Inferring Principles of Cell Cycle Regulation from Lineage Correlations in Cancer Cells

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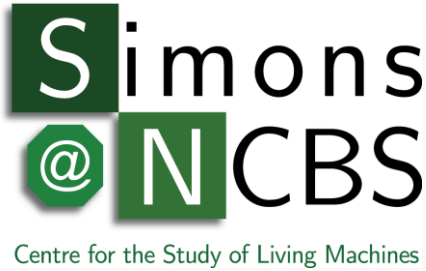
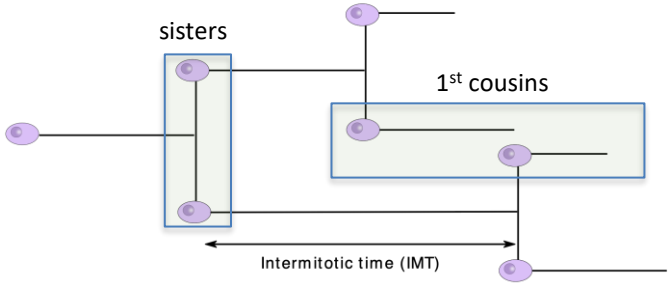
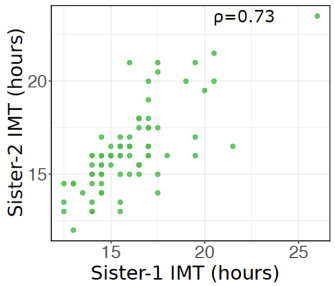


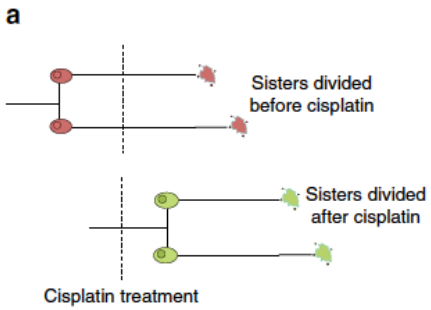
Cellular lineage tracking with time-lapse microscopy

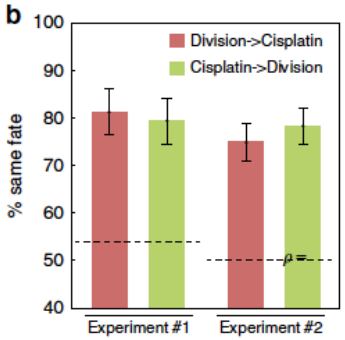
Cell line: HEK293T
Average division time: 24 hours
Duration of movie: 32 hours
Fluorescence: H2B – Cyan Fluorescent Protein

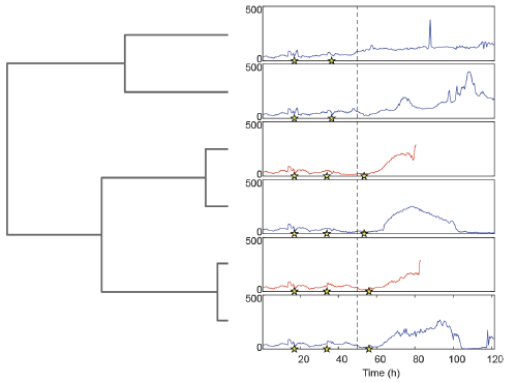
What can we learn from lineage correlations?





