Use of the Metropolis-Hastings Algorithm in the Calibration of a Patient Level Simulation of Prostate Cancer Screening

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Introduction

- Designing cancer screening programmes requires an understanding of epidemiology, disease natural history and screening test characteristics.
- Many of these aspects of the decision problem are unobservable and data can only tell us about their joint uncertainty.
- A Metropolis-Hastings algorithm was used to calibrate a patient level simulation model of the natural history of prostate cancer to national cancer registry and international trial data.
- This method correctly represents the joint uncertainty amongst the model parameters by drawing efficiently from a high dimensional correlated parameter space.
- The calibration approach estimates the probability of developing prostate cancer, the rate of disease progression and sensitivity of the screening test.
- This is then used to estimate the impact of prostate cancer screening in the UK.
- This case study demonstrates that the Bayesian approach to calibration can be used to appropriately characterise the uncertainty alongside computationally expensive simulation models.

Aim of cancer screening:

- Reduce cancer mortality, morbidity and treatment costs through early diagnosis and intervention.

Challenges:

- Effectiveness of different screening programmes unknown.
- Scarce data around disease process due to its unobservable nature.
- Multiple unknown parameters in cancer screening model.

Solution:

- Develop loosely parameterised cancer screening simulation model.
- Calibrate unobservable model parameters to observed data.
- Estimate impact of prostate cancer screening using calibrated model.

Model Structure

A patient level simulation was implemented in Simul8,[i] dynamically linked to Excel [ii] whereby the calibration process was run using Visual Basic. Figure 1 depicts the structure of the disease natural history model.

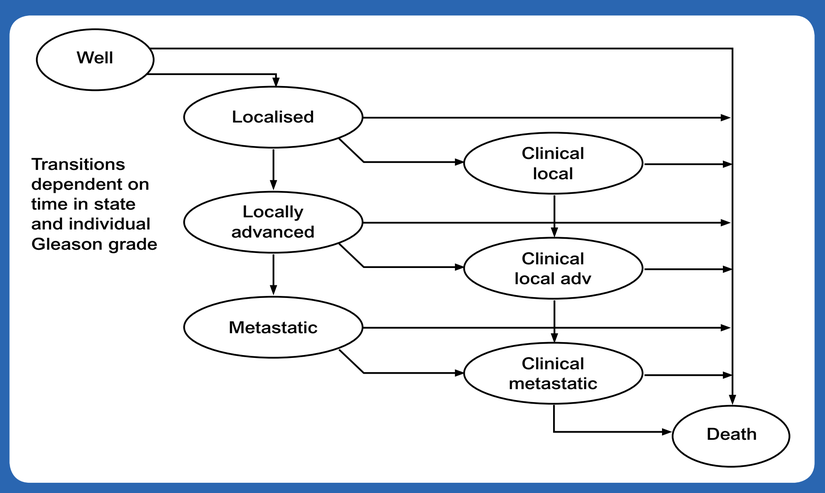
Key features of the model include:

- Three progressively worse disease states from localised disease (confined to prostate) to metastatic disease (spread to surrounding organs and bones).
- Three grades of disease aggressiveness described in terms of Gleason score (G<7, G=7, G>7).

Patients move through the model according to:

- If they have prostate cancer or not
- Aggressiveness of their prostate cancer
- Sensitivity of screening test
- Specificity of screening test
- Hazard of prostate cancer death
- Hazard of other cause death
- Risk of clinical detection; which is assumed to increase with age and stage of prostate cancer.

