Promoting extinction or minimizing growth? The impact of treatment on trait trajectories in evolving populations

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Submitted by Michael Raatz 18 Jun 2022 08:44

Abstract

When cancers or bacterial infections establish, small populations of cells have to free themselves from homoeostatic regulations that prevent their expansion. Trait evolution allows these populations to evade this regulation, escape stochastic extinction and climb up the fitness landscape. In this study, we analyse this complex process and investigate the fate of a cell population that underlies the basic processes of birth, death and mutation. We find that the shape of the fitness landscape dictates a circular adaptation trajectory in trait space. We show that successful adaptation is less likely for parental populations with higher turnover (higher birth and death rates). Including density- or trait-affecting treatment we find that these treatment types change the adaptation dynamics in agreement with geometrically derived hypotheses. Treatment strategies that simultaneously target birth and death rates are most effective, but also increase evolvability. By mapping physiological adaptation pathways and molecular drug mechanisms to traits and treatments with clear eco-evolutionary consequences, we can achieve a much better understanding of the adaptation dynamics and the eco-evolutionary mechanisms at play in the dynamics of cancer and bacterial infections.

Keywords: Evolutionary rescue, Resistance evolution, Dormancy, Competitive release, Immune evasion

Round #1
by Dominik Wodarz, 08 Oct 2022 06:13
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Minor Revisions

The paper seems very interesting, and in general is viewed positively by the reviewers. The reviewers make a number of useful suggestions and have some questions, which should be straightforward to address in a revision; this might benefit the paper.

We thank you for this overall positive assessment. We found the suggestions from the reviewers very helpful and have implemented most of them. Particularly, we have better indicated the focus of this study on the initial phase of the adaptation process. Also, we are now more explicit about the assumptions behind our model and analysis. We found the suggestions to look at multiplicative mutational effects very interesting and implemented them now in a supplementary figure, actually supporting our previous interpretation of the declining rescue probability with increasing turnover in the additive mutational effects model. We are grateful for the constructive criticism and feel that the paper has improved considerably. Please see our point-by-point response below.

Reviews

Reviewed by Rob Noble, 05 Jul 2022 09:54

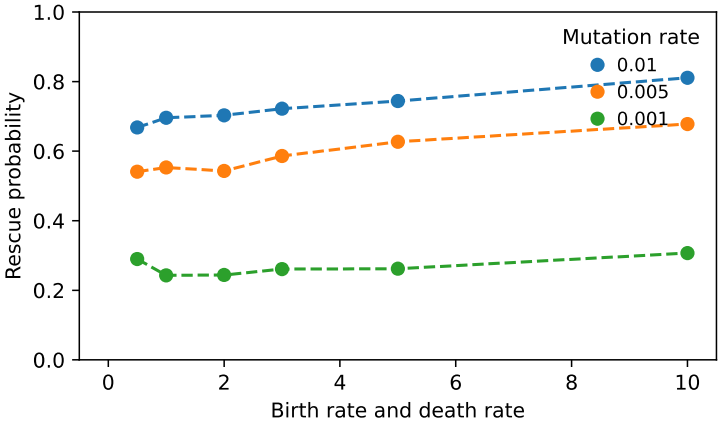
This study investigates evolution during the early growth of tumours or bacterial populations and predicts which treatment strategies will most effectively steer the dynamics towards extinction. The analytical and numerical methods are well chosen. The paper is clearly written and logically structured. I have a few comments about the model assumptions. These concerns don't necessarily require the generation of new results but I think they should at least be discussed in the paper.

Whereas the focus is on mutations that modify birth and death rates, and thus effective carrying capacities, isn't it plausible also to have selection on the third trait, K? For example, bacteria could evolve to upregulate production of beneficial public goods, or cancer cells could evolve lower sensitivity to hypoxia, enabling them to achieve larger population sizes even while maintaining their initial basic birth and death rates. How might mutations modifying K change the results?

