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Deterministic and stochastic modeling for PDGF-driven gliomas reveals a classification of gliomas

Tuan Anh Phan[1,3] · Hai Dang Nguyen[2] · Jianjun Paul Tian[1]

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Abstract
Motivated by our study of infiltrating dynamics of immune cells into tumors, we propose a stochastic model in terms of Ito stochastic differential equations to study how two parameters, the chemoattractant production rate and the chemotactic coefficient, influence immune cell migration and how these parameters distinguish two types of gliomas. We conduct a detailed analysis of the stochastic model and its deterministic counterpart. The deterministic model can differentiate two types of gliomas according to the range of the chemoattractant production rate as two equilibrium solutions, while the stochastic model also can differentiate two types of gliomas according to the ranges of the chemoattractant production rate and chemotactic coefficient with thresholds as one non-zero ergodic invariant measure and one weak persistent state when the noise intensities are small. When the noise intensities are large comparing with the chemotactic coefficient, there is only one type of glioma that corresponds to a non-zero ergodic invariant measure. Using our experimental data, numerical simulations are carried out to demonstrate properties of our models, and we give medical interpretations and implications for our analytical results and numerical simulations. This study also confirms some of our results about IDH gliomas.

Keywords Ergodic invariant measure · Weak persistence · Stochastic differential equation · muIDH glioma · wtIDH glioma

Mathematics Subject Classification 37C40 · 37H10 · 60H10 · 92B05

1 Introduction

It is significant for many cancers to have infiltrated immune cells (Quail and Joyce 2013). There are lots of studies to explore the impacts of tumor-infiltrated immune cells (Kitamura et al. 2015). Some studies showed that direct contact between immune cells and tumor cells can reduce the tumor size while other studies indicated that increased immune cells in the tumor may facilitate tumor cell invasion (Nosho et al. 2010;

Extended author information available on the last page of the article

Gannot et al. 2002; Calzascia et al. 2003). Although the reason for these contradictory observations remains elusive, it is important to understand how the migration of immune cells into the tumor is regulated (Kesarwani et al. 2017). Recently, our group performed a series of experimental studies about how tumor-associated immune cells are regulated (Amankulor et al. 2017). Gliomas have two types, CIMP and non-CIMP, according to CpG island methylator phenotype (CIMP) (Noushmehr et al. 2010). CIMP gliomas have some mutations in isocitrate dehydrogenase 1/2 (IDH1/2). Non-CIMP wild-type IDH1/2 (wtIDH1/2) gliomas are more malicious comparing with their CIMP counterparts, CIMP mutant IDH1/2 (muIDH1/2). In our experiments with human tissues, we compared the infiltrated immune cell amounts of wtIDH1 and muIDH1 and found human CIMP gliomas have lower numbers of several immune cell types compared with non-CIMP tumors. To understand the difference in vivo, we utilized the RCAS/tva system to create isogenic glioma pairs from PDGF-driven mouse glioma models whose initiating events differed only in the presence or absence of muIDH1. Our experimental results showed that the muIDH1 mouse gliomas have significant reduced immune cell contents, and showed a regulatory role of muIDH1 on the infiltration of immune cells into gliomas with the secretion of several chemoattractants (Amankulor et al. 2017). However, to comprehend how IDH1 mutants regulate the infiltration of immune cells into gliomas and how they affect the aggressiveness of gliomas, it is necessary to integrate our experimental data into a dynamical system to acquire a complete understanding of subtle regulation of immune cell infiltration.

In our study (Niu et al. 2020), we formulated a mathematical model of 3-dimensional glioma driven by PDGF. We consider a radially symmetrical tumor and denote by r the distance from a point to the center of the tumor. The tumor boundary is denoted by $r = R(t)$. Let $G(r,t)$ be the number density of glioma cells, $H(r,t)$ the number density of necrotic cells, $N(r,t)$ the number density of infiltrated immune cells, and $A(r,t)$ the concentration of chemoattractants produced by tumor cells. The proliferation and removal of cells cause movements of cells within the tumor, with a convection term, for tumor cells G, which is of the form $\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 G(r,t)V(r,t))$, where $V(r,t)$ is the velocity and $V(0,t) = 0$. The necrotic cells undergo the same convection while the chemoattractants undergo diffusion. The immune cells migrate along the gradient field generated by chemoattractants into the tumor, and then undergo the same convection besides chemotaxis within the tumor. By mass conservation laws, the model we proposed in Niu et al. (2020) is as follows:

$$\frac{\partial G(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}[r^2 G(r,t)V(r,t)] = \lambda G(r,t) - \mu G(r,t), \ r \in [0, R(t)),$$

$$\frac{\partial H(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}[r^2 H(r,t)V(r,t)] = \mu G(r,t) - \delta H(r,t), \ r \in [0, R(t)),$$

$$\frac{\partial A(r,t)}{\partial t} = D\frac{1}{r^2}\frac{\partial}{\partial r}\left[r^2\frac{\partial A(r,t)}{\partial r}\right] + \frac{mG(r,t)}{\beta + G(r,t)} - \gamma A(r,t), \ r \in [0, \infty),$$

$$\frac{\partial N(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}[r^2 N(r,t)V(r,t)] = -\alpha\frac{1}{r^2}\frac{\partial}{\partial r}[r^2 N(r,t)\frac{\partial A(r,t)}{\partial r}]$$
$$- \rho N(r,t), \ r \in [0, R(t)).$$

We assumed that all cells have the same size. Since the number density of the tissue is constant, we have $G(r,t) + H(r,t) + N(r,t) = \theta$ within the tumor. Combining these equations, we have the equation for the velocity,

$$\frac{\theta}{r^2}\frac{\partial}{\partial r}[r^2 V(r,t)] = \lambda G(r,t) - \delta H(r,t) - \alpha \frac{1}{r^2}\frac{\partial}{\partial r}[r^2 N(r,t)\frac{\partial A(r,t)}{\partial r}] - \rho N(r,t).$$

The free boundary condition is given by $\frac{dR(t)}{dt} = V(R(t),t)$. The initial conditions are specified as $R(0) = \epsilon$, where ϵ is a very small number; $G(r,0)$, $H(r,0)$, $N(r,0)$, for $0 < r < \epsilon$; and $A(r,0)$, $0 < r < \infty$. The boundary conditions for the chemoattractant $A(r,t)$ are specified as $\frac{\partial}{\partial r}A(0,t) = 0$ and $A(r,t)$ vanishes at infinity, and $V(0,t) = 0$ for $t \geq 0$. We did computational studies to verify our model and made numerical predications in Niu et al. (2020). Particularly, we found two parameters, the chemoattractant production rate m and chemotactic coefficient α, play important roles. The chemoattractant production rate m can distinguish two types of tumors, wtIDH1 and muIDH1, according to the range of its value. The chemotactic coefficient α determines the possibilities of immune cell migration along chemoattractant gradient fields. However, as these two parameters are perturbed or in a noisy environment which actually is the case in reality, we would like to explore how stable our conclusion about these two parameters are. This is a medical relevant question. There are several factors which contribute randomness of parameter values (Phan et al. 2021). We mentioned parameter sensitivity analysis in Niu et al. (2020). However, the influence of randomness and noise on parameters is a different question.

Therefore, in this article, we conduct some analysis of how these two parameters will affect the dynamics of immune cells infiltrating into the tumor site if they are perturbed. In order to grasp the essence of the problem, we first reduce our PDE system above to a system of ordinary differential equations and then perturb two parameters to obtain a system of Ito stochastic differential equations.

The simplified ODE system is as follows:

$$\begin{aligned}
\frac{dG}{dt} &= \lambda G\left(1 - \frac{G+N}{C}\right),\\
\frac{dA}{dt} &= \frac{mG}{\beta+G} - \gamma A,\\
\frac{dN}{dt} &= \alpha AN - \rho N.
\end{aligned} \tag{1.1}$$

where $G = G(t)$ is the number density of glioma cells at time t, $A = A(t)$ is the concentration of chemoattractants at time t, and $N = N(t)$ is the number density of infiltrated immune cells at time t. We use logistic growth to model the growth of glioma cells with the proliferation rate λ and carrying capacity C. The necrotic cells is not needed since it is built in logistic growth function. Chemoattractants is produced by glioma cells and the Michaelis-Menten Kinetics is used to model the production rate of chemoattractants which is proportional to $\frac{mG}{\beta+G}$, where β is Michaelis constant. The parameter γ denotes the chemoattractant degradation rate. The parameter ρ is the immune clearance rate. The last two parameters m and α, represent the chemoattractant

production rate and the chemotactic coefficient, respectively. This ODE model may be regarded as a simplified version of our PDE model without spatial distributions, but inherits dynamical properties in time, particularly, which we are interested in most are about these two parameters.

Aforementioned, we are interested in parameters m and α. The chemoattractant production rate m describes how much chemoattractants are produced in unit volume and unit time. The randomness or noise for m mainly comes from how much chemoattractants are in the tumor, or its variation can be described by variation of chemoattractant concentrations. Specifically, we may assume that each chemoattractant molecule make almost same contribution to the stochastic effects and receive the same environmental noise. Then, the environmental noise and randomness for chemoattractant production can be represented by $\tau_1 A\xi$, where ξ is the unit noise and τ_1 can be regarded as a way to measure average variation of each chemoattractant molecule (Phan et al. 2021). As usual, we take the white noise $\xi = \frac{dW}{dt}$, and W_t represents the standard Wiener process. Thus, we will change m to $m + \tau_1 A\frac{dW_1}{dt}$. The chemotactic coefficient α describes how much area or volume of the gradient can be generated per unit of chemoattractant and time. In other words, the chemotactic coefficient describes how much possibility that chemoattractant substance can make immune cell move forward. The randomness and noise for α mainly is from the environment. We may represent the noise by $\tau_2\xi$, where τ_2 measure an average variation of the environmental contribution (Phan and Tian 2020). We then replace α with $\alpha + \tau_2\frac{dW_2}{dt}$. It should be mentioned that W_1 and W_2 are mutually independent one dimensional Wiener processes. Therefore, we get the following system of Ito stochastic differential equations.

$$\begin{aligned} dG &= \lambda G\left(1 - \frac{G+N}{C}\right)dt, \\ dA &= \left(\frac{mG}{\beta+G} - \gamma A\right)dt + \frac{\tau_1 AG}{\beta+G}\,dW_1, \\ dN &= (\alpha AN - \rho N)\,dt + \tau_2 AN\,dW_2. \end{aligned} \tag{1.2}$$

As the way we incorporate randomness and noise is not usually to simply add additive or linear noise, our stochastic model does not satisfy usual boundedness conditions (Benaïm 2018; Hening and Nguyen 2018). This creates difficulties in analyzing our stochastic model. Based on significant progress in the theory of stochastic persistence (Benaïm 2018; Schreiber et al. 2011; Hening and Nguyen 2018), we develop delicate and new estimates for our model. Meanwhile, we conduct numerical studies using our experimental data with detailed biological interpretations and implications.

The rest of the article is organized as follows. In Sect. 2, we non-dimensionalize the systems (1.1) and (1.2), present main analytical results, and provide medical interpretations. In Sect. 3, using our experimental data, we provide numerical simulations for two systems with biological explanations, we discuss some aspects of stochastic modeling and list several open problems. In Sect. 4, an analysis of the deterministic counterpart of our stochastic model is presented and the main theorem for this system is proved. In Sect. 5, we analyze our stochastic model by studying the long-term

behaviors near the boundary of the positive invariant domain. The article ends with Acknowledgements and References.

2 Results and interpretations

In this section, we list our major analytical results and give some biological interpretations. For simplicity, we non-dimensionalize the system (1.2) by setting $G = C\overline{G}$, $A = C\overline{A}$, $N = C\overline{N}$, $T = \gamma t$, and rename parameters $r = \frac{\lambda}{\gamma}$, $a = \frac{m}{\gamma C}$, $b = \frac{\beta}{C}$, $c = \frac{\alpha C}{\gamma}$, $d = \frac{\rho}{\gamma}$, $\overline{\tau}_1 = \frac{\tau_1}{C}$, and $\overline{\tau}_2 = \frac{\tau_2}{C}$. Then the system (1.2) becomes

$$\begin{aligned} d\overline{G} &= r\overline{G}(1-\overline{G}-\overline{N})\,dT, \\ d\overline{A} &= \left(\frac{a\overline{G}}{b+\overline{G}} - \overline{A}\right) dT + \frac{\overline{\tau}_1 \overline{AG}}{b+\overline{G}}\, dW_1, \\ d\overline{N} &= (c\overline{AN} - d\overline{N})\,dT + \overline{\tau}_2 \overline{AN}\, dW_2. \end{aligned}$$

For convenience, drop all the bars over the variables and write T as t, we get

$$\begin{aligned} dG &= rG(1-G-N)\,dt, \\ dA &= \left(\frac{aG}{b+G} - A\right) dt + \frac{\tau_1 AG}{b+G}\, dW_1, \\ dN &= (cAN - dN)\,dt + \tau_2 AN\, dW_2, \end{aligned} \tag{2.1}$$

and the corresponding deterministic system of (2.1) is

$$\begin{aligned} \frac{dG}{dt} &= rG(1-G-N), \\ \frac{dA}{dt} &= \frac{aG}{b+G} - A, \\ \frac{dN}{dt} &= cAN - dN. \end{aligned} \tag{2.2}$$

It is assumed that all parameters are nonnegative.

For the deterministic system (2.2), it is straightforward to find the positive invariant domain which is biologically meaningful as

$$D = \{(G, A, N) : 0 \le G \le 1,\ A \ge 0,\ N \ge 0\}.$$

Now, the parameter a represents the chemoattractant production rate and c represents chemotactic coefficient. We find the first critical value for the parameter a, $a_{s_1} = \frac{bd+d}{c}$, by determining three equilibrium solutions $E_0 = (0, 0, 0)$, $E_1 = (1, \frac{a}{b+1}, 0)$, and $E_2 = \left(\frac{bd}{ac-d}, \frac{d}{c}, \frac{ac-d-bd}{ac-d}\right)$. We linearize the system (2.2) at these equilibria to study their local stability. We also use center manifold theorem to study the global and local

stability of the equilibria on the boundary of D. To investigate Hopf bifurcations, we develop a family of coefficient parameterized polynomials and take advantage of properties of Routh–Hurwitz determinant to obtain the second critical value for the parameter a, $a_{s_2} = \frac{y_3^*+d}{c}$, where y_3^* is the unique positive root of the cubic polynomial $\Phi(y) = -y^3 + (b+bd)y^2 + bd(br+1)y + b^2d^2r$. The main result for the dynamics of the system (2.2) can be summarized in the following theorem.

Theorem 2.1 *The system (2.2) has three equilibrium solutions E_0, E_1, and the positive equilibrium E_2. E_0 is always unstable for all positive values of a. E_1 is globally asymptotically stable when $0 < a < a_{s_1}$, and it is unstable when $a > a_{s_1}$. At $a = a_{s_1}$, E_1 is locally asymptotically stable and the positive equilibrium E_2 moves into the positive invariant domain D, a similar type of transcritical bifurcation occurs with E_1 and E_2. As $a_{s_1} < a < a_{s_2}$, E_2 is locally asymptotically stable; when $a > a_{s_2}$, E_2 is unstable. Only one Hopf bifurcation occurs at $a = a_{s_2}$, and this bifurcation gives rise to one family of periodical solutions. As a becomes large enough, $E_2 \approx (O(\frac{1}{a}), \frac{d}{c}, 1)$.*

This theorem has some biological interpretations or implications. From our study in Niu et al. (2020), we know that the chemoattractant production rate m or a now can distinguish two type of gliomas, wtIDH1 and muIDH1. Gliomas of wtIDH1 have more infiltrated immune cells. We may give the following interpretations.

Interpretation 2.1 *With the deterministic system (2.2), two types of gliomas can be distinguished by their chemoattractant production rate. If the chemoattractant production rate is smaller than a critical value, a_{s_1}, then the tumor belongs to muIDH1 type. If the chemoattractant production rate is greater than a_{s_1}, then the tumor belongs to wtIDH1 type. When the chemoattractant production rate is even larger, the tumor will attract more immune cells and is more aggressive.*

For the stochastic system (2.1), we specify an appropriate completed filtered probability space. Let $\Omega = \{\omega \in C(\mathbb{R}, \mathbb{R}^2), \omega(0) = 0\}$, $\mathcal{F}$ the Borel σ-algebra on Ω and $\mathbb{P}$ the measure induced by $\{W_t\}_{t\in\mathbb{R}}$, a two-sided 2-dimensional Wiener process. Then the elements of Ω can be identified with paths of a Wiener process $\omega(t) = W_t(\omega)$. Now we consider the $\mathbb{P}$-completion of $\mathcal{F}$, also denoted by $\mathcal{F}$, that is $\mathcal{F}$ contains all $\mathbb{P}$-null sets. The filtration $\mathcal{F}_t$ is given by the canonical filtration generated by the Wiener process completed by all $\mathbb{P}$-null sets of $\mathcal{F}$. Denote the probability measure given by the extension of $\mathbb{P}$ to the completed $\mathcal{F}$ again by $\mathbb{P}$. Thus, a completed filtered probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\in\mathbb{R}}, \mathbb{P})$ is obtained. We denote the drift term and the diffusion term of the system (2.1) by

$$f(U) = \begin{bmatrix} rG(1-G-N) \\ \frac{aG}{b+G} - A \\ cAN - dN \end{bmatrix}, \text{ and } g(U) = \begin{bmatrix} 0 & 0 \\ \frac{\tau_1 AG}{b+G} & 0 \\ 0 & \tau_2 AN \end{bmatrix}.$$

The process given by the solution to (2.1) will be denoted by U or $U(t) = (G(t), A(t), N(t))$, $t \geq 0$. Let $\mathcal{L}$ be the infinitesimal generator of the process U and, for any smooth enough functions $F : \mathbb{R}^3_+ := [0, \infty)^3 \to \mathbb{R}$, the generator $\mathcal{L}$ acts

as

$$\mathcal{L}F(u) = F_u \cdot f(u) + \frac{1}{2}\text{trace}(g(u)g(u)^T F_{uu}),$$

where F_u is the gradient of F and F_{uu} is the Hessian matrix of F. We use $\mathbb{P}_u$ to denote the probability law on Ω when the solution path starts at $u = (G, A, N)$ and $\mathbb{E}_u$ is the expectation corresponding to $\mathbb{P}_u$.

