The Effect of The Structure of The Host Tissue on Intratumor Heterogeneity, Metastasis And Immune Surveillance

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Movement behavior of biological entities plays a crucial role in their destiny through regulating their intraspecific and interspecific interactions as well as their interaction with surrounding environment. In spite of various models for population dynamics, the effect of movement behavior and heterogeneity of environment on population dynamics has remained poorly understood. We introduced an extended version of Kolmogorov equation which captures movement behavior. We translated our model to a biased random walk on percolation lattice and explored the effect of mentioned topic on population dynamics. Then we applied our findings to intratumor heterogeneity, metastasis and immune surveillance. In the case of tumor, our result reveals that communication between cell colons and the structure of host tissue together regulate the intratumor heterogeneity. For metastasis, our model predicts that the interplay between the structure of metastatic niche and interactions between metastatic cells arrived from different colons determines that which kind of seeds, polyclonal or monoclonal, can successfully metastasized there. Finally, studying the immune cells-tumor cells interaction in this context reveals the negative effect of the homogeneous structure of host tissue on immune surveillance.

Introduction: Population Dynamics is the approach to the study of how populations change in size and structure over time under effect of other populations or environmental cues. Because of similarities between different entities in their intraspecific and interspecific interactions, as well as the generality of assumptions in population dynamics models, wide range of biological problems have been studied through this method such as interaction between cancer cells and host tissue [1], intratumor heterogeneity [2, 3], immune system activation [4] and its interaction with tumor cells [5] and interactions between animals [6]. Consequently, key questions in population dynamics, if addressed properly, can shed light on vast biological problems.

Fate of each specie is directly under effect of its encounters with conspecifics [7], other species [8] and environment [9]. Respectively, a population as the collection of single entities is under effect of those factors as well. In many cases, these interactive entities are spatially separate and they need to move and search for each other [10]. Thus, they relay on spatial migration to interact more efficiently with the target entities, escape threats or find new sources [11]. There is a continuum range in entities movement from uninformed migration (simple random walk) towards informed migration (biased random walk) [12, 13]. Thanks to movement ecology studies, the role of movement behavior is clear in many aspects [14,18], but the effect of single entities movement behavior within environment on population dynamics has remained poorly understood [10]. Besides, these movements happens within an environment which is heterogeneous [19,21] and can directly alter their intended motion dynamics. As a result, for a comprehensive understanding of population dynamics, we need to consider entities movement and the heterogeneity of environment [22,23].

Theoretically, single population dynamics has been studied by logistic equation [24] which lacks expression of spatial distributions of interactive entities. Fisher’s equation, also known as Kolmogorov-Petrovsky-Piskunov (KPP) equation and Fisher-KPP equation, as a reaction-diffusion equation and a spatially extended version of logistic model [25] have been used to study single population dynamics [26,29]. For interactive groups, the Lotka-Volterra equations [31,32] and their generalized version, the Kolmogorov equation [33,34] have been used. These traditional mean field models assume well-mixed populations with many individuals in which interactions can be defined as functions of overall density. Whereas in real world, each member of population experiences a different situation and encounter rate for populations is not simply proportional to their density. To include two important factors in entities interaction, movement behavior and the heterogeneity of the structure of environment [10], which play crucial roles in population dynamics [11], we need to modify traditional models and extend them. Through this paper we develop a model for population dynamics which not only contains different movement modes, but it also captures the structure of environment and will let us analyze effects of movement behavior and physical heterogeneity of environment on population dynamics.

Model: We introduce an extended version of the Kolmogorov equation which contains active movement behavior for all interactive entities. By adding active motions to the Kolmogorov equation, we will have the following equations for two interactive populations:

\[
\frac{\partial P_1(x, y, t)}{\partial t} = D_1 \nabla^2 P_1(x, y, t) + v_1 \frac{\partial P_1(x, y, t)}{\partial t}
\]  

(1)
in which $D_1$ and $D_2$ are diffusion constants. During this paper we consider $D_1 = D_2 = \text{constant}$ (see SI for the effect of $D$) and $K_1 = K_2 = 1$. $R_{11}$ and $R_{22}$ are growth rate of each population. $R_{12}$ and $R_{21}$ are effect of each population on the other one which could be positive or negative. $v_1$ and $v_2$ are drift velocities of cells by which they follow or escape other cells. Analytical solution is not available for these equations and spatial heterogeneity of environment can not be considered readily. As a result, we translate this model to a group of interactive walkers on a $100 \times 100$ percolation square lattice with occupancy equal to $1 - p$ (Figure 1). Each coefficient would be translated to its corresponding value.

