Population dynamics of epigenetic oncogenesis

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***Short Abstract* — The role of the tumour microenvironment in cancer initiation is poorly understood. We present and analyze a microenvironment population dynamics model motivated by an attractor landscape view of cellular states. Cell types are regarded as stable minima of a quasi-potential function that harbours additional spurious minima, some of which may be pre-cancerous. Stochastic transitions between healthy and mutagenic minima enable mutation acquisition at the population level (oncogenesis). This transition rate may be amplified by tumour signals, causing positive feedback. A three-state ODE model describes this process. We analyze its dynamics with and without tumour feedback, discussing implications for cancer initiation.**

I. Purpose

THE role of the tumour microenvironment in the early stages of cancer initiation remains poorly understood. We rigorously investigate its potential role using a model inspired by an attractor landscape view of cellular phenotypes. This view associates a cell's "state" with its set of gene transcript levels [1,2]. Physiological cell types are interpreted as minima of a quasi-potential function that captures epigenetic regulatory interactions. Due to the high-dimensionality of the corresponding landscape, it is generally the case that unexpected or "spurious" stable points will exist, some of which could exhibit deleterious phenotypes and have been hypothesized to be pre-cancerous [2,3].

The subset of spurious phenotypes with mutagenic potential (e.g. via p53 dysregulation) is hypothesized to be a precursor to the emergence of cells with cancer driver mutations [2,3]. Accordingly, the role of tumour microenvironment signalling is of particular interest, as evidence suggests tumour signals may amplify the transition rate from healthy to spurious cell types (e.g. via tumour exosomes [4]). Our modelling formalizes these hypotheses and investigates their effects on cancer initiation.

II. Model

A minimal three-state ODE system is constructed by considering three cell classes: x (the set of non-mutagenic or healthy attractors), y (the mutagenic spurious attractors), and z (cells which have acquired irreversible cancer driver mutations). The total population $N = x + y + z$ is dynamically conserved, representing pre-cancerous metaplasia (i.e. no outgrowth). Cells can switch reversibly (epigenetically) between the x and y attractor sets, but only cells which have entered the y state can acquire mutations at non-negligible rates. Our model accounts for state transitions, growth, immigration, and population-regulating cell death.

III. Analysis

We consider the model's behaviour in two scenarios: 1) fixed transition rates, and 2) positive feedback in the form of mutant population-dependent transition rate between x and y.

Without feedback there is exactly one physical and stable fixed point of the dynamics for all physical parameter values. As parameters such as the growth rates of states y or z are varied, the stable fixed point undergoes a continuous transcritical bifurcation between two regimes: "all-z" ($z_\infty = N$) and "low-z" ($0 \leq z_\infty < N$). These regimes can be interpreted as pre-cancer and cancer-free states, respectively.

Positive feedback on the x-to-y transition rate leads to rich dynamics, including bistability (via a pitchfork bifurcation) of the all-z and low-z fixed points over a wide range of parameters. We investigate switching between the monostable and bistable regimes as a function of y and z growth rates. The resulting "phase diagram" is reminiscent of a liquid-gas transition (discontinuous phase switching below a critical point but continuous switching beyond this point). Stochastic simulation of the first-passage time to acquire a second driver mutation in each regime indicates that small deviations in mutation and subpopulation growth rates can accelerate or inhibit tumour development.

IV. Conclusion

Analysis of our minimal population dynamics model reveals significant consequences of positive feedback in the tumour microenvironment. Namely, if tumour signals can induce reprogramming to spurious phenotypes in healthy surrounding tissue, then mutated cells can dominate the total population even if they grow much more slowly than healthy cells. In addition, mutants can fixate with a mutation rate that is orders of magnitude lower than what is needed in the absence of signalling. This suggests that blocking pro-tumour microenvironment signals alone (i.e. without direct targeting of tumour cells) could inhibit tumour development.

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