Our aim for studying the stochastic system (2.1) is to explore how environmental noise and parameter randomness affect our tumor classification and the dynamics of the system (2.2). Our method is to analyze solutions of (2.1) on the boundary of D. Our analysis shows that there are two ergodic invariant measures $\mu_1 = \boldsymbol{\delta}_0^* \times \boldsymbol{\delta}_0^* \times \boldsymbol{\delta}_0^*$ and $\mu_2 = \boldsymbol{\delta}_1^* \times \pi \times \boldsymbol{\delta}_0^*$ on the boundary ∂D. Here $\boldsymbol{\delta}_1^*$ and $\boldsymbol{\delta}_0^*$ denote the Dirac measures with mass at 1 and 0, respectively. The invariant measure π is the inverse gamma distribution: $\pi \sim \text{IG}\left(2(\frac{b+1}{\tau_1})^2 + 1, \frac{2a(b+1)}{\tau_1^2}\right)$. From these measures, we derive the sufficient and almost necessary condition for weak persistence of the SDE system (2.1). Our main result for the dynamics of the system (2.1) is stated in the following theorem.

Theorem 2.2 *Assume that* $\tau_1 < (b+1)\sqrt{2}$ *and define the threshold*

$$\boldsymbol{\lambda} := \frac{ac}{b+1} - d - \frac{\tau_2^2 a^2}{2(b+1)^2 - \tau_1^2}.$$

If $\boldsymbol{\lambda} < 0$ *then for any initial value* $u = (G, A, N)$ *in the interior of* D, D°, *the solution* $U(t) = (G(t), A(t), N(t))$ *of the system* (2.1) *converges to* μ_2 *in the sense that* $G(t)$ *converges to* 1 *a.s.,* $A(t)$ *converges weakly to* π, *and* $N(t)$ *converges to* 0 *exponentially fast with the rate* $\boldsymbol{\lambda}$. *If* $\boldsymbol{\lambda} > 0$, *then* $\limsup_{t\to\infty} \mathbb{E}_u \frac{1}{t}\int_0^t \ln(N(s)+1)ds > 0$ *that is* $N(t)$ *cannot converge to* 0 *in "log-moment"time average sense, which also implies that* $\limsup_{t\to\infty} \mathbb{E}_u \frac{1}{t}\int_0^t N^p(s)ds > 0$, $p \in (0,1)$. *In this case,* μ_2 *becomes a repeller and the system* (2.1) *becomes weakly persistent in the sense that solution* $U(t)$ *does not converge to* μ_2 *a.s.*

In order to interpret this theorem and give some biological implications, we need to find relations between $\boldsymbol{\lambda}$, a, and noise intensities. We consider $\boldsymbol{\lambda} = \boldsymbol{\lambda}(a, \tau_1, \tau_2)$ as a function of the parameter a, τ_1, and τ_2. The following lemma lists some possible relations among these parameters.

Lemma 2.1 *The existence of the second moment of the invariant measure* π *requires the noise intensity* τ_1 *is bounded as* $\tau_1^2 < 2(b+1)^2$.

(1) *When* $\frac{1}{4d}(\frac{c}{b+1})^2\tau_1^2 + \tau_2^2 \geq \frac{c^2}{2d}$ *and* $\tau_1^2 < 2(b+1)^2$, *we have* $\boldsymbol{\lambda} < 0$.

(2) *When* $\frac{1}{4d}(\frac{c}{b+1})^2\tau_1^2 + \tau_2^2 < \frac{c^2}{2d}$, *there exist the values* a_1 *and* a_2 *of the parameter* a *with* $a_{s_1} < a_1$ *and* $a_1 < a_2$, *where* $\boldsymbol{\lambda}(a_1) = \boldsymbol{\lambda}(a_2) = 0$. *We have two cases:*

- *if* $a \in (0, a_1) \cup (a_2, \infty)$, *then* $\boldsymbol{\lambda} < 0$;
- *if* $a \in (a_1, a_2)$, *then* $\boldsymbol{\lambda} > 0$.

In the case of $\frac{1}{4d}(\frac{c}{b+1})^2\tau_1^2 + \tau_2^2 < \frac{c^2}{2d}$, a_2 *can be considered as a function of* τ_1 *and* τ_2 *and then it is increasing with two noise intensities;* $a_2 > a_{s_2}$ *for small values of* τ_1 *and* τ_2 *while* $a_2 < a_{s_2}$ *for large values of* τ_1 *and* τ_2.

It is easy to see that the mean of the inverse gamma distribution π approaches $\frac{a}{b+1}$ when (τ_1, τ_2) approaches $(0, 0)$. Hence, we may say that the ergodic invariant measures of the stochastic system (2.1), μ_1 and μ_2, correspond to the equilibrium solutions of the deterministic system (2.2), E_0 and E_1, respectively. There should exist another ergodic invariant measure of the system (2.1) which corresponds to the equilibrium solution E_2 of the system (2.2). However, it is difficult to prove this property because our model has a rational function noise term and lacks boundedness. We will list this as an open problem for future studies. We only can say that, when $\boldsymbol{\lambda} > 0$, any solution starting in the interior of the positive invariant domain D will not approach neither μ_1 nor μ_2 on the boundary ∂D. In other words, this solution will stay at the interior of D; it may either approach an invariant measure supported by the interior of D or stochastically oscillate.

Biologically, we obtain more subtle implications related to two parameters, a and c, and noise intensities from our stochastic model (2.1).

Interpretation 2.2 *If the noise of chemotactic coefficient* c *is big enough,* $\tau_2^2 \geq \frac{c^2}{2d}$ *while* $\tau_1^2 < 2(b+1)^2$, *then the tumor always belongs to type muIDH1 no matter how large the chemoattractant production rate* a *is. In this case, the tumor type is determined by the chemotactic coefficient. This is a new situation when randomness and stochastic effects are introduced into the model.*

When both noise intensities are not big, namely $\tau_2^2 < \frac{c^2}{2d}$ *and* $\tau_1^2 < 2(b+1)^2$, *the tumor type is largely determined by the chemoattractant production rate which is similar as the deterministic model (2.2). However, we have more subtle situations. The critical value of the chemoattractant production rate that determines tumor type in the stochastic model is greater than that in the deterministic model which is the case* $a_{s_1} < a_1$. *This is reasonable because the stochastic model counts parameter randomness and environmental noise. Another new situation is that, when the value of the chemoattractant production rate is greater than* a_2, *the tumor type seems to be switched again. A reasonable interpretation may be as follows. The tumor type is not changed again, but periodic solutions or pulse solutions with low immune cell contents appear.*

It is clear that the stochastic model confirms the result about tumor type classification from our PDE model by the chemoattractant production rate with emphasizing the importance of the chemotactic coefficient. The classification of tumor types with these parameters in either model is stable in the sense of parameter perturbations.

3 Numerical simulations and discussion

3.1 Numerical simulations with biological interpretations

In order to illustrate our analytical results, we utilize some data from our previous research (see Niu et al. 2020) to simulate our model of deterministic type and stochas-

Table 1 Parameters and their values

Parameters	Description	Values	Dimensions
λ	Proliferation rate of glioma cells	0.48	day^{-1}
m	Maximum of chemoattractant production rate	0.7–17	10^5 pg/ml day
β	Michaelis constant	0.1	10^6 cells/mm^3
γ	Chemoattractant degradation rate	2.185	10^2/day
α	Chemotactic coefficient	0.6	mm^2 ml/day pg
ρ	Clearance rate of immune cells	0.9	day^{-1}
C	Cell density of tumor tissue	1	10^6 cells/mm^3

tic type. Before we do so, we would like to explain some connection between our current models and previous PDE model and related experimental work. In our study (Niu et al. 2020), our PDE model fits our experimental results, for example, tumor volume changes over time in under several conditions. In these simplified models, there is no spatial variable. However, our quantities are now still cell number densities and chemoattractant concentration as in our PDE model, not cell numbers and chemoattractant quantity in general ODE/SDE models. In this way, our current models inherit dynamical behaviors and some sort of spatial information, and we will be able to use the parameter values from our previous work which were estimated from our experimental results. All parameters of the system (1.2), except the noise intensities τ_1 and τ_2, are listed in Table 1, which are from our study (Niu et al. 2020). After non-dimensionalization, the parameters of the stochastic system (2.1) and its corresponding deterministic system (2.2) are $r = 0.22$, $b = 0.1$, $c = 0.275$, and $d = 0.412$. For the sake of simplicity, we conduct numerical simulations based on the non-dimensionalized SDE system (2.1) and ODE system (2.2). Thus, the units of glioma cells, concentration of chemoattractants, and infiltrated immune cells are not absolute number densities but relative numbers. The quantities such as G, A, and N are, the portion of glioma cells, concentration of chemoattractants, and infiltrated immune cells over the tumor carrying capacity, respectively. We just indicate them as relative glioma cells and so on in the figures. For the time, it can be regarded as relative time since $\tau = \gamma t$. In all the figures below, we will simulate the trajectories of the ODE system (2.2) and the SDE system (2.1) with initial value $(0.5, 0.1, 0.1)$ and all parameters fixed except the parameter a and the noise intensities τ_1 and τ_2.

In Sect. 4, we found two thresholds of the parameter a which are $a_{s_1} = 1.65$ and $a_{s_2} = 2.5579$. The parameter a measures how much chemoattractants can be produced by tumor cells in a unit time. The analysis in Sect. 4 shows this parameter plays a central role in determining the dynamics of the ODE system (2.2).

When a is below a_{s_1}, Fig. 1 indicates that relative glioma cells are increasing to its carrying capacity while relative infiltrated immune cells decay to zero. This can be explained as follows. At the beginning, glioma cells secrete chemoattractants that form a dynamic gradient field to facilitate migration of immune cells into the tumor. However, the concentration of chemoattractants is not strong enough to attract immune

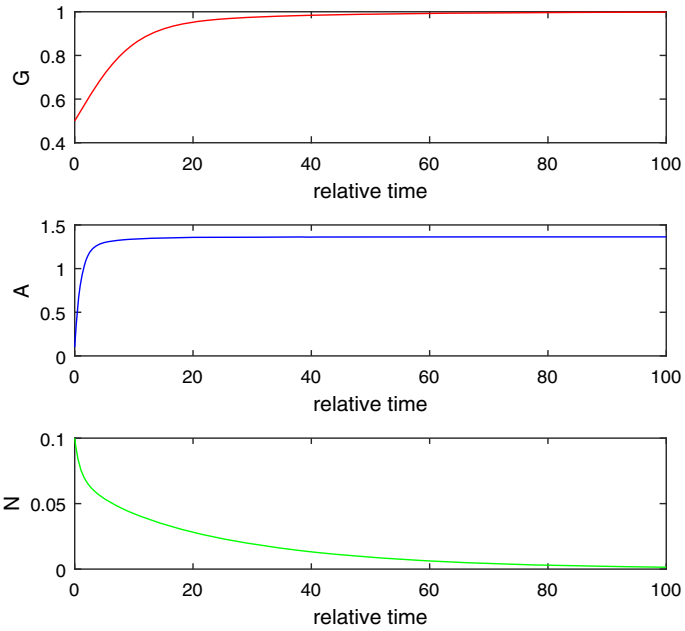

Fig. 1 Deterministic solution paths when $a = 1.5$

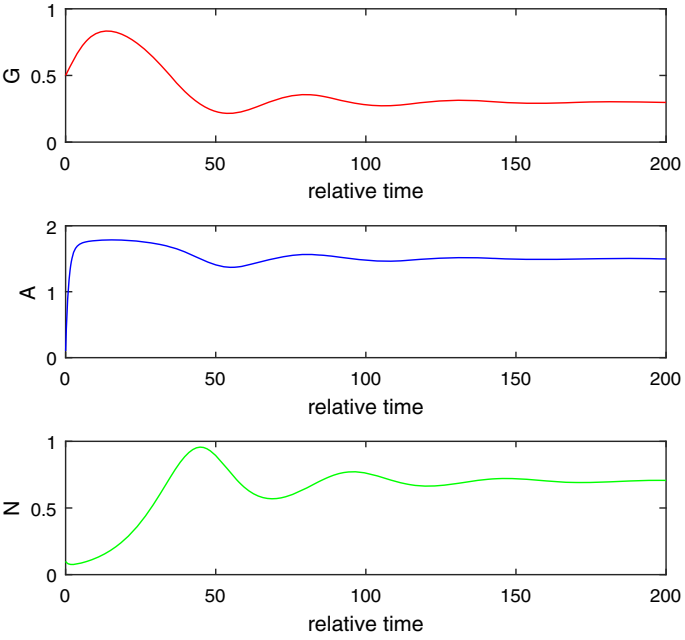

Fig. 2 Deterministic solution paths when $a = 2$

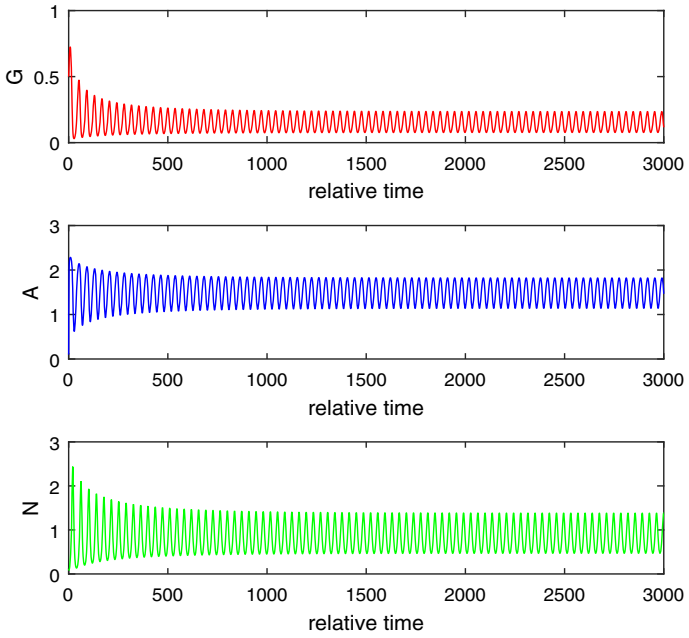

Fig. 3 Deterministic solution paths when $a = 2.6$

cells. So the number density of infiltrated immune cells goes down while the number density of glioma cells keep growing.

When a is between a_{s_1} and a_{s_2}, Fig. 2 shows relative glioma cells, relative concentration of chemoattractants, and relative infiltrated immune cells eventually settle down into an equilibrium state (which is the positive equilibrium E_2). This is because after recruiting a portion of immune cells, the number density of glioma cells becomes oscillatory and starts reaching a steady state. But then the concentration of chemoattractants becomes saturated, consequently immune cell migration undergoes a slowdown phase and finally its number density reaches an equilibrium state.

When a is slightly bigger than a_{s_2}, Fig. 3 indicates that the populations of glioma cells and infiltrated immune cells and concentration of chemoattractants undergo an oscillating process. As in the proof of Sect. 4, there is only one stable periodic solution arising from the Hopf bifurcation at $a_{s_2} = 2.5579$. This solution represents the predator-prey dynamics among glioma cells, chemoattractants, and infiltrated immune cells.

As a is becoming large, say $a = 5$, the solution behaves differently. Figure 4 shows populations of glioma cells and infiltrated immune cells can reach a very small value. It represents a pulsating oscillation. The minimum of the pulsating oscillation solution is decreasing as a increases.

