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Migrastatic therapy as a potential game-changer in adaptive cancer treatment

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Adaptive therapy, which anticipates and counters the evolution of resistance in cancer cells, has gained significant traction, especially following the success of the Zhang et al.'s protocol in treating metastatic castrate-resistant prostate cancer. While several adaptive therapies have now advanced to clinical trials, none currently incorporates migrastatics, i.e. treatments designed to inhibit cancer cell metastasis. In this study, we propose integrating migrastatics into adaptive therapy protocols and evaluate its potential benefits through a spatial game-theoretic model. Our results demonstrate that combining adaptive therapy with migrastatics effectively delays the onset of metastases and reduces both the number and size of metastases in most cancer scenarios analyzed. Including migrastatics to adaptive therapy not only extends the time to the first metastasis, but also enhances the overall efficacy of adaptive therapies. Our findings suggest a promising new direction for cancer treatment, where adaptive therapy, in combination with migrastatic agents, can target both the evolution of resistance and the metastatic spread of cancer cells.

Cancer represents the second leading cause of death worldwide. Moreover, recent trends show that cancer may become the first leading cause of death by 2030[1,2]. Cancer treatment typically targets uncontrolled cancer cell proliferation with the aim to eradicate tumors[3–5].

In standard of care, patients are typically given the maximum tolerated dose (MTD), which is the highest dose that a mean patient can handle without experiencing intolerable toxicity[4,6,7]. While MTD-based therapy offers survival benefits, it often comes with severe side effects. Moreover, recurrence is almost inevitable due to the emergence of therapeutic resistance[8–12]. To address these challenges, adaptive therapy (AT), also known as evolutionary therapy, has been proposed[13–20]. AT involves adjusting treatment dosing and timing based on cancer's response to therapy. Mathematical models informed by known cancer biology and data have been crucial in its development[5,16,18,21–23]. Often, AT aims at maintaining a sufficient population of drug-sensitive cells, enabling them to outcompete drug-resistant cells when treatment is not applied, and hereby control the tumor burden longer. A pilot example of AT is Zhang et al.'s protocol in metastatic castrate-resistant prostate cancer (mCRPC)[24,25]. In this clinical trial, mCRPC is treated with MTD until the total tumor burden is halved compared to its initial size. Upon reaching this threshold, the treatment is stopped and the tumor is allowed to regrow to its original size, allowing for competition between drug-sensitive and resistant cells. When the total tumor burden reaches its initial size, treatment with MTD is reinstated and a new treatment cycle begins. Zhang et al.'s protocol aims to control the tumor burden through limiting the development of uncontrollable drug resistance rather than cancer eradication and nearly triples patients' time to progression [24,25].

Existing AT protocols aim at tumor containment, control or eradication[16,18,21,22,24,26], and they do not target spread of the disease. However, up to 90% of mortality in solid tumors is due to metastasizing rather than cancer growth alone[27,28]. In order for the primary tumor to successfully metastasize, cancer cells need to complete a number of sequential events, the so-called invasion-metastatic cascade[29–31].

Conventional cytotoxic and/or cytostatic therapeutics target uncontrollable proliferation, which ultimately results in Darwinian selection of resistant clones within the tumor[32]. These approaches ignore the invasive

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potential of cancer cells, and may support metastasizing[33]. To effectively treat cancer, cancer cell motility and invasion need to be successfully targeted.

Therefore, inhibiting cell motility via migrastatics, i.e. drugs targeting invasion and migration, has been proposed as a novel therapeutic approach[34–36]. Unlike cytotoxic drugs that target proliferation, migrastatics interfere with invasion mechanisms, addressing cancer's motility to prevent metastasis.

Moreover, migrastatic strategies possess some significant advantages compared to cytotoxic therapies. While cytotoxic therapy can result in tumor shrinkage, the migration capacity and metastatic potential of resistant cells are not affected. Although the migrastatics are neither cytotoxic nor cystostatic they significantly reduce the motility of cancer cells. Thus, one of migrastatics' most significant advantages lies in the potential reduction of high-dose cytotoxic treatment.

As novel drugs, migrastatics do not have a defined administration regime yet, and since their effect is distinct from that of cytotoxics, it is crucial to adopt a new approach for their administration. Three specific regimens of therapeutic use of migrastatic drugs have been proposed to combat the formation and progression of metastases[36]. Firstly, the neoadjuvant/adjuvant therapy suggests the administration of migrastatics before and after surgical procedures. The inclusion of migrastatics seeks to counteract and/or to minimize the risk of tumor cells initiating a metastatic program as a result of pro-invasive changes in their environment caused by wound-healing processes (pro-migratory effect of cytokines) and post-operative treatments (anticoagulants)[37]. Secondly, the combination of cytotoxic and migrastatic drugs is proposed to effectively reduce the development of metastases. Combining these two treatments aims to target both the primary tumor and the migratory potential of cancer cells, reducing the likelihood of metastatic spread. Lastly, migrastatic therapy aims to minimize the long-term risk of metastasis. It can be used alone to slow down or even prevent metastasis. Alternatively, it can be used in combination with either non-systemic treatment targeting only the primary tumor, such as surgery or radiotherapy, or in combination with immunotherapy[38].

We believe that incorporating migrastatics into both classical and adaptive therapy protocols has strong potential to control tumor growth while simultaneously preventing metastasis. To demonstrate the potential of including migrastatics into the existing treatment protocols, we utilize a spatial game-theoretic model that is conceptually similar to that of You et al. (2017)[39]. The model allows us to examine a potential impact of applying both cytotoxic and migrastatic treatments and that of applying migrastatic treatment only. As treatment strategies, we investigate both the standard of care and an AT approach.

