outcomes

Full cholesterol model



Overview of cholesterol metabolism



Formulation of equations in the model

- Most first order mass action kinetics representing transfer from one compartment or protein or form to another

$$[\mathrm{PCSK9}_{\mathrm{icH}\rightarrow\mathrm{pl}}] = PCSK9\_ic\_H\_to\_pl\_release\_rate\_k \cdot \mathrm{PCSK9}_{\mathrm{icH}}$$
$$[\mathrm{VLDL}_{\mathrm{pl}\rightarrow}\mathrm{LDL}_{\mathrm{pl}}] = VLDL\_to\_LDL\_conversion\_rate\_k \cdot \mathrm{VLDL\_pl}$$

- Association of two proteins is proportional to their product

$$[PCKS9_{pl} + LDLR \rightarrow PCSK9{:}LDLR] = PCSK9\_LDLR\_pl\_association\_rate\_k \cdot \frac{\mathrm{PCSK9}_{\mathrm{pl}} \cdot \mathrm{LDLR}}{Vol_{pl}}$$

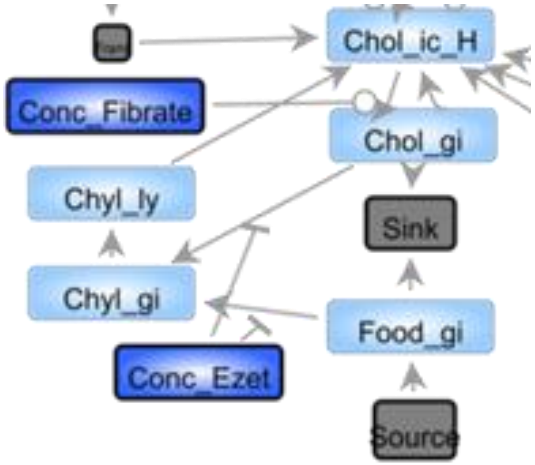
$$[\mathrm{LDL}_{\mathrm{en}} + \mathrm{LDL}R_{\mathrm{en}} \rightarrow \mathrm{LDL}_{\mathrm{en}}{:}\mathrm{LDL}R_{\mathrm{en}}] = LDL\_LDLR\_en\_association\_rate\_k \cdot \frac{LDL_{en} \cdot LDLR_{en}}{Vol_{en}}$$

- Regulatory proteins act through hill functions

$$[\mathrm{PCSK9}_{0\rightarrow\mathrm{icH}}] = PCSK9\_ic\_H\_production\_rate\_k \cdot \frac{\mathrm{SREBP2_H}^{n1}}{PCSK9\_EC50^{n1} + \mathrm{SREBP2_H}^{n1}}$$

$$[\mathrm{LDL-R}_{0\rightarrow\mathrm{icH}}] = LDLR\_ic\_H\_production\_rate\_k \cdot \frac{\mathrm{SREBP2_H}^{n2}}{\mathrm{LDL-R}\_EC50^{n2} + \mathrm{SREBP2_H}^{n2}}$$

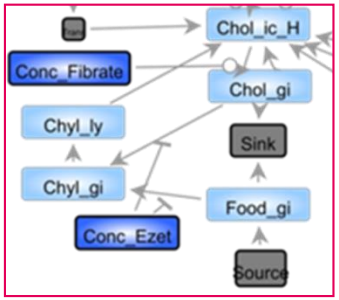
Gastrointestinal processing of cholesterol



- Intake of food (represented as a constant source over the course of the day or as a discontinuous source present during three daily meals)
- Transfer of hepatic cholesterol to GI cholesterol pool
- Elimination of cholesterol from food and from the GI cholesterol pool
- Encapsulation of food and pooled GI cholesterol into chylomicrons
- Transfer of chylomicrons to hepatic intracellular cholesterol pool through lymph

Equations for gastrointestinal processing of cholesterol

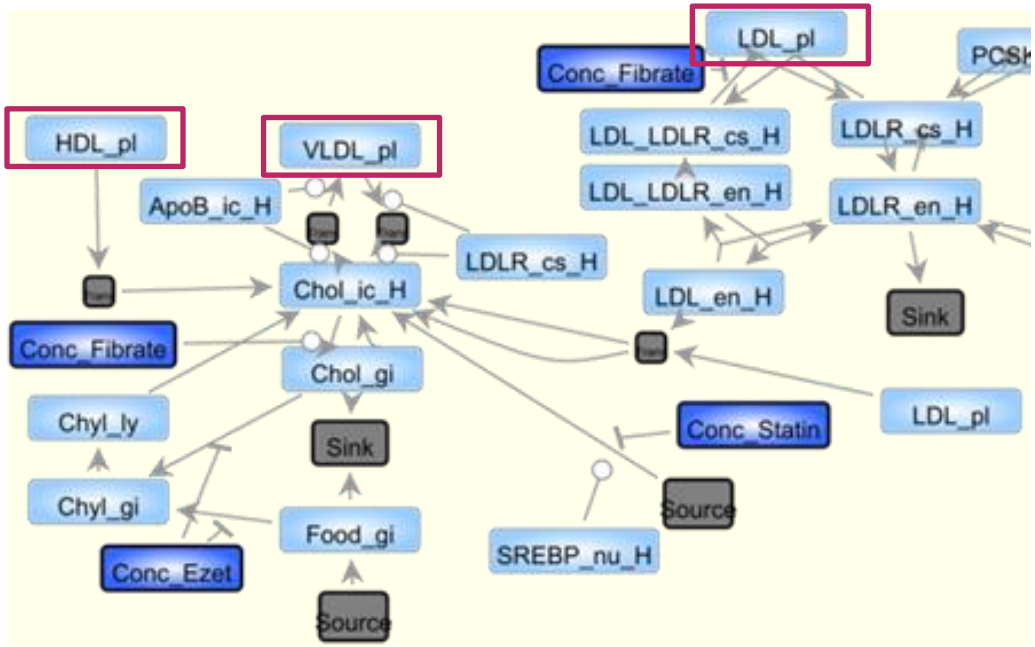
- All equations follow rules outlined above
- Effect of drugs in this system (ezetimibe and fibrate) is represented through hill functions



$$\frac{d(Chol\_gi)}{dt} = Chol\_ic\_H \cdot (biliary\_chol\_secretion\_rate\_k + bileacid\_chol\_secretion\_rate\_k)$$
$$\cdot (Fibrate\_bile\_Emax \cdot \frac{Conc\_Fibrate^{Fibrate\_bile\_nh}}{Conc\_Fibrate^{Fibrate\_bile\_nh} + Fibrate\_bile\_EC50^{Fibrate\_bile\_nh}} + 1) - Chol\_gi \cdot Chol\_gi\_excretion\_rate\_k + Chol\_gi \cdot Chol\_to\_Chyl\_gi\_absorption\_rate\_k$$
$$\cdot ((Ezet\_Chyl\_Imax \cdot \frac{Conc\_Ezet^{Ezet\_Chyl\_nh}}{Conc\_Ezet^{Ezet\_Chyl\_nh} + Ezet\_Chyl\_IC50^{Ezet\_Chyl\_nh}} - 1) - Chol\_gi \cdot bileacid\_chol\_absorption\_rate\_k$$

