

Modelling metastatic progression using metMHN

Kevin Rupp¹, Andreas Lösch², Y. Linda Hu², Rudolf Schill¹, Chenxi Nie¹, Maren Klever³, Simon Pfahler⁴, Stefan Hansch², Stefan Vocht², Tilo Wettig⁴, Lars Grasedyck³, Niko Beerenwinkel¹, Rainer Spang²



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¹DBSSE, ETH Zürich;

²Department of Informatics and Data Science, University of Regensburg;

³Institute for Geometry and Applied Mathematics, RWTH Aachen;

⁴Department of Physics, University of Regensburg

Summary

- Metastasis is defined as the spread of cancer cells from a primary tumor to a distant site in a patient's body.
- Metastasis is a major contributor to cancer related mortality, yet (genetic) factors driving formation and successful colonization are poorly understood.
- We extended Mutual Hazard Networks (MHN)^[1] to infer the impact of mutational events driving metastasis formation and subsequent colonization of the distant site

4 Results and Discussion

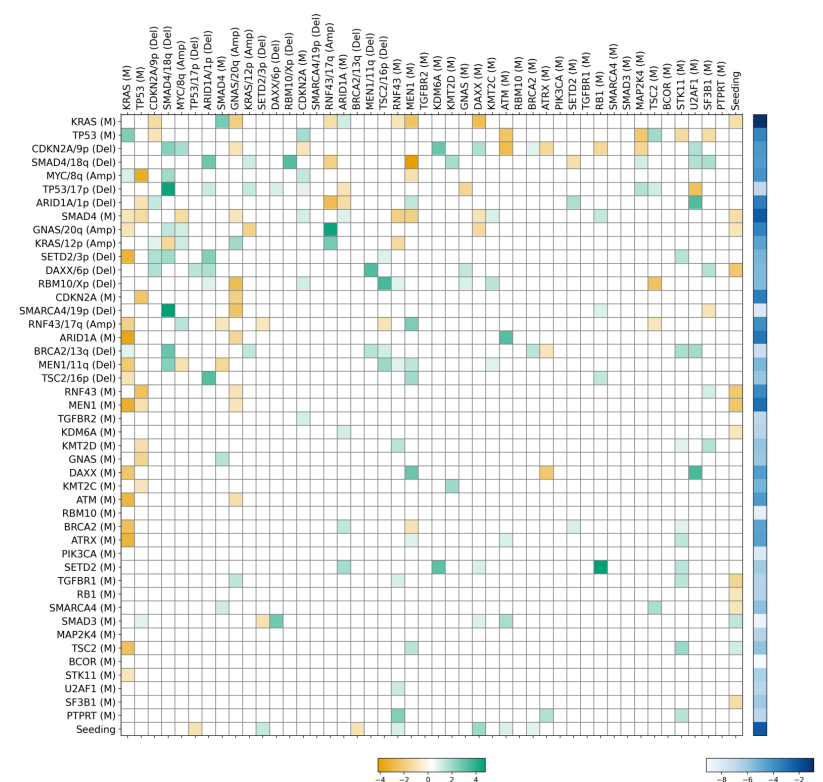
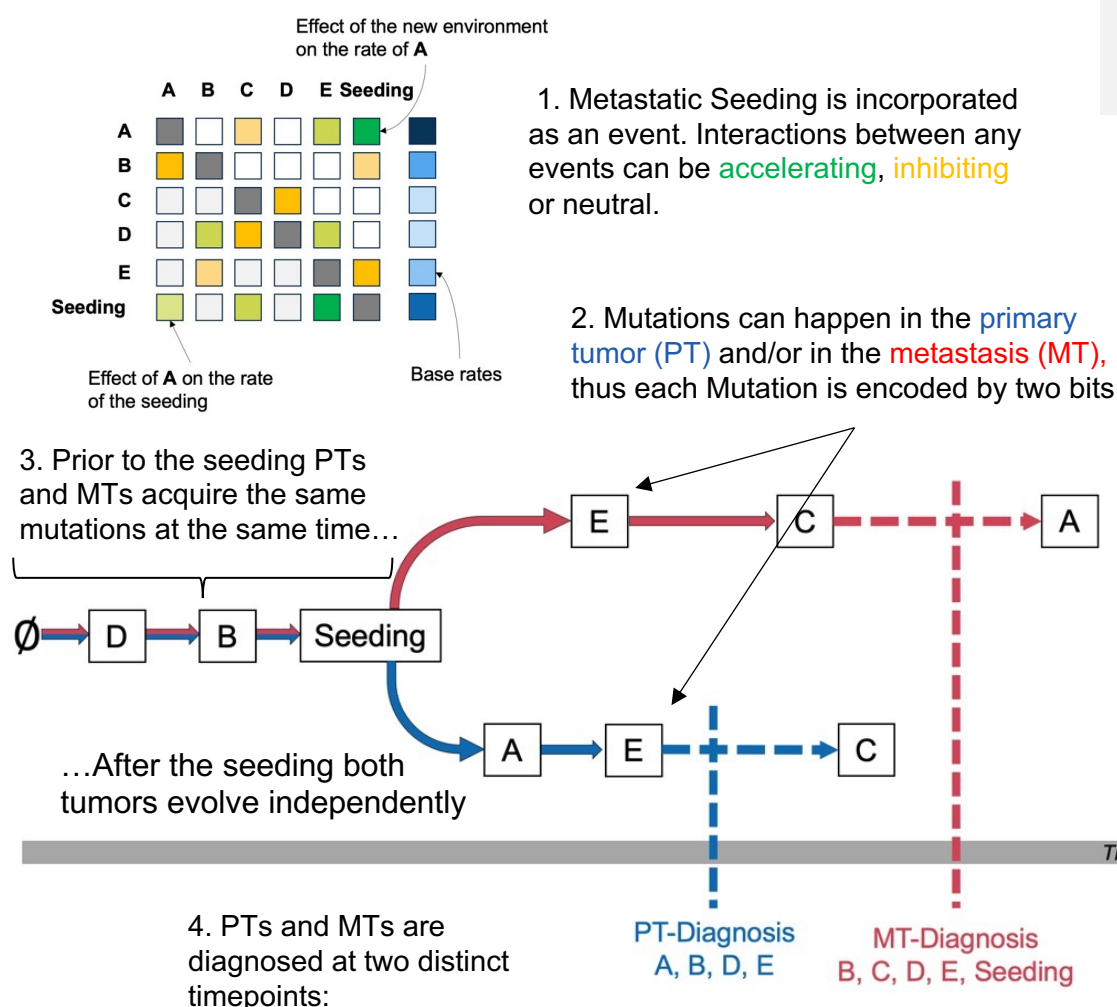
metMHN was fit to pancreatic adenocarcinoma (PAAD) and pancreatic neuroendocrine (PANET) tumors from Nguyen et al. (2022)^[2]. For point mutations, we selected the 30 most frequently functionally mutated genes. For CNAs, 15 events were defined and selected manually on the basis of either frequently altered minimal common regions per chromosome or frequent alterations covering driver genes of interest.