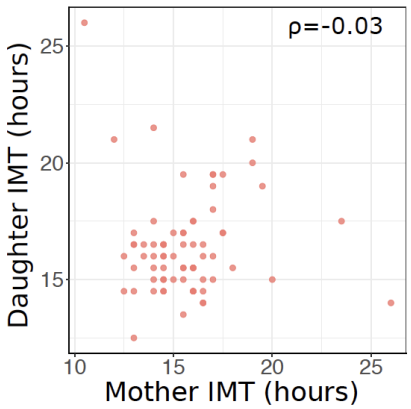


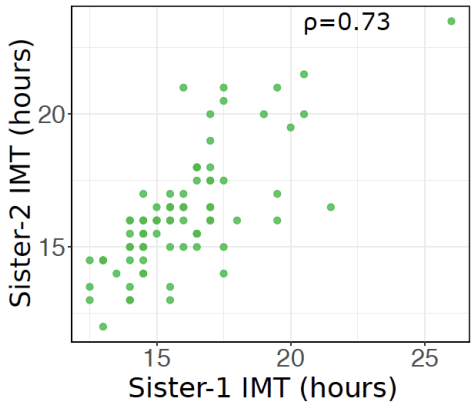


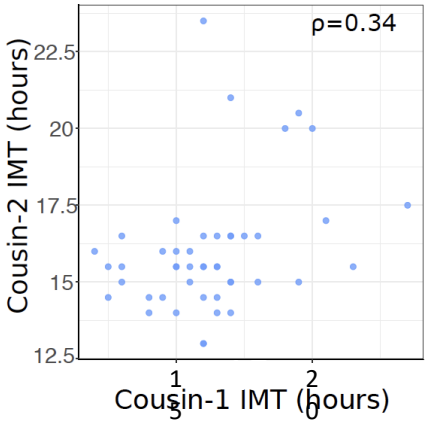


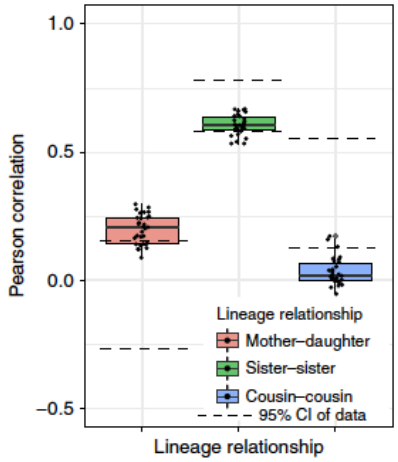
Simple cell cycle models cannot explain lineage correlations

