Review of the LIFE method and final projects

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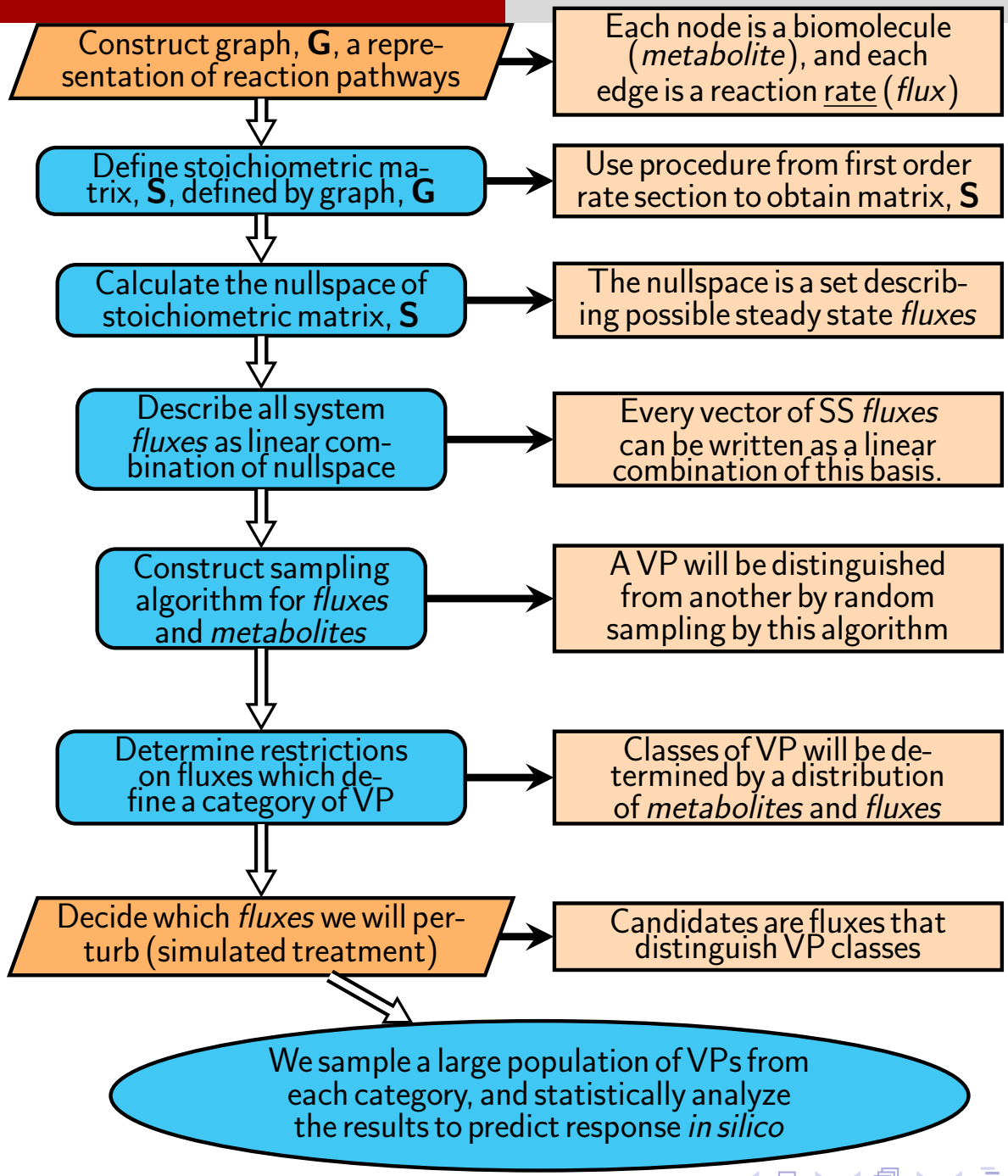
April 17, 2018