We study the different possibilities in species interactions and explore the effect of movement behavior on population dynamics. To quantify our results, we will use two characteristic times, the half-time of a population as the time taken for the population to decline to half its size, $HT$, and the double-time of a population, $DT$, as the time taken for the population to increase to twice its size. Consequently, $HT$ would be the indicative of species extinction time and $DT$ would be the indicative of species dominance time. To distinguish intraspecific interactions from interspecific interactions we consider two approaches: 1) The single mode in which only one member of each population is added to system and their interaction is studied until one of them duplicates (until $TD$) or dies (until $HT$). In this approach only interspecific interactions would effect the system 2) The collective mode in which 1000 entities of each population are added to model and we track the evolution until the time which the one population exceeds 2000 (time recorded as $TD$) or falls off 500 (time recorded as $HT$).

At single mode, the status of walker would be updated as follows: i) duplicates to an empty nearest neighbor (for $r_{11} + r_{21}P_2(x, y, t) > 0$) with probability $r_{11} + r_{21}P_2(x, y, t)$ or would be eliminated (for $r_{11} + r_{21}P_2(x, y, t) < 0$) with probability of $1 - r_{11} + r_{21}P_2(x, y, t)$, ii) survived walker moves based on corresponding Langevin equation, $\dot{X}_i = \eta(x_i, y, t) + v_i$ in which $\eta(x, y) = \left[\begin{array}{c} b_1(x, y) \\ b_2(x, y) \end{array}\right]$ with $b_1 = \delta(r(x, y) - l(x, y))/\tau$, and $b_2 = \delta(u(x, y) - d(x, y))/\tau$. $r(x, y)$, $l(x, y)$, $u(x, y)$ and $d(x, y)$ are the probabilities of going right, left, up and the down and using Keller-Segel model [37] we have $r_1(x_1, y_1, x_2, y_2) = [1 - E(x_1^+, y_1)]e^{-\gamma|x_1^+ - x_2|}/S_1(x_1, y_1)$. Where $x_1$ and $x_2$ are positions of the first and second cells. $E(x_1^+, y_1)$ represents physical barriers and turns the probability to zero if there would be solid line in the right side of $(x_1, y_1)$. $\gamma$ determines the walkers response magnitude and direction. We consider directionality the same for both populations (see SI for $\gamma_1 \neq \gamma_2$). $S$ is the normalization factor (for $l(x, y)$, $u(x, y)$, $d(x, y)$ and more details see SI). At collective mode we use Monte Carlo method for simulation direction of motion is towards the center of mass of the other population.

This approach provides a frame work to decompose interspecific, intraspecific and environmental factors. Then we study the behavior of $DT$ (and $HT$ if it would be applicable) per directionality of motion($\gamma$) for Obligate symbiosis, Facultative mutualism, Interference competition and Predator-prey at different environments.

Result: Obligate symbiosis also known as obligate mutualism refers to tow populations which can survive only together like fungus and alga. In such a case we have: $R_{21} = R_{12} > 0$ and $R_{11} = R_{22} = 0$. $DT$ versus $\gamma$ for $p = 0$ and $p = 0.35$ at single and collective modes was obtained (see Figure 2a). Comparing $p = 0$ and $p = 0.35$ for single mode shows that heterogeneity of environment can increase the value of $DT$ and change its dynamics. Comparing the result of single mode and collective mode for $p = 0$ shows that intraspecific interactions can both increase and decrease the value of $DT$ based on motion dynamics. $\gamma = 2, \gamma = 0.9, \gamma = 0.4$ and $\gamma = 0.4$ respectively minimize $DT$ for single mode with $p = 0$, single mode with $p = 0.35$, collective mode with $p = 0$ and collective mode with $p = 0.35$.

