A NONLOCAL SAMPLE DEPENDENCE SDE-PDE SYSTEM MODELING PROTON DYNAMICS IN A TUMOR

ABSTRACT. A nonlocal stochastic model for intra- and extracellular proton dynamics in a tumor is proposed. The intracellular dynamics is governed by an SDE coupled to a reaction-diffusion equation for the extracellular proton concentration on the macroscale. In a more general context the existence and uniqueness of solutions for local and nonlocal SDE-PDE systems are established allowing, in particular, to analyze the proton dynamics model both, in its local version and the case with nonlocal path dependence. Numerical simulations are performed to illustrate the behavior of solutions, providing some insights into the effects of randomness on tumor acidity.

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1. INTRODUCTION

This work is motivated by modeling the interactions between extracellular and intracellular proton dynamics in the context of tumor growth. Hypoxia is a characteristic of invasive tumors, resulting from an imbalance between oxygen supply and its consumption at the cellular level. The increased glycolysis metabolism in cancer cells leads to acidification of the peritumoral region, hence conferring an advantage against normal cells, which -unlike neoplastic tissue- are known to have a reduced capability of surviving at low pH values, see e.g. [17, 21]. The reversed pH gradient between tumors and normal tissue promotes tumor invasion and proliferation [24]. Starting with the model by Gatenby and Gawlinski [11] involving reaction-diffusion equations for the dynamics of extracellular protons in interaction with tumor and normal cell densities, several classes of models extending that setting have been proposed and analyzed, see e.g., [16, 21] or [6, 7, 23, 18] for more recent, multiscale approaches coupling the dynamics of intra- and extracellular protons with the evolution of tumor cells and normal

tissue. Focusing on the proton dynamics, Webb et al. [27] proposed some models for the interdependence between the activity of several membrane-based ion transport systems and the changes in the peritumoral space. The models involve even more biological details, like intracellular proton buffering, effects on the expression/activation of matrix metalloproteinases (MMPs) and proton removal by vasculature. While all these approaches are deterministic, stochasticity needs to be included, as it is a relevant feature inherent to many biological processes occurring on all modeling levels. In particular, it seems to greatly influence subcellular dynamics and individual cell behavior, see e.g. [25].

Experimental findings suggest stochasticity in pH dynamics: Although all cells follow the same biochemical mechanisms, there are variations and uncertainties (essentially due to a random environment) in the behavior of every single cell. Furthermore, the distribution of intracellular pH (pH_i) at any value of extracellular pH (pH_e) was found to be broader than what was predicted by theoretical models based on machine noise and stochastic variation in the activity of membrane-based mechanisms regulating pH_i [14]. Moreover, excess current fluctuations have been observed in the gating of the ion channels [8]. Recent models by Hiremath and Surulescu [6, 7] take into account stochastic fluctuations in the intracellular proton dynamics; the latter is described with the aid of a random ODE featuring a stochastic term and coupled to a reaction-diffusion PDE for extracellular proton concentration and two further PDEs for the evolution of normal and cancer cell densities. In this work we concentrate on the interplay between intra- and extracellular protons, the concentration of the former satisfying a stochastic differential equation (SDE), hence (due to the coupling) opening the possibility of carrying the stochasticity from the microscopic, subcellular level to the macroscopic level of protons diffusing in the tumor microenvironment. The PDE for the latter dynamics is hence a random PDE (shortly RPDE). We also introduce a model with nonlocal sample dependence, in which the PDE for the extracellular proton concentration features only the averaged random fluctuations from the subcellular level. This new setting has the advantage of the PDE being genuinely deterministic.

Scalar SDEs with nonlocal sample dependence relating to, but extending mean-field SDEs like those in [26, 10] have been proposed and analyzed in [12]. Our nonlocal (here also called mean-field) model is analyzed w.r.t. well-posedness of solutions and preserving invariance. Actually, the analytical results are established in a more general setting for coupled systems of SDEs and random reaction-diffusion PDEs. The paper is organized as follows: In Section 2 we state the concrete nonlocal proton dynamics model and the setting for general SDE-RPDE systems. In Section 3 we proceed with the formulation and analysis of its local versions. Using the results for local SDE-RPDE systems we prove the existence and uniqueness of solutions for nonlocal systems in Section 4, which implies the well-posedness of the model stated in Section 2. Finally, the numerical simulations in Section 5 illustrate the proton dynamics for the model in Section 2.

2. Model set-up

We consider the following system modeling proton dynamics:

$$dX_t = \big(d\Delta X_t + r(X_t, \mathbb{E}(Y_t)) - \alpha X_t\big)dt$$
$$\partial_\nu X_t|_{\partial D} = 0, \quad X_0 = \zeta,$$
$$dY_t = (-r(X_t, Y_t) - \beta Y_t + \varphi(t, Y_t))dt + \gamma Y_t(1 - Y_t)dW_t$$
$$Y_0 = \eta,$$

where $D \subset \mathbb{R}^n, n = 1, 2, 3$, is a bounded domain with smooth boundary ∂D and W_t is a standard scalar Wiener process.

The model variables are: X, the extracellular proton concentration, and Y, the intracellular proton concentration. Both are normalized w.r.t. the maximum concentration, i.e., X and Y take values within the unit interval $(0, 1)$. Thus, X_t is a deterministic quantity satisfying a reaction-diffusion equation, while Y_t is a stochastic process evolving according to an Itô SDE. The evolution of X_t is influenced by diffusion, the source term $r(X_t, \mathbb{E}(Y_t))$ modeling the proton extrusion through the cell membrane into the extracellular environment, and a decay term with a rate α characterizing the loss of extracellular protons by processes other than membrane based transport into the tumor cells (e.g., uptake by vasculature, normal cells, buffering etc.). The dependence of r on $\mathbb{E}(Y_t)$ instead of Y_t highlights that the effects of H^+ coming from the intracellular regions of a set of tumors are averaged when considering the proton concentration in the extracellular space. In the intracellular space, however, Y_t is seen as a genuine stochastic process influencing as such the proton extrusion. The function φ models production of Y by glycolysis (which in cancer cells is much amplified when compared to normal cells and hence non-negligible). The decay term βY_t describes the loss of protons by intracellular buffering (e.g., by organelles), and the diffusion coefficient $g(Y) = \gamma Y(1 - Y)$ quantifies the (stochastic) variability in the production/decay of intracellular H^+. It accounts for the Y_t values ranging between 0 (complete alkalinization) and 1 (maximum acidification), both bounds being lethal for the cell and hence leading to no variability. Also, a maximum threshold is achieved in the middle of this interval, suggesting that larger spreads of the Y_t distribution are not allowed.

For a concrete choice of the membrane-based transport terms we use the setting in [23], which in turn was motivated by the choices in [6, 27] using the quantitative information in [1], where rates of H^+ flux due to NDCBE, NHE, and AE transporters were measured. [1] Hence, the above function r will take the form

$$r(x, y) = a_1 \frac{y}{1 + y^2 + a_2 x^2} - a_3 \frac{x}{1 + a_4 y^2},$$

where $a_i, i = 1, \ldots, 4$, are positive constants.

Thus, for the interaction functions we have

$$
\begin{aligned}
f_1(X_t, \mathbb{E}(Y_t)) &:= r(X_t, \mathbb{E}(Y_t)) - \alpha X_t \\
&= a_1 \frac{\mathbb{E}(Y_t)}{1 + \mathbb{E}(Y_t)^2 + a_2 X_t^2} - a_3 \frac{X_t}{1 + a_4 \mathbb{E}(Y_t)^2} - \alpha X_t \\
f_2(t, X_t, Y_t) &:= -r(X_t, Y_t) - \beta Y_t + \varphi(t) \\
&= -a_1 \frac{Y_t}{1 + Y_t^2 + a_2 X_t^2} + a_3 \frac{X_t}{1 + a_4 Y_t^2} - \beta Y_t + \varphi(t, Y_t).
\end{aligned}
$$

The space dependent function ζ is positive and bounded by one, and the random variable η can only have realizations within the unit interval, as well.

In the following section we establish the well-posedness for a more general class of models including the above mathematical description of proton dynamics as a particular case.

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[1] NDCBE (Na$^+$ dependent Cl$^-$-HCO$_3^-$ exchanger), NHE (Na$^+$ and H^+ exchanger) and AE (Cl$^-$-HCO$_3^-$ or anion exchanger) are specific ion transporters on the cell membrane.

Namely, we consider coupled, nonlocal SDE-PDE systems of the form

$$
\begin{aligned}
dX_t &= \{\Delta X_t + f_1(t, X_t, Y_t, \mathbb{E}(X_t), \mathbb{E}(Y_t))\}\, dt, \\
\partial_\nu X_t|_{\partial D} &= 0, \qquad X_0 = \zeta, \\
dY_t &= f_2(t, X_t, Y_t, \mathbb{E}(X_t), \mathbb{E}(Y_t))dt + g(t, X_t, Y_t, \mathbb{E}(X_t), \mathbb{E}(Y_t))dW_t, \\
Y_0 &= \eta,
\end{aligned}
\tag{1}
$$

with notations corresponding to the previous ones.

We will first analyze local SDE-RPDE systems in 3 and then apply these results to show the well-posedness of system (1).

3. Well-posedness of a local SDE–PDE system

Existence and uniqueness of the solution. Let $(\Omega, \mathcal{F}, \mathbb{P})$ be a complete probability space with a normal filtration $(\mathcal{F}_t)_{t \geq 0}$, let $(W_t)_{t \geq 0}$ be a standard scalar Wiener process and dW_t denote the corresponding Itô differential. In this section we prove the well-posedness of stochastic systems of the form

$$
\begin{aligned}
dX_t &= (\Delta X_t + f_1(t, X_t, Y_t))\, dt \\
\partial_\nu X_t|_{\partial D} &= 0, \qquad X_0 = \zeta, \\
dY_t &= f_2(t, X_t, Y_t)dt + g(t, X_t, Y_t)dW_t, \\
Y_0 &= \eta,
\end{aligned}
\tag{2}
$$

where $D \subset \mathbb{R}^n, n = 1, 2, 3$, is a bounded domain with smooth boundary ∂D. Moreover, $\Delta = \Delta_x$ denotes the Laplace operator with respect to the spatial variable $x \in D$, and ∂_ν the outward normal derivative on the boundary. The initial data ζ, η are $\mathcal{F}_0$-adapted random variables in $L^2(D)$ such that $\mathbb{E}\|\zeta\|^2_{L^2(D)} < \infty$ and $\mathbb{E}\|\eta\|^2_{L^2(D)} < \infty$.

