A Multistage Carcinogenesis Framework to Study Cancer Recurrence

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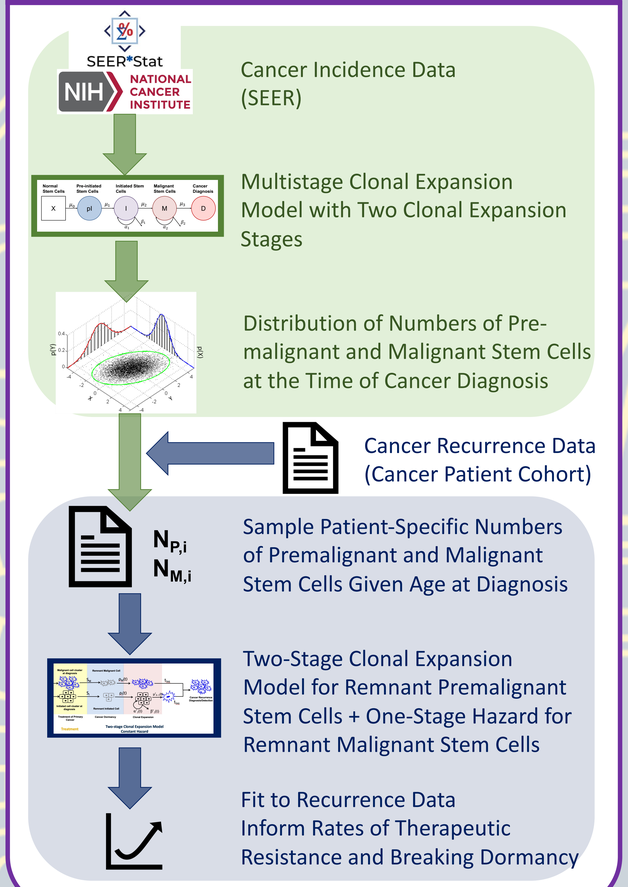
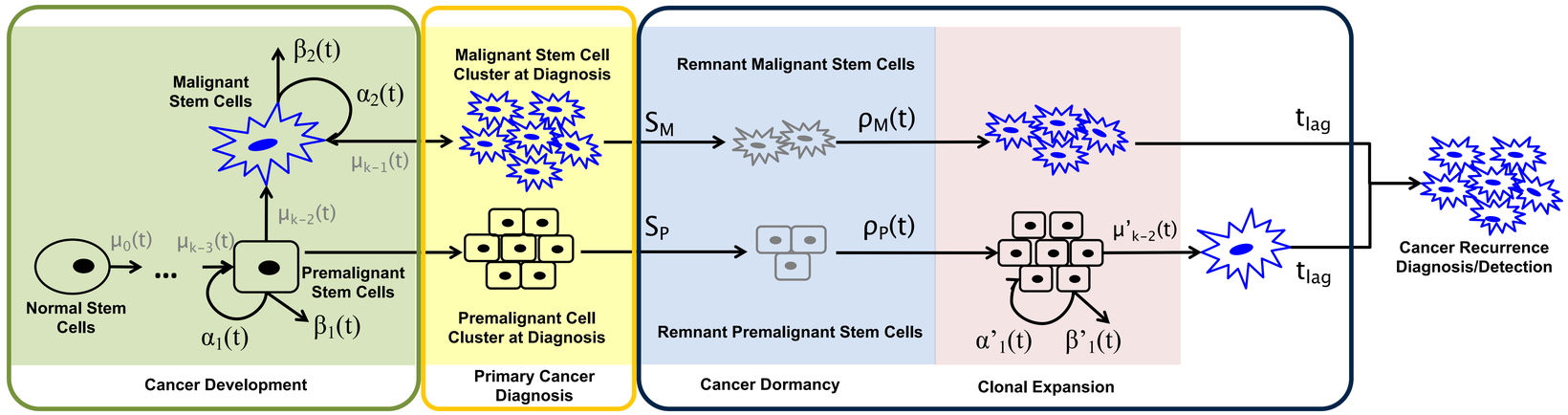
Introduction

- Multistage carcinogenesis models, e.g., the Two-Stage Clonal Expansion model, have been widely used to study cancer mechanisms, incidence, and mortality risk. However, these models have not yet been used to study potential mechanisms of cancer recurrence
- We present a novel mechanistic modeling framework for cancer recurrence, which
  - Provides insights into biological mechanisms driving cancer recurrence: **therapeutic resistance** and **cancer dormancy**
  - Allows for parameter estimations using cancer survivor cohorts
  - Adaptable to various cancer sites
  - Has the potential to include time-varying covariates

