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Extrapolating discrete-time disease evolution data in limited series of transition probability matrices: A continuous-time Markov chain approach

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Disclosures

- This study is conducted by Evidinno Outcomes Research Inc. in collaboration with Bristol Myers Squibb, which provided financial sponsorship
- Yuanhui Zhang and Murat Kurt report employment by Bristol Myers Squibb
- Behnam Sharif and Nishu Gaind are contracted and employed, respectively, by Evidinno Outcomes Research Inc. (Vancouver, BC, Canada)

Background

- Within each disease model, patients move through health states as the disease progresses, each with different signs, symptoms, mortality, morbidity, burden, medical needs, and costs
- Multi-state Markov models are commonly used to describe the long-term disease progression through various health states over time in discrete or continuous scales. Examples include decline in lung function during chronic obstructive pulmonary disease, decline in glomerular filtration rates during chronic kidney disease,[1] and change in HbA1c levels over time in diabetes.[2,3] Dynamics of progression are often represented via transition probability matrices (TPMs)
- Multi-state Markov models have also been used by clinicians to guide treatment decisions.[4,5] Examples include optimizing initiation of statins to control lipid levels for lowering the risk of coronary heart disease and stroke in patients with type 2 diabetes,[5,6] or optimizing the management of blood pressure and cholesterol to improve quality of life[7]
- Limited follow-up data from clinical trials warrants the use of extrapolation methods for lifetime disease models; however, unlike time-to-event outcomes there is a gap in the literature for advanced analytical methods to extrapolate data available in the form of discrete-time TPMs. Long-term TPMs are often cited to be uncertain, with common assumptions such as holding TPMs constant or no state occupancy changes.
- Continuous-time hidden Markov chain is a suitable alternative to discrete-time Markov chain for modelling long-term disease progression when changes in disease occur irregularly. With the advent of modern optimization tools that can tackle complex maximum likelihood optimization problems and elicit the underlying transition rate matrix of continuous-time hidden Markov chains, limited data in discrete-time can be easily projected for long-run-term quality adjusted life years (QALY) and cost evaluations[8,9,10]

1. Hoogendoorn M, et al. *Value Health* 2011;14(8):1039-1047. 2. Zhang Y, et al. *Diabetes Care. 2014;37(5):1338-1345*. 3. Johnson SR, et al. *Diabetes Care* 2019;42(1):69-76. 4. Denton BT, et al. *Med Decis Making* 2009;29(3):351-367. 5. Kurt M, et al. *IIE Trans Healthc Syst Eng* 2011;1(1):49-65. 6. Mason JE, et al. *Med Decis Making* 2012;32(1):154-166. 7. Mason JE, et al. *Eur J Oper Res* 2014;233(3):727-738. 8. Bladt M, et al. *J R Stat Soc Series B Stat Methodol* 2005;67(3):395-410. 9. Liu YY, et al. *Adv Neural Inf Process Syst* 2015;28:3599-3607. 10. Liu Y-Y, et al. arXiv 2021:2110.13998.