Results

Migrastatics prevent metastases and tumor growth

The spatial game-theoretic model has been tested with 5 alternative fitness matrices, representing potential interactions between treatment sensitive and resistant cells. For details, see methods. Firstly, we evaluate the effect of migrastatics alone with these five fitness matrices. Figure 1 summarizes this effect for fitness matrix A_1, while Appendix A summarizes the outcomes with the other fitness matrices. In all case studies, including migrastatics slows down the increase of total tumor burden when compared to no treatment (Fig. 1A). This is likely due to the limitation of space when the probability of migration is lowered, making the placement of an offspring less likely. As expected, with migrastatics, the number of metastases is lower, while time to the first metastasis is longer (Fig. 1B). In addition to a lower total tumor burden and later metastasizing, the formed metastases contain less cells (Fig. 1C).

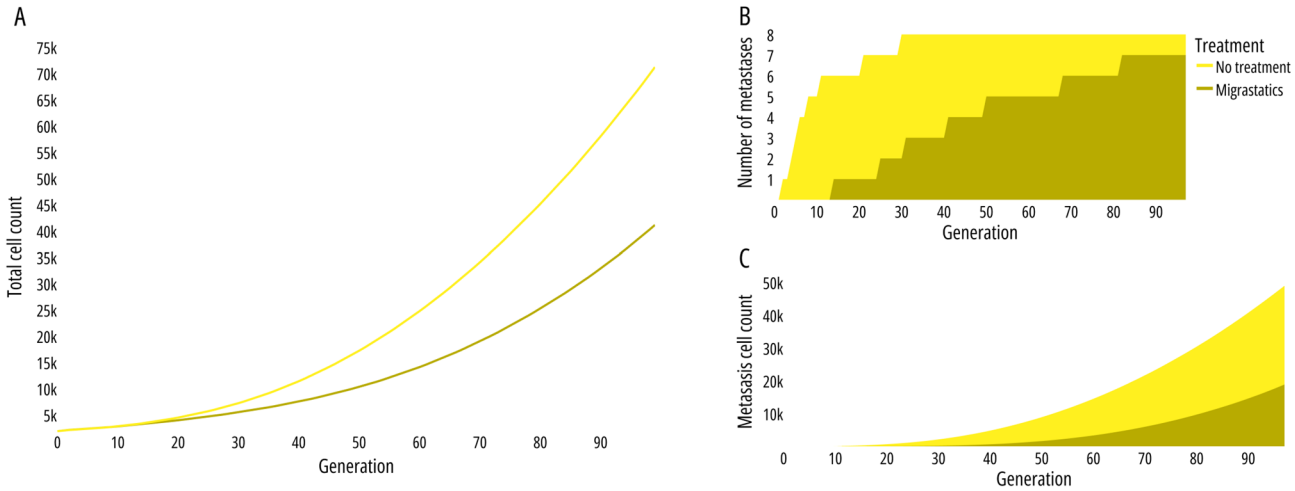

Fig. 1. Dynamics of cancer cells under migrastatic treatment for the case study with the fitness matrix A_1: Migrastatic treatment reduces the total tumor burden (**A**) by decreasing both metastasis formation (**B**) and size of metastases (**C**). Time to first metastasis increases, and average metastasis size decreases. In all panels the results are averaged over 50 simulations.

Combining adaptive therapy and migrastatics hinders metastasizing

Hereafter we analyze the effect of migrastatics combined with cytotoxic treatments. Firstly, we note that the addition of migrastatics to Zhang et al.'s AT protocol does not alter the tumor burden's expected oscillatory behavior in all evaluated cases (Figs. 2, 3, 4, 5 and 6).

In all but one of the cases AT prolongs time to progression. In the case of the fitness matrix A_5, AT becomes ineffective around the 20th generation, due to all sensitive cells being killed by the cytotoxic drugs (Fig. 3B). This is in correspondence with the fully resistant ESS of this fitness matrix. After the 20th generation, the increase of the total tumor burden of MTD and AT per generation becomes similar, and as the cell population at that generation is larger with AT, the total tumor burden of AT becomes higher than that of MTD.

With the fitness matrix A_4, AT still facilitates oscillations at the end of the simulation (Fig. 2B) and cells sensitive to the cytotoxic treatment are more frequent than resistant cells at this generation (Fig. 2A). Similarly to the case of the fitness matrix A_5, the addition of migrastatics to the cytotoxic treatment prolongs time to the first metastasis. Metastases occur first in conditions treated with AT, followed by MTD and last in MTD combined with migrastatics. With both fitness matrices A_4 and A_5, the average number of cells per metastasis when migrastatics are applied is low. In the case of the fitness matrix A_4, metastases occur earlier when migrastatics are combined with AT, followed by migrastatics combined with MTD. However, at the end of the simulation, there are no sensitive cells present for MTD with migrastatics, while they are still present when AT and migrastatics are combined. Additionally, at this generation, both the number of metastases and the cell growth are lower when AT is combined with migrastatics, compared to those of MTD with migrastatics.

In the case of the fitness matrix A_3, only resistant cells remain halfway through the simulation (Fig. 4A) and AT becomes ineffective (Fig. 4B). In the two other anti-coordination cases, A_1 and A_2 (Figs. 5 and 6), the application of AT prolongs time to progression, as sensitive cells are still present halfway through the simulation, with total tumor burden still oscillating at the end of the simulation for the case of A_1 (Fig. 5A). In all cases where sensitive and resistant cells are expected to coexist at the ESS, migrastatic treatment prolongs time to metastasizing, and the final average metastasis size is smaller, with best results for AT combined with migrastatics.

Discussion

The aim of this study was to identify a treatment strategy that not only aims to inhibit tumor growth while limiting the number of resistant cancer cells but also reduces the formation of metastases. This was to demonstrate a high potential that migrastatic treatment may have, especially in combination with AT treatments.

