Supplementary Figures

Figure S1. Schematic view of the model as described in Methods.

Figure S2. Examples of the adaptive cancer fitness landscapes used in this study.

These examples illustrate how the fitness landscapes look like when different parameters are used. **a-d**, four different selection intensities are used in this study: $\sigma^2 = 10$ (**a**), $\sigma^2 = 40$ (**b**), $\sigma^2 = 70$ (**c**) and $\sigma^2 = 100$ (**d**). **e-f**, to illustrate how selections are correlated along traits in the fitness landscape two selection correlations are used (see equations (9) and Methods for more details): $\sigma^2 = 10$, $\rho_s = 0.9$ (**e**) and $\sigma^2 = 10$, $\rho_s = 0.5$ (**f**).

Figure S3. Cancer evolution trajectories with a static TME optimum and different initial conditions.

These results demonstrate that under a static TME optimum the initial fitness of cancer cell determines whether subsequent new driver mutations could be observed. If the initial fitness is high ($w_0 = 1$) there is no observation of any new driver mutation (**a**). If a lower fitness is assumed ($w_0 < 1$), there is a maximum of three driver mutations observed (**b**). However, if we assume the mutational variance $m^2 = 1 \times 10^{-5}$ and the selection intensity $\sigma^2 = 1$, the cancer with an initial fitness $w_0 = 0.9$ can adapt to the static TME optimum (**c**) by many "mini driver" mutations (**d**).

Figure S4. Mean cancer cell fitness under various selection intensities and TME conditions.

These results indicate that selection intensity and TME changing speed can significantly affect the evolutionary trajectories of a cancer. Cancer populations evolve under four different rates of TME change ($v_1 = 0.05$, $v_1 = 5 \times 10^{-3}$, $v_1 = 0.05$, $v_1 = 5 \times 10^{-4}$ and $v_1 = 5 \times 10^{-5}$) with $\sigma^2 = 10$ (**a**), $\sigma^2 = 40$ (**b**), $\sigma^2 = 70$ (**c**) and $\sigma^2 = 100$ (**d**). Error bars are s.e.m. and each point represents 100 independent simulations. The line represents a simple linear regression fit. Due to immediate population extinction data are not shown for $v_1 = 0.5$. The dash line represents mean fitness 0.5. When mean population fitness reaches this value it is destined to be extinct.

Figure S5. Mean selection coefficients of adaptive mutations as per figure S4.

These results indicate the selection intensity and TME changing speed play a significant role in cancer adaptive evolution.

Figure S6. *Cancer adaptive evolution with different rates of selection correlation between traits.*

In a slowly changing TME the phenotypic effects of fixed mutations faithfully capture the selection correlation, which is defined by the fitness function (see equation (9) and Figure S2 for different shapes of the fitness landscape due different selection correlation values). Populations evolve under four different selection correlations and TME change rates. **a**, **e**, **i** and **m**, $\rho_s = 0.25$. **b**, **f**, **j** and **n**, $\rho_s = 0.5$. **c**, **g**, **k** and **o**, $\rho_s = 0.75$. **d**, **h**, **l** and **p**, $\rho_s = 0.9$.

Figure S7. *Mean fitness and selection coefficient of cancer adaptation in a randomly changing TME.*

These results show that the increased variance in random changes of the TME acts against adaptive cancer evolution, which leads to decreased mean population fitness and increased selection coefficients of fixed mutations. The mean fitness (**a**) and selection coefficient (**b**) are plotted against different standard deviations (SD) of the random TME change. Error bars are the standard error of the mean (s.e.m.), and each point represents 100 independent simulations.

Figure S8. *Mean fitness and selection coefficient of cancer adaptation in a directionally changing TME with a random component.*

Here it is similar to Figure S7 that increased variance in the directionally changing TME acts against adaptive cancer evolution. The mean fitness (**a**) and selection coefficient (**b**) are plotted against different standard deviations (SD) of the random change. Different colours represent different speed of the directional change. Error bars are the standard error of the mean (s.e.m.), and each point represents 100 independent simulations.

Figure S9. *Mean fitness and selection coefficient of cancer adaptation in a cyclically/periodically changing TME.*

These results suggest that when the period of the cyclically changing TME is fixed the increased amplitude can decrease mean population fitness and increase the selection coefficients of fixed mutations, which act against adaptive cancer evolution. The mean fitness (**a**) and selection coefficient (**b**) are plotted against different amplitudes of the TME change. The period is set at $P = 360$. Error bars are the standard error of the mean (s.e.m.), and each point represents 100 independent simulations.