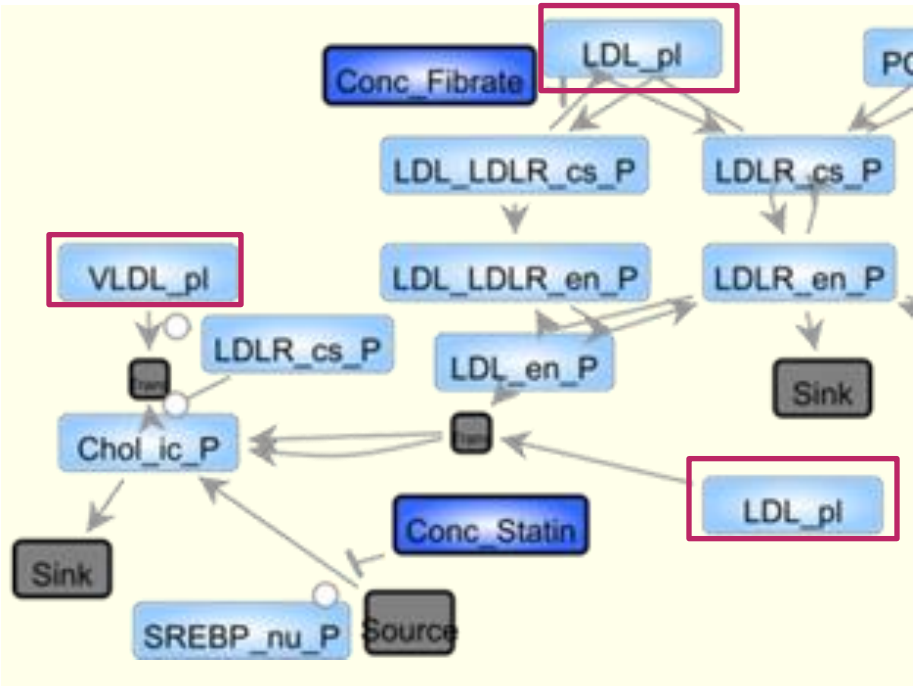
Hepatic compartment of the model captures cholesterol production and reabsorption

- Production of intracellular cholesterol is mediated by activated SREBP-2
- Cholesterol is also formed from internalization of the plasma lipoproteins
- VLDL-C is produced from intracellular cholesterol and ApoB lipoprotein and secreted into plasma
- LDL, VLDL, and HDL enter the cells through LDLR-dependent and independent pathways



Peripheral compartment of the model reflects cholesterol processing in non-hepatic cells

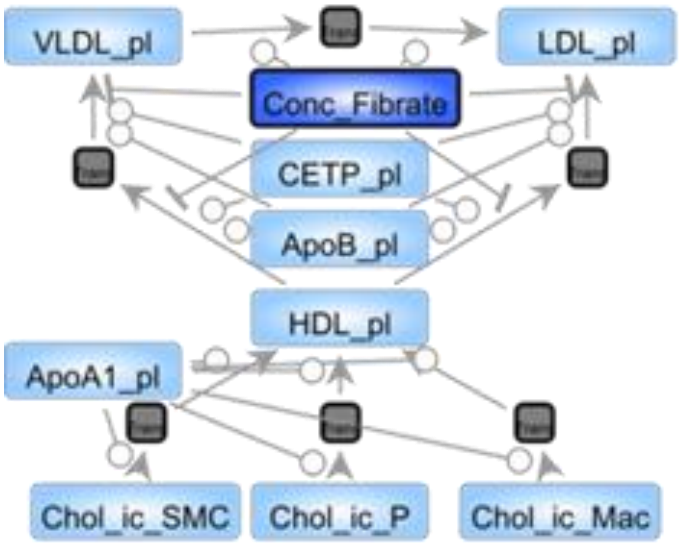
- Intracellular cholesterol production is mediated by activated SREBP-2
- LDL-C in plasma contributes to hepatic intracellular cholesterol through LDL-R internalization or independently
- VLDL-C is internalized through LDL-R binding and contributes to intracellular cholesterol



Equations for hepatic and peripheral cholesterol metabolism

- *Disassociation rates are written in terms of association rates and Kd's to make use of the wider ability to obtain references for Kd values*
  - $\frac{d(\boldsymbol{LDL\_en\_H})}{dt} = LDL\_LDLR\_en\_association\_rate\_k \cdot LDL\_LDLR\_en\_Kd \cdot LDL\_LDLR\_en\_H - \frac{(LDL\_LDLR\_en\_association\_rate\_k \cdot LDL\_en\_H \cdot LDLR\_en\_H)}{volume\_en\_H} - LDL\_en\_to\_Chol\_ic\_H\_rate\_k \cdot LDL\_en\_H$
- $\frac{d\left(Chol_{ic_H}\right)}{dt}$ terms of interest:
  - *Conversion rate is used to represent amount of cholesterol per lipoprotein*
    - $LDL\_en\_to\_Chol\_ic\_H\_rate\_k \cdot chol\_per\_LDL\_particle \cdot LDL\_en\_H$
    - $HDL_{pl} \cdot HDL_{pl}\_uptake\_rate\_k \cdot chol\_per\_HDL$
  - *HDL particle above directly contributes to cholesterol whereas LDL and VLDL con contribute through LDLR uptake into endosome or through LDLR-independent mechanisms*
    - $LDL\_pl \cdot LDL\_pl\_LDLRind\_H\_uptake\_rate\_k \cdot chol\_per\_LDL\_particle$
    - $LDL\_en\_H \cdot LDL\_en\_to\_Chol\_ic\_H\_rate\_k \cdot chol\_per\_LDL$
  - *Regulation of cholesterol and VLDL production is represented through hill functions*
    - $Chol\_ic\_H\_production\_rate\_k \cdot \frac{SREBP\_nu\_H^{SREBP\_Chol\_nh}}{(SREBP\_nu\_H^{SREBP\_Chol\_nh} + SREBP\_Chol\_EC50^{SREBP\_Chol\_nh})}$
    - $VLDL\_pl\_production\_rate\_k \cdot Chol\_ic\_H \cdot \frac{(ApoB\_ic\_H^{ApoB\_VLDL\_nh})}{(ApoB\_ic\_H^{ApoB\_VLDL\_nh} + ApoB\_VLDL\_EC50^{ApoB\_VLDL\_nh})} +$