In Sect. 5, we analyzed the SDE system (2.1) which is obtained from the ODE system (2.2) by perturbing the parameter a, the relative maximum of the chemoattractant production rate, and the parameter c, the relative chemotactic coefficient. We found a

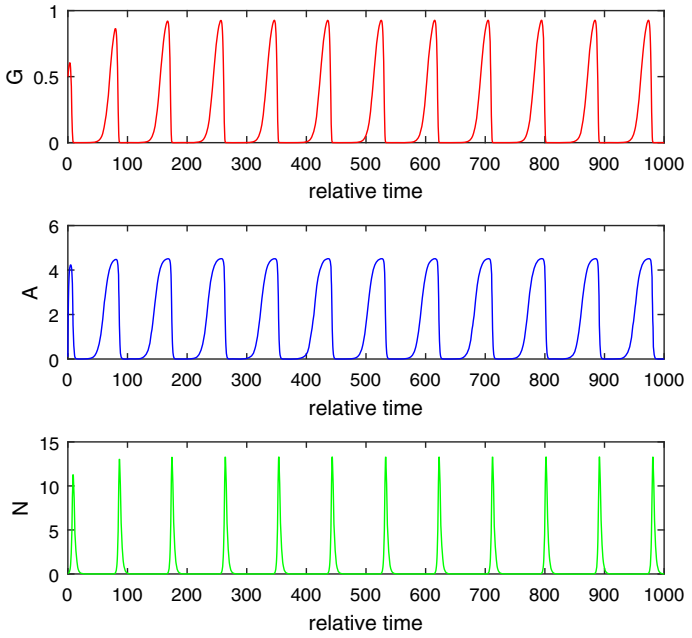

Fig. 4 Deterministic solution paths when $a = 5$

threshold

$$\boldsymbol{\lambda} = \boldsymbol{\lambda}(a, \tau_1, \tau_2) = \frac{ac}{b+1} - d - \frac{\tau_2^2 a^2}{2(b+1)^2 - \tau_1^2}, \tag{3.1}$$

to determine the extinction and weak persistence of the SDE system (2.1) provided $\tau_1 < (b+1)\sqrt{2}$. According to Lemma 2.1, we can regard $\boldsymbol{\lambda}$ as a function of a, τ_1, and τ_2. Actually, $\boldsymbol{\lambda}$ is a quadratic function of a with negative leading coefficient, which has two positive real solutions

$$a_{1,2} = \frac{c(2(b+1)^2 - \tau_1^2)}{2\tau_2^2(b+1)} \mp \frac{\sqrt{2(b+1)^2 - \tau_1^2}}{\tau_2} \sqrt{\frac{c^2(2(b+1)^2 - \tau_1^2)}{4\tau_2^2(b+1)^2} - d}$$

provided that $\frac{1}{4d}(\frac{c}{b+1})^2\tau_1^2 + \tau_2^2 < \frac{c^2}{2d}$. The main theorem 2.2 showed that population of glioma cells reaches its carrying capacity and population of infiltrated immune cells goes extinct when $\boldsymbol{\lambda} < 0$. By Lemma 2.1, this condition is equivalent to either $\frac{1}{4d}(\frac{c}{b+1})^2\tau_1^2 + \tau_2^2 \geq \frac{c^2}{2d}$, $\tau_1 < (b+1)\sqrt{2}$ or $\frac{1}{4d}(\frac{c}{b+1})^2\tau_1^2 + \tau_2^2 < \frac{c^2}{2d}$, $a \in (0, a_1) \cup (a_2, \infty)$. We observe that the condition for the extinction of the system (2.1) is quite subtle and complicated. Particularly, when noise intensities are small and a is large enough, the solution of the system (2.1) approaches the boundary of the positive invariant domain and hence the system goes extinct. Furthermore, when noise intensities are large enough, the solution of the system (2.1) is suppressed to approach

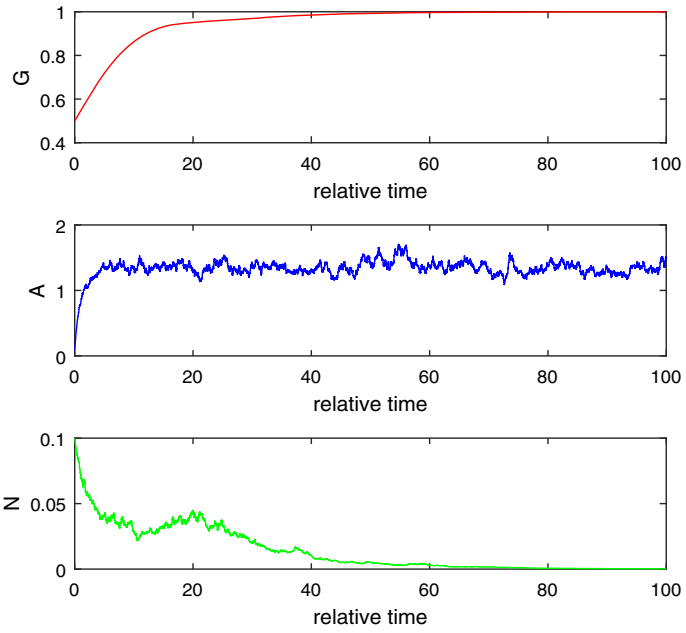

Fig. 5 Stochastic solution paths when $a = 1.5$, $\tau_1 = \tau_2 = 0.1$

the boundary no matter how large the value of a is. Contrary to the complexity of the extinction conditions, the weak persistent condition for the system (2.1) is quite simple. All populations become weakly persistent when $\boldsymbol{\lambda} > 0$, which is equivalent to $\frac{1}{4d}(\frac{c}{b+1})^2\tau_1^2 + \tau_2^2 < \frac{c^2}{2d}$ and $a_1 < a < a_2$. With parameters as in simulating ODE system (2.2), we illustrate the extinction and weak persistence of the SDE system (2.1) in the following two examples.

Example 1. We demonstrate the situation when $\boldsymbol{\lambda} < 0$. Take $a = 1.5$, $\tau_1 = \tau_2 = 0.1$ in Fig. 5 and take $a = 5$, $\tau_1 = 0.1$, $\tau_2 = 0.4$ in Fig. 6. Both figures indicate that in a short period of time glioma cells increases to the tumor carrying capacity and infiltrated immune cells decay to zero exponentially fast, while the concentration of chemoattractants becomes saturated.

Example 2. We simulate the stochastic trajectories when $\boldsymbol{\lambda} > 0$. Take $a = 2.5$, $\tau_1 = \tau_2 = 0.1$ in Fig. 7. This picture shows that glioma cells, chemoattractants, and infiltrated immune cells coexist and interact in the predator-type dynamics. Even though the solution path represents an oscillatory behavior as in the deterministic case, its pattern cannot be predicted. Next, take $a = 5$, $\tau_1 = \tau_2 = 0.1$ in Fig. 8. This figure indicates the solution path still weakly persist but represents a pulsating oscillation.

Our PDGF models of the deterministic type and stochastic type are able to predict the dynamical behavior of these two types of gliomas. As an example, the mathematical model of PDE type in Niu et al. (2020) predicted that the wild-type tumor mice will survive longer if the immune cells are blocked to migrate into the tumor. The infiltrated immune cells help to drive the aggressiveness of gliomas and then increase

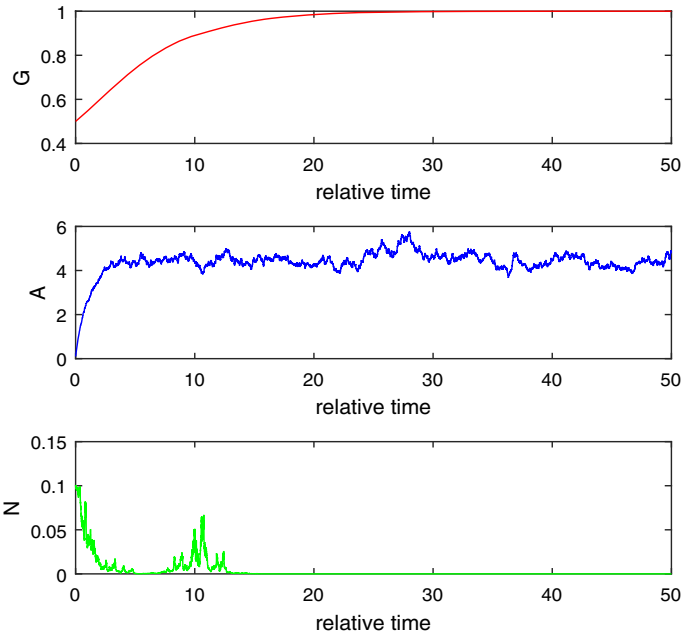

Fig. 6 Stochastic solution paths when $a = 5$, $\tau_1 = 0.1$, $\tau_2 = 0.4$

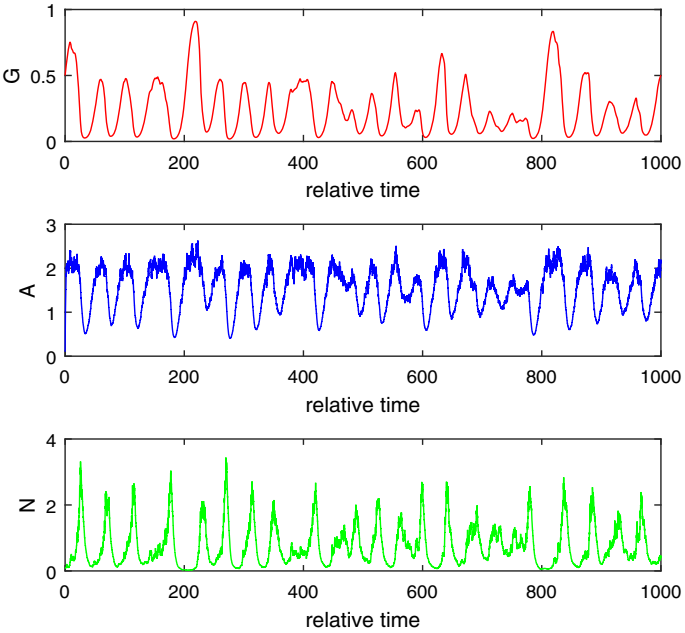

Fig. 7 Stochastic solution paths when $a = 2.5$, $\tau_1 = \tau_2 = 0.1$

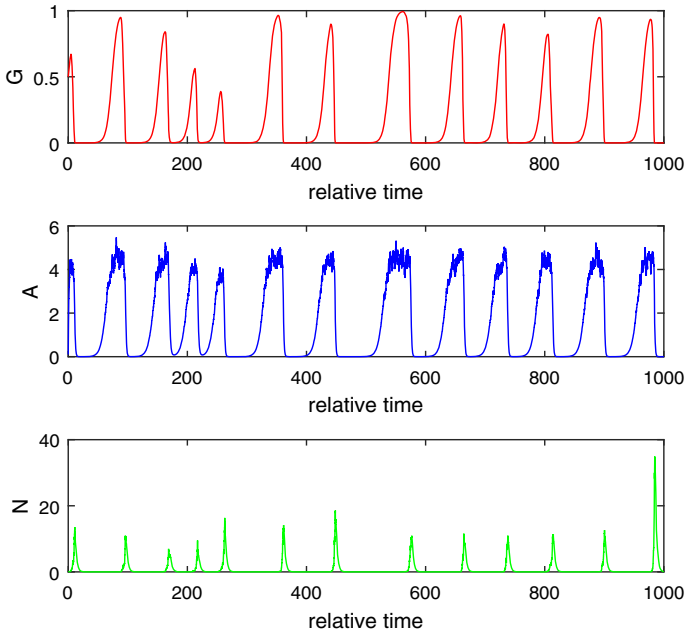

Fig. 8 Stochastic solution paths when $a = 5$, $\tau_1 = \tau_2 = 0.1$

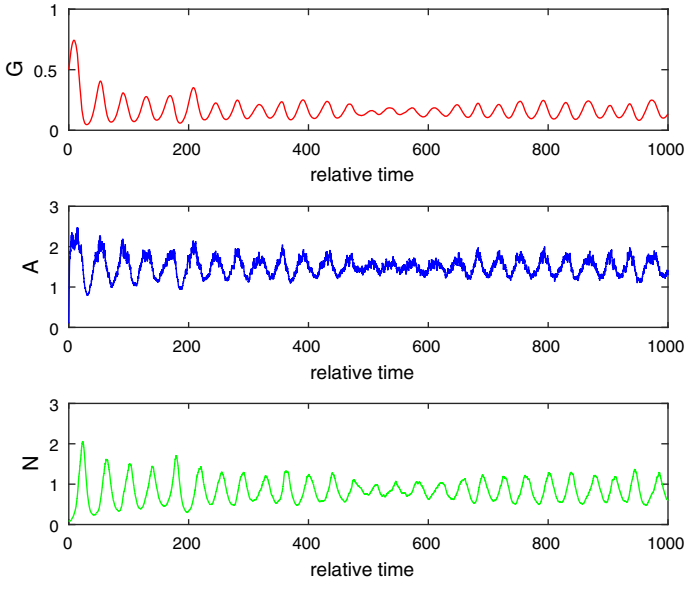

Fig. 9 Stochastic solution paths when $a = 2.5$, $\tau_1 = 0.1$, $\tau_2 = 0.01$

production of chemoattractants. So in order to block immune cells to infiltrate into the tumor, we can reduce the chemotactic strength which is represented by the relative chemotactic coefficient and its corresponding noise intensity τ_2. Using our SDE model, take $a = 2.5$, $\tau_1 = 0.1$ as in Fig. 7 but τ_2 is decreased to 0.01. Fig. 9 shows that the solution oscillates less wildly and hence glioma cells of wild type become less aggressive.

It should be noticed that we only plot one realization for each case above for demonstration purpose. We actually simulated many realizations for each case, and observed that these realizations share a similar pattern in each case. Therefore, we present one typical path for each case.

3.2 Discussion

The motivation of this study is to understand the roles of two parameters, the chemoattractant production rate and chemotactic coefficient, in the infiltrating dynamics of immune cells into tumors. In our experiments and modeling of immune cells infiltrating to tumor sites in terms of PDE free boundary problem, we computationally found these two parameters are very important. The chemoattractant production rate by tumor cells determines two types of gliomas according to the range of its value, or aggressiveness of gliomas, while the chemotactic coefficient determines the possibilities of immune cells migrating to tumor sites. We would like to know how stable our conclusion about these two parameters are when they are perturbed or when stochastic effects are counted in noisy tumor growth environments. This is a medical relevant question because there are many randomness and stochastic effects in medical problems. Due to difficulties of analysis of free boundary problem, we propose to utilize stochastic differential equations to explore this question. The first step is to reduce the free boundary PDE system to an ODE system. We then add white noises to these two parameters according to their properties, and obtain a system of Ito stochastic differential equations. We carry out detailed studies about these two models. We see the correspondence between equilibrium solutions of the deterministic system and ergodic invariant measures of the stochastic system according to different value range of the chemoattractant production rate and chemotactic coefficient. For the stochastic system, there appears some new features. For example, when both noise intensities are not big comparing with the chemotactic coefficient, the stochastic model behaves more or less similarly as the deterministic counterpart. However, when both noise intensities are big, particularly when the noise intensity of the chemotactic coefficient is greater than a scaled chemotactic coefficient, the occupation measure of the stochastic solution converges to the invariant measure μ_2 and hence the stochastic system behaves uniformly as muIDH gliomas.

Mathematically, the noise term for the chemoattractant production rate is of a rational function which creates difficulties for analysis. For the deterministic system, there is a stable equilibrium solution E_2 which is in the interior of the positive invariant domain D. We expect that there is a ergodic invariant measure for the stochastic system which corresponds to E_2. However, it is not easy to show the existence of such

invariant measure supported by the interior of the positive invariant domain D. We would like to list this question as an open problem.

For the deterministic system, we show there is a Hopf bifurcation and appearance of one family of periodic solutions when the value of the chemoattractant production rate passes through a second critical value. For the stochastic model, we observe some periodical solution paths. However, it is difficult to show the existence of Hopf bifurcations in stochastic models. We would also like to list this question as an open problem.

Although the stochastic model is obtained by a simplification of PDE model, it is interesting on its own. Besides the two open problems mentioned above, it will be interesting to explore what new features we can obtain if we also perturb the tumor growth rate, because one way to model aggressiveness of tumors is to increase growth rate. We plan to study this problem in the future.

4 Analysis of the ODE model

This section is devoted to the proof of Theorem 2.1 for the ODE system (2.2).

4.1 Preliminaries

Since the right-hand side of each equation of the system (2.2) is a continuously differentiable function with respect G, A, and N, by existence and uniqueness theorem of an ODE system [see Theorem 1 on page 89 in Perko (2006)], the system (2.2) with initial value $(G(0), A(0), N(0))$ always has a unique solution $(G(t), A(t), N(t))$ defined on the maximal interval $[0, \zeta)$. It is important to know if the solution exists for all time $t \geq 0$. Our result is summarized in the following theorem.

Theorem 4.1 *If $G(0) \geq 0$, $A(0) \geq 0$, and $N(0) \geq 0$ then $G(t) \geq 0$, $A(t) \geq 0$, and $N(t) \geq 0$ for all $t \in [0, \zeta)$. Furthermore, if $0 \leq G(0) \leq 1$, $0 \leq A(0) \leq \frac{a}{b+1}$, and $N(0) \geq 0$ then $0 \leq G(t) \leq 1$, $0 \leq A(t) \leq \frac{a}{b+1}$, $N(t) \geq 0$ for all $t \in [0, \zeta)$. Finally, we can conclude that the solution $(G(t), A(t), N(t))$ exists for all time $t \geq 0$, i.e. $\zeta = \infty$.*

Proof First, assume that $G(0) \geq 0$, $A(0) \geq 0$, and $N(0) \geq 0$. By the first equation of (2.2), for all $t \in (0, \zeta)$

$$G(t) = G(0) \exp\left\{\int_0^t r(1 - G(s) - N(s))ds\right\},$$

which implies that $G(t) \geq 0$ for all $t \in (0, \zeta)$ because $G(0) \geq 0$. The second equation of (2.2) implies for $t \in (0, \zeta)$

$$A(t) = A(0)e^{-t} + e^{-t} \int_0^t \frac{aG(s)}{b + G(s)} e^s ds.$$

Since $A(0) \geq 0$ and $G(s) \geq 0$ for all $s \in [0, \zeta)$, $A(t) \geq 0$ for all $t \in (0, \zeta)$. From the last equation of (2.2), we get for all $t \in (0, \zeta)$

$$N(t) = N(0) \exp\left\{\int_0^t [cA(s) - d]ds\right\}.$$

As $N(0) \geq 0$, so $N(t) \geq 0$ for all $t \in (0, \zeta)$.