Objectives

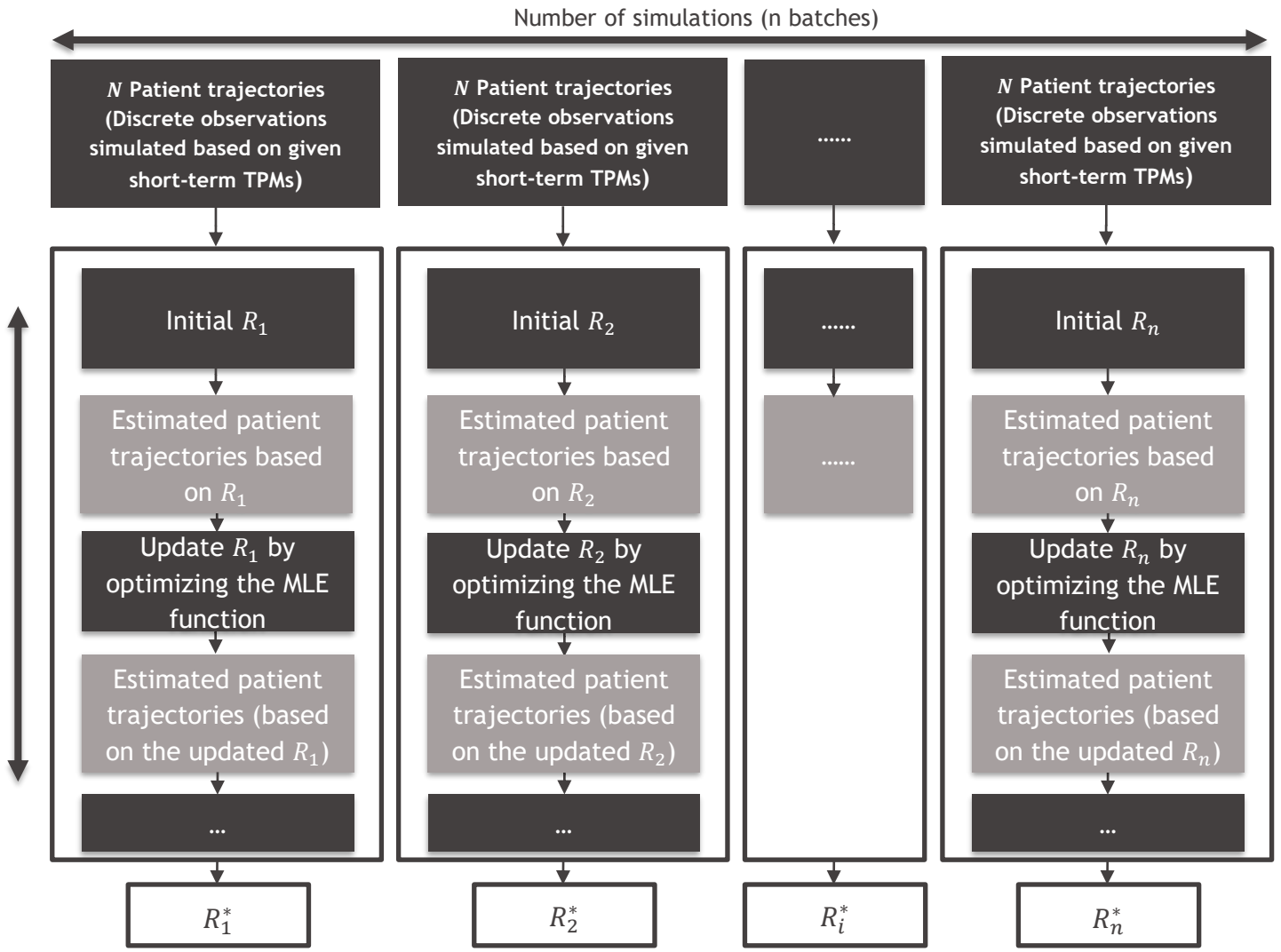
- The objective of this study was to
  - Devise a continuous-time Markov chain (CTMC) algorithm to estimate transition rates and corresponding state occupancy measures using limited aggregated level data
  - Compare the long-term predictive performance of the CTMC approach to a traditional approach which assumes no transitions among health states after the follow-up

Method: CTMC algorithm

- Assumption: The evolution of disease happens in continuous-time according to a time-homogeneous hidden Markov chain
- The algorithm used simulated event and censoring times from the observed discrete-time TPMs to estimate the underlying transition rate matrix (Matrix R) for long-term prediction

$$R = \begin{bmatrix} -r_1 & r_{12} & r_{13} \\ r_{21} & -r_2 & r_{23} \\ r_{31} & r_{32} & -r_3 \end{bmatrix}$$

- State-of-the-art optimization approach was used to numerically optimize the discrete maximum likelihood estimator (MLE) according to Liu et al. 2015[9]

