Peer Community In Mathematical & Computational Biology

Modelling within-host evolutionary dynamics of antimicrobial resistance

Krasimira Tsaneva *based on reviews by 2 anonymous reviewers*

A recommendation of:

Within-host evolutionary dynamics of antimicrobial quantitative resistance

Ramsès Djidjou-Demasse, Mircea T. Sofonea, Marc Choisy, Samuel Alizon *(2021), HAL, hal-03194023, ver. 4 peer-reviewed and recommended by Peer Community in Mathematical and Computational Biology* ***https://hal.archives-ouvertes.fr/hal-03194023***

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Recommendation

Antimicrobial resistance (AMR) arises due to two main reasons: pathogens are either intrinsically resistant to the antimicrobials, or they can develop new resistance mechanisms in a continuous fashion over time and space. The latter has been referred to as within-host evolution of antimicrobial resistance and studied in infectious disease settings such as Tuberculosis [1]. During antibiotic treatment for example within-host evolutionary AMR dynamics plays an important role [2] and presents significant challenges in terms of optimizing treatment dosage. The study by Djidjou-Demasse et al. [3] contributes to addressing such challenges by developing a modelling approach that utilizes integro-differential equations to mathematically capture continuity in the space of the bacterial resistance levels.

Given its importance as a major public health concern with enormous societal consequences around the world, the evolution of drug resistance in the context of various pathogens has been extensively studied using population genetics approaches [4]. This problem has been also addressed using mathematical modelling approaches including Ordinary Differential Equations (ODE)-based [5. 6] and more recently Stochastic Differential Equations (SDE)-based models [7]. In [3] the authors propose a model of within-host AMR evolution in the absence and presence of drug treatment. The advantage of the proposed modelling approach is that it allows for AMR to be represented as a continuous quantitative trait, describing the level of resistance of the bacterial population termed quantitative AMR (qAMR) in [3]. Moreover, consistent with recent experimental evidence [2] integro-differential equations take into account both, the dynamics of the bacterial population density, referred to as “bottleneck size” in [2] as well as the evolution of its level of resistance due to drug-induced selection.

The model proposed in [3] has been extensively and rigorously analysed to address various scenarios including the significance of host immune response in drug efficiency,

treatment failure and preventive strategies. The drug treatment chosen to be investigated in this study, namely chemotherapy, has been characterised in terms of the level of evolved resistance by the bacterial population in presence of antimicrobial pressure at equilibrium.

Furthermore, the minimal duration of drug administration on bacterial growth and the emergence of AMR has been probed in the model by changing the initial population size and average resistance levels. A potential limitation of the proposed model is the assumption that mutations occur frequently (i.e. during growth), which may not be necessarily the case in certain experimental and/or clinical situations.

References

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Reviews

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Evaluation round #2

DOI or URL of the preprint: *https://hal.archives-ouvertes.fr/hal-03194023*

Version of the preprint: 2

Author's Reply

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Decision by Krasimira Tsaneva, 13 Dec 2021

Dear Authors,

You have now received the second round of review(s) for your manuscript that have identified a couple of outstanding issues which need to be resolved before recommendation for publication.

Could you please address these issues in a revised manuscript and provide detailed response in due course.

Sincerely, Krasimira

Reviewed by anonymous reviewer, 18 Oct 2021

I appreciate that the authors have addressed most of my concerns and I think the paper has improved. Regarding my previous comment #4 about the Langevin equation, I think my questions (i) and (ii) were probably not very clear, so I will try to rephrase them.

In the formulation of the time dynamics in equations 2.1 and 2.2, the authors deviate from classical population genetics literature (cf. e.g. Wright, Genetics, 1931; Kimura "The Neutral Theory of Molecular Evolution", 1983). They do not cite any paper that would explain the reasoning behind these deviations, hence I consider it important that they are carefully explained and motivated.

The main deviations that I see are the following (where I am going to just focus on Eq. 2.1, since 2.2 is just a special case of 2.1):

(1) In the first term of Eq. 2.1, the authors multiply a mutation term, J(x-y), with a growth term, p(y). In the classical formulation, these are, however, two separate terms. The growth term describes the relative fitness of the genotype x (relative to the other genotypes in the population) and is proportional to p(x)*b(x). On the other hand, the (separate) mutation term is usually applied to the current subpopulation sizes, i.e. to b(x) and b(y).
(2) This leads to the second point. While the given expression contains the incoming mutations from state y to state x, it appears to be missing a term for the outgoing mutations from x to y. This term should be proportional to -J(y-x)*b(x).

