How Order of Mutations Affects Cancer Progression

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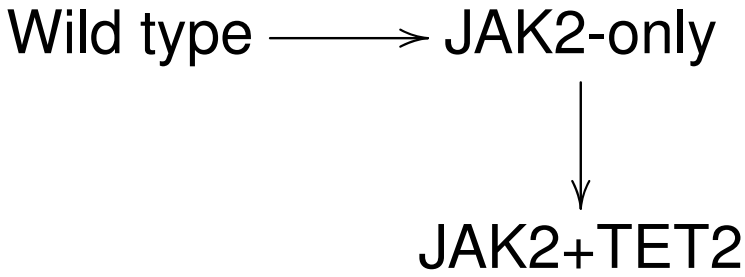
Introduction

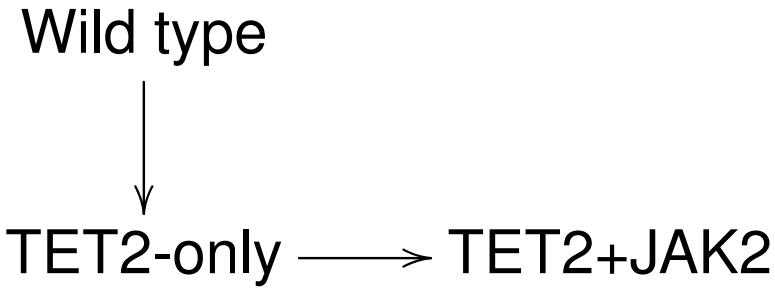
- Myeloproliferative neoplasms (MPNs) are a group of cancers that start in the bone marrow and cause an increase in the number of blood cells.
- Different genetic mutations are found in MPN patients. These mutations are known to have different effects on cell behavior.
- We focus on two common mutations in MPN, JAK2 V617F (henceforth abbreviated as JAK2) and TET2.
- For MPN patients with JAK2 and TET2 mutations, it is possible to find cells with different numbers of mutations: wild type cells (no mutation), cells with only one mutation (either JAK2 or TET2), cells with both mutations.
- For some patients, we can determine the appearance order of mutations.

Introduction

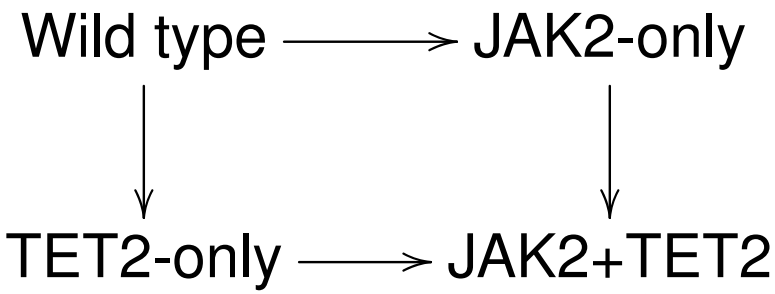
- JAK2 mutation appears before TET2 mutation, and such patients are called JAK2-first patients.



- JAK2 mutation appears after TET2 mutation, and such patients are called TET2-first patients.



- The order of mutations cannot be determined.



Introduction

- For MPN patients that the order of JAK2 and TET2 mutations can be determined, Ortmann et al. made various observations.
- JAK2-first patients and TET2-first patients have differences regarding gene expression, cell population, and cancer progression.
- We build an ordinary differential equation model to explain observations regarding gene expression.
- We build a generalized Moran process model to explain observations regarding cell population and cancer progression.

Clinical observations

- Observation **(1)**: Some genes are up-regulated (or down-regulated) by JAK2 mutation only if TET2 mutation is not present. If the TET2 mutation is also present, gene expression is not affected.
- Observation **(2)**: Some other genes are up-regulated (or down-regulated) by JAK2 mutation only if TET2 mutation is also present; but they are not affected if the TET2 mutation is not present.
- Observation **(3)**: Ten genes (AURKB, FHOD1, HTRA2, IDH2, MCM2, MCM4, MCM5, TK1, UQCRC1, WDR34) are up-regulated by JAK2 mutation if TET2 mutation is not present, but they are down-regulated by JAK2 mutation if TET2 mutation is present.