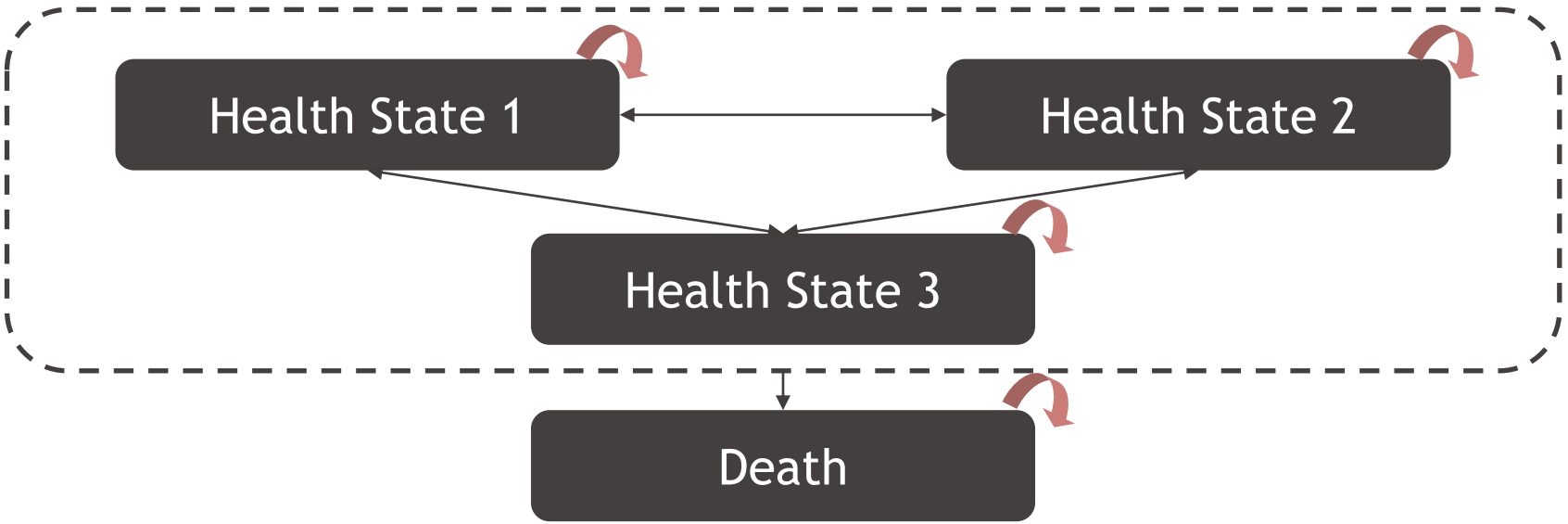


R, unknown rate matrix; R*, the calculated rate matrix from maximum likelihood estimation.

9. Liu YY, et al. *Adv Neural Inf Process Syst* 2015;28:3599-3607.

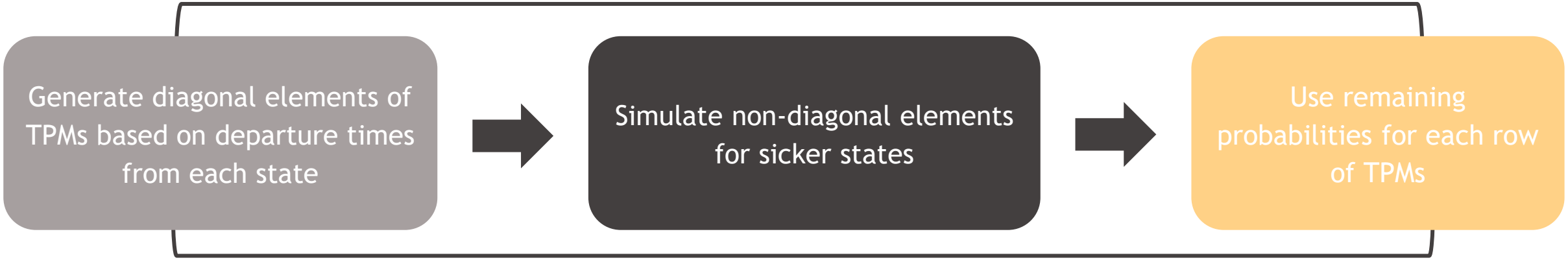
Illustrative case study: A hypothetical 4-state model

- An internal validation was conducted to first establish the convergence of the CTMC approach and tested its predictive ability using synthetic data sets. Experiments showed <1% prediction error
- The CTMC algorithm was applied to a hypothetical disease setting, severity of which was classified by three health states excluding death. Transitions from each of the 3 health states were permissible to any health state (including death)



Synthetic disease data generation

- Simulated sojourn times in each state and frequency of movements across different health states were used in a maximum likelihood estimation framework to elicit the generator matrix of an underlying CTMC which can be run forward to predict the proportion of patients in each health state beyond the trial follow-up
- The process was simulated for 1,000 times to sample from TPMs' distribution. For each simulation, the posterior state probabilities were estimated using the CTMC approach to calculate the underlying generator matrix. The mean generator matrix and confidence intervals (CI) of all elements were then calculated across all simulations to account for the uncertainty in the simulation process



TPMs, transition probability matrices.