Figure S10*. Cancer phylogenetic trees under different changing TME dynamics.*

These results demonstrate that it is possible to use phylogenetics to infer the underlying TME selection dynamics. Example phylogenetic trees are shown for simulated cancers

under three different TME dynamics, which were longitudinally sampled every 100 generations for a fixed period of time. **a-d**, four illustrative phylogenetic trees are shown for a directionally changing TME with four different speeds: $v_1 = 0$ (static TME, **a**), $v_1 = 5\times10^{-5}$ (**b**), $v_1 = 5\times10^{-4}$ (**c**) and $v_1 = 5\times10^{-3}$ (**d**). A static or slowly changing TME (**a-b**) leads to long internal branches expanding in parallel for long periods of time indicating weak stabilizing selection, while a moderately changing TME (**c**) leads to continual selection of branches with beneficial mutations and therefore promote adaptive evolution. A fast-changing TME (**d**) leads to strong selection and shorter side branches indicating fast extinction of these branches. **e-h**, four phylogenetic trees are shown for a randomly changing TME with four different standard deviations: $\delta = 0.5$ (**e**), $\delta = 1$ (**f**), $\delta = 1.5$ (**g**) and $\delta = 2$ (**h**). Here the higher variance of the random TME changing dynamics leads to shorter side branches indicating higher rates of stochastic death of these cancer cells, which obviously does not promote adaptive evolution as no obvious "imbalanced" trees can be observed. **i-l**, four phylogenetic trees are shown for a cyclically changing TME with four different amplitudes: (**i**), $A = 2$ (**j**), $A = 4$ (**k**) and $A = 6$ (**l**). Here low amplitude of TME changing cycle leads to a phylogeny showing recent clonal expansion indicating relatively stable population size under weak selection (**i**). Interestingly, we show above that moderate amplitudes promote adaptive evolution (**j**), which is evident here from the phylogenies' ladder-like and spindly tree topology (strongly imbalanced) with long trunk and shorter side branches. The temporal signals in the phylogeny also reflect a cyclic selection pattern, where long branches and ladder-like shorter branches appear in tandem (e.g., see **j**). Note that the clonal interference is apparent in all cases particularly when the TME changing dynamics lead to strong selection, e.g., a faster changing TME (**d**) obviously leads to strong clonal competition and faster extinction of these shorter side branches comparing with a slower changing TME if there are no additional large beneficial mutations supplied (**c**). All cancers are simulated for 10000 generations except (**d**), where the cancer went extinct at approximately 2300 generations. The maximum population size is set at $N = 10^5$. The scale bar represents the number of cell divisions.

Figure S11. *Illustration of the fitness landscape shifts due to different anticancer treatment strategies.*

These figures illustrate how the optimum of a fitness landscape moves quantitatively and how the reduced selection intensity leads to a "flatter" fitness landscape in cancer treatments. **a**, fitness landscape changes with different (constant) TME optimum due to different treatments. **b**, the optimum of the fitness landscape changes from $z_0^{opt} = 0$ to $z_1^{opt} = 5$. **c**, fitness landscape optimum changes from $z_0^{opt} = 0$ to $z_1^{opt} = 8$. **d**, fitness landscape optimum changes from $z_0^{opt} = 0$ to $z_1^{opt} = 8$ and selection intensity from $\sigma^2 = 10$ to $\sigma^2 = 40$. Clearly, the shorter distance that an optimum travels gives a less "steep" valley for the cancer cells to cross (evolve resistance). Similarly, the reduced selection intensity (a "flatter" fitness landscape) also gives the cancer cells a less "steep" valley to cross from the original fitness landscape to the new one (compare **c** and **d**).

Figure S12. *Cancer adaptation with different resistance mechanisms under treatment strategies maintaining a constant TME optimum.*

Different resistance mechanisms lead to different 3D spatio-temporal patterns of sub-clonal evolution. Example 3D snapshots are taken sequentially after the sudden change of TME optimum ($z_1^{opt}=8, \sigma^2=10$) due to treatments (**a-d**), however, the population has three different resistance mechanisms to avoid population extinction. **a**, the cancer cells have more loci contributing to adaptation ($L=50$). We find two adaptive mutations at generation 113 and generation 1033, which are born in generation 101 and 228 with $s=38.281$ and $s=0.5976$, respectively. **b**, the cancer cells have higher mutation rates($\mu=4\times10^{-4}$). In this case we find one adaptive mutation at generation 977 born at generation 101 with a very large selection coefficient, $s=57.3361$, indicating very strong selection leading to the fixation of this mutation with very large fitness effect. **c**, the cancer cells evolve in a fitness landscape with lower selection intensity($\sigma^2=40$). The population fitness is summarized in **d** for each treatment strategy.