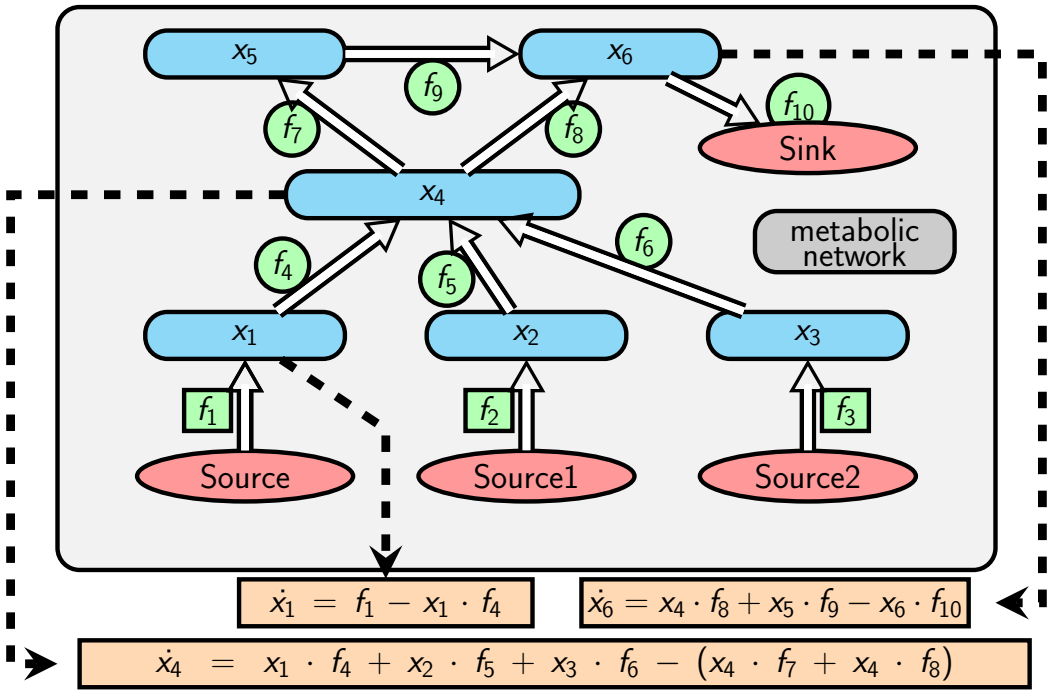
Steps of LIFE

- Define stoichiometric matrix $S(x)$ from Graph.
- Find basis for nullspace of $S(x)$, $\mathcal{N}(S(x))$.
- Sample from nullspace using appropriate parameters.
- Solve the system with a stiff ODE solver, such as ode15s in matlab

For this project, you must determine the sources and sinks that connect the two submodels you are given.


Construct graph, **G**, a representation of reaction pathways
Each node is a biomolecule (*metabolite*), and each edge is a reaction rate (*flux*)
Define stoichiometric matrix, **S**, defined by graph, **G**
Use procedure from first order rate section to obtain matrix, **S**
Calculate the nullspace of stoichiometric matrix, **S**
The nullspace is a set describing possible steady state *fluxes*
Describe all system *fluxes* as linear combination of nullspace
Every vector of SS *fluxes* can be written as a linear combination of this basis.
Construct sampling algorithm for *fluxes* and *metabolites*
A VP will be distinguished from another by random sampling by this algorithm
Determine restrictions on fluxes which define a category of VP
Classes of VP will be determined by a distribution of *metabolites* and *fluxes*
Decide which *fluxes* we will perturb (simulated treatment)
Candidates are fluxes that distinguish VP classes
We sample a large population of VPs from each category, and statistically analyze the results to predict response *in silico*