Other model parameters

- For the calculation of long-term health outcomes, the following assumptions were made:
  - 60% males with mean age of 60 years and 40-year time horizon
  - Annual rates of discount (cost and effects) as well as treatment discontinuation rates were both 3%; utilities were assumed to be 0.9, 0.8, and 0.7 for states 1, 2, and 3, respectively
  - Patients in state 1 were assumed to follow age- and sex-adjusted US background mortality rates. Compared to state 1, relative mortality risk was 3 and 9 in state 2 and state 3, respectively

Methods: Application of CTMC algorithm

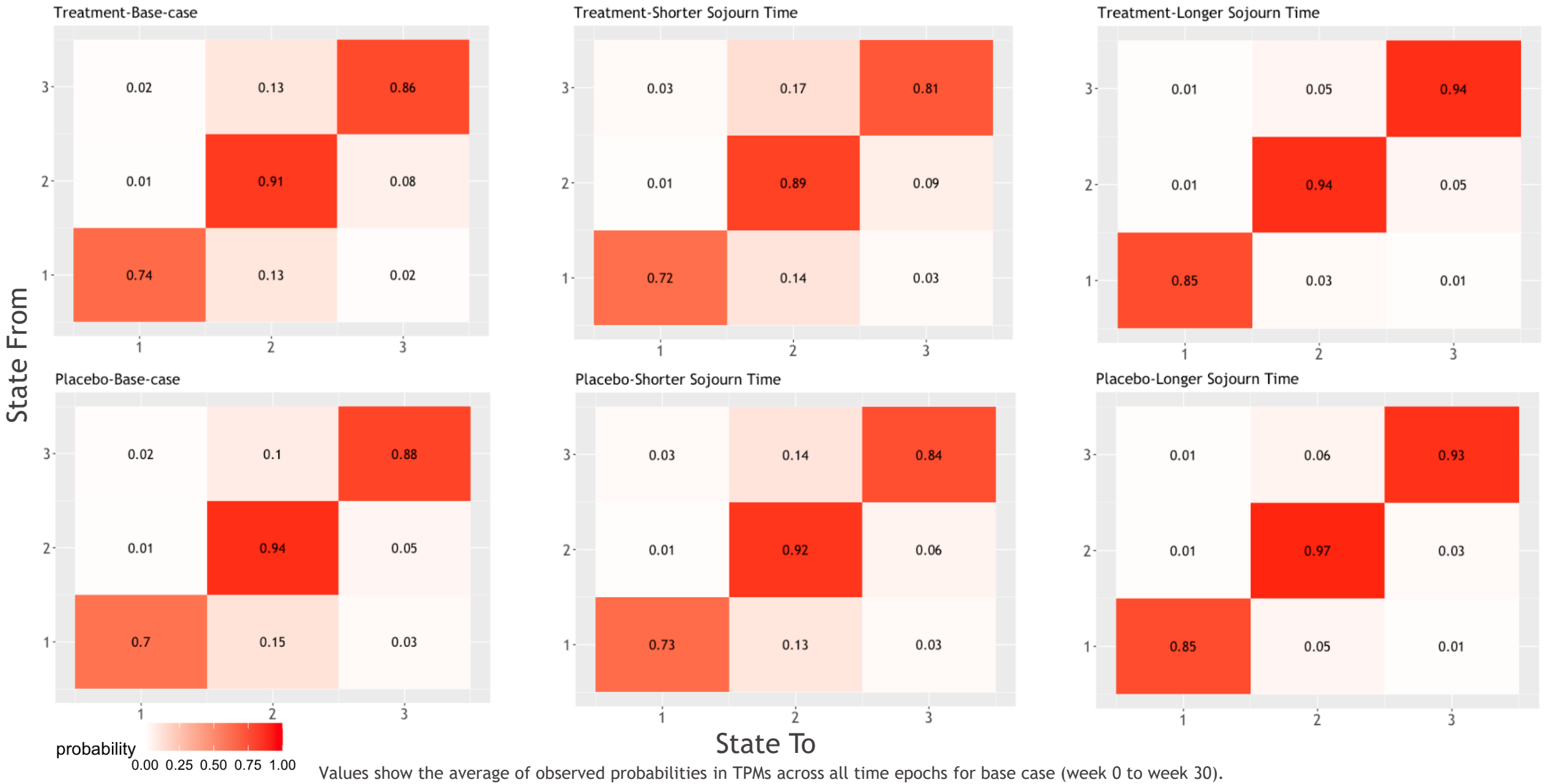
- Scenario analyses on different initial state distributions were conducted
- Sensitivity analyses were conducted to explore assumptions on simulated sojourn times for synthetic data*