We have demonstrated that Zhang et al.'s AT protocol[24,25] is successful in postponing time to progression when compared to the standard of care for most scenarios studied. This is because this protocol prevents outgrowth of resistant cell types and successfully facilitates the survival of drug-sensitive cancer cell populations. However, due to the high total tumor burden the Zhang et al.'s protocol maintains, it may promote cancer cell migration and the formation of metastases. This often results in earlier metastasizing of the tumor and larger

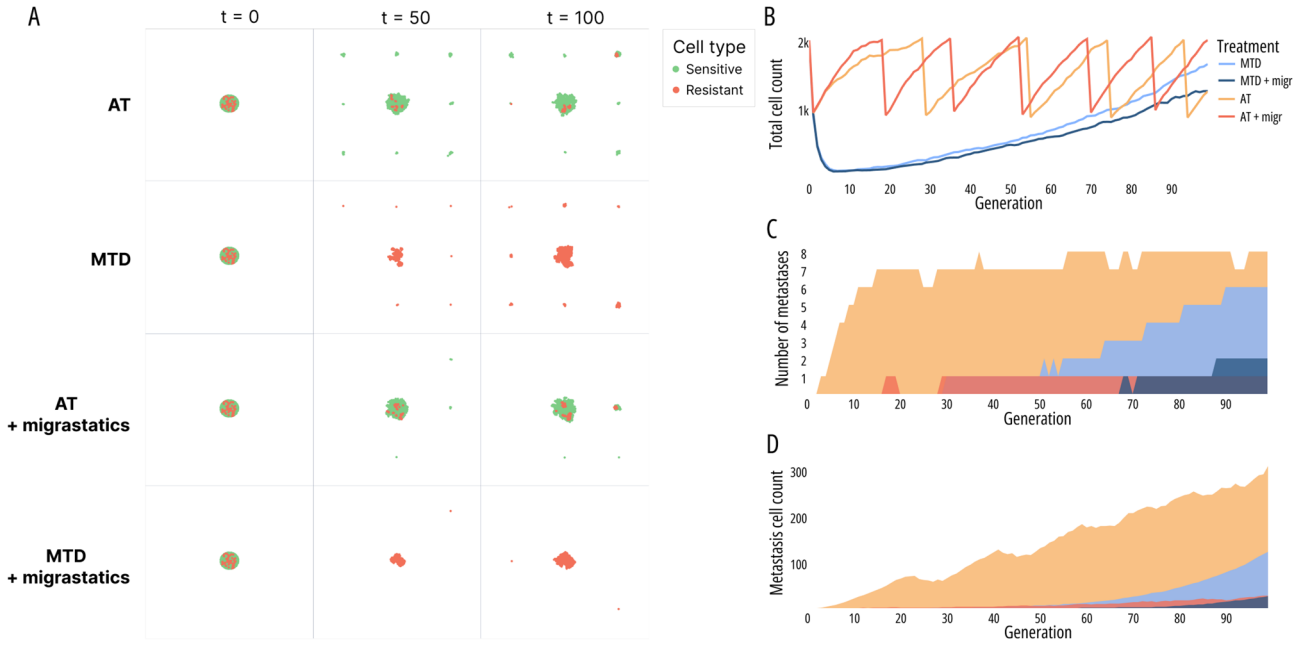

Fig. 2. Cancer cell growth with the fitness matrix A_4 with four treatments combining Adaptive Therapy (AT) or Maximum Tolerable Dose (MTD) with and without migrastatics. (**A**) Reduced metastases and persistence of sensitive cells with AT. (**B**) Migrastatics do not inhibit overall growth. (**C**) Delayed and reduced metastases, especially with AT. (**D**) Smaller, delayed metastases with migrastatics. Figures in panels **C** and **D** are averaged over 50 runs.

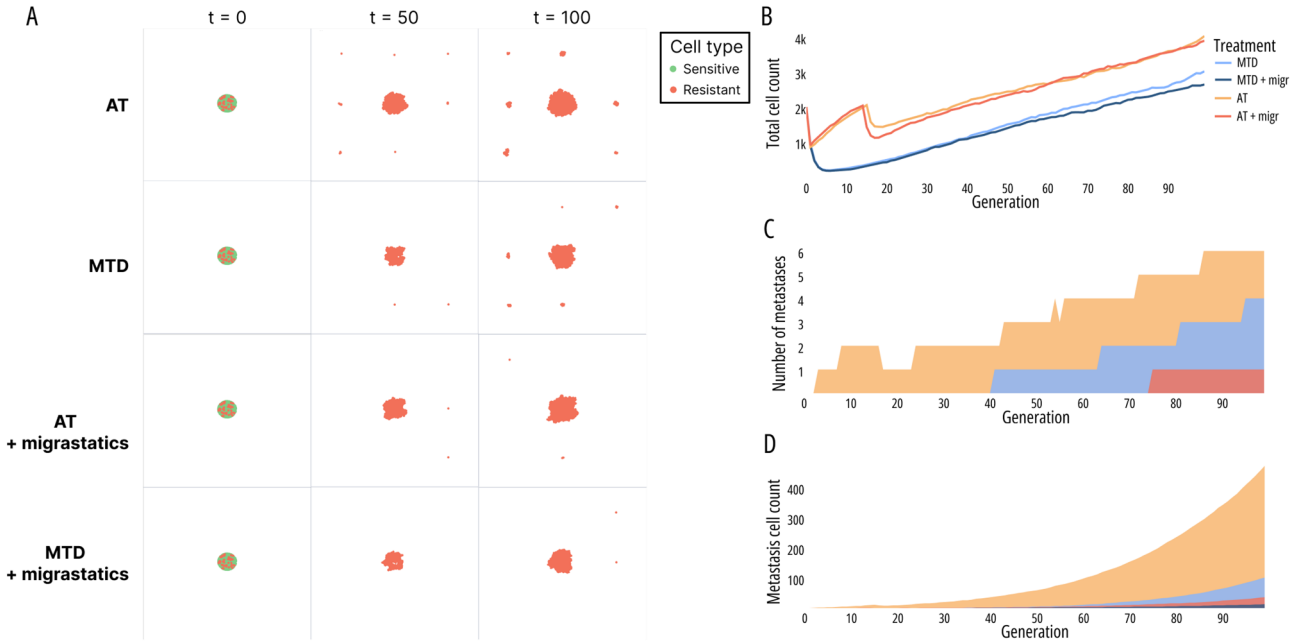

Fig. 3. Cancer cell growth with the fitness matrix A_5 with four treatments combining Adaptive Therapy (AT) or Maximum Tolerable Dose (MTD) with and without migrastatics. (**A**) Reduced metastases. (**B**) Migrastatics do not inhibit overall growth and AT fails with tumors becoming fully resistant. (**C**) Delayed and reduced metastases with migrastatics, earlier but fewer metastases with AT. (**D**) Smaller, delayed metastases with migrastatics. Figures in panels **C** and **D** are averaged over 50 runs.

