A Stochastic Micro-Macro Model for Cancer Cell Proton Dynamics

Peter E. Kloeden, Stefanie Sonner, Christina Surulescu

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Plan

Introduction
- Acid mediated tumor invasion
- Extra- and intracellular proton dynamics

Stochastic models for proton dynamics
- Stochastic micro-macro models
- Nonlocal SDE-PDE systems

Mathematical analysis
- Local well-posedness and invariance
- Numerical simulations

Concluding remarks
Acid mediated tumor invasion

- most tumors characterized by acidic and hypoxic regions
- increased production and release of protons
- acidic environment promotes apoptosis of normal cells, facilitates invasion

[Gatenby-Gawlinsky, 2003]
Introduction

Extra- and intracellular proton dynamics

Acid mediated tumor invasion

- despite of extracellular acidification intracellular pH at normal rates
- regulation through buffering and membrane based transport systems

[Pouysségur-Dayan-Mazure, 2006]
Some mathematical models

Deterministic models

- Reaction diffusion models for cancer invasion

- Intra- and extracellular proton dynamics

- Multiscale models for acid-mediated tumor invasion
  [Stinner-Meral-Surulescu 2014]

Stochasticity essential in intracellular dynamics

- Multiscale models including random effects
  [Hiremath-Surulescu 2014]

- Stochastic model for proton dynamics
  [Kloeden-S.-Surulescu, preprint]
A stochastic model for proton dynamics

\( X, Y \) extracellular, intracellular proton concentration

\[
\begin{align*}
dX_t &= \left[ d\Delta X_t + r(X_t, Y_t) - \alpha X_t \right] dt \\
\frac{\partial \nu X_t}{\partial D} &= 0
\end{align*}
\]

\[
dY_t = \left[ -r(X_t, Y_t) - \beta Y_t + \varphi(Y_t) \right] dt + g(Y_t)dW_t
\]

\( X|_{t=0} = X_0, \quad Y|_{t=0} = Y_0. \)

\( X, Y \) stochastic processes on \( D \times [0, T] \times \Omega, D \subset \mathbb{R}^n \) bounded.

- \( r \) membrane based transport systems
- \( \varphi \) intracellular proton production
- \( g \) stochastic perturbation
- constant decay of \( X \) and \( Y \), diffusion of \( X \)
Nonlocal stochastic models

Assuming effects of intracellular protons are averaged on extracellular level:

\[
\begin{align*}
    dX_t &= \left[ d\Delta X_t + r(X_t, \mathbb{E}(Y_t)) - \alpha X_t \right] dt \\
    dY_t &= \left[ -r(X_t, Y_t) - \beta Y_t + \varphi(Y_t) \right] dt + g(Y_t)dW_t
\end{align*}
\]

Nonlocal stochastic models

- arise in different fields [Hu-Wu 2014] ; [Yong 2013] ; etc.
- scalar meanfield SDEs [Kloeden-Lorenz 2010]

**Aim:** Analysis for general (nonlocal) SDE-PDE systems
We consider general *nonlocal* SDE-PDE systems

\[
    dX_t = \left[ \Delta X_t + f_1(X_t, Y_t, \mathbb{E}(X_t), \mathbb{E}(Y_t)) \right] dt \\
    \partial_n X_t |_{\partial D} = 0 \\
    dY_t = f_2(X_t, Y_t, \mathbb{E}(X_t), \mathbb{E}(Y_t)) dt + g(X_t, Y_t, \mathbb{E}(X_t), \mathbb{E}(Y_t)) dW_t \\
    X|_{t=0} = X_0, \quad Y|_{t=0} = Y_0.
\]

We show

- local well-posedness
- invariance:

  *for any* \(0 \leq X_0, Y_0 \leq 1\) *the solutions take values in* \((0, 1)\).

  \((X, Y\) normalized w.r.t. maximum concentrations)
Sketch of the proof

Construct approximate solutions \((X^n, Y^n)\) on equidistant partitions of \([0, T]\)

\[
dX_t^n = \left[ \Delta X_t^n + f_1(X_t^n, Y_t^n, \mathbb{E}(X^n_{t_k}), \mathbb{E}(Y^n_{t_k})) \right] dt \\
dY_t^n = f_2(X_t^n, Y_t^n, \mathbb{E}(X^n_{t_k}), \mathbb{E}(Y^n_{t_k})) dt + g(X_t^n, Y_t^n, \mathbb{E}(X^n_{t_k}), \mathbb{E}(Y^n_{t_k})) dW_t
\]

on \([t^n_k, t^n_{k+1}]\), where \(t^n_k = \frac{kT}{2^n}, 1 \leq k \leq 2^n - 1\).