We denote by A the operator $-\Delta$ in D with homogeneous Neumann boundary conditions and by $e^{-At}, t \geq 0$, the analytic semigroup in $L^2(D)$ generated by A.

Definition 1. *We call $(X, Y) : D \times [0, T] \times \Omega \to \mathbb{R}^2$ a mild solution of system (2) if X and Y are $\mathcal{F}_t$-adapted mean-square continuous $L^2(D)$-valued processes in $[0, T]$ that satisfy the integral equations*

$$
X_t = e^{-At}\zeta + \int_0^t e^{-A(t-s)} f_1(s, X_s, Y_s)ds
$$

$$
Y_t = e^{-t}\eta + \int_0^t e^{-(t-s)} \left(f_2(s, X_s, Y_s) + Y_s\right) ds + \int_0^t e^{-(t-s)} g(s, X_s, Y_s)dW_s.
$$

We remark that the stochastic integral equation in Definition 1 is equivalent to the identity

$$
Y_t = \eta + \int_0^t f_2(s, X_s, Y_s)ds + \int_0^t g(s, X_s, Y_s)dW_s.
$$

Assumptions

(A_1) The functions $f = (f_1, f_2) : [0, T] \times \mathbb{R}^2 \to \mathbb{R}^2$ and $g : [0, T] \times \mathbb{R}^2 \to \mathbb{R}$ are continuous, and there exists a constant $c \geq 0$ such that

$$
|f(t, x)| + |g(t, x)| \leq c(1 + |x|)
$$

$$
|f(t, x) - f(t, \tilde{x})| + |g(t, x) - g(t, \tilde{x})| \leq c(|x - \tilde{x}|),
$$

for all $t \in [0, T], x = (x_1, x_2) \in \mathbb{R}^2$, where $|\cdot|$ denotes the Euclidean norm in $\mathbb{R}^n$.

Here and in the sequel, we use the following notations

$$(H, \|\cdot\|) = (L^2(D), \|\cdot\|_{L^2(D)}), \qquad \mathcal{H} = H \times H,$$
$$\langle\cdot,\cdot\rangle = \langle\cdot,\cdot\rangle_{L^2(D)}, \qquad \langle\cdot,\cdot\rangle_{\mathcal{H}} = \langle\cdot,\cdot\rangle + \langle\cdot,\cdot\rangle, \qquad \|\cdot\|_{\mathcal{H}} = \|\cdot\| + \|\cdot\|.$$

Theorem 2. *We assume (A_1) is satisfied. Then, for every $T > 0, p \geq 1$ and $\mathcal{F}_0$-adapted initial data $(\zeta, \eta) \in L^{2p}(\Omega; \mathcal{H})$ there exists a unique mild solution of problem (2) such that $(X, Y) \in C([0,T]; L^{2p}(\Omega; \mathcal{H}))$. Moreover, if $p > 1$ the solution has continuous sample paths, i.e., $(X, Y) \in L^{2p}(\Omega; C([0,T]; \mathcal{H}))$,*

$$\mathbb{P}\left(\cup_{t \in [0,T]}\{\omega \in \Omega \mid \limsup_{s \to t}(\|X_s(\omega) - X_t(\omega)\| + \|Y_s(\omega) - Y_t(\omega)\|) > 0\}\right) = 0$$

and the following estimate holds

$$\mathbb{E} \sup_{t \in [0,T]} (\|X_t\|^{2p} + \|Y_t\|^{2p}) \leq c \left(1 + \|\zeta\|^{2p} + \|\eta\|^{2p}\right), \tag{3}$$

for some constant $c \geq 0$ depending on T.

Proof. We do the proof for $p > 1$; the case $p = 1$ follows similarly. For a constant $\lambda > 0$ that will be chosen below and $p > 1$ we denote by $\Xi_{p,\lambda}$ the space of $\mathcal{F}_t$-adapted, continuous processes in H such that

$$\mathbb{E}\left(\sup_{t \in [0,T]} \{e^{-2p\lambda t}\|X_t\|^{2p}\}\right) < \infty.$$

Then, $\Xi_{p,\lambda}$ is a Banach space equipped with the norm

$$\|X\|_{p,\lambda} := \left(\mathbb{E}\left(\sup_{t \in [0,T]} \{e^{-2p\lambda t}\|X_t\|^{2p}\}\right)\right)^{\frac{1}{2p}}.$$

We define $\mathcal{X} := \Xi_{p,\lambda} \times \Xi_{p,\lambda}$ with norm $\|(X,Y)\|_{\mathcal{X}} := \left(\|X\|_{p,\lambda}^{2p} + \|Y\|_{p,\lambda}^{2p}\right)^{\frac{1}{2p}}$ and show that the mapping $\Phi : \mathcal{X} \to \mathcal{X}$,

$$\Phi(X,Y)_t = \begin{pmatrix} \Phi_1(X,Y)_t \\ \Phi_2(X,Y)_t \end{pmatrix} := \begin{pmatrix} e^{-At}\zeta + \int_0^t e^{-A(t-s)}f_1(s, X_s, Y_s)ds \\ \eta + \int_0^t f_2(s, X_s, Y_s)ds + \int_0^t g(s, X_s, Y_s)dW_s \end{pmatrix},$$

is well-defined, Lipschitz-continuous, and has a unique fixed point in $\mathcal{X}$.

From now on, the letter C will always denote a non-negative constant, independent of T, that may vary in each occurrence and from line to line.

Step 1: Φ is a well-defined, bounded operator and satisfies the estimate

$$\|\Phi(X,Y)\|_{\mathcal{X}} \leq c_T \left(1 + \|(\zeta, \eta)\|_{\mathcal{X}} + \|(X,Y)\|_{\mathcal{X}}\right) \qquad (X,Y) \in \mathcal{X}, \tag{4}$$

for some constant $c_T > 0$ depending on T.

Here and in the sequel, we use the notation $Z_t = (X_t, Y_t)$. By assumption (A_1) we obtain

$$e^{-2p\lambda t}\|\int_0^t e^{-A(t-s)}f_1(s, Z_s)ds\|^{2p} \leq e^{-2p\lambda t}\left(\int_0^t \|e^{-A(t-s)}\|_{\mathcal{L}(H)}\|f_1(s, Z_s)\|ds\right)^{2p}$$

$$\leq C\left(\int_0^t e^{-\lambda t}\|f_1(s, Z_s)\|ds\right)^{2p} \leq C\left(\int_0^t (1 + \|Z_s\|_{\mathcal{H}})e^{-\lambda s}e^{-\lambda(t-s)}ds\right)^{2p},$$

where we used the estimate $\|e^{-A(t-s)}\|_{\mathcal{L}(H)} \leq Ce^{-C(t-s)}$ and $\mathcal{L}(H)$ denotes as usual the space of linear and continuous functions on H. Now taking the supremum and expectation value in the above inequality it follows that

$$
\left\| \int_0^{\cdot} e^{-A(\cdot-s)} f_1(s, Z_s) ds \right\|_{p,\lambda}^{2p}
$$

$$
\leq C\, \mathbb{E} \sup_{t \in [0,T]} \left(\int_0^t (1 + \|Z_s\|_{\mathcal{H}}) e^{-\lambda s} e^{-\lambda(t-s)} ds \right)^{2p}
$$

$$
\leq C\, \mathbb{E} \sup_{t \in [0,T]} \left(\sup_{s \in [0,t]} \left\{ (1 + \|Z_s\|_{\mathcal{H}}) e^{-\lambda s} \right\} \int_0^t e^{-\lambda(t-s)} ds \right)^{2p}
$$

$$
\leq C\, \mathbb{E} \sup_{t \in [0,T]} \left(\left\{ 1 + e^{-\lambda t} (\|Z_t\|_{\mathcal{H}}) \right\} \frac{1}{\lambda} \left(1 - e^{-\lambda t} \right) \right)^{2p} \leq \frac{C}{\lambda^{2p}} \left(1 + \|Z\|_{\mathcal{X}}^{2p} \right).
$$

Similarly, we derive the estimate

$$
\left\| \int_0^{\cdot} f_2(s, Z_s) ds \right\|_{p,\lambda}^{2p} \leq \frac{C}{\lambda^{2p}} \left(1 + \|Z\|_{\mathcal{X}}^{2p} \right).
$$

Theorem I.7.2, p.40, in [15] and hypothesis (A_1) further imply that

$$
\left\| \int_0^{\cdot} g(s, Z_s) dW_s \right\|_{p,\lambda}^{2p} = \mathbb{E} \sup_{t \in [0,T]} \left\| \int_0^t e^{-\lambda t} g(s, Z_s) dW_s \right\|^{2p}
$$

$$
\leq CT^{p-1} \mathbb{E} \int_0^T e^{-2p\lambda T} (1 + \|Z_s\|_{\mathcal{H}})^{2p} ds \leq CT^{p-1} (1 + \|Z\|_{\mathcal{X}}^{2p}) \int_0^T e^{-2p\lambda(T-s)} ds
$$

$$
\leq \frac{C}{2p\lambda} T^{p-1} (1 + \|Z\|_{\mathcal{X}}^{2p}).
$$

Summing up we obtain

$$
\|\Phi_1(X,Y)\|_{p,\lambda}^{2p} + \|\Phi_2(X,Y)\|_{p,\lambda}^{2p}
$$

$$
\leq C \max \left\{ \frac{1}{\lambda^{2p}}, \frac{T^{p-1}}{2p\lambda} \right\} \left(1 + \mathbb{E}\|\zeta\|^{2p} + \mathbb{E}\|\eta\|^{2p} + \|X\|_{p,\lambda}^{2p} + \|Y\|_{p,\lambda}^{2p} \right),
$$

for some constant $C \geq 0$, which implies estimate (4).