Scenario	State 1	State 2	State 3
1 (Base-case)	0.00%	75.00%	25.00%
2	75.00%	0.00%	25.00%
3	75.00%	25.00%	0.00%
4	100.00%	0.00%	0.00%
5	0.00%	100.00%	0.00%
6	0.00%	0.00%	100.00%
7	33.34%	33.34%	33.34%

Analyses were focused generally on scenarios with a higher proportion of patients starting in healthier state (i.e., 3:1), along with testing of other scenarios of equal distribution across different states and extreme cases (i.e., 100% in one state)

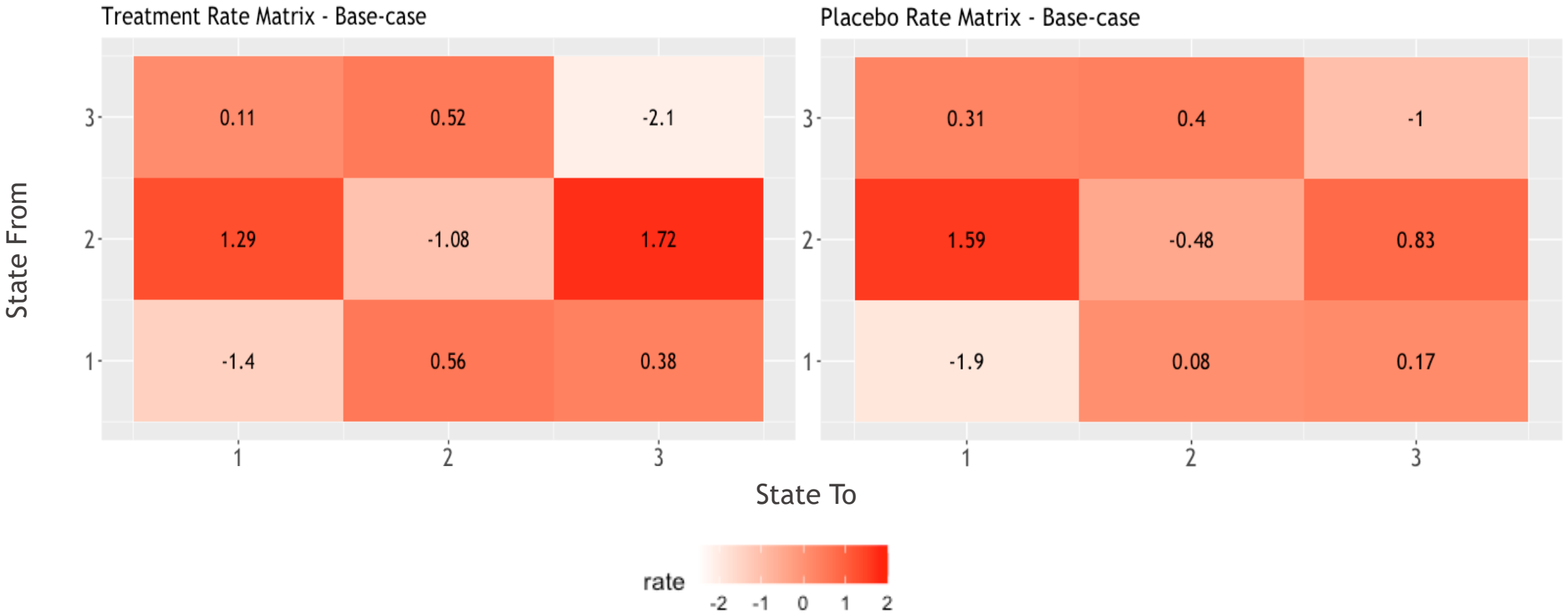
* Shorter sojourn time setting: Diagonal entries of the TPMs were assumed to be lower than those in the base-case setting.
Longer sojourn time setting: Diagonal entries of the TPMs were assumed to be higher than those in the base-case setting.

