Modeling Fibrosis Progression in NAFLD and NASH

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Introduction

- Prevalence of advanced fibrosis progression has grown to over 4 million people in the US and there are currently no approved treatment options for NAFLD or NASH
- Variability in disease progression can be attributed to biopsy sample variability, pathologist reading in addition to biological factors governing disease progression
- Lack of prior knowledge of a patients fibrosis status also adds to the challenge of accurately predicting disease progression

Objective

The specific pathways, timescales, and dynamics driving the progression of fibrosis in NAFLD and NASH are not yet well understood. The objective of this work was to develop a continuous-time Markov chain model [1] to capture the heterogeneity of fibrosis progression and regression observed in the clinic.

Methods

Published studies involving paired liver biopsies with varying trial duration were identified [2-8]. We then employed a continuous-time Marko Chain model (Fig. 1A) to estimate the average time of disease progression through the various stages of fibrosis. A sensitivity analysis was performed to identify which parameters have the most influence on the average change in fibrosis score.

CTMC Model

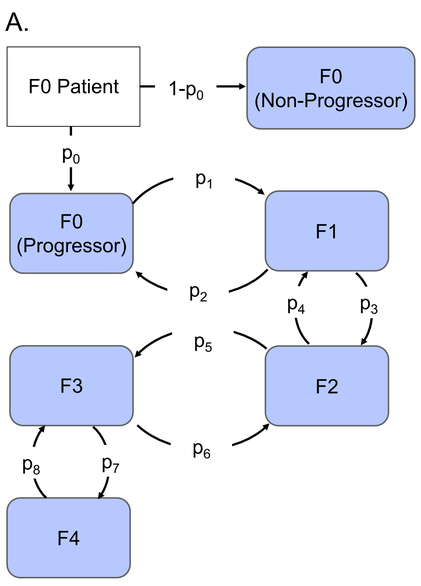
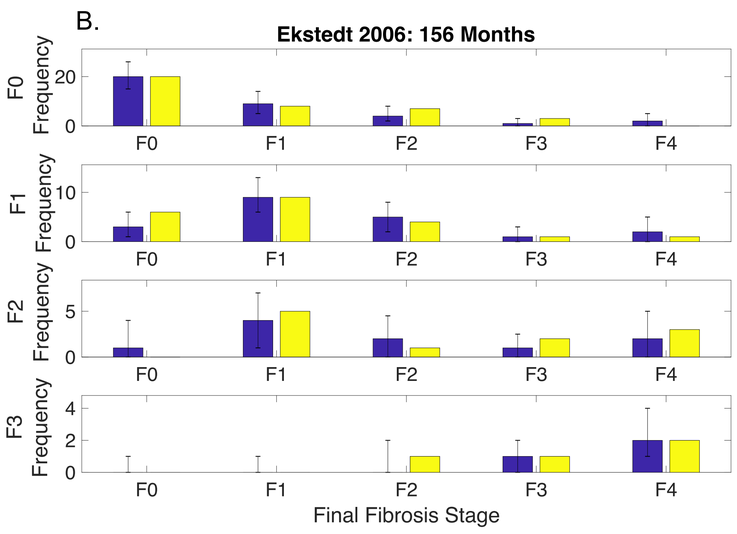


Figure 1. *CTMC model structure and fitting at 156 months.*

(A) F0 patients are either progressors or non-progressors. Each stage of fibrosis has an associated progression or regression rate.

(B) Representative model fitting of observed data (yellow bars) and model fitted data (blue bars) [3]. Error bars represent the SD following 200 simulations.

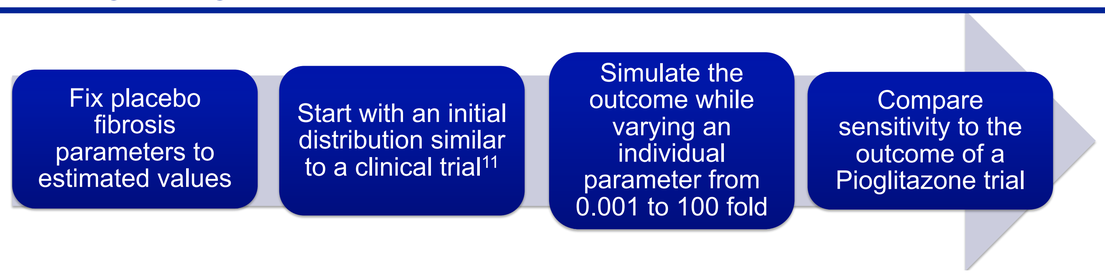


- Probability is time independent and therefore each time point has the same probability of progression
- Model is able is agnostic to the sources of variability and is able to simulate the heterogeneity of disease progression in patient populations