"Cousin-mother inequality" in the HCT116 cell line





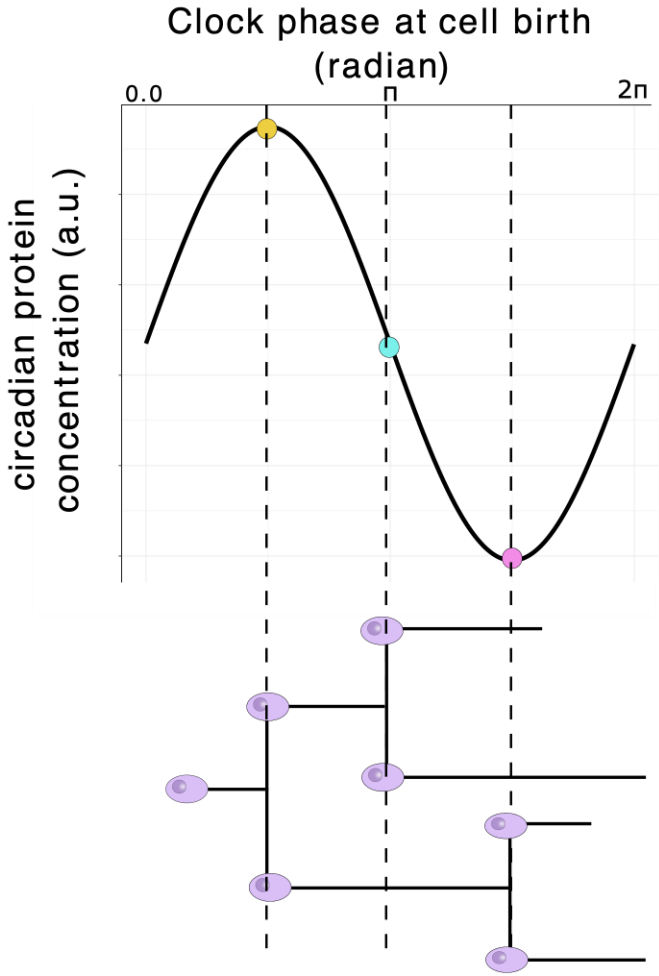




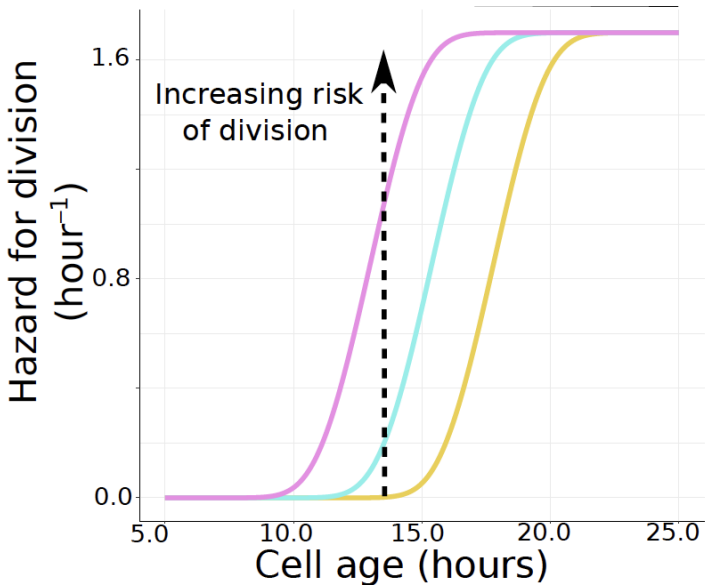
Sandler et al, Nature 2015

Chakrabarti, Paek et al (Nat Comm, 2018)

A model of circadian-controlled cell fate probability