Since these questions pertain to the fundamental model underlying the paper, I think it is important to resolve them before recommendation for publication. In particular, the presented results might change under the canonical population genetics formulation of the model.

Evaluation round #1

DOI or URL of the preprint: *https://hal.archives-ouvertes.fr/hal-03194023*

Version of the preprint: 1

Author's Reply

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Decision by Krasimira Tsaneva, 13 Jun 2021

Dear Authors,

As with all preprints that have been selected for potential recommendation by the PCI Maths & Comp Biol, your manuscript was reviewed by members of the managing board of PCI Math Comp Biol and by several independent reviewers. The reviewers appreciated the attention to an important topic. Based on the reviews, we are likely to consider this preprint for recommendation, providing that you modify the manuscript according to the review recommendations.

In particular, this manuscript deals with a complex combination of detailed modelling and biomedical interpretations, and the exact combination of model parameters and biological significance that give rise to

each finding are not always immediately obvious to the reader. It is crucial that sufficient detail is provided to allow these simulations (and their results) to be replicated. Hence, I encourage the authors to make a concerted effort to simplify, clarify and improve the comprehensibility of the methods for each set of simulations. I would also strongly recommend that their code is made available online, to further this aim.

Please prepare and submit your revised preprint within 30 days. If you anticipate any delay, please let us know the expected resubmission date by replying to this email.

When you are ready to resubmit, please provide the following:

[1] A letter containing a detailed list of your responses to all review comments, and a description of the changes you have made in the manuscript. Please note while forming your response, if your article is accepted, the peer review history will be made publicly available. The record will include editor decision letters (with reviews) and your responses to reviewer comments.

[2] Two versions of the revised manuscript: one with either highlights or tracked changes denoting where the text has been changed; the other a clean version (uploaded as the manuscript file).

Important additional instructions are given below as part of the reviewer comments.

We hope that our recommendation process has been constructive so far, and we welcome your feedback at any time. Please don't hesitate to contact us if you have any questions or comments.

Sincerely,

Krasimira Tsaneva-Atanasova

PCI Maths & Comp Biol recommender

Reviewed by anonymous reviewer, 14 May 2021

Overview: This paper deals with the construction and analysis of a mathematical model to understand the efficacy of chemotherapy on bacterial growth and evolution. The authors focus on non-binary levels of resistance (i.e. resistance that is continuously changing above and below the minimum inhibitory concentration (MIC)). They use their integro-differential equation mdodel to provide quantitative descriptions of bacterial growth and population size and the evolution of its level of resistance.

General comments:

This is a pertinent topic with potential extensions outside of bacterial growth (e.g. in cancer and cancer therapy). A continuous description of the level of evolved resistance is a nice construction to better understand how resistance is established given chemotherapy. The paper is sometimes hard to follow, and would benefit from clearer statements of biological interpretation. There is some discussion of evaluating potential treatments given the analytic, but I find that this was not examined with enough of an eye for actionable suggestions. Of note, I evaluated primarily the main text (outside of appendices).

1) Is it true that A(C)->infinity as C-> infinity? It's usually thought of as saturating at a threshold level of activity (what does it mean to have infinite antimicrobial activity?).

2) "From this intuitive approach, it follows that there exists C* in (0,infinity) such that A(C*) is equal to the intrinsic growth of a bacterial population, all else being equal. This threshold concentration at which a bacterial population does not grow in vitro is called the Minimum Inhibitory Concentration (MIC)." The relationship between A(C*) being equal to the intrinsic growth rate and the MIC isn't clear to me, and this statement seems to contradict a later statement providing the precise definition of MIC. Suggest clarifying/adding details.

3) I found it a curious choice to let x (the level of resistance) be a real number, such that there is "negative" resistance. The intuition behind this wasn't clear, and it leads to some difficulties understanding the meaning of various model terms. For example, k(x) goes to infinity as x-> -infinity so x<0 is highest resistance? Clarifications may be needed.

4) How were parameter values determined For example, why is the intrinsic growth rate of the reference sensitive strain 0.95p_m? References are noted in the column headers of Table 1, but none are given. This comes up again in Fig. 2 and on, it is important to understand where chosen parameter values come from.

5) In Eq. 3.4, should the x for the feedback of resident x be interpreted the same as level of resistance x?

6) In Fig. 3, I suggest using a text label for (1-(p_1/p_m))^-1 and (1-(p_0/p_m))^-1 to help the reader.