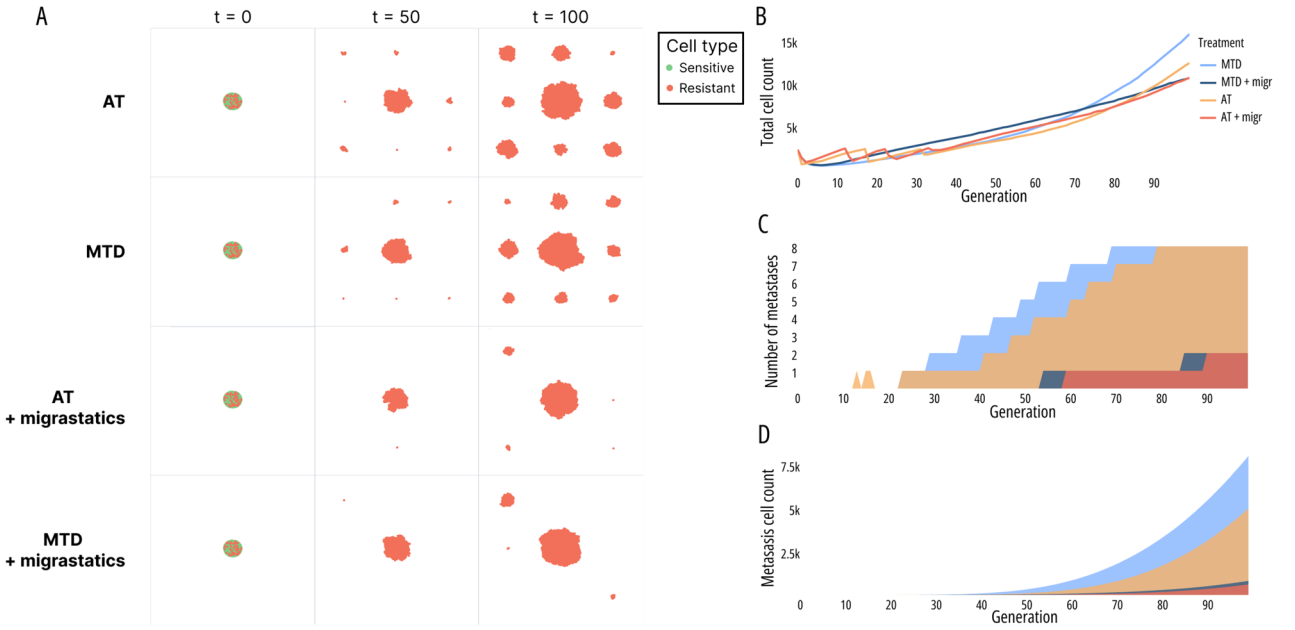

Fig. 4. Cancer cell growth with the fitness matrix A_3 and treatments combining Adaptive Therapy (AT) or Maximum Tolerable Dose (MTD) with and without migrastatics. (**A**) Reduced metastases with migrastatics. (**B**) Migrastatics do not inhibit overall cancer growth; AT fails with completely resistant tumors. (**C**) Delayed and reduced metastases with migrastatics. (**D**) Smaller, delayed metastases with migrastatics. Figures in panels (**C**,**D**) are averaged over 50 runs.

metastases. These results point to the need to expand the scope of adaptive therapies beyond drug resistance alone and include targeting cancer cells' invasiveness.

When migrastatics were added to both the MTD and AT treatment protocols, we observed both a decrease in the number and size of metastases and an increase in the time to metastasis for all cases evaluated here.