Figure S13. *Cancer adaptation under treatment strategies that continuously change the TME optimum.*

Treatment strategies continuously modify the TME optimum leading to different 3D patterns of spatio-temporal patterns of sub-clonal evolution and evolutionary trajectories. Example 3D snapshots are taken sequentially after treatments (**a-d**). Three different treatments maintaining three different rates of TME change: $v_1=0.5$ (**a**), $v_1=0.05$ (**b**) and $v_1=0.005$ (**c**), respectively. The population fitness plotted against generation time is summarized in **d** for each treatment strategy. Note that the sample is taken for every generation, and the dashed line indicates when the treatment starts (after generation 100).

Supplementary Movies

Movie S1. A simulation movie showing 3D cancer adaptation under a static TME with $v_1 = 0$.

Movie S2. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 0.5$.

Movie S3. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 0.05$.

Movie S4. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-3}$.

Movie S5. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-4}$.

Movie S6. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-5}$.

Movie S7. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-5}$. In this simulation we have initial fitness $w = 0.1$, initial population size $N = 10^4$.

Movie S8. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 0.05$, initial fitness $w = 0.1$, initial population size $N = 10^7$.

Movie S9. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-3}$, initial fitness $w = 0.1$, initial population size $N = 10^7$.

Movie S10. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-4}$, initial fitness $w = 0.1$, initial population size $N = 10^7$.

Movie S11. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-5}$, initial fitness $w = 0.1$, initial population size $N = 10^7$.

Movie S12. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 0.05$, initial fitness $w = 0.5$, initial population size $N = 10^7$.

Movie S13. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-3}$, initial fitness $w = 0.5$, initial population size $N = 10^7$.

Movie S14. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-4}$, initial fitness $w = 0.5$, initial population size $N = 10^7$.

Movie S15. A simulation movie showing 3D cancer adaptation under a TME change rate $v_1 = 5\times10^{-5}$, initial fitness $w = 0.5$, initial population size $N = 10^7$.

Movie S16. A simulation movie showing 3D cancer adaptation under a cyclically changing TME. The amplitude is set at $A = 4$ with period $P = 360$.

Movie S17. A simulation movie showing 3D cancer adaptation under a cyclically changing TME. The amplitude is set at $A = 6$ with period $P = 360$.

Movie S18. A simulation movie showing 3D cancer adaptation under a treatment strategy maintaining a constant TME optimum $z_1^{opt} = 5$.

Movie S19. A simulation movie showing 3D cancer adaptation under a treatment strategy maintaining a constant TME optimum $z_1^{opt} = 6$.

Movie S20. A simulation movie showing 3D cancer adaptation under a treatment strategy maintaining a constant TME optimum $z_1^{opt} = 7$.

Movie S21. A simulation movie showing 3D cancer adaptation under a treatment strategy maintaining a constant TME optimum $z_1^{opt} = 8$. Note that in this simulation the cancer population went extinct.

Movie S22. A simulation movie showing 3D cancer adaptation with a resistance mechanism under a treatment strategy maintaining a constant TME optimum at $z_1^{opt} = 8$. The resistance mechanism here is the number of loci contributing to adaptation is increased to $L = 50$ from $L = 5$. Comparing to Movie S20, the population extinction is avoided.

Movie S23. A simulation movie showing 3D cancer adaptation with a resistance mechanism under a treatment strategy maintaining a constant TME optimum at $z_1^{opt} = 8$. The resistance mechanism here is increased mutation rate from $\mu = 4\times10^{-5}$ to $\mu = 4\times10^{-4}$. Comparing to Movie S20, the population extinction is also avoided.

Movie S24. A simulation movie showing 3D cancer adaptation with a resistance mechanism under a treatment strategy maintaining a constant TME optimum at $z_1^{opt} = 8$. The resistance mechanism here is that the TME selection intensity is reduced from $\sigma^2 = 10$ to $\sigma^2 = 40$ (the width is increased see Supplementary Figure S2a and 2b). Comparing to Movie S20, the population extinction is also avoided.