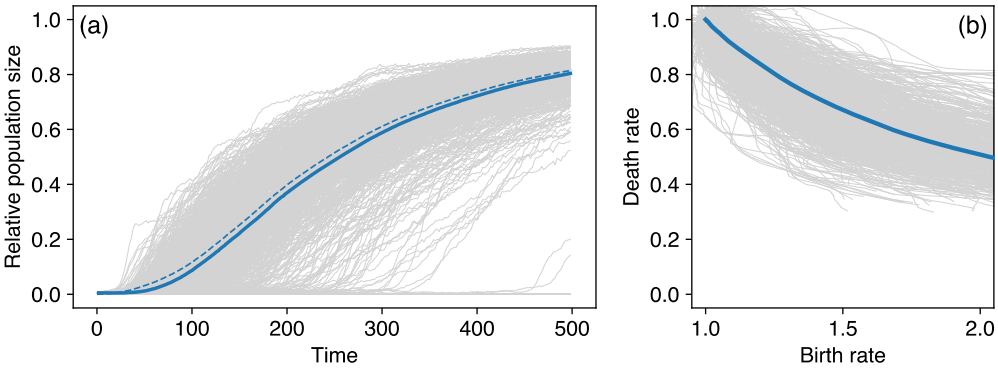
We agree that mutations in K are possible and constitute an interesting next step. However, we focused on mutating only b and d as we aimed to constrain ourselves to the initial establishment phase where the population has not reached the carrying capacity yet. The main reason for this is that the population is very unlikely to go extinct once it has reached sizes close to the carrying capacity (see e.g. Fig. 5). In agreement with this, treatment success typically occurs after the first or second treatment cycle in our setting, i.e. when the population size is still small. As soon as the population size gets close to the carrying capacity, many mechanisms that are not modelled in our system may become important (e.g. vascularization, spatial structuring within the tumour, …). We added a clarification of our focus in lines 104/105.

Mutation effects are assumed to be additive (equation 1), yet many other evolutionary models instead assume multiplicative effects. How might assuming multiplicative effects change the results? In the model "increasing both the initial birth and death rate equally, increases the number of extinct replicate population" (line 249) because "the same adaptation step in trait space gains a smaller increase in the survival probability of fast-turnover cells than in slow-turnover cells" (line 406). Would this result still hold if the model were to assume multiplicative effects?

We agree that it's *a priori* unclear whether mutation effects are additive, multiplicative, or even more complex. For multiplicative mutational effects we would not expect this pattern as higher turnover lineages also perform larger steps in trait space. To check this hypothesis, we conducted a brief analysis of multiplicative mutational effects, where we assumed b_mutant = b_parental*(1+s), s ~ N(0, sigma) (as opposed to b_mutant = b_parental + s, s ~ N(0, sigma)). Similar terms were used for the death rate. We find that assuming multiplicative mutational effects result in rescue probabilities that are largely independent of turnover, confirming our geometrical explanation (see below figure, now added as new Fig. S3).



Multiplicative effects also distort the adaptation trajectories as birth-rate components of adaptive steps are on average larger than death-rate components. This introduces a bias in the adaptive steps and prevents that the fitness gradients are tracked (see the figure below showing the untreated ensemble dynamics for multiplicative mutational effects).



The other findings remain qualitatively the same (e.g. the treatment effects). Exploring the emergent differences further seems to merit an investigation on its own, but this would go beyond the scope of the current manuscript. We thank the reviewer for pointing out the importance of the mutational effects model that we chose and we have emphasized our choice more clearly now (line 100).

How realistic and general is it to assume that “mortality during treatment is higher for less fit lineages” (line 462)? Chemotherapy, for example, targets the most rapidly dividing cells.

We agree. This assumption holds only for additive treatment effects. Chemotherapy that targets rapidly dividing cells preferentially should be modelled as a multiplicative effect, i.e. a mortality term of form -c*b*N. In this study, we limited ourselves to additive treatment effects on the traits, as we also assumed additive mutational effects (see above).

The choice of initial condition N(0) = 100 requires justification. In reality, every lineage begins with a single cell and much of the interesting dynamics occurs when the population size is below 100. If we assume the founder cell has equal birth and death rates, neglect density-dependent effects, ignore deleterious mutations (as the authors do throughout), and assume the population size follows a random walk (equivalent to gambler’s ruin) then the probability of this cell giving rise to a population of 100 cells before going extinct is 1%. That is, w/A, where w = 1 is the initial size and A = 100 is the target. So such lineages aren’t unreasonably rare. However, the shortest time until the population can grow from 1 to 100

cells is 99 generations and almost all lineages will take much longer than this. The expected waiting time is (w^2 – A^2)/3 = 3,333 generations. Given the assumed mutation rate of 0.005 per generation, almost all lineages will acquire multiple mutations by the time they reach 100 cells, and hence birth and death rates will vary both within and between 100-cell populations. Even if we instead assume that the birth rate is initially less than the death rate (inconsistent with homeostasis), it's unclear whether 100-cell populations with equal birth and death rates will often arise. The authors should explain why they nevertheless chose to start with homogeneous 100-cell populations and discuss how this might limit the scope of their findings.