Model Development



Multistage Carcinogenesis – Recurrence Modeling Framework



Multistage Clonal Expansion Model | **Treatment** | **Remnant Premalignant Stem Cells: Two-Stage Clonal Expansion Model**
Remnant Malignant Stem Cells: One-Stage Model

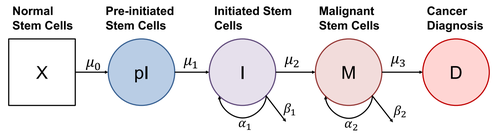
Incidence Model

Methods

- Multi-stage clonal expansion model with two clonal expansion stages of premalignant and malignant stem cells, respectively, with cancer detection/diagnosis as end point

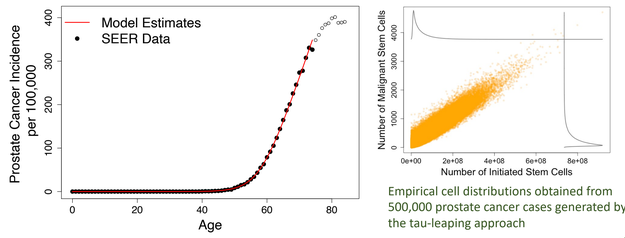
Example – Prostate Cancer

- SEER Prostate cancer incidence data
- Years: 1975-1990 and ages: 0-75



Preliminary Results

α_1	α_2	μ_3	$\mu_0 = \mu_1 = \mu_2$	$\alpha_1 - \beta_1 - \mu_2$	$\alpha_2 - \beta_2 - \mu_3$
Fixed			Fitted		
2	3	7E-4	1.075E-6 (1.009E-6, 1.147E-6)	0.279 (0.278,0.280)	0.095 (0.084,0.108)



Empirical cell distributions obtained from 500,000 prostate cancer cases generated by the tau-leaping approach

Recurrence Model

Methods

- $h(t + t_{lag}) = N_M S_M \rho_M + \frac{N_P S_P \rho_P}{\alpha_1'} \frac{pq(e^{-qt} - e^{-pt})}{qe^{-pt} - pe^{-qt}}$,

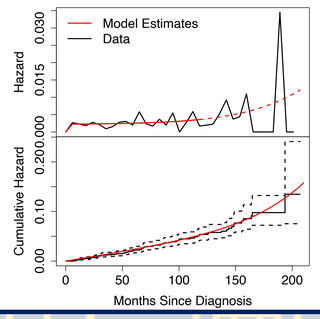
where $p,q = \frac{1}{2}[-(\alpha_1' - \beta_1' - \mu_2') \mp \sqrt{(\alpha_1' - \beta_1' - \mu_2')^2 + 4\alpha_1'\mu_2'}$

- N_M and N_P obtained from tau-leaping procedure
- Assume $\alpha_1' = \alpha_1, \beta_1' = \beta_1, \mu_2' = \mu_2$
- Fit S_M, S_P, ρ_M, ρ_P

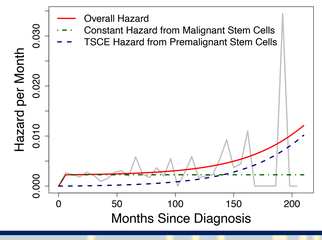
Example – Prostate Cancer

- Prostate cancer patient cohort from University of Michigan Health System
- ~4,500 patients

Preliminary Results



S_M	S_P	ρ_M	ρ_P
2.31E-6	1.77E-7	5.94	5.97



Discussion

- Early prostate cancer recurrence may be dominated by remnant malignant stem cells, whereas later increase in recurrence rate may be driven by remnant premalignant stem cells
- Estimated treatment failure rate was higher among malignant stem cells (S_M vs. S_P)
- The rate of breaking from cancer dormancy was similar between these two types of cells (ρ_M vs. ρ_P)
- This modeling framework shows the potential to inform mechanisms of cancer recurrence with mechanistic models and incidence/recurrence data
- Future steps:
  - Fit the multistage incidence model using using localized/regional prostate cancer incidence data
  - Test the robustness of model parameters
  - Validate model in other datasets and incorporate clinical experts' feedbacks

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