Generalized Graph of Metabolic Network



$$\dot{X} = S(f)X \qquad S(f) \text{ is a } 6 \times 6 \text{ matrix}$$

Linear-In-Flux-Expressions (LIFE) Method

$$\dot{X} = S(X) \cdot f$$

$$\dot{X} = \begin{pmatrix} 1 & 0 & 0 & -x_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & -x_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & -x_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & x_1 & x_2 & x_3 & -x_4 & -x_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & x_4 & 0 & -x_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & x_4 & x_5 & -x_6 \end{pmatrix} \cdot \begin{pmatrix} f1 \\ f2 \\ f3 \\ f4 \\ f5 \\ f6 \\ f7 \\ f8 \\ f9 \\ f10 \end{pmatrix}$$

$S(x)$ is a 6×10 matrix $\qquad \operatorname{rank} S(x) = 6$

LIFE cont'd

flux $f \subset \ker S(x)$ if $S(x) \cdot f = 0$

LIFE cont'd

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$$\begin{pmatrix} f1 \\ f2 \\ f3 \\ f4 \\ f5 \\ f6 \\ f7 \\ f8 \\ f9 \\ f10 \end{pmatrix} = a_1 \begin{bmatrix} X6 \\ 0 \\ 0 \\ \frac{X6}{X1} \\ 0 \\ 0 \\ 0 \\ \frac{X6}{X4} \\ 0 \\ 1 \end{bmatrix} + a_2 \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \frac{X5}{X4} \\ \frac{-X5}{X4} \\ 1 \\ 0 \end{bmatrix} + a_3 \begin{bmatrix} -X3 \\ 0 \\ X3 \\ \frac{-X3}{X1} \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + a_4 \begin{bmatrix} -X2 \\ X2 \\ 0 \\ \frac{-X2}{X1} \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

LIFE cont'd

flux $f \subset \ker S(x)$ if $S(x) \cdot f = 0$

$$\begin{pmatrix} f1 \\ f2 \\ f3 \\ f4 \\ f5 \\ f6 \\ f7 \\ f8 \\ f9 \\ f10 \end{pmatrix} = a_1 \begin{bmatrix} X6 \\ 0 \\ 0 \\ \frac{X6}{X1} \\ 0 \\ 0 \\ 0 \\ \frac{X6}{X4} \\ 0 \\ 1 \end{bmatrix} + a_2 \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \frac{X5}{X4} \\ \frac{-X5}{X4} \\ 1 \\ 0 \end{bmatrix} + a_3 \begin{bmatrix} -X3 \\ 0 \\ X3 \\ \frac{-X3}{X1} \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + a_4 \begin{bmatrix} -X2 \\ X2 \\ 0 \\ \frac{-X2}{X1} \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{pmatrix} a_1 x_6 - a_3 x_3 - a_4 x_2 \\ a_4 \cdot x_2 \\ a_3 \cdot x_3 \\ \frac{a_1 x_6}{x_1} - \frac{a_3 x_3}{x_1} - \frac{a_4 x_2}{x_1} \\ \mathbf{a_4} \\ \mathbf{a_3} \\ \frac{a_2 x_5}{x_4} \\ \frac{a_1 x_6}{x_4} - \frac{a_2 x_2}{x_4} \\ \mathbf{a_2} \\ \mathbf{a_1} \end{pmatrix}$$