Reverse cholesterol transport

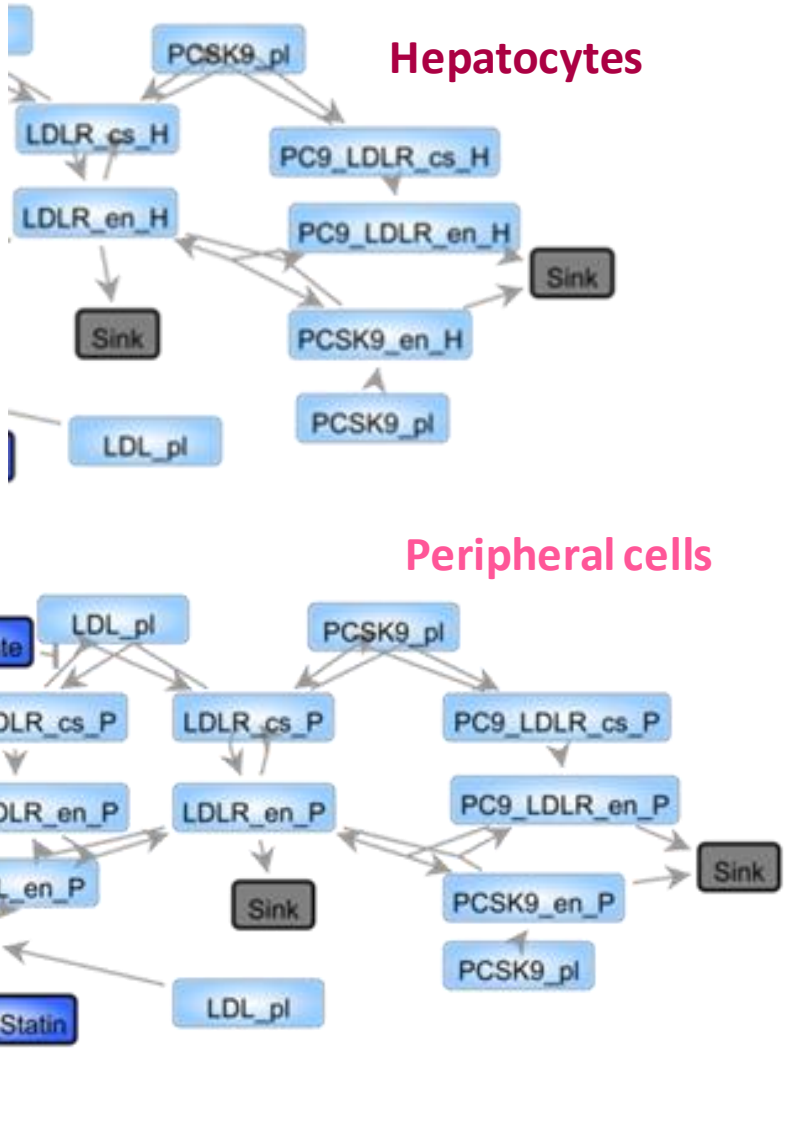


- Excess intracellular cholesterol from peripheral cells is transferred to ApoA1-containing HDL particles
- Cholesterol from circulating HDL particles can be exchanged onto ApoB-containing VLDL or LDL particles by the action of CETP
- VLDL conversion into LDL in plasma is represented here

Equations for reverse cholesterol transport

- $\frac{d(HDL_{pl})}{dt}$ *terms of interest*
  - $(HDL\_pl \cdot \boldsymbol{HDL\_to\_LDL\_exchange\_rate\_k} \cdot weight\_CETP\_HDL\_LDL \cdot weight\_ApoB\_HDL\_LDL \cdot Fibrate\_CETP\_Imax \cdot \frac{Conc_{Fibrate}^{Fibrate_{CETP_{nh}}}}{\left(Conc_{Fibrate}^{Fibrate_{CETP_{nh}}} + Fibrate_{CETP_{IC50}}^{Fibrate_{CETP_{nh}}} - 1\right)} \cdot \frac{ApoB_{pl}^{ApoB_{HDL_{LDL_{nh}}}}}{\left(ApoB_{pl}^{ApoB_{HDL_{LDL_{nh}}}} + ApoB_{HDL_{LDL_{EC50}}}^{ApoB_{HDL_{LDL_{nh}}}}\right)} \cdot \frac{CETP_{pl}^{CETP_{HDL_{LDL_{nh}}}}}{\left(CETP_{pl}^{CETP_{HDL_{LDL_{nh}}}} + CETP_{HDL_{LDL_{EC50}}}^{CETP_{HDL_{LDL_{nh}}}}\right)}$
  - $Chol\_ic\_P \cdot \boldsymbol{Chol\_ic\_P\_to\_HDL\_pl\_rate\_k} \cdot \frac{ApoA1_{pl}^{ApoA1_{RCT_{nh}}}}{chol_{per_{HDL_{particle}}} \cdot \left(ApoA1_{pl}^{ApoA1_{RCT_{nh}}} + ApoA1_{RCT_{EC50}}^{ApoA1_{RCT_{nh}}}\right)}$

Role of PCSK9 in cholesterol metabolism



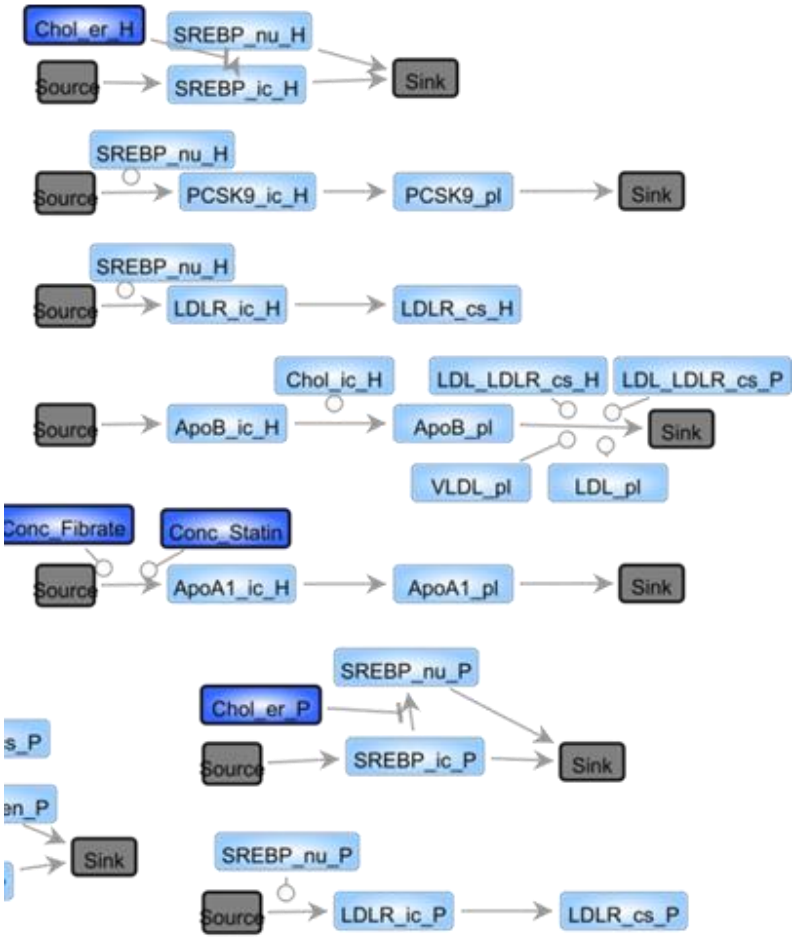
- PCSK9 binds and internalizes LDLR in hepatic and peripheral cells
- PCSK9-LDLR in both localizations can be degraded whereas LDL-LDLR cannot

Equations for PCSK9 interactions in cholesterol system

- Binding to LDLR at the cell surface is first represented, followed by internalization of this complex

$$-\frac{d(PC9\_LDLR\_en\_H)}{dt} = LDLR\_internalization\_fraction\_H \cdot PC9\_LDLR\_cs\_H \cdot PCSK9\_LDLR\_H\_internalization\_rate\_k - PC9\_LDLR\_en\_H \cdot PCSK9\_LDLR\_en\_Kd \cdot PCSK9\_LDLR\_en\_association\_rate\_k + \frac{(LDLR\_en\_H \cdot PCSK9\_en\_H \cdot PCSK9\_LDLR\_en\_association\_rate\_k)}{volume\_en\_H} - PC9\_LDLR\_en\_H \cdot PC9\_LDLR\_en\_H\_degradation\_rate\_k$$

Feedback regulates intracellular production of cholesterol proteins



- Synthesis and activation of SREBP provides a feedback mechanism between intracellular ER cholesterol levels and the expression of SREBP-regulated genes (including PCSK9, LDLR, and HMG-CoA reductase).
- SREBP activation is regulated by intracellular cholesterol
- ApoB and ApoA1 synthesis, release into circulation, and clearance determine the levels available for VLDL/LDL formation and HDL formation.
  - The transfer of intracellular ApoB to circulation is coupled to the formation of VLDL and therefore also to the intracellular cholesterol level.
  - Likewise, clearance of ApoB from circulation is coupled to the LDLR-mediated clearance of ApoB-containing particles (VLDL and LDL).
- PCSK9 synthesis, release into circulation, and clearance determine the circulating levels of PCSK9 available for interaction with either the LDLR or anti-PCSK9.