Starting at N=100, and also the settings for the other parameters (mutation rate, standard deviation of mutation kernel, carrying capacity) was a practical choice to avoid requiring a very large number of replicates to be able to track successful adaptation events and efficiently sample the trajectory (see Fig. 4, formerly Fig. S2). We now indicated this more clearly in the caption to Tab. 1. Also, we want to note that we actually do not ignore deleterious mutations, but they are out-competed (see Fig. 2b, left upper corner, there are at least two lineages with b<1 and d>1).

Minor comments:

In the Abstract, "geometrically derived hypotheses" (line 14) is unclear. I suggest something like "a geometrical analysis of fitness gradients".

Done, thanks!

Besides "space restriction and nutrient limitation" (line 94), I suggest mentioning oxygen, which is typically what limits initial tumour growth.

Thanks!

The letter f is used for both a fitness function (line 142) and a treatment effect (line 277). Consider using different letters for clarity.

Well spotted, thanks. We changed the fitness function name to phi.

The caption of Figure S1 refers to a "black dashed line" that I can't find in the figure. I guess it should be "blue line".

Thanks, indeed we were referring to the blue line. The caption has been corrected.

Reviewed by anonymous reviewer, 29 Aug 2022 19:15

Raatz and Traulsen use mathematical simulations to investigate the evolutionary dynamics of the cellular traits, birth and death rate, in the absence or presence of density- or trait-affecting treatment strategies. They find that adaptation follows a circular trajectory, increasing birth rates and lowering death rates, which favors lower turnover rates for evolutionary adaptation. If the creation of more mutant lineages also leads to higher evolvability is however determined by the treatment strategy determines. The authors further use geometric arguments to determine how different fitness components change the adaptive trajectories and suggest that net growth maximization could be a stronger determinant than survival probability.

Overall, this manuscript makes an important contribution to understanding the evolutionary landscape of crucial cellular traits, particularly under various treatment strategies. The authors present a thorough theoretical analysis and the manuscript is well-organized. As such I have only minor comments.

Thank you!

Strength:

A particular strength of the manuscript is its use of a geometric analysis that helps visualize the results and provides a nice way to extend the results without running every single simulation. The results of the analysis are additionally thoroughly tested using stochastic and deterministic simulations.

The authors study a range of different treatment strategies including bacteriostatic and bactericidal strategies, which is only considered in the minority of studies on evolution under treatment.

The results are generally presented in a clear and structured manner and connected to clinically relevant examples.

Thank you!

Weaknesses:

In some places the manuscript could benefit from a bit more clarification however:

- The abstract itself is to some extend difficult do understand as the reader doesn't necessarily know what is meant by 'circular adaptation trajectory' and 'geometrically derived hypotheses'.

Agreed, we specified the trait space dimensions (line 11). In line with the comments by Rev#1 we reworded "geometrically derived hypotheses" to "geometrical analysis of fitness gradients" which is more descriptive.

- Where do the model parameter values come from and what exactly is the genetic variance in the birth and death rate intuitively? (Also, the table says genetic variance in death rate twice.)

Thanks for catching this. Regarding the intuitive meaning of the Gs, we have now added that they capture the additive genetic variance (l. 145). We clarified that we chose the parameters such that about half of the replicate simulations would show successful adaptation without treatment (caption to Tab. 1).

- Similarly, is there empirical evidence for the truncated Gaussian distribution used for the mutated trait values.

We clarified the reasoning and consequences of this choice in line 130ff. Unfortunately, we are unaware of empirical evidence on the distribution of mutational effects for these traits, which is probably also unlikely to exist as these rates are seldomly measured. Surely, this would be of interest and we regard it as one aim of our study to advocate for actually tracking these traits over time.

- Where do the equations for minimizing growth and maximizing extinction in Figure 1 come from?

Thanks for pointing out this unclarity, we extended their description in lines 208-212.

- The geometric presentation of treatment effects on different fitness effects could benefit from giving a bit more intuitive explanation on how the trait points and fitness isoclines change.

Indeed, indicating the isocline rotations and the displacements in trait space is helpful here and has been added to the description of Fig. 6 (lines 270ff).

20000 seems to be quite low as a carrying capacity when thinking about bacterial populations and as the carrying capacity seems to have some influence on trait evolution, it would be good to discuss this parameter in realistic ranges as well.

Setting K=20000 was a practical choice to have a sufficiently high rescue probability to visualize the adaptation trajectory, but not too many cells (lineages) to slow down the simulations too much. For smaller K, the rescue probability drops quickly, while for higher K computation time increases rapidly as each lineage is tracked individually. Also, our main focus is to investigate the initial adaptation process and not what happens close to K (please see also our response to Reviewer 1 in this respect).

Phenotypic plasticity is mentioned in the beginning of the results part but could be discussed a bit more compared to genetic changes.

