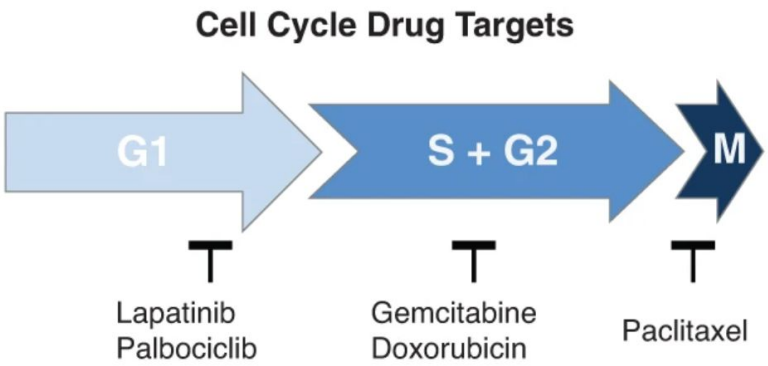
“Analysis and modeling of cancer drug responses using cell cycle phase-specific rate effects”

Prof. Aaron Meyer

Tommy Thach
C&S Bio 185 (Winter 2024)

Area of Focus: Cell Cycle of Cancer Cells



- Response to typical cancer drugs
- Identifying treatment strategies

Knowledge Gap: Specific Influence of Drugs

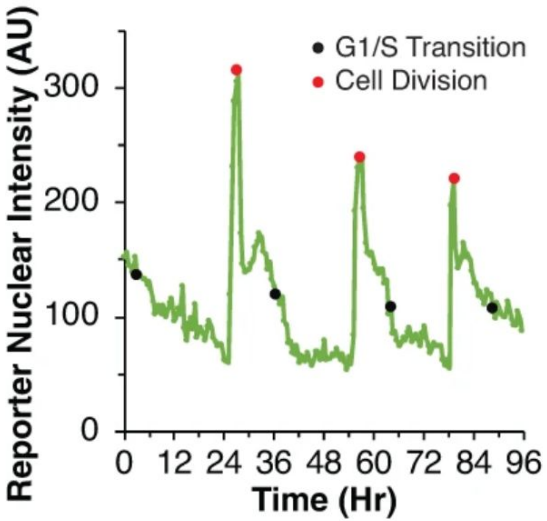
Quantifying effects on the specific phases and the progression through the cell cycle?

Modeling to predict and identify effective treatment?

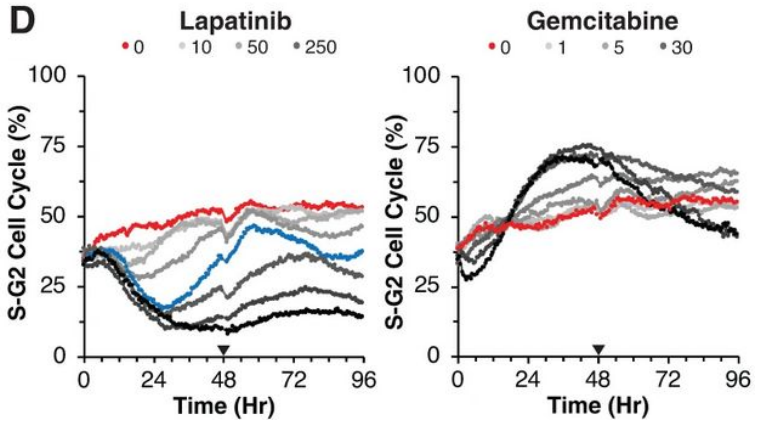
Experimental Method: Breast Cancer Cells + Drugs

Breast cancer cells (HER2+ AU565)
→ engineered to express cell cycle reporter

Treated with varying doses of five drugs



Results: Effects vary with dose and drug

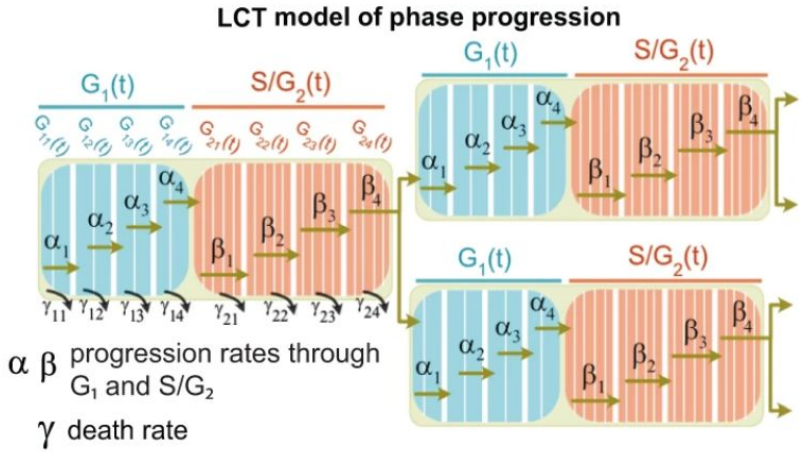


- Reduction of cells vary with dose
- Differences in fraction of S-G_2 cells

Computational Method: Linear Chain Trick (LCT)