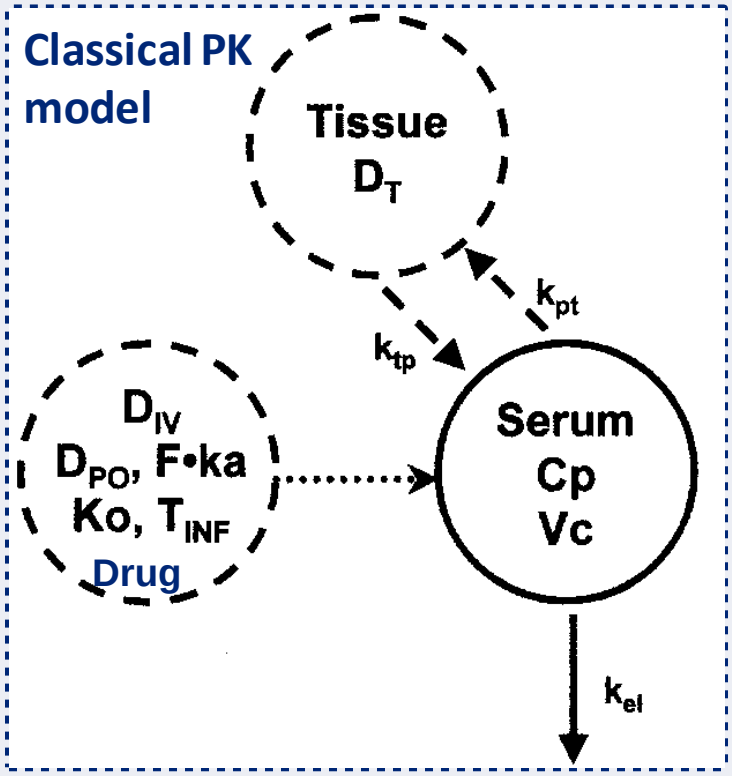
Equations for intracellular production of cholesterol proteins

- Regulation of production and activation is generally represented by hill functions

$$\frac{d(SREBP\_ic\_H)}{dt} = SREBP\_ic\_H\_production\_rate\_k - SREBP\_ic\_H \cdot SREBP\_ic\_H\_degradation\_rate\_k - SREBP\_ic\_H \cdot SREBP\_ic\_to\_nu\_H\_activation\_rate\_k \cdot Chol\_SREBP\_Imax \cdot \left(1 - \frac{Chol\_er\_H^{Chol\_SREBP\_nh}}{Chol\_er\_H^{Chol\_SREBP\_nh} + Chol\_er\_H\_base^{Chol\_SREBP\_nh}}\right)$$

$$\frac{d(ApoB\_ic\_H)}{dt} = ApoB\_ic\_H\_production\_rate\_k \cdot \frac{LDL\_pl}{ApoB\_pl} - ApoB\_ic\_H \cdot ApoB\_ic\_H\_to\_pl\_release\_rate\_k \cdot \frac{(LDL\_pl + VLDL\_pl)}{ApoB\_pl} - Chol\_ic\_H \cdot VLDL\_pl\_production\_rate\_k \cdot \frac{ApoB\_ic\_H^{ApoB\_VLDL\_nh}}{chol\_per\_VLDL\_particle \cdot (ApoB\_ic\_H^{ApoB\_VLDL\_nh} + ApoB\_VLDL\_EC50^{ApoB\_VLDL\_nh})}$$

Pharmacokinetic models are designed to predict the concentration of drug in a patient's plasma over time

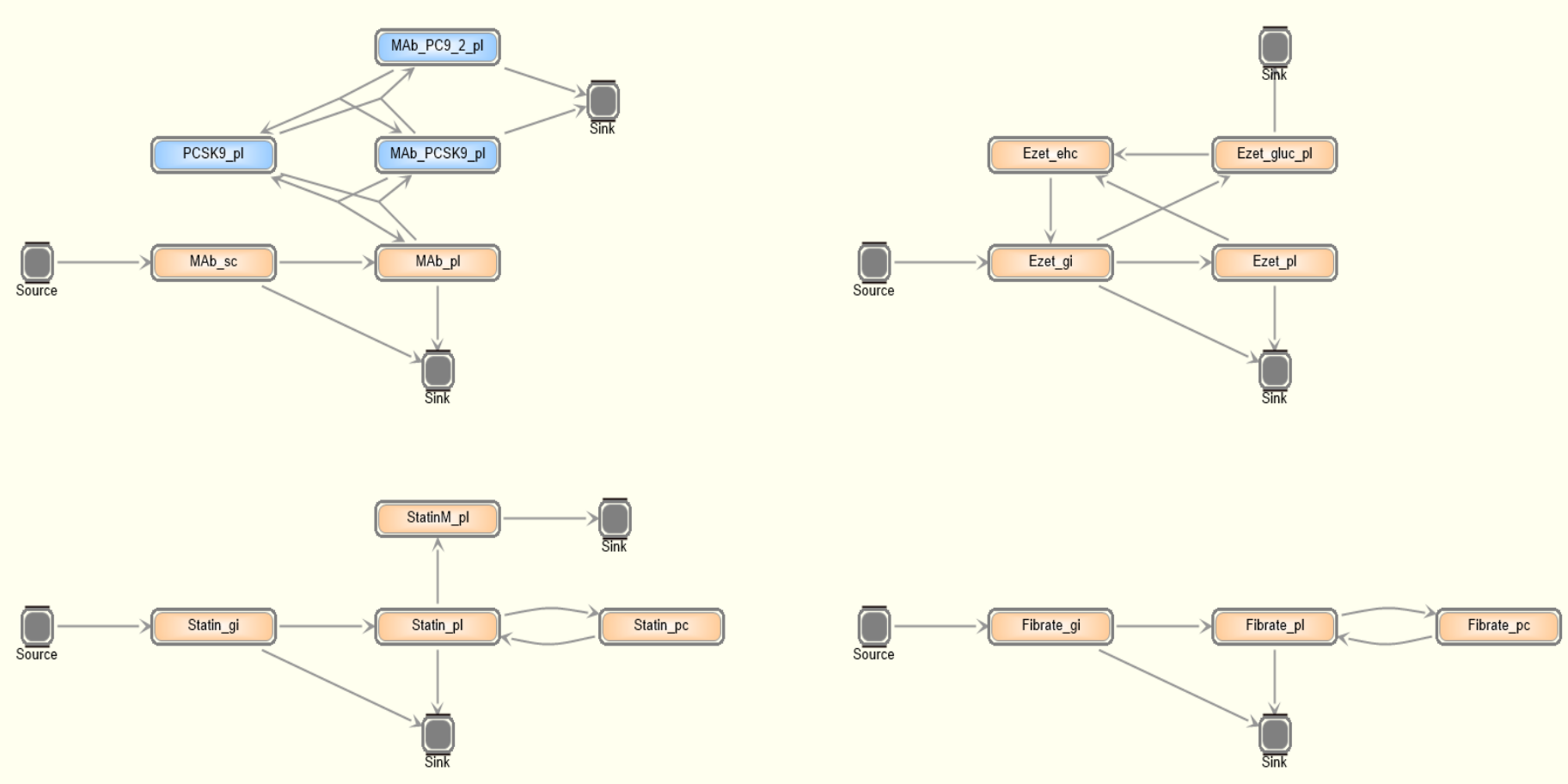


- Pharmacokinetic models describe the ADME characteristics of a drug
- Classical pharmacokinetic models consist of:
  - Absorption into the central (plasma) compartment, which represents plasma and well-perfused organs
  - Clearance of the drug from the central compartment
  - A "peripheral" compartment representing organs with lower perfusion
- Compartment design and parameter values are done empirically to fit data
  - Peripheral compartment and transition and clearance rates are "lumped" and do not correspond to specific parts or mechanisms
- Classical PK models predict average drug kinetics whereas Population Pharmacokinetics models (PopPK) predict variability in kinetics across a patient population

Mager, D.E. and Jusko, W.J. **General Pharmacokinetic Model for Drugs Exhibiting Target-Mediated Drug Disposition**. Journal of Pharmacokinetics and Pharmacodynamics. 28:6:507-532 (2001)

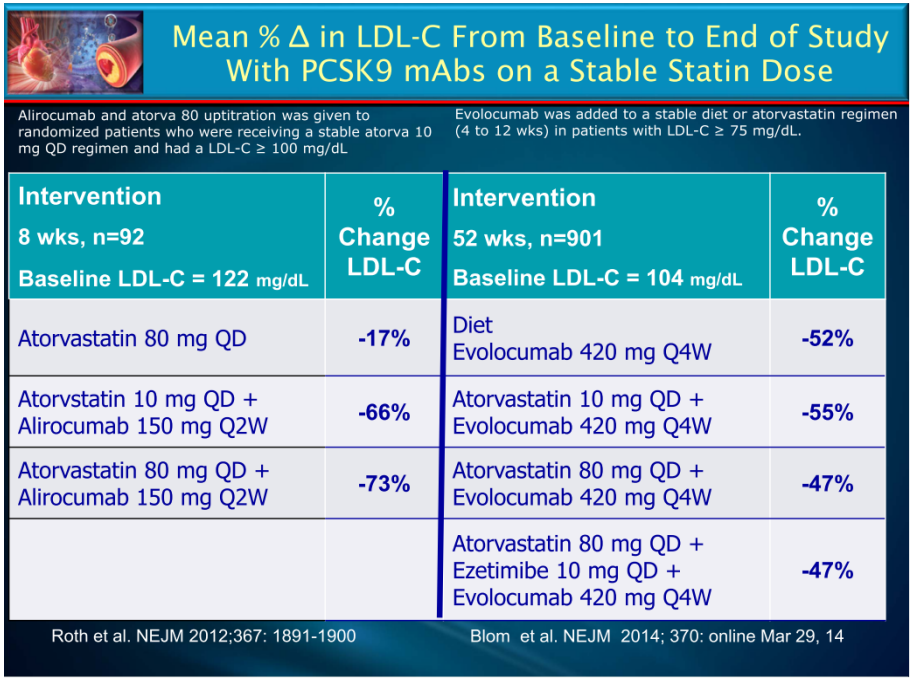
Pharmacokinetic submodels

- The model represents oral dosing of statin, fibrate, and ezetimibe along with subcutaneous dosing of the PCSK9 monoclonal antibody (Mab)
- Active metabolites of Ezetimibe and Statin are represented
- Distribution of drugs is represented through depot compartment, plasma, and other major localizations (peripheral or EHC compartments)



Model of statin therapy

- We included known mechanisms of action for statins into the model and calibrated the parameters influencing the pharmacodynamic effect of this drug to the average clinical response across clinical trial data reported in the literature.



Mean % Δ in LDL-C From Baseline to End of Study With PCSK9 mAbs on a Stable Statin Dose

Alirocumab and atorva 80 uptitration was given to randomized patients who were receiving a stable atorva 10 mg QD regimen and had a LDL-C ≥ 100 mg/dL

Evolocumab was added to a stable diet or atorvastatin regimen (4 to 12 wks) in patients with LDL-C ≥ 75 mg/dL.

Intervention 8 wks, n=92 Baseline LDL-C = 122 mg/dL	% Change LDL-C	Intervention 52 wks, n=901 Baseline LDL-C = 104 mg/dL	% Change LDL-C
Atorvastatin 80 mg QD	-17%	Diet Evolocumab 420 mg Q4W	-52%
Atorvstatin 10 mg QD + Alirocumab 150 mg Q2W	-66%	Atorvastatin 10 mg QD + Evolocumab 420 mg Q4W	-55%
Atorvastatin 80 mg QD + Alirocumab 150 mg Q2W	-73%	Atorvastatin 80 mg QD + Evolocumab 420 mg Q4W	-47%
		Atorvastatin 80 mg QD + Ezetimibe 10 mg QD + Evolocumab 420 mg Q4W	-47%

Roth et al. NEJM 2012;367: 1891-1900

Blom et al. NEJM 2014; 370: online Mar 29, 14

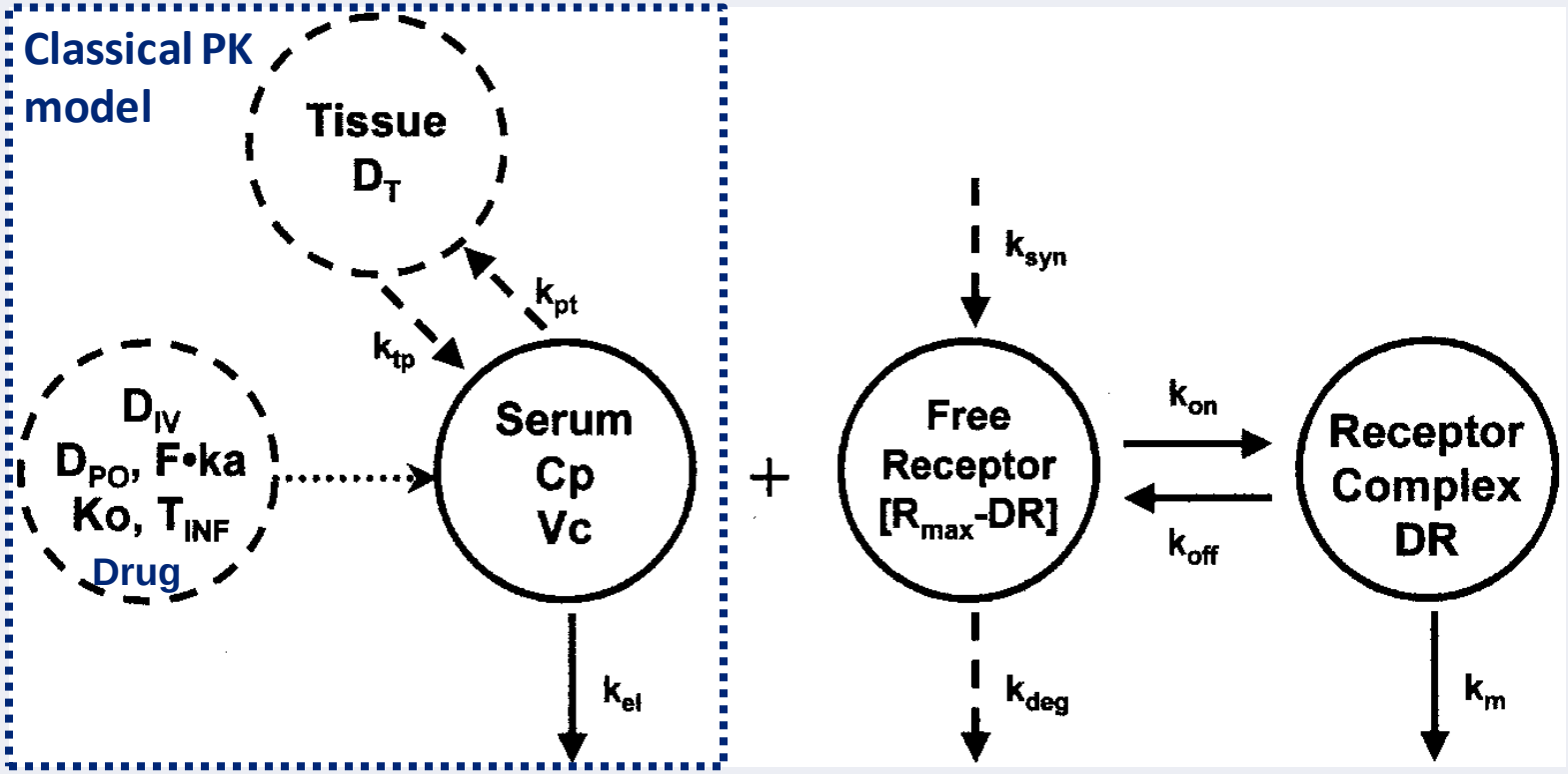
- *Roth EM, et. al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med. 2012;367:1891–1900.*
- *Vaughan CJ, Gotto AM. Update on statins: 2003. Circulation. 2004;110:886–892.*
- *Blom, D. J., et. al. 2014. "A 52-week placebo-controlled trial of evolocumab in hyperlipidemia." N Engl J Med 370 (19):1809-19.*