Clinical observations

- Observation **(4)**: When JAK2 and TET2 mutations are both present, different orders of appearances for JAK2 and TET2 mutations lead to different expression levels of certain genes. These conclusions are inferred from other indirect evidence (e.g., JAK2-first cells are more sensitive to ruxolitinib than TET2-first cells).
- Observation **(5)**: In TET2-first patients, the percentage of cells with just one mutation (TET2) is significantly higher than the percentage of JAK2-only cells in JAK2-first patients.
- Observation **(6)**: At diagnosis, JAK2-first patients are significantly younger than TET2-first patients.

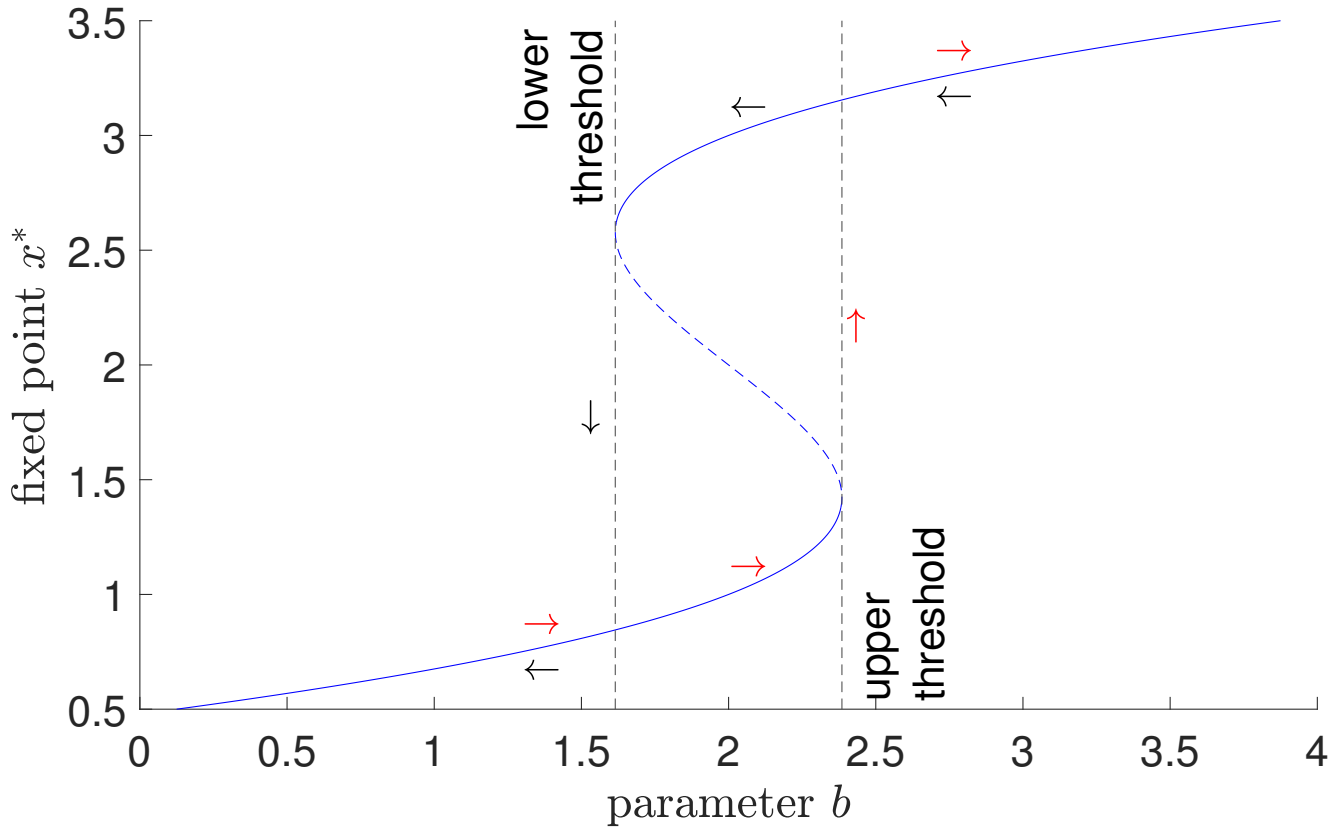
Mathematical model for Observations (1–4)