Flux values for different classes of Virtual Patient

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

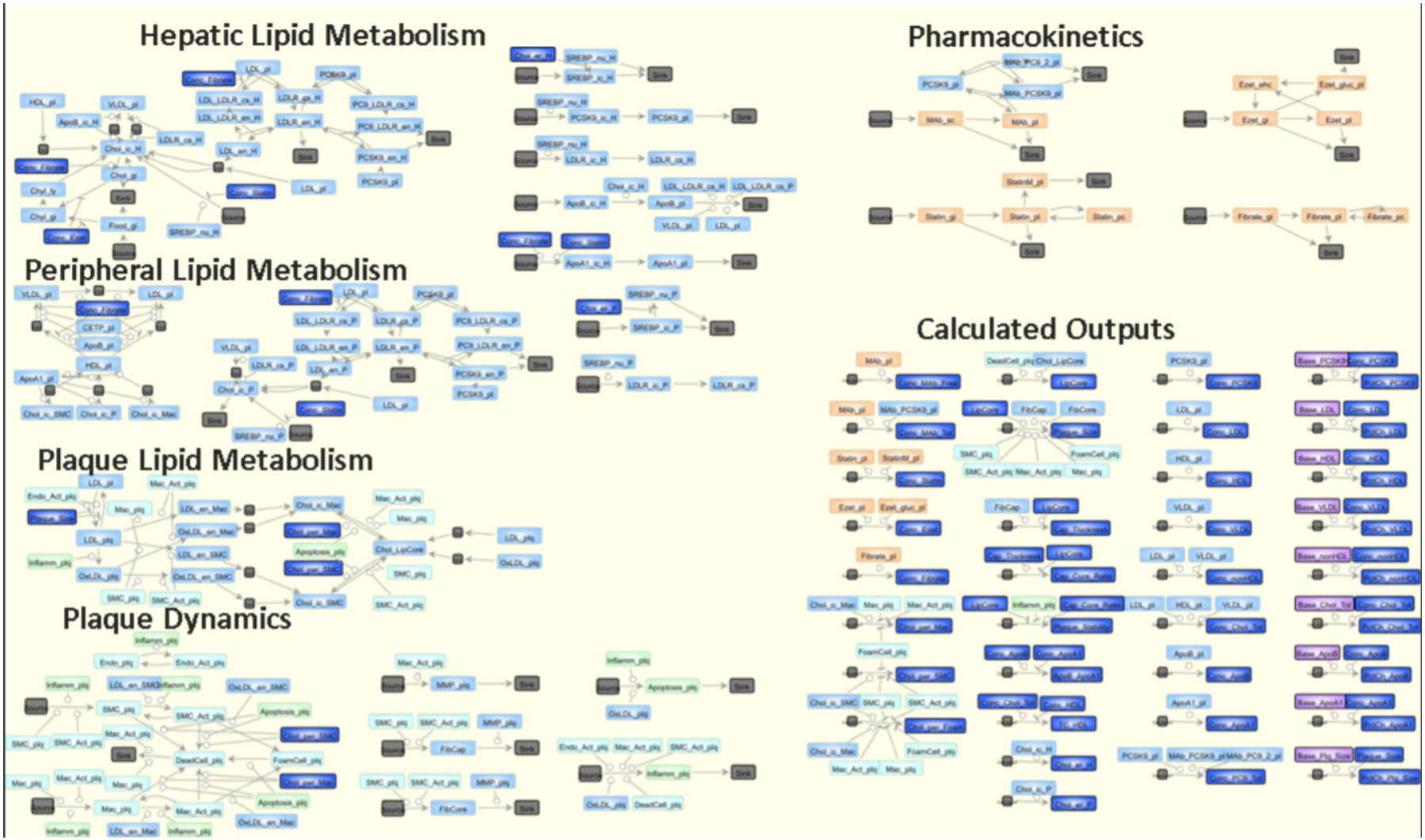
Virtual Patients as Parameterizations of the Model

Sample $a_1, \ldots, a_4$ and plug in baseline metabolites $x_1, \ldots, x_6$. Then we have a single virtual patient.