Facultative mutualism refers to two interacting species which derive benefit from each other but can survive without the symbiotic partner. For this case we have: $R_{21} = R_{12} > 0$ and $R_{11} = R_{22} > 0$. $DT$ versus $\gamma$ for $p = 0$ and $p = 0.35$ at single and collective modes was obtained. As Figure 2b shows, heterogeneity of environment has a minor effect on $DT$ but interspecific interactions can change the dynamics of $DT$. When we increase directionality, we always mean to increase the interspecific encounter rate but we already have changed the intraspecific interactions. These intraspecific interactions come to play for $\gamma > 0.2$ and in spite of higher
encounter rate for this range, intraspecific competition prohibits any further decrease in $DT$ and even increases it. $\gamma = 2$, $\gamma = 1.3$, $\gamma = 0.2$ and $\gamma = 0.2$ respectively minimize $DT$ for single mode with $p = 0$, single mode with $p = 0.35$, collective mode with $p = 0$ and collective mode with $p = 0.35$.

FIG. 2: a) Double-time, $DT$, for two identical dependent populations versus $\gamma$. Walker follow (avoid) each others for $\gamma > 0$ ($\gamma < 0$). As we expect, in all cases species only have chance to duplicate if move towards each others. Otherwise, they have no chance. Environment structure slightly increase the duplication time. b) Double-time, $DT$, for two identical cooperative populations versus $\gamma$. While for single mode, $DT$ versus $\gamma$ is almost univocal, for collective mode behavior changes. $\gamma = \pm 2$ have larger $DT$ in respect to $\gamma = 0.2$ with minimum $DT$. This behavior comes from inter-specific interactions. High drift velocity aggregates species to a limited area and their duplication would be prohibited because of limited space.

Interference competition refers to two competitive populations which interfere with foraging, survival, reproduction and etc. of each other. For such a case we have: $R_{11} = R_{22} > 0$ and $R_{21} = R_{12} < 0$. $HT$ and $DT$ per $\gamma$ for $p = 0$ and $p = 0.35$ were obtained (Figure 3). At single mode, species have almost zero chance to meet each others for $\gamma < 0$. Consequently $DT$ does not depend on $\gamma$ and $HT$ diverges at this range (Figure 3). For $\gamma > 0$, higher directionality leads to higher interspecific encounter rate and higher $DT$. Heterogeneity of environment decreases encounter rates and increase $HT$ and decreases $DT$. For collective mode, when directionality decreases, at $-2 < \gamma < -0.2$, interspecific encounter rate remains almost the same but intraspecific competition for space decreases and leads to a lower $DT$. $HT$ at this range remained unlimited. For $\gamma > -0.2$ interspecific encounter rate increases and leads to higher values of $DT$. At $\gamma \sim 2$ both intraspecific and interspecific competition reach to highest value and maximize the $DT$. For homogenous environment, higher directionality of motion always leads to higher encounter rate and lower $HT$. But in heterogeneous environment, an intermediate value of directionality, corresponding to $\gamma = 1$, maximizes the encounter rate and consequently minimizes the $HT$.

Predator-prey interaction refers to a case in which an specie (predator) feeds on an other specie (prey). By considering $P_1$ as the prey and $P_2$ as predator we have: $R_{11} = -R_{21} = 2R_{12} > 0$ and $R_{22} = 0$. $HT$ and $DT$ per $\gamma$ for $p = 0$ and $p = 0.35$ were obtained (see Figure 4).

FIG. 3: a) Double-time, $DT$, for two identical competitive populations versus $\gamma_1 = \gamma_2$. For single mode, $DT$ has almost univocally increases versus $\gamma$. In collective mode, $\gamma = -0.2$ minimizes the $DT$ in which both interspecific and intraspecific encounter rates are low. b) Half-time, $HT$, for two identical competitive populations versus $\gamma$. The structure of environment plays determinant role in $HT$ of these cases and change its behavior versus $\gamma$. At homogeneous environment $\gamma = 3.5$ minimizes $HT$ but at heterogeneous environment $\gamma = 1$ minimizes $HT$.

At single mode, species have almost zero chance to meet each other for all values $\gamma < 0$. Consequently, $DT$ for predator and $HT$ for prey diverge. Heterogeneity of environment decreases the encounter rate and increases the value and alters the dynamics of $DT$ and $HT$ in respect to homogeneous case. At collective mode, predators have higher chance (roughly $10^4$ times larger at $\gamma = 0$) to meet prey in respect to corresponding single mode. As a result, in collective mode, predators got the chance to duplicate at $\gamma \sim -0.2$. That is why both $DT$ and $HT$ have limited values in this range. When we increase $\gamma$, encounter rate will increase and $DT$ decreases. But for larger values of $\gamma$, intraspecific interaction come to play and competition for space limits predators duplication (Figure 4) but $HT$ for prey continues to decrease because of high encounters (Figure 4).