Results: Average view of TPMs



Values show the average of observed probabilities in TPMs across all time epochs for base case (week 0 to week 30).

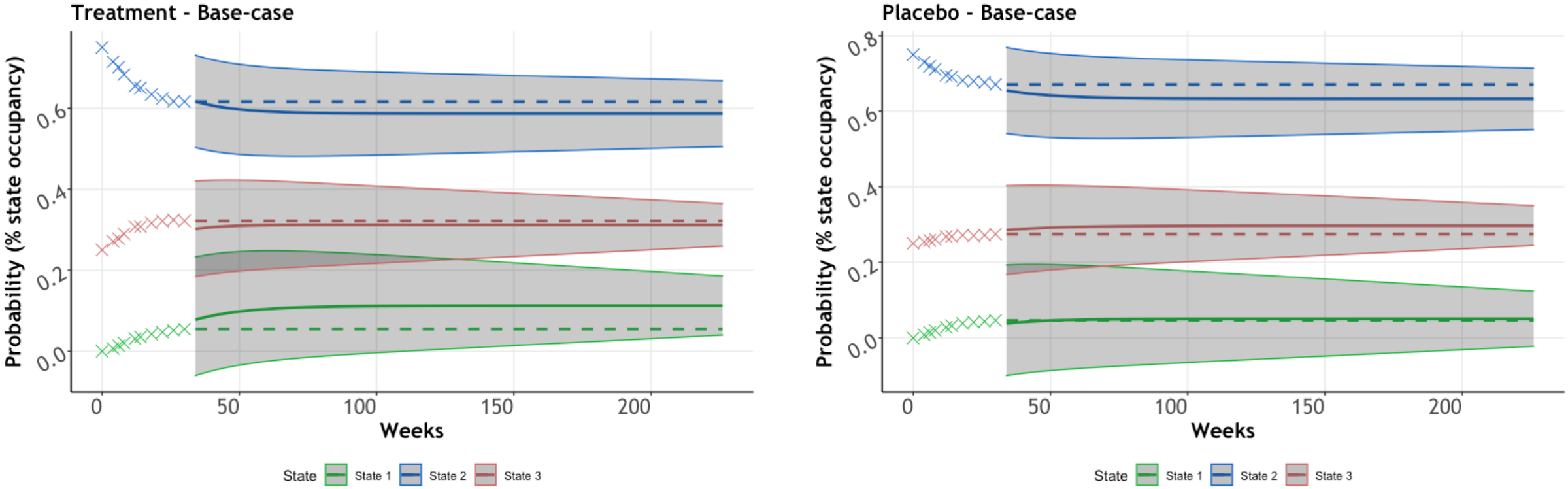
Results: Average view of generator matrices



Values in the cells show the mean estimated rates based on CTMC approach based on 1000 simulations.

Results: State occupancy projections

- Projected conditional state occupancies for Scenario 1 were compared between the CTMC and the traditional approach



The traditional approach was discrete-time Markov chain, which assumes no transitions among health states after the follow-up.
Grey shaded areas represent 95% CIs around conditional state occupancies for the CTMC approach.