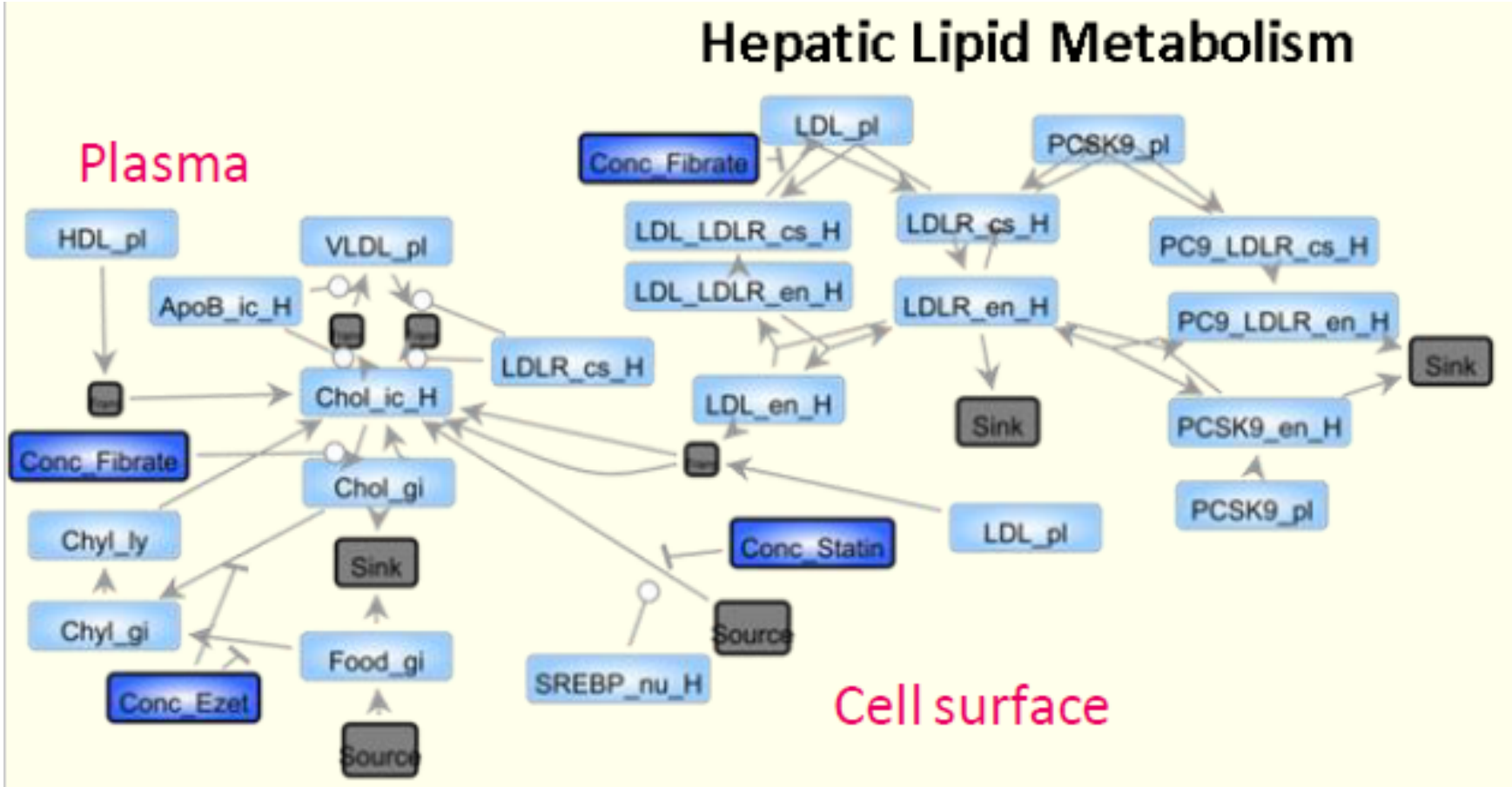
$$\begin{pmatrix} a_1 x_6 - a_3 x_3 - a_4 x_2 \\ a_4 \cdot x_2 \\ a_3 \cdot x_3 \\ \frac{a_1 x_6}{x_1} - \frac{a_3 x_3}{x_1} - \frac{a_4 x_2}{x_1} \\ \mathbf{a_4} \\ \mathbf{a_3} \\ \frac{a_2 x_5}{x_4} \\ \frac{a_1 x_6}{x_4} - \frac{a_2 x_2}{x_4} \\ \mathbf{a_2} \\ \mathbf{a_1} \end{pmatrix} = \begin{pmatrix} f1 \\ f2 \\ f3 \\ f4 \\ f5 \\ f6 \\ f7 \\ f8 \\ f9 \\ f10 \end{pmatrix} \tag{1}$$

Classes of virtual patient are defined by the distribution from which we sample $a_1, \ldots, a_4$. In the past, we have used lognormal distributions with various mean and standard deviation matching clinical data.

