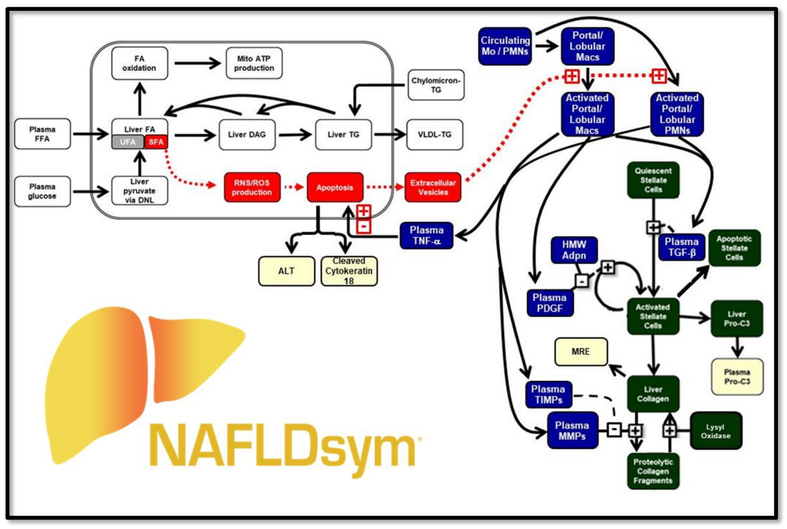
Virtual Patient Generation Strategies for Non-Alcoholic Fatty Liver Disease

Fulya Akpinar Singh[1], Scott Q Siler[2], Grant T Generaux[2], Diane M Longo[2], Lisl Shoda[2], Christina Battista[2], Zackary R Kenz[2], Craig Thalhauser[1], Tarek Leil[1]

[1] [1]Bristol-Myers Squibb, Princeton, NJ, USA; [2] DILIsym Services, Inc., Research Triangle Park, NC



NAFLDsym QSP model.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are of growing concern within developed countries, with recent estimates suggesting up to 30% of the US population may be affected[1]. NAFLDsym v2A is a QSP model of NAFLD and NASH that represents the primary pathophysiologic components of the disease, including steatosis, lipotoxicity, inflammation, dyslipidemia, and fibrosis. The model consists of a system of ordinary differential equations (ODEs) which describe these processes in the three primary acinar zones of the liver.

Weight gain is thought to play a substantial role in NAFLD/NASH disease progression. Steatosis, NAS, and fibrosis scores have been shown to correlate with weight gain[2], and improvement with each has also been reported with weight loss[3]. NAFLDsym is capable of reproducing these behaviors[4].

METHODS

SimPops in NAFLDsym v2A, reflecting inter-patient heterogeneity in steatosis, lipotoxicity, inflammation, and fibrosis, can be generated multiple ways. Two different approaches to generating SimPops, in particular, are described and compared.

In both methods, parameter values were adjusted and combined. These included parameters describing body weight, glycemia, plasma TG clearance, serum adiponectin, de novo lipogenesis (DNL), adipose fatty acid release, VLDL-TG release, sensitivity to SFA-induced oxidative stress, hepatocellular TG lipolysis, fatty acid esterification, hepatocyte bioenergetics, sensitivity to apoptosis, hepatocellular proliferation, hepatocyte extracellular vesicle release, macrophage activation and mediator release, stellate cell activation/proliferation, and collagen synthesis/degradation.

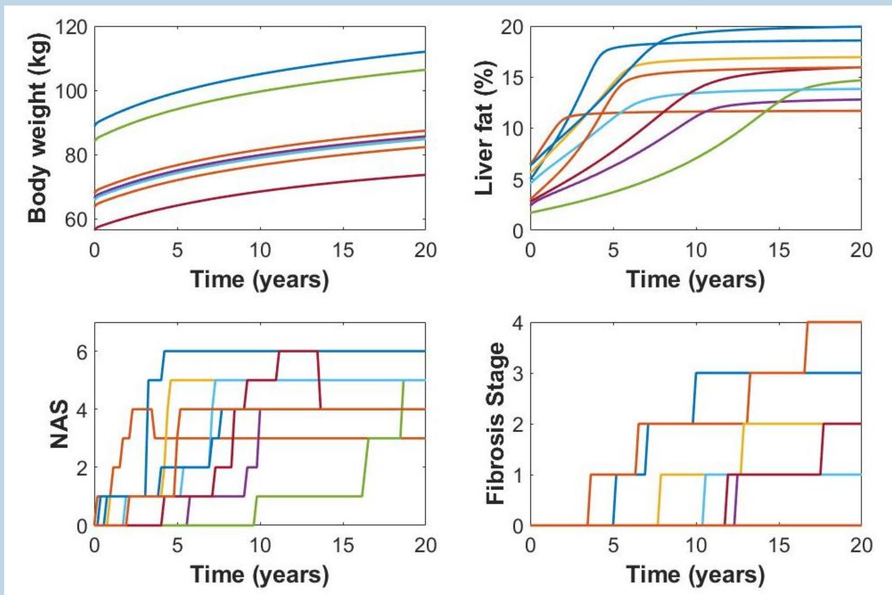
In one method, each simulated patient within the SimPops is allowed to reach steady state over 3-12 simulated years while maintaining body weight with isocaloric food intake. Numerous simulated measurements for the steady state SimPops are compared with multiple measured data sets to ensure validity.

