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De-coupling cell-autonomous and non-cell-autonomous fitness effects allows solution of the Fokker-Planck equation for the evolution of interacting populations

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De-coupling cell-autonomous and non-cell-autonomous fitness effects allows solution of the Fokker-Planck equation for the evolution of interacting populations

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Evolutionary therapy and particularly evolutionary control are of key interest in tackling drug resistance in patients. Ideally we can derive control protocols, such as those described in *(Iram et. al, Nat. Phys)*, to steer a population towards a genotype that is necessarily resistant to one drug whilst sensitive to another. In effect controlling evolution is controlling treatability. In order to derive such precise control protocols we require accurate mathematical descriptions of our evolving system. Many of the population genetics models of evolution developed thus far lack sufficient complexity to predict tumor evolution in the clinic. In particular, the standard Wright-Fisher approach taken from population genetics neither considers nor accurately predicts the heterogeneity that we see in patients. One reason for this is that growth rates or fitnesses of cells in mixed populations are assumed to be the same as that in monoculture. In both simple bacterial systems and complex tumor systems, experiments have shown that these assumptions break down and frequency dependent fitness effects are observed. Even the Fokker-Planck formalism, used in the derivations and simulations of counterdiabatic control mentioned earlier, currently lacks the incorporation of cell-cell interactions. To incorporate these interactions into our Fokker-Planck description we take the payoff matrix description from within game theory and associated replicator dynamics and decouple the cell-autonomous selection and non-cell-autonomous interaction terms. We solve the Fokker-Planck equation using this decoupled description for the interacting case and examine the steady state solution analytically and numerically across a range of interaction and selection parameters. We demonstrate the impact that games have in accelerating and decelerating evolution and their role in regulating access to regions of the solution space. This work demonstrates a new framework for eco-evolutionary modelling and emphasizes that the emergence of a dominant cell-type can be caused by both ecological and genotypic factors and conversely that an underlying autonomous genotypic landscape does not need to be neutral for heterogeneity to persist.