- We built an ordinary differential equation model to explain Observations (1–4).
- The expression level of gene X is

$$\mathrm{d}x/\mathrm{d}t = b + f(x) - x.$$

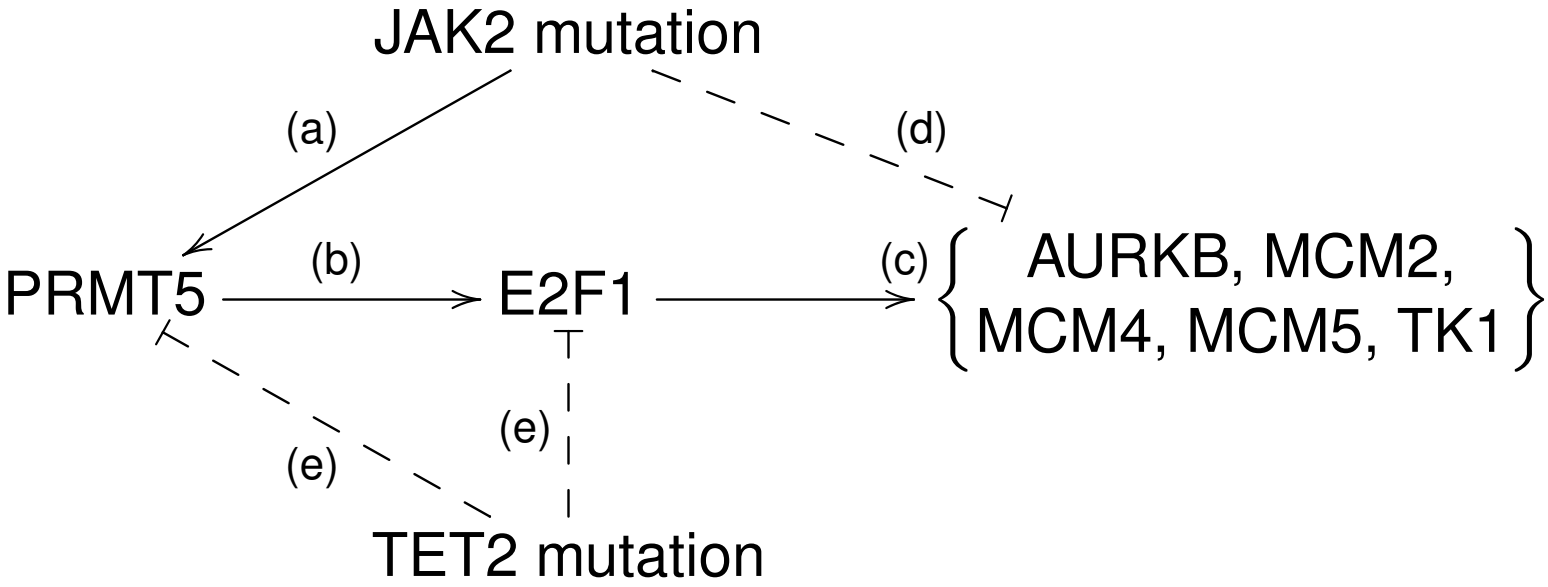
- $b = b_0 \pm \mathbb{1}_{\mathrm{J}} \pm \mathbb{1}_{\mathrm{T}}$ is the synthesis term, depending on whether JAK2 and TET2 are present.
- $f(x) = -(x-2)^3 + 2(x-2)$ is the autoregulation of X.
- $-x$ is the degradation term.

Mathematical model for Observations (1–4)



When $b = 0.5 + \mathbb{1}_{\mathrm{J}} + \mathbb{1}_{\mathrm{T}}$, x^* will be at the high state only if both JAK2 and TET2 are present. Thus JAK2 up-regulates X only if TET2 is present. Other cases for Observations **(1,2)** can be explained similarly.