Table 1. Parameter Estimates

Progressor Fraction	**Forward τ (mo.)**	$1/p_1$: 2.44	$1/p_3$: 82.6	$1/p_5$: 147	$1/p_7$: 15.0
	90% Range	[0.13, 7.3]	[4.2, 247]	[7.5, 440]	[0.77, 45]
p_0 : 0.556	**Reverse τ (mo.)**	$1/p_2$: 6.62	$1/p_4$: 48.8	$1/p_6$: 138	$1/p_8$: 40.8
	90% Range	[0.34, 19.8]	[2.5, 146]	[7.0, 413]	[2.0, 122]

Sensitivity Analysis



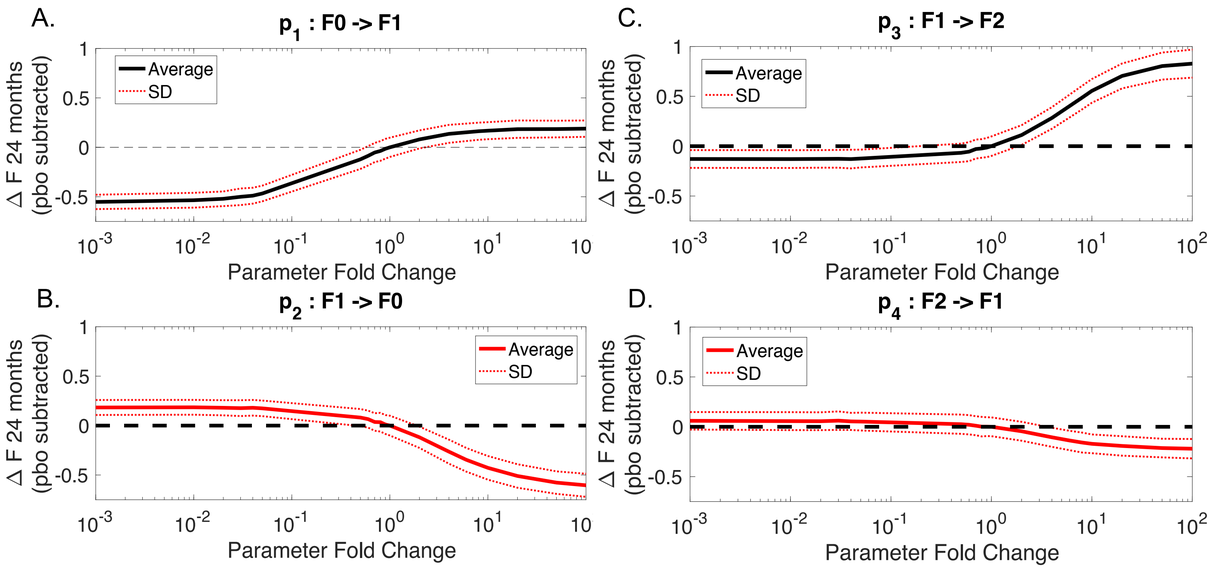
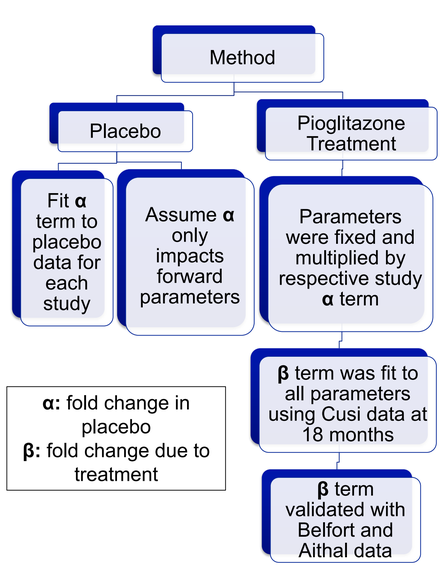


Figure 2. *Sensitivity analysis demonstrates intervention at stages F0, F1 and F2 have the greatest impact on average fibrosis score.*

For each parameter the placebo subtracted change in fibrosis score is plotted against the fold change in transition rate parameter. **(A)** F0 to F1, p_1 **(B)** F1 to F0, p_2 **(C)** F1 to F2, p_3 **(D)** F2 to F1, p_4 .