It remains to prove continuity of the image function $t \mapsto \Phi(Z)_t$. Let $0 \leq s < t \leq T$. For the second equation we obtain

$$
\Phi_2(Z)_t - \Phi_2(Z)_s = \int_s^t f_2(\tau, Z_\tau) d\tau + \int_s^t g(\tau, Z_\tau) dW_\tau,
$$

and consequently, by a version of the Burkholder-Gundy-Davis inequality (see Theorem 7.1, p.39, in [15]) it follows that

$$
\mathbb{E}\|\Phi_2(Z)_t - \Phi_2(Z)_s\|^{2p}
$$

$$
\leq C \left\{ \mathbb{E} \left(\int_s^t \|f_2(\tau, Z_\tau)\| d\tau \right)^{2p} + \mathbb{E} \left\| \int_s^t g(\tau, Z_\tau) dW_\tau \right\|^{2p} \right\}
$$

$$
\leq C \left(\mathbb{E} \left(\int_s^t \|f_2(\tau, Z_\tau)\| d\tau \right)^{2p} + |t-s|^{p-1} \mathbb{E} \int_s^t \|g(\tau, Z_\tau)\|^{2p} d\tau \right)
$$

$$
\leq C \left(\mathbb{E} \left(\int_s^t 1 + \|Z_\tau\|_{\mathcal{H}} d\tau \right)^{2p} + |t-s|^{p-1} \mathbb{E} \int_s^t (1 + \|Z_\tau\|_{\mathcal{H}}^{2p}) d\tau \right)
$$

$$
\leq C \left(|t-s|^{2p} + |t-s|^p \right) \left(1 + \mathbb{E} \sup_{\tau \in [0,T]} \|Z_\tau\|_{\mathcal{H}}^{2p} \right)
$$

$$
\leq C |t-s|^p (T^p + 1) \left(1 + \mathbb{E} \sup_{\tau \in [0,T]} \|Z_\tau\|_{\mathcal{H}}^{2p} \right).
$$

Moreover, since

$$
\mathbb{E} \{ \sup_{\tau \in [0,T]} \|Z_\tau\|_{\mathcal{H}}^{2p} \} \leq e^{2p\lambda T} \|Z\|_{\mathcal{X}}^{2p}
$$

Kolmogorov's continuity criterion (Theorem 2.1 and the subsequent remark , p.6, in [2]) implies the continuity of $t \mapsto \Phi_2(X,Y)_t$. For the first component we obtain

$$
\|\Phi_1(Z)_t - \Phi_1(Z)_s\|
$$

$$
\leq \|(e^{-At} - e^{-As})\zeta\| + \|\int_0^t e^{-A(t-\tau)} f_1(\tau, Z_\tau) d\tau - \int_0^s e^{-A(s-\tau)} f_1(\tau, Z_\tau) d\tau\|
$$

$$
\leq \|e^{-As}(e^{-A(t-s)} - \mathrm{Id})\zeta\| + \|\int_s^t e^{-A(t-\tau)} f_1(\tau, Z_\tau) d\tau\|
$$

$$
+ \|\int_0^s (e^{-A(t-\tau)} - e^{-A(s-\tau)}) f_1(\tau, Z_\tau) d\tau\|
$$

$$
= I_1 + I_2 + I_3.
$$

Semigroup estimates imply

$$
I_1 \leq C \|(e^{-A(t-s)} - \mathrm{Id})\zeta\| \leq C|t-s|\|\zeta\|,
$$

and using (A_1) for the second term it follows that

$$
I_2 \leq \int_s^t \|e^{-A(t-\tau)} f_1(\tau, Z_\tau)\| d\tau \leq C \int_s^t \|f_1(\tau, Z_\tau)\| d\tau \leq C \int_s^t (1 + \|Z_\tau\|_{\mathcal{H}}) d\tau.
$$

The last integral can be estimated by

$$I_3 \le \int_0^s \|(e^{-A(t-s)} - \mathrm{Id})e^{-A(s-\tau)} f_1(\tau, Z_\tau)\| d\tau$$

$$\le C \int_0^s |t-s| \|e^{-A(s-\tau)} f_1(\tau, Z_\tau)\| d\tau$$

$$\le C|t-s| \int_0^s \|f_1(\tau, Z_\tau)\| d\tau \le C|t-s| \int_0^s (1 + \|Z_\tau\|_{\mathcal{H}}) d\tau.$$

Taking the $2p$-th power and expectation value and summing up we obtain

$$\mathbb{E}\|\Phi_1(Z)_t - \Phi_1(Z)_s\|^{2p} \le C \,\mathbb{E}(\|I_1\|^{2p} + \|I_2\|^{2p} + \|I_3\|^{2p})$$

$$\le C|t-s|^{2p} \Big\{ \|\zeta\|^{2p} + (1 + T^{2p}) \Big(1 + \mathbb{E} \sup_{\tau \in [0,T]} \|Z_\tau\|_{\mathcal{H}}^{2p} \Big) \Big\}.$$

As before, the continuity of $t \mapsto \Phi_1(X, Y)_t$ now follows from Kolmogorov's continuity criterion.

Step 2: For λ sufficiently large Φ is a contraction in $\mathcal{X}$.

We assume $Z = (X, Y)$ and $\widetilde{Z} = (\widetilde{X}, \widetilde{Y})$ are processes in $\mathcal{X}$. Then, $\Phi(X, Y) - \Phi(\widetilde{X}, \widetilde{Y})$ satisfies the system

$$\Phi_1(Z)_t - \Phi_1(\widetilde{Z})_t = \int_0^t e^{-A(t-s)} \Big(f_1(s, Z_s) - f_1(s, \widetilde{Z}_s) \Big) ds,$$

$$\Phi_2(Z)_t - \Phi_2(\widetilde{Z})_t = \int_0^t \Big(f_2(s, Z_s) - f_2(s, \widetilde{Z}_s) \Big) ds + \int_0^t \Big(g(s, Z_s) - g(s, \widetilde{Z}_s) \Big) dW_s.$$

Assumption (A_1) implies for the first equation

$$e^{-2p\lambda t} \|\Phi_1(Z)_t - \Phi_1(\widetilde{Z})_t\|^{2p} \le C \left(\int_0^t e^{-\lambda t} \|f_1(s, Z_s) - f_1(s, \widetilde{Z}_s)\| ds \right)^{2p}$$

$$\le C \left(\int_0^t \|Z_s - \widetilde{Z}_s\|_{\mathcal{H}} e^{-\lambda s} e^{-\lambda(t-s)} ds \right)^{2p},$$

and taking the supremum and expectation value we obtain

$$\|\Phi_1(Z) - \Phi_1(\widetilde{Z})\|_{p,\lambda}^{2p} \le C \left(\|Z - \widetilde{Z}\|_{\mathcal{X}}^{2p} \right) \left(\int_0^T e^{-\lambda(t-s)} ds \right)^{2p} \le \frac{C_T}{\lambda^{2p}} \|Z - \widetilde{Z}\|_{\mathcal{X}}^{2p},$$

for some constant $C_T \ge 0$. Similarly, we derive a bound for the first integral in the second equation

$$\left\| \int_0^{\cdot} f_2(s, Z_s) - f_2(s, \widetilde{Z}_s) ds \right\|_{p,\lambda}^{2p} \le \frac{C}{\lambda^{2p}} \|Z - \widetilde{Z}\|_{\mathcal{X}}^{2p}.$$

To estimate the remaining term we use Theorem I.7.2, p.40, in [11] and hypothesis (A_1)

$$\mathbb{E} \sup_{t \in [0,T]} \left\| e^{-\lambda t} \int_0^t g(s, Z_s) - g(s, \widetilde{Z}_s) dW_s \right\|^{2p}$$

$$\leq CT^{p-1} \mathbb{E} \int_0^T e^{-2p\lambda T} \|g(s, Z_s) - g(s, \widetilde{Z}_s)\|^{2p} ds$$

$$\leq CT^{p-1} \mathbb{E} \int_0^T e^{-2p\lambda s} \|Z_s - \widetilde{Z}_s\|_{\mathcal{H}}^{2p} e^{-2p\lambda(T-s)} ds \leq \frac{C}{2p\lambda} T^{p-1} \|Z - \widetilde{Z}\|_{\mathcal{X}}^{2p}.$$

Adding the inequalities deduced above we obtain

$$\|\Phi(Z) - \Phi(\widetilde{Z})\|_{\mathcal{X}}^{2p} \leq C \max \left\{ \frac{1}{\lambda^{2p}}, \frac{T^{p-1}}{2p\lambda} \right\} \|Z - \widetilde{Z}\|_{\mathcal{X}}^{2p},$$

for some constant $C \geq 0$. Consequently, if $\lambda > 0$ is sufficiently large Φ is a contraction in $\mathcal{X} = \Xi_{p,\lambda} \times \Xi_{p,\lambda}$.

Step 3: Existence and uniqueness.

For λ large enough Φ is a contraction in $\mathcal{X} = \Xi_{p,\lambda} \times \Xi_{p,\lambda}$. By Banach's fixed point theorem it possesses a unique fixed point (X, Y), which is the unique mild solution of the initial value problem (2).

Step 4: Estimate (3).