Cholesterol network

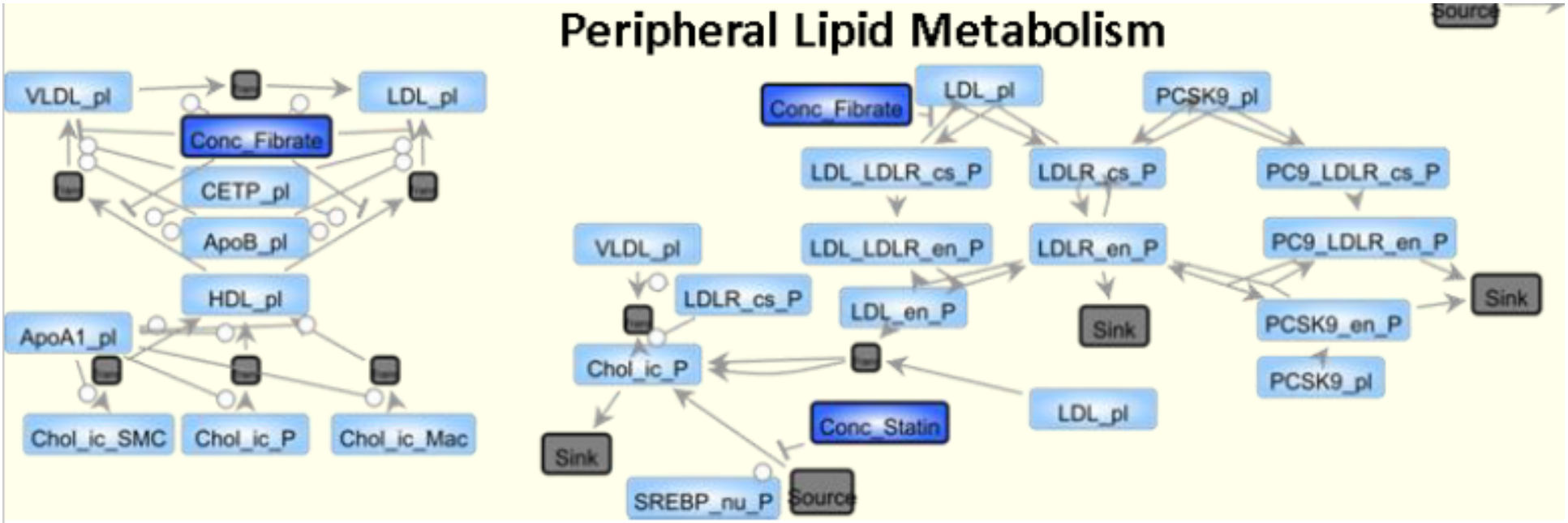


Hepatic subsystem



Team a: Nate, Ravi, Linlin.

Peripheral subsystem



Team α: Zheming, Heather, Dan.

Analysis of subnetworks

For the final project, teams must:

- Understand the connections between the two submodels. Teams must identify those metabolites which are present in both networks, such as LDL_pl and PCSK9_pl.
- Identify levels of sources for equilibria.
- Run the program for the assigned submodel with the appropriate sources and sinks resulting from the network being split.
- Apply the life method to identify all equilibria.
- Run the simulation with a new dosing regimen for the pcsk9 antibody therapy.

Plot of LDL_pl over time: