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Optimizing adaptive cancer therapy: dynamic programming and evolutionary game theory

Mark Gluzman, Jacob G. Scott and Alexander Vladimirsky

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Original submission:	11 March 2019
1st revised submission:	31 October 2019
2nd revised submission:	18 February 2020
Final acceptance:	26 March 2020

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Review History

RSPB-2019-0570.R0 (Original submission)

Review form: Reviewer 1

Recommendation
Accept with minor revision (please list in comments)

Comments to the Author
I enjoyed reading this paper. It is very well written and presents the material clearly. Although it is quite mathematical, it can be readily understood by non-mathematicians. I do have some advice that the authors might consider. The article is focused on clinical therapy and the role of evolution in resistance. However, the parameters in the model are related to angiogenesis and tumor metabolism. The treatment target is the GLY cells which is a strategy not currently in clinical use. If possible, I suggest reframing the model so that the populations represent a subpopulations in a recognizable clinical treatment protocol.

Review form: Reviewer 2

Recommendation
Accept with minor revision (please list in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Excellent

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Acceptable

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
Yes

Is it clear?
Yes

Is it adequate?
Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
This is an intersting contribution to a rising strategy (i.e., Adaptive Therapy) first theorized by the Gatemby group and that now has reached the age of clinical application.
The paper focus on a specific model of cancer evolutionand aims at providing clinicians with decision-making tool to optimize adaptive therapy strategy.
I cannot comment the intrinsic mathematics but the authors are requested to fix the following issues:
-presentation of metronomics in the Introduction section is somewhat biased. Metronomics is indeed better tolerated but its development is not driven by safety issues but to seek higher efficacy through alternate mechanisms of actions such as anti-angiogenesis and immunostimulating properties. Please refer to the pivotal work from the Folkman and the Bob Kerbel groups to precise this.
-reported inconsistencies in clinical efficacy with metronomic regimen could actually come from the empirical nature of current clinical applications. To what extent pharmacometrics could help to fix this issue should be better discussed, especially since several groups have published models

regarding optimal dosing and scheduling.
- When presenting optimal control theory and associated paper, the authors have missed a critical clinical trial (Revisiting dosing regimen using PK/PD modeling: the MODEL1 phase I/II trial of docetaxel plus epirubicin in metastatic breast cancer patients. Hénin E, Meille C, Barbolosi D, You B, Guitton J, Iliadis A, Freyer G. Breast Cancer Res Treat. 2016 Apr;156(2):331-41. doi: 10.1007/s10549-016-3760-9.). To the best of my knowledge, this was the first time ever that a clinical study has been prospectively designed and performed using a constraints model based upon Optimal Control Theory.
- The authors should better discuss future steps and applications of their work - what kind of further validation steps (i.e., through running non-clinical studies to test the performances of their models to identify an optimal adaptive therapy strategy, unless they feel ready to a early-phase clinical trial in humans) should we expect to bridge the gap between theory and actual application?

Decision letter (RSPB-2019-0570.R0)

10-May-2019

Dear Dr Vladimirsky:

I am writing to inform you that your manuscript RSPB-2019-0570 entitled "Optimizing adaptive cancer therapy: dynamic programming and evolutionary game theory" has, in its current form, been rejected for publication in Proceedings B.

This action has been taken on the advice of referees, who have recommended that substantial revisions are necessary. With this in mind we would be happy to consider a resubmission, provided the comments of the referees are fully addressed. However please note that this is not a provisional acceptance.

The resubmission will be treated as a new manuscript. However, we will approach the same reviewers if they are available and it is deemed appropriate to do so by the Editor. Please note that resubmissions must be submitted within six months of the date of this email. In exceptional circumstances, extensions may be possible if agreed with the Editorial Office. Manuscripts submitted after this date will be automatically rejected.

Please find below the comments made by the referees, not including confidential reports to the Editor, which I hope you will find useful. If you do choose to resubmit your manuscript, please upload the following:

1) A 'response to referees' document including details of how you have responded to the comments, and the adjustments you have made.
2) A clean copy of the manuscript and one with 'tracked changes' indicating your 'response to referees' comments document.
3) Line numbers in your main document.

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Sincerely,
Proceedings B
mailto: proceedingsb@royalsociety.org

Associate Editor
Comments to Author:
Thank you for submitting your paper to PRSB. I have now received two referees reports on your paper and have looked at it myself. As you can see they are both positive about your work and we all think that you should be congratulated for your ability to present your theoretical results in an accessible way. Both referees do make important comments however that need to be addressed before we can make a decision on the paper. This may result in more work but at least the issues around the clinical context need to be addressed. While doing this it would help the presentation of the work to put more of the theoretical work into supplementary material and to also pay special attention to the journal format, particularly for the abstract. My sense is that this will result in a much improved and impactful manuscript.

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s)
I enjoyed reading this paper. It is very well written and presents the material clearly. Although it is quite mathematical, it can be readily understood by non-mathematicians. I do have some advice that the authors might consider. The article is focused on clinical therapy and the role of evolution in resistance. However, the parameters in the model are related to angiogenesis and tumor metabolism. The treatment target is the GLY cells which is a strategy not currently in clinical use. If possible, I suggest reframing the model so that the populations represent a subpopulations in a recognizable clinical treatment protocol.

Referee: 2

Comments to the Author(s)
This is an intersting contribution to a rising strategy (i.e., Adaptive Therapy) first theorized by the Gatemby group and that now has reached the age of clinical application.
The paper focus on a specific model of cancer evolutionand aims at providing clinicians with decision-making tool to optimize adaptive therapy strategy.
I cannot comment the intrinsic mathematics but the authors are requested to fix the following issues:
-presentation of metronomics in the Introduction section is somewhat biased. Metronomics is indeed better tolerated but its development is not driven by safety issues but to seek higher efficacy through alternate mechanisms of actions such as anti-angiogenesis and immunostimulating properties. Please refer to the pivotal work from the Folkman and the Bob Kerbel groups to precise this.
-reported inconsistencies in clinical efficacy with metronomic regimen could actually come from the empirical nature of current clinical applications. To what extent pharmacometrics could help to fix this issue should be better discussed, especially since several groups have published models regarding optimal dosing and scheduling.
- When presenting optimal control theory and associated paper, the authors have missed a critical clinical trial (Revisiting dosing regimen using PK/PD modeling: the MODEL1 phase I/II trial of docetaxel plus epirubicin in metastatic breast cancer patients. Hénin E, Meille C, Barbolosi D, You B, Guitton J, Iliadis A, Freyer G. Breast Cancer Res Treat. 2016 Apr;156(2):331-41. doi: 10.1007/s10549-016-3760-9.). To the best of my knowledge, this was the first time ever that a clinical study has been prospectively designed and performed using a constraints model based upon Optimal Control Theory.
- The authors should better discuss future steps and applications of their work - what kind of further validation steps (i.e., through running non-clinical studies to test the performances of their models to identify an optimal adaptive therapy strategy, unless they feel ready to a early-

phase clinical trial in humans) should we expect to bridge the gap between theory and actual application?

Author's Response to Decision Letter for (RSPB-2019-0570.R0)

See Appendix A.

RSPB-2019-2454.R0

Review form: Reviewer 1

Recommendation
Accept with minor revision (please list in comments)

Comments to the Author
This is a very nice well-written manuscript and I support its publication. My major concern is that the imposition of treatment on the pre-existing model (e.g. GLY) is a bit forced and potentially confusing. Rather than just saying they are "targeting" GLY cells I suggest they name a specific therapy, specific cells, and resistance mechanisms. They might start by suggesting serum ligands (e.g. EGF) can be treated as substrate similar to glucose and then simply extend from there

Review form: Reviewer 3

Recommendation
Major revision is needed (please make suggestions in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Acceptable

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
N/A

Is it clear?
N/A

Is it adequate?
N/A

Do you have any ethical concerns with this paper?
No

Comments to the Author
See the attached file (See Appendix B).

Decision letter (RSPB-2019-2454.R0)

08-Jan-2020

Dear Dr Vladimirsky,

Your manuscript has now been peer reviewed and the reviews have been assessed by an Associate Editor. The reviewers' comments (not including confidential comments to the Editor) and the comments from the Associate Editor are included at the end of this email for your reference. As you will see, the reviewers and the Editors have raised some concerns with your manuscript and we would like to invite you to revise your manuscript to address them.

We do not allow multiple rounds of revision so we urge you to make every effort to fully address all of the comments at this stage. If deemed necessary by the Associate Editor, your manuscript will be sent back to one or more of the original reviewers for assessment. If the original reviewers are not available we may invite new reviewers. Please note that we cannot guarantee eventual acceptance of your manuscript at this stage.

To submit your revision please log into http://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions", click on "Create a Revision". Your manuscript number has been appended to denote a revision.

When submitting your revision please upload a file under "Response to Referees" in the "File Upload" section. This should document, point by point, how you have responded to the reviewers' and Editors' comments, and the adjustments you have made to the manuscript. We require a copy of the manuscript with revisions made since the previous version marked as 'tracked changes' to be included in the 'response to referees' document.

Your main manuscript should be submitted as a text file (doc, txt, rtf or tex), not a PDF. Your figures should be submitted as separate files and not included within the main manuscript file.

When revising your manuscript you should also ensure that it adheres to our editorial policies

(https://royalsociety.org/journals/ethics-policies/). You should pay particular attention to the following:

Research ethics:
If your study contains research on humans please ensure that you detail in the methods section whether you obtained ethical approval from your local research ethics committee and gained informed consent to participate from each of the participants.

Use of animals and field studies:
If your study uses animals please include details in the methods section of any approval and licences given to carry out the study and include full details of how animal welfare standards were ensured. Field studies should be conducted in accordance with local legislation; please include details of the appropriate permission and licences that you obtained to carry out the field work.

Data accessibility and data citation:
It is a condition of publication that you make available the data and research materials supporting the results in the article. Datasets should be deposited in an appropriate publicly available repository and details of the associated accession number, link or DOI to the datasets must be included in the Data Accessibility section of the article (https://royalsociety.org/journals/ethics-policies/data-sharing-mining/). Reference(s) to datasets should also be included in the reference list of the article with DOIs (where available).

In order to ensure effective and robust dissemination and appropriate credit to authors the dataset(s) used should also be fully cited and listed in the references.

If you wish to submit your data to Dryad (http://datadryad.org/) and have not already done so you can submit your data via this link
http://datadryad.org/submit?journalID=RSPB&manu=(Document not available), which will take you to your unique entry in the Dryad repository.

If you have already submitted your data to dryad you can make any necessary revisions to your dataset by following the above link.

For more information please see our open data policy http://royalsocietypublishing.org/data-sharing.

Electronic supplementary material:
All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI. Please try to submit all supplementary material as a single file.

Online supplementary material will also carry the title and description provided during submission, so please ensure these are accurate and informative. Note that the Royal Society will not edit or typeset supplementary material and it will be hosted as provided. Please ensure that the supplementary material includes the paper details (authors, title, journal name, article DOI). Your article DOI will be 10.1098/rspb.[paper ID in form xxxx.xxxx e.g. 10.1098/rspb.2016.0049].

Please submit a copy of your revised paper within three weeks. If we do not hear from you within this time your manuscript will be rejected. If you are unable to meet this deadline please let us know as soon as possible, as we may be able to grant a short extension.

Thank you for submitting your manuscript to Proceedings B; we look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Best wishes,
Loeske Kruuk
Editor
mailto: proceedingsb@royalsociety.org

Associate Editor
Comments to Author:
I have received two referees report. My sense is the paper is nearly there - but I agree with the referee that you should have the equations in the paper so people don't need to refer to previous work and they also make a number of other good suggestions that I would like you to address. My sense is that this will improve the paper.

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s).
This is a very nice well-written manuscript and I support its publication. My major concern is that the imposition of treatment on the pre-existing model (e.g. GLY) is a bit forced and potentially confusing. Rather than just saying they are "targeting" GLY cells I suggest they name a specific therapy, specific cells, and resistance mechanisms. They might start by suggesting serum ligands (e.g. EGF) can be treated as substrate similar to glucose and then simply extend from there

Referee: 3

Comments to the Author(s).
See the attached file.

Author's Response to Decision Letter for (RSPB-2019-2454.R0)

See Appendix C.

RSPB-2019-2454.R1 (Revision)

Review form: Reviewer 1

Recommendation
Accept as is

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
N/A

Is it clear?
N/A

Is it adequate?
N/A

Do you have any ethical concerns with this paper?
No

Comments to the Author
This revision has addressed all my questions, I have no more comment. I think the paper can be accepted for publishing.

Decision letter (RSPB-2019-2454.R1)

26-Mar-2020

Dear Dr Vladimirsky

I am pleased to inform you that your manuscript entitled "Optimizing adaptive cancer therapy: dynamic programming and evolutionary game theory" has been accepted for publication in Proceedings B.

You can expect to receive a proof of your article from our Production office in due course, please check your spam filter if you do not receive it. PLEASE NOTE: you will be given the exact page length of your paper which may be different from the estimation from Editorial and you may be asked to reduce your paper if it goes over the 10 page limit.

If you are likely to be away from e-mail contact please let us know. Due to rapid publication and an extremely tight schedule, if comments are not received, we may publish the paper as it stands.

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Electronic supplementary material:
All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI.

Thank you for your excellent contribution. On behalf of the Editors of the Proceedings B, we look forward to your continued contributions to the Journal.

Finally, all the best for dealing with the challenges of the current COVID-19 situation: I hope you all stay safe.

Yours sincerely,
Professor Loeske Kruuk
Editor, Proceedings B
mailto: proceedingsb@royalsociety.org

Associate Editor:
Board Member: 1
Comments to Author:
(There are no comments.)

Board Member: 2
Comments to Author:
(There are no comments.)

Appendix A

Response to Associate Editor

We are very grateful to the editor and referees for their positive review and constructive comments. We believe our manuscript became better as a result of addressing them. In addition, we have changed the abstract, streamlined the exposition (with the changed portions highlighted in blue), shortened the figure captions, and moved one section to Supplementary Materials. Once it is formatted per journal style, we estimate that the revised version will be 9.5 pages long. We hope that it is now suitable for publication in PRSB.

Below we go through all issues in detail, with the review text quoted in black and our response in blue.

General review:

Thank you for submitting your paper to PRSB. I have now received two referees reports on your paper and have looked at it myself. As you can see they are both positive about your work and we all think that you should be congratulated for your ability to present your theoretical results in an accessible way. Both referees do make important comments however that need to be addressed before we can make a decision on the paper. This may result in more work but at least the issues around the clinical context need to be addressed.

Many thanks for the positive review. In particular, we are very pleased that our presentation of theoretical results was found to be accessible, as this was something we spent significant time discussing and working on. Presenting theoretical work to a broad audience is never easy, especially in cases like this where our aim is truly to engage audiences from mathematics, cancer biology and clinical oncology.

Specific comments:

While doing this it would help the presentation of the work to put more of the theoretical work into supplementary material and to also pay special attention to the journal format, particularly for the abstract. My sense is that this will result in a much improved and impactful manuscript.

We have rewritten the presentation of the cancer evolution model in a more compact form. Boxes 1 and 2 have been merged: equations (1) and (3) in the old version have been removed, and equation (7) has been moved to the first box. The specific evolutionary game theory model presented in Box 1 – while central to our illustrative results, is not the focus of this paper – and interested readers can find medical motivation and mathematical justification of the model in Kaznatcheev et al. (2017) where it was first presented. We have moved a discussion of optimization trade-off between total administered drugs versus time to recovery into Section 4S of Supplementary Materials.

We have also changed the formatting of our abstract, making it shorter and removing the division into sections. We now also explain the acronym "MTD" before using it in the second half

of the abstract.

Response to Reviewer #1

General review:

I enjoyed reading this paper. It is very well written and presents the material clearly. Although it is quite mathematical, it can be readily understood by non-mathematicians.

Many thanks for this positive comment. We spent a lot of time trying to make it accessible – as we are truly interested in communicating our method to a broad audience so that it can be used!

Specific comments:

I do have some advice that the authors might consider. The article is focused on clinical therapy and the role of evolution in resistance. However, the parameters in the model are related to angiogenesis and tumor metabolism. The treatment target is the GLY cells which is a strategy not currently in clinical use. If possible, I suggest reframing the model so that the populations represent subpopulations in a recognizable clinical treatment protocol.