Results: LY gain for CTMC vs. traditional approach (1/2)

Scenarios for initial distribution of patients across states	Settings for the generation of diagonal entries of TPMs	Long-term LY gain (treatment vs. placebo)		
		CTMC (95% CI)	Traditional Approach	CTMC vs. Traditional Approach (95% CI)
Scenario 1 (0%, 75%, 25%)	**Base-case**	3.04 (2.43,3.93)	0.99	2.05 (1.44,2.94)
	Shorter sojourn times†	2.98 (2.04,3.77)	2.63	0.35 (-0.59,1.14)
	Longer sojourn times‡	1.14 (0.54,2.11)	0.67	0.47 (-0.13,1.44)
Scenario 2 (75%, 0%, 25%)	**Base-case**	0.86 (0.11,1.60)	0.52	0.34 (-0.41,1.08)
	Shorter sojourn times†	0.79 (0.36,1.54)	0.72	0.07 (-0.36,0.82)
	Longer sojourn times‡	0.54 (0.12,1.17)	0.32	0.22 (-0.20,0.85)
Scenario 3 (75%, 25%, 0%)	**Base-case**	0.76 (0.26,1.67)	0.42	0.34 (-0.16,1.25)
	Shorter sojourn times†	0.77 (0.30,1.63)	0.61	0.09 (-0.31,1.02)
	Longer sojourn times‡	0.55 (0.22,1.43)	0.21	0.34 (0.01,1.22)
Scenario 4 (100%, 0%, 0%)	**Base-case**	1.56 (0.71,3.02)	0.88	0.68 (-0.17,2.14)
	Shorter sojourn times†	1.22 (0.69,2.55)	0.92	0.30 (-0.30,1.63)
	Longer sojourn times‡	1.03 (0.51,2.14)	0.67	0.36 (-0.16,1.47)

†Diagonal entries of the TPMs in the "shorter sojourn time setting" were assumed to be lower than those in the base-case setting. ‡Diagonal entries of the TPMs in the "longer sojourn time setting" were assumed to be higher than those in the base-case setting.

Values highlighted in green represents settings where LY differential is estimated to be more significant.

Results: LY gain for CTMC vs. traditional approach (2/2)

Scenarios for initial distribution of patients across states	Settings for the generation of diagonal entries of TPMs	Long-term LY gain (treatment vs. placebo)		
		CTMC (95% CI)	Traditional Approach	CTMC vs. Traditional Approach (95% CI)
Scenario 5 (0%, 100%, 0%)	**Base-case**	2.99 (2.29,3.70)	0.52	2.47 (1.77,3.18)
	Shorter sojourn times†	2.95 (1.89,3.42)	0.32	2.63 (1.57,3.10)
	Longer sojourn times‡	1.30 (0.68,2.86)	0.62	0.68 (0.06,2.24)
Scenario 6 (0%, 0%, 100%)	**Base-case**	3.25 (1.21,4.89)	2.36	0.89 (-1.15,2.53)
	Shorter sojourn times†	3.01 (1.01,4.42)	2.53	0.48 (-1.52,1.89)
	Longer sojourn times‡	2.40 (1.23,3.87)	1.92	0.50 (-0.69,1.95)
Scenario 7 (33.34%, 33.34%, 33.34%)	**Base-case**	2.90 (1.44,3.97)	1.31	1.59 (0.13,2.66)
	Shorter sojourn times†	2.53 (1.14,3.65)	1.90	0.63 (-0.76,1.75)
	Longer sojourn times‡	1.2 (0.44,2.36)	0.84	0.36 (-0.40,1.52)

†Diagonal entries of the TPMs in the "shorter sojourn time setting" were assumed to be lower than those in the base-case setting. ‡Diagonal entries of the TPMs in the "longer sojourn time setting" were assumed to be higher than those in the base-case setting.

Values highlighted in green represents settings where LY differential is estimated to be more significant.

Results: QALY gain for CTMC vs. traditional approach (1/2)