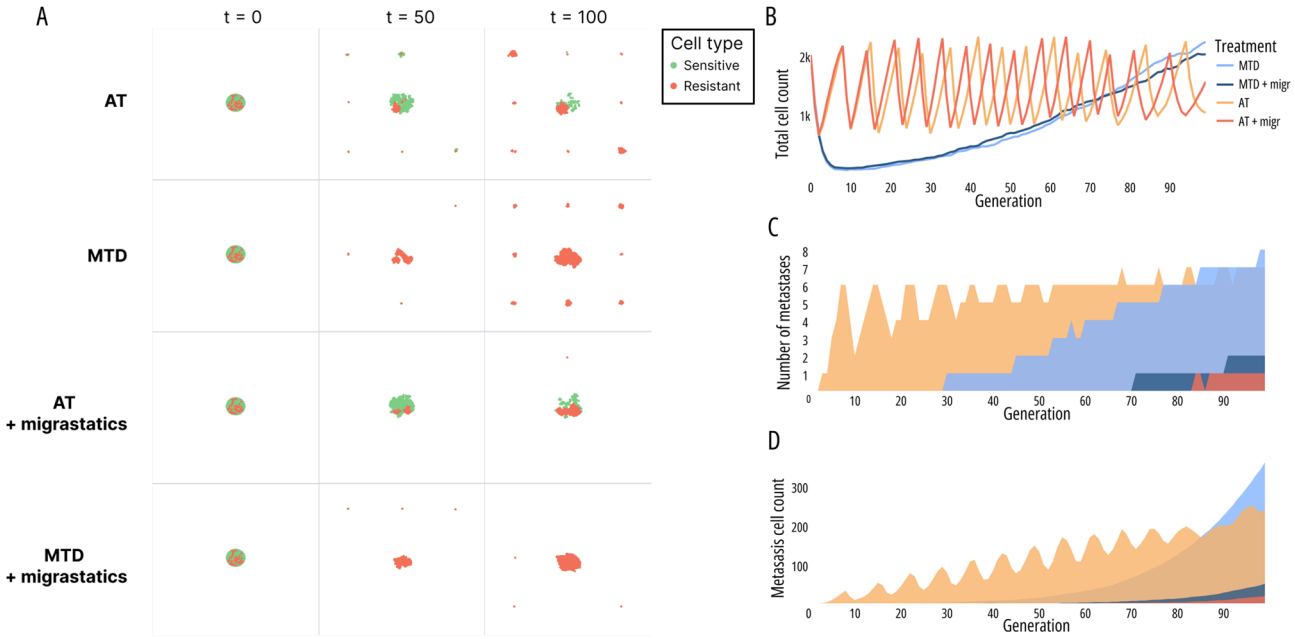

Fig. 5. Cancer cell growth with the fitness matrix A_1 under four treatments: Adaptive Therapy (AT), Maximum Tolerable Dose (MTD), with and without migrastatics. (**A**) AT preserves sensitive cells; MTD leads to resistance. In all treatment strategies, migrastatic treatment reduces metastasis. (**B**) Migrastatics does not affect overall tumor growth. (**C**) Delayed, reduced metastasis with migrastatics. Metastases form earlier with AT. (**D**) Smaller, delayed metastases with migrastatics, smaller metastates with AT. Results in panels **C** and **D** are averaged over 50 runs.

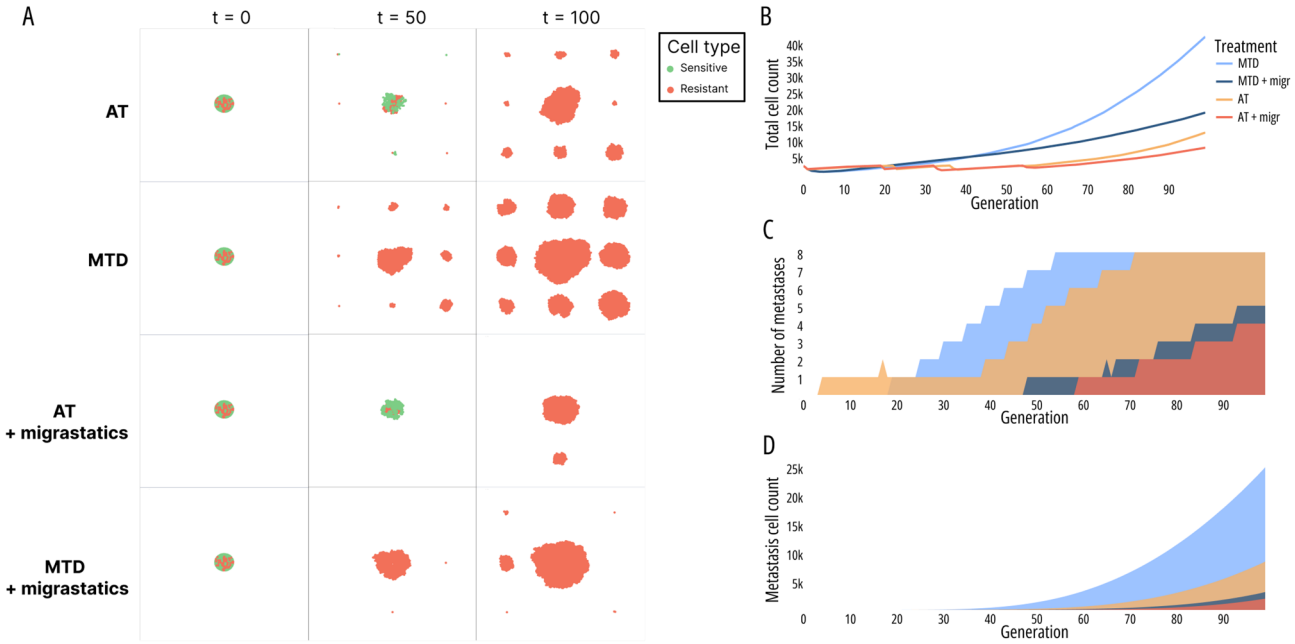

Fig. 6. Cancer cell growth with the fitness matrix A_2 under four treatments: Adaptive Therapy (AT), Maximum Tolerable Dose (MTD), with and without migrastatics. (**A**) Migrastatics reduces metastasis formation. (**B**) Migrastatics inhibits overall cell growth; AT fails after three cycles due to resistance. (**C**) Migrastatics delays and reduces metastasis; earlier but fewer metastases with AT. (**D**) Migrastatics leads to smaller, delayed metastases, with the fewest cells in AT combined with migrastatics. Figures in panels **C** and **D** are averaged over 50 runs.

Importantly, adding migrastatics does not interfere with the dynamics of total tumor burden and the oscillatory behavior of AT. For fitness matrices where AT prolonged time to treatment failure, addition of migrastatics to the AT improved the time to progression, number of metastases, and time to the first metastasis. Together, our modeling results demonstrate that the combination of migrastatics with AT can help target both tumor resistance and metastasizing.

While there is implicitly no reason for the prevalence of cells which would eventually get resistant to migrastatics, because such resistance would not give them a proliferative advantage[32,36,40], the synergistic effect with AT will have yet to be validated in preclinical and clinical studies. Initially, the combination of AT with migrastatic therapy will be tested in a 3D spheroid model[41], and subsequently in a suitable mouse model of metastasis, tailored for testing of migrastatic drug efficacy, e.g., model from[42]. Data collected during these experimental studies can be used to validate our models and optimize AT enhanced by migrastatics.

Our model assumes a fixed location of the primary site and potential metastatic sites. Future studies should validate our results when assuming varying potential number of metastases as well as varying locations of both the primary site and potential metastatic sites. The location of the primary tumor may be a determining factor to where metastases will form and the metastasis locations are correlated with patient survival[43,44].

In our game-theoretic model only resistance to the cytotoxic drug is assumed. This is because we expect that little to no resistance against migrastatics will develop in the tumor cell population[32]. This is hypothesized because while standard drugs drive selection of resistant cell populations by targeting cell proliferation, migrastatics do not disrupt proliferative signaling. Therefore, as migrastatics are not expected to reduce tumor growth, no proliferative advantage would be gained by migrastatic resistance, limiting the enrichment for migrastatic resistant cell types in the tumor environment. Our future work will validate this hypothesis in *in vivo* and *in vitro* studies.