Thank you for this constructive comment. We agree with the reviewer that the model we have chosen to illustrate our method does not represent a commonly assumed scenario. Our goal was to show how **any** *(three strategy) model could be optimized, and the central result of the paper is the method itself and the opportunities that it can present. We, in fact, wanted to stay away from specific clinical scenarios (like, for example, the one posited in the Zhang and Gatenby paper). Instead, we want to illustrate how, as we hopefully approach an era of* **measured games***, as per Kaznatcheev et al., 2019 (Nature Ecology and Evolution) a theoretical approach can be used to optimize any given ecological dynamic over a range of parameters. Further, having chosen a previously published model, we were able to focus on the results of the optimization method we present, rather than any results specific to the model, which would detract from our message. To this end, while we understand the reviewer's desire for a more directly clinically applicable result, we would like to withhold this for future work.*

Response to Reviewer #2

General review:

This is an intersting contribution to a rising strategy (i.e., Adaptive Therapy) first theorized by the Gatemby group and that now has reached the age of clinical application. The paper focus on a specific model of cancer evolution and aims at providing clinicians with decision-making tool to optimize adaptive therapy strategy. I cannot comment the intrinsic mathematics but the authors are requested to fix the following issues:

We are glad that the reviewer has found our paper interesting. The main focus and novelty of the article is our method of optimizing adaptive policies for an EGT model of cancer dynamics. The model from Kaznatcheev et al. (2017) is used to illustrate how optimal adaptive policies can be found in many game theory based models.

Specific comments:

1. presentation of metronomics in the Introduction section is somewhat biased. Metronomics is indeed better tolerated but its development is not driven by safety issues but to seek higher efficacy through alternate mechanisms of actions such as anti-angiogenesis and immunostimulating properties. Please refer to the pivotal work from the Folkman and the Bob Kerbel groups to precise this.

We agree with the reviewer that our exposition of metronomic policy was somewhat brief and insufficiently nuanced. We have rewritten the corresponding paragraph and hope that our discussion of metronomics is more accurate now (please, see page 2 lines 40-48).

2. reported inconsistencies in clinical efficacy with metronomic regimens could actually come from the empirical nature of current clinical applications. To what extent pharmacometrics could help to fix this issue should be better discussed, especially since several groups have published models regarding optimal dosing and scheduling.

*We 100% agree that the failures of metronomic therapy are likely based on the fact that the designs themselves are empiric. Our results, and those of Zhang and Gatenby (along with work to optimize their own game using closed-loop methods from Stankova) suggest that *there does not exist* a single empirical protocol that would succeed. The thrust of our (and their) work instead suggests that for each specific (model-driven) clinical scenario, a different regimen should be used to optimize. While the threshold-based method of Zhang has produced better results than any previous empiric method, they themselves suggest it is not optimal, only 'better', with optimization left to further work. The approach we present here represents one such method, and we are eager to see it implemented by groups for their specific models (e.g. Zhang et al. Nat Comms or Archetti et al. PNAS).*

3. When presenting optimal control theory and associated paper, the authors have missed a critical clinical trial (Revisiting dosing regimen using PK/PD modeling: the MODEL1 phase I/II trial of docetaxel plus epirubicin in metastatic breast cancer patients. Hnin E, Meille C, Barbolosi D, You B, Guitton J, Iliadis A, Freyer G. Breast Cancer Res Treat. 2016 Apr;156(2):331-41. doi: 10.1007/s10549-016-3760-9.). To the best of my knowledge, this was the first time ever that a clinical study has been prospectively designed and performed using a constraints model based upon Optimal Control Theory.

We thank the reviewer for bringing this important paper to our attention. We have added a discussion of this work on page 2 lines 45-48. Hnin et. al.(2016) optimizes dosing regimen for original PK/PD models and then evaluates the model-driven dosage protocol in a clinical study. The results demonstrate that the proposed model-driven dosage regimes can decrease therapy-related toxicity and improve cancer treatment efficacy. This clinical study supports our belief that model-driven treatment strategies can be more efficient than conventional protocols. But it is also important **which treatment aspects** *are optimized to choose a model-driven strategy. In Hnin et. al.(2016) the authors optimize dosage "distribution", fixing the total drug amount per cycle and the time schedule. The method that we propose provides optimal adaptive strategies optimizing the dosage intensity* **and** *the time schedule. Clinical studies of optimal adaptive strategy should yield even better results in the setting of Hnin et. al.(2016) if the underlying mathematical model is realistic. On the other hand, the failure of an optimal model-driven strategy in a clinical study would imply that the model does not capture some important parameters of the real cancer dynamics.*

4. The authors should better discuss future steps and applications of their work - what kind of further validation steps (i.e., through running non-clinical studies to test the performances of their models to identify an optimal adaptive therapy strategy, unless they feel ready to a early-phase clinical trial in humans) should we expect to bridge the gap between theory and actual application?

We are excited to discuss these future steps, and now present an aspirational paragraph to address this on lines 278-287, pages 12-13.