$$\mu = \mu_0 + A\sin(\Phi)$$



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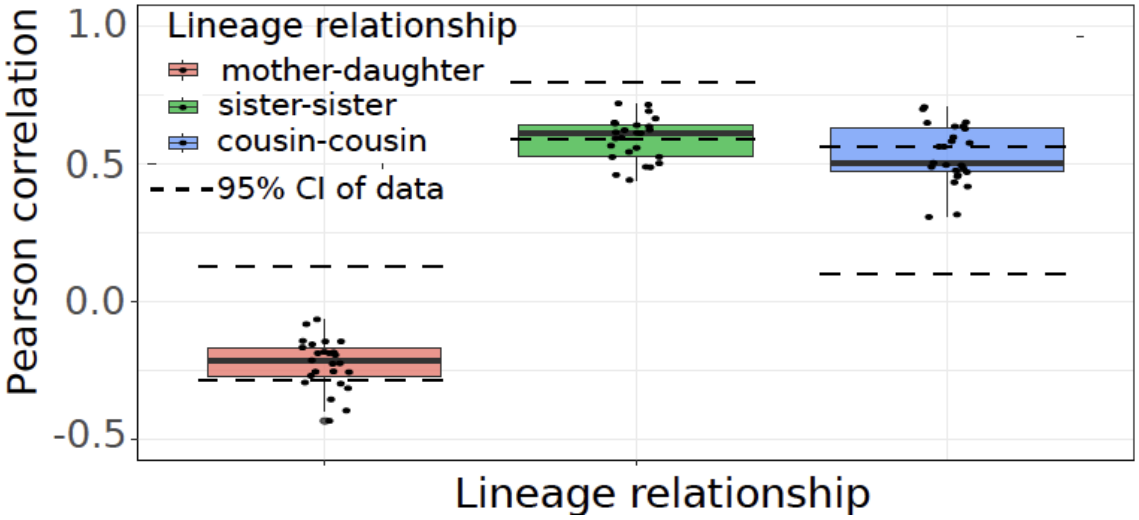
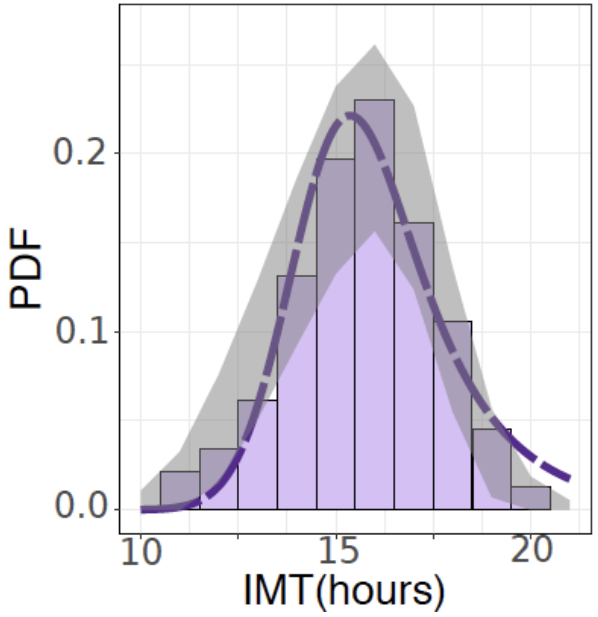
Coupling to circadian rhythm recapitulates correlations and IMT distribution