We have decided to remove the mention of ‘phenotypic plasticity’ at the beginning of the results part. Given that in our model traits only change upon birth and not during the lifetime of organisms we feel that ‘phenotypic plasticity’ was actually misleading. Thanks for catching this!

The trait trajectories in Fig. 7b do not look extremely different. Maybe the authors could elaborate a bit more if they consider these differences still significant under clinical conditions.

We would be careful to deduce any clinical implication from our basic model, other than the mechanistic consequence that treatment can alter the trait trajectory. Such an endeavour would potentially require more sophisticated models, but at least a careful parametrization of our model for the problem at hand.

In the discussion section (L435-438), the authors state that the observed prognosis regarding tumor growth does not fit with their observations. How do the authors explain this discrepancy?

Unfortunately, we did not fully finish this line of thought in the original submission. We now added a sentence indicating the resolution of this discrepancy (line 455ff). Basically, prognosis is a composite measure that is affected by many more factors than mere tumour birth and death rate, and that there might be an observer's bias in that we pay particular attention to the few high-turnover, aggressive ones that have managed to escape extinction. Thanks!

Reviewed by anonymous reviewer, 06 Sep 2022 14:37

In this work the authors study a computational model for the evolution of cells under a different types of selective challenges. In their model cells can divide, die and mutate. Cell division is limited by a carrying capactiy, and mutations cause a random effect on birth and death rates. This model is developed to model the treatment of either cancer cells or bacteria. The authors consider a variety of treatment types. First there are what the author calls 'density-affecting' treatments, which immediately reduces the total population of cells. Second there are 'trait-affecting' treatments which can reduce cell birth rates (cyto-static), increase cell death rates (cyto-toxic), or affect both birth and death rates. The authors then study the evolution of the average birth death rates under a variety of treatment types. They find that 'density-affecting' treatments result in slower growing populations (conditional on survival) because of a less thorough exploration of trait-space. In contrast, 'trait-affecting' treatments will result in faster growing populations (conditional on survival). Overall, I thought this paper addressed interesting question in a reasonably clear fashion. Some of the critiques (some minor typos) I have are listed below.

1) Equation 1, summation should be over an index other than i.

Thank you, this has been corrected now.

2) Equation 3, I had a hard time understanding the role of 'f'. Perhaps they can add some more text clarifyting this function.

To prevent further confusion, we added a reference to the next paragraph where the fitness functions that replace f (now phi) are defined.

3) Page 7, lines 152-153. It seems like the process you described will never have negative cell numbers regardless of the effective carrying capacity. Cell deaths are proportional to the number of cells, so no cells means no deaths.

As we assume Poisson-distributed numbers of birth and death events in our model, there is a non-zero probability that more death events should occur than there are alive cells. Besides this technicality, we wanted to point out that the population size only tracks the effective carrying capacity for positive values and not for negative. Thus, we feel that is statement is necessary.

4) Page 7, line 157. 'not unambiguous' is a double negative.

Changed to “ambiguous”.

5) Figure 4. The authors don't really provide an explanation of this phenomena until the discussion. I think it would be good to have some discussion of Figure 4 in Section 3.

We feel that discussing this in section 3 already would break the story line. Thus, we prefer to leave these explanations in the discussion section.

6) Page 15, line 277. Label 'f' is re-used for a new purpose. Better to use a new symbol here.

Thanks, this was sloppy on our side. The fitness functions name has been changed to phi now, so ‘f’ is now uniquely defined as the bottleneck factor.

7) Figure 7. I believe these are plots of population size conditioned on survival, however it's not clear. Please adjust the figure caption to state that these are plots conditioned on survival.

Indeed, it is good to point this out again. We added this statement to the caption.

8) Page 23, lines 386-387. The authors should specify the evidence for circular adaptive trajectories in trait space, i.e., reference figures.

We agree that this might be helpful here and have added references to the figures in the first paragraph of the discussion.

9) Page 24, line 410-415. I'm not convinced that the lower survival probability in high turnover cells is due to faster decline. In particular, mutations in your model are tied to births, and at least to me it would seem like the number of births prior to extinction should be the same regardless of turnover.