Next, assume that $0 \leq G(0) \leq 1$, $0 \leq A(0) \leq \frac{a}{b+1}$, and $N(0) \geq 0$. By the above proof $G(t)$, $A(t)$, and $N(t)$ are non-negative for all $t \in [0, \zeta)$. Since $N(t) \geq 0$, $G' = rG(1 - G - N) \leq rG(1 - G)$. Because $G(0) \leq 1$, by comparison theorem $G(t) \leq 1$ for all $t \in [0, \zeta)$. But, then from the second equation we have $A' = \frac{aG}{b+G} - A \leq \frac{a}{b+1} - A$. Again the comparison theorem implies $A(t) \leq \frac{a}{b+1} - (\frac{a}{b+1} - A(0))e^{-t}$. Since $A(0) \leq \frac{a}{b+1}$, $A(t) \leq \frac{a}{b+1}$ for all $t \in [0, \zeta)$. Now define the domain

$$E = \left\{(G, A, N) : 0 \leq G \leq 1,\ 0 \leq A \leq \frac{a}{b+1},\ N \geq 0\right\}.$$

We have proved that given any $(G(0), A(0), N(0)) \in E$ the system (2.2) with this initial value has a unique solution $(G(t), A(t), N(t)) \in E$ defined on the maximal interval $[0, \zeta)$. In order to prove that $\zeta = \infty$, consider the following compact set contained in E

$$K = \left\{(G, A, N) : 0 \leq G \leq 1,\ 0 \leq A \leq \frac{a}{b+1},\ 0 \leq N \leq M\right\}$$

for some constant M which is to be chosen. By way of contradiction, assume that $\zeta < \infty$. Notice that we can assume that $A(0)$ and $N(0)$ are very small initial values that is close to 0 because $A(0)$ and $N(0)$ represent relative concentration of chemoattractant and relative number density of infiltrated immune cells at the beginning, respectively. Then we can suppose that $A(0) \leq \frac{a}{b+1}$, by above proof $A(t) \leq \frac{a}{b+1}$ for all $t \in [0, \zeta)$. The third equation of the system (2.2) implies that $N'(t) \leq \frac{ac-bd-d}{b+1}N$ and then by comparison theorem $N(t) \leq N(0)\exp\left\{\frac{ac-bd-d}{b+1}t\right\}$. Choose $M > 0$ big enough so that for all finite times $t \in (0, \zeta)$

$$N(0)\exp\left\{\frac{ac - bd - d}{b+1}t\right\} \leq M.$$

Thus $N(t) \leq M$ for all $t \in (0, \zeta)$ and hence $(G(t), A(t), N(t)) \in K$ for all $t \in (0, \zeta)$. This contradicts the conclusion of Theorem 3 on page 91 in Perko (2006). Therefore $\zeta = \infty$. □

4.2 Equilibrium analysis

Define the domain $D = \{(G, A, N) : 0 \leq G \leq 1, A \geq 0, N \geq 0\}$. By the Theorem 4.1, D is a positive invariant domain for the system (2.2). So we refer it as

a "global" domain. Let $U = (G, A, N)^T$ and $f(U) = (rG(1 - G - N), \frac{aG}{b+G} - A, cAN - dN)^T$. The equilibrium solutions of (2.2) are the solutions to $f(U) = 0$, which is equivalent to

$$\begin{aligned} &rG(1 - G - N) = 0, \\ &\frac{aG}{b + G} = A, \\ &(cA - d)N = 0. \end{aligned}$$

It is easy to obtain equilibrium solutions as follows.

- If $0 < ac \leq d + bd$ then the system (2.2) has 2 equilibrium solutions $E_0 = (0, 0, 0)$ and $E_1 = (1, \frac{a}{b+1}, 0)$.
- If $ac > d + bd$ then the system (2.2) has 3 equilibrium solutions which are E_0, E_1, and the unique positive equilibrium solution $E_2 = \left(\frac{bd}{ac-d}, \frac{d}{c}, \frac{ac-d-bd}{ac-d}\right)$.

Now we analyze the stability of all equilibrium solutions when the parameter a is varied. First, the variational matrix of the system (2.2) is given by

$$Df(U) = \begin{bmatrix} r - 2rG - rN & 0 & -rG \\ \frac{ab}{(b+G)^2} & -1 & 0 \\ 0 & cN & cA - d \end{bmatrix}.$$

A. At $E_0 = (0, 0, 0)$, the variational matrix is $Df(E_0) = \begin{bmatrix} r & 0 & 0 \\ a/b & -1 & 0 \\ 0 & 0 & -d \end{bmatrix}$, having r, -1, and $-d$ as its eigenvalues. Since $r > 0$, E_0 is unstable.
B. At $E_1 = (1, \frac{a}{b+1}, 0)$, the variational matrix is

$$Df(E_1) = \begin{bmatrix} -r & 0 & -r \\ \frac{ab}{(b+1)^2} & -1 & 0 \\ 0 & 0 & \frac{ac-d-bd}{b+1} \end{bmatrix}$$

which has 3 eigenvalues $\lambda_1 = -r$, $\lambda_2 = -1$, and $\lambda_3 = \frac{ac-d-bd}{b+1}$. If $0 < ac < bd + d$ then $\lambda_3 < 0$, so E_1 is locally asymptotically stable. If $ac > bd + d$ then $\lambda_3 > 0$, hence E_1 is unstable.
C. In fact, when $0 < ac < bd + d$, we can show that E_1 is globally stable. For convenience, we make a translation of variables $G = 1 - \overline{G}$, $A = \frac{a}{b+1} - \overline{A}$, and $N = \overline{N}$. The equilibrium solution E_1 is translated to $\overline{E}_1 = (0, 0, 0)$. Then, after dropping all the bars over variables, the system (2.2) becomes

$$\begin{aligned} \frac{dG}{dt} &= r(1 - G)(N - G), \\ \frac{dA}{dt} &= \frac{a}{b + 1} - A - \frac{a(1 - G)}{b + 1 - G}, \end{aligned}$$

$$\frac{dN}{dt} = -cAN + \frac{ac - bd - d}{b+1}N, \tag{4.1}$$

while the domain D is translated into $D_1 = \{(G, A, N) : 0 \le G \le 1, A \le \frac{a}{b+1}, N \ge 0\}$. Let $(G(0), A(0), N(0)) \in D_1$, then by Theorem 4.1 we have $(G(t), A(t), N(t)) \in D_1$ for $t \ge 0$. Since $-cAN \le 0$, the third equation implies $N' \le \frac{ac-bd-d}{b+1}N$. By comparison theorem, $0 \le N(t) \le N(0)\exp\{\frac{ac-bd-d}{b+1}t\} \to 0$ as $t \to \infty$ since $ac - bd - d < 0$. Thus $N(t)$ decays to 0 exponentially fast. Now it makes sense to assume that $G(0) < 1$ because if $G(0) = 1$ then it would mean that originally we don't have any glioma cells in tumor tissue. Then $0 < G(t) < 1$ for all $t \ge 0$. So by the first equation of (4.1) we have

$$\frac{dG(t)}{1 - G(t)} = r(N(t) - G(t)).$$

Integrating both sides from 0 to t yields

$$G(t) = 1 - \frac{1 - G(0)}{\exp\{\int_0^t r(N(s) - G(s))\, ds\}}. \tag{4.2}$$

Since $N(t) \ge 0$ for all $t \ge 0$ and $N(t) \to 0$ exponentially as $t \to \infty$, $\lim_{t\to\infty} \exp\{\int_0^t N(s)ds\}$ exists and is positively finite. As $-\int_0^t G(s)ds$ is decreasing with respect to t, so $\lim_{t\to\infty} \exp\{-\int_0^t G(s)ds\}$ exists and is either zero or positively finite. This follows that $\lim_{t\to\infty} \exp\{\int_0^t r(N(s) - G(s))ds\}$ exists and is either zero or positively finite. Thus $\lim_{t\to\infty} G(t)$ exists. As $0 < G(t) < 1$ for all $t \ge 0$, so $0 \le \lim_{t\to\infty} G(t) \le 1$. Due to (4.2), $\lim_{t\to\infty} \exp\{\int_0^t r(N(s) - G(s))ds\}$ cannot be zero. Therefore $\lim_{t\to\infty} \exp\{\int_0^t r(N(s) - G(s))ds\}$ is positively finite. Since $G(0) < 1$, by (4.2) we obtain $\lim_{t\to\infty} G(t) < 1$. Again, by the first equation of (4.1)

$$\frac{dG(t)}{dt} = rN(t)(1 - G(t)) - rG(t)(1 - G(t)).$$

Integrating both sides from 0 to t and then dividing by t give

$$\frac{G(t) - G(0)}{t} = \frac{1}{t}\int_0^t rN(s)(1 - G(s))ds - \frac{1}{t}\int_0^t rG(s)(1 - G(s))ds. \tag{4.3}$$

Since $0 \le 1 - G(s) \le 1$ for all $s \ge 0$ and $N(s) \ge 0$ for all $s \ge 0$,

$$0 \le \frac{1}{t}\int_0^t rN(s)(1 - G(s))ds \le \frac{1}{t}\int_0^t rN(s)ds.$$

By L'Hospital's Rule (Lee 1977, p. 28), since $\lim_{t\to\infty} N(t) = 0$, $\lim_{t\to\infty} \frac{1}{t}\int_0^t rN(s)ds = \lim_{t\to\infty} rN(t) = 0$. So letting $t \to \infty$ in (4.3) yields

$$\lim_{t\to\infty} \frac{1}{t}\int_0^t rG(s)(1-G(s))ds = 0.$$

By the above proof, $\lim_{t\to\infty} G(t)(1-G(t))$ exists and hence, by L'Hospital's Rule we get

$$\lim_{t\to\infty} G(t)(1-G(t)) = \lim_{t\to\infty} \frac{1}{t}\int_0^t rG(s)(1-G(s))ds = 0.$$

Since $\lim_{t\to\infty} G(t) < 1$, $\lim_{t\to\infty} G(t) = 0$. Finally, we show that $\lim_{t\to\infty} A(t) = 0$. From the second equation of (4.1), we have

$$A(t) = A(0)e^{-t} + e^{-t}\int_0^t \left(\frac{a}{b+1} - \frac{a(1-G(s))}{b+1-G(s)}\right)e^s ds.$$

By L'Hospital's Rule,

$$\begin{aligned}
\lim_{t\to\infty} e^{-t}\int_0^t \left(\frac{a}{b+1} - \frac{a(1-G(s))}{b+1-G(s)}\right)e^s\, ds &= \lim_{t\to\infty} \frac{\int_0^t \left(\frac{a}{b+1} - \frac{a(1-G(s))}{b+1-G(s)}\right)e^s\, ds}{e^t} \\
&= \lim_{t\to\infty} \frac{\left(\frac{a}{b+1} - \frac{a(1-G(t))}{b+1-G(t)}\right)e^t}{e^t} \\
&= \lim_{t\to\infty} \left(\frac{a}{b+1} - \frac{a(1-G(t))}{b+1-G(t)}\right) \\
&= \frac{a}{b+1} - \frac{a}{b+1} = 0.
\end{aligned}$$

Thus $\lim_{t\to\infty} A(t) = 0$. Therefore, $\overline{E}_1$ is globally stable with respect to the system (4.1). In other words, the system (2.2) has a global attractor E_1.

D. When $ac = bd + d$, the system (4.1) becomes

$$\begin{aligned}
\frac{dG}{dt} &= r(1-G)(N-G), \\
\frac{dA}{dt} &= \frac{a}{b+1} - A - \frac{a(1-G)}{b+1-G}, \\
\frac{dN}{dt} &= -cAN.
\end{aligned} \tag{4.4}$$

Let $U=(G, A, N)^T$ and $F(U)=\left(r(1-G)(N-G), \frac{a}{b+1}-A-\frac{a(1-G)}{b+1-G}, -cAN\right)^T$, then the variational matrix at $\overline{E}_1$ is

$$L := DF(\overline{E}_1) = \begin{bmatrix} -r & 0 & r \\ \frac{ab}{(b+1)^2} & -1 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

which has two negative eigenvalues $\lambda_1 = -r$, $\lambda_2 = -1$, and one eigenvalue $\lambda_3 = 0$. To study the stability of the equilibrium solution $\overline{E}_1$, we will utilize the center manifold theorem to reduce the system (4.4) into a center manifold, and then look at the reduced system. Without loss of generality, assume that $r \neq 1$. Then 3 corresponding eigenvectors with respect λ_1, λ_2, and λ_3 are $V_1 = \left(\frac{(1-r)(b+1)^2}{ab}, 1, 0\right)^T$, $V_2 = (0, 1, 0)^T$, and $V_3 = \left(1, \frac{ab}{(b+1)^2}, 1\right)^T$. We set a transformation matrix to be $T = (V_1, V_2, V_3)$. Then the system (4.4) can be written as $\frac{dX}{dt} = LX + F_1$, where $F_1 = \left(-rGN + rG^2, \frac{a}{b+1} - \frac{a(1-G)}{b+1-G} - \frac{ab}{(b+1)^2}G, -cAN\right)^T$. Set $U = TY$ where $Y = (y_1, y_2, y_3)^T$, then the system (4.4) is equivalent to

$$\frac{dY}{dt} = T^{-1}LTY + T^{-1}F_1,$$

where $T^{-1}LT = \text{diag}(-r, -1, 0)$, and $G = \frac{(1-r)(b+1)^2}{ab}y_1 + y_3$, $A = y_1 + y_2 + \frac{ab}{(b+1)^2}y_3$, and $N = y_3$. Denote $T^{-1}F_1 = (f_1, f_2, f_3)^T$, then

$$\begin{aligned}
f_1 &= \frac{ab}{(1-r)(b+1)^2}\left[\frac{r(1-r)^2(b+1)^4}{a^2b^2}y_1^2\right. \\
&\quad \left. + \left(\frac{r(1-r)(b+1)^2}{ab} + c\right)y_1y_3 + cy_2y_3 + \frac{abc}{(b+1)^2}y_3^2\right] \\
&= A_{11}y_1^2 + A_{13}y_1y_3 + A_{23}y_2y_3 + A_{33}y_3^2, \\
f_2 &= \frac{rab}{(1-r)(b+1)^2}\left[-\frac{(1-r)^2(b+1)^4}{a^2b^2}y_1^2 - \left(\frac{(1-r)(b+1)^2}{ab} + c\right)y_1y_3\right. \\
&\quad \left. -cy_2y_3 - \frac{abc}{(b+1)^2}y_3^2\right] \\
&\quad + \frac{a}{b+1} - \frac{a - \frac{(1-r)(b+1)^2}{b}y_1 - ay_3}{b+1-\frac{(1-r)(b+1)^2}{ab}y_1 - y_3} - (1-r)y_1 - \frac{ab}{(b+1)^2}y_3 \\
&= B_{11}y_1^2 + B_{13}y_1y_3 + B_{23}y_2y_3 + B_{33}y_3^2 + \frac{a}{b+1} - \frac{a - B_1y_1 - ay_3}{b+1-B_2y_1-y_3} + B_3y_1 + B_4y_3 \\
&= B_{11}y_1^2 + B_{13}y_1y_3 + B_{23}y_2y_3 + B_{33}y_3^2 + K(y_1, y_2, y_3),
\end{aligned}$$

$$f_3 = -cy_1y_3 - cy_2y_3 - \frac{abc}{(b+1)^2}y_3^2$$
$$= C_{13}y_1y_3 + C_{23}y_2y_3 + C_{33}y_3^2,$$

where A_{ij}, B_{ij}, C_{ij}, and B_i are easily determined and

$$K(y_1, y_2, y_3) = \frac{a}{b+1} - \frac{a - B_1y_1 - ay_3}{b+1-B_2y_1-y_3} + B_3y_1 + B_4y_3.$$

Note that $g \in C^\infty$, $K(0,0,0) = 0$, and $DK(0,0,0) = 0$. Using the Taylor series, we can rewritten K as an infinite polynomial of y_1, y_2, and y_3 with degree at least 2. Next, the transformed system can be written as

$$\begin{aligned} \frac{dZ}{dt} &= BZ + \begin{pmatrix} f_1 \\ f_2 \end{pmatrix}, \\ \frac{dy_3}{dt} &= 0y_3 + f_3, \end{aligned} \tag{4.5}$$

where $B = \text{diag}(-r, -1)$ and $Z = (y_1, y_2)^T$. It is straightforward to check that the functions f_k's are C^2 functions, $f_k(0,0,0) = 0$ and $Df_k(0,0,0) = 0$, where $k = 1, 2, 3$, and Df is the first derivative of the function f. Thus, by the Center Manifold Theorem (see Tian 2011; Carr 1981), there exists a center manifold given by $Z = h(y_3) = (h_1(y_3), h_2(y_3))^T$ with $h \in C^2$, $h(0) = Dh(0) = 0$, and it satisfies

$$Bh(y_3) + \begin{pmatrix} f_1(h(y_3), y_3) \\ f_2(h(y_3), y_3) \end{pmatrix} = Dh(y_3)\, f_3(h(y_3), y_3).$$

We can assume that $y_1 = h_1(y_3) = e_2y_3^2 + e_3y_3^3 + \text{o}(y_3^3)$ and $y_2 = m_2y_3^2 + m_3y_3^3 + \text{o}(y_3^3)$. Then $f_3(h(y_3), y_3) = C_{33}y_3^2 + \text{o}(y_3^2)$, where $C_{33} = -\frac{abc}{(b+1)^2} < 0$. The behavior of zero solution of the system (4.5) is governed by that of the single equation $\frac{dy_3}{dt} = f_3(h(y_3), y_3)$ or $\frac{dy_3}{dt} = C_{33}y_3^2 + \text{o}(y_3^2)$. Since $C_{33} < 0$, $y_3 = 0$ is locally asymptotically stable. Therefore $E_1 = (1, \frac{a}{b+1}, 0)$ is also locally asymptotically stable when $ac = bd + d$.