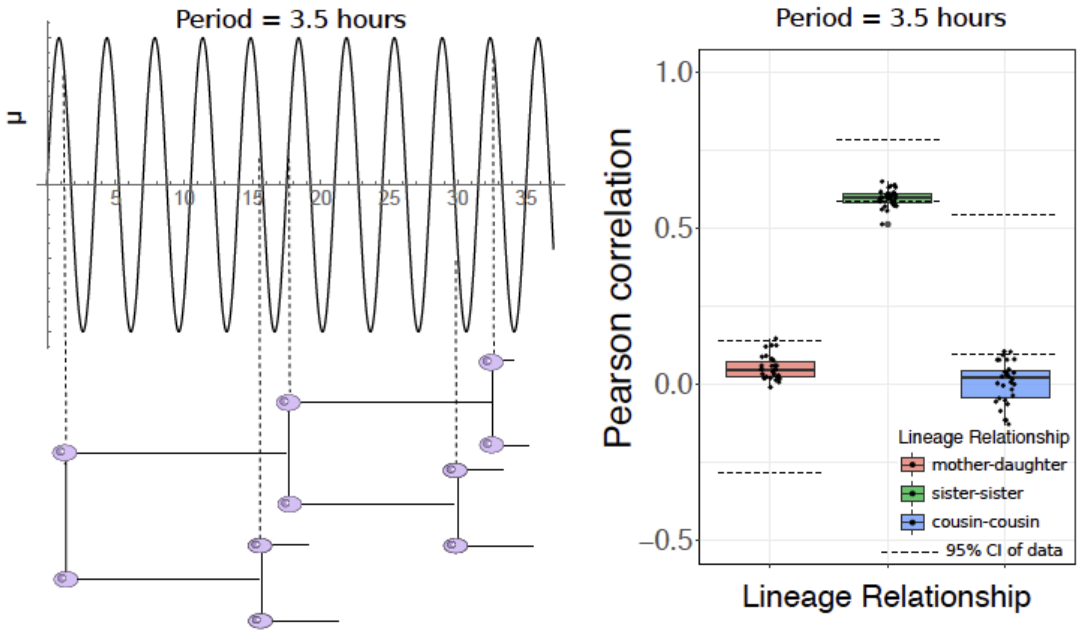




Only 4 free parameters

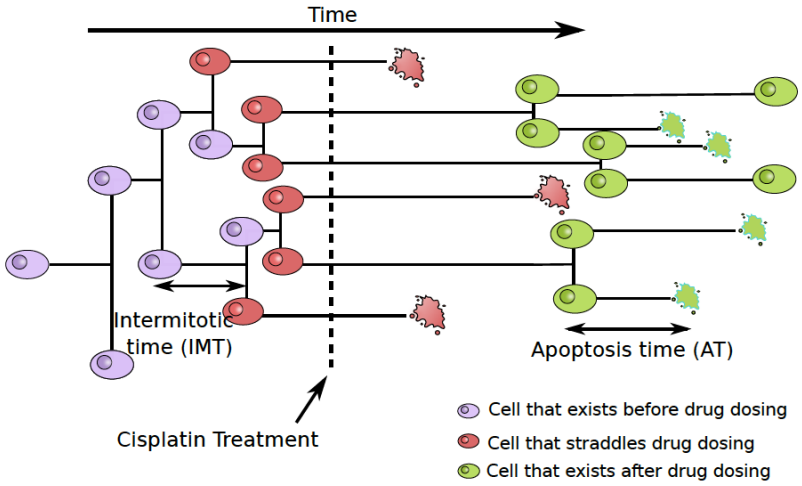
Chakrabarti, Paek et al (Nat Comm, 2018)

Coupling to ultradian rhythms *cannot* explain correlations

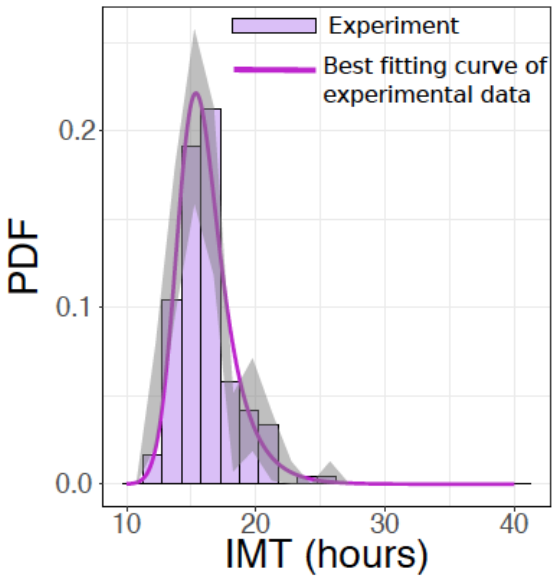


Chakrabarti, Paek et al (Nat Comm, 2018)

