

## MICHAEL NICHOLSON

### Pathways to resistance in growing populations over fitness valleys

We consider a multitype branching process in which cells undergo birth, death, and mutation. Motivated by the measured cost of resistance in bacteria and models of imperfect drug penetration (interpreting some mutational events as migrations), the type-1 cells have the largest fitness, inducing a fitness valley. We wait until the first time a given, arbitrary number of mutations has accumulated, indicating resistance has emerged. This time is characterised in the limit of small mutation rates. The ordering in which the mutations arose gives different pathways to resistance. Explicit, intuitive expressions are derived for the probability that resistance stemmed from any given pathway, again for small mutation rates. The impact of imperfect drug penetration will be considered as an application.