A Stochastic Micro-Macro Model for Cancer Cell Proton Dynamics

Peter E. Kloeden, Stefanie Sonner, Christina Surulescu

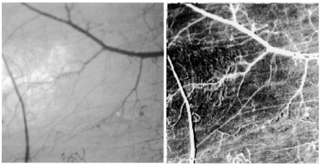
Micro and Macro Systems in Life Sciences

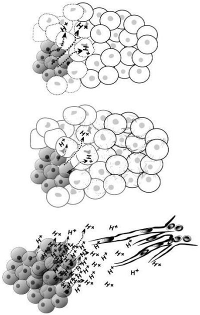
Bedlewo, June 8 2015

Plan

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

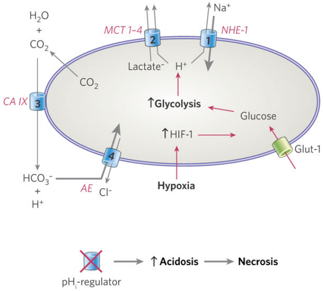




[Gatenby-Gawlinsky, 2003]

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

  [Gatenby-Gawlinski 1996] ; [Martin-Gatenby-Gawlinsky-Maini 2010] ; etc.

- Intra- and extracellular proton dynamics

  [Webb-Sherratt-Fish 1999] ; [Boyer-Tannock 1992]

- 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

$$\begin{aligned} dX_t &= \left[d\Delta X_t + r(X_t, Y_t) - \alpha X_t\right] dt \\ \partial_\nu X_t|_{\partial D} &= 0 \\ dY_t &= \left[-r(X_t, Y_t) - \beta Y_t + \varphi(Y_t)\right] dt + g(Y_t) dW_t \\ X|_{t=0} &= X_0, \quad Y|_{t=0} = Y_0. \end{aligned}$$

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

- r membrane based transport systems
- φ 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:

$$dX_t = \big[d\Delta X_t + r(X_t, \mathbb{E}(Y_t)) - \alpha X_t\big] dt$$
$$dY_t = \big[- r(X_t, Y_t) - \beta Y_t + \varphi(Y_t)\big] dt + g(Y_t) dW_t$$

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

Mathematical analysis

We consider general *nonlocal* SDE-PDE systems

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

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 $[0, T]$

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

on $[t_k^n, t_{k+1}^n]$, where $t_n^k = \frac{kT}{2^n}$, $1 \le k \le 2^n - 1$.

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

Sketch of the proof: *local* systems

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

W_t standard scalar Wiener process, dW_t Itô differential.

Solutions $X, Y : D \times [0, T] \times \Omega \to \mathbb{R}^2$ 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,

$$|f(x)|+|g(x)|\le c(1+|x|),$$
$$|f(x)-f(\tilde{x})|+|g(x)-g(\tilde{x})|\le c(|x-\tilde{x}|),\quad x\in\mathbb{R}^2.$$

Theorem

Let (A_1) be satisfied. Then, for every $T>0, p\ge 1$ 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]

(A_2) Interaction functions

$$f_1(0,y) \geq 0, \qquad f_1(1,y) \leq 0,$$
$$f_2(x,0) \geq 0, \qquad f_2(x,1) \leq 0, \qquad \forall\, x,y \in [0,1].$$

Stochastic perturbation

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

Theorem

If (A_1), (A_2) hold and $0 \leq X_0, Y_0 \leq 1$. Then, X and Y are almost surely non-negative and uniformly bounded by 1.

Numerical simulations: proton dynamics model

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

- proton transporters [Stinner-Meral-Surulescu 2014]

$$r(x, y) = c_1 \frac{y}{1 + y^2 + c_2 x^2} - c_3 \frac{x}{1 + y^2}$$

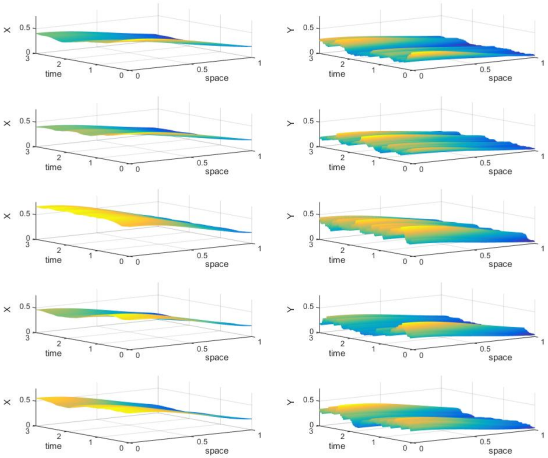
- intracellular proton production

$$\varphi(y) = c_4 y(1 - y)$$

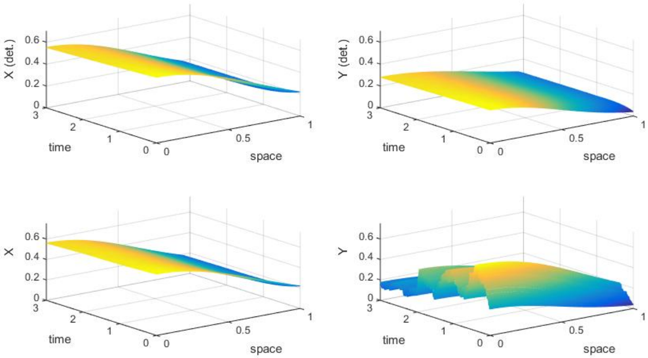
- stochastic perturbation

$$g(y) = c_5 y(1 - y)$$

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-posedess 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, ...