E. Now assume that $ac > bd + d$. Then there is a third equilibrium solution $E_2 = \left(\frac{bd}{ac-d}, \frac{d}{c}, \frac{ac-d-bd}{ac-d}\right)$, which is the unique positive equilibrium of the system (2.2). The variational matrix at this point is

$$Df(E_2) = \begin{bmatrix} -\frac{rbd}{ac-d} & 0 & -\frac{rbd}{ac-d} \\ \frac{(ac-d)^2}{abc^2} & -1 & 0 \\ 0 & \frac{c(ac-d-bd)}{ac-d} & 0 \end{bmatrix}.$$

The $|Df(E_2) - \lambda I| = 0$ is equivalent to

$$p(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0,$$

where $a_1 = \frac{rbd}{ac-d} + 1$, $a_2 = \frac{rbd}{ac-d}$, and $a_3 = \frac{rd(ac-d-bd)}{ac}$. Since $ac > bd + d$, all the coefficients a_i's are positive. By the Routh–Hurwitz Criterion, all roots of $p(\lambda) = 0$ have negative real parts iff $H_1 = a_1 > 0$, $H_2 = \begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix} = a_1a_2 - a_3 > 0$, and $H_3 = \begin{vmatrix} a_1 & a_3 & 0 \\ 1 & a_2 & 0 \\ 0 & a_1 & a_3 \end{vmatrix} = a_3H_2 > 0$. Since $H_1 = a_1 > 0$ and $a_3 > 0$, these conditions are the same as $H_2 > 0$. We have

$$H_2 = a_1a_2 - a_3 = \left(\frac{rbd}{ac-d} + 1\right)\frac{rbd}{ac-d} - \frac{rd(ac-d-bd)}{ac} > 0$$

is equivalent to $\frac{(rbd+ac-d)a}{(ac-d)^2(ac-d-bd)} > \frac{1}{bc}$. Define $\varphi(a) = \frac{(rbd+ac-d)a}{(ac-d)^2(ac-d-bd)}$, then we can conclude that if $\varphi(a) > \frac{1}{bc}$ then the positive equilibrium solution E_2 is locally asymptotically stable.

4.3 Hopf bifurcations

Now, we study the function $H(a) = H_2$ to get insight into the Hopf bifurcation that occurs when $ac > bd+d$. Note that we fix all the parameters except a and we consider H_2 as a function of the variable a. Then we have

$$H(a) = \frac{rd}{ac(ac-d)^2}[abc(rbd + ac - d) - (ac-d)^2(ac-d-bd)].$$

Set $y = ac - d$, then $ac = y + d$. Since $ac > bd + d$, $y > bd$. So

$$H(a) = \frac{rd\,\Phi(y)}{ac(ac-d)^2}$$

where $\Phi(y) := b(y+d)(rbd+y) - y^2(y-bd) = -y^3 + (b+bd)y^2 + bd(rb+1)y + rb^2d^2$ is a cubic polynomial of y. Clearly, $H(a)$ and $\Phi(ac-d)$ have the same roots. It is easy to compute

$$\Phi(bd) = b^2d^2(r+1)(b+1) > 0.$$

Since $\lim_{y\to\infty}\Phi(y) = -\infty$, $\Phi(y) = 0$ has at least one real root, say y_3^*, bigger than bd. On the other hand,

$$\Phi'(y) = -3y^2 + 2(b+bd)y + bd(rb+1) = 0$$

has 2 distinct real roots $y_{2,1} = \frac{1}{3}\left(b + bd \pm \sqrt{(b+bd)^2 + 3bd(rb+1)}\right)$. Note that $y_2 > 0 > y_1$ and $\Phi(0) = rb^2d^2 > 0$. As $\Phi(y) = \left(\frac{y}{3} - \frac{b+bd}{9}\right)\Phi'(y) + r(y)$ and $r(y) = \left[\frac{2}{3}bd(rb+1) + \frac{2}{9}(b+bd)^2\right]y + rb^2d^2 + bd(b+bd)(rb+1)$, so $\Phi(y_2) = r(y_2) > 0$. There are 3 cases. First, if $\Phi(y_1) < 0$ then, since $\lim_{y\to-\infty}\Phi(y) = \infty$, Φ

has at least one real root, say y_1^*, less than y_1. Since $\Phi(0) > 0$, Φ has at least another real root, say y_2^*, between y_1 and 0. Thus Φ has 3 distinct real roots $y_1^* < y_1 < y_2^* < 0 < bd < y_3^*$. Second, if $\Phi(y_1) = 0$ then, since $\Phi'(y_1) = 0$, Φ has one repeated real root $y_1^* = y_1$. So Φ has 2 distinct real roots $y_1^* < 0 < bd < y_3^*$. Lastly, if $\Phi(y_1) > 0$ then Φ has a unique real root $y_3^* > bd$.

Lemma 4.1 *The equation $H(a) = 0$ has only one root a_0 bigger than $a_{s_1} := \frac{d(b+1)}{c}$. Furthermore, there is a small neighborhood of a_0, $(a_0 - \delta_1, a_0 + \delta_1)$, where $\delta_1 < a_0 - a_{s_1}$, such that $H'(a_0) \neq 0$ and $H(a)$ is monotonically decreasing in this interval.*

Proof From the above argument, in any case y_3^* is the unique positive root of $\Phi(y) = 0$. Let $a_0 = \frac{y_3^*+d}{c}$, since $\Phi(y_3^*) = 0$, $H(a_0) = 0$. As $y_3^* > bd$, so $a_0 > a_{s_1}$. Note that $\Phi'(y_3^*) < 0$ since $y_3^* > y_2 > y_1$. It is easy to compute

$$H'(a_0) = \frac{rd\Phi'(y_3^*)}{a_0(a_0c - d)^2} < 0.$$

Since $H'(a)$ is continuous, there exists a $\delta_1 > 0$ that can be made smaller than $a_0 - a_{s_1}$ so that $H'(a) < 0$ for all $a \in (a_0 - \delta_1, a_0 + \delta_1)$. We're done. □

Let $a_{s_2} = a_0$, then $H(a) > 0$ when $a_{s_1} < a < a_{s_2}$, $H(a_{s_2}) = 0$, and $H(a) < 0$ when $a > a_{s_2}$. From Lemma 4.1, a_{s_2} is a unique positive value that zeroes out the function $H(a)$ and after a_{s_2} the function $H(a)$ is always negative.

In order to show that the Hopf bifurcation occurs in the system (2.2) when a passes through the critical value a_{s_2}, we need following two lemmas whose proofs can be found in Tian (2011), Phan and Tian (2017).

Lemma 4.2 *A cubic polynomial $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$ with real coefficients has a pair of pure imaginary roots iff $a_2 > 0$ and $a_3 = a_1a_2$. When it has pure imaginary roots, the pure imaginary roots are $\pm i\sqrt{a_2}$, the real root is $-a_1$, and $a_1a_3 \geq 0$. Furthermore, the real part of two complex roots of the above cubic polynomial is positive iff $a_2 > 0$ and $a_3 - a_1a_2 > 0$.*

Lemma 4.3 *Consider a coefficient parametrized polynomial $\lambda^3 + a_1(\tau)\lambda^2 + a_2(\tau)\lambda + a_3(\tau) = 0$, where the coefficients $a_k(\tau)$, k=1,2,3, are C^1 real-valued functions. Denote its complex roots by $\lambda(\tau) = \alpha(\tau) + i\beta(\tau)$. Suppose there is a τ_0 such that $\alpha(\tau_0) = 0$ and $\beta(\tau_0) \neq 0$, i.e. $\lambda(\tau_0) = i\beta(\tau_0)$. If $\alpha'(\tau_0) = 0$ then $a_2'(\tau_0)a_3(\tau_0) = a_2(\tau_0)(a_3'(\tau_0) - a_2(\tau_0)a_1'(\tau_0))$.*

Now we consider each coefficient of the characteristic polynomial $p(\lambda)$ to be a function of the parameter a. So

$$p(\lambda) = \lambda^3 + a_1(a)\lambda^2 + a_2(a)\lambda + a_3(a), \tag{4.6}$$

where $a_1(a) = \frac{rbd}{ac-d} + 1$, $a_2(a) = \frac{rbd}{ac-d}$, and $a_3(a) = \frac{rd(ac-d-bd)}{ac}$. Since $ac > bd + d$, all the coefficients $a_k(a)$'s are positive. Denote the complex roots of (4.6) by $\lambda(a) = \alpha(a) \pm i\beta(a)$. By Lemma 4.1, $H(a)$ is monotonically decreasing in a neighborhood

of a_0, $(a_0-\delta_1, a_0+\delta_1)$. When $a_0-\delta_1 < a < a_0$, $H_2 = H(a) > 0$, and we know that $H_1 = a_1(a) > 0$ and $H_3 = a_3(a)H_2 > 0$. By the Routh–Hurwitz Criterion, $\alpha(a) < 0$. When $a_0 < a < a_0+\delta_1$, $H(a) < 0$ which implies that $a_3(a) - a_1(a)a_2(a) > 0$. Due to Lemma 4.2, $\alpha(a)$ must be positive. When $a = a_0$, $H(a_0) = 0$ which means that $a_3(a_0) = a_1(a_0)a_2(a_0)$. Since $a_2(a_0) > 0$, by Lemma 4.2 the cubic equation $p(\lambda) = 0$ has a pair of pure imaginary roots and hence $\alpha(a_0) = 0$. Thus we have proved that the real part $\alpha(a)$ changes sign as a passes through a_0. Finally, we state a theorem that guarantees the occurrence of Hopf bifurcation for the system (2.2) as the parameter a passes through the critical value a_0.

Theorem 4.2 *There exists a neighborhood of a_0, $(a_0-\delta_0, a_0+\delta_0)$, such that for each a in this interval the characteristic polynomial (4.6) has a pair of complex conjugate eigenvalues $\lambda(a) = \alpha(a) \pm i\beta(a)$, in which $\alpha(a)$ changes sign when a passes through a_0 and $\beta(a) > 0$ in the interval. Furthermore, when $a = a_0$, (4.6) has a pair of pure imaginary roots and one negative real root, and $\alpha'(a_0) \neq 0$.*

Proof When $a = a_0$, from the above argument, $p(\lambda) = 0$ has a pair of pure imaginary roots $\lambda(a_0) = \pm i\beta(a_0)$. In light of Lemma 4.3, $\beta(a_0) = \sqrt{a_2(a_0)} = \sqrt{\frac{rbd}{a_0c-d}} > 0$. Since $\beta(a)$ is continuous with respect to a, there is a neighborhood of a_0 so that $\beta(a) > 0$ in this neighborhood. The radius δ_0 of the neighborhood can be taken small enough so that $\delta_0 < \delta_1$ in Lemma 4.1. Hence when $a \in (a_0-\delta_0, a_0+\delta_0)$ the cubic equation $p(\lambda) = 0$ has a pair of complex conjugate eigenvalues with positive imaginary parts and real parts change sign when a passes through a_0. It remains to prove that $\alpha'(a_0) \neq 0$. Indeed, if $\alpha'(a_0) = 0$ then Lemma 4.3 implies that $a_3'(a_0) - a_1'(a_0)a_2(a_0) = \frac{a_2'(a_0)a_3(a_0)}{a_2(a_0)}$. On the other hand,

$$\begin{aligned} H'(a_0) &= a_1'(a_0)a_2(a_0) + a_1(a_0)a_2'(a_0) - a_3'(a_0) \\ &= a_1(a_0)a_2'(a_0) - \frac{a_2'(a_0)a_3(a_0)}{a_2(a_0)} \\ &= \frac{(a_1(a_0)a_2(a_0) - a_3(a_0))a_2'(a_0)}{a_2(a_0)} = \frac{H(a_0)a_2'(a_0)}{a_2(a_0)} = 0, \end{aligned}$$

which is a contradiction since $H'(a_0) \neq 0$ by Lemma 4.1. This completes the proof. □

Because we cannot find exactly algebraic expression for a_0, it is very difficult to gain insight into the nature of periodical solutions that occur around the equilibrium point E_2 as a is close to a_0 such as their amplitudes, periods, and their stability. But we know that $a_{s_2} := a_0$ is the unique critical point after a_{s_1} at which the function $H(a)$ has zeros and so we can have only one Hopf bifurcation at $a = a_{s_2}$. Thus, there will be only one family of periodical solutions rising from this bifurcation. We will use numerical simulations to demonstrate some typical dynamics of periodical solutions for the system. However, we can make some statements about the general properties of periodical solutions occurring around E_2 as in the following corollary.

Corollary 4.1 *If E_2 is stable but not asymptotically stable at $a = a_0$ then all solutions of the system (2.2) in a neighborhood of E_2 are periodical in a surface. If E_2 is asymptotically stable or unstable at $b = b_0$ then there is an asymptotically stable periodical solution in a neighborhood of E_2 as a is close to a_0.*

We now look at the relation between equilibria E_1 and E_2. When $a < a_{s_1}$, we showed that E_1 is globally asymptotically stable; furthermore, the equilibrium E_2 is not in the positive invariant domain D. As a increases to $a_{s_1} = \frac{bd+d}{c}$, the equilibrium E_2 moves into D, and it coalesces with the equilibrium E_1. At $a = a_{s_1}$, $E_1 \equiv E_2$ and we proved that it is locally asymptotically stable. When $a > a_{s_1}$ and a is in a neighborhood of a_{s_1}, E_2 is still locally asymptotically stable while E_1 becomes unstable. This demonstrates a similar type of transcritical bifurcation occurs at $a = a_{s_1}$. Therefore, we prove the main Theorem 2.1.

5 Analysis of the SDE system

This section is devoted to deriving a sufficient and almost necessary condition for weak persistence of the SDE system (2.1), in other words, the condition for distinguishing two types of gliomas.

5.1 Preliminaries

In previous section, we proved that $D = \{(G, A, N) : 0 \le G \le 1,\ A \ge 0,\ N \ge 0\}$ is the positive invariant domain of the deterministic system (2.2). It is natural to expect D is also the almost sure positive invariant domain for the stochastic system (2.1). We prove this fact in the following theorem.

Theorem 5.1 *For any initial value $u = (G, A, N) \in D$, there exists a unique a.s. continuous global solution $U(t) = (G(t), A(t), N(t))$, $t \ge 0$, for the system (2.1) that remains in D a.s. Particularly, if $N = 0$ then $\mathbb{P}_u\{N(t) = 0\ \forall\, t > 0\} = 1$, and if $N > 0$ then $\mathbb{P}_u\{N(t) > 0\ \forall\, t > 0\} = 1$. Similarly, if $G = 0$ then $\mathbb{P}_u\{G(t) = 0\ \forall\, t > 0\} = 1$, and if $0 < G \le 1$ and $N \ge 0$ then $\mathbb{P}_u\{0 < G(t) \le 1\ \forall\, t > 0\} = 1$. If either $G > 0$ or $A > 0$ then $\mathbb{P}_u\{A(t) > 0\ \forall\, t > 0\} = 1$. Finally, the solution $U(t)$ is a strong Markov process that possesses the Feller property.*

Proof Since the coefficients $f(U)$ and $g(U)$ are locally Lipschitz continuous on $(-b, \infty) \times \mathbb{R}^2$, there exists a unique a.s. continuous local solution $U(t) = (G(t), A(t), N(t))^T$ up to the explosion time

$$\tau_e = \inf\left\{t > 0 : \min\left\{\frac{G(t)}{b + G(t)}, A(t), N(t)\right\} = -\infty \text{ or } \max\{A(t), N(t)\} = \infty\right\}$$

with any initial value in $(-b, \infty) \times \mathbb{R}^2$ and, furthermore, the solution $U(t)$ with $t \in [0, \tau_e)$ is a strong Markov process with Feller-Markov property (see Khasminskii 2012). Next, we will show that $\mathbb{P}_u\{\tau_e = \infty\} = 1$ when the initial value is in D. Indeed,

by the equation of $N(t)$, we have

$$N(t) = N \exp\left\{\int_0^t \left[cA(s) - d - \frac{\tau_2^2}{2}A^2(s)\right]ds + \tau_2 \int_0^t A(s)dW_2(s)\right\}.$$

It follows that if $N = 0$ then $N(t) = 0$ for all $t \in (0, \tau_e)$ a.s. and if $N > 0$ then $N(t) > 0$ for all $t \in (0, \tau_e)$ a.s. Next, the equation for $G(t)$ implies

$$G(t) = G \exp\left\{\int_0^t r(1 - G(s) - N(s))ds\right\}.$$

So it is obvious that if $G = 0$ then $G(t) = 0$ for all $t \in (0, \tau_e)$ a.s. and if $0 < G \leq 1$ and $N \geq 0$ then $G(t) > 0$ for all $t \in (0, \tau_e)$ a.s. and $N(t) \geq 0$ for all $t \in (0, \tau_e)$ a.s. By comparison theorem for the equation of $G(t)$, $dG(t) = rG(t)(1 - G(t) - N(t))dt \leq rG(t)(1 - G(t))dt$. This implies that $0 < G(t) \leq 1$ for all $t \in (0, \tau_e)$ a.s. From the equation of $A(t)$, we get

$$A(t) = \phi_t \left[A + \int_0^t \phi_s^{-1} \frac{aG(s)}{b + G(s)}ds\right] \tag{5.1}$$

where

$$\phi_t = \exp\left\{\int_0^t \left[-1 - \frac{\tau_1^2}{2}\frac{G^2(s)}{(b + G(s))^2}\right]ds + \int_0^t \frac{\tau_1 G(s)}{b + G(s)}dW_1(s)\right\}. \tag{5.2}$$

If $A = 0$ and $G > 0$ then $G(t) > 0$ for all $t \in (0, \tau_e)$ a.s. and it implies that for a.s.

$$A(t) = \phi_t \int_0^t \phi_s^{-1} \frac{aG(s)}{b + G(s)}ds > 0 \quad \forall\, t \in (0, \tau_e).$$

If $A > 0$ and $G = 0$ then $G(t) = 0$ for all $t \in (0, \tau_e)$ a.s. Thus $A(t) = \phi_t A(0) > 0$ for all $t \in (0, \tau_e)$ a.s. It is clear that if $A > 0$ and $G > 0$ then we have $A(t) > 0$ for all $t \in (0, \tau_e)$ a.s. Therefore, we have shown that if the initial value $u = (G, A, N)$ is in D then for a.s. $0 \leq G(t) \leq 1$, $A(t) \geq 0$, and $N(t) \geq 0$ for all $t \in (0, \tau_e)$.

