Study of the numerical method for an inverse problem of a simplified intestinal crypt

Marie Haghebaert, Béatrice Laroche, Mauricio A. Sepulveda Cortes

STUDY OF THE NUMERICAL METHOD FOR AN INVERSE PROBLEM OF A SIMPLIFIED INTESTINAL CRYPT.

MARIE HAGHEBAERT, BEATRICE LAROCHE,
AND MAURICIO A. SEPÚLVEDA CORTÉS

Abstract. In this work we consider the study of an inverse problem for an intestinal crypt model. The original model is based on the interaction of epithelial cells with microbiota-derived chemicals diffusing in the crypt from the gut lumen. The 5 types of cells considered in the original model [3] were reduced in this work to 3 types of cells for simplifications of the inverse problem. The inverse problem consists of determining the shape of the secretory cells of the deep crypt from observations of the stem cells and progenitor cells at a fixed time. The method used is the calculation of the adjoint state associated with the second-order BGK numerical scheme considered in [3], which allows calculating the critical points of the Lagrangian associated with the inverse problem, and applying a gradient method in order to minimize the cost function. The algorithm is described, and some numerical examples are given.

1. The simplified intestinal crypt model

1.1. **The stem-progenitor interaction model.** We consider a model of epithelial cells interacting with the microbiota-derived chemicals diffusing in the crypt from the gut lumen. The original model, derived from an individual-based PDMP model (piecewise deterministic Markov process model, see [3]) treats 5 well-differentiated cell types: stem cells (SC); progenitor cells (PC); enterocytes (ENT); globet cells (GC); and deep crypt secretory cells (DCS). For a simplification of the original model in the process of studying the inverse problem, we will consider at first, only the SC, PC and DCS cells. We set $\rho_{tot} = \rho_{sc} + \rho_{dcs} + \rho_{pc}$ and solve equations on ρ_{sc} and ρ_{pc}, with $\rho_{dcs} = \rho_{dcs}(z)$ independent of t. In this reduced model the system of equations is given by:

(1.1)
$$\begin{cases} \partial_t \rho_{sc} - \mathcal{W}\partial_z \left(\phi(z)\rho_{sc}\partial_z \rho_{tot}\right) = H_1(z, \rho_{dcs}, \rho_{sc}, \rho_{pc}), & 0 < z < z_{max},\ t > 0, \\ \rho_{sc}(t,0) = \rho_{sc}^{bot}, \qquad \partial_z \rho_{sc}(t, z_{max}) = 0, & t > 0, \\ \rho_{sc}(x,0) = \rho_{sc}^{init}(x), & 0 < z < z_{max}, \end{cases}$$

Date: December 9, 2023.

This work was supported by INRIA-ANACONDA project associated to the team INRIA-MUSCA. MH's contribution was permitted in part by funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Grant agreement ERC-2017-AdG No. 788191 - Homo.symbiosus. MS was supported by Fondecyt-ANID project 1220869, ANID-Chile through Centro de Modelamiento Matemático (FB210005), and Jean d'Alembert fellowship program, Université Paris-Saclay.

where $H_1(z,\rho_{dcs},\rho_{sc},\rho_{pc}) = [q_{sc}(1-R_n(z))(1-R_{sc}(D\rho_{tot})) - q_{diff}R_n(z)]\,\rho_{sc}$ with

$$R_n(z) = R(z, Z_{niche}, \kappa_{niche})$$
$$R_{sc}(\varrho) = R(\varrho, K_{sc}, \kappa_{dens})$$

(1.2)
$$\begin{cases} \partial_t\rho_{pc} - \mathcal{W}\partial_z\left(\phi(z)\rho_{pc}\partial_z\rho_{tot}\right) = H_2(z,\rho_{dcs},\rho_{sc},\rho_{pc}), & 0 < z < z_{max},\ t > 0, \\ \rho_{pc}(t,0) = 0, \qquad \partial_z\rho_{pc}(t,z_{max}) = 0, & t > 0, \\ \rho_{pc}(x,0) = \rho_{pc}^{init}(x), & 0 < z < z_{max}. \end{cases}$$

where $H_2(z,\rho_{dcs},\rho_{sc},\rho_{pc}) = [q_{pc}(1-R_t(z))(1-R_{pc}(D\rho_{tot})) - q_{ex}R_e(z)R_{pc}(D\rho_{tot})]\,\rho_{pc} + q_{diff}R_n(z)\rho_{sc}$ with

$$R_t(z) = R(z, Z_{tiers}, \kappa_{tiers}),$$
$$R_e(z) = R(z, Z_{ex}, \kappa_{ex}),$$
$$R_{pc}(\varrho) = R(\varrho, K_{pc}, \kappa_{dens}).$$

We use a generic regulation function $R(y,K,\kappa)$ for $y \geq 0$, $K \geq 0$ and $\kappa \geq 0$ that model the regulation of cell fate event according to variable y. The function R is a piecewise polynomial function in $\mathcal{C}^1(0,z_{max})$ defined as :

$$R(y,K,\kappa) = \begin{cases} 0 & \text{if } y \geq K-\kappa, \\ \dfrac{-y^3+3Ky^2-(3K^2-3\kappa^2)y+(K^3+2\kappa^3-3K\kappa^2)}{4\kappa^3} & \text{if } K-\kappa < y < K+\kappa, \\ 1 & \text{if } K+\kappa \geq y. \end{cases}$$

Additionally $\phi \in \mathcal{C}^1(0,z_{max})$, such that $\phi(0) = \phi(z_{max}) = 0$, $\phi(z) = 1$ in $[r_0 -$

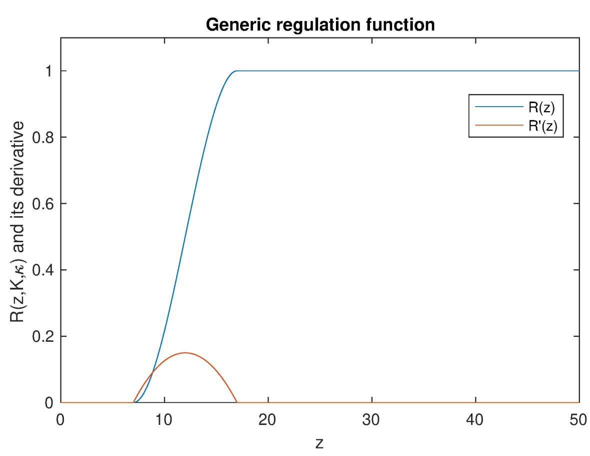

FIGURE 1. Generic regulation function and its derivative, with $K = 12$, $\kappa = 5$.

$\varepsilon, z_{max} - r_0 + \varepsilon]$, and $\phi(z) \geq 0$, represents a corrective function taking into account the impact of curvature on mechanical forces modelling by [3]:

$$\phi(z) = \begin{cases} \frac{\sqrt{(\varepsilon+z)\,(2\,r_0-\varepsilon-z)}-\sqrt{\varepsilon\,(2\,r_0-\varepsilon)}}{r_0-\sqrt{\varepsilon\,(2\,r_0-\varepsilon)}} & \text{if } z \leq r_0 - \varepsilon \\ 1 & \text{if } r_0 - \varepsilon < z < z_{max} - r_0 + \varepsilon \\ \frac{2\,r_0-\sqrt{\varepsilon\,(2\,r_0-\varepsilon)}}{r_0} - \frac{2\,r_0-\sqrt{(\varepsilon-z+z_{\max})\,(2\,r_0-\varepsilon+z-z_{\max})}}{r_0-\sqrt{\varepsilon\,(2\,r_0-\varepsilon)}} & \text{if } z \geq z_{max} - r_0 + \varepsilon \end{cases}$$

