Mitotic Count Simulation

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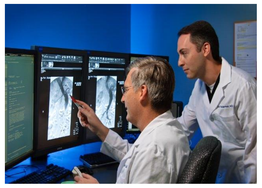
Clinical area: Digitization of Pathology, Division: DIDSR/OSEL/CDRH

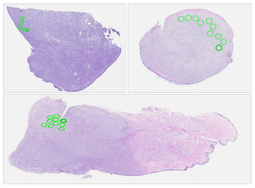
Regulatory Relevance

Shapes digital pathology's pathway to market by comparing pathologists' performance with digital images to the microscope.

Summary

We are generating a number of Monte Carlo (MC) trials. In each trial, there are a number of readers and a number of cases. Each case has a number of locations of interests. The readers provide counts to each case location on multiple modalities. We analyze the simulation results to understand the sampling variability of the agreement between survival time and counts and to evaluate novel variance of the sampling variability.





Simulation Configuration (Inputs)

Size: number of MC trials, readers, cases, locations per cases

Model Parameters:

- mean survival time, mean censoring time, mean counts (negative exponential distributions)
- variances describing random effects for readers, cases, locations, and interactions (zero-mean normal distributions)

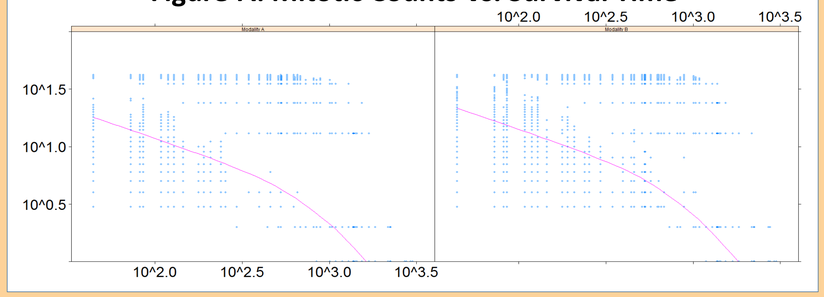
Simulation Outputs for One Trial

- **Survival time**
- **Censoring time**
- **Noise**: the sources are readers, cases, modalities and interactions, also referred to as random effects
- **Mitotic counts:** given by readers to each case-location
- **Reader-averaged agreement measure:** between survival times and counts (correlation, concordance, agreement)
- **Variance** of reader-averaged agreement measure (new methods to be evaluated)

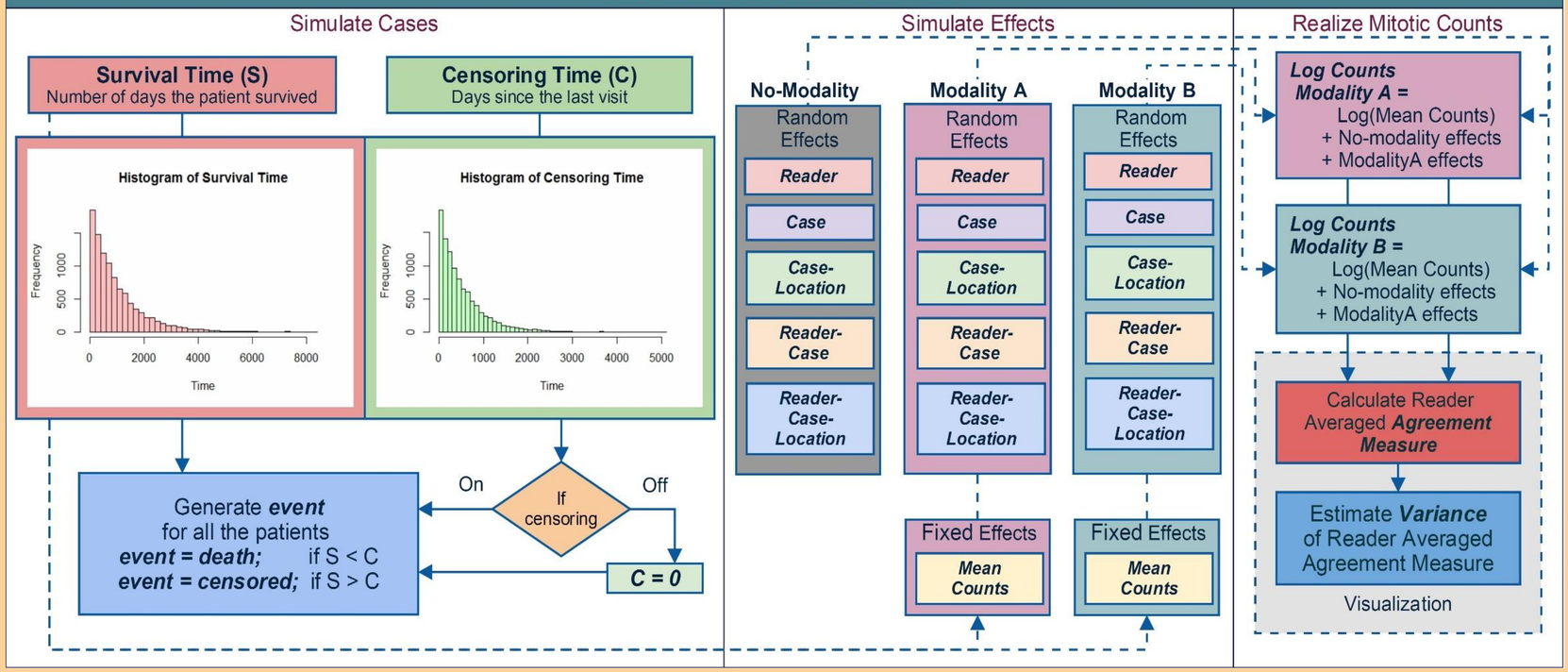
Visualization of One Trial: Mitotic Counts Vs. Survival Time