- \((X^n, Y^n)\) Cauchy sequence in \(L^2([0, T]; L^2(\Omega; H))\), and \((X^n, Y^n) \rightarrow (X, Y)\) as \(n \rightarrow \infty\).
- requires several results for local SDE-PDE systems
- based on method for nonlocal scalar SDEs \[\text{[Lorenz-Kloeden 2010]}\]
- invariance criteria for SDEs \[\text{[Cresson-Puig-S. 2013]}\]
Sketch of the proof: *local* systems

\[ dX_t = \left[ \Delta X_t + f_1(X_t, Y_t) \right] dt \]
\[ \partial_\nu X_t |_{\partial D} = 0 \]
\[ dY_t = f_2(X_t, Y_t) dt + g(X_t, Y_t) dW_t \]
\[ Y|_{t=0} = Y_0, \quad X|_{t=0} = X_0, \]

\( W_t \) standard scalar Wiener process, \( dW_t \) Itô differential.

Solutions \( X, Y : D \times [0, T] \times \Omega \rightarrow \mathbb{R}^2 \) are \( L^2(D) \)-valued stochastic processes.
Local well-posedness

\((A_1)\) \(f = (f_1, f_2) : \mathbb{R}^2 \to \mathbb{R}^2\) and \(g : \mathbb{R}^2 \to \mathbb{R}\) continuous,

\[ |f(x)| + |g(x)| \leq c(1 + |x|), \]

\[ |f(x) - f(\tilde{x})| + |g(x) - g(\tilde{x})| \leq c(|x - \tilde{x}|), \quad x \in \mathbb{R}^2. \]

**Theorem**

*Let \((A_1)\) be satisfied. Then, for every \(T > 0, p \geq 1\) and \(\mathcal{F}_0\)-adapted \((X_0, Y_0) \in L^{2p}(\Omega; H)\) there exists a unique mild solution \((X, Y) \in C([0, T]; L^{2p}(\Omega; H)). \)

*If \(p > 1\), then \((X, Y)\) has continuous sample paths.*

Here, \(H = L^2(D) \times L^2(D). \)
Invariance

Important property in biological applications [Cresson-Puig-S. 2013]

(A₂) Interaction functions

\[
\begin{align*}
  f_1(0, y) &\geq 0, & f_1(1, y) &\leq 0, \\
  f_2(x, 0) &\geq 0, & f_2(x, 1) &\leq 0, & \forall x, y \in [0, 1].
\end{align*}
\]

Stochastic perturbation

\[
g(x, 0) = g(x, 1) = 0 \quad \forall x \in [0, 1].
\]

**Theorem**

*If (A₁), (A₂) hold and \(0 \leq X_0, Y_0 \leq 1\). Then, \(X\) and \(Y\) are almost surely non-negative and uniformly bounded by 1.*
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Numerical simulations: proton dynamics model

\[ dX_t = \left[ d\Delta X_t + r(X_t, Y_t) - \alpha X_t \right] dt \]
\[ dY_t = \left[ - r(X_t, Y_t) - \beta Y_t + \varphi(Y_t) \right] dt + g(Y_t) dW_t \]

- **proton transporters** [Stinner-Meral-Surulescu 2014]
  \[ r(x, y) = c_1 \frac{y}{1 + y^2 + c_2 x^2} - c_3 \frac{x}{1 + y^2} \]

- **intracellular proton production**
  \[ \varphi(y) = c_4 y (1 - y) \]

- **stochastic perturbation**
  \[ g(y) = c_5 y (1 - y) \]
The local SDE-PDE-model: five sample paths
Deterministic model and nonlocal stochastic model

Time evolution of extracellular and intracellular protons
Concluding remarks

- Stochasticity important in intracellular dynamics
- SDE-PDE models for cancer cell proton dynamics
- Well-posedness and invariance for general nonlocal SDE-PDE systems
- Analytical results extend to more general settings

Outlook

- Model extensions including cancer cells and normal tissue (ODE-SDE-PDE systems, nonlinear diffusion, taxis effects)
- Numerical simulations, model validation, ...