- The maximum decrease in average fibrosis score by altering any single parameter is -0.5

Pioglitazone Case Study



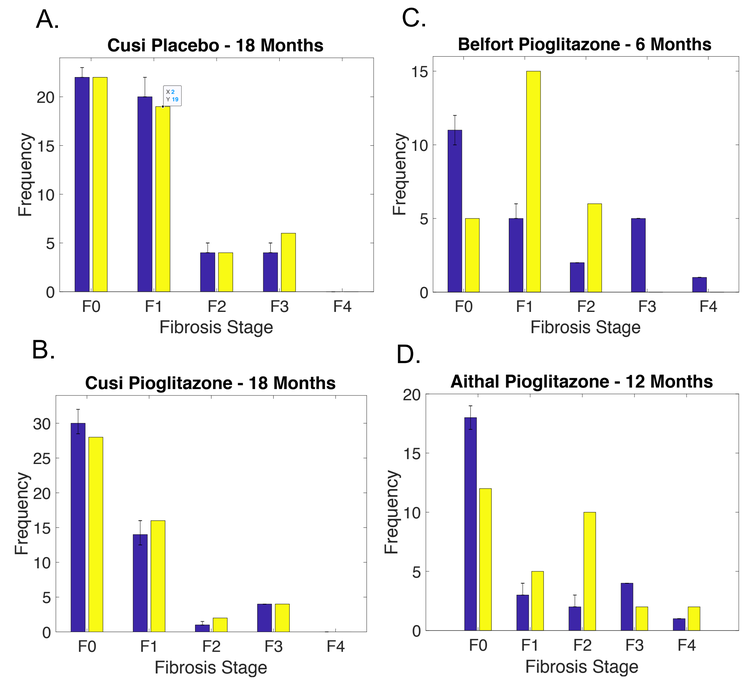


Figure 3. *Model refitted to pioglitazone response captures training set but under-predicts progression from F1 to F2 in different patient populations.*

(A) Fitting of placebo response (α) to Cusi placebo data. **(B)** Fitting of pioglitazone response (β) to Cusi data. **(C)** Simulated outcome of Belfort pioglitazone response (β). **(D)** Simulated outcome of Aithal pioglitazone response (β).

Table 2. Pioglitazone Parameters

Placebo (mo.)	$1/p_1$: 3.75	$1/p_3$: 182	$1/p_5$: 85.6	$1/p_7$: 131
Pioglitazone (mo.)	$1/p_1$: 33.4	$1/p_3$: 702	$1/p_5$: 375	$1/p_7$: 199
	$1/p_2$: 16.5	$1/p_4$: 5.32	$1/p_6$: 17.4	$1/p_8$: 3.88