readers = 50, cases = 50, locations = 10,
mean survival time = 1000 days, mean censoring time = 500 days
mean counts A = 5, mean counts B = 6,
all variance components = 0.1

Figure-A: Mitotic Counts Vs. Survival Time



Simulation Flow for One Trial



Analysis of All Trials

Number of MC Trials = 10000

Figure-B: Distribution of Agreement Measures

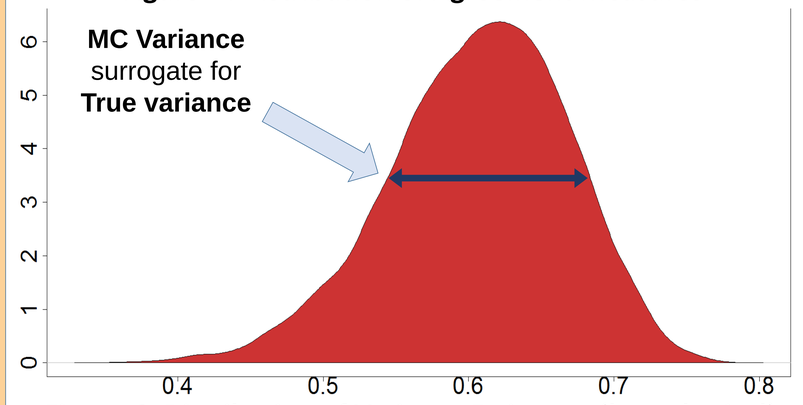
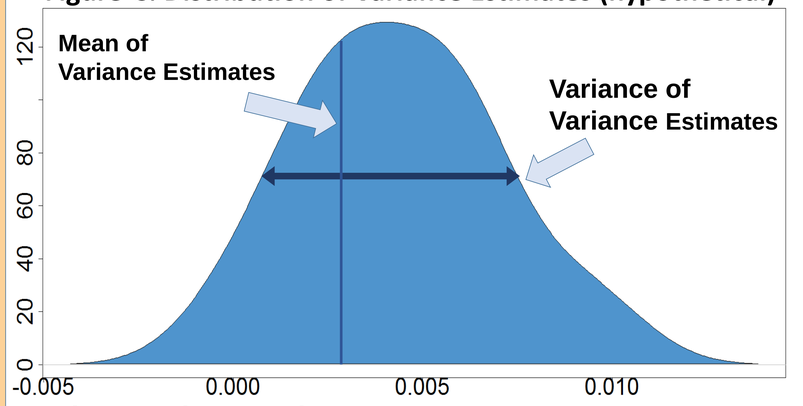


Figure-C: Distribution of Variance Estimates (hypothetical)



Evaluate Variance Estimators:

- **Bias** = Difference between true variance and mean of variance estimates
- **Precision** = Variance of variance estimates

Results and Future Work

- The simulation allows us to understand the sampling variability of the agreement between survival time and counts **(Figure-A)** and to evaluate novel variance estimates of the sampling variability **(Figure A&B).**
- Code is written in R, runs on R Console, linux command line, cloud (NCIP hub access on request)
- Source and documentation available at (private project until release) https://github.com/DIDSR/mitoticCountSimulation
- In future, we want to parallelize the code and develop a GUI for a better user experience

Acknowledgement

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