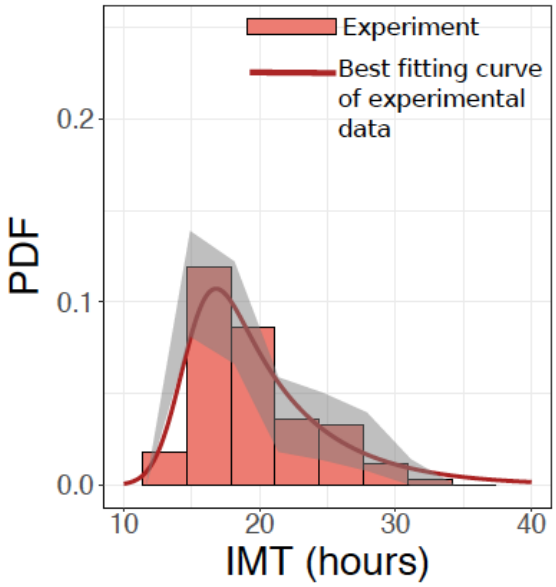
Cisplatin increases the heterogeneity of cell division times



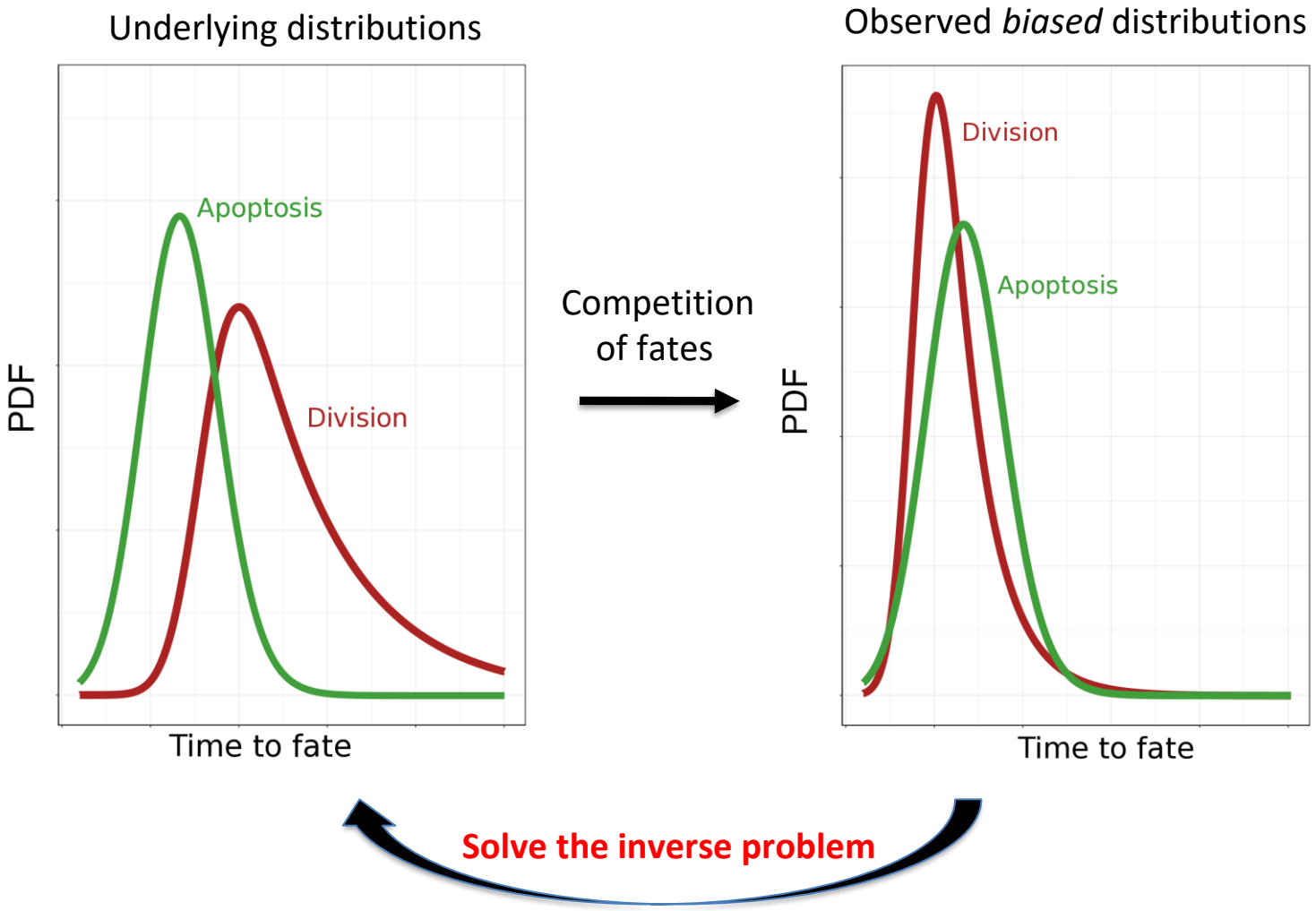
Before drug



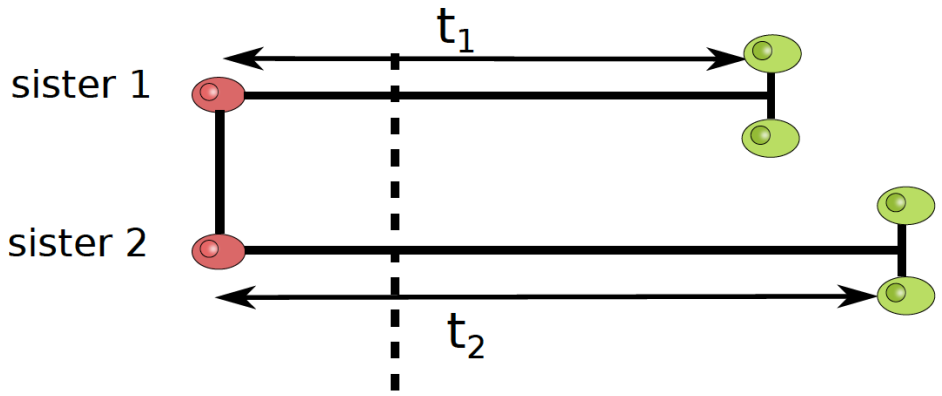
After drug



Stochastic competition of fates biases observed distributions



An algorithm to infer hidden heterogeneity induced by cisplatin



Cisplatin treatment

$$S(t) = \Pr(T > t) = 1 - F(t)$$ (Survival function)

$h(t)$ = Hazard function

$$f_i\left(t_1^i, t_2^i; \boldsymbol{\theta}\right) = c_z\left(1 - S^i\left(t_1^i\right), 1 - S^i\left(t_2^i\right)\right)\ S^i\left(t_1^i\right) h\left(t_1^i; \boldsymbol{\theta}\right)\ S^i\left(t_2^i\right) h\left(t_2^i; \boldsymbol{\theta}\right)$$