Let $(X, Y) = Z = \Phi(Z)$ be the mild solution of (2). By Hölder's inequality and (A_1) it follows that

$$\mathbb{E} \sup_{t \in [0,T]} \|X_t\|^{2p} \leq C \left(\mathbb{E}\|\zeta\|^{2p} + \mathbb{E} \sup_{t \in [0,T]} \left(\int_0^t \|f_1(s, Z_s)\| ds \right)^{2p} \right)$$

$$\leq C \left(\mathbb{E}\|\zeta\|^{2p} + T^{2p-1} \mathbb{E} \int_0^T \|f_1(s, Z_s)\|^{2p} ds \right)$$

$$\leq C \left(\mathbb{E}\|\zeta\|^{2p} + T^{2p-1} \mathbb{E} \int_0^T (1 + \|Z_s\|_{\mathcal{H}}^{2p}) ds \right)$$

$$\leq C \left(\mathbb{E}\|\zeta\|^{2p} + T^{2p} + T^{2p-1} \int_0^T \mathbb{E} \sup_{s \in [0,t]} \|Z_s\|_{\mathcal{H}}^{2p} dt \right)$$

and similarly,

$$\mathbb{E} \sup_{t \in [0,T]} \|Y_t\|^{2p} \leq C \left(\mathbb{E}\|\eta\|^{2p} + T^{2p} + T^{2p-1} \int_0^T \mathbb{E} \sup_{s \in [0,t]} \|Z_s\|_{\mathcal{H}}^{2p} dt \right)$$

$$+ \mathbb{E} \sup_{t \in [0,T]} \left\| \int_0^t g(s, X_s, Y_s) dW_s \right\|^{2p}.$$

To estimate the stochastic integral we use again Theorem I.7.2, p.40, in [15] and (A_1),

$$\mathbb{E} \sup_{t \in [0,T]} \left\| \int_0^t g(s, Z_s) dW_s \right\|^{2p} \leq CT^{p-1} \mathbb{E} \int_0^T \|g(s, Z_s)\|^{2p} ds$$

$$\leq CT^{p-1} \mathbb{E} \int_0^T (1 + \|Z_s\|_{\mathcal{H}}^{2p}) ds \leq C \left(T^p + T^{p-1} \int_0^T \mathbb{E} \sup_{s \in [0,t]} \|Z_s\|_{\mathcal{H}}^{2p} dt \right).$$

Adding the relevant inequalities we obtain

$$
\mathbb{E} \sup_{t \in [0,T]} \left(\|X_t\|^{2p} + \|Y_t\|^{2p} \right)
$$

$$
\leq C \Big(\mathbb{E}(\|\zeta\|^{2p} + \|\eta\|^{2p}) + T^p + T^{2p}
$$

$$
+ (T^{p-1} + T^{2p-1}) \int_0^T \mathbb{E} \sup_{s \in [0,t]} \left(\|X_s\|^{2p} + \|Y_s\|^{2p} \right) dt \Big),
$$

for some constant $C \geq 0$, which by Gronwall's lemma implies (3). $\qquad\square$

3.1. **Invariance.** The solutions of mathematical models in biology often describe quantities that are non-negative and bounded by a maximum value. The following conditions ensure that solutions emanating from viable initial data remain within the admissible range.

(A_2) There exist constants $m_1^*, m_2^* > 0$ such that f_1 and f_2 satisfy

$$
\begin{array}{lll}
f_1(t, 0, x_2) \geq 0, & f_1(t, m_1^*, x_2) \leq 0 & \forall\, 0 \leq x_2 \leq m_2^*,\ t \in [0,T], \\
f_2(t, x_1, 0) \geq 0, & f_2(t, x_1, m_2^*) \leq 0 & \forall\, 0 \leq x_1 \leq m_1^*,\ t \in [0,T],
\end{array}
$$

and the stochastic perturbation fulfills

$$
g(t, x_1, 0) = g(t, x_1, m_2^*) = 0 \qquad \forall\, 0 \leq x_1 \leq m_1^*,\ t \in [0,T].
$$

Remark 1. *Hypothesis (A_2) implies that the set $[0, m_1^*] \times [0, m_2^*]$ is invariant for system (2); i.e., solutions corresponding to initial data (ζ, η) such that $0 \leq \zeta \leq m_1^*, 0 \leq \eta \leq m_2^*$ are almost surely non-negative and uniformly bounded by m_1^* and m_2^*.*

An admissible stochastic perturbation is, e.g., the function

$$
g(Y) = \sigma Y (m_2^* - Y), \qquad \sigma \in \mathbb{R},
$$

on the invariant set $[0, m_1^*] \times [0, m_2^*]$.

Theorem 3. *In addition to the hypotheses of Theorem 2 we assume that (A_2) holds and the initial data (ζ, η) are deterministic and satisfy $0 \leq \zeta \leq m_1^*$, $0 \leq \eta \leq m_2^*$ in D. Then, the solutions are almost surely non-negative and uniformly bounded by m_1^* and m_2^*, respectively.*

Proof. Let (ζ, η) be given initial data satisfying the stated assumptions. We first assume that $f = (f_1, f_2)$ and g satisfy the conditions in (A_2) for all $(x_1, x_2) \in \mathbb{R}^2$, $t \in [0,T]$. We denote by $\tilde{f} = (\tilde{f}_1, \tilde{f}_2)$ and $\tilde{g}$ the modified functions that coincide on $[0, m_1^*] \times [0, m_2^*]$ with f and g. Moeover, we denote the solutions of the corresponding modified system by $\widetilde{X}$ and $\widetilde{Y}$. Due to the continuity of solutions shown in Step 1 the first equation can be considered pathwise. By deterministic comparison principles for scalar parabolic equations it follows that $\widetilde{X}$ remains pathwise non-negative and bounded by m_1^*. On the other hand, for every fixed $x \in D$ the SDE in (2) fulfills the hypothesis of the stochastic invariance criterion (see [19] or [3]), which implies that $\widetilde{Y}$ takes values within the interval $[0, m_2^*]$ with probability 1.

Finally, the solutions $\widetilde{X}$ and $\widetilde{Y}$ satisfy the original system with $f = (f_1, f_2)$ and g, and by the uniqueness of solutions we conclude that the set $[0, m_1^*] \times [0, m_2^*]$ is invariant for the original problem (2). Consequently, solutions corresponding to initial data within the given range are non-negative, uniformly bounded and exist globally.

$\qquad\square$

3.2. **Boundedness properties of the solutions.** We will need the following properties of solutions of (2) to show the well-posedness of stochastic mean-field models.

Proposition 4. *Under the hypotheses of Theorem 2, the solutions of system* (2) *satisfy*

$$\sup_{s\in[0,t]} \left(\mathbb{E}\|X_s\|^2 + \mathbb{E}\|Y_s\|^2 \right) \leq \left(\mathbb{E}\|\zeta\|^2 + \mathbb{E}\|\eta\|^2 + c_1 t \right) e^{c_1 t} \qquad \forall t \in [0,T],$$

for some constant $c_1 \geq 0$ depending on T.

Proof. Let $Z = (X,Y)$ be the mild solution of (2). Itô's formula and the previous invariance result imply that $\|Y_t\|^2$ satisfies the SDE

$$\|Y_t\|^2$$
$$= \|\eta\|^2 + 2 \int_0^t Y_s f_2(s, X_s, Y_s) ds + 2 \int_0^t (g(s, X_s, Y_s))^2 ds + 2 \int_0^t Y_s g(s, X_s, Y_s) dW_s.$$

Since

$$\mathbb{E}\left(\int_0^t Y_s g(s, X_s, Y_s) dW_s \right) = 0,$$

taking the expectation value in the above equality we obtain

$$\mathbb{E}\|Y_t\|^2 = \mathbb{E}\|\eta\|^2 + 2 \int_0^t \mathbb{E}(Y_s f_2(s, X_s, Y_s)) ds + 2 \int_0^t \mathbb{E}(g(s, X_s, Y_s))^2 ds$$

$$\leq \mathbb{E}\|\eta\|^2 + C \left(\int_0^t \mathbb{E}(1 + \|Y_s\|^2 + \|X_s\|^2) ds \right)$$

$$= \mathbb{E}\|\eta\|^2 + Ct + C \int_0^t \mathbb{E}(\|Y_s\|^2 + \|X_s\|^2) ds,$$

where we used hypothesis (A_1).

On the other hand, multiplying the PDE in (2) by X and integrating over Ω leads to

$$\frac{1}{2}\frac{d}{dt}\|X_t\|^2 = -\int_\Omega |\nabla X_t|^2 dx + \int_\Omega X_t f_1(t, X_t, Y_t) dx.$$

We integrate the equation from 0 to t, disregard the negative term, and use (A_1) to conclude

$$\|X_t\|^2 - \|\zeta\|^2 = -2 \int_0^t \int_\Omega |\nabla X_s|^2 dx ds + 2 \int_0^t \int_\Omega X_s f_1(s, X_s, Y_s) dx ds$$

$$\leq C \int_0^t \int_\Omega |X_s|(1 + |X_s| + |Y_s|) dx ds$$

$$\leq C \int_0^t \int_\Omega (1 + |X_s|^2 + |Y_s|^2) dx ds.$$

Taking expectation values we obtain

$$\mathbb{E}\|X_t\|^2 \leq \mathbb{E}\|\zeta\|^2 + Ct + C \int_0^t \mathbb{E}\|X_s\|^2 + \mathbb{E}\|Y_s\|^2 ds.$$

Adding both estimates leads to

$$\mathbb{E}(\|X_t\|^2 + |Y_t\|^2) \leq \mathbb{E}\|\zeta\|^2 + \mathbb{E}\|\eta\|^2 + Ct + C \int_0^t \mathbb{E}(\|X_s\|^2 + \|Y_s\|^2) ds,$$

and the proposition follows from Gronwall's Lemma. $\qquad\square$

Proposition 5. *Under the hypotheses of Theorem 2, for every $p \in \mathbb{N}$ the solutions of system (2) satisfy the estimate*

$$\mathbb{E}(\|X_t - X_s\|^{2p} + \|Y_t - Y_s\|^{2p}) \leq c_2 |t - s|^p \left(\mathbb{E}\|\zeta\|^{2p} + \mathbb{E}\|\eta\|^{2p} + 1\right) \qquad \forall t, s \in [0, T],$$

for some constant $c_2 \geq 0$ depending on T.