Statin therapy equations

- $\frac{d(Statin\_gi)}{dt} = -Statin\_F \cdot Statin\_Ka \cdot Statin\_gi + Statin\_Ka \cdot Statin\_gi \cdot (Statin\_F - 1) + Statin\_dose$
-
- $\frac{d(Statin\_pl)}{dt} = Statin\_F \cdot Statin\_Ka \cdot Statin\_gi - Statin\_pl \cdot Statin\_kel - Statin\_pl \cdot Statin\_kmet - Statin\_pl \cdot Statin\_pl\_to\_pc\_rate\_k + Statin\_pc \cdot Statin\_pc\_to\_pl\_rate\_k$
-
- $\frac{d(StatinM\_pl)}{dt} = Statin\_pl \cdot Statin\_kmet - StatinM\_pl \cdot StatinM\_kel$
- $\frac{d(Statin\_pc)}{dt} = Statin\_pl \cdot Statin\_pl\_to\_pc\_rate\_k - Statin\_pc \cdot Statin\_pc\_to\_pl\_rate\_k$
- $Conc\_Statin = convert\_nM\_to\_uM \cdot (\frac{Statin\_pl}{Statin\_Vd} + \frac{StatinM\_pl}{StatinM\_Vd})$

Target-Mediated Drug Distribution (TMDD) models are used in place of classical PK models when the clearance and localization of a therapeutic are inextricably linked to its target

TMDD Model



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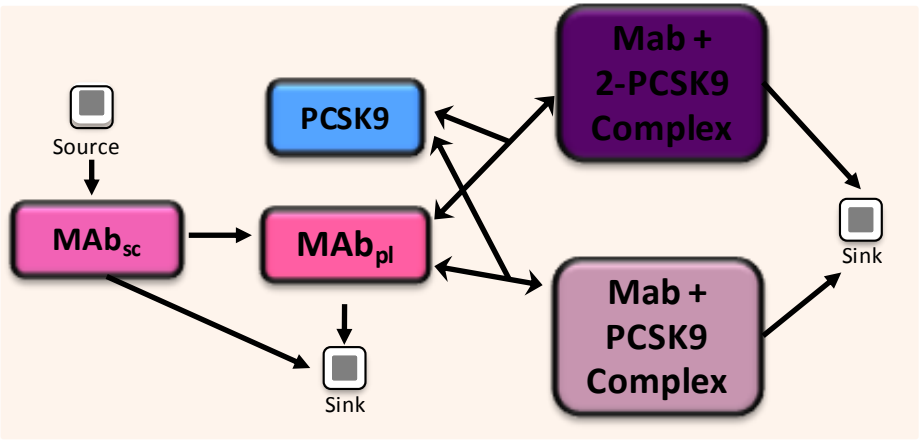
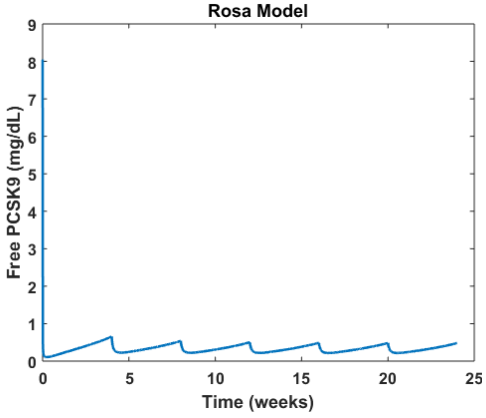
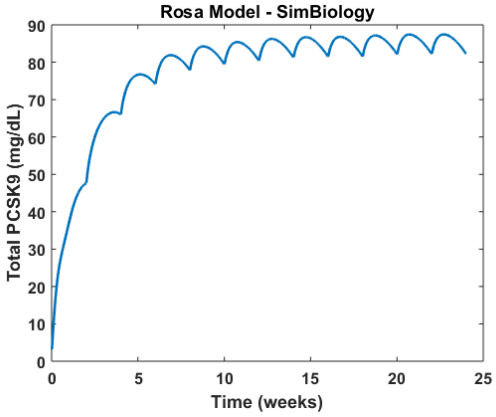
Representation of PCSK9 therapy in the QSP model







- Anti-PCSK9 antibodies are administered into the subcutaneous compartment and absorbed into the plasma compartment
- This model includes dual PCSK9 binding by each antibody
- Direct binding of PCSK9 and MAb in plasma is represented here

The model was developed for an average patient first and then parameterized for four different patient types

- One important feature of QSP models, since they encompass so much biological detail, is the ability to represent specific patient phenotypes and study their response to drug
- For the cholesterol model, we were interested in the following patients:
  - Statin responders
  - Statin non-responders
  - Anti-PCSK9 therapy responders
  - Anti-PCSK9 therapy non-responders

Parameter values adjusted to create virtual patients representing varied response to statin and alirocumab therapy