Mathematical model for Observations (1–4)

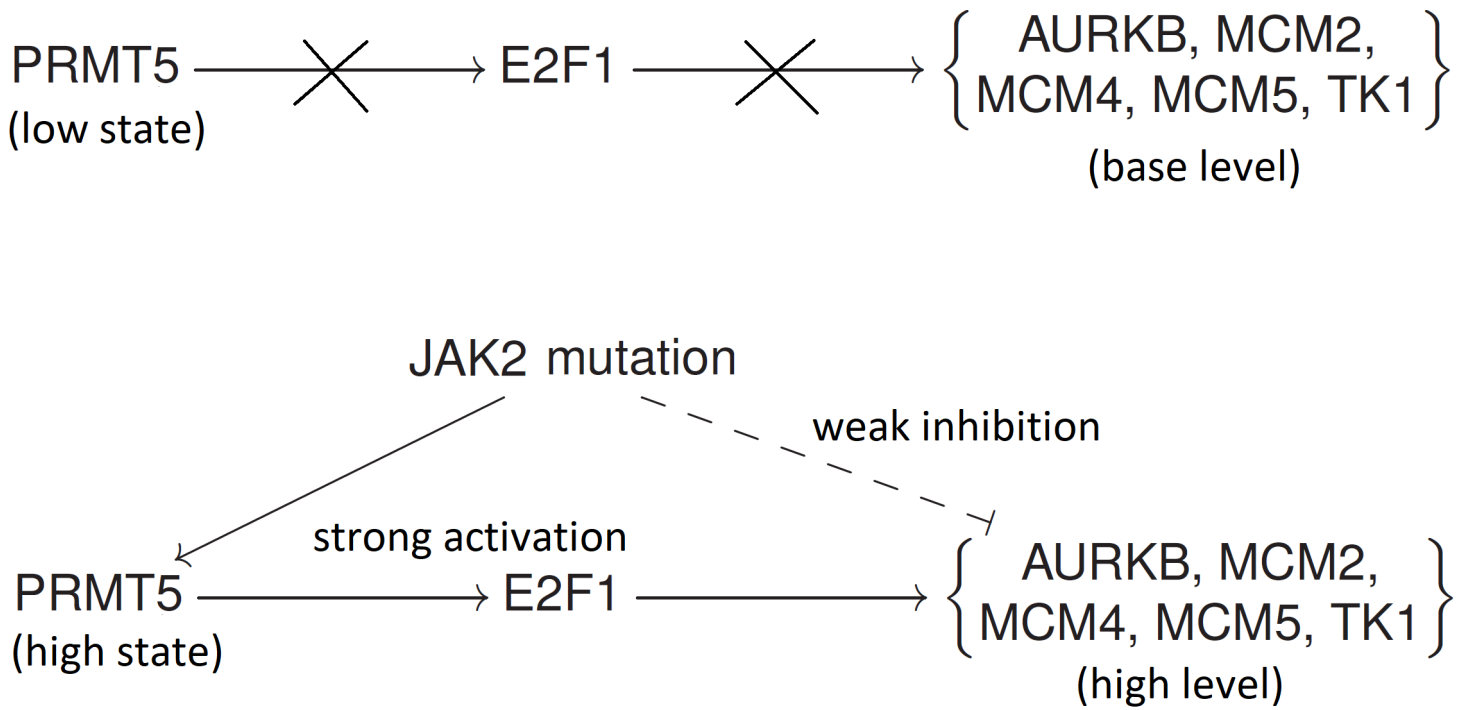


- Regulations (a,b,c) are known. Regulations (d,e) are hypothetical. One can verify them experimentally.
- This regulatory network can be used to explain Observation (3) for five genes.

