Sir,

We read with great interest Dr McEvoy’s comments on our paper. His attempt to ‘give a simplified explanation of the underlying concepts to a non-mathematical physician’ resulted in an over-simplification, which we would like to clarify from the start. Strictly speaking, our manuscript discusses multiple myeloma (MM) as an ‘evolutionary game’ between three interacting cell types, which are viewed as different strategies of a cell population. In reducing the interplay of cell lineages to hawks and doves, in whatever variant of the game, Dr McEvoy is pictorially moving along the edges of the simplex (triangles) in Figures 2–4, which, in our view, is too much of a simplification, given that MM development proceeds across the simplex, as explicitly shown in our paper. Nonetheless, along the edges of the triangle, hawks and doves play a coexistence game, never a prisoner’s dilemma. This is an important point, as most of the evolutionary thinking in cancer has been considered as a simplified version of a prisoner’s dilemma between two cell lineages, something that is explicitly abandoned in our work.

Whenever reproduction, mutation and selection occur, evolution is a natural consequence (Cairns, 1975; Tomlinson and Bodmer, 1999). Viewed in this way, cancer is an evolutionary process, albeit an undesirable one with respect to the host. Cancer is clearly a problem of multicellularity and an almost inevitable process, albeit an undesirable one with respect to the host. Cancer cells have a fitness advantage owing to their mutation profile (Cairns, 1975; Tomlinson and Bodmer, 1999; Beerenwinkel et al, 2007). In our model, we do not consider additional mutations that change this profile, as this would mean introducing new strategies in the cell population. Their fitness, however, does not result solely from their mutation profile – it is also dependent on their microenvironment. We purposefully chose MM because its interactions with osteoclasts and osteoblasts are well defined and the general response of the three cell populations to the exchange of cytokines is well accepted. Of course, similar principles can be
readily generalised and applied to other tumours and even non-malignant disorders.

We disagree with Dr McEvoy that 'any ESS reached by treatment can only at best achieve an ESS where normal cells coexist with malignant cells'. In fact, Figure 2b shows precisely that this need not be the case, although at present the cure scenario, although possible, is not under our control. Hence, although it may be difficult to cure a tumour, this depends on where the populations lie with respect to the saddle point (unstable equilibrium) as shown in Figure 2b. If therapies can alter the values of the interacting parameters such that the patient reaches a state to the left of this equilibrium point, in the absence of further mutations, natural selection will eliminate the malignant clone, although this may take time. Therapies that can reduce the fitness of malignant cells compared with their normal counterparts exist, with imatinib (and other tyrosine kinase inhibitors, such as dasatinib or nilotinib) being perhaps the best example. Indeed, we have shown that this is the reason for its well-known efficacy in chronic myeloid leukaemia (Dingli et al, 2008). We believe it is only a matter of time before other tumours can be treated in a similar manner. Furthermore, reducing the fitness of a cell does not imply reversing the process of carcinogenesis. For instance, the reversible nature of imatinib means that, once treatment is stopped, the disease may relapse. Consequently, imatinib does not eliminate bcr–abl oncoprotein expression but abrogates its function and therefore reduces the relative fitness of cancer cells.

As a final remark, we would like to point out that our results suggest that the path to win the 'war on cancer' is perhaps not to fulfil the goal pictured in the cover of the Economist in September 2008, in which all cancers cells must be targeted for elimination. Instead, we may look for our allies in the right place and at the right scale, which, with a small yet intelligent push from our side, may do the job much better, by taking advantage of the same ruthless power of evolution that favoured cancer in the start of the process.

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