Now we consider $V(G, A, N) = A + \frac{1}{c}\log(1 + N)$. Then it is easy to compute for all $t \in (0, \tau_e)$

$$\mathcal{L}V(t) = \frac{aG(t)}{b + G(t)} - \frac{A(t)}{N(t) + 1} - \frac{d}{c}\frac{N(t)}{N(t) + 1} - \frac{\tau_2^2}{2c}\frac{A^2(t)N^2(t)}{(N(t) + 1)^2} \leq \frac{a}{b + 1}.$$

Let $\xi_n = \inf\{t \in [0, \tau_e) : A(t) > n \text{ or } N(t) > n\}$. Clearly, ξ_n is increasing as $n \to \infty$. Set

$$\tau_\infty := \lim_{n\to\infty} \xi_n = \inf\{t \in [0, \tau_e) : A(t) = \infty \text{ or } N(t) = \infty\}.$$

Since $\max\{A(\tau_e), N(\tau_e)\} = \infty$, $\tau_\infty \le \tau_e$ a.s. Thus it suffices to show that $\mathbb{P}_u\{\tau_\infty = \infty\} = 1$. Fix $t > 0$, applying Itô's formula for V gives

$$\begin{aligned}\mathbb{E}_u V(t \wedge \xi_n) &:= \mathbb{E}_u V(G(t \wedge \xi_n), A(t \wedge \xi_n), N(t \wedge \xi_n)) \\ &= V(G(0), A(0), N(0)) + \mathbb{E}_u \int_0^{t\wedge\xi_n} \mathcal{L}V(G(s), A(s), N(s))ds \\ &\le K + \frac{a}{b+1}(t \wedge \xi_n) \le K + \frac{at}{b+1}\end{aligned}$$

where $K = V(G(0), A(0), N(0))$ is a positive constant. On the other hand,

$$\mathbb{E}_u V(t \wedge \xi_n) \ge \int_{\{\xi_n < t\}} V(t \wedge \xi_n) d\mathbb{P}_u = \int_{\{\xi_n < t\}} V(G(\xi_n), A(\xi_n), N(\xi_n)) d\mathbb{P}_u.$$

But, since $V(G(\xi_n), A(\xi_n), N(\xi_n)) = A(\xi_n) + \frac{1}{c}\log(1+N(\xi_n)) \ge n \wedge \frac{1}{c}\log(1+n) =: h(n)$,

$$\mathbb{P}_u\{\xi_n < t\} \le \frac{K + at/(b+1)}{h(n)} \to 0 \text{ as } n \to \infty$$

and so $\mathbb{P}_u\{\tau_\infty < t\} = 0$. As $t > 0$ is arbitrary, so $\mathbb{P}_u\{\tau_\infty = \infty\} = 1$. This completes the proof. □

5.2 Ergodic invariant measures on the boundary

To investigate the long-term behavior of the SDE system, we first find possible ergodic invariant measures of the system (2.1) on the boundary ∂D.

A. When $N(0) = 0$, $N(t) = 0$ for all $t > 0$ a.s. The system (2.1) becomes

$$\begin{aligned} dG &= rG(1-G)dt, \\ dA &= \left[\frac{aG}{b+G} - A\right]dt + \tau_1 \frac{AG}{b+G} dW_1. \end{aligned} \tag{5.3}$$

If $G(0) = 0$ then, from the first equation above, $G(t) = 0$ for all $t > 0$ a.s. But then the second equation becomes $dA = -Adt$, which implies that $A(t) = A(0)e^{-t} \to 0$ a.s. as $t \to \infty$. So we obtain an ergodic invariant measure $\mu_1 = \delta_0^* \times \delta_0^* \times \delta_0^*$ for solutions of (2.1) on ∂D.

B. If $0 < G(0) \le 1$ then the first equation of (5.3) implies that $\lim_{t\to\infty} G(t) = 1$ a.s. If $G = 1$ then the second equation becomes

$$d\tilde{A} = \left(\frac{a}{b+1} - \tilde{A}\right)dt + \frac{\tau_1}{b+1}\tilde{A}dW_1. \tag{5.4}$$

Let $c > 0$ and consider

$$s(\tilde{A}) = \int_c^{\tilde{A}} \exp\left\{-\int_c^y \frac{2(\frac{a}{b+1} - u)}{(\frac{\tau_1 u}{b+1})^2}\right\} dy = C_1 \int_c^{\tilde{A}} y^{\frac{2(b+1)^2}{\tau_1^2}} \exp\left\{\frac{2a(b+1)}{\tau_1^2}\frac{1}{y}\right\} dy$$

for some positive constant C_1. Rewrite the integrand as

$$y^{\frac{2(b+1)^2}{\tau_1^2}}\left[1 + \frac{2a(b+1)}{\tau_1^2}\frac{1}{y} + \frac{1}{2!}\frac{4a^2(b+1)^2}{\tau_1^4}\frac{1}{y^2} + \cdots\right].$$

Clearly, there is a $k \in \mathbb{Z}_+$ such that $\frac{2(b+1)^2}{\tau_1^2} - k < -1$ and hence $s(0+) := \lim_{\tilde{A}\downarrow 0} s(\tilde{A}) = -\infty$. Of course, $s(\infty) := \lim_{\tilde{A}\uparrow\infty} s(\tilde{A}) = \infty$. Then $\tilde{A}(t)$ oscillates between 0 and ∞. Hence (5.4) has a unique invariant measure π on $\mathbb{R}_+$ whose density $p = p(x)$ solves the associated Fokker-Planck equation

$$-\frac{d}{dx}\left[\left(\frac{a}{b+1} - x\right)p(x)\right] + \frac{d^2}{dx^2}\left[\frac{1}{2}\frac{\tau_1^2 x^2}{(b+1)^2}p(x)\right] = 0. \tag{5.5}$$

Set $y(x) = \frac{1}{2}\frac{\tau_1^2 x^2}{(b+1)^2}p(x)$, and $\gamma(x) = \frac{2(b+1)^2}{\tau_1^2}[\frac{a}{b+1}\frac{1}{x^2} - \frac{1}{x}]$. Then (5.5) is equivalent to

$$y'(x) - \gamma(x)y(x) = -C$$

for some constant C. The solution of this equation is given by

$$y(x) = A(x)\left[K + C\int_x^1 \frac{dt}{A(t)}\right]$$

for some positive constant K. It is easy to show that p is a density iff $C = 0$. Note that

$$A(t) = \exp\left\{\int_1^t \gamma(u)du\right\} = \exp\left\{\frac{2a(b+1)}{\tau_1^2}\right\} t^{-\frac{2(b+1)^2}{\tau_1^2}} \exp\left\{-\frac{2a(b+1)}{\tau_1^2}\frac{1}{t}\right\}.$$

Thus

$$p(x) = K\frac{2(b+1)^2}{\tau_1^2}\exp\left\{\frac{2a(b+1)}{\tau_1^2}\right\} x^{-\frac{2(b+1)^2}{\tau_1^2}} \exp\left\{-\frac{2a(b+1)}{\tau_1^2}\frac{1}{x}\right\}.$$

Let $\alpha := 2(\frac{b+1}{\tau_1})^2 + 1$ and $\beta := \frac{2a(b+1)}{\tau_1^2}$, then $p(x) = \underline{K}\, x^{-\alpha-1}e^{-\beta/x}$ where

$$\underline{K} = \left(\int_0^\infty x^{-\alpha-1}e^{-\beta/x}dx\right)^{-1}$$

is the normalizing constant. By changing variable $u = \frac{\beta}{x}$, we get

$$\int_0^\infty x^{-\alpha-1}e^{-\beta/x}dx = \beta^{-\alpha}\int_0^\infty \left(\frac{\beta}{x}\right)^{\alpha-1} e^{-\beta/x}\frac{\beta}{x^2}dx$$
$$= \beta^{-\alpha}\int_0^\infty u^{\alpha-1}e^{-u}du = \beta^{-\alpha}\Gamma(\alpha),$$

where Γ is the Gamma function. Hence $p(x) = \dfrac{\beta^\alpha}{\Gamma(\alpha)}x^{-\alpha-1}e^{-\beta/x}$. In other words, the invariant measure π is the Inverse-Gamma distribution with parameters α and β. Therefore $\mu_2 = \delta_1^* \times \pi \times \delta_0^*$ is an ergodic invariant measure for solutions of (2.1) on ∂D.

From now on, we assume that $(\frac{\tau_1}{b+1})^2 < 2$ in order for the second moment of the invariant measure π exists.

C. We state and prove several lemmas that are needed to prove the main theorem 2.2.

Lemma 5.1 $\mathbb{E}_u A^4(t) \le e^{\overline{K}t}(A(0) + \overline{K})$ *for some constant* $\overline{K} > 0$. *There exist* $c_p, K_p > 0$ *such that* $\mathbb{E}_u A^{2+p}(t) < A^{2+p}(0)\, e^{-c_p t} + K_p$ *for some small constant* $p > 0$.

Proof We can easily obtain that $\mathcal{L}A^4 \le C_1(1 + A^4)$ for some constant C_1, then standard arguments [see e.g. Mao (2007, Section 2.4)] can be applied to prove the first part of the lemma.

To prove the second part, noting from Itô's formula for A^{2+p} $(p > 0)$ that

$$\mathcal{L}(A^{2+p}) = (2+p)A^{1+p}\left(\frac{aG}{b+G} - A\right) + (2+p)(1+p)\frac{\tau_1^2}{2}\left(\frac{G}{b+G}\right)^2 A^{2+p}$$
$$= (2+p)\frac{aG}{b+G}A^{1+p} - (2+p)\left[1 - (1+p)\frac{\tau_1^2}{2}\left(\frac{G}{b+G}\right)^2\right]A^{2+p}$$
$$\le \frac{a(2+p)}{b+1}A^{1+p} - (2+p)\left[1 - \frac{1+p}{2}\left(\frac{\tau_1}{b+1}\right)^2\right]A^{2+p}.$$

Notice that $\lim\limits_{p\to 0^+}\left[1 - \frac{1+p}{2}(\frac{\tau_1}{b+1})^2\right] = 1 - \frac{1}{2}(\frac{\tau_1}{b+1})^2 > 0$ and $\lim\limits_{p\to 0^+}\mathbb{E}_u A^{1+p} = \mathbb{E}_u A$. Since $\frac{d}{dt}\mathbb{E}_u A \le \frac{a}{b+1} - \mathbb{E}_u A$, $\mathbb{E}_u A \le \frac{a}{b+1}$. Thus, for $p > 0$ small enough, $1 - \frac{1+p}{2}(\frac{\tau_1}{b+1})^2 > 0$ and $\mathbb{E}_u A^{1+p} \le \frac{a}{b+1}$. Hence $\mathbb{E}_u\mathcal{L}(A^{2+p}) \le H_p - c_p A^{2+p}$ for $p > 0$ small and for some positive constants H_p and c_p. We show that $\limsup_{t\to\infty}\mathbb{E}_u A^{2+p} \le \frac{H_p}{c_p}$. In fact,

$$\mathbb{E}_u L(e^{c_p t}A^{2+p}(t)) \le e^{c_p t}\left[(H_p - c_p\mathbb{E}_u A^{2+p}) + c_p\mathbb{E}_u A^{2+p}\right] = H_p e^{c_p t},$$

and then, by Itô's formula, we get

$$\mathbb{E}_u\left(e^{c_p t}A^{2+p}(t)\right) = \mathbb{E}_u A^{2+p}(0) + \mathbb{E}_u\int_0^t \mathcal{L}(e^{c_p t}A^{2+p}(s))ds$$
$$\leq \mathbb{E}_u A^{2+p}(0) + H_p\int_0^t e^{c_p s}ds = \mathbb{E}_u A^{2+p}(0) + \frac{H_p}{c_p}(e^{c_p t}-1).$$

Dividing both sides by $e^{c_p t}$ gets

$$\mathbb{E}_u A^{2+p}(t) \leq \mathbb{E}_u A^{2+p}(0)e^{-c_p t} + \frac{H_p}{c_p}(1-e^{-c_p t}).$$

This implies that $\limsup_{t\to\infty}\mathbb{E}_u A^{2+p}(t) \leq \frac{H_p}{c_p}$. □

Lemma 5.2 $\mathbb{E}_u \sup_{t\in[0,T]} N^q(t) \leq K_T\, N^q(0)$ *for* $q \in (0, \frac{1}{2})$ *sufficiently small and any* $T > 0$.

Proof Apply Itô's formula for N^q $(0 < q < 1)$, we have for all $t \in [0, T]$

$$N^q(t) = N^q(0) + \int_0^t \mathcal{L}(N^q(s))ds + \int_0^t q\tau_2 N^q(s)A(s)dW_2(s)$$

where

$$\mathcal{L}(N^q) = qN^q\left[cA - d + \frac{1}{2}(q-1)\tau_2^2 A^2\right] \leq H_q N^q$$

for some positive constant H_q. Then

$$\mathbb{E}_u N^q(t) \leq N^q(0) + H_q\int_0^t \mathbb{E}_u N^q(s)ds.$$

By Gronwall's inequality, for all $t \in [0, T]$ and $q \in (0, 1)$,

$$\mathbb{E}_u N^q(t) \leq N^q(0)\exp\{H_q t\} \leq H_1 N^q(0).$$

Now we have

$$\mathbb{E}_u \sup_{t\in[0,T]} N^q(t) \leq N^q(0) + \mathbb{E}_u \sup_{t\in[0,T]}\int_0^t \mathcal{L}(N^q(s))ds$$
$$+ \mathbb{E}_u \sup_{t\in[0,T]} q\tau_2\left|\int_0^t N^q(s)A(s)dW_2(s)\right|.$$

It is clear that

$$\mathbb{E}_u \sup_{t\in[0,T]} \int_0^t \mathcal{L}(N^q(s))ds \le \mathbb{E}_u \sup_{t\in[0,T]} H_q \int_0^t N^q(s)ds = H_q \int_0^T \mathbb{E}_u N^q(s)ds \le H_2 N^q(0).$$

On the other hand, by the Burkholder–Davis–Gundy inequality (Revuz and Yor 1999, p. 160), for some constant $C_1 > 0$

$$\begin{aligned}\mathbb{E}_u \sup_{t\in[0,T]} q\tau_2 \left| \int_0^t N^q(s)A(s)dW_2(s) \right| &\le C_1 \mathbb{E}_u \left[\int_0^T N^{2q}(s)A^2(s)ds \right]^{1/2} \\ &\le C_1 \left[\left(\mathbb{E}_u \int_0^T N^{2q(2+p)/p}(s)ds \right)^{p/(2+p)} \left(\mathbb{E}_u \int_0^T A^{2+p}(s) \right)^{2/(2+p)} \right]^{1/2}\end{aligned}$$

here we have used the Holder's inequality in the last one. By Lemma 5.1, choose $p > 0$ small enough so that $\mathbb{E}_u \int_0^T A^{2+p}(s)ds < \infty$ for any $T > 0$. For $q < \frac{p}{2(2+p)}$ sufficiently small, we have for some positive constant H_3

$$\mathbb{E}_u \int_0^T N^{2q(2+p)/p}(s)ds \le H_3 N^{2q(2+p)/p}(0).$$

Thus

$$\mathbb{E}_u \sup_{t\in[0,T]} q\tau_2 \left| \int_0^t N^q(s)A(s)dW_2(s) \right| \le H_4 N^q(0)$$

for some positive constant H_4. This completes the proof. □

Lemma 5.3 *There exists a compact set $\tilde{K} \subseteq D$ such that for any initial value $u = (G, A, N) \in D^\circ$, the solution process $U(t) = (G(t), A(t), N(t))$ is recurrent relative to $\tilde{K}$.*

Proof By Theorem 3.9 p.89 in Khasminskii (2012), it suffices to construct a non-negative twice differentiable function $V = V(G, A, N)$ so that $\mathcal{L}V < 0$ for all $(G, A, N) \in \tilde{K}^c$. Now we consider $V(G, A, N) = G + 2cA + \ln(1 + N)$, then

$$\begin{aligned}\mathcal{L}V &= rG(1 - G - N) + \frac{2caG}{b + G} - 2cA + \frac{(cA - d)N}{N + 1} - \frac{\tau_2^2}{2}\frac{A^2N^2}{(1 + N)^2} \\ &\le rG(1 - G) + \frac{2caG}{b + G} - cA - \frac{dN}{1 + N} \\ &\le H_5 \mathbf{1}_{\{G+A+N\le R\}} - H_6 \mathbf{1}_{\{G+A+N>R\}}\end{aligned}$$

for some positive constants H_5, H_6, and R. Hence

$$\tilde{K} = \{(G, A, N) \in D : G + A + N \le R\}$$

is the desired compact set. □

D. Next, we will prove the following claim that is also needed for the proof the main theorem 2.2.

Claim 5.1 *If* $\limsup_{t\to\infty} \frac{\ln N(t)}{t} < -r'$ *a.s for some constant* $r' > 0$ *then* $\lim_{t\to\infty} |A(t) - \tilde{A}(t)| = 0$ *a.s.*

Proof Under the hypothesis of the claim and the first ODE in (2.1), we can easily show that $\limsup_{t\to\infty} e^{\rho t}|G(t) - 1| = 0$ for some constant $\rho > 0$. As a result, for any $\varepsilon > 0$, there exists K_ε such that

$$\mathbb{P}_u \left\{ e^{\rho t}|G(t) - 1| \le K_\varepsilon, t \ge 0 \right\} \ge 1 - \varepsilon. \tag{5.6}$$

