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Evolutionary cancer therapy

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Heterogeneity in cancer is increasingly being recognized as a key determinant of tumour progression and response to therapy. However, much of our current understanding of this heterogeneity has been driven by our ability to measure it, and therefore has largely focused on the genomic scale. Ultimately such heterogeneity is realized through the generation of distinct phenotypes. In recent years there has been a deeper appreciation for how phenotypic variation is modulated by a range of biological mechanisms over different spatial scales - specifically epigenetic, metabolic and microenvironmental. Within a growing tumour, multiple cellular phenotypes and a spatiotemporally-varying microenvironment form a complex ecosystem that exhibits unintuitive, nonlinear behaviour.

Treatment of advanced cancers has benefited from new agents that supplement or bypass conventional therapies. However, even effective therapies fail as a heterogeneous tumour cell population deploys a wide range of resistance strategies. We propose that evolutionary dynamics ultimately determine survival and proliferation of resistant cells, therefore evolutionary treatment strategies should be used with conventional therapies to delay or prevent resistance. Using an agent-based framework to model spatial competition among sensitive and resistant populations, we apply anti-proliferative drug treatments to varying ratios of sensitive and resistant cells. We compare a continuous maximum tolerated dose schedule with an adaptive schedule aimed at tumour control through competition between sensitive and resistant cells. We find that continuous treatment cures mostly sensitive tumours, but with any resistant cells, recurrence is inevitable. We identify two adaptive strategies that control heterogeneous tumours: dose modulation controls most tumours with less drug, while a more vacation-oriented schedule can control more invasive tumours.

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