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Modelling metastatic progression using metMHN

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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

Mutual Hazard Networks (MHN)

- Mutations are treated as binary events. Their accumulation in a tumor is modelled as a continous 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:

1. Metastatic Seeding is incorporated as an event. Interactions between any events can be accelerating, inhibiting or neutral.

2. Mutations can happen in the primary tumor (PT) and/or in the metastasis (MT), thus each Mutation is encoded by two bits

3. Prior to the seeding PTs and MTs acquire the same mutations at the same time…

…After the seeding both tumors evolve independently

4. PTs and MTs are diagnosed at two distinct timepoints:

PT-Diagnosis
A, B, D, E

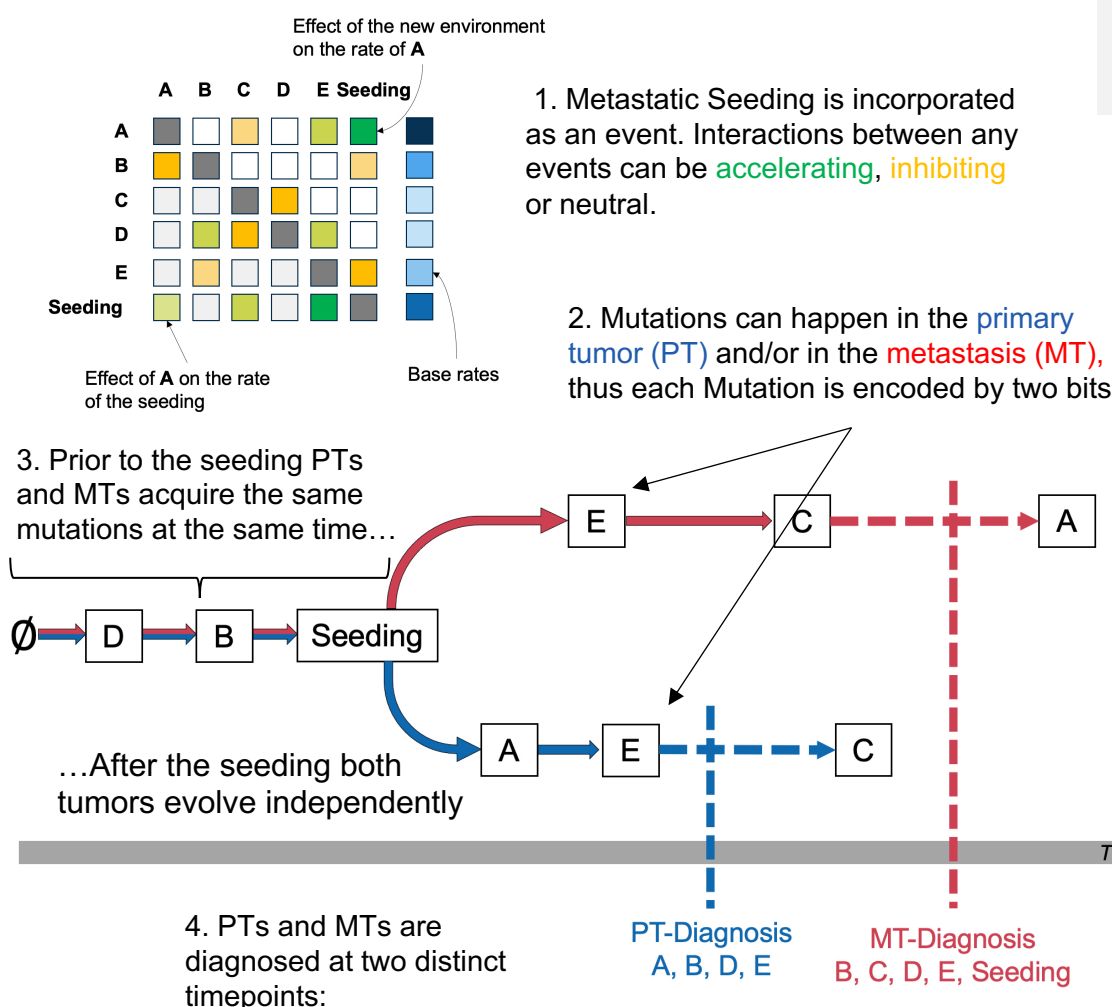MT-Diagnosis
B, C, D, E, Seeding

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.

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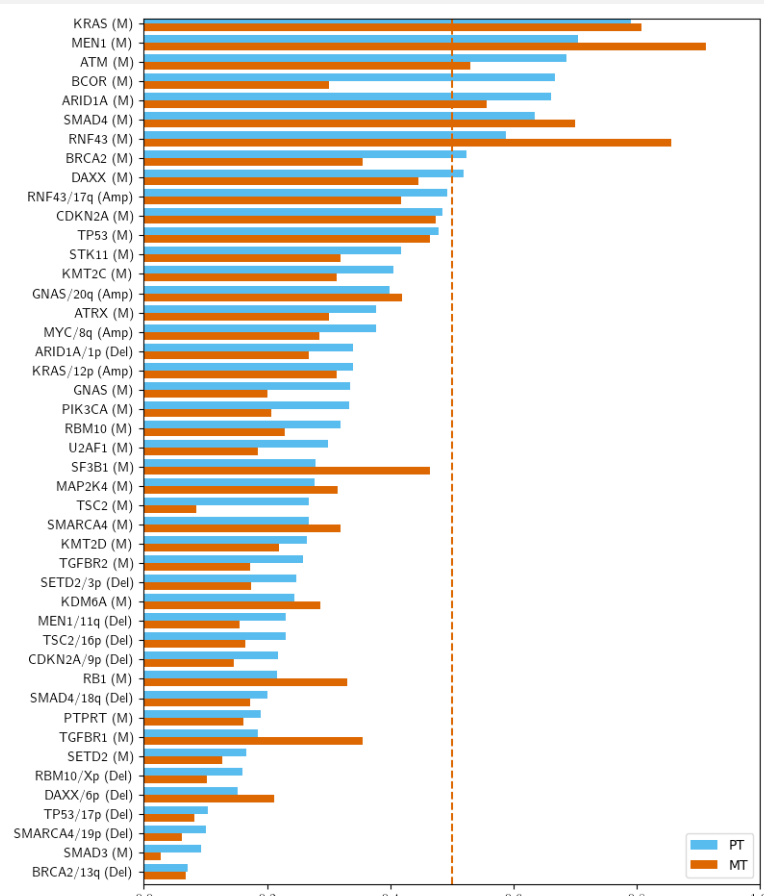
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2. Nguyen et al. (2022). Genomic characterization of metastatic patterns from prospective clinical sequencing of 25,000 patients. Cell, 185(3) https://doi.org/10.1016/j.cell.2022.01.003