Mutual Hazard Networks (MHN)

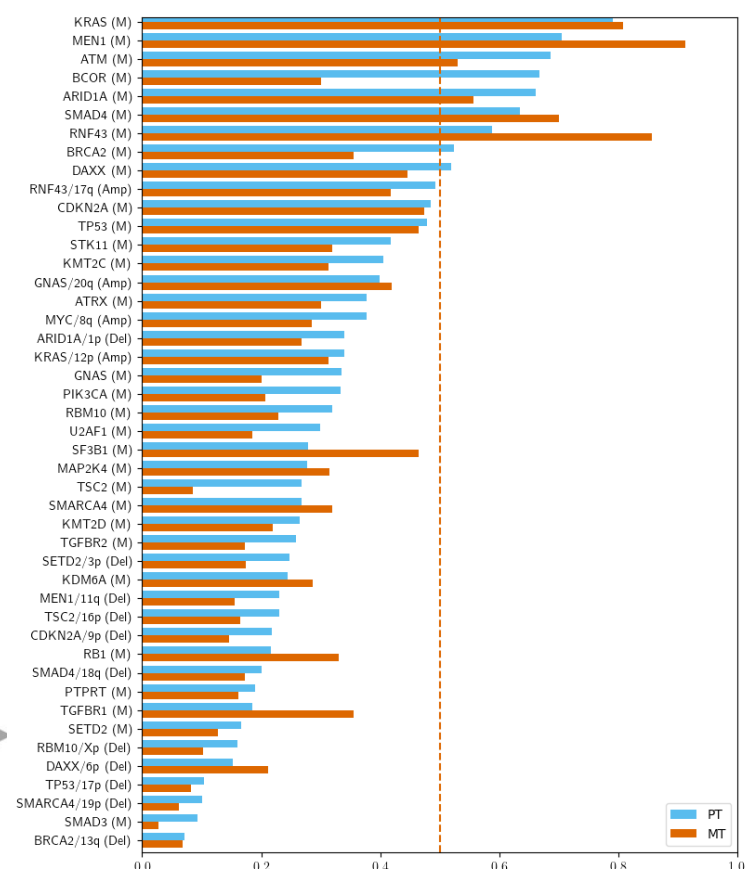
- Mutations are treated as binary events. Their accumulation in a tumor is modelled as a continuous time Markov chain.
- Each mutation is characterized by its base rate of appearance and by promoting/inhibiting effects on the accumulation rates of other mutations
- New Mutations are acquired at rates proportional to the product of their base rates and the multiplicative effects of mutations already present.

Mutual Hazard Networks for metastases (metMHN)

To account for the branching nature of metastatic progression we adapted the MHN in four different aspects:



metMHN can answer questions such as: Given a mutation is detectable at diagnosis in the **primary tumor** and/or the **metastasis**, how likely is it that it happened before the seeding?



1. R. Schill, S. Solbrig, T. Wettig, and R. Spang (2020). Modelling cancer progression using Mutual Hazard Networks. Bioinformatics, 36(1) <https://doi.org/10.1093/bioinformatics/btz513>

2. Nguyen et al. (2022). Genomic characterization of metastatic patterns from prospective clinical sequencing of 25,000 patients. Cell, 185(3) <https://doi.org/10.1016/j.cell.2022.01.003>