Mathematical model for Observations (1–4)

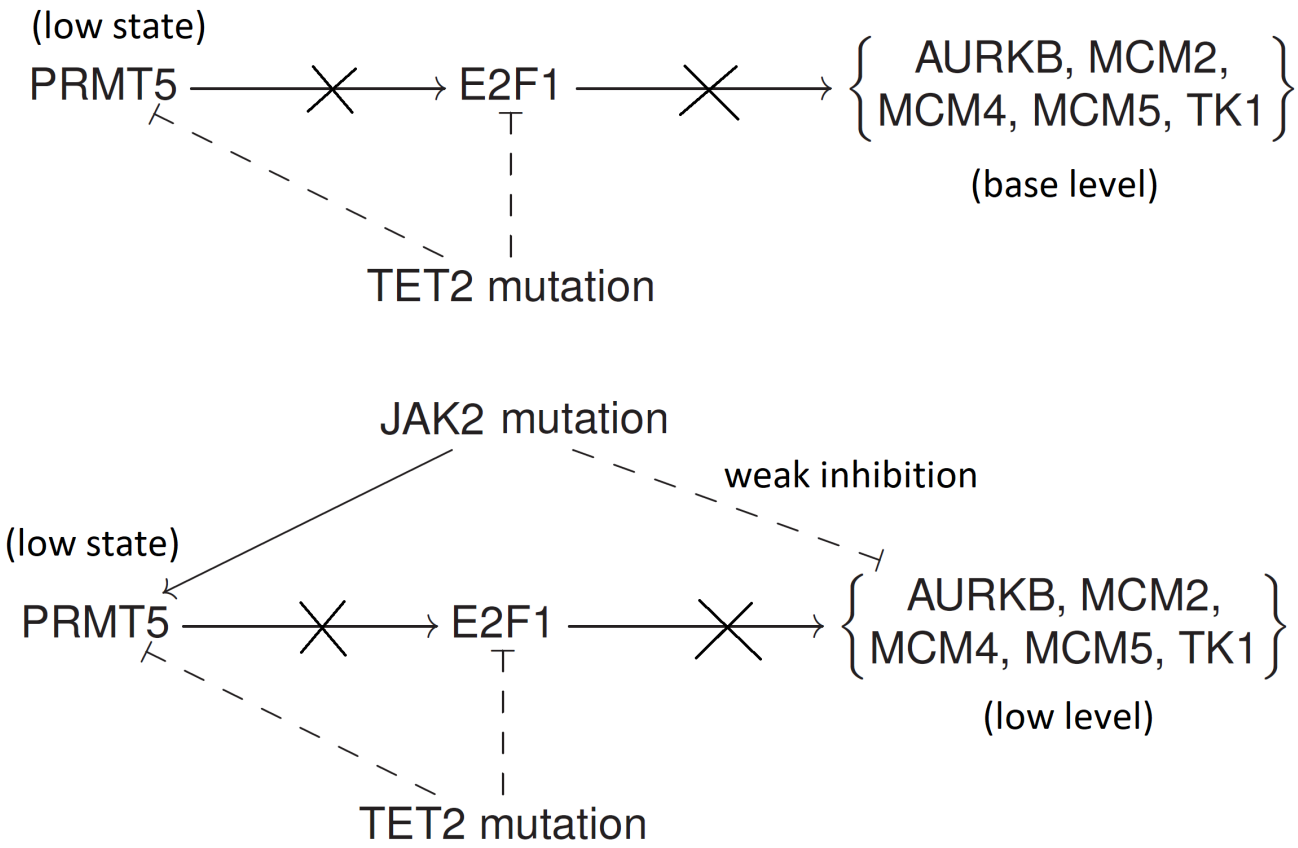
- PRMT5 satisfies $\mathrm{d}p/\mathrm{d}t = b + f(p) - p$ with $b = 1.5 + \mathbb{1}_{\mathrm{J}} - \mathbb{1}_{\mathrm{T}}$. AURKB etc. satisfies $\mathrm{d}a/\mathrm{d}t = 1 - \mathbb{1}_{\mathrm{J}} + p - a$.
- PRMT5 has two expression levels: low state and high state.
- If TET2 mutation is present, PRMT5 is locked to the low state, and cannot regulate AURKB etc.
- If TET2 mutation is not present, JAK2 mutation can activate PRMT5 from the low state to the high state, and strongly promote AURKB etc. through E2F1.