The system (1.1)-(1.2) can be rewritten as

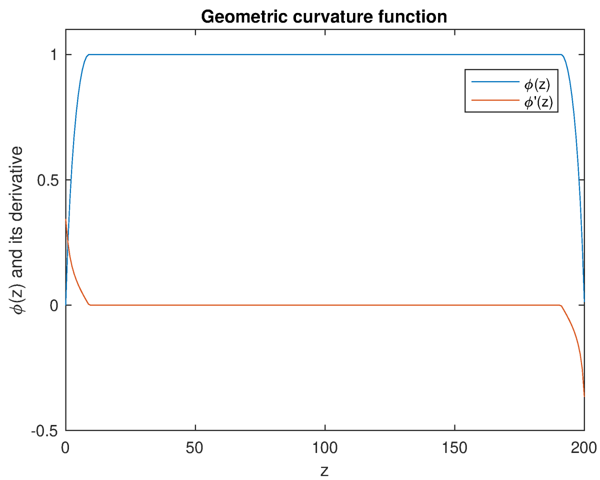

FIGURE 2. Graph of the geometric curvature function and its derivative, with $z_{max} = 200$, $r_0 = 10$, $\varepsilon = 1$.

$$(1.3) \qquad \begin{cases} \partial_t \rho_{sc} + \partial_z A_{sc} = \partial_{zz} B(\rho_{sc}) + H_1, & 0 < z < z_{max},\ t > 0, \\ \partial_t \rho_{pc} + \partial_z A_{pc} = \partial_{zz} B(\rho_{pc}) + H_2, & 0 < z < z_{max},\ t > 0, \\ \rho_{sc}(t,0) = \rho_{sc}^{bot}, \qquad \rho_{pc}(t,0) = 0, & t > 0, \\ \partial_z \rho_{sc}(t, z_{max}) = \partial_z \rho_{pc}(t, z_{max}) = 0, & t > 0, \\ \rho_{sc}(x,0) = \rho_{sc}^{init}(x), \quad \rho_{pc}(x,0) = \rho_{pc}^{init}(x), & 0 < z < z_{max}. \end{cases}$$

whose semiconservative structure (conservative in its convective and diffusive terms but with nonlinear source terms), allows us to consider a relaxation scheme as in [1]. The system (1.3) is equivalent to (1.1)-(1.2), through the relations:

$$\begin{aligned} A_{sc} &= A(z, \rho'_{dcs}, \partial_z \rho_{pc}, \rho_{sc}) \\ A_{pc} &= A(z, \rho'_{dcs}, \partial_z \rho_{sc}, \rho_{pc}) \\ A(z, \xi, \eta, \rho) &= -\mathcal{W}\left[\phi(\xi+\eta)\rho - \phi' \rho^2/2)\right], \\ B(\rho) &= B(z,\rho) = \mathcal{W}\phi\rho^2/2. \end{aligned}$$

When H_1 and H_2 does not depend on ρ_{pc}, ρ_{sc} and

$$H_1, H_2 \in L^\infty((0, z_{max} \times (0,T)),$$

the problem (1.3) is well posed and there is a unique entropy solution in $L^\infty((0, z_{max} \times (0,T))$ such that $B(\rho) \in L^2(0,T; H^1(0,z_{max}))$ (see for example [2, 5]). On the other hand, the weak solution of the system (1.3) verifies

$$E(\rho_{sc}, \rho_{pc}, w_{sc}, w_{pc}; \rho_{dcs}) = 0, \qquad \text{for all } w_{sc}, w_{pc}$$

with w_{sc}, w_{pc} smooth test functions on $[0,T] \times [0, z_{max}]$, such that for all t, $w_{pc}(t,0) = w_{pc}(t, z_{max}) = 0$ and $w_{sc}(t,0) = w_{sc}(t, z_{max}) = 0$ and

$$\begin{aligned} &E(\rho_{sc}, \rho_{pc}, w_{sc}, w_{pc}; \rho_{dcs}) := \\ &\quad \int_0^T \int_0^{z_{max}} \left[\rho_{sc}\partial_t w_{sc} + A_{sc}\partial_z w_{sc} + B(\rho_{sc})\partial_{zz} w_{sc} + H_1 w_{sc}\right] dz\, dt \\ &\quad + \int_0^T \int_0^{z_{max}} \left[\rho_{pc}\partial_t w_{pc} + A_{pc}\partial_z w_{pc} + B(\rho_{pc})\partial_{zz} w_{pc} + H_2 w_{pc}\right] dz\, dt \\ &\quad - \int_0^{z_{max}} \rho_{sc}(z,T) w_{sc}(z,T)\, dz + \int_0^{z_{max}} \rho_{sc}^{init}(z) w_{sc}(z,0)\, dz \\ &\quad - \int_0^{z_{max}} \rho_{pc}(z,T) w_{pc}(z,T)\, dz + \int_0^{z_{max}} \rho_{pc}^{init}(z) w_{pc}(z,0)\, dz \end{aligned} \tag{1.4}$$

2. Inverse Problem.

2.1. The problem of identifying the function $\rho_{dcs}(z)$.

1) Given $\rho_{sc}^{obs}(z,T)$ and $\rho_{pc}^{obs}(z,T)$ (experimental, observed or measured data), find $\rho_{dcs} \in \mathcal{C}(0, z_{max}) \cap L^\infty(0, z_{max})$, such that $\rho_{sc}(z,T) \approx \rho_{sc}^{obs}(z,T)$ and $\rho_{pc}(z,T) \approx \rho_{pc}^{obs}(z,T)$.

Equivalently, assuming a parametrization of the ρ_{dcs} density by a vector θ of N real parameters

$$\rho_{dcs}(z) = \bar{\rho}_{dcs}(z, \theta)$$

the identification problem is expressed as

2) Given $\rho_{sc}^{obs}(z,T)$ and $\rho_{pc}^{obs}(z,T)$ (experimental, observed or measured data), find $\theta \in \mathcal{A} \subset \mathbb{R}^N$, such that $\rho_{sc}(z,T) \approx \rho_{sc}^{obs}(z,T)$ and $\rho_{pc}(z,T) \approx \rho_{pc}^{obs}(z,T)$.

We define the cost function, with α, $\beta > 0$, as

$$\begin{aligned} J(\rho_{sc}, \rho_{pc}) := \frac{\alpha}{2} \int_0^{z_{max}} |\rho_{sc}(z,T) - \rho_{sc}^{obs}(z,T)|^2 dz \\ + \frac{\beta}{2} \int_0^{z_{max}} |\rho_{pc}(z,T) - \rho_{pc}^{obs}(z,T)|^2 dz \end{aligned} \tag{2.1}$$

The inverse problem consists of

$$\begin{cases} \text{find } \theta \in \mathcal{A}, \text{ such that} \\ J(\{\rho_{sc}, \rho_{pc}\}(\bar{\theta})) = \min_{\theta \in \mathcal{A}} J(\rho_{sc}, \rho_{pc}) \end{cases}$$

We define the Lagrangian

$$\mathcal{L}(\rho_{sc}, \rho_{pc}, w_{sc}, w_{pc}; \rho_{dcs}) := J(\rho_{sc}, \rho_{pc}) + E(\rho_{sc}, \rho_{pc}, w_{sc}, w_{pc}; \rho_{dcs}) \tag{2.2}$$

The derivative of $\mathcal{L}$ respect of ρ_{sc} and ρ_{pc} in the directions $\delta\rho_{sc}$ and $\delta\rho_{pc}$, respectively are given by

$$\left\langle \frac{\partial \mathcal{L}}{\partial \rho_{sc}}, \delta\rho_{sc} \right\rangle = \alpha \int_0^{z_{max}} (\rho_{sc}(z,T) - \rho_{sc}^{obs}(z,T))\delta\rho_{sc}(z,T)dz + \left\langle \frac{\partial E}{\partial \rho_{sc}}, \delta\rho_{sc} \right\rangle = 0 \tag{2.3}$$

$$\left\langle \frac{\partial \mathcal{L}}{\partial \rho_{pc}}, \delta\rho_{pc} \right\rangle = \beta \int_0^{z_{max}} (\rho_{pc}(z,T) - \rho_{pc}^{obs}(z,T))\delta\rho_{pc}(z,T)dz + \left\langle \frac{\partial E}{\partial \rho_{pc}}, \delta\rho_{pc} \right\rangle = 0 \tag{2.4}$$

Derivating (1.4) respect of ρ_{sc} and ρ_{pc} and replacing in (2.3)-(2.4), allows us to establish the adjoint problem given by:

$$\begin{cases} \partial_t w_{sc} + \dfrac{\partial A}{\partial \rho}(z, \rho'_{dcs}, \partial\rho_{pc}, \rho_{sc})\partial_z w_{sc} - \partial_z\left[\left(\dfrac{\partial A}{\partial \eta}(z, \rho'_{dcs}, \partial\rho_{sc}, \rho_{pc})\right)\partial_z w_{pc}\right] \\ \qquad = \dfrac{\partial B}{\partial \rho}(\rho_{sc})\partial_{zz} w_{sc} + \dfrac{\partial H_1}{\partial \rho_{sc}} w_{sc} + \dfrac{\partial H_2}{\partial \rho_{sc}} w_{pc}, \\ w_{sc}(z_{max}, t) = w_{sc}(0,t) = 0, \\ w_{sc}(z,T) = \alpha(\rho_{sc}(z,T) - \rho_{sc}^{obs}(z,T)) \\ \partial_t w_{pc} + \dfrac{\partial A}{\partial \rho}(z, \rho'_{dcs}, \partial\rho_{sc}, \rho_{pc})\partial_z w_{pc} - \partial_z\left[\left(\dfrac{\partial A}{\partial \eta}(z, \rho'_{dcs}, \partial\rho_{pc}, \rho_{sc})\right)\partial_z w_{sc}\right] \\ \qquad = \dfrac{\partial B}{\partial \rho}(\rho_{pc})\partial_{zz} w_{pc} + \dfrac{\partial H_1}{\partial \rho_{pc}} w_{sc} + \dfrac{\partial H_2}{\partial \rho_{pc}} w_{pc}, \\ w_{pc}(z_{max}, t) = w_{pc}(0,t) = 0, \\ w_{pc}(z,T) = \beta(\rho_{pc}(z,T) - \rho_{pc}^{obs}(z,T)) \end{cases}$$

We suppose that $\rho_{dcs} = \rho_{dcs}(\theta)$ is of class $\mathcal{C}^1$ with respect to θ, the finite set of parameters to identify, and we suppose that $\rho'_{dcs} = \rho'_{dcs}(\theta)$ is also of class $\mathcal{C}^1$ with respect to θ. The derivative of the cost function with respect of θ_i is given by

$$\begin{aligned} \frac{\partial J}{\partial \theta_i} &= \frac{\partial \mathcal{L}}{\partial \theta_i} + \left\langle \frac{\partial \mathcal{L}}{\partial \rho_{sc}}, \frac{\partial \rho_{sc}}{\partial \theta_i} \right\rangle + \left\langle \frac{\partial \mathcal{L}}{\partial \rho_{pc}}, \frac{\partial \rho_{pc}}{\partial \theta_i} \right\rangle = \frac{\partial}{\partial \theta_i}\left[E(\rho_{sc}, \rho_{pc}, w_{sc}, w_{pc}; \rho_{dcs})\right] \\ &= \left\langle \frac{\partial E}{\partial \rho_{dcs}}, \frac{\partial \rho_{dcs}}{\partial \theta_i} \right\rangle + \left\langle \frac{\partial E}{\partial \rho'_{dcs}}, \frac{\partial \rho'_{dcs}}{\partial \theta_i} \right\rangle \\ &= -\int_0^T \int_0^{z_{max}} \mathcal{W}\phi(z)(\rho_{sc}\partial_z w_{sc} + \rho_{pc}\partial_z w_{pc})\frac{\partial \rho'_{dcs}}{\partial \theta_i}\, dz\, dt \\ &\quad + \int_0^T \int_0^{z_{max}} \left(\frac{\partial H_1}{\partial \rho_{dcs}}\frac{\partial \rho_{dcs}}{\partial \theta_i} w_{sc} + \frac{\partial H_2}{\partial \rho_{dcs}}\frac{\partial \rho_{dcs}}{\partial \theta_i} w\right) dz\, dt \\ &= -\int_0^T \int_0^{z_{max}} \mathcal{W}\phi(z)(\rho_{sc}\partial_z w_{sc} + \rho_{pc}\partial_z w_{pc})\frac{\partial \rho'_{dcs}}{\partial \theta_i}\, dz\, dt \\ &\quad - \int_0^T \int_0^{z_{max}} D q_{sc}(1 - R_n)R'_{sc}\rho_{sc} w_{sc}\frac{\partial \rho_{dcs}}{\partial \theta_i}\, dz\, dt \\ &\quad - \int_0^T \int_0^{z_{max}} D\left[q_{pc}R_t + q_e(1 - R_e)\right]R'_{pc}\rho_{pc} w_{pc}\frac{\partial \rho_{dcs}}{\partial \theta_i}\, dz\, dt \end{aligned}$$

This calculation is formal, and the derivative of the cost function is not guaranteed. However, it establishes a necessary condition criterion of optimality:

$$\int_0^T \int_0^{z_{max}} \mathcal{W}\partial_z \left[\phi(z)(\rho_{sc}\partial_z w_{sc} + \rho_{pc}\partial_z w_{pc})\right] \delta\rho_{dcs}\, dz\, dt$$
$$- \int_0^T \int_0^{z_{max}} Dq_{sc}(1-R_n)R'_{sc}\rho_{sc}w_{sc}\delta\rho_{dcs}\, dz\, dt$$
$$- \int_0^T \int_0^{z_{max}} D\left[q_{pc}R_t + q_e(1-R_e)\right] R'_{pc}\rho_{pc}w_{pc}\delta\rho_{dcs}\, dz\, dt \geqslant 0, \qquad \text{for all } \delta\rho_{dcs}.$$

2.2. **Example of ρ_{dcs} shapes and $\delta\rho_{dcs}$ directions :**

(1) Trapezoidal shape. Let

(2.5)
$$\rho_{trapz}(z) = (d(z-z_d)+1)\mathbb{1}_{[z_d-1/d,z_d]}(z) + \mathbb{1}_{]z_d,z_u[}(z) + (1+u(z-z_u))\mathbb{1}_{[z_u,z_u-1/u]}(z),$$

with its derivative

$$\rho'_{trapz}(z) = d\mathbb{1}_{[z_d-1/d,z_d]}(z) + u\mathbb{1}_{[z_u,z_u-1/u]}(z),$$

where $\mathbb{1}[a,b](z) = H(x-a) - H(x-b)$ is the characteristic function for the interval $[a,b]$. We consider the renormalization:

$$\rho_{dcs} = \frac{N_{dcs}}{\int_0^{z_{max}} \rho_{trapz}(z)\, dz}\rho_{trapz}(z), \qquad \rho'_{dcs} = \frac{N_{dcs}}{\int_0^{z_{max}} \rho_{trapz}(z)\, dz}\rho'_{trapz}(z)$$

Taking $N_{dcs} \in \mathbb{R}_+$, and $(d,u,z_d,z_u) \in \mathcal{A} := \{0 < \frac{1}{d} \leqslant z_d \leqslant z_u \leqslant z_{max} - \frac{1}{u} < z_{max}\}$. We deduce

$$\frac{\partial}{\partial d}\rho_{trapz} = (z-z_d)\mathbb{1}_{[z_d-1/d,z_d]}(z) \qquad \frac{\partial}{\partial z_d}\rho_{trapz} = -d\mathbb{1}_{[z_d-1/d,z_d]}(z)$$
$$\frac{\partial}{\partial u}\rho_{trapz} = (z-z_u)\mathbb{1}_{[z_u,z_u-1/u]}(z) \qquad \frac{\partial}{\partial z_u}\rho_{trapz} = -u\mathbb{1}_{[z_u,z_u-1/u]}(z)$$
$$\frac{\partial}{\partial d}\rho'_{trapz} = \mathbb{1}_{[z_d-1/d,z_d]}(z) - (1/d)\delta(z-z_d+1/d),$$
$$\frac{\partial}{\partial u}\rho'_{trapz} = \mathbb{1}_{[z_u,z_u-1/u]}(z) + (1/u)\delta(z-z_u+1/u),$$
$$\frac{\partial}{\partial z_d}\rho'_{trapz} = -d\left(\delta(z-z_d+1/d) - \delta(z-z_d)\right)$$
$$\frac{\partial}{\partial z_u}\rho'_{trapz} = -u\left(\delta(z-z_u) - \delta(z-z_u+1/u)\right)$$

and then

$$\frac{\partial\rho_{dcs}}{\partial N_{dcs}} = \frac{\rho_{trapz}}{\int_0^{z_{max}} \rho_{trapz}\, dz}, \qquad \frac{\partial\rho'_{dcs}}{\partial N_{dcs}} = \frac{\rho'_{trapz}}{\int_0^{z_{max}} \rho_{trapz}\, dz}$$

$$\frac{\partial\rho_{dcs}}{\partial\theta_i} = N_{dcs}\left(1 - \frac{\rho_{trapz}}{\left(\int_0^{z_{max}} \rho_{trapz}\, dz\right)^2}\right)\frac{\partial\rho_{trapz}}{\partial\theta_i}, \quad \frac{\partial\rho'_{dcs}}{\partial\theta_i} = N_{dcs}\frac{\partial\rho'_{trapz}}{\partial\theta_i} - \frac{N_{dcs}\rho_{trapz}\dfrac{\partial\rho_{trapz}}{\partial\theta_i}}{\left(\int_0^{z_{max}} \rho_{trapz}\, dz\right)^2}$$

for $i = 2,\dots,5$, $\theta_1 = N_{dcs}$, $\theta_2 = d$, $\theta_3 = u$, $\theta_4 = z_d$ and $\theta_5 = z_u$.

(2) Smoothing of the trapezoidal shape.

We can take $\rho^{\varepsilon}_{dcs} = \varrho_{\varepsilon} \star \rho_{dcs}$ a smooth approximation of the trapezoidal shape via convolution with mollifiers. In this case, the derivatives are applied with practically the same formulas as in the previous case, thanks to the commutativity properties of the derivative with the convolution product.

(3) Simplification of the parameters.

In order to simplify the number of parameters limiting them to 3, and considering those that play a role in the main modifications of the shape of the DCS population distribution, namely: height, width and center of the distribution, let us assume a predetermined shape $\rho^{0}_{dcs}(z)$, which can be, for example, the trapezoidal shape (ρ_{trapz}) or smooth form (ρ^{ε}_{dcs}) described above. We define the DCS population distribution as

$$\rho_{NLz_0}(z) := \rho_{dcs}(z; N, L, z_0) = N\rho^{0}_{dcs}(Lz + z_0) = N\rho^{0}_{dcs}(y).$$

with it derivative $\rho'_{NLz_0}(z) = NL\{\rho^{0}_{dcs}\}'(y)$, where $y = Lz + z_0$. For example, taking the trapezoidal shape $\rho^{0}_{dcs} = \rho_{trapz}$ given by (2.5), we obtain:

$$\begin{aligned}
\frac{\partial}{\partial N}\rho_{NLz_0}(z) &= \rho_{trapz}(y), & \frac{\partial}{\partial N}\rho'_{NLz_0}(z) &= L\rho'_{trapz}(y)\\
\frac{\partial}{\partial z_0}\rho_{NLz_0}(z) &= N\rho'_{trapz}(y), & \frac{\partial}{\partial z_0}\rho'_{NLz_0}(z) &= NL\rho''_{trapz}(y)\\
\frac{\partial}{\partial L}\rho_{NLz_0}(z) &= Nz\rho'_{trapz}(y), & \frac{\partial}{\partial L}\rho'_{NLz_0}(z) &= N\rho'_{trapz}(y) + NLz\rho''_{trapz}(y)
\end{aligned}$$

where

$$\begin{aligned}
&\rho_{trapz}(y) \text{ is given by (2.5) with } y = Lz + z_0\\
&\rho'_{trapz}(y) = \rho'_{trapz}(y(z)) = d\mathbb{1}_{[z_1,z_2]}(z) + u\mathbb{1}_{[z_3,z_4]}(z)\\
&\rho''_{trapz}(y) = \rho''_{trapz}(y(z)) = d\,(\delta_{z_1} - \delta_{z_2}) + u\,(\delta_{z_3} - \delta_{z_4})
\end{aligned}$$

with $z_1 = \dfrac{z_d - z_0}{L} - \dfrac{1}{Ld}$, $z_2 = \dfrac{z_d - z_0}{L}$, $z_3 = \dfrac{z_u - z_0}{L}$ and $z_4 = \dfrac{z_u - z_0}{L} - \dfrac{1}{Lu}$.

For instance

$$
\begin{aligned}
\frac{\partial J}{\partial L} = -\mathcal{W}N \int_0^T & \left[d \int_{z_1}^{z_2} \phi(z)(\rho_{sc}\partial_z w_{sc} + \rho_{pc}\partial_z w_{pc})\, dz \right. \\
& \left. + u \int_{z_3}^{z_4} \phi(z)(\rho_{sc}\partial_z w_{sc} + \rho_{pc}\partial_z w_{pc})\, dz \right] dt \\
& -\mathcal{W}NL \left[dz_1 \phi(z_1) \int_0^T (\rho_{sc}\partial_z w_{sc} + \rho_{pc}\partial_z w_{pc})\Big|_{z=z_1} dt \right. \\
& \quad - dz_2 \phi(z_2) \int_0^T (\rho_{sc}\partial_z w_{sc} + \rho_{pc}\partial_z w_{pc})\Big|_{z=z_2} dt \\
& \quad + uz_3 \phi(z_3) \int_0^T (\rho_{sc}\partial_z w_{sc} + \rho_{pc}\partial_z w_{pc})\Big|_{z=z_3} dt \\
& \quad \left. - uz_4 \phi(z_4) \int_0^T (\rho_{sc}\partial_z w_{sc} + \rho_{pc}\partial_z w_{pc})\Big|_{z=z_4} dt \right] \\
& -DNq_{sc} \int_0^T \left(d \int_{z_1}^{z_2} z(1-R_n) R'_{sc} \rho_{sc} w_{sc}\, dz \right. \\
& \quad \left. + u \int_{z_3}^{z_4} z(1-R_n) R'_{sc} \rho_{sc} w_{sc}\, dz \right) dt \\
& -DN \int_0^T \left(d \int_{z_1}^{z_2} z \left[q_{pc} R_t + q_e(1-R_e) \right] R'_{pc} \rho_{pc} w_{pc}\, dz \right. \\
& \quad \left. + u \int_{z_3}^{z_4} z \left[q_{pc} R_t + q_e(1-R_e) \right] R'_{pc} \rho_{pc} w_{pc}\, dz \right) dt
\end{aligned}
$$

3. Numerical approximation.

3.1. **BGK schemes for the direct problem.** Based on the explicit diffusive kinetic schemes introduced by [1], we obtain a general 5-points scheme in a conservative form described in details in [4]:

$$\delta z(\rho_{sc,i}^{\varepsilon,n+1} - \rho_{sc,i}^{\varepsilon,n}) + \delta t(\mathcal{F}_{sc,i+1/2}^{\varepsilon,n} - \mathcal{F}_{sc,i-1/2}^{\varepsilon,n}) = \delta t \delta z H_1(z, \rho_{dcs}, \rho_{sc,i}^{\varepsilon,n}, \rho_{pc,i}^{\varepsilon,n}) \tag{3.1}$$

$$\rho_{sc,i}^0 = \rho_{sc,i}^{init}, \tag{3.2}$$

$$\delta z(\rho_{pc,i}^{\varepsilon,n+1} - \rho_{pc,i}^{\varepsilon,n}) + \delta t(\mathcal{F}_{pc,i+1/2}^{\varepsilon,n} - \mathcal{F}_{pc,i-1/2}^{\varepsilon,n}) = \delta t \delta z H_2(z, \rho_{dcs}, \rho_{sc,i}^{\varepsilon,n}, \rho_{pc,i}^{\varepsilon,n}), \tag{3.3}$$

$$\rho_{pc,i}^0 = \rho_{pc,i}^{init}, \tag{3.4}$$

where

$$
\begin{aligned}
\mathcal{F}_{sc,i+1/2}^{\varepsilon,n} &= \sum_{\ell=1}^{4} \lambda_\ell F_\ell({}^{sc}M_{i-1,\ell}^{\varepsilon,n}, {}^{sc}M_{i,\ell}^{\varepsilon,n}, {}^{sc}M_{i+1,\ell}^{\varepsilon,n}) \\
\mathcal{F}_{pc,i+1/2}^{\varepsilon,n} &= \sum_{\ell=1}^{4} \lambda_\ell F_\ell({}^{pc}M_{i-1,\ell}^{\varepsilon,n}, {}^{pc}M_{i,\ell}^{\varepsilon,n}, {}^{pc}M_{i+1,\ell}^{\varepsilon,n})
\end{aligned}
$$

with $\lambda_1 = \lambda$, $\lambda_2 = -\lambda$, $\lambda_3 = \lambda + \dfrac{\theta}{\sqrt{\varepsilon}}$, $\lambda_4 = -\lambda - \dfrac{\theta}{\sqrt{\varepsilon}}$,

$$\begin{aligned}
F_{1,2}(M_{i-1}, M_i, M_{i+1}) &= F^L(M_i, M_{i+1}) \\
&\quad + \varphi^{Superbee}(M_{i-1}, M_i, M_{i+1}) \left(F^H(M_i, M_{i+1}) - F^L(M_i, M_{i+1})\right) \\
F_3(M_{i-1}, M_i, M_{i+1}) &= F_3(M_i, M_{i+1}) = M_i + b_0(M_{i+1} - M_i) \\
F_4(M_{i-1}, M_i, M_{i+1}) &= F_4(M_i, M_{i+1}) = M_{i+1} + b_0(M_i - M_{i+1})
\end{aligned}$$

and

$$\begin{aligned}
{}^{sc}M^{\varepsilon,n}_{i,1} &= \frac{1}{2\lambda}\left(\lambda(\rho^n_{sc,i} - \frac{B(i\delta z, \rho^n_{sc,i})}{\theta^2}) + A^{sc}_{i+\frac{1}{2}}\right) \\
{}^{sc}M^{\varepsilon,n}_{i,2} &= \frac{1}{2\lambda}\left(\lambda(\rho^n_{sc,i} - \frac{B(i\delta z, \rho^n_{sc,i})}{\theta^2}) - A^{sc}_{i+\frac{1}{2}}\right) \\
{}^{sc}M^{\varepsilon,n}_{i,3} = {}^{sc}M^{\varepsilon,n}_{i,4} &= \frac{B(i\delta z, \rho^n_{sc,i})}{2\theta^2} \\
{}^{pc}M^{\varepsilon,n}_{i,1} &= \frac{1}{2\lambda}\left(\lambda(\rho^n_{pc,i} - \frac{B(i\delta z, \rho^n_{pc,i})}{\theta^2}) + A^{pc}_{i+\frac{1}{2}}\right) \\
{}^{pc}M^{\varepsilon,n}_{i,2} &= \frac{1}{2\lambda}\left(\lambda(\rho^n_{pc,i} - \frac{B(i\delta z, \rho^n_{pc,i})}{\theta^2}) - A^{pc}_{i+\frac{1}{2}}\right) \\
{}^{pc}M^{\varepsilon,n}_{i,3} = {}^{pc}M^{\varepsilon,n}_{i,4} &= \frac{B(i\delta z, \rho^n_{pc,i})}{2\theta^2}.
\end{aligned}$$

where

$$A_{i+\frac{1}{2}} = V^+_{i+\frac{1}{2}}\rho_i + V^-_{i+\frac{1}{2}}\rho_{i+1} + \mathcal{W}(\phi'_{i+\frac{1}{2}})^+\rho_i^2/2 + \mathcal{W}(\phi'_{i+\frac{1}{2}})^-\rho_{i+1}^2/2$$

with $v^+ = \max(v, 0)$, and $v^- = \min(v, 0)$, $\phi'_{i+\frac{1}{2}} = \frac{\phi'(i\delta z) + \phi'((i+1)\delta z)}{2}$, and

$$\begin{aligned}
V^{sc}_{i+\frac{1}{2}} &= -\mathcal{W}\left[(\phi\rho'_{dcs})_{i+\frac{1}{2}} + \phi_{i+\frac{1}{2}} D^+\rho_{pc,i}\right] \\
V^{pc}_{i+\frac{1}{2}} &= -\mathcal{W}\left[(\phi\rho'_{dcs})_{i+\frac{1}{2}} + \phi_{i+\frac{1}{2}} D^+\rho_{sc,i}\right]
\end{aligned}$$

with $D^+\rho_i = \dfrac{\rho_{i+1} - \rho_i}{\delta z}$. Additionally, the parameter λ and θ are chosen as

$$\theta = \sqrt{\frac{\max\{B'(\rho_l)\}}{\alpha - 1}} + \delta, \qquad \lambda = \max\left\{\frac{\partial}{\partial \rho_l} A^l_{i+\frac{1}{2}}\right\} + \delta$$

$l = sc, pc$. Replicating these formulas independently for both ρ and ρ_{sc}, thus obtaining the parameter pairs (θ, λ) and $(\theta_{sc} = \delta, \lambda_{sc})$, respectively, and the CFL condition

$$\delta t \leqslant \min\left\{\frac{\delta z^2}{2\theta^2}, \frac{\delta z}{\lambda_{sc}}, \frac{\delta z}{\lambda_{pc}}\right\} \tag{3.5}$$

3.2. **Adjoint scheme associate to BGK scheme.** Let $\rho_{sc,\delta} = (\rho^n_{sc,i})_{i,n}$, $\rho_{pc,\delta} = (\rho^n_{pc,i})_{i,n}$ Multiplying (3.1)-(3.4) by $w^n_{sc,i}$, $w^n_{pc,i}$, and summing by parts, we obtain

$$E_\delta(\rho_{sc,\delta}, \rho_{pc,\delta}, w_{sc,\delta}, w_{pc,\delta}; \rho_{dcs}) = 0, \qquad \text{for all } w_{sc,\delta}, w_{pc,\delta}$$

with

$$E_\delta(\rho_{sc,\delta}, \rho_{pc,\delta}, w_{sc,\delta}, w_{pc,\delta}; \rho_{dcs}) = E_{1,\delta}(\rho_{sc,\delta}, \rho_{pc,\delta}, w_{sc,\delta}; \rho_{dcs}) + E_{2,\delta}(\rho_{sc,\delta}, \rho_{pc,\delta}, w_{pc,\delta}; \rho_{dcs})$$

where

(3.6)

$$E_{1,\delta}(\rho_{sc,\delta}, \rho_{pc,\delta}, w_{sc,\delta}; \rho_{dcs}) := \sum_{n=1}^{N} \sum_{i=1}^{\lfloor \frac{zmax}{\delta z} \rfloor -1} \left[\rho_{sc,i}^{\varepsilon,n} \left(w_{sc,i}^{n} - w_{sc,i}^{n-1} \right) \delta z + \mathcal{F}_{sc,i+1/2}^{\varepsilon,n} \left(w_{sc,i+1}^{n} - w_{sc,i}^{n} \right) \delta t + H_{1,i}^{n} w_{sc,i}^{n} \delta z \delta t \right] - \sum_{i=1}^{\lfloor \frac{zmax}{\delta z} \rfloor -1} (\rho_{sc,i}^{N} w_{sc,i}^{N} - \rho_{sc,i}^{init} w_{sc,i}^{0}) \delta z$$

(3.7)

$$E_{2,\delta}(\rho_{sc,\delta}, \rho_{pc,\delta}, w_{pc,\delta}; \rho_{dcs}) := \sum_{n=1}^{N} \sum_{i=1}^{\lfloor \frac{zmax}{\delta z} \rfloor -1} \left[\rho_{pc,i}^{\varepsilon,n} \left(w_{pc,i}^{n} - w_{pc,i}^{n-1} \right) \delta z + \mathcal{F}_{pc,i+1/2}^{\varepsilon,n} \left(w_{pc,i+1}^{n} - w_{pc,i}^{n} \right) \delta t + H_{2,i}^{n} w_{pc,i}^{n} \delta z \delta t \right] - \sum_{i=1}^{\lfloor \frac{zmax}{\delta z} \rfloor -1} (\rho_{pc,i}^{N} w_{pc,i}^{N} - \rho_{pc,i}^{init} w_{pc,i}^{0}) \delta z$$

3.3. **Discrete inverse problem.** The discrete cost function is given by

$$J_{\delta}(\rho_{\delta}, \rho_{sc,\delta}) := \frac{\alpha}{2} \sum_{i=1}^{\lfloor \frac{zmax}{\delta z} \rfloor -1} |\rho_{sc,i}^{N} - \rho_{sc,i}^{obs}|^2 \delta z + \frac{\beta}{2} \sum_{i=1}^{\lfloor \frac{zmax}{\delta z} \rfloor -1} |\rho_{pc,i}^{N} - \rho_{pc,i}^{obs}|^2 \delta z \quad (3.8)$$

Thus derivating of the discrete Lagrangian

$$\mathcal{L}_{\delta}(\rho_{sc,\delta}, \rho_{pc,\delta}, w_{sc,\delta}, w_{pc,\delta}; \rho_{dcs}) := J_{\delta}(\rho_{sc,\delta}, \rho_{pc,\delta}) + E_{\delta}(\rho_{sc,\delta}, \rho_{pc,\delta}, w_{sc,\delta}, w_{pc,\delta}; \rho_{dcs})$$

with respect to $\rho_{sc,i}^{n}$ and $\rho_{pc,i}^{n}$, we obtain the discrete adjoint scheme

$$\begin{aligned} w_{sc,i}^{n-1} &= w_{sc,i}^{n} + \frac{\delta t}{\delta z} \sum_{k=1}^{4} \frac{\partial}{\partial \rho_{sc,k-2}} \left[\mathcal{F}_{sc,i-k+5/2}^{\varepsilon,n} \right] \left(w_{sc,i-k+3}^{n} - w_{sc,i-k+2}^{n} \right) \\ &\quad + \frac{\delta t}{\delta z} \sum_{k=1}^{4} \frac{\partial}{\partial \rho_{sc,k-2}} \left[\mathcal{F}_{pc,i-k+5/2}^{\varepsilon,n} \right] \left(w_{pc,i-k+3}^{n} - w_{pc,i-k+2}^{n} \right) \\ &\quad + \delta t \frac{\partial H_{1,i}^{n}}{\partial \rho_{sc,i}^{n}} w_{sc,i}^{n} + \delta t \frac{\partial H_{2,i}^{n}}{\partial \rho_{sc,i}^{n}} w_{pc,i}^{n}, \end{aligned} \quad (3.9)$$

$$\begin{aligned} w_{pc,i}^{n-1} &= w_{pc,i}^{n} + \frac{\delta t}{\delta z} \sum_{k=1}^{4} \frac{\partial}{\partial \rho_{pc,k-2}} \left[\mathcal{F}_{sc,i-k+5/2}^{\varepsilon,n} \right] \left(w_{sc,i-k+3}^{n} - w_{sc,i-k+2}^{n} \right) \\ &\quad + \frac{\delta t}{\delta z} \sum_{k=1}^{4} \frac{\partial}{\partial \rho_{pc,k-2}} \left[\mathcal{F}_{pc,i-k+5/2}^{\varepsilon,n} \right] \left(w_{pc,i-k+3}^{n} - w_{pc,i-k+2}^{n} \right) \\ &\quad + \delta t \frac{\partial H_{1,i}^{n}}{\partial \rho_{pc,i}^{n}} w_{sc,i}^{n} + \delta t \frac{\partial H_{2,i}^{n}}{\partial \rho_{pc,i}^{n}} w_{pc,i}^{n}, \end{aligned} \quad (3.10)$$

$$w_{sc,i}^{N-1} = \alpha \left(\rho_{sc,i}^{N} - \rho_{sc,i}^{obs} \right) \quad (3.11)$$

$$w_{pc,i}^{N-1} = \beta \left(\rho_{pc,i}^{N} - \rho_{pc,i}^{obs} \right) \quad (3.12)$$

Because $\left\langle \dfrac{\partial M_{k,\ell}^{\varepsilon,n}}{\partial \rho'_{dcs}}, \delta\rho'_{dcs} \right\rangle = -\dfrac{\mathcal{W}\phi_k}{2}\rho_k^n$, we deduce that the derivative of the discrete cost function is given by:

$$\begin{aligned}\left\langle \frac{\partial J_\delta}{\partial \rho_{dcs}}, \delta\rho_{dcs} \right\rangle &= \delta t \sum_{n=1}^{N} \sum_{i=1}^{\lfloor \frac{z_{max}}{\delta z} \rfloor - 1} \sum_{k=1}^{4} \frac{\partial}{\partial \rho'_{dcs,k-2}} \left[\mathcal{F}_{sc,i+1/2}^{\varepsilon,n}\right] \left(w_{sc,i+1}^n - w_{sc,i}^n\right) \\ &+ \delta t \sum_{n=1}^{N} \sum_{i=1}^{\lfloor \frac{z_{max}}{\delta z} \rfloor - 1} \sum_{k=1}^{4} \frac{\partial}{\partial \rho'_{dcs,k-2}} \left[\mathcal{F}_{pc,i+1/2}^{\varepsilon,n}\right] \left(w_{pc,i+1}^n - w_{pc,i}^n\right) \\ &+ \delta t \delta z \sum_{n=1}^{N} \sum_{i=1}^{\lfloor \frac{z_{max}}{\delta z} \rfloor - 1} \left(\frac{\partial H_{1,i}^n}{\partial \rho_{dcs}} w_{sc,i}^n + \frac{\partial H_{2,i}^n}{\partial \rho_{dcs}} w_{pc,i}^n \right),\end{aligned} \tag{3.13}$$

4. Numerical Examples

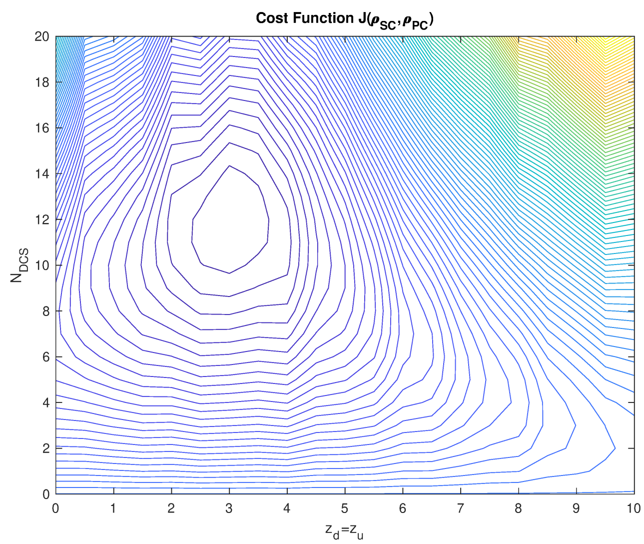

Figure 3. Cost function $J(\rho_{sc}, \rho_{pc}) = \dfrac{1}{2}\displaystyle\int_0^{z_{max}} \left|\rho_{sc}^{obs}(z) - \rho_{sc}(z,T)\right|^2 dz + \dfrac{1}{2}\displaystyle\int_0^{z_{max}} \left|\rho_{pc}^{obs}(z) - \rho_{pc}(z,T)\right|^2 dz.$

We make here a simulation for $z_{max} = 200$ and $T = 20$. We choose a reasonable discretization with $N = 250$, which gives $dz = z_{max}/(N-1) = 0.8032$. Additionally, the values proposed in [3] for the physical-biological parameters of the model are considered, that is: $\mathcal{W} = 6.01/8$, $q_{SC} = 0.15$, $Z_{niche} = 12.0$, $k_{niche} = 5.0$, $D = 12.07$, $K_{SC} = 53$, $k_{dens} = 6$, $q_{diff} = 0.2$, $q_{PC} = 0.22$, $Z_{tiers} = 40.0$, $k_{tiers} = 40.0$, $K_{PC} = 41.0$, $q_{ex} = 0.34$, $Z_{ex} = 190.0$, $k_{ex} = 15.0$. As for the geometric parameters of the crypt, these are given by $r_0 = 10$, $\varepsilon_0 = 0.1 r_0$. Regarding the DCS cells, we initially consider the same trapezoidal shape of [3], with the parameters $d = 2.25$, $u = -1/8$ and $0 \leqslant N_{DCS} \leqslant 20$, $0 \leqslant z_d = z_u \leqslant 10$.

Firstly, we experimentally confirmed that a trapezoidal shape for the DCS cells, although they generate regular solutions, they do not behave regularly in the face of

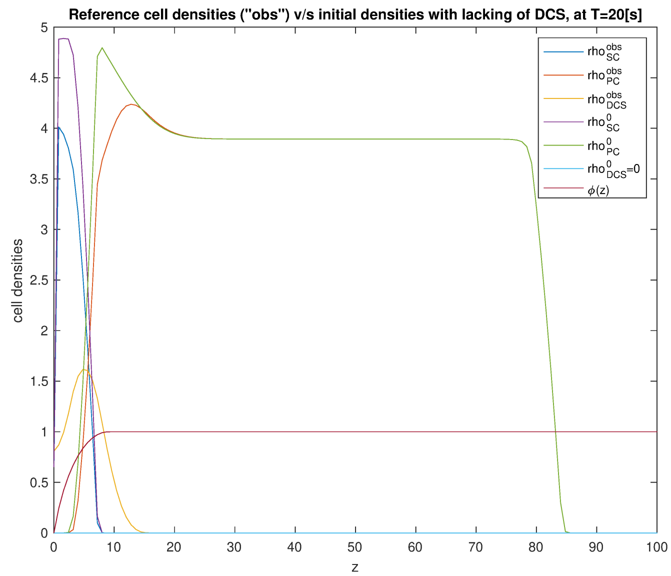

FIGURE 4. Evolution of cell population: Simulation of the interaction SC-PC with the presence of a smooth form for the distribution of DCS v/s simulation with lacking of DCS. Testing of the inverse problem: starting from the case with lacking of DCS, reconstruct their shape, using the numerical simulation of the case with DCS as a reference (observation) for the objective function.

small variations in the parameters of said trapezoid. Although there is a continuity of the solution with respect to these parameters, we observe through some numerical tests that the cost function (2.1) and its approximation (3.8) contain oscillations and therefore several local minima that are uncomfortable to minimize. Therefore we choose to approximate the DCS cell distribution function by regularizing it through convolution with molliifier functions.

On the other hand, since in this instance we do not have real experimental observations, we consider a reference simulation with $N_{DCS} = 12$ and $z_d = z_u = 3$ (chosen values of [3]) at which we will call observed data. We then start from a simulation without DCS cells, that is, $N_{DCS} = 0$ and $z_d = z_u = 0$, and we try to reconstruct the shape of the DCS cells for the observed solution by solving the inverse problem 2.1.*2)* and minimizing the cost function (3.8).

Additionally, the parameters $\delta = 10^{-5}$, $\alpha = 0.9$ and $b_0 = 1$ were chosen for the description of the BGK scheme and the calculation of the values of λ_ℓ and θ. We consider a CFL condition (3.5) sufficiently strict that it covers all the range of values that $N_{DCS} \in [0; 20]$ and $z_d = z_u \in [0; 10]$ can take. This gives a value $\delta t = 3.2257 \cdot 10^{-5}$ for the set of physical, geometric and meshing parameters described here.

Figure 3 shows the simulated cost function for various values of N_{DCS} varying from 0 to 20, and various values of $z_d = z_u$ varying from 0 to 10. The trapezoid of the DCS cell distribution function is smoothed using the smooth1DconvNE2xConv()

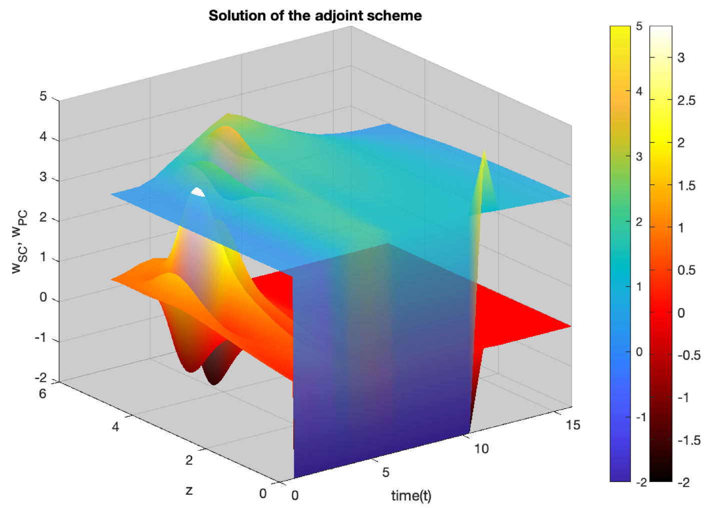

FIGURE 5. Solutions of the adjoint scheme associated to the BGK scheme of the cell distributions: w_{sc} in a hot color map, and $w_{pc}+3$ (in order to be able to visualize it differentiated from w_{sc}) in a slightly transparent "parula" color map and above of the w_{sc} graph.

function of matlab [6]. This smoothed function can be seen in figure 4 (yellow graph). Based on this, a cost function is obtained with a single, clearly defined minimum, locally convex, and sufficiently sensitive to data perturbation. It should be noted that the sum of two functionals $\frac{1}{2}\int_0^{z_{max}} \left|\rho_{sc}^{obs}(z) - \rho_{sc}(z,T)\right|^2 dz$ and $\frac{1}{2}\int_0^{z_{max}} \left|\rho_{pc}^{obs}(z) - \rho_{pc}(z,T)\right|^2 dz$ is being minimized in that each of them alone does not have a locally convex shape as defined as the sum of both.