Figure 1: Model structure and natural history of prostate cancer



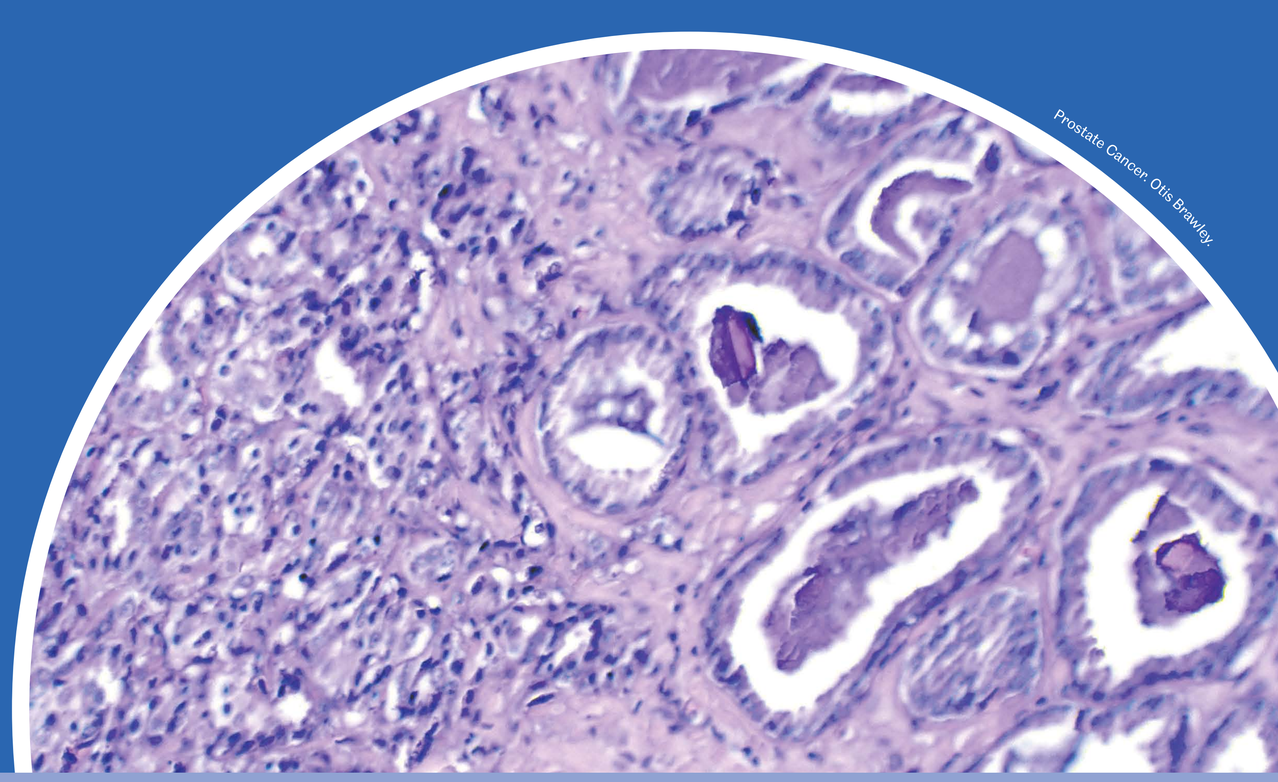
Data Sources

This study utilised data from national cancer registries and international randomised controlled trials (RCTs). Table 1 lists the data and their sources used to calibrate the model.

Table 1: Sources of data used in calibration process

Data	Source
Age specific cancer incidence	UK Office of National Statistics (ONS)
Cancer stage distributions	ProtecT[1] RCT UK Cancer Registry (ECRIC[2])
Gleason score (cancer aggressiveness) distributions	ProtecT[1] RCT UK Cancer Registry (ECRIC[2])
PSA/biopsy test characteristics	ERSPC[3] RCT (Rotterdam section)
Progression Free Survival[4]	ERSPC[3] RCT (Rotterdam section)
Overall Survival[4]	ERSPC[3] RCT (Rotterdam section)

[1] Prostate Testing for Cancer and Treatment.
[2] Eastern Cancer Registry and Information Centre.
[3] European Randomised Study of Screening for Prostate Cancer.
[4] Screen detected non-metastatic cancers.



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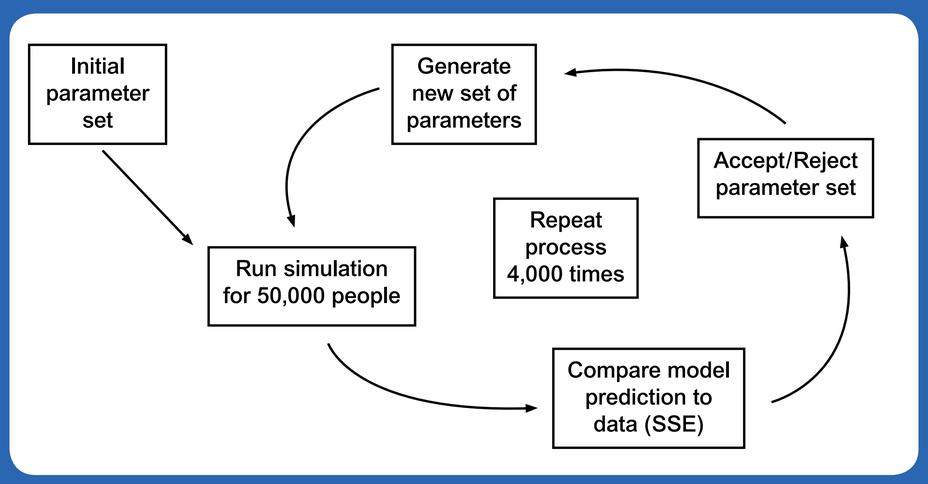
Calibration Method