Mathematical model for Observations (1–4)



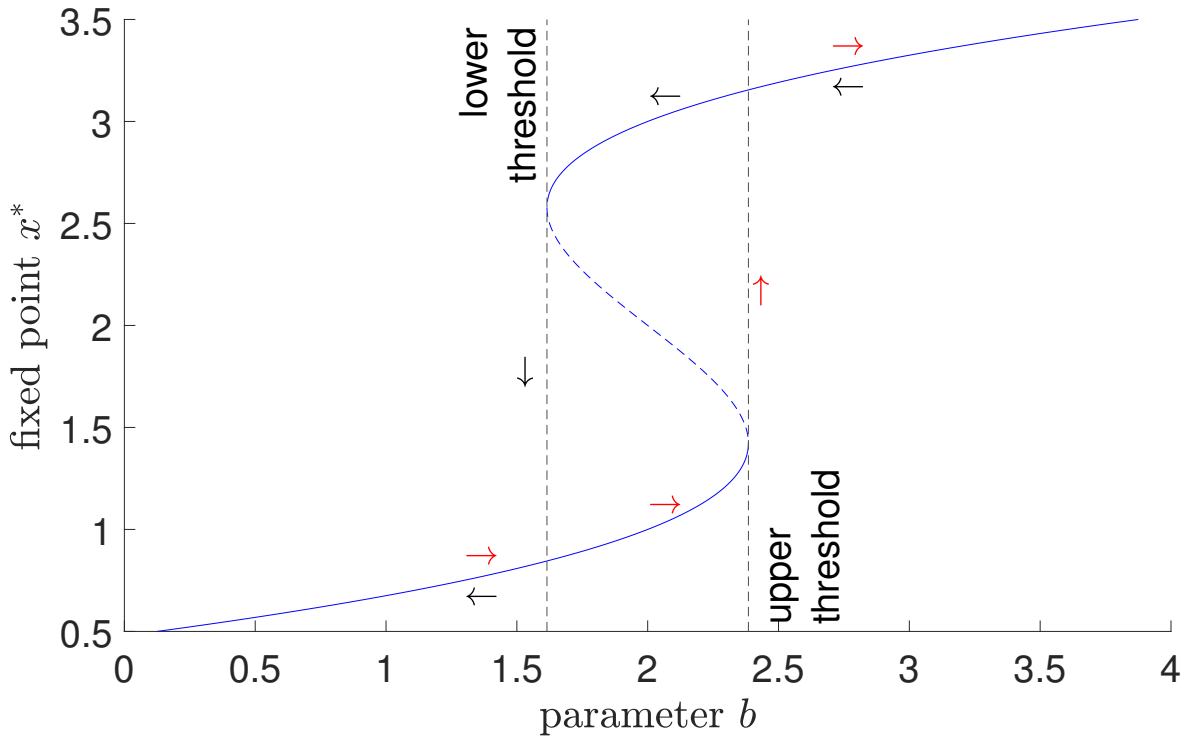
Without TET2 mutation, JAK2 mutation can up-regulate AURKB etc.

Mathematical model for Observations (1–4)



With TET2 mutation, JAK2 mutation can down-regulate AURKB etc. This explains Observation (3).

Mathematical model for Observations (1–4)