7) "Our analysis emphasizes that treatment strategies that promote synergy between host immunity (mu) and the antimicrobial activity (k_0) are a key component in achieving our TTO objective." Host immunity is not generally something that is known when determining treatment strategies. It would be nice to explore more clinically-actionable scheduling guided by the results of the analysis. For example, what are the effects of intermittent dosing or non-continuous dosing given the chemotherapy's pharmacokinetics?

Minor comments:

1) There are typos throughout that should be corrected:

-"...example of such impact, which is the evolution..." suggest "example of such impact, the evolution..."

-"...two or three order of magnitudes of antimicrobial concentrations." missing a) after concentrations

-"...in the case of Neisseria gonorrhoeae" missing a , after gonorrhoeae

-"killing rate k(x) of the bacterial population with resistance level x due to the exposure of an antimicrobial" should it be "killing rate k(x) of the antimicrobial on the bacterial population with resistance level x"?

-caption to Fig. 1: "rihgt" should be "right"

-caption to Fig. 2: "os" should be "of"

2) I would suggest reordering panel figures to have A, B, C on top and D, E on the bottom (or something similar).

Reviewed by anonymous reviewer, 09 Jun 2021

In this manuscript, the authors provide an analysis of the dynamics of resistance evolution in bacterial populations exposed to a chemotherapy treatment. In the model, resistance is treated as a continuous random variable and the variance in the distribution of resistances among the bacterial population is considered explicitly. I think the described formalism is useful, particularly compared to approaches in which resistance is considered a binary trait. It allows the authors to make quantitative statements about expected trajectories of bacterial populations with respect to treatment success (i.e. eradication of the bacterial population) and asymptotically evolved resistance levels. However, I see some open questions regarding the modeling assumptions.

1. b(t,x) and B(t) are sometimes denoted as population densities and sometimes as population sizes. It is necessary to define this very clearly and give the value range in Table 1.

2. How is the functional form of the killing rate k(x) (p. 3) motivated?

3. How is the functional form of the intrinsic growth rate p(x) (p. 3) motivated? What about the scenario in which population size is constant and p(x)=0?

4. Eq. (2.1) is the Langevin equation describing the dynamics of b(t,x). Regarding its formulation, several questions arise:
i. In the first term, which describes the influx into sub-population b(t,x) due to mutations from sub-populations b(t,y), what is the role of the intrinsic growth rate p(y)? This somehow makes sense for y=x, which corresponds to the influx to b(t,x) due to growth of sub-population x (i.e. when no mutations happen). However, otherwise it appears that mutations from y!=x can only occur proportionally to the growth rate p(y), whereas in reality even in a sub-population y of constant size mutations can be introduced (as some cells die and others divide, and the latter is associated with the mutational process).
ii. The equation does not contain a term that accounts for mutations away from sub-population x

(proportional to J(y-x)*b(t,x)).
iii. How is the pre-factor (1+B(t))^alpha motivated? What is the range of B(t) (see point 1)? What is the meaning of the scaling constant alpha? What is the impact of alpha on all downstream results?
iv. The equation does not contain any noise term. However, b(t,x) can become small enough for stochasticity to matter. How robust are the results under such random fluctuations?

5. It appears that Eq. (3.4) is incorrect. Do the authors mean the reproduction number of the rare mutant strategy on the LHS? Otherwise, it appears that unity should be subtracted on the RHS.

6. Eq. (3.5): Based on Eq. (C.6)ff., it appears that the substitution used when going from Eq. (3.4) to Eq. (3.5) only holds when R_0(x)>1. Is this always satisfied? For example, if x is the resistance of the reference sensitive strain, certainly its R_0(x)<0 under chemotherapy. Another question in this context is how was Eq. (C.7) derived?

7. In Figs. 4 and 5, it is a bit confusing that even though m_0 is supposedly the same in all cases (m_0=0.05), the size of the bacterial population (green filled curve) in the panels showing drug efficiency is varying.

8. p. 12, paragraph 5: "This phenomenon is in accordance with the strong relationship between the rate of emergence mutant and the antimicrobial dose [10, 11]." If I interpreted the phrasing correctly, it appears that the authors here conflate the probability with which resistant mutants arise (i.e. treatment failure) with the resistance, x, conditioning on treatment failure. Figure 3 shows, however, that the probability of treatment failure monotonically decreases for increasing dosage.

9. What is meant by "In addition to the death and birth rates, bacterial population resistance level mitigates the antimicrobial activity of the drug" (p. 2)? I do not quite see how resistance has effects outside of modulating birth and death rates.

10. The grammar (see e.g. last paragraph on p. 2) and orthography of the manuscript need some improvement. There are a lot of extra plurals and missing definite articles.