Proof. Let $Z = (X, Y)$ be the mild solution of (2) and $t, s \in [0, T]$ be such that $t > s$. For the first component we obtain

$$\|X_t - X_s\|$$
$$\leq \|(e^{-At} - e^{-As})\zeta\| + \left\| \int_0^t e^{-A(t-\tau)} f_1(\tau, Z_\tau) d\tau - \int_0^s e^{-A(s-\tau)} f_1(\tau, Z_\tau) d\tau \right\|$$
$$\leq \|e^{-As}(e^{-A(t-s)} - \mathrm{Id})\zeta\| + \left\| \int_s^t e^{-A(t-\tau)} f_1(\tau, Z_\tau) d\tau \right\|$$
$$\quad + \left\| \int_0^s (e^{-A(t-\tau)} - e^{-A(s-\tau)}) f_1(\tau, Z_\tau) d\tau \right\|$$
$$= J_1 + J_2 + J_3.$$

Semigroup estimates imply

$$J_1 \leq C\|(e^{-A(t-s)} - \mathrm{Id})\zeta\| \leq C|t - s|\|\zeta\|,$$

and using (A_1) the second term can be estimated by

$$J_2 \leq \int_s^t \|e^{-A(t-\tau)} f_1(\tau, Z_\tau)\| d\tau \leq C \int_s^t \|f_1(\tau, Z_\tau)\| d\tau \leq C \int_s^t (1 + \|Z_\tau\|_{\mathcal{H}}) d\tau.$$

Taking the $2p$-th power and expectation value and using Hölder's inequality we obtain

$$\mathbb{E}\|J_2\|^{2p} \leq C|t - s|^{2p-1} \int_s^t \mathbb{E}(1 + \|Z_\tau\|_{\mathcal{H}}^{2p}) d\tau$$
$$\leq C\left(|t - s|^{2p} + |t - s|^{2p-1} \int_s^t \mathbb{E}\|Z_\tau\|_{\mathcal{H}}^{2p} d\tau\right).$$

Furthermore,

$$J_3 \leq \int_0^s \|(e^{-A(t-s)} - \mathrm{Id})e^{-A(s-\tau)} f_1(\tau, Z_\tau)\| d\tau$$
$$\leq C \int_0^s |t - s| \|e^{-A(s-\tau)} f_1(\tau, Z_\tau)\| d\tau \leq C|t - s| \int_0^s \|f_1(\tau, Z_\tau)\| d\tau$$
$$\leq C|t - s| \int_0^s (1 + \|Z_\tau\|) d\tau \leq C|t - s| \left(s + \int_0^s \|Z_\tau\| d\tau\right).$$

Taking the $2p$-th power and expectation value it follows by Hölder's inequality that

$$\mathbb{E}\|J_3\|^{2p} \leq C|t - s|^{2p} \left(s^{2p} + s^{2p-1} \int_0^s \mathbb{E}\|Z_\tau\|_{\mathcal{H}}^{2p} d\tau\right)$$
$$\leq C|t - s|^{2p} s^{2p} \left(1 + \left(\mathbb{E}\|Z_0\|_{\mathcal{H}}^{2p} + c_1 s\right) e^{c_1 s}\right) \leq C_T |t - s|^{2p} \left(1 + \mathbb{E}\|Z_0\|_{\mathcal{H}}^{2p}\right),$$

for some constant $C_T \geq 0$, where we used Proposition 4 in the second inequality. The solution of the SDE satisfies

$$Y_t - Y_s = \int_s^t f_2(\tau, Z_\tau) d\tau + \int_s^t g(\tau, Z_\tau) dW_\tau.$$

The first integral can be estimated similarly to J_2,

$$\mathbb{E}\left(\int_s^t \|f_2(\tau, Z_\tau)\| d\tau\right)^{2p} \leq C\left(|t-s|^{2p} + |t-s|^{2p-1} \int_s^t \mathbb{E}\|Z_\tau\|_{\mathcal{H}}^{2p} d\tau\right),$$

and the stochastic integral by applying Theorem I.7.1, p.39, in [15],

$$\mathbb{E}\left\|\int_s^t g(\tau, Z_\tau) dW_\tau\right\|^{2p} \leq C|t-s|^{p-1} \int_s^t \mathbb{E}\|g(\tau, Z_\tau)\|^{2p} d\tau$$

$$\leq C|t-s|^{p-1} \int_s^t \mathbb{E}(1 + \|Z_\tau\|_{\mathcal{H}}^{2p}) d\tau$$

$$= C\left(|t-s|^p + |t-s|^{p-1} \int_s^t \mathbb{E}\|Z_\tau\|_{\mathcal{H}}^{2p} d\tau\right).$$

Summing up all previous estimates we obtain

$$\mathbb{E}(\|Z_t - Z_s\|_{\mathcal{H}}^{2p}) \leq C_T \left(|t-s|^p(\mathbb{E}\|Z_0\|_{\mathcal{H}}^{2p} + 1) + |t-s|^{p-1} \int_s^t \mathbb{E}\|Z_\tau\|_{\mathcal{H}}^{2p} d\tau\right)$$

$$\leq C_T \left(|t-s|^p(\mathbb{E}\|Z_0\|_{\mathcal{H}}^{2p} + 1) + |t-s|^p(\mathbb{E}\|Z_0\|_{\mathcal{H}}^{2p} + c_1 T)e^{c_1 T}\right),$$

for some constant $C_T \geq 0$, hence obtaining the stated inequality. $\square$

4. The nonlocal SDE-PDE system

4.1. **Well-posedness of the nonlocal model.** To prove the well-posedness of (1) we use the results for local SDE–PDE systems in Section 3 and ideas applied in [12] about scalar SDEs with nonlocal sample dependence.

Assumptions

(H_1) The functions $f = (f_1, f_2) : [0,T] \times \mathbb{R}^4 \to \mathbb{R}^2$ and $g : [0,T] \times \mathbb{R}^4 \to \mathbb{R}$ are continuous, and there exists a constant $c \geq 0$ such that

$$|f(t,x,y)| + |g(t,x,y)| \leq c(1 + |x|),$$

$$|f(t,x,y) - f(t,\tilde{x},y)| + |g(t,x,y) - g(t,\tilde{x},y)| \leq c|x - \tilde{x}|,$$

for all $t \in [0,T], (x,y) \in \mathbb{R}^4, \tilde{x} \in \mathbb{R}^2$.

(H_2) For all $r > 0$ there exists a constant c_r such that

$$|f(t,x,y) - f(t,x,\tilde{y})| + |g(t,x,y) - g(t,x,\tilde{y})| \leq c_r|y - \tilde{y}|(1 + |x|),$$

for all $t \in [0,T], x \in \mathbb{R}^2$ and $y, \tilde{y} \in \mathbb{R}^2$ such that $|y| \leq r$.

Theorem 6. *We assume (H_1) and (H_2) are satisfied. Then, for every $\mathcal{F}_0$-adapted initial data $(\zeta, \eta) \in L^2(\Omega; \mathcal{H})$ there exists a unique mild solution $u \in C([0,T]; L^2(\Omega; \mathcal{H}))$ of problem (1) such that*

$$\sup_{t \in [0,T]} \mathbb{E}(\|X_t\|^2 + \|Y_t\|^2) \leq c\left(1 + \mathbb{E}\|\zeta\|^2 + \mathbb{E}\|\eta\|^2\right),$$

for some constant $c \geq 0$ depending on T. Moreover, if the initial data belongs to $L^{2p}(\Omega; \mathcal{H})$ with $p > 1$, then the solution (X, Y) has continuous sample paths.

Proof. We construct approximate solutions on equidistant partitions of the interval $[0, T]$. This will provide a Cauchy sequence in $C([0, T]; L^2(\Omega; \mathcal{H}))$ that converges to the solution of the original model (1).

For $n \in \mathbb{N}$ such that $2^n > T$ we set $h_n := \frac{T}{2^n}$ and $t_k^n := k h_n$ for $k = 0, \ldots, 2^n$. We denote by $Z^n = (X^n, Y^n)$ the approximate solution obtained by successively solving the local systems

$$
\begin{aligned}
dX_t^n &= \left\{ \Delta X_t^n + f_1\big(t, X_t^n, Y_t^n, \mathbb{E}(X_{t_k^n}^n), \mathbb{E}(Y_{t_k^n}^n)\big) \right\} dt, \\
\partial_\nu X_t^n|_{\partial D} &= 0, \\
dY_t^n &= f_2\big(t, X_t^n, Y_t^n, \mathbb{E}(X_{t_k^n}^n), \mathbb{E}(Y_{t_k^n}^n)\big) dt + g\big(t, X_t^n, Y_t^n, \mathbb{E}(X_{t_k^n}^n), \mathbb{E}(Y_{t_k^n}^n)\big) dW_t,
\end{aligned}
$$

on the intervals $[t_k^n, t_{k+1}^n]$ with initial data $Z^n(t_k^n) = Z_{t_k^n}^n$, $k = 0, \ldots, 2^n - 1$. On every such subinterval there exist unique mild solutions $Z^n \in C([t_k^n, t_{k+1}^n]; L^2(\Omega; \mathcal{H}))$, by hypothesis (H_1) and Theorem 2.

From Proposition 4 and Proposition 5 we deduce that there exist constants $c_1 \geq 0$ and $c_2 \geq 0$ independent of n such that

$$
\begin{aligned}
\mathbb{E}\|Z_s^n\|_{\mathcal{H}}^2 &\leq \big(\mathbb{E}\|(\zeta, \eta)\|_{\mathcal{H}}^2 + c_1 s\big) e^{c_1 s} \leq \big(\mathbb{E}\|(\zeta, \eta)\|_{\mathcal{H}}^2 + 1\big) e^{2c_1 T}, \\
\mathbb{E}\|Z_{[s^n]}^n - Z_s^n\|_{\mathcal{H}}^2 &\leq c_2 h_n (\mathbb{E}\|(\zeta, \eta)\|_{\mathcal{H}}^2 + 1),
\end{aligned} \tag{5}
$$

for all $s \in [0, T]$ and $n \in \mathbb{N}$, where $[s^n] := \max\{t_k^n \,|\, t_k^n \leq s, \, k \in \mathbb{N}\}$. For given initial data $Z_0 = (\zeta, \eta)$ we set $r := \big(\mathbb{E}\|Z_0\|_{\mathcal{H}}^2 + 1\big) e^{2c_1 T}$, and c_r denotes the corresponding constant in (H_2).