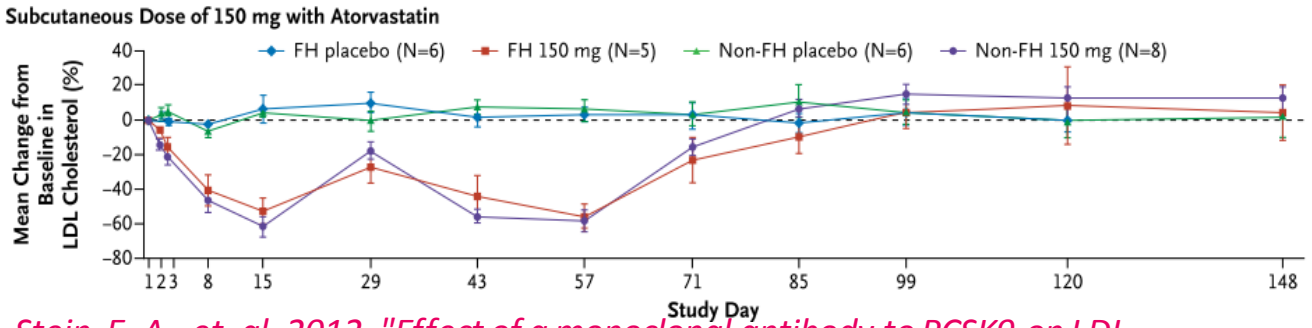
Process	Parameter	VP0	VP1	VP2	VP3	VP4	Unit	Reference/calculation
Rate of bile salt entering GI	Bile_acid_chol_secretion_rate_k	0.0143	0.01235	0.0135	0.011	0.017	1/h	Adjusted to achieve desired baseline LDL
Hepatic cholesterol synthesis	Chol_ic_H_production_rate_k	70000	100000	40000	70000	40000	nmol/h	Adjusted to represent high or low cholesterol synthesis
Hepatic unbound LDL-R degradation rate	LDL-R_en_H_degradation_rate_k	0.035	0.035	0.035	0.02	0.08	1/h	Estimated from LDL-R turnover rate
Peripheral unbound LDL-R degradation rate	LDL-R_en_P_degradation_rate_k	0.035	0.035	0.035	0.02	0.08	1/h	Estimated from LDL-R turnover rate
LDL-R synthesis rate, hepatocytes	LDL-R_ic_H_production_rate_k	2	2.9	1.8	2.4	1.56	nmol/h	Calculated to balance LDL-R turnover rate
LDL-R synthesis rate, peripheral	LDL-R_ic_P_production_rate_k	0.7	0.9	0.6	0.8	0.5	nmol/h	Calculated to balance LDL-R turnover rate
PCSK9 synthesis	PCSK9_ic_H_production_rate_k	3.5	3.5	3.5	3.1	5	nmol/h	Based on clearance and steady-state amount in plasma, (Konrad, Troutt, and Cao 2011)
Affinity of PCSK9 for LDL-R at acidic pH	PCSK9_LDL-R_en_Kd	10	10	10	5	20	nM	(Cunningham et al. 2007, Piper et al. 2007)
Affinity of PCSK9 for LDL-R at neutral pH	PCSK9_LDL-R_pl_Kd	350	350	350	175	700	nM	(Cunningham et al. 2007, Piper et al. 2007)
PCSK9 clearance	PCSK9_pl_clearance_rate_k	0.1	0.1	0.1	0.05	0.3	1/h	Adjusted to achieve desired PCSK9 level
Transfer of cholesterol from HDL to VLDL	HDL_to_VLDL_exchange_rate_k	0.0158	0.0238	0.0238	0.0238	0.0238	1/h	Calculated based on Giugliano et al., 2012; McAuley et al., 2012
Transfer of cholesterol from HDL to LDL	HDL_to_LDL_exchange_rate_k	0.0017	0.0026	0.0026	0.0026	0.0026	1/h	Calculated based on Giugliano et al., 2012; McAuley et al., 2012
Hill coefficient for SREBP-2-regulated PCSK9 synthesis	SREBP_PCSK9_nh	4	2	4	4	4	Unitless	Adjusted to provide varying degrees of response to SREBP-2 activation
Hill coefficient for SREBP-2-regulated LDL-R synthesis	SREBP_LDL-R_nh	4	4	3	4	4	Unitless	Adjusted to provide varying degrees of response to SREBP-2 activation

VPs 1 and 2 are statin responders and non-responders, respectively. VPs 3 and 4 are alirocumab responders and non-responders, respectively.

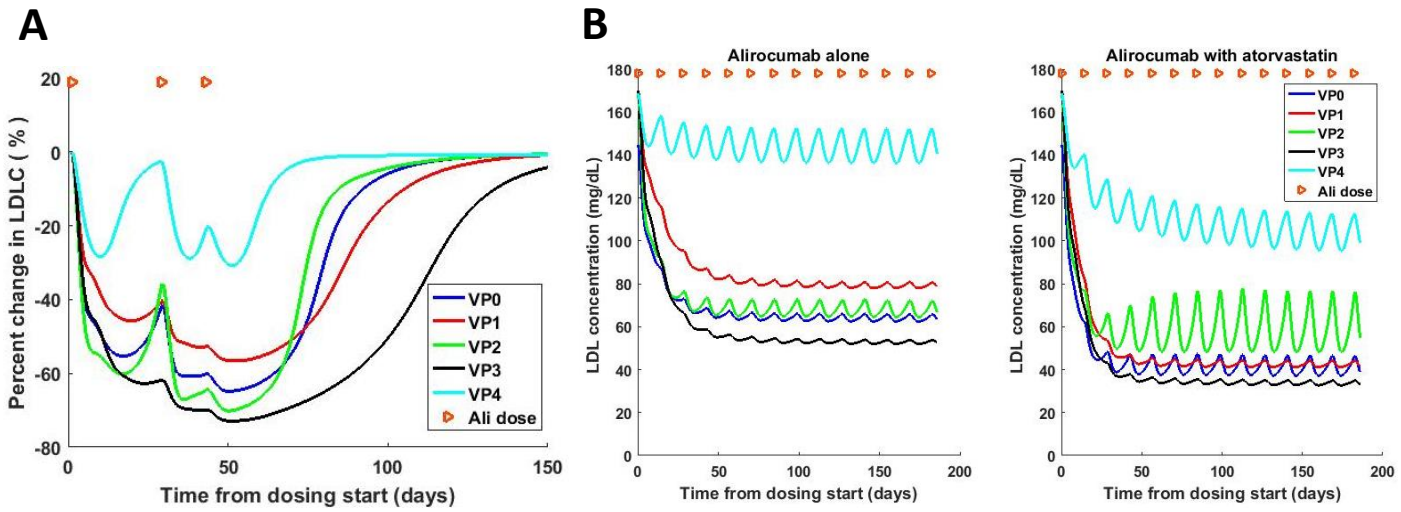
Baseline characteristics of Virtual Patients prior to therapy

Cholesterol	VP0	VP1	VP2	VP3	VP4
LDL	145 mg/dL	169 mg/dL	168 mg/dL	170 mg/dL	169 mg/dL
Total cholesterol	223 mg/dL	241 mg/dL	239 mg/dL	242 mg/dL	239 mg/dL
ApoB-100	1.15 g/L	1.25 g/L	1.25 g/L	1.25 g/L	1.28 g/L
HDL	55.0 mg/dL	46.3 mg/dL	46.2 mg/dL	46.3 mg/dL	46.0 mg/dL
VLDL	23.7 mg/dL	25.5 mg/dL	25.1 mg/dL	25.6 mg/dL	24.6 mg/dL
Non-HDL-C	168 mg/dL	195 mg/dL	193 mg/dL	196 mg/dL	193 mg/dL
PCSK9					
Free	3.3 nM (238 ng/mL)	3.0 nM (216 ng/mL)	4.5 nM (324 ng/mL)	1.8 nM (130 ng/mL)	4.7 nM (338 ng/mL)
Plaque					
Plaque volume	78 mm^3	85 mm^3	84 mm^3	84 mm^3	84 mm^3
Lipid core	31 mm^3	38 mm^3	37 mm^3	37 mm^3	37 mm^3