In another method, simulated patients were placed on hypercaloric diets, eliciting weight gain over time. The increased caloric consumption augmented DNL within the simulated patients[5]; increased adipose fatty acid release due to increased adipose depot size[6] combines with increased DNL to amplify the hepatic lipid burden. This simulated progression of NASH also generates valid simulated patients and SimPops. Simulated patients can be sampled and validated at various points in disease progression.

SimPops generated with the two approaches described above can be used to predict the responses to treatments and understand underlying mechanisms contributing to predicted responses.

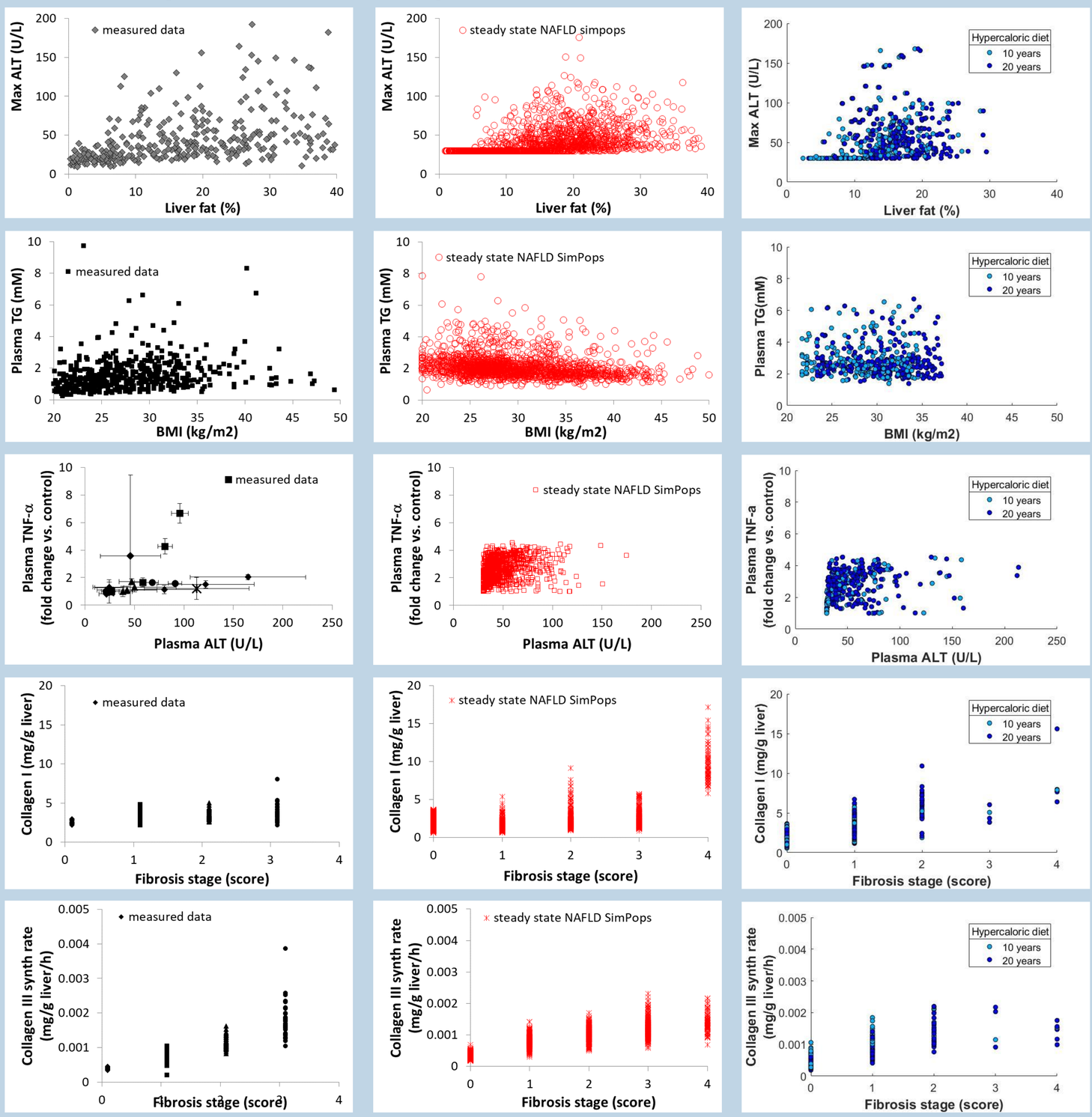
RESULTS

Simulations of Disease Progression within NAFLDsym



- 2% increase in caloric intake over 20 years resulted in ~20%-30% body weight gain by design[17].
- Liver fat levels of some patients have increased fast and reached a steady state, while some showed a slow and steady increase.
- Varying the aforementioned parameters allowed simulation of inter-patient variability in progression of NAS score and Fibrosis stage.

Comparison of SimPops Generated with Different Methods



- Simulated patients generated using the two different methods show similarities in dynamics of steatosis, lipotoxicity, inflammation and fibrosis.
- Simulating diet-induced disease progression produced only 9/232 patients (<4%) at F3 and F4 stage over 20 years, in agreement with the slow progression rates for NASH patients reported in literature.

CONCLUSIONS

- NAFLDsym SimPops are able to represent inter-patient variability in key pathophysiologic and clinical characteristics of patients with NASH and NAFLD
- NAFLDsym can simulate disease progression to generate SimPops, sampling patients at various points in disease progression (simple steatosis, NASH, fibrosis)
- SimPops generation in NAFLDsym can be achieved by allowing patients to reach steady state following changes in key parameters, as well as by simulating hypercaloric diet that induces weight gain and NAFLD development. While the first approach is computationally faster, the second one allows exploration of disease progression.

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