For $m < n$ the difference of two approximations satisfies

$$
\begin{aligned}
X_t^n - X_t^m &= \int_0^t e^{-A(t-s)} \big(f_1(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_1(s, Z_s^m, \mathbb{E}(Z_{[s^m]}^m))\big) ds, \\
Y_t^n - Y_t^m &= \int_0^t f_2(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_2(s, Z_s^m, \mathbb{E}(Z_{[s^m]}^m)) ds \\
&\quad + \int_0^t g(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - g(s, Z_s^m, \mathbb{E}(Z_{[s^m]}^m)) dW_s.
\end{aligned}
$$

Assumptions (H_1), (H_2) and Hölder's inequality imply

$$\|X_t^n - X_t^m\|^2 \le t \int_0^t \|e^{-A(t-s)}\|_{\mathcal{L}(H)}^2 \big\|f_1(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_1(s, Z_s^m, \mathbb{E}(Z_{[s^m]}^m))\big\|^2 ds$$

$$\le Ct \int_0^t \Big(\big\|f_1(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_1(s, Z_s^n, \mathbb{E}(Z_s^n))\big\|^2$$

$$+ \big\|f_1(s, Z_s^n, \mathbb{E}(Z_s^n)) - f_1(s, Z_s^m, \mathbb{E}(Z_s^n))\big\|^2$$

$$+ \big\|f_1(s, Z_s^m, \mathbb{E}(Z_s^n)) - f_1(s, Z_s^m, \mathbb{E}(Z_s^m))\big\|^2$$

$$+ \big\|f_1(s, Z_s^m, \mathbb{E}(Z_s^m)) - f_1(s, Z_s^m, \mathbb{E}(Z_{[s^m]}^m))\big\|^2\Big) ds$$

$$\le Ct \int_0^t \Big(\|\mathbb{E}(Z_{[s^n]}^n - Z_s^n)\|_{\mathcal{H}}^2 (1 + \|Z_s^n\|_{\mathcal{H}}^2)$$

$$+ \|Z_s^n - Z_s^m\|_{\mathcal{H}}^2 + \big\|\mathbb{E}(Z_s^n - Z_s^m)\big\|_{\mathcal{H}}^2 (1 + \|Z_s^m\|_{\mathcal{H}}^2)$$

$$+ \big\|\mathbb{E}(Z_s^m - Z_{[s^m]}^m)\big\|_{\mathcal{H}}^2 (1 + \|Z_s^m\|_{\mathcal{H}}^2)\Big) ds.$$

Similarly, we can estimate the first integral in the second equation,

$$\Big\| \int_0^t f_2(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_2(s, Z_s^m, \mathbb{E}(Z_{[s^m]}^m)) ds \Big\|^2$$

$$\le Ct \int_0^t \Big(\|\mathbb{E}(Z_{[s^n]}^n - Z_s^n)\|^2 (1 + \|Z_s^n\|_{\mathcal{H}}^2)$$

$$+ \|Z_s^n - Z_s^m\|_{\mathcal{H}}^2 + \big\|\mathbb{E}(Z_s^n - Z_s^m)\big\|_{\mathcal{H}}^2 (1 + \|Z_s^m\|_{\mathcal{H}}^2)$$

$$+ \big\|\mathbb{E}(Z_s^m - Z_{[s^m]}^m)\big\|^2 (1 + \|Z_s^m\|_{\mathcal{H}}^2)\Big) ds,$$

and for the stochastic integral Itô's isometry implies that

$$\mathbb{E}\Big\| \int_0^t g(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - g(s, Z_s^m, \mathbb{E}(Z_{[s^m]}^m)) dW_s \Big\|^2$$

$$\le \mathbb{E} \int_0^t \big\|g(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - g(s, Z_s^m, \mathbb{E}(Z_{[s^m]}^m))\big\|^2 ds.$$

Estimating this integral accordingly and taking the expectation value in the previous inequalities we arrive at

$$\mathbb{E}\|Z_t^n - Z_t^m\|_{\mathcal{H}}^2$$

$$\le Ce^t \int_0^t \Big(\|\mathbb{E}(Z_{[s^n]}^n - Z_s^n)\|_{\mathcal{H}}^2 (1 + \mathbb{E}\|Z_s^n\|_{\mathcal{H}}^2) + \|\mathbb{E}(Z_s^n - Z_s^m)\|_{\mathcal{H}}^2$$

$$+ \mathbb{E}\|Z_s^n - Z_s^m\|_{\mathcal{H}}^2 (1 + \mathbb{E}\|Z_s^m\|_{\mathcal{H}}^2) + \mathbb{E}\|Z_s^m - Z_{[s^m]}^m\|_{\mathcal{H}}^2 (1 + \mathbb{E}\|Z_s^m\|_{\mathcal{H}}^2)\Big) ds$$

$$\le Ce^t \int_0^t \Big(\mathbb{E}\|Z_{[s^n]}^n - Z_s^n\|_{\mathcal{H}}^2 (1 + \mathbb{E}\|Z_s^n\|_{\mathcal{H}}^2) + \mathbb{E}\|Z_s^n - Z_s^m\|_{\mathcal{H}}^2 (1 + \mathbb{E}\|Z_s^m\|_{\mathcal{H}}^2)$$

$$+ \mathbb{E}\|Z_s^m - Z_{[s^m]}^m\|_{\mathcal{H}}^2 (1 + \mathbb{E}\|Z_s^m\|_{\mathcal{H}}^2)\Big) ds.$$

Moreover, using (5) we obtain

$$\mathbb{E}\|Z_t^n - Z_t^m\|_{\mathcal{H}}^2$$

$$\leq Ce^t \int_0^t \Big(2h_m(\mathbb{E}\|(\zeta,\eta)\|_{\mathcal{H}}^2 + 1)\big(1 + (\mathbb{E}\|(\zeta,\eta)\|_{\mathcal{H}}^2 + 1)e^{2c_1 T}\big)$$

$$+ \mathbb{E}\|Z_s^n - Z_s^m\|_{\mathcal{H}}^2 \big(1 + (\mathbb{E}\|(\zeta,\eta)\|_{\mathcal{H}}^2 + 1)e^{2c_1 T}\big) \Big) ds$$

$$\leq C_T(\mathbb{E}\|(\zeta,\eta)\|_{\mathcal{H}}^2 + 1)\Big(h_m(\mathbb{E}\|(\zeta,\eta)\|_{\mathcal{H}}^2 + 1) + \int_0^t \mathbb{E}\|Z_s^n - Z_s^m\|_{\mathcal{H}}^2 ds \Big),$$

and Gronwall's lemma yields a uniform bound for the mean square difference

$$\sup_{n>m} \sup_{t\in[0,T]} \mathbb{E}\|Z_t^n - Z_t^m\|_{\mathcal{H}}^2 \leq h_m C_T(1 + \mathbb{E}\|(\zeta,\eta)\|_{\mathcal{H}}^2)^2 e^{C_T T(1+\mathbb{E}\|(\zeta,\eta)\|_{\mathcal{H}}^2)}.$$

Consequently, Z^n is a Cauchy sequence in $C([0,T]; L^2(\Omega; \mathcal{H}))$, and we denote its limit by Z.

We will show that $Z = (X, Y)$ is the unique mild solution of the mean-field system (1). To this end we consider the local system

$$\begin{aligned} dU_t &= \{\Delta U_t + f_1(t, U_t, V_t, \mathbb{E}(X_t), \mathbb{E}(Y_t))\}\, dt, \\ \partial_\nu U_t|_{\partial D} &= 0, \\ dV_t &= f_2(t, U_t, V_t, \mathbb{E}(X_t), \mathbb{E}(Y_t))dt + g(t, U_t, V_t, \mathbb{E}(X_t), \mathbb{E}(Y_t))dW_t, \end{aligned} \tag{6}$$

with initial data $(U_0, V_0) = (\zeta, \eta)$. A unique mild solution $S = (U, V)$ exists by Theorem 2. To assess the difference between S and Z^n consider the system

$$X_t^n - U_t = \int_0^t e^{-A(t-s)}\big(f_1(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_1(s, S_s, \mathbb{E}(Z_s))\big)ds,$$

$$Y_t^n - V_t = \int_0^t f_2(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_2(s, S_s, \mathbb{E}(Z_s))ds$$

$$+ \int_0^t g(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - g(s, S_s, \mathbb{E}(Z_s))dW_s.$$

We split the difference for f_1 as follows:

$$\big\|f_1(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_1(s, S_s, \mathbb{E}(Z_s))\big\| \leq \big\|f_1(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_1(s, Z_s^n, \mathbb{E}(Z_s^n)\big\|$$

$$+ \big\|f_1(s, Z_s^n, \mathbb{E}(Z_s^n)) - f_1(s, Z_s^n, \mathbb{E}(Z_s))\big\| + \big\|f_1(s, Z_s^n, \mathbb{E}(Z_s)) - f_1(s, S_s, \mathbb{E}(Z_s))\big\|,$$

and hypotheses (H_1) and (H_2) lead to

$$\mathbb{E}\big\| \int_0^t e^{-A(t-s)}\big(f_1(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_1(s, S_s, \mathbb{E}(Z_s))\big)ds \big\|^2$$

$$\leq Ct \int_0^t \mathbb{E}\big\|f_1(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_1(s, S_s, \mathbb{E}(Z_s))\big\|^2 ds$$

$$\leq Ct \int_0^t \Big((\|\mathbb{E}(Z_{[s^n]}^n - Z_s^n)\|_{\mathcal{H}}^2 + \|\mathbb{E}(Z_s^n - Z_s)\|_{\mathcal{H}}^2)(1 + \mathbb{E}\|Z_s^n\|_{\mathcal{H}}^2) + \mathbb{E}\|Z_s^n - S_s\|^2 \Big) ds.$$

The other integrals can be estimated accordingly. Summing up and using Itô's isometry and (5) we arrive at

$$
\begin{aligned}
&\mathbb{E}\big\|Z_t^n - S_t\big\|_{\mathcal{H}}^2 \\
&\leq Ct \int_0^t \mathbb{E}\big\|f_1(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_1(s, S_s, \mathbb{E}(Z_s))\big\|^2 ds \\
&\quad + Ct \int_0^t \mathbb{E}\big\|f_2(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - f_2(s, S_s, \mathbb{E}(Z_s))\big\|^2 ds \\
&\quad + C \int_0^t \mathbb{E}\big\|g(s, Z_s^n, \mathbb{E}(Z_{[s^n]}^n)) - g(s, S_s, \mathbb{E}(Z_s))\big\|^2 ds \\
&\leq Ce^t \int_0^t \big(\|\mathbb{E}(Z_{[s^n]}^n) - Z_s^n)\|_{\mathcal{H}}^2 + \|\mathbb{E}(Z_s^n - Z_s)\|_{\mathcal{H}}^2\big)\big(1 + \mathbb{E}\|Z_s^n\|_{\mathcal{H}}^2\big) + \mathbb{E}\|Z_s^n - S_s\|^2 ds \\
&\leq Ce^t \int_0^t \big(h_n(\mathbb{E}\|(\zeta, \eta)\|_{\mathcal{H}}^2 + 1) + \mathbb{E}\|Z_s^n - Z_s\|_{\mathcal{H}}^2\big)\big(1 + (\mathbb{E}\|(\zeta, \eta)\|_{\mathcal{H}}^2 + 1)e^{2c_1 T}\big) \\
&\quad + \mathbb{E}\|Z_s^n - S_s\|_{\mathcal{H}}^2 ds \\
&\leq C_T\Big(\big(h_n(\mathbb{E}\|(\zeta, \eta)\|_{\mathcal{H}}^2 + 1)\big)^2 + (\mathbb{E}\|(\zeta, \eta)\|_{\mathcal{H}}^2 + 1)\sup_{s \in [0,T]} \mathbb{E}\|Z_s^n - Z_s\|_{\mathcal{H}}^2\Big) \\
&\quad + \int_0^t \mathbb{E}\|Z_s^n - S_s\|_{\mathcal{H}}^2 ds\Big).
\end{aligned}
$$

Using the fact that Z is the limit of the sequence Z^n, it follows by Gronwall's lemma that Z_n converges to S in $C([0,T]; L^2(\Omega; \mathcal{H}))$, which implies $Z = S$. The sample path continuity of $S = Z$ follows from Proposition 5.