Clinical Trial Design

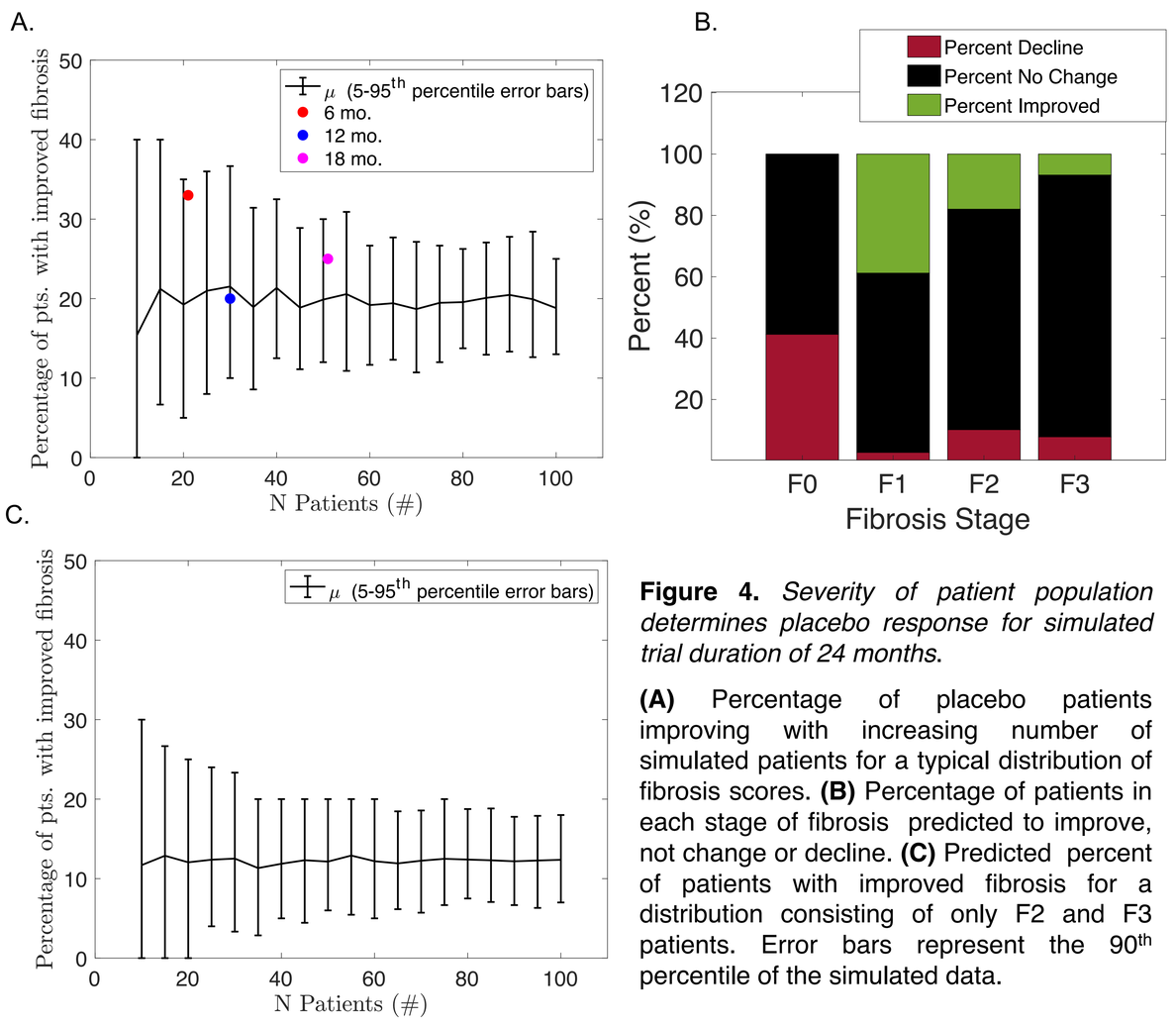


Figure 4. *Severity of patient population determines placebo response for simulated trial duration of 24 months.*

(A) Percentage of placebo patients improving with increasing number of simulated patients for a typical distribution of fibrosis scores. **(B)** Percentage of patients in each stage of fibrosis predicted to improve, not change or decline. **(C)** Predicted percent of patients with improved fibrosis for a distribution consisting of only F2 and F3 patients. Error bars represent the 90th percentile of the simulated data.

Results

Model fitting suggests the average duration of progression from stage F0 to F1 is 2.44 months and 90% of patients transitioned from F0 to F1 between 0.13 and 7.3 months. This rate accounts for misclassification and is independent of time spent in a particular stage. Reverse rates were also estimated to account for disease regression. Sensitivity analysis revealed intervention at stage 1 and stage 2 results in improved overall average fibrosis scores for a typical patient cohort distribution (Fig. 2). These results were in good agreement with a retrospective analysis of placebo controlled pioglitazone clinical trials for the treatment of NAFLD and NASH [9-11].

Conclusions

The CTMC modeling approach enabled us to estimate forward and reverse parameters for fibrosis in NAFLD and NASH. Accounting for sample error variability and pathologist variability allows us to make more robust predictions about potential clinical outcomes. As more data becomes available, we will be able to increase confidence in parameter estimates which will allow us to make better predictions to aid clinical trial design.

References

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