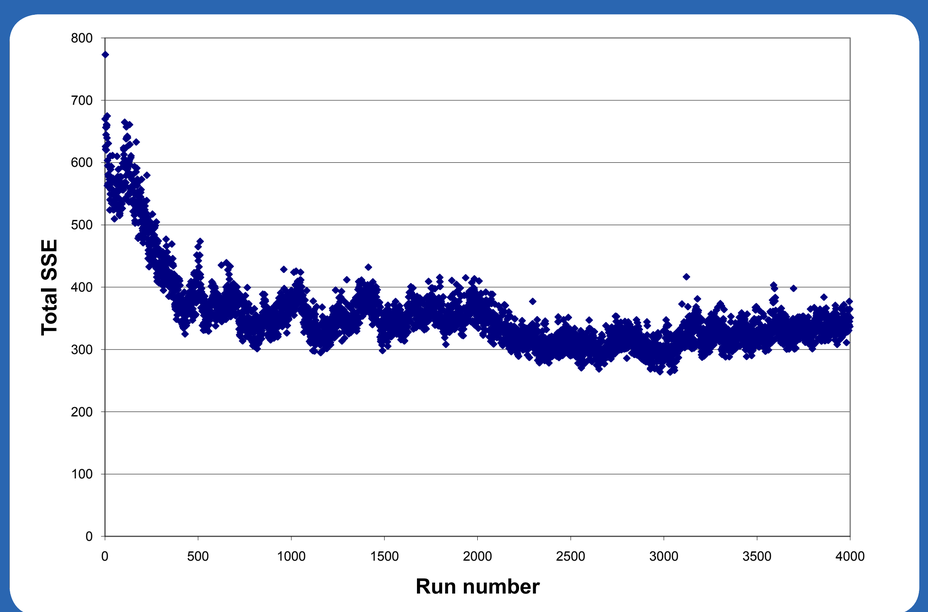
A Metropolis-Hastings algorithm was used to estimate joint posterior probability distributions of model parameters. Figure 2 represents the iterative algorithm.

Figure 2: Calibration process



- Figure 3 shows how the total sum of squared errors (SSE) changes during the calibration process.
- The total SSE quickly reduces at the start of the calibration process as the parameter sets converge.
- The middle section depicts how the total SSE can increase as the algorithm permits sets with a worse SSE in order that the complete parameter space is explored rather than stopping at a local minimum.
- The objective is for the calibration to converge to a global minimum region.

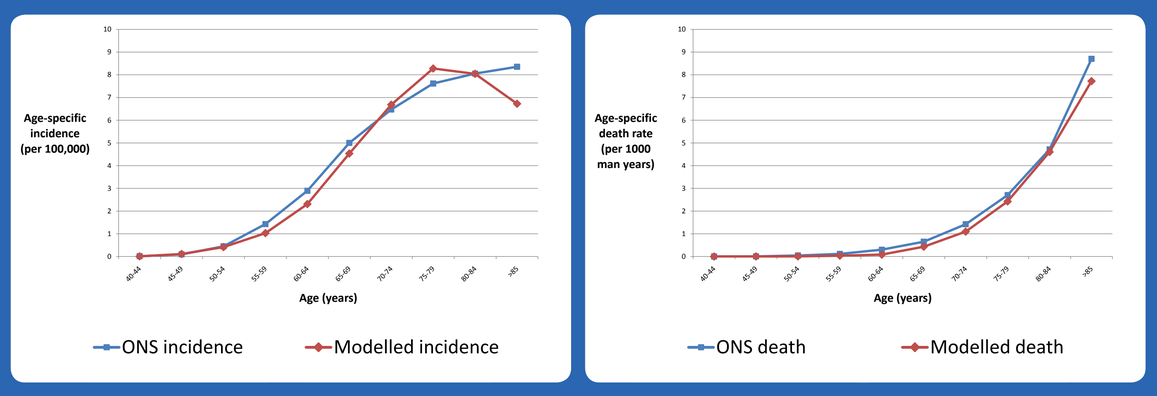
Figure 3: The total SSE during the calibration process.