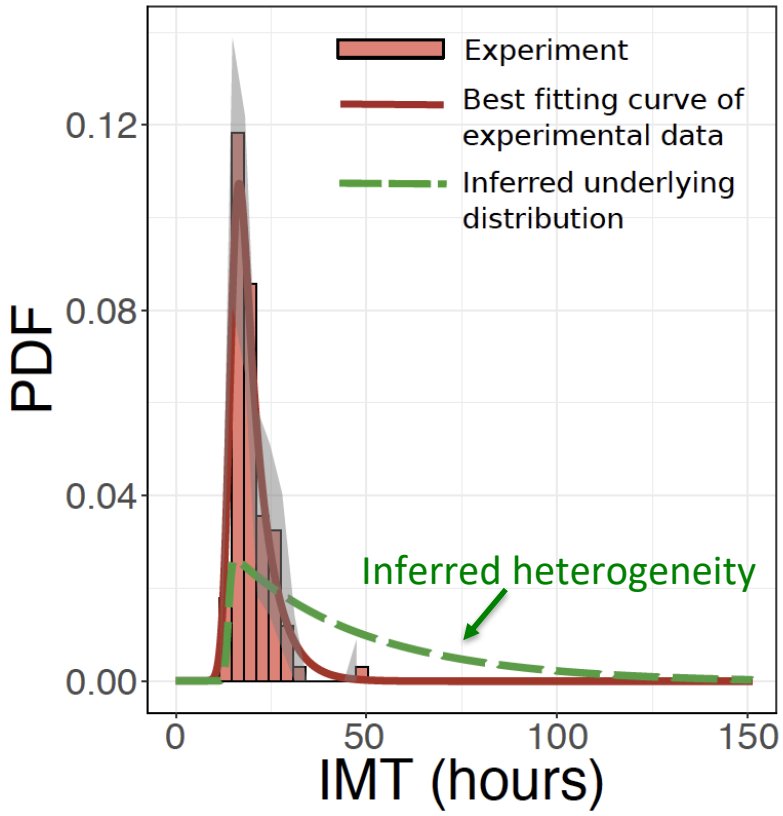
Joint density of the two sisters

Copula accounts for sister correlations

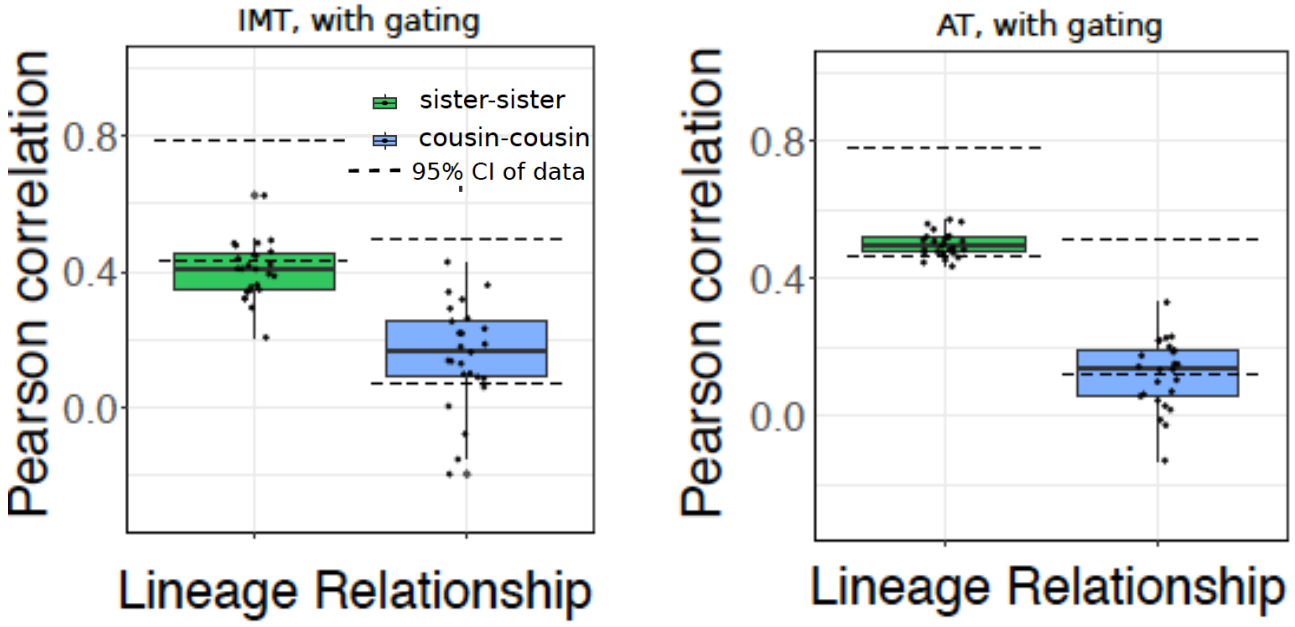
Marginal density of sister 1

Marginal density of sister 2

Hidden heterogeneity in cell division times after cisplatin administration



Correlations after cisplatin treatment can also be explained by the circadian gating model



Summary

- Current understanding of cell fate control based on stochastic protein production/degradation cannot explain the cousin-mother inequality.

- A mathematical model based on hazard functions provides a general framework to describe gating of cell division and death.

- Coupling of circadian, not ultradian oscillations to cell division explains the cousin-mother inequality

- A computational algorithm to infer the true underlying distributions of cell division and death times in the presence of competing fates.

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