To prove uniqueness of solutions we assume that $Z = (X, Y)$ and $S = (U, V)$ are two solutions corresponding to the initial data (ζ, η). To assess their difference consider the system

$$
\begin{aligned}
X_t - U_t &= \int_0^t e^{-A(t-s)}\big(f_1(s, Z_s, \mathbb{E}(Z_s)) - f_1(s, S_s, \mathbb{E}(S_s))\big) ds, \\
Y_t - V_t &= \int_0^t f_2(s, Z_s, \mathbb{E}(Z_s)) - f_2(s, S_s, \mathbb{E}(S_s)) ds \\
&\quad + \int_0^t g(s, Z_s, \mathbb{E}(Z_s)) - g(s, S_s, \mathbb{E}(S_s)) dW_s.
\end{aligned}
$$

We split the difference for f_1 as follows:

$$
\begin{aligned}
&\big\|f_1(s, Z_s, \mathbb{E}(Z_s)) - f_1(s, S_s, \mathbb{E}(S_s))\big\| \\
&\leq \big\|f_1(s, Z_s, \mathbb{E}(Z_s)) - f_1(s, Z_s, \mathbb{E}(S_s))\big\| + \big\|f_1(s, Z_s, \mathbb{E}(S_s)) - f_1(s, S_s, \mathbb{E}(S_s))\big\|,
\end{aligned}
$$

and obtain for the first integral

$$\mathbb{E}\Big\| \int_0^t e^{-A(t-s)}\big(f_1(s, Z_s, \mathbb{E}(Z_s)) - f_1(s, S_s, \mathbb{E}(S_s))\big)ds\Big\|^2$$

$$\leq Ct \int_0^t \mathbb{E}\big\| f_1(s, Z_s, \mathbb{E}(Z_s)) - f_1(s, Z_s, \mathbb{E}(S_s))\big\|^2$$

$$+ \big\| f_1(s, Z_s, \mathbb{E}(S_s)) - f_1(s, S_s, \mathbb{E}(S_s))\big\|^2 ds$$

$$\leq Ct \int_0^t \|\mathbb{E}(Z_s - S_s)\|^2_{\mathcal{H}}(1 + \mathbb{E}\|Z_s\|^2_{\mathcal{H}}) + \|\mathbb{E}(Z_s - S_s)\|^2_{\mathcal{H}} ds$$

$$\leq C_T(1 + \mathbb{E}\|(\zeta, \eta)\|^2_{\mathcal{H}}) \int_0^t \mathbb{E}\|Z_s - S_s\|^2_{\mathcal{H}} ds,$$

where we used (H_1), (H_2) and (5). The other integrals can be estimated similarly. It follows that

$$\mathbb{E}\|Z_t - S_t\|^2_{\mathcal{H}} \leq C_T(1 + \mathbb{E}\|(\zeta, \eta)\|^2_{\mathcal{H}}) \int_0^t \mathbb{E}\|Z_s - S_s\|^2_{\mathcal{H}} ds,$$

and Gronwall's lemma implies that $S = Z$, which concludes the proof.

The solution (X, Y) is the limit of the Cauchy sequence (X^n, Y^n) and coincides with the solution (U, V) of the local system (6). Hence, if the initial data belong to $L^{2p}(\Omega; \mathcal{H})$, the pathwise continuity follows from Theorem 2. □

4.2. Invariance.
For its relevance in modeling applications we formulate conditions ensuring that solutions of the mean-field system (1) are non-negative and bounded by a certain maximum value.

(H_3) There exist constants $m_1^*, m_2^* > 0$ such that f_1 and f_2 satisfy

$$f_1(t, 0, x_2, y) \geq 0, \qquad f_1(t, m_1^*, x_2, y) \leq 0 \qquad \forall\, 0 \leq x_2 \leq m_2^*,\ t \in [0, T], y \in \mathbb{R}^2$$

$$f_2(t, x_1, 0, y) \geq 0, \qquad f_2(t, x_1, m_2^*, y) \leq 0 \qquad \forall\, 0 \leq x_1 \leq m_1^*,\ t \in [0, T], y \in \mathbb{R}^2,$$

and the stochastic perturbation fulfills

$$g(t, x_1, 0, y) = g(t, x_1, m_2^*, y) = 0 \qquad \forall\, 0 \leq x_1 \leq m_1^*,\ t \in [0, T], y \in \mathbb{R}^2.$$

Theorem 7. *In addition to the hypotheses of Theorem 6 we assume that (H_3) holds and the initial data (ζ, η) is deterministic and satisfies $0 \leq \zeta \leq m_1^*$, $0 \leq \eta \leq m_2^*$ in D. Then, the solutions are almost surely non-negative and uniformly bounded by m_1^* and m_2^*, respectively.*

Proof. The solution (X, Y) is the limit of the Cauchy sequence (X^n, Y^n) in the proof of Theorem 6. Moreover, it coincides with the solution (U, V) of the local system (6). Theorem 3 and hypothesis (H_3) imply that the solution (U, V) takes values within the set $[0, m_1^*] \times [0, m_2^*]$ almost surely, which proves the invariance of the mean-field model. □

5. NUMERICAL SIMULATIONS

To illustrate the qualitative behavior of solutions we present numerical simulations for the proton dynamics model in Section 2,

$$dX_t = \big(d\Delta X_t + r(X_t, \mathbb{E}(Y_t)) - \alpha X_t\big)dt$$
$$dY_t = (-r(X_t, Y_t) - \beta Y_t + \varphi(t, Y_t))dt + \gamma Y_t(1 - Y_t)dW_t, \tag{7}$$

as well as for its local version

$$dX_t = \big(d\Delta X_t + r(X_t, Y_t) - \alpha X_t\big)dt$$
$$dY_t = (-r(X_t, Y_t) - \beta Y_t + \varphi(t, Y_t))dt + \gamma Y_t(1 - Y_t)dW_t, \tag{8}$$

in $D \times [0, T] = (0, 1) \times [0, T]$. The extracellular proton concentration X and the intracellular proton concentration Y are normalized w.r.t. the maximum concentration, i.e., the dependent variables X and Y take values within the unit interval $(0, 1)$. We endow the system with the initial and boundary values

$$\partial_x X_t|_{x=0} = 0, \qquad\qquad \partial_x X_t|_{x=1} = \mu,$$
$$X_0 = \zeta, \qquad\qquad Y_0 = \eta$$

where μ is a positive constant and the (deterministic) functions ζ and η are non-negative and bounded by 1 in $D = (0, 1)$. We use the functions in [23] for the membrane-based transport terms

$$r(x, y) = a_1 \frac{y}{1 + y^2 + a_2 x^2} - a_3 \frac{x}{1 + a_4 y^2},$$

and assume that the production of intracellular protons by glycolysis is determined by

$$\varphi(t, y) = \varphi_0 \frac{y}{1 + a_2 y},$$

where the constant φ_0 is positive, and where $a_i, i = 1, \ldots, 4$ are positive constants.

TABLE 1. Parameters used in the simulations

parameter	symbol	value
diffusion coefficient	d	0.0001
decay rate for X	α	1
decay rate for Y	β	2
activity of transporter 1	a_1	2
normalization constant	a_2	0.001
activity of transporter 2	a_3	0.5
normalization constant	a_4	0.1
production rate of Y	φ_0	2
intensity of the stochastic perturbation	γ	1
Neumann boundary conditions at $x = 1$	μ	0.5

We use finite differences and an explicit Euler scheme to solve the PDE and the Euler-Mayurama method for the SDE. The parameters used in the simulations are summarized in Table 1, and the initial data is chosen as

$$\zeta(x) = 0.6e^{-x^2}, \qquad \eta(x) = 0.3e^{-2x^2}, \qquad x \in D.$$

Observe that for this choice of interaction functions and parameter values the conditions ensuring invariance are satisfied, i.e., for any initial data $0 \le \zeta \le 1, 0 \le \eta \le 1$ the proton concentrations X and Y are non-negative and bounded by 1. The shape of the initial conditions is motivated by the assumption that the tumor is located at the left end of the space interval and the cancer cells emit protons, rendering the tumor microenvironment acidic. The acidity is supposed to decrease towards the tumor edge (hence with advancing space). The concentration of intracellular protons should be lower than that of their extracellular counterparts,