Results

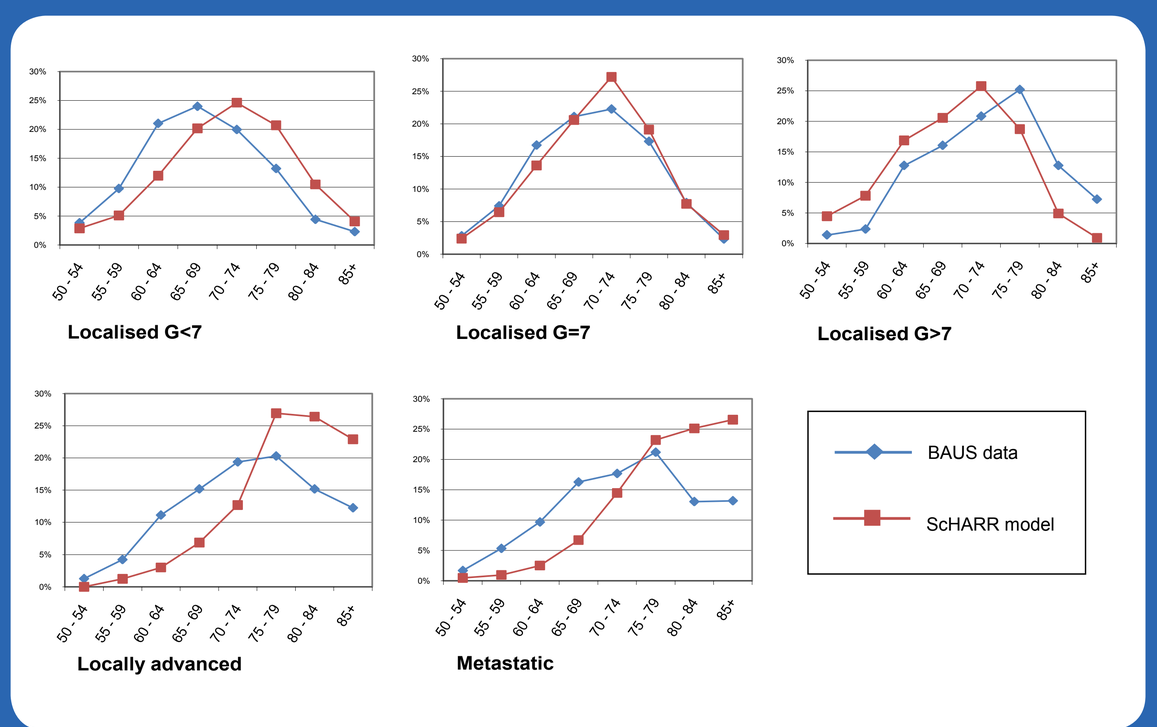
- Figure 4 presents plots of the model predicted age specific incidence of prostate cancer and prostate cancer mortality under no organised screening against UK national statistics from 2004.
- Model predicted age specific incidence and prostate cancer mortality closely matches reported statistics.

Figure 4: Observed and modelled age specific incidence and mortality of prostate cancer under no organised screening.



- The model was validated against age- stage and Gleason grade data from the British Association of Urological Surgeons (BAUS) Cancer Registry for the year 2008 (see Figure 5).
- Model estimated age and stage distributions correspond well to cancer registry data.

Figure 5: Model predicted age and stage distributions of prostate cancer validated against BAUS cancer registry data.



Conclusion

Parameterising complex conceptual models containing unobservable elements is a challenging process.

A Metropolis-Hastings algorithm was used to calibrate these unobservable model parameters such that model outputs were comparable with observed data.

This Bayesian approach to calibration has wider applications than health, and can be used to appropriately characterise uncertainty in other fields including within computationally expensive simulation models.

Impact of Screening in the UK

The cost-effectiveness of different screening options is currently being investigated on behalf of the UK National Screening Committee using the calibrated model. Preliminary results suggest that single screening strategies have little impact on overall age specific prostate cancer incidence and mortality rates. Any overall survival benefit is likely to be small; approximately 1 day for single screening strategies and 11 days for repeat screening.

Acknowledgements

Dr Anne Mackie and Prof Julietta Patnick at the UK National Screening Committee; the South West Public Health Observatory; the British Association of Urological Surgeons; and the ProtecT team.

References

[i] Simul8 software, Version 15.0. Copyright 2008 Simul8® Simul8 Corporation.

[ii] Microsoft Office Excel 2007 software, Version 12.0. Copyright 2006 Excel® Microsoft Corporation.

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