Let $\overline{A}(t)$ satisfying

$$d\overline{A} = \left(\frac{a\overline{G}}{b + \overline{G}} - \overline{A} \right) dt + \frac{\tau_1 \overline{A}\,\overline{G}}{b + \overline{G}} dW_1 \text{ with } \overline{A}(0) = A(0) \tag{5.7}$$

where $\overline{G}(t) = G(t \wedge \xi_\varepsilon)$, $\xi_\varepsilon = \inf\{t \ge 0 : e^{\rho t}|G(t) - 1| \ge K_\varepsilon\}$. From the equation (5.4) and (5.7), we get

$$d(\overline{A}(t) - \tilde{A}(t)) = \left[\frac{a\overline{G}(t)}{b + \overline{G}(t)} - \frac{a}{b+1} - (\overline{A}(t) - \tilde{A}(t)) \right] dt + \left(\frac{\tau_1 \overline{A}(t)\overline{G}(t)}{b + \overline{G}(t)} - \frac{\tau_1 \tilde{A}(t)}{b+1} \right) dW_1$$

and then

$$\begin{aligned} d(\overline{A}(t) - \tilde{A}(t))^2 = & \left\{ -\theta(\overline{A}(t) - \tilde{A}(t))^2 + 2a \left(\frac{\overline{G}(t)}{b + \overline{G}(t)} - \frac{1}{b+1} \right) (\overline{A}(t) - \tilde{A}(t)) \right. \\ & + \tau_1^2 \left[\left(\frac{\overline{G}(t)}{b + \overline{G}(t)} \right. \right. \\ & \left. \left. + \frac{1}{b+1} \right) \overline{A}(t)^2 - \frac{2}{b+1} \overline{A}(t)\tilde{A}(t) \right] \frac{b(\overline{G}(t) - 1)}{(b+1)(b + \overline{G}(t))} \Bigg\} dt \\ & + 2\tau_1 \left(\frac{\overline{A}(t)\overline{G}(t)}{b + \overline{G}(t)} - \frac{\tilde{A}(t)}{b+1} \right) (\overline{A}(t) - \tilde{A}(t)) dW_1 \\ = & -\theta(\overline{A}(t) - \tilde{A}(t))^2 dt + h_1(t)(\overline{A}(t) - \tilde{A}(t)) dt \\ & + \left[\left(\frac{\overline{G}(t)}{b + \overline{G}(t)} + \frac{1}{b+1} \right) \overline{A}(t)^2 - \frac{2}{b+1} \overline{A}(t)\tilde{A}(t) \right] h_2(t) dt + h_3(t) dW_1 \end{aligned} \tag{5.8}$$

where $\theta := 2 - \frac{\tau_1^2}{(b+1)^2}$, $h_1(t) := 2a\left(\frac{\overline{G}(t)}{b+\overline{G}(t)} - \frac{1}{b+1}\right)$, $h_2(t) := \frac{\tau_1^2 b(\overline{G}(t)-1)}{(b+1)(b+\overline{G}(t))}$, and

$$h_3(t) := 2\tau_1\left(\frac{\overline{A}(t)\overline{G}(t)}{b+\overline{G}(t)} - \frac{\tilde{A}(t)}{b+1}\right)(\overline{A}(t) - \tilde{A}(t)).$$

One can easily obtain that from the fact that $\limsup_{t\to\infty} e^{\rho t}(\overline{G}(t)-1) = 0$ that

$$\sup_{t>0} e^{\rho t/2}(|h_1(t)| + |h_2(t)|) < K_\varepsilon' \tag{5.9}$$

for some non-random constant K_ε'.

Hence, for some positive constants r, K_1 and K_2, there exists $t_0 > 0$ such that $t > t_0$ implies

$$\begin{aligned}\mathbb{E}_u\mathcal{L}(\overline{A}(t)-\tilde{A}(t))^2 \le -\theta\,\mathbb{E}_u(\overline{A}(t)-\tilde{A}(t))^2 + K_1e^{-rt}\mathbb{E}_u|\overline{A}(t)-\tilde{A}(t)| \\ + K_2e^{-rt}\mathbb{E}_u\left|\left(\frac{\overline{G}(t)}{b+\overline{G}(t)} + \frac{1}{b+1}\right)\overline{A}(t)^2 - \frac{2}{b+1}\overline{A}(t)\tilde{A}(t)\right|.\end{aligned}$$

It is clear that $\mathbb{E}_u\tilde{A}(t)^2$ is uniformly bounded for $u \in D^\circ$ and, by Lemma 5.1 with slight modification, so is $\mathbb{E}_u\overline{A}(t)^2$. Hence both $\mathbb{E}_u|\overline{A}(t)-\tilde{A}(t)|$ and $\mathbb{E}_u(\overline{A}(t)\tilde{A}(t))$ are uniformly bounded. Thus

$$\mathbb{E}_u\mathcal{L}(\overline{A}(t)-\tilde{A}(t))^2 \le -\theta\,\mathbb{E}_u(\overline{A}(t)-\tilde{A}(t))^2 + K_3e^{-rt}$$

for all $t > t_0$ and some positive constant K_3. Let $0 < \theta_0 < \min\{\theta, r\}$, then for all $t > 0$

$$\begin{aligned}\mathbb{E}_u\mathcal{L}\left(e^{\theta_0 t}(\overline{A}(t)-\tilde{A}(t))^2\right) &\le e^{\theta_0 t}\left[\theta_0\mathbb{E}_u(\overline{A}(t)-\tilde{A}(t))^2 - \theta\mathbb{E}_u(\overline{A}(t)-\tilde{A}(t))^2 + K_3e^{-rt}\right] \\ &\le K_3e^{-(r-\theta_0)t}.\end{aligned}$$

Again by Itô's formula,

$$\begin{aligned}\mathbb{E}_u e^{\theta_0 t}(\overline{A}(t)-\tilde{A}(t))^2 &= e^{\theta_0 0}\mathbb{E}_u(\overline{A}(0)-\tilde{A}(0))^2 + \mathbb{E}_u\int_0^t \mathcal{L}\left(e^{\theta_0 s}(\overline{A}(s)-\tilde{A}(s))^2\right) \\ &\le \mathbb{E}_u(\overline{A}(0)-\tilde{A}(0))^2 + K_3\int_0^t e^{-(r-\theta_0)s}ds \\ &= \mathbb{E}_u(\overline{A}(0)-\tilde{A}(0))^2 + \frac{K_3}{r-\theta_0}\left[1-e^{-(r-\theta_0)t}\right],\end{aligned}$$

which follows that $\mathbb{E}_u(\overline{A}(t)-\tilde{A}(t))^2 \le K_4e^{-\theta_0 t}$ for all $t > 0$ and for some positive constant K_4. By Holder's inequality, $\mathbb{E}_u|\overline{A}(t)-\tilde{A}(t)| \le \sqrt{K_4}\,e^{-\theta_0 t/2}$ for all $t > 0$.

Now we have for any $n \geq 1$

$$\mathbb{E}_u \sup_{t\in[n,n+1]} |\overline{A}(t) - \tilde{A}(t)| \leq \mathbb{E}_u |\overline{A}(n) - \tilde{A}(n)| + \mathbb{E}_u \sup_{t\in[n,n+1]} \left| \int_n^t \mathcal{L}(\overline{A}(s) - \tilde{A}(s)) ds \right| + \mathbb{E}_u \sup_{t\in[n,n+1]} \left| \int_n^t \tau_1 \left(\frac{\overline{A}(s)\overline{G}(s)}{b + \overline{G}(s)} - \frac{\tilde{A}(s)}{b+1} \right) dW_1(s) \right|.$$

When $n > t_0$, for some positive constant K_5

$$\begin{aligned}
\mathbb{E}_u \sup_{t\in[n,n+1]} \left| \int_n^t \mathcal{L}(\overline{A}(s) - \tilde{A}(s)) ds \right| &\leq \mathbb{E}_u \int_n^{n+1} |\mathcal{L}(\overline{A}(s) - \tilde{A}(s))| ds \\
&\leq \mathbb{E}_u \int_n^{n+1} \left| \frac{a\overline{G}(s)}{b + \overline{G}(s)} - \frac{a}{b+1} \right| ds + \mathbb{E}_u \int_n^{n+1} |\overline{A}(s) - \tilde{A}(s)| ds \\
&\leq \frac{aK}{b+1} \int_n^{n+1} e^{-rs} ds + \sqrt{K_4} \int_n^{n+1} e^{-\theta_0 s/2} ds \leq K_5 e^{-\theta_0 n/2}.
\end{aligned}$$

On the other hand, by the Burkholder–Davis–Gundy inequality (Revuz and Yor 1999, p. 160), there is a positive constant $C > 0$ such that

$$\begin{aligned}
&\mathbb{E}_u \sup_{t\in[n,n+1]} \left| \int_n^t \tau_1 \left(\frac{\overline{A}(s)\overline{G}(s)}{b + \overline{G}(s)} - \frac{\tilde{A}(s)}{b+1} \right) dW_1(s) \right| \\
&\leq C\tau_1 \mathbb{E}_u \sqrt{\int_n^{n+1} \left(\frac{\overline{A}(s)\overline{G}(s)}{b + \overline{G}(s)} - \frac{\tilde{A}(s)}{b+1} \right)^2 ds} \\
&= C\tau_1 \mathbb{E}_u \sqrt{\int_n^{n+1} \left[\overline{A}(s) \left(\frac{\overline{G}(s)}{b + \overline{G}(s)} - \frac{1}{b+1} \right) + \frac{1}{b+1} (\overline{A}(s) - \tilde{A}(s)) \right]^2 ds} \\
&\leq C\tau_1 \sqrt{2} \sqrt{\mathbb{E}_u \int_n^{n+1} \overline{A}^2(s) \left(\frac{\overline{G}(s)}{b + \overline{G}(s)} - \frac{1}{b+1} \right)^2 ds} \\
&\quad + C\tau_1 \sqrt{2} \sqrt{\mathbb{E}_u \int_n^{n+1} \left(\frac{\overline{A}(s) - \tilde{A}(s)}{b+1} \right)^2 ds} \\
&\leq C\tau_1 \sqrt{2} \frac{K}{b+1} e^{-rn} \sqrt{\mathbb{E}_u \int_n^{n+1} \overline{A}^2(s) ds} + \frac{C\tau_1 \sqrt{2} \sqrt{K_4}}{b+1} e^{-\theta_0 n/2} \leq K_6 e^{-\theta_0 n/2},
\end{aligned}$$

for some positive constant K_6. Thus for all $n > 0$ we get

$$\mathbb{E}_u \sup_{t\in[n,n+1]} |\overline{A}(t) - \tilde{A}(t)| \leq K_7 e^{-\theta_0 n/2}$$

for some constant $K_7 > 0$. Then the Markov's inequality implies for all $n > 0$

$$\mathbb{P}_u\left\{\sup_{t\in[n,n+1]}|\overline{A}(t)-\tilde{A}(t)|\geq e^{-\theta_0 n/4}\right\}\leq e^{\theta_0 n/4}\mathbb{E}_u\sup_{t\in[n,n+1]}|\overline{A}(t)-\tilde{A}(t)|\leq K_7 e^{-\theta_0 n/4}.$$

Since $\sum_{n>0} K_7(e^{-\theta_0/4})^n < \infty$, Borel-Cantelli's lemma implies with probability 1 there exists a n_0 such that for all $n > n_0$ we get

$$\sup_{t\in[n,n+1]}|\overline{A}(t)-\tilde{A}(t)| < e^{-\theta_0 n/4}.$$

Hence $|\overline{A}(t)-\tilde{A}(t)|\to 0$ a.s. It is obvious that $\mathbb{P}_u\{\xi_\varepsilon=\infty\}\geq 1-\varepsilon$ and $\overline{A}(t)=A(t)$ for any $t\geq 0$ if $\xi_\varepsilon=\infty$. Since $\varepsilon > 0$ is chosen arbitrarily, we can easily obtain the desired result. □

Remark 5.1 Since π is the invariant measure of (5.4), it follows from the strong law of large numbers that for a.s.

$$\lim_{t\to\infty}\frac{1}{t}\mathbb{E}\int_0^t\tilde{A}(s)ds=\int_0^\infty\tilde{A}\pi(d\tilde{A})=\frac{\beta}{\alpha-1}=\frac{a}{b+1}$$

and

$$\lim_{t\to\infty}\frac{1}{t}\mathbb{E}\int_0^t\tilde{A}^2(s)ds=\int_0^\infty\tilde{A}^2\pi(d\tilde{A})=\frac{\beta^2}{(\alpha-1)(\alpha-2)}=\frac{2a^2}{2(b+1)^2-\tau_1^2}.$$

We can see that $\mu_2 := \boldsymbol{\delta}_1\times\pi\times\boldsymbol{\delta}_0$ is the unique invariant measure of $U(t)$ on the set $\{u=(G,A,N): N=0\}$ where $\boldsymbol{\delta}_0, \boldsymbol{\delta}_1$ are the Dirac measures with mass at 0 and 1 respectively.

E. To give an idea how to determine the long term behavior of (2.1), we look at the Lyapunov exponents of μ_1. Now, from the first equation of (2.1),

$$\frac{\ln G(t)}{t}=\frac{\ln G(0)}{t}+\frac{1}{t}\int_0^t r(1-G(s)-N(s))ds.$$

When the solution $U(t)$ is close to the support of μ_1 for a long time, $\frac{\ln G(t)}{t}$ can be approximated by the average with respect to μ_1

$$\lambda_1(\mu_1):=\int_{\partial D} r(1-G-N)d\mu_1=r,$$

which is the Lyapunov exponent of the ergodic invariant measure μ_1 along the solution component G. Since $\lambda_1(\mu_1)=r>0$, the ergodic invariant measure μ_1 is always a repeller.

By the third equation of (2.1), using Itô's formula we get

$$\frac{\ln N(t)}{t} = \frac{\ln N(0)}{t} + \frac{1}{t}\int_0^t \left[cA(s) - d - \frac{\tau_2^2}{2}A^2(s)\right] ds + \frac{1}{t}\int_0^t \tau_2 A(s) dW_2(s).$$

If the solution $U(t)$ is close to the support of μ_2 for a long time, $\frac{\ln N(0)}{t}$ and $\frac{1}{t}\int_0^t \tau_2 A(s) dW_2(s)$ approximate zero for t large enough while $\frac{\ln N(t)}{t}$ can be approximated by the average with respect to μ_2

$$\lambda_3(\mu_2) := \int_{\partial D} \left[cA - d - \frac{\tau_2^2}{2}A^2\right] d\mu_2 = \frac{ac}{b+1} - d - \frac{\tau_2^2 a^2}{2(b+1)^2 - \tau_1^2},$$

which is the Lyapunov exponent of the ergodic invariant measure μ_2 along the solution component $N(t)$. Let

$$\boldsymbol{\lambda} := \lambda_3(\mu_2) = \frac{ac}{b+1} - d - \frac{\tau_2^2 a^2}{2(b+1)^2 - \tau_1^2}.$$

When $\boldsymbol{\lambda} < 0$, $N(t)$ approaches 0 a.s. By the same argument as in Sect. 3, $G(t)$ approaches 1 a.s. and the occupation measure of $A(t)$ converges weakly to π a.s. due to Claim 5.1. Hence μ_2 is a local attractor. When $\boldsymbol{\lambda} > 0$, μ_2 becomes a repeller. In fact, our main theorem 2.2 claims that if $\boldsymbol{\lambda} < 0$ then μ_2 is a global attractor and if $\boldsymbol{\lambda} > 0$ then the solution does not converge to μ_2 a.s.

5.3 Proof of the main theorem 2.2

It is ready now to give the detailed proof of the main theorem 2.2.