In our understanding, there are three factors acting here: 1) the geometrical structure of the radial survival probability isoclines which suggest that larger or more adaptive steps are needed to significantly increase survival probability at large turnover. 2) Higher birth rates β_0 (assuming equally high death rates) lead to a faster decline of the parental (wild type) population as the declining population size is given by $N_0(t) = \frac{K\, N_0(0)}{K+\beta_0\, t\, N_0(0)}$.
3) A higher birth rate leads to more mutations occurring in the declining population. Neglecting the carrying capacity term in the birth rate, the number of expected mutations until time t is given by $K\mu \log\left(1+\frac{\beta_0\, t\, N_o(0)}{K}\right)$.
Factors 1) and 2) suggest a lower rescue probability for higher turnover, factor 3) suggests a higher rescue probability. Particularly, the non-trivial dependencies of factors 2) and 3) on the birth rate prevent that these two factors neutralize each other and thus we don’t see why the number of births prior to extinction should be independent of turnover. Our simulation results then show that indeed factors 1) and 2) outweigh factor 3).

Reviewed by anonymous reviewer, 20 Sep 2022 01:38

This paper aims to explore a general theoretical framework for understanding adaptation of population cells using a two-dimensional trait space consisting of birth and death rates. In the study, treatment that affects the population of cells is not explicitly modeled, but rather is characterized by its impacts on the population size vs birth and/or death rates. The work has interesting modeling ideas and biological realism could have been strengthened.

It would be helpful to validate the robustness of the closed-form approximation formula S1 with respect to its dependence on the carrying capacity K. K= 20 000 is used in the paper. If K gets too small, would that formula still hold?

No, this approximation assumes density-independence, i.e. large K. Below, we motivate the explicit inclusion of K. The validity of Eq. S1 is therefore not the focus of our study and we would refer the interested reader to the original source (Xue and Leibler 2017).

Line 98 - 99: We assume that mutations in the two traits can occur independently and without correlation. Would this be necessarily true? Should the cost of mutation (or some tradeoff between increasing birth rate and reducing death rate) be considered as well?

Including some form of correlation or trade-off between mutational steps in birth and death rate would introduce biases in the direction of adaptation and thus distort the adaptation trajectory. Our aim was to leave the adaptation process entirely driven by fitness measures within imposing constraints. For a specific system, however, it is very likely that such constraints exist. Considering these constraints or trade-offs would go beyond the scope of our study though.

In the simulations, death rates approach to sufficiently small. If I understand correctly, would these living cells are now almost immortal and can live forever? This might be biologically implausible.

Reaching quasi-immortality for sure is an unrealistic outcome. However, we focus in this study on the initial phase of adaptation, which would end before the death rate becomes too small. To circumvent this, others have included trait-space constraints (e.g. Kuosmanen et al. 2022 bioRxiv. 10.1101/2022.07.11.499527). We wanted to study the unconstrained adaptation however.

In the x-axis where death rate is zero, what is the direction of selection for birth rate? Can the birth rates (slowly or fast, depending on the model parameters) evolve as large as possible if one does not stop the simulation after t = 500.

A further adaptation for larger times would be affected by non-modelled factors that become important after the initial adaptation phase. Indeed, adaptation would proceed towards higher birth rates, but without treatment and thus with almost no mortality, birth events would be very rare and adaptation speed vanish.

To continue the comment above, what happens for much longer simulations? The current simulations stop at 500. If we let the simulation run as long as possible, what are the observations there?

This scenario was not the focus of our study and the model would not describe its biology well enough to make any solid statements. For large population sizes (relative to the carrying capacity) K itself would be under selection and in a tumour oxygen deprivation, acidification and vascularization would become important, all of which are not included in our model.

Is there any potential conflict between minimizing extinction and maximizing growth? For simple one-stage birth-death models there seems no (as discussed in 3.3). But my intuition is that there might exist such a tradeoff in general multi-stage age-dependent reproduction models. See, e.g., though for a different system:
https://onlinelibrary.wiley.com/doi/pdf/10.1111/ele.12392

Initially, we were somewhat expecting conflicts between these two fitness measures but it turned out that the angle between adaptive steps of minimizing extinction and maximizing growth are always between zero and 45 degrees, i.e. they never have opposing components. We have now included this in lines 396-398.

Minor remarks

Line 20: Keywords include dormancy. But the present model does not address dormancy at all, if I understand correctly their model.

We were picturing the slow-turnover cells as dormant. We have now indicated this more clearly in the text (line 413).

Line 65: These adaptations have lead to the development of drugs that
-> These adaptations have led to the development of drugs that

Thanks for your attentive reading!

The paper draws insights from two big fields: cancer and bacteria (actually Schematic Figure 1 includes cancer cells and bacteria cells altogether). Although it is appealing to use general purpose models to shed light simultaneously on both systems, they are drastically different in their population dynamics. Thus it is very important to note this limitation when interpreting their findings in both fields, especially given that the present study is a conceptual study based entirely on simple birth-death models.

True, but as we have laid out with multiple literature references, similar processes occur in both systems on the level of abstraction from our model. Only on this abstract level, our model can improve understanding.