In the present model, sensitive and resistant cancer cell types are fixed and no transitions between these two cell types occur. This deliberate simplifying assumption allows us to focus on competition between pre-existing resistant and sensitive cells, a scenario commonly used in spatial agent-based models of cancer[45,46]. In general, phenotypic switching or mutation can be incorporated by allowing probabilistic type of changes during the birth–death process, as is standard in many spatial ABMs[47]. While our current formulation captures treatment effects only through phenotype-specific birth and death rates[39] and migration, future extensions could include quantitative resistance or mixed qualitative–quantitative resistance, as well as switching along fitness gradients[23,48–50]. We expect that introducing low-rate transitions between sensitive and resistant cancer cells would modulate the relative frequencies of the phenotypes but would not alter the qualitative treatment outcomes observed here.

The five fitness matrices (A_1–A_5) used in the current study were chosen to represent qualitatively distinct evolutionary games relevant to cancer eco-evolutionary dynamics. Matrices A_1–A_3 instantiate anti–coordination games with mixed ESSs, whereas matrices A_4 and A_5 represent coordination games with pure ESSs. The latter instantiate the same type of games analyzed in recent works on coordination games in cancer[51–53] . Our numerical choices were designed to instantiate these distinct game classes rather than to represent one specific biological system. We do not expect that moderate variations in the fitness matrix entries alter the qualitative treatment ranking or the advantages of combining migrastatics with adaptive therapy, because the evolutionary game types remain the same.

While our model makes assumptions regarding resistance and initial conditions, these choices were selected to represent key biological mechanisms at a tractable level of abstraction. In addition to resistance structure, two further parameters are particularly relevant for interpreting treatment outcomes: the effectivity of the cytotoxic drug and the initial tumor size. To evaluate the robustness of our findings, we examined the influence of these two assumptions. In our baseline simulations, cytotoxic therapy removed 60% of sensitive cells per generation, reflecting a strong but non-eradicating drug response under MTD-like dosing, while resistant cells remained unaffected. This value was chosen to represent substantial therapeutic pressure without collapsing competitive dynamics and an average affect of treatment. Importantly, this kill fraction lies within the previously reported biologically plausible range of cytotoxic effectivity (40–90%)[54]. Moreover, changing the cytotoxic effectivity within this range produced qualitatively similar outcomes. Because the model is not tailored to any specific cancer type or drug, we consider this value of 60% as a general and biologically plausible magnitude of the cytotoxic effect[55].

Likewise, all simulations were initiated with 2,000 cells (97.5% sensitive, 2.5% resistant), representing a small heterogeneous tumor with a pre-existing resistant subpopulation. Sensitivity analyses across different initial tumor sizes did not alter the relative superiority of migrastatic-augmented adaptive therapy, indicating that our conclusions are robust to variation in initial conditions. Together, these results show that the qualitative advantage of adding migrastatics to adaptive therapy does not depend strongly on the magnitude of cytotoxic efficacy or starting tumor size. This robustness strengthens confidence that the combined strategy may remain effective under realistic biological variability.

The fitness matrices used here are chosen to describe qualitatively different scenarios and demonstrate the effect of different treatments in such scenarios. These results show that AT can be successfully applied in cases of games with mixed-strategy ESSs. However, when resistant cells have the highest benefit from interacting with their own type, compared to the proliferation probabilities of sensitive ones, AT does not improve time to progression when compared to MTD. Here the resistant cells outcompete the sensitive cells and the tumors become fully resistant, causing earlier treatment failure.

However, even when AT is ineffective, we demonstrated that addition of migrastatics to the standard cytotoxic treatment is still effective in reducing metastases. Moreover, one can consider other forms of AT than Zhang et al.'s protocol, such as double-bind or extinction multi-drug evolutionary therapies[15,56], which will likely be

more effective and can still be combined with migrastatics. Treatment optimization to choose the best treatment timing and dosing using optimal control theory is also a potential next step of our research[57–59].

A valuable direction for future work is to parameterize our model directly through *in vivo* and *in vitro* data. Many of the parameters, such as proliferation and death rates, resistance acquisition probabilities, and migration probabilities, can be derived from existing experimental setups. For example, migration rates can be informed by spheroid invasion assays or in-vivo tracking via intravital microscopy[60], resistance rates can be estimated from fluctuation assays or relapse kinetics, and frequency-dependent fitness values can be measured using game assays in co-culture experiments[53,61,62]. Agent-based models have also been calibrated to image-based tumor patterns[63] and experimental metastasis data[64]. Incorporating such empirical parameterization into our framework will enhance its clinical interpretability and predictive power.

In our simulations, we initiated the primary tumor with 2000 cells, representing a small but spatially structured neoplastic population. This magnitude is comparable to typical seeding densities used in 3D in vitro tumor models, such as spheroid and organoid assays, where 1000–3000 cells per well are commonly used and 2000 cells often serve as a standard seeding density for robust spheroid formation and invasion assays[65–67]. Although larger initial tumors could in principle be simulated, increasing N_0 substantially raises computational cost while not altering the qualitative behavior: sensitivity analyses showed that the qualitative outcomes regarding treatment effect and the benefits of combining migrastatics with adaptive therapy remain unchanged. This robustness reflects that the eco-evolutionary dynamics in our model are governed primarily by local interaction structure and spatial competition, which scale consistently with system size.

We have demonstrated that by combining Zhang et al.'s AT protocol[24] with migrastatics both resistance and metastasis can be controlled longer and treatment failure is hereby delayed. This points to a promising new treatment strategy combating both the proliferative and invasive aspects of cancer. Future work should focus on extending the current model and validating these findings with *in vivo* and *in vitro* data, similarly to how it has been done for other mathematical models[53,61,68,69].