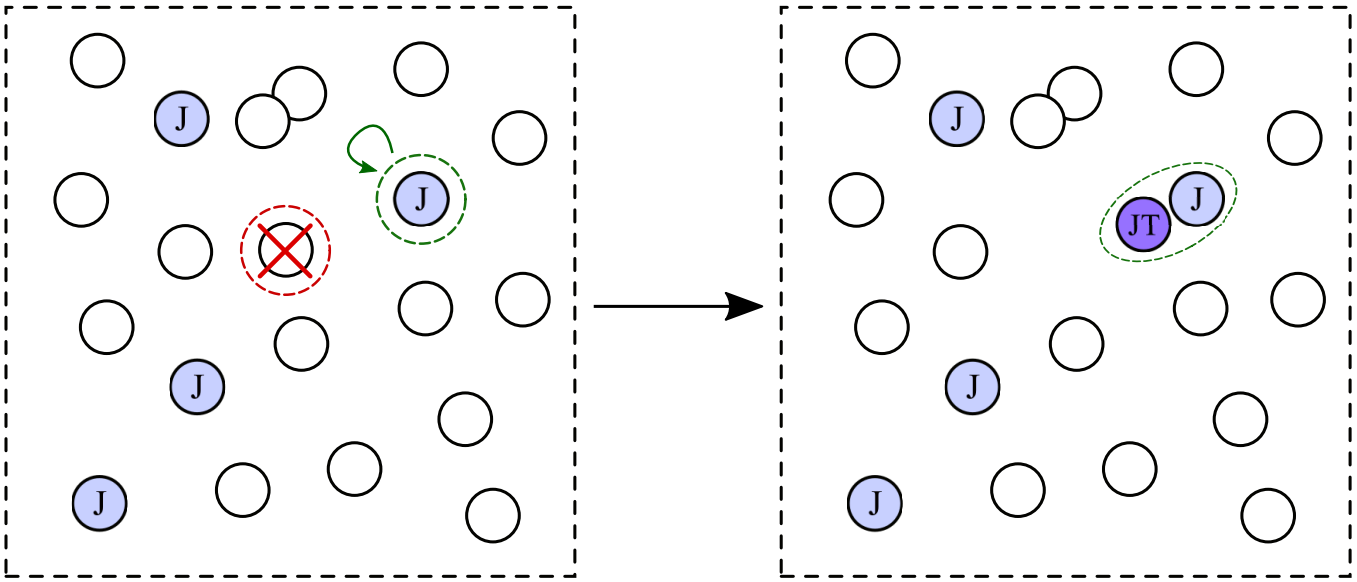


- Consider $\mathrm{d}x/\mathrm{d}t = b + f(x) - x$ with $b = 2 + \mathbb{1}_{\mathrm{J}} - \mathbb{1}_{\mathrm{T}}$. If the order of mutations is JAK2-TET2, the final x^* is in the high state; if the order of mutations is TET2-JAK2, the final x^* is in the low state. Thus the order of mutations affects gene expressions, which explains Observation **(4)**.

Mathematical model for Observations (5,6)

- Consider a generalized Moran process.
- Initially, there are N cells with no mutation (wild type).
- For each round, a cell is randomly chosen (with equal probability) to die.
- Then a cell is randomly chosen to divide. A cell with mutations is more likely to be chosen.
- After division, for the most time, two daughter cells have the same mutation configuration with the mother cell. With a small probability, one daughter cell can acquire a new mutation.

Mathematical model for Observations (5,6)



- We measure the time when the first cell with both mutations appears (corresponding to the age at diagnosis) and the JAK2-only or TET2-only cell percentage at this time.
- We want to explain Observation (5) (different percentages of one-mutation cells) and Observation (6) (different ages at diagnosis).

Mathematical model for Observations (5,6)

- We propose three biological mechanisms regarding the difference between JAK2 mutation and TET2 mutation.
- Mechanism A: JAK2 mutation can slightly increase growth rate (probability of being chosen to divide), while TET2 mutation can significantly increase growth rate.
- Mechanism B: The mutation rate of JAK2 is lower than the mutation rate of TET2.
- Mechanism C: Cells with the JAK2 mutation carry a higher mutation rate for TET2 mutation. This means JAK2 induces TET2 mutation.
- In simulations, we find that each of these mechanisms can reproduce Observations (5,6). Since different mutations generally have different mutation rates, we think Mechanism B is more convincing.

Summary

- The appearance order of cancer-related mutations can affect gene expression, cell population, and cancer progression.
- We build two mathematical models to explain such clinical observations.
- We make some predictions that can be verified by experiments.

References

- Wang, Y., Shtylla, B., & Chou, T. (2023). Order-of-mutation effects on cancer progression: models for myeloproliferative neoplasm. arXiv preprint arXiv:2308.09941.
- Ortmann, C. A., Kent, D. G., Nangalia, J., Silber, Y., Wedge, D. C., Grinfeld, J., ... & Green, A. R. (2015). Effect of mutation order on myeloproliferative neoplasms. New England Journal of Medicine, 372(7), 601-612.