Scenarios for initial distribution of patients across states	Settings for the generation of diagonal entries of TPMs	Long-term QALY gain (treatment vs. placebo)		
		CTMC (95% CI)	Traditional Approach	CTMC vs. Traditional Approach (95% CI)
Scenario 1 (0%, 75%, 25%)	**Base-case**	3.20 (2.44,3.96)	1.38	1.82 (1.06,2.58)
	Shorter sojourn times†	3.14 (2.12,3.72)	3.01	0.13 (-0.89,0.71)
	Longer sojourn times‡	1.03 (0.13,2.27)	0.75	0.28 (-0.62,1.52)
Scenario 2 (75%, 0%, 25%)	**Base-case**	1.33 (0.61,2.55)	0.74	0.59 (-0.13,1.81)
	Shorter sojourn times†	0.96 (0.21,1.98)	0.87	0.09 (-0.66,1.11)
	Longer sojourn times‡	0.71 (0.13,1.69)	0.48	0.23 (-0.35,1.21)
Scenario 3 (75%, 25%, 0%)	**Base-case**	1.03 (0.43,2.59)	0.61	0.42 (-0.18,1.98)
	Shorter sojourn times†	0.97 (0.31,1.89)	0.84	0.13 (-0.53,1.05)
	Longer sojourn times‡	0.69 (0.22,1.44)	0.41	0.28 (-0.19,1.03)
Scenario 4 (100%, 0%, 0%)	**Base-case**	1.76 (0.78,3.32)	1.03	0.73 (-0.25,2.29)
	Shorter sojourn times†	1.42 (0.67,2.68)	1.14	0.28 (-0.47,1.53)
	Longer sojourn times‡	1.20 (0.58,2.51)	0.78	0.42 (-0.20,1.73)

†Diagonal entries of the TPMs in the "shorter sojourn time setting" were assumed to be lower than those in the base-case setting. ‡Diagonal entries of the TPMs in the "longer sojourn time setting" were assumed to be higher than those in the base-case setting.

Values highlighted in green represents settings where QALY differential is estimated to be more significant.

Results: QALY gain for CTMC vs. traditional approach (2/2)

Scenarios for initial distribution of patients across states	Settings for the generation of diagonal entries of TPMs	Long-term QALY gain (treatment vs. placebo)		
		CTMC (95% CI)	Traditional Approach	CTMC vs. Traditional Approach (95% CI)
Scenario 5 (0%, 100%, 0%)	**Base-case**	3.16 (2.64,3.70)	0.93	2.23 (1.71,2.77)
	Shorter sojourn times†	3.12 (2.52,3.80)	0.42	2.70 (2.10,3.38)
	Longer sojourn times‡	1.19 (0.55,2.26)	0.71	0.48 (-0.16,1.55)
Scenario 6 (0%, 0%, 100%)	**Base-case**	3.57 (1.52,4.43)	2.66	0.91 (-1.14,1.77)
	Shorter sojourn times†	3.07 (1.22,4.31)	2.88	0.19 (-1.66,1.43)
	Longer sojourn times‡	2.7 (1.01,3.11)	2.2	0.50 (-1.19,0.91)
Scenario 7 (33.34%, 33.34%, 33.34%)	**Base-case**	3.1 (1.52,4.03)	1.96	1.14 (-0.44,2.07)
	Shorter sojourn times†	2.8 (1.33,3.78)	2.30	0.50 (-0.97,1.48)
	Longer sojourn times‡	1.4 (0.77,2.49)	0.98	0.42 (-0.21,1.51)

†Diagonal entries of the TPMs in the "shorter sojourn time setting" were assumed to be lower than those in the base-case setting. ‡Diagonal entries of the TPMs in the "longer sojourn time setting" were assumed to be higher than those in the base-case setting.

Values highlighted in green represents settings where QALY differential is estimated to be more significant.

Conclusions

- Sensitivity analyses confirmed the robustness of the results. Increase in LY and QALY gains by the CTMC approach was sustained across various scenarios
- In multiple settings with respect to initial distribution of patients across states and construction of synthetic data, the traditional approach can underestimate the long-term LY and QALY gains by treatment compared to the CTMC approach. Based on the calculated CIs, most of the differentials in LY and QALY gains between the two approaches were statistically non-significant
- Our study emphasized the need of a structurally rigorous approach for the extrapolation of disease progression data encapsulated in TPMs
- The CTMC algorithm was developed based on state-of-the-art optimization methodologies to estimate the underlying continuous generator matrix. This approach is flexible and scalable to larger Markov models
- Unlike some recent studies,[11] our CTMC approach does not quantify the impact of confounders such as comorbidity on long-term predictions
- Future studies can leverage external long-term follow-up data for validation of state occupancy projections for the CTMC approach versus other traditional approaches

11. Oflaz Z, et al. *Stat Methods Med Res* 2023 Apr;32(4):829-849. doi: 10.1177/09622802231155100.

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Thank you!

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