Methods

To examine the potential of migrastatics in the standard of care and adaptive treatments, we have developed a continuous-space evolutionary game-theoretic model of metastatic cancer growth and its spread to potential metastatic sites. This model allows us to explore the impact of cytotoxic and migrastatic treatments on the tumor growth, formation of metastases, and composition of these metastases. The model includes the primary tumor and eight possible metastatic sites. The cancer cells are either sensitive or resistant to the cytotoxic treatment and may migrate and potentially form metastases. Our model includes both frequency-dependent and density-dependent selection, as cancer cells' probability of producing daughter cells is given by their pairwise interaction with other cells within their neighborhood and is captured by the fitness matrix. Different fitness matrices correspond to different scenarios regarding the likelihood of sensitive cancer cells being able to outcompete the resistant ones with and without treatment, also seen through different evolutionarily stable strategies (ESSs). We select examples with different fitness matrices for our case studies, to demonstrate the qualitative results corresponding to different assumptions on cancer cells' competition. Our spatial game-theoretic model was implemented in Java, version 11.0.

Model dynamics

Our continuous-space model contains one primary tumor site with 8 possible migration sites, Figure 7 shows a graphical overview of our spatial game-theoretic agent-based model. The field is defined as a square $[-L, L] \times [-L, L] \subset \mathbb{R}^2$ where L is sufficiently large to avoid boundary effects. The primary site is in the center of the field and is defined as a disc of a predefined radius with a center at (0, 0). We assume that metastases can potentially form at 8 metastasis sites, which are located at discs with a predefined radius equal to the interaction radius and placed in the field. While theoretically, metastatic sites could be put at any position in the field, in our simulations we assume that their centers are at predefined locations. See Table 1 for all parameter values.

At the onset of the simulation, a predetermined number of cells are randomly distributed within the primary site, comprising a predefined fraction of cells sensitive (type *S*) and resistant (type *R*) to cytotoxic treatment. Of these cells, a predefined fraction is selected as invasive and can potentially migrate to one of the eight metastatic sites, or from one of the migration sites to the primary tumor. The same starting configuration, i.e. the placement of the cells of the primary site, is used for all case studies.

Interactions take place in generations, similarly to You et al. (2017)[39]. Within each generation, each cell in the field is selected as a focal cell in a random order and undergoes the following steps:

1. *Death*: The focal cell may die according to a predefined death probability, which is equal for all cells in the simulation. If the cell survives, it proceeds to the next step.
2. *Migration*: If the focal cell survives and possesses the property to be invasive, it migrates to a randomly selected site among the eight possible metastatic sites with a predefined probability. Upon migration, a predefined survival probability determines the cell's survival at the new location. Surviving cells can proceed to the next step.
3. *Proliferation*: In the final stage of each generation, cells have the potential to proliferate. To do so, an interaction partner is randomly selected from the focal cell's interaction neighborhood, which is defined as a disc centered on the focal cell with a radius equal to the interaction radius. Proliferation occurs only if the total number of cells within this neighborhood remains below the predefined local carrying capacity. The probability of the focal cell producing an offspring of its own type is determined by the fitness matrix $A = (a_{ij})_{2\times 2}$. For a focal cell of type i interacting with a partner of type j, where $i, j \in \{S, R\}$, the element a_{ij} in the matrix A defines the probability that the focal cell generates a daughter cell of its own type i. When

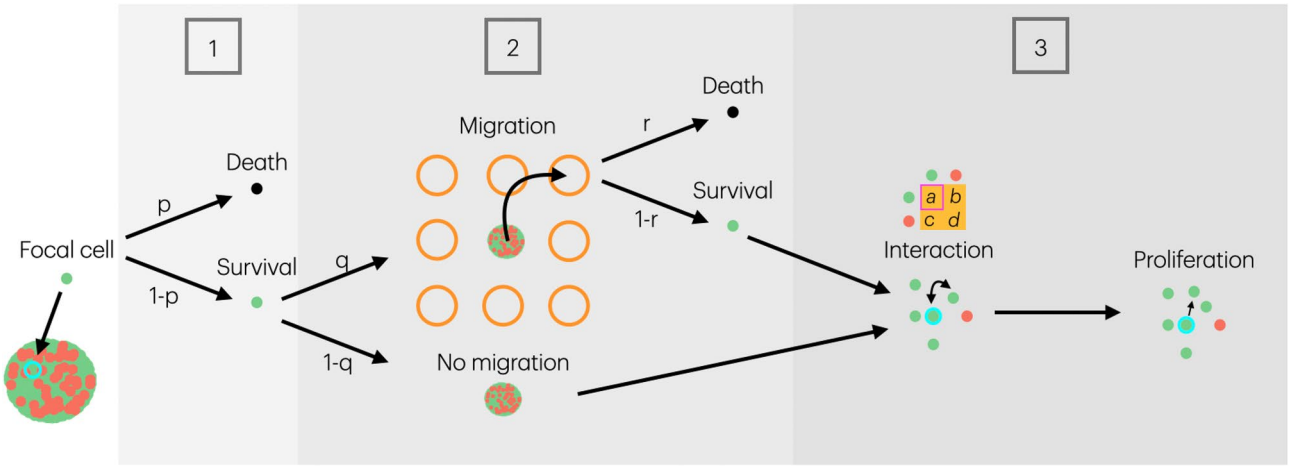

Fig. 7. Schematic overview of the main steps of the spatial game-theoretic agent-based model, happening per generation. In each generation, all cells are selected as focal cells in a random order. Once selected, each focal cell undergoes up to 3 sequential phases. First, the focal cell may die with probability p. Dead cells are removed from the simulation at the end of every generation when the total population is updated. If the cell survives, it proceeds to the second phase, where it may migrate to one of the eight metastasis locations with probability q. A migrating cell experiences an additional death probability r. A surviving cell (whether it migrated or remained at its original location) then enters the third phase, where it interacts with a randomly selected cell within its interaction radius. The element a_{ij} of the fitness matrix $(A_{ij})_{2\times 2}$ defines the probability that the focal cell of type i produces a daughter cell of its own type when interacting with a cell of type j. All daughter cells are added to the random place within focal cells' interaction radius between generations and therefore cannot act as focal cells or interaction partners within the current generation.