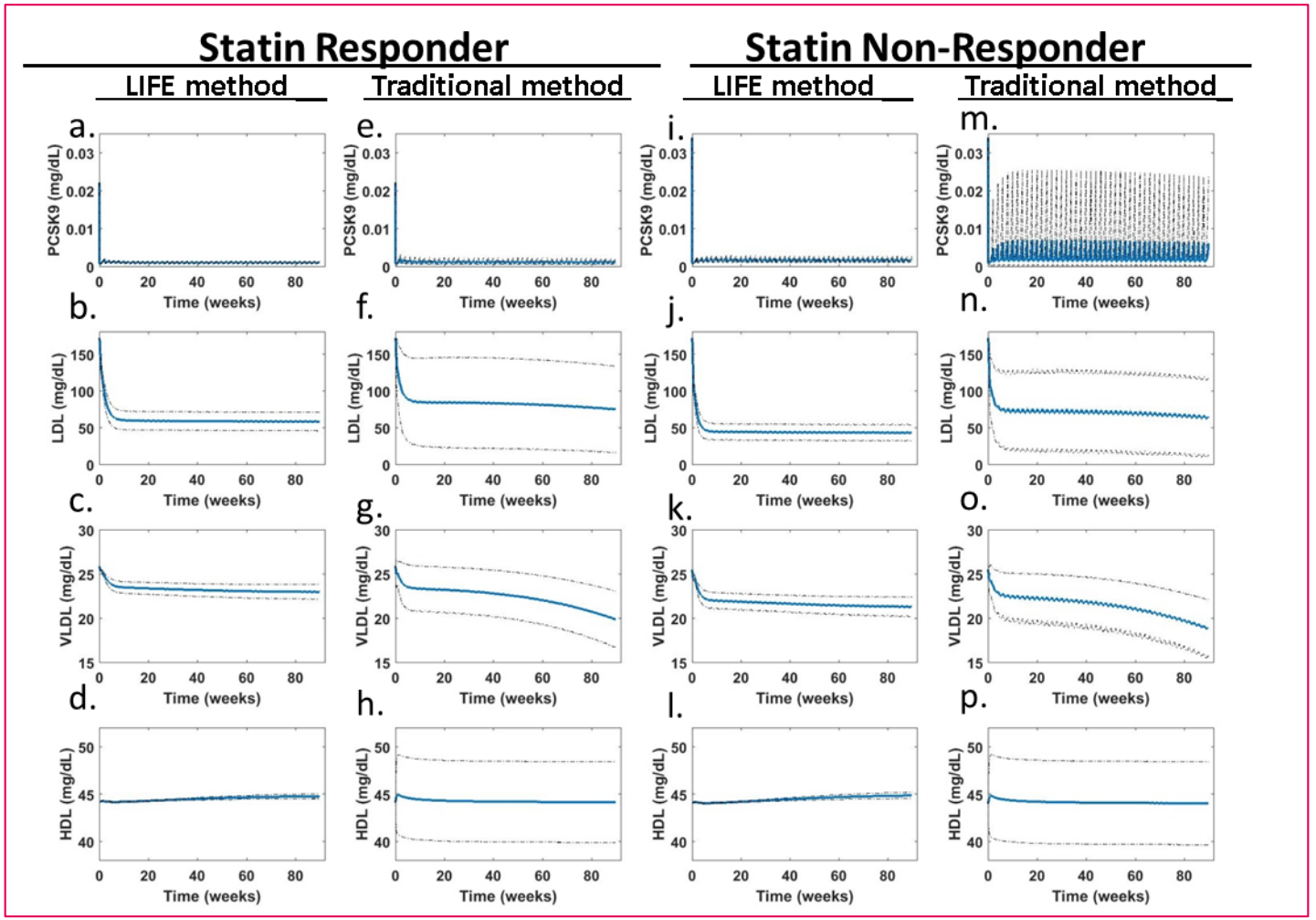
Virtual patients encompass a range of therapy responses seen clinically to anti-PCSK9 and statin therapy



Stein, E. A., et. al. 2012. "Effect of a monoclonal antibody to PCSK9 on LDL cholesterol." N Engl J Med 366 (12):1108-180

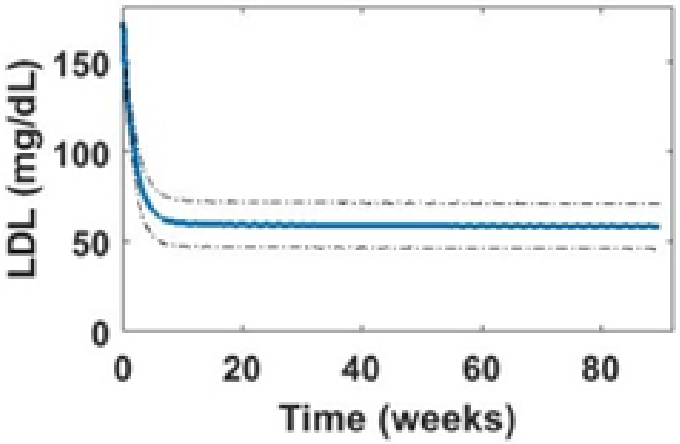


The LIFE method was better able to differentiate response of statin responders vs. non-responder virtual patients to PCSK9 therapy

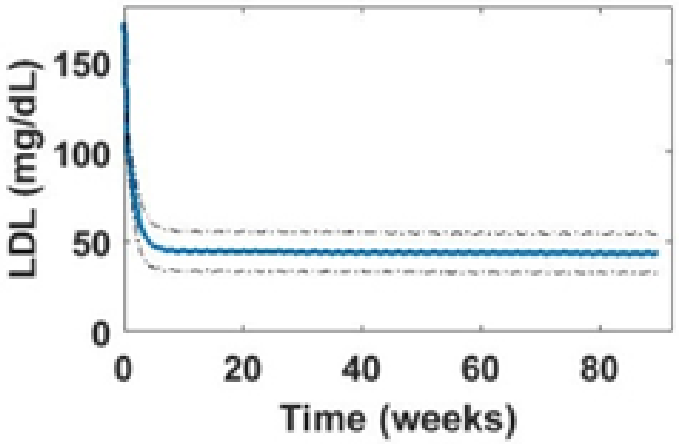


The LIFE method was better able to differentiate response of statin responders vs. non-responders to PCSK9 therapy

Statin Responder



Statin Non-Responder



Conclusion from these studies

- We predict that Statin non-responders will better respond to Praluent therapy
  - the baseline PCSK9 levels of these patients are higher and so PCSK9 has a larger role in causing high cholesterol levels
- However both statin responders and non-responders will see a significant reduction in their LDL-C levels of from baseline
- In conclusion, all types of patients would benefit from Praluent therapy and should be offered it, but statin non-responders will see a slightly more dramatic response

To consider when constructing your projects

- What are the important species and parameters implicated in the question
- What can you learn from the LIFE equations before performing an optimization?
- What changes do you need to make in the model to ensure consistency – any changes that you make do not conflict with existing assumptions or representations in the model

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QUESTIONS ON TALK

- Goal: Presentation to last 1.5-2 h of April 3 class
- Do I need references for all summaries?
- Is this the right level of detail?
- What should I have prepared in terms of the cholesterol model for the students to use? Do I need to create any submodels?