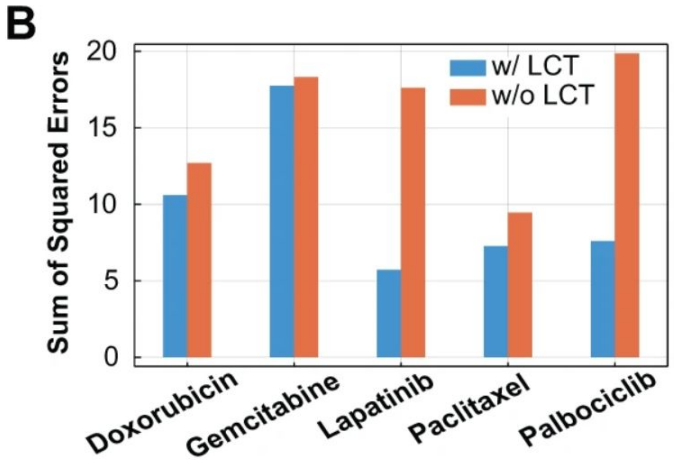
G_1/S-G_2 phase durations follow Gamma distribution + uncorrelated

Mean-field system of ordinary differential equations (ODEs) derived from LCT



Results: LCT Model captured essential aspects

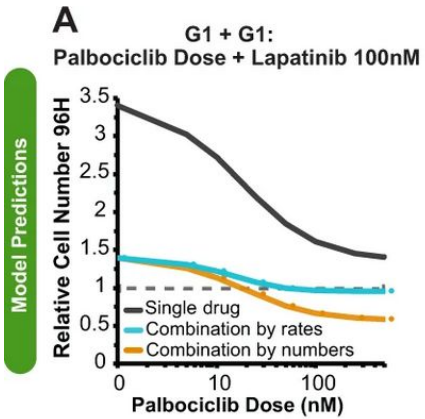
- Lower error compared to exponential model
- Captured oscillation and dose-dependent effects

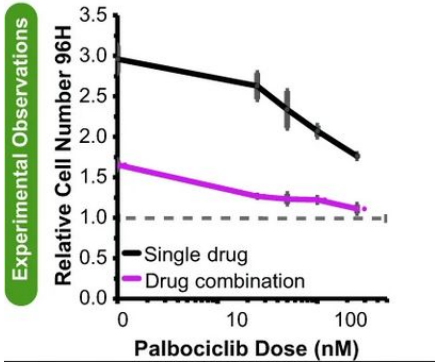


Implications: LCT Model predicts interactions

- Predictions of interactions agrees with experimental results

- Can help identify effective treatment plans





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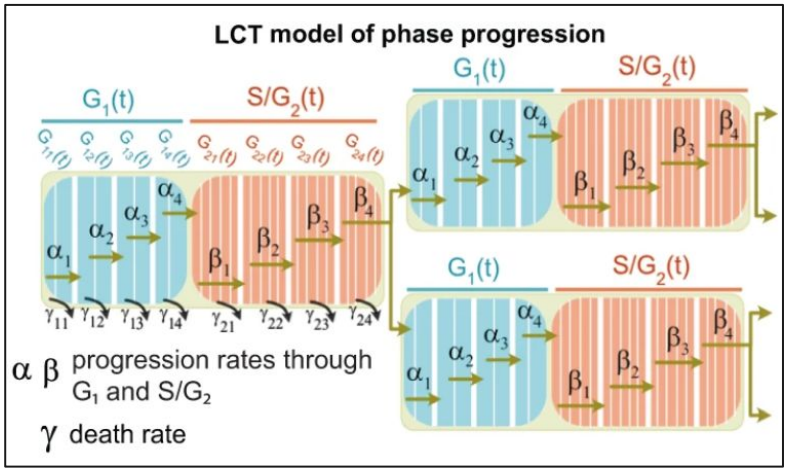
Identifying effective therapeutic treatment strategies is a major challenge to improving outcomes for patients with breast cancer. To gain a comprehensive understanding of how clinically relevant anti-cancer agents modulate cell cycle progression, here we use genetically engineered breast cancer cell lines to track drug-induced changes in cell number and cell cycle phase to reveal drug-specific cell cycle effects that vary across time. We use a linear chain trick (LCT) computational model, which faithfully captures drug-induced dynamic responses, correctly infers drug effects, and reproduces influences on specific cell cycle phases. We use the LCT model to predict the effects of unseen drug combinations and confirm these in independent validation experiments. Our integrated experimental and modeling approach opens avenues to assess drug responses, predict effective drug combinations, and identify optimal drug sequencing strategies.



Pitch:
Recreate the model while changing the number of sub-phases within each phase

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