Description	Value
Number of simulation runs	50
Number of initial cells	2000
Initial cell type distribution	97.5% sensitive cells,
	2.5% resistant cells
Local carrying capacity (cells per unit area)	6
Natural death probability	0.15 (A_1–A_3) 0.10 (A_4 & A_5)
Density radius	1
Reproduction radius	1
Interaction radius	1
Number of metastatic sites	8
Survival probability at a new site	0.1
Fraction of invasive cells	0.1
Migration probability without migrastatics	0.1
Migration probability with migrastatics	0.01
Metastasis center locations	$(-60, 60)$, $(0, 60)$, $(60, 60)$, $(-60, 0)$ $(60, 0)$, $(-60, 60)$,$(0, -60)$,$(60, -60)$

Table 1. Parameters common for all evaluated scenarios.

the cell is determined to proliferate, the newly produced cell of the same type as the focal cell is then placed randomly within the interaction neighborhood. Daughter cells in the current generation cannot be chosen as interaction partners until the next generation, but are taken into account when evaluating whether the carrying capacity has not been reached. New cells are therefore effectively only placed between generations.

In all simulations, sensitive and resistant phenotypes are fixed: no transitions between the sensitive and resistant cells occur.

Case studies

We investigate the impact of different treatment schedules for our model with 5 different fitness matrices, each corresponding to a different type of interactions between the sensitive and resistant cancer cells. An element a_{ij}

of the fitness matrix $(a_{ij})_{2\times 2}$ defines the probability that cancer cell of type *i* produces an offspring of its own type when interacting with cell of type *j*.

Three of these matrices represent competition between sensitive and resistant cell populations. In these three matrices, interactions of a cell with its own type result in a proliferation probability of 0.2 for both sensitive and resistant cell types, while proliferation probabilities when interacting with a cell of different type vary.

The first matrix, A_1, corresponds to an anti-coordination game[52]:

$$\begin{array}{cc} & \begin{array}{cc} S & R \end{array} \\ \begin{array}{c} S \\ R \end{array} & \begin{bmatrix} 0.2 & 0.7 \\ 0.3 & 0.2 \end{bmatrix} \end{array}$$

This fitness matrix has a mixed evolutionarily stable strategy (ESS). Here, either type of cell has a higher probability of proliferating when interacting with cells of the other type than when interacting with cells of its own type. In the mostly resistant environment, sensitive cells will grow more than resistant cells, while in the mostly sensitive environment, resistant cells will grow more than the sensitive cells.

The second matrix, A_2, corresponds to an anti-coordination game[52], which switches the roles of the sensitive and resistant cells in comparison to matrix A_1:

$$\begin{array}{cc} & \begin{array}{cc} S & R \end{array} \\ \begin{array}{c} S \\ R \end{array} & \begin{bmatrix} 0.2 & 0.3 \\ 0.7 & 0.2 \end{bmatrix} \end{array}$$

This matrix has a mixed-strategy ESS, too. Here, in a mostly resistant environment, resistant cells will grow more than the sensitive ones, whereas when the environment consists of mostly sensitive cells, resistant cells will grow more than the sensitive ones.

The third matrix, A_3, corresponds to a symmetric anti-coordination game, containing one mixed-strategy ESS[52]:

$$\begin{array}{cc} & \begin{array}{cc} S & R \end{array} \\ \begin{array}{c} S \\ R \end{array} & \begin{bmatrix} 0.2 & 0.5 \\ 0.5 & 0.2 \end{bmatrix} \end{array}$$

Here, neither sensitive nor resistant cells outcompete each other when interacting with a cell of the other type.

Cancer cells of the same type could also cooperate with each other during tumor growth. Here we evaluate two cases, one where sensitive cells benefit from interactions with their own type, with ESS containing only sensitive cells, and another one, where the same holds for the resistant cells, and there is a fully resistant ESS. These games are defined via fitness matrices A_4 and A_5, respectively:

$$\begin{array}{cc} & \begin{array}{cc} S & R \end{array} \\ \begin{array}{c} S \\ R \end{array} & \begin{bmatrix} 0.8 & 0.2 \\ 0.2 & 0.2 \end{bmatrix} \end{array} \quad \text{and} \quad \begin{array}{cc} & \begin{array}{cc} S & R \end{array} \\ \begin{array}{c} S \\ R \end{array} & \begin{bmatrix} 0.2 & 0.2 \\ 0.2 & 0.8 \end{bmatrix} \end{array}$$

For each of the five fitness matrices, four treatment strategies are compared to each other and to no treatment, in terms of the time to progression. The four treatment strategies combine two treatments:

1. *Cytotoxic treatment*: When cytotoxic treatment is applied, 60% of all sensitive cells are killed and removed immediately in step the treatment is applied. Resistant cells are not affected.
2. *Migrastatic treatment*: When migrastatic treatment is applied, the probability of migration of all cells is lowered to 0.01.

We compare (i) no treatment, (ii) applying migrastatics only, (iii) cytotoxic MTD treatment without migrastatics, (iv) cytotoxic MTD treatment with migrastatics, (v) adaptive cytotoxic treatment (AT) without migrastatics, and (vi) adaptive cytotoxic treatment with migrastatics. Here AT refers to Zhang et al.'s protocol[24,25]. In this on- and off- treatment strategy, MTD is administered until the overall tumor burden has been reduced to 50% of its initial size. Once this reduction is achieved, therapy is paused, allowing the tumor to regrow to its initial size, when the therapy is resumed and a new treatment cycle starts.

Data availability

The simulations were performed using the Migrastatics simulation software, implemented as a Java application, version 11.0. The source code and executable JAR file are publicly available at https://gitlab.tudelft.nl/evolutionary-game-theory-lab/Migrastatics.git. The Java platform is available from https://www.oracle.com/nl/java/technologies/downloads/#java21.

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Declarations

Competing interests
The authors declare no competing interests.

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