Appendix B

This paper considers an interesting issue related to cancer treatment, the optimizing adaptive cancer therapy. The authors applied the Evolutionary Game Theory (EGT) to problem, which gives the Hamilton-Jaccobi-Bellman (HJB) equations. The optimizing therapy protocol can be obtained by solving the HJB equation. This method is mathematically meaningful. The authors discussed the outcomes based on the optimal strategies and the maximum tolerated dose (MTD) method. Based on the studies, the authors conclude that the optimal control method can improve the MTD-based method, and yields less costs. The topic and results and this paper are interesting. However, there are some issues need to be addressed.

1. This paper mainly refer the model in previous studies (ref. [19]). I suggest that the authors need to provide more details about the model setup so that the paper is self-contained. Not every reader want to check the original paper for the model details. For example, how the three type cells interact to each other? How the equation (2) was derived from the interactions between there type cells?

2. In the model equation, it is a key condition to assume that the total cell number of three type cells is a constant. Clinically, how can we justify this assumption? Cancer is a disease of abnormal growth, and treatment tends to kill cancer cells. Therefore, it is not obvious to assume the constant total cell number during treatment. The authors need to provide more discussions on this assumption. In particularly, how about the conclusions when this assumption is invalid?

3. Do “heterogeneous regime” means the parameter to have oscillatory solutions? Please clarify.

4. Any clinical facts to support the oscillation solution under control (without treatment) condition?

5. How the parameter values in the study are selected? I don’t find the value of d_max. The parameter values spread over the paper. I suggest the authors to summarize the parameter values through a table.

6. Based on the current presentation, it is very difficult to understand the meaning of the yellow region in Figures 3-4, and how these regions depend on the parameters. If I understand correctly, the regions are given by equation (14) in the supplementary materials, and the optimal method is succeeds if the ON region intersect with the boundary of therapy succeeds, the optimal method is fails is the ON region intersect with the boundary of therapy fails. I suggest the authors state clearly these relations.

Appendix C

Response to Associate Editor

I have received two referees report. My sense is the paper is nearly there - but I agree with the referee that you should have the equations in the paper so people don't need to refer to previous work and they also make a number of other good suggestions that I would like you to address. My sense is that this will improve the paper.

We thank the reviewers for their positive evaluation and constructive suggestions. We agree that the paper should be self-contained. We have added Section 1S in Supplementary Material to provide details on Kaznatcheev et al. model and summarize the key steps of model derivation. We have addressed the reviewers' comments and also shortened the "discussion" section to conform to ProcB page limits.

Response to Reviewer #1

This is a very nice well-written manuscript and I support its publication. My major concern is that the imposition of treatment on the pre-existing model (e.g. GLY) is a bit forced and potentially confusing. Rather than just saying they are "targeting" GLY cells I suggest they name a specific therapy, specific cells, and resistance mechanisms. They might start by suggesting serum ligands (e.g. EGF) can be treated as substrate similar to glucose and then simply extend from there

We thank the reviewer for their positive comments, and agree (to a degree) about inclusion of specifics of the model to give the reader a better intuitive grasp of the biology underlying the model assumptions – specifically regarding therapy and cell phenotypes. To this end, we have added descriptions of each phenotype as requested when the model is introduced, found on lines 113–124, page 4, in blue text. However, given this paper's focus on the novel method to optimize ***any model*** *of tumor growth, we would like to refrain from any additional discussion beyond what we have now added.*

Response to Reviewer #3

General review:

This paper considers an interesting issue related to cancer treatment, the optimizing adaptive cancer therapy. The authors applied the Evolutionary Game Theory (EGT) to problem, which gives the Hamilton-Jaccobi-Bellman (HJB) equations. The optimizing therapy protocol can be obtained by solving the HJB equation. This method is mathematically meaningful. The authors discussed the outcomes based on the optimal strategies and the maximum tolerated dose (MTD) method. Based on the studies, the authors conclude that the optimal control method

can improve the MTD-based method, and yields less costs. The topic and results and this paper are interesting. However, there are some issues need to be addressed.

Specific comments:

1. This paper mainly refer the model in previous studies (ref. [19]). I suggest that the authors need to provide more details about the model setup so that the paper is self-contained. Not every reader want to check the original paper for the model details. For example, how the three type cells interact to each other? How the equation (2) was derived from the interactions between there type cells?