in order to allow the survival and proliferation of tumor cells (thus the maintenance of proton dynamics).
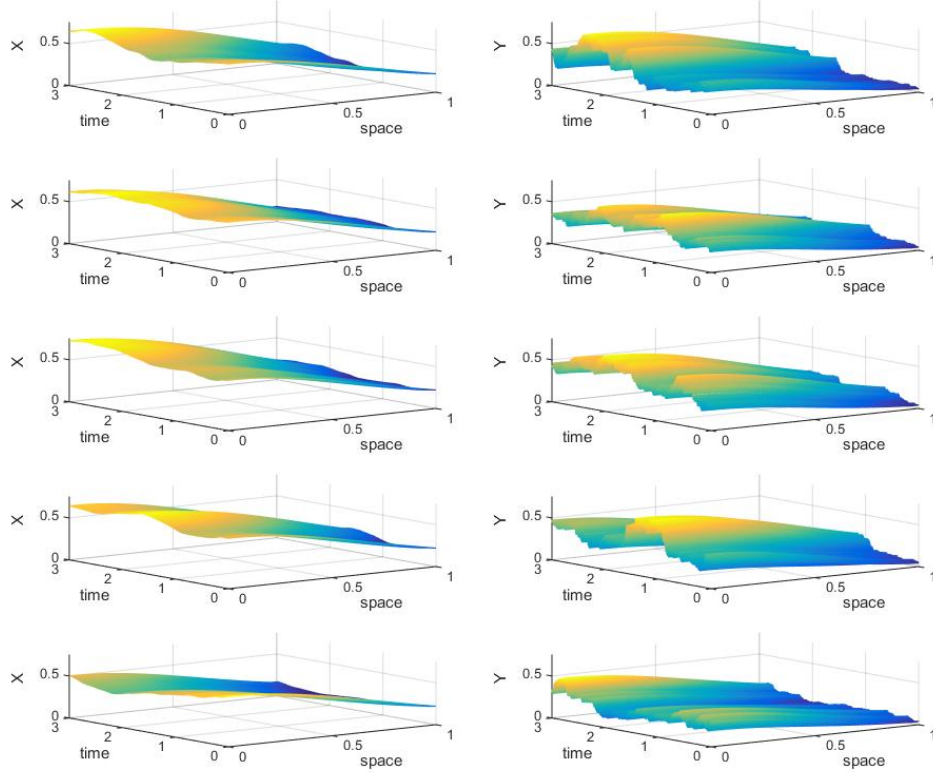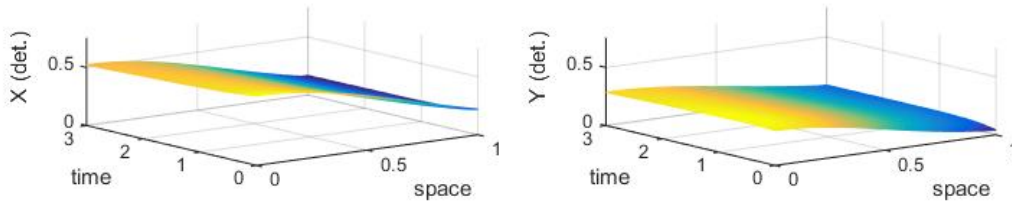

FIGURE 1. Five sample paths for the solutions of the local SDE-PDE model. Left column: concentration X of extracellular protons. Right column: concentration Y of intracellular protons.

Figure 1 shows the time evolution of extra- and intracellular protons. We plotted five sample paths for solutions of the local model (8). Notice the inter-path differences in both proton populations, suggesting corresponding tumor-to-tumor variability w.r.t. acidity, although the same type of cancer is considered.

Figure 2 shows the behavior of solutions of the deterministic model and of the nonlocal system (7). The expectation values involved in the PDE for extracellular protons were computed by averaging over 20 (Figure 2b) and 1000 sample paths (Figure 2c). Figure 2a shows the solutions of the deterministic model, i.e., the model with $\gamma = 0$, while each of Figures 2b and 2c shows the solution X of the mean-field SDE-PDE system and one sample path for the intracellular protons Y. As expected, when averaging over a large number of tumors the differences between the nonlocal model and the pure deterministic one are small. However, in the case of a much reduced number of tumors (corresponding to a less frequent cancer
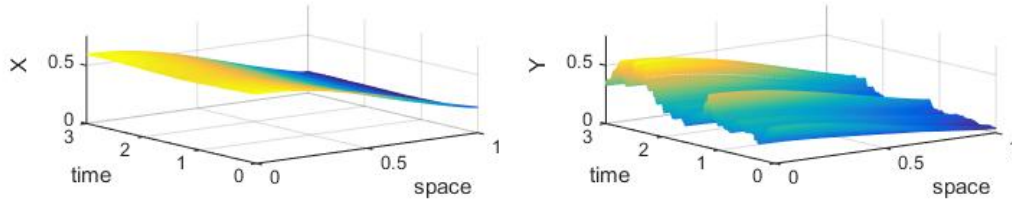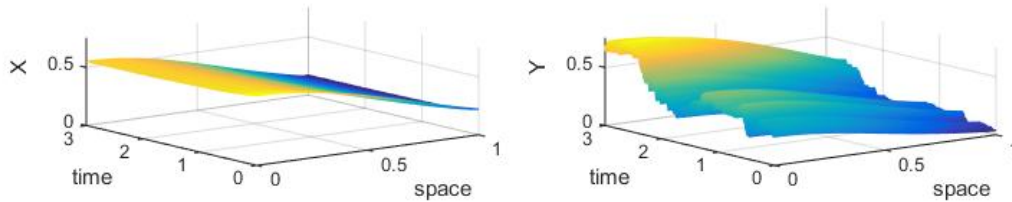
(A) deterministic ODE-PDE model

(B) nonlocal SDE-PDE model: X by using the average over 20 sample paths (left) and sample path for Y (right)

(C) nonlocal SDE-PDE model: X by using the average over 1000 sample paths (left) and sample path for Y (right)

FIGURE 2. Simulations for the deterministic and nonlocal SDE-PDE model. Left column: concentration X of extracellular protons. Right column: concentration Y of intracellular protons.

type) the randomness (inter-tumor variations) seems to play a significant role in acidification. This can be relevant for the sensitivity against therapies and for tumor aggressiveness, as it is well known by now that the low extracellular pH (pH_e) and the gradients between intracellular (pH_i) and pH_e significantly influence the response of tumors to various treatments like radiotherapy and chemotherapy [4, 22, 20]. Our findings seem to endorse the necessity of paying particular attention to individualized treatment, especially for rare tumors, where it is difficult to rely on clinical experience aquired with a rather small number of patients.

The next step will be to include the dynamics of tumor cells and normal tissue and assess the behavior of the two cell populations under the influence of the stochastic proton dynamics studied here. This is ongoing work.

References

[1] M. J. Boyer and I. F. Tannock, Regulation of intracellular pH in tumor cell lines: influence of microenvironmental conditions, *Cancer Research*, **52** (1992), 4441–4447.

[2] P. L. Chow, *Stochastic Partial Differential Equations*, Chapman & Hall /CRC, Boca Raton, 2007.

[3] J. Cresson, B. Puig and S. Sonner, Stochastic models in biology and the invariance problem, submitted.

[4] M.L. Freeman and E. Sierra, An acidic extracellular environment reduces the fixation of radiation damage. *Radiat. Resist.*, **97** (1984), 154–161.

[5] D. Henry, *Geometric Theory of Semilinear Parabolic Equations*, Lecture Notes in Mathematics, Springer, Berlin, Heidelberg, New York, 1981.

[6] S. Hiremath and C. Surulescu, A stochastic multiscale model for acid mediated cancer invasion, *Nonlinear Analysis: Real World Applications*, **22** (2015), 176–205.

[7] S. Hiremath and C. Surulescu, A stochastic model featuring acid induced gaps during tumor progression, *preprint TU Kaiserslautern* (2015), submitted.

[8] E. Jakobsson and S. W. Chiu, Stochastic theory of ion movement in channels with single-ion occupancy. Application to sodium permeation of gramicidin channel,, *Biophys. J.*, **52** (1987), 33–45.

[9] A. Jentzen and P.E. Kloeden, *Taylor Approximations for Stochastic Partial Differential Equations*, CBMS-NSF Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, 2011.

[10] Y. Jiongmin, Linear-quadratic optimal control problems for mean-field stochastic differential equations, *SIAM J. Control Optim.*, **51** (2013), 2809–2838.

[11] R. A. Gatenby and E. T. Gawlinski, A reaction-diffusion model of cancer invasion, *Cancer Research*, **56** (1996), 5745–5753.

[12] P. E. Kloeden and T. Lorenz, Stochastic differential equations with nonlocal sample dependence, *Stochastic Analysis and Applications*, **28** (2010), 937–945.

[13] P. E. Kloeden and E. Platen, *Numerical Solution of Stochastic Differential Equations*, Springer-Verlag, Berlin-Heidelberg, 1992.

[14] A. H. Lee and I. F. Tannock, Heterogeneity of intracellular pH and of mechanisms that regulate intracellular pH in populations of cultured cells, *Cancer Research*, **58** (1998), 1901–1908.

[15] X. Mao, *Stochastic Differential Equations and Applications*, 2nd edition, Woodhead Publishing, Cambridge, 2007.

[16] N. K. Martin, R. A. Gatenby, E. T. Gawlinski and P. K. Maini, Tumor-stromal interactions in acid-mediated invasion: a mathematical model, *J. Theor. Biol.*, **267** (2010), 461–470.

[17] R. Martínez-Zaguilán, E. A. Seftor, R. E. B. Seftor, Y. W. Chu, R. J. Gillies and M. J. C. Hendrix, Acidic pH enhances the invasive behavior of human melanoma cells, *Clin. Exp. Metastasis*, **14** (1996), 176–186.

[18] G. Meral, C. Stinner and C. Surulescu, A multiscale model for acid-mediated tumor invasion: therapy approaches, *J. Coupled Systems and Multiscale Dynamics*, to appear.

[19] A. Milian, Stochastic viability and comparison theorem, *Colloquium Mathematicum*, **LXVIII** (1995), 297–316.

[20] A. De Milito and S. Fais, Tumor acidity, chemoresistance and proton pump inhibitors. *Future Oncol.*, **1 (2005)**, 779–786.

[21] K. Smallbone, D. J. Gavaghan, R. A. Gatenby and P. K. Maini, The role of acidity in solid tumor growth and invasion, *J. Theor. Biol.*, **235** (2005), 476–484.

[22] C.W. Song, R. Griffin, and H.J. Park, Influence of Tumor pH on Therapeutic Response, in *Cancer Drug Resistance*, Edited B. Teicher, Humana Press Inc., Totowa, NJ (2006).

[23] C. Stinner, C. Surulescu and G. Meral, A multiscale model for pH-tactic invasion with time-varying carrying capacities, *IMA J. Appl. Math.*, doi:10.1093/imamat/hxu055 (2014).

[24] C. Stock and A. Schwab, Protons make tumor cells move like clockwork, *Pflugers Arch. - European J. Physiology*, **458** (2009), 981–992.

[25] C. L. Stokes, D. A. Lauffenburger and S. K. Williams, Migration of individual microvessel endothelial cells: stochastic model and parameter measurement, *J. Cell Science*, **99** (1991), 419–430.

[26] J. Touboul, G. Herrmann and O. Faugeras, Noise-induced behaviors in neural mean field dynamics, *SIAM J. Applied Dynamical Systems*, **11** (2012), 49–81.

[27] S. D. Webb, J. A. Sherratt and R. G. Fish, Mathematical modelling of tumour acidity: regulation of intracellular pH, *J. Theor. Biol.*, **196** (1999), 237–250.

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