These result indicate that the movement behavior of entities can alter population dynamics through regulat-
ing three main factors in population dynamics: a) interspecies interactions and encounter which plays a crucial role in population dynamics b) intraspecies interactions which comes to play when there is a limited source, namely space. c) specie-environment interactions which leads to alteration in above cases.

Case Studies: Clonal diversity between tumor cells (also known as intratumor heterogeneity, ITH) has been identified long ago [39]. The interactions between these colonies which are spatially separated in many cases [2, 40–48] and are equivalent to allopatric speciation [49], has been studied through ecological approaches [50, 51]. We need to view cancer as an ecosystem of subclones that may act cooperatively or antagonistically [49]. However, the relation between physical structure of host tissue and ITH needs more clarification. By considering the interactive entities as the members of different colons, we can apply our result to this field. Based on this analogy, the physical structure of host tissue can both promote and prohibit the ITH based on the nature of sub-clonal interactions. For cooperative sub-colons, physical barriers can prohibit the clonal diversity. As our result indicates (Figure 2), large number of barrier at environment bans these encounters and leads to lower diversity through elimination of such a dependent populations. On the other hand, for competitive sub-colons, as our result shows (Figure 3), barriers help them to survive and finally increase ITH.

Metastasis as an initiation of new population can be studied as an ecological process [52]. Experimental result shows colonies competition [43, 46, 53] and cooperation [54, 56] during metastasis. Besides, metastatic spread has been reported to be monophyletic (composed of single colon cells) [58, 59] and polyphyletic (composed of more than one colon cells) [58, 60]. Based on experimental results, patterns of metastatic outgrowth is site-specific. Whereas peritoneal lesions remained polyclonal, liver and lung lesions drifted toward monoclonality [52], presumably reflecting different selective pressures at these metastatic sites. By considering seeds from different colons as the interactive species of our model, we can applying our findings to this case and find a deeper understanding of how metastatic sites can impose such a difference on metastatic seeds success. As our results (Figure 2) show, cells of tow competitive (dependent) colons can reach each other easier in structures with no barriers and can grow faster. Consequently, cooperative colons have a higher chance to create a polyphyletic seed at tissue with lower density of ECM in respect to a tissue with high density of ECM. On the other hand, as our results show (Figure 3), cells of tow competitive colons have higher chance to create a polyphyletic seed in tissue with higher density of barriers in respect to a tissue with lower density of barrier. Based on this analogy, the physical structure of the host tissue and communications between colons together play essential role in the nature seed of metastasis and where they can land.

The immune system plays crucial roles in human body including detection and elimination of cancerous cells [61]. The process of detecting and attacking tumor antigen presenting cells by immune system is referred to as immune surveillance [62]. This ability of immune system has triggered cancer immunotherapy studies [63] and has led to promising results [64]. Identifying the role of different players in immune surveillance, including the structure of host tissue [66], may help us to overcome current challenges [65] and improve the immune system ability to fight cancer. Before immune suppression, immune cells only prohibit tumor growth and this has lead to developing predator-prey model for immune cell and tumor cell interaction [67]. Traditional population dynamics models lack cells movement behavior and environment structure [68] while there are growing evidences for presence and profound effect immune cells random/informed migration [4, 69]. Besides, the structure of environment has been reported to regulate the immune cells migration and immune cells function [20, 66]. By considering immune cells as predator and cancer cells as prey, we can apply our result to immune surveillance. Through comparing with Figure 4 we can conclude that the structure of environment increases the immune surveillance failure chance. On the other hand, it shows that immune cells self-interactions can lead to immune surveillance success.

Conclusion: We developed a model to study the effect of movement behavior and environmental heterogeneity on population dynamics by extending a previously well known model. Based on our result, movement behavior can alter population dynamics through regulating interspecific and intraspecific interactions and environment controls how species can interact. Applying our result to ITH shows that the interplay between subcolonial interactions and the structure of environment regulates ITH. For metastasis, our result predicts that the structure of the host tissue and the interaction between arriving cells determines the seed to be monophyletic or polyphyletic. Finally, our results reveals that the structure of ECM is able to lead to immune surveillance failure and immunotherapeutic approaches should use ECM degrading drugs too.

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