We totally agree that a summary of setup and derivation of the Kaznatcheev et al.[19] model will improve understanding of our paper. We have added Section 1S in Supplementary Material. In this section we list the model assumptions on cells interaction, tumor growth, GLY-targeting therapy effect, etc, and summarize the main steps of deriving the system of equations (2).

2. In the model equation, it is a key condition to assume that the total cell number of three type cells is a constant. Clinically, how can we justify this assumption? Cancer is a disease of abnormal growth, and treatment tends to kill cancer cells. Therefore, it is not obvious to assume the constant total cell number during treatment. The authors need to provide more discussions on this assumption. In particularly, how about the conclusions when this assumption is invalid?

The replicator equations can be derived with an assumption of either constant or exponentially growing population. We have added the corresponding footnote on page 2 to inform the readers about the assumption. In Section 1S of Supplementary Material we show the derivation of the model under the exponential growth assumption, and add several references to the Methods section where this generalization is also performed. We want to emphasize that the model from Kaznatcheev et al. (2017) is used as an example. The main purpose of the paper is to illustrate how optimal adaptive policies can be found in many models based on evolutionary game theory.

3. Do “heterogeneous regime” means the parameter to have oscillatory solutions? Please clarify.

In brief, yes. We mean here that the tumor always remains heterogeneous (i.e., if we start in the interior of the state space triangle, all cell phenotypes remain present and their fractions remain bounded away from zero even asymptotically). In the previous paper from Kaznatcheev, it is proven that periodic orbits exist in this regime. As this is not a central point for the current paper, we would not like to confuse the readers with a more detailed discussion.

4. Any clinical facts to support the oscillation solution under control (without treatment) condition?

This is an excellent question, but one which we believe is beyond the scope of this paper. It is generally found that tumors are heterogeneous (please see the two references included below), but knowledge of highly temporally resolved levels of heterogeneity are beyond the scope of current knowledge.

Marusyk A., Polyak K.
"Tumor heterogeneity: causes and consequences"
Biochim Biophys Acta. 2010 1805(1):105–117.

Marusyk A., Almendro V., Polyak K.
"Intra-tumour heterogeneity: a looking glass for cancer?"
Nat Rev Cancer. 2012 12(5):323–334.

5. How the parameter values in the study are selected? I dont find the value of d_{max}. The parameter values spread over the paper. I suggest the authors to summarize the parameter values through a table.

We thank the reviewer for pointing out that we have not listed a set of parameters for Figure 2 and 3 in the main text. Now we provide it on lines 177,180; pages 7,8. The parameters for all figures are summarized in Section 4S of Supplementary Materials.

6. Based on the current presentation, it is very difficult to understand the meaning of the yellow region in Figures 3-4, and how these regions depend on the parameters. If I understand correctly, the regions are given by equation (14) in the supplementary materials, and the optimal method is succeeds if the ON region intersect with the boundary of therapy succeeds, the optimal method is fails is the ON region intersect with the boundary of therapy fails. I suggest the authors state clearly these relations.

We apologize if our description of colors used in the state space was confusing. We have tried to clarify in the revised version by adding legends to Figures 2,3,5. The coloring convention is also explained in the corresponding Figure captions.

As the reviewer correctly points out, these colors indicate parts of the state space where the drugs should be administered at the maximum tolerable rate (yellow regions) or not at all (blue regions). This yellow/blue decomposition can be used to encode any bang-bang policy, including the optimal one (computed by our algorithm), the non-treatment policy (everything is blue), and the MTD-based policy (everything is yellow). For the optimal policy, this decomposition is indeed based on finding the maximizing value of d in formula (14) of Supplementary Material in the previously submitted version of manuscript (formula (18) in the revised version).

However, the success of treatment under a given feedback policy also depends on the ***initial state*** *of the system. E.g., in Figures 2 and 3, the optimal policy leads to "success" from* ***every*** *initial state below the ($x_G = 1 - f_b$) failure barrier; please see the lines 203–207 on page 10 of the manuscript. For many of those initial states, the success/recovery is achieved under*

the "natural dynamics" (travelling through the blue region only – without any use of drugs). In contrast, in Figure 4, all 3 policies (drugs-off, MTD-based, and optimal adaptive) are successful for only ***some*** *of the initial states. But we emphasize that such "incurable regions" (shown in green in Figure 5) are much smaller for the optimal policy.*