Case 1. Assume that $\boldsymbol{\lambda} < 0$. By Theorem 5.1, there are only two ergodic invariant measures for the process $(G(t), A(t), N(t))$ on the boundary ∂D, which are $\mu_1 = \delta_0^* \times \delta_0^* \times \delta_0^*$ and $\mu_2 = \delta_1^* \times \pi \times \delta_0^*$. Notice that

$$\int_{\partial D} (cA - d - \tau_2^2 A^2/2) d\mu_1 = -d < 0,$$
$$\int_{\partial D} (cA - d - \tau_2^2 A^2/2) d\mu_2 = \boldsymbol{\lambda} < 0.$$

Applying Itô's formula for N^q $(0 < q < 1)$

$$d(N^q) = qN^q \left[cA - d + \frac{1}{2}(q-1)\tau_2^2 A^2\right] dt + q\tau_2 N^q A\, dW_2. \tag{5.10}$$

For $q = \frac{1}{2}$, let $M > 0$ such that $\mathcal{L}(\sqrt{N}) \le -\sqrt{N}$ if $A \ge M$. Set $H = \sup_{A \ge 0}[cA - d - \frac{1}{4}\tau_2^2 A^2]$, then $H > 0$ and $\mathcal{L}(\sqrt{N}) \le H\sqrt{N}$ for all $N \ge 0$. Now let $n^* > 8(H+1)$,

and define the family of occupation measures

$$\Pi_t^u(\cdot) := \frac{1}{t}\int_0^t \mathbb{P}_u\{U(s) \in \cdot\}ds.$$

By the Fubini–Tonelli's theorem (Revuz and Yor 1999, p. 160),

$$\begin{aligned}\int_D (cA - d - \tau_2^2 A^2/2)\Pi_t^u(dv) &= \int_D (cA - d - \tau_2^2 A^2/2)\frac{1}{t}\int_0^t \mathbb{P}_u\{U(s) \in dv\}ds \\ &= \frac{1}{t}\int_0^t \left[\int_D (cA - d - \tau_2^2 A^2/2)\mathbb{P}_u\{U(s) \in dv\}\right] ds \\ &= \frac{1}{t}\int_0^t \mathbb{E}_u(cA(s) - d - \tau_2^2 A^2(s)/2)ds.\end{aligned}$$

Due to Lemma 5.1, when the initial value $u = (G, A, N)$ is in $\{G > 0, A > 0, N = 0\} \subseteq \partial D$ such that $G \leq 1$ and $A \leq M$, we have

$$\sup_{A\leq M, t>0} \frac{1}{t}\int_0^t \mathbb{E}_u(cA(s) - d - \tau_2^2 A^2(s)/2)ds < \infty.$$

This means that $\{\Pi_t^u\}_{t\geq 0}$ is tight in ∂D. Then there is a sequence $\{t_k\}_{k\geq 1}$ such that $t_k \uparrow \infty$ and $\Pi_{t_k}^u$ converges weakly to some invariant measure of $U(t)$ supported by $\{G > 0, A > 0, N = 0\}$. But, since μ_2 is the unique ergodic invariant measure on there, by lemma 3.4 in Hening and Nguyen (2018),

$$\lim_{k\to\infty} \frac{1}{t_k}\int_0^{t_k} \mathbb{E}_u(cA(s) - d - \tau_2^2 A^2(s)/2)ds = \int_{\partial D} (cA - d - \tau_2^2 A^2/2)d\mu_2 = \boldsymbol{\lambda} < 0.$$

Use the argument as in Lemma 4.1 in Hening and Nguyen (2018), we can show that there is a $T^* > 0$ such that for any initial value $u = (G, A, N) \in (0, 1] \times (0, M] \times \{0\}$ and for all $T \geq T^*$

$$\mathbb{E}_u \int_0^T [cA(t) - d - \tau_2^2 A^2(t)/2]dt \leq \frac{\boldsymbol{\lambda} T}{2}.$$

Because of the Feller propery of $U(t)$ [see Remark 3.1 in Hening and Nguyen (2018)], and the uniform boundedness of $\mathbb{E}_u A^{2+p}$ by Lemma 5.1, we get

$$\mathbb{E}_u \int_0^T [cA(t) - d - \tau_2^2 A^2(t)/2]dt \leq \frac{\boldsymbol{\lambda} T}{2} \tag{5.11}$$

for all $T \in [T^*, n^*T^*]$ and for any initial value $u = (G, A, N) \in (0, 1] \times (0, M] \times (0, \delta]$, where δ is some positive constant. By (5.10), we get for any $q \in (0, 1)$ and $T \in [T^*, n^*T^*]$

$$\ln N^q(T) = \ln N^q(0) + q\, m(T)$$

where

$$m(T) = \int_0^T [cA(t) - d - \tau_2^2 A^2(t)/2]dt + \int_0^T \tau_2 A(t) dW_2(t).$$

Let $\phi_{u,T}(q) = \mathbb{E}_u \exp\{qm(T)\}$, then standard calculus shows that

$$\frac{d\phi_{u,T}}{dq}(0) = \mathbb{E}_u m(T) = \mathbb{E}_u \int_0^T [cA(t) - d - \tau_2^2 A^2(t)/2]dt$$

and

$$\frac{d^2\phi_{u,T}}{dq^2} = \mathbb{E}_u m^2(T) e^{qm(T)} \leq C\mathbb{E}_u m^2(T) + \mathbb{E}_u e^{\frac{1}{2}m(T)}, q \in [0, \frac{1}{4}]$$

Since $\mathcal{L}N^{\frac{1}{2}} \leq HN^{\frac{1}{2}}$, we have $\mathbb{E}_u e^{\frac{1}{2}m(T)} = \frac{\mathbb{E}_u N^{\frac{1}{2}}(T)}{N^{\frac{1}{2}}} \leq e^{HT}$. Due to Lemma 5.1, we have $\mathbb{E}_u m^2(T) \leq K_{T,M}$ for some constant K depending on T, M. Then

$$\frac{d^2\phi_{u,T}}{dq^2} = \mathbb{E}_u m^2(T) e^{qm(T)} \leq \tilde{C} := C(K_{T,M} + e^{HT}), q \in [0, \frac{1}{4}]$$

As a result, for any initial value $u = (G, A, N) \in (0, 1] \times (0, M] \times (0, \delta]$, $T \in [T^*, n^*T^*]$, and $q \in (0, \frac{1}{4})$ sufficiently small, Taylor expansion around $q = 0$ for $\phi_{u,T}$, reads

$$\phi_{u,T}(q) \leq 1 + q\frac{d\phi_{u,T}}{dq}(0) + \frac{\tilde{C}}{2}q^2 \leq 1 - \frac{\boldsymbol{\lambda} T}{4}q + \frac{\tilde{C}}{2}q^2.$$

For sufficiently small q, we have

$$\mathbb{E}_u(N(T)^q/N(0)^q) = \mathbb{E}_u \exp\{qm(T)\} = \phi_{u,T}(q) \leq 1 - \frac{q\boldsymbol{\lambda} T}{8} < 1$$

for $u = (G, A, N) \in (0, 1] \times (0, M] \times (0, \delta]$ and $T \in [T^*, n^*T^*]$. Since $\mathcal{L}N^{\frac{1}{2}} \leq -N^{\frac{1}{2}}$ if $A > M$, we can mimic the argument in Hening and Nguyen (2018, Theorem 5.1) to show that

$$\mathbb{E}_u(N(n^*T^*)^q/N(0)^q) \leq \rho, \text{ for any } u = (G, A, N) \in (0, 1] \times (0, \infty) \times (0, \delta_0],$$

for some δ_0, and $\rho \in (0, 1)$. Define

$$Y(k) = \frac{N^q(kn^*T^*) \wedge \delta_0^q}{\rho^k}, k \in \mathbb{N}.$$

Then

$$\mathbb{E}_u(N^q(n^*T^*) \wedge \delta^q) \le \mathbb{E}_u N^q(n^*T^*) \le N^q(0) \exp\left\{\frac{q\boldsymbol{\lambda} n^*T^*}{2}\right\} = N^q(0)\rho.$$

It follows that $\mathbb{E}_u Y(1) \le N^q(0) = Y(0)$, this combined with the Markov property of $U(t)$ implies that $Y(k)$ is a super-martingale. Now, for $\epsilon \in (0, \delta_0)$, let $\eta_\epsilon := \inf\{k \in \mathbb{N} : Y(k) > \epsilon\}$, $Z(k) := \mathbf{1}_{\{\eta_\epsilon > k\}} N^q(kn^*T^*)$, and $B_k := [kn^*T^*, (k+1)n^*T^*]$. By Lemma 5.2, we have for some positive constant K_*

$$\mathbb{E}_u \sup_{t\in[0,n^*T^*]} N^q(t) \le K_* N^q(0). \tag{5.12}$$

By Markov's property and due to (5.12),

$$\begin{aligned}\mathbb{E}_u \sup_{t\in B_k} \mathbf{1}_{\{\eta_\epsilon > t\}} N^q(t) &= \mathbb{E}_u \left\{\mathbf{1}_{\{\eta_\epsilon > k\}} \mathbb{E}_{U(kn^*T^*)}\left[\sup_{t\in[0,n^*T^*]} \mathbf{1}_{\{\eta_\epsilon > t\}} N^q(t)\right]\right\} \\ &\le K_* \mathbb{E}_u\left[\mathbf{1}_{\{\eta_\epsilon > k\}} N^q(kn^*T^*)\right] \\ &\le K_* \rho^k N^q(0).\end{aligned} \tag{5.13}$$

Here the last inequality follows from the fact that $Y(t)$ is a super martingale. As a result, we have from applying Markov's inequality to (5.13) that

$$\begin{aligned}\mathbb{P}_u\left\{\sup_{t\in B_k} \mathbf{1}_{\{\eta_\epsilon=\infty\}} N^q(t) > \rho^{k/2}\right\} &\le \mathbb{P}_u\left\{\sup_{t\in B_k} \mathbf{1}_{\{\eta_\epsilon > t\}} N^q(t) > \rho^{k/2}\right\} \\ &\le K_* N^q(0)\rho^{k/2}.\end{aligned}$$

Since $\sum_{k=1}^{\infty} K_* N^q(0)\rho^{k/2} < \infty$, Borel-Cantelli Lemma shows that, wp1, there exists a k_0 so that $k > k_0$ implies $\mathbf{1}_{\{\eta_\epsilon=\infty\}} N^q(t) \le \rho^{k/2}$ for all $t \in B_k$. As a result, $\limsup_{t\to\infty} \frac{\ln(N^q(t))}{t} < -r'' < 0$ a.s. on the event $\{\eta_\epsilon = \infty\}$ for a nonrandom positive constant r''. On the other hand, since $Y(k)$ is a super-martingale,

$$\mathbb{P}_u\{\eta_\epsilon < k\} = \mathbb{P}_u\{Y(k) > \epsilon\} \le \frac{\mathbb{E}_u Y(k)}{\epsilon} \le \frac{N^q(0)}{\epsilon}$$

for all $k \ge 1$, and hence $\mathbb{P}_u\{\eta_\epsilon < \infty\} \le \frac{N^q(0)}{\epsilon}$. Thus

$$\mathbb{P}_u\left\{\frac{\ln(N^q(t))}{t} < -r''\right\} = \mathbb{P}_u\{\eta_\epsilon = \infty\} \ge 1 - \frac{N^q(0)}{\epsilon}.$$

We have shown that for any $\epsilon' > 0$ there exists a $\delta' > 0$ so that

$$N < \delta' \text{ implies } \mathbb{P}_u\left\{\frac{\ln(N^q(t))}{t} < -r''\right\} > 1 - \epsilon'. \tag{5.14}$$

Next, we want to show that for some $T > 0$

$$\inf_{u \in K} \mathbb{P}_u\{G(T) \le 1,\ A(T) \le M,\ N(T) < \delta'\} > 0 \tag{5.15}$$

for any compact set K in D. Indeed, consider the control system associated with (2.1)

$$\begin{aligned}
\dot{G_\phi} &= rG_\phi(1 - G_\phi - N_\phi),\\
\dot{A_\phi} &= \frac{aG_\phi}{b + G_\phi} - A_\phi - \frac{\tau_1^2}{2}\frac{A_\phi G_\phi^2}{(b + G_\phi)^2} + \frac{\tau_1 A_\phi G_\phi}{b + G_\phi}\phi_1,\\
\dot{N_\phi} &= cA_\phi N_\phi - dN_\phi - \frac{\tau_2^2}{2}A_\phi^2 N_\phi + \tau_2 A_\phi N_\phi \phi_2,
\end{aligned}$$

where $\phi(t) = (\phi_1(t), \phi_2(t))^T$ is a piece-wise continuous control. It is clear that $G_\phi(t) \le 1$ for all $t \ge 0$ and any control ϕ. With the controls $\phi_1(t) \le -\tilde{H}$ and $\phi_2(t) \le -\tilde{H}$ for sufficiently large $\tilde{H} > 0$, we can get $A_\phi(T) \le M$ and $N_\phi(T) < \delta'$ for some $T > 0$. For any compact set K in D, by the support theorem [see Theorem 8.1 p. 518 in Ikeda and Watanabe (1989)],

$$\mathbb{P}_u\{U(T) \in V_{\delta'}\} > 0$$

for any initial value $u = (G, A, N) \in K$, where $V_{\delta'} = (0, 1] \times (0, M] \times (0, \delta')$. Then the uniform bound (5.15) follows from the Feller property of $U(t)$. In view of Lemma 5.3, for any initial value $u = (G, A, N)$ in the interior of D, the process $U(t) = (G(t), A(t), N(t))$ is recurrent relative to some compact set $\tilde{K}$ in D°. That is, $\zeta_k < \infty$ a.s. for all $k \ge 1$ where $\zeta_0 = 0$,

$$\begin{aligned}
\zeta_1 &= \inf\{t > 0 : U(t) \in \tilde{K}\},\\
\zeta_{k+1} &= \inf\{t > \zeta_k + T : U(t) \in \tilde{K}\}.
\end{aligned}$$

Let $C_k := \{U(t) \notin V_{\delta'}\ \forall t \in [\zeta_k, \zeta_{k+1}]\}$. By (5.15), there is a $\rho^* > 0$ such that $\mathbb{P}(C_k^c) \ge \rho^*$ for all $k \ge 1$ and for any initial value u in D°. Using the Strong Markov Property of the process $U(t)$, it is easy to show that

$$\mathbb{P}(\cap_{k=1}^n C_k) \le (1 - \rho^*)^n \to 0 \quad \text{as} \quad n \to \infty$$

and hence $\mathbb{P}\left(\cup_{k=1}^\infty C_k^c\right) = 1$. This means that for any initial value u in D°, the process $U(t)$ will eventually enter the set $\{G \le 1,\ A \le M,\ N < \delta'\}$ in a finite time with probability 1. Combining this with (5.14) and using the strong Markov property, we can conclude that

$$\mathbb{P}_u\left\{\frac{\ln(N^q(t))}{t} < -r''\right\} \ge 1 - \epsilon'$$

for any $\epsilon' > 0$ and for any initial value u in D°. Therefore, $\lim_{t\to\infty} \frac{\ln N(t)}{t} < -\frac{r''}{q} < 0$ a.s. Using Claim 5.1, we obtain $|A(t) - \tilde{A}(t)| \to 0$ a.s. and hence $A(t)$ converges weakly to the ergodic invariant measure π. Now, the equation of $N(t)$ implies

$$\begin{aligned}\lim_{t\to\infty} \frac{\ln N(t)}{t} &= \lim_{t\to\infty} \frac{\ln N}{t} + \lim_{t\to\infty} \frac{1}{t}\int_0^t [cA(s) - d - \tau_2^2 A^2(s)/2]ds \\ &\quad + \lim_{t\to\infty} \frac{1}{t}\int_0^t \tau_2 A(s) dW_2(s) \\ &= \boldsymbol{\lambda} + \lim_{t\to\infty} \frac{1}{t}\int_0^t \tau_2 A(s) dW_2(s).\end{aligned}$$

In view of Theorem 3.4 in Mao (2007), since $\int_0^t \tau_2 A(s) dW_2(s), t \geq 0$, is a real-valued continuous local martingale vanishing at $t = 0$ and

$$\limsup_{t\to\infty} \frac{1}{t}\int_0^t \tau_2^2 A^2(s) ds = \frac{2a^2\tau_2^2}{2(b+1)^2 - \tau_1^2} < \infty,$$

we have

$$\lim_{t\to\infty} \frac{1}{t}\int_0^t \tau_2 A(s) dW_2(s) = 0 \ a.s.$$

Thus

$$\lim_{t\to\infty} \frac{\ln N(t)}{t} = \boldsymbol{\lambda} \ a.s.$$

That is $N(t)$ decays a.s. to 0 exponentially fast with the rate $\boldsymbol{\lambda}$.

Case 2. Suppose that $\lambda > 0$ and the initial value $u = (G, A, N) \in D^\circ$. By way of contradiction, assume that $\limsup_{t\to\infty} \mathbb{E}_u \frac{1}{t}\int_0^t \ln(N(s) + 1) ds = 0$. By generalized L'Hospital's Rule (Lee 1977, p. 28), it implies that $\liminf_{t\to\infty} \mathbb{E}_u \ln(N(t) + 1) = 0$. Then Fatou's lemma implies that $\mathbb{E}_u \liminf_{t\to\infty} \ln(N(t) + 1) = 0$ and hence $\liminf_{t\to\infty} \ln(N(t) + 1) = 0$ a.s. So there exists a sequence of positive real numbers $\{t_k\}_k$ such that $t_k \uparrow \infty$ and $\ln(N(t_k) + 1) \to 0$ as $k \to \infty$ a.s. Hence $N(t_k) \to 0$ as $k \to \infty$ a.s. By Claim 5.1, $G(t_k) \to 1$ a.s. and $|A(t_k) - \tilde{A}(t_k)| \to 0$ a.s. This means the family of occupation measures $\{\Pi_{t_k}^{u_k}(\cdot)\}$, where $u_k = U(t_k)$, is tight on ∂D and converges weakly to the invariant measure μ_2. But, using Lemma 5.2 and (Hening and Nguyen 2018, Lemma 3.4), we get

$$\begin{aligned}&\lim_{k\to\infty} \frac{1}{t_k}\mathbb{E}_u \ln N(t_k) \\ &= \lim_{k\to\infty} \frac{1}{t_k}\int_0^{t_k} \mathbb{E}_u(cA(s) - d - \tau_2^2 A^2(s)/2) ds = \int_{\partial D} (cA - d - \tau_2^2 A^2/2) d\mu_2 = \boldsymbol{\lambda} > 0\end{aligned}$$

which contradicts the hypothesis that $\limsup_{t\to\infty} \mathbb{E}_u \frac{1}{t}\int_0^t \ln(N(s)+1)ds = 0$. Therefore, the proof of Theorem 2.2 is completed. □

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Authors and Affiliations

Tuan Anh Phan[1,3] · Hai Dang Nguyen[2] · Jianjun Paul Tian[1]

✉ Jianjun Paul Tian
jtian@nmsu.edu

Tuan Anh Phan
tuanpa86@nmsu.edu

Hai Dang Nguyen
hnguyen4@ua.edu

1 Department of Mathematical Sciences, New Mexico State University, Las Cruces, NM 88001, USA

2 Department of Mathematics, The University of Alabama, Tuscaloosa, AL 35401, USA

3 Present Address: Institute for Modeling Collaboration and Innovation, 875 Perimeter Drive, MS 1122, Moscow, ID 83844, USA