4.1. **Inverse problem results.** In Figure 4, the distribution of reference densities (considered as "observations") for the stem cells (cyan color) and for the progenitor cells (red color) are plotted. Additionally, the distribution of smoothed DCS cells is graphed (in yellow) that allows simulating such results, and corresponds to the shape that is desired to be reconstructed through the method of solving the inverse problem. Then, for comparison, the simulation of the distributions corresponding to the starting point for the resolution using gradient descent of the minimization problem is graphed, this is simulation without the presence of DCS cells ($N_{DCS} = z_d = z_u = 0$) : stem cells (in purple) and progenitor cells (in light green). Additionally and as a reference, the representative function of the geometry of the crypt $\phi(z)$ is graphed.

We compute the adjoint state of the BGK numerical scheme, in order to obtain the critical points of the Lagrangian (2.2). The numerical simulation of the adjoint state (3.9)-(3.10) is graphed in Figure 5. In order to simultaneously display both w_{sc} and w_{pc} in the same figure, the constant 3 is added to w_{pc} to graph it in

Identification indicators	Values
Number of iterations	17
Evaluations of $J(\cdot)$	72
$J(\rho_{sc}^{Identif}, \rho_{pc}^{Identif})$	2.62119e-13
$(N_{DCS}^{Identif}; z_d^{Identif})$	(12; 3)
$N_{DCS}^{Identif} - N_{DCS}^{obs}$	-3.8188e-06
$z_d^{Identif} - z_d^{obs}$	4.6803e-07
$\nabla J(\rho_{sc}^{Identif}, \rho_{pc}^{Identif})^T$	(-0.1863e-06; -0.4405e-06)
Hessian of $J(\rho_{sc}^{Identif}, \rho_{pc}^{Identif})$	$\begin{pmatrix} 0.0741 & 0.1925 \\ 0.1925 & 0.6007 \end{pmatrix}$

Table 1. Numerical result of the inverse problem test

a slightly transparent "parula" color map , in contrast to the reddish map for w_{sc}. Like Lagange multipliers, these quantities are related to the derivatives of the constraints (in this case the equations that characterize the BGK scheme), and their stability is important for the calculation of the gradient. In this case we observe a stability of the solution except in $z = 0$ where there is a singularity in its neighborhood, and for a time $t \leqslant t^*$ with $t^* \approx 12$. This could become problematic if we want to identify, for example, the boundary condition at the bottom of the crypt ($z = 0$), which is surely an ill-posed problem.

In the Table 1 a summary of the identification of the parameters can be observed. Indeed, based on a situation without DCS cells, we managed to rebuild the parameters of the distribution of reference DCS cells in 17 gradient iterations and 72 evaluations of the cost function, reaching the values $N_{DCS}^{Identif} = 12$ and $z_u^{Identif} = 3$ with an error of less than $4 \cdot 10^{-6}$.

Acknowledgment

The inverse problem for the model studied in this work was discussed during the third author's long-stay visit to the MaIAGE unit of INRAE and the MUSCA team of INRIA, Université Paris-Saclay, France. The third author MS thanks these laboratories of applied mathematics and modeling for their kind support and hospitality.

References

[1] D. Aregba-Driollet, R. Natalini, and S. Tang. *Explicit Diffusive Kinetic Schemes for Nonlinear Degenerate Parabolic Systems.* Mathematics of Computation 73, no. 245 (2004): 63-94.

[2] J. Carrillo. *Entropy solutions for nonlinear degenerate problems.* Arch. Ration. Mech. Anal. 147 (1999), no. 4, 269-361. El problema inverso

[3] L. Darrigade, M. Haghebaert, C. Cherbuy, S. Labarthe, B. Laroche. *A PDMP model of the epithelial cell turn-over in the intestinal crypt including microbiota-derived regulations.* J Math Biol. 2022 Jun 23;84(7):60.

[4] M. Haghebaert, B. Laroche. *Personal communication concerning the Thesis of M. Haghebaert.* 2023.

[5] C. Mascia, A. Porretta, A. Terracina, *Nonhomogeneous Dirichlet problems for degenerate parabolic-hyperbolic equations.* Arch. Ration. Mech. Anal. 163 (2002), no. 2, 87-124.
[6] Peter Seibold (2023). Smoothing 1D not equidistant curve by convolution (https://www.mathworks.com/matlabcentral/fileexchange/132528-smoothing-1d-not-equidistant-curve-by-convolution), MATLAB Central File Exchange.

Annexes

Appendix A. Derivative of the flux for 5-points schemes

A.1. **Derivative of the flux respect of ρ_{sc} and ρ_{pc}.** We consider the descomposition

$$\mathcal{F}^{\varepsilon,n}_{\sigma,i+1/2} = \sum_{\ell=1}^{4} \lambda_\ell F_{\sigma,\ell,i+1/2} = \sum_{\ell=1}^{4} \lambda_\ell F_\ell(M^n_{\sigma,i-1,\ell}, M^n_{\sigma,i,\ell}, M^n_{\sigma,i+1,\ell})$$

for $\sigma = sc, pc$, with $\lambda_1 = \lambda$, $\lambda_2 = -\lambda$, $\lambda_3 = \lambda + \dfrac{\theta}{\sqrt{\varepsilon}}$, $\lambda_4 = -\lambda - \dfrac{\theta}{\sqrt{\varepsilon}}$. In this sense, we have

$$\begin{aligned}
\frac{\partial}{\partial \rho_{\varpi,-1}} \left[\mathcal{F}^{\varepsilon,n}_{\sigma,i+3/2}\right] &= \sum_{\ell=1}^{4} \lambda_\ell \frac{\partial F_{\sigma,\ell,i+3/2}}{\partial M_{\sigma,-1,\ell}} \frac{\partial M_{\sigma,i,\ell}}{\partial \rho_{\varpi,0}} \\
\frac{\partial}{\partial \rho_{\varpi,0}} \left[\mathcal{F}^{\varepsilon,n}_{\sigma,i+1/2}\right] &= \sum_{\ell=1}^{4} \lambda_\ell \left[\frac{\partial F_{\sigma,\ell,i+1/2}}{\partial M_{\sigma,-1,\ell}} \frac{\partial M_{\sigma,i-1,\ell}}{\partial \rho_{\varpi,,1}} + \frac{\partial F_{\sigma,\ell,i+1/2}}{\partial M_{\sigma,0,\ell}} \frac{\partial M_{\sigma,i,\ell}}{\partial \rho_{\varpi,,0}}\right] \\
\frac{\partial}{\partial \rho_{\varpi,1}} \left[\mathcal{F}^{\varepsilon,n}_{\sigma,i-1/2}\right] &= \sum_{\ell=1}^{4} \lambda_\ell \left[\frac{\partial F_{\sigma,\ell,i-1/2}}{\partial M_{\sigma,0,\ell}} \frac{\partial M_{\sigma,i-1,\ell}}{\partial \rho_{\varpi,,1}} + \frac{\partial F_{\sigma,\ell,i-1/2}}{\partial M_{\sigma,1,\ell}} \frac{\partial M_{\sigma,i,\ell}}{\partial \rho_{\varpi,,0}}\right] \\
\frac{\partial}{\partial \rho_{\varpi,2}} \left[\mathcal{F}^{\varepsilon,n}_{\sigma,i-3/2}\right] &= \sum_{\ell=1}^{4} \lambda_\ell \frac{\partial F_{\sigma,\ell,i-3/2}}{\partial M_{\sigma,1,\ell}} \frac{\partial M_{\sigma,i-1,\ell}}{\partial \rho_{\varpi,,1}}
\end{aligned}$$

with $\sigma = sc, pc$ and $\varpi = sc, pc$. Then, we can replace directly this expressions on (3.9) and (3.10).

A.2. **Derivative of the flux respect of ρ'_{dcs}.** We have

$$\begin{aligned}
\frac{\partial}{\partial \rho'_{dcs,-1}} \left[\mathcal{F}^{\varepsilon,n}_{\sigma,i+1/2}\right] &= \sum_{\ell=1}^{4} \lambda_\ell \frac{\partial F_{\sigma,\ell,i+1/2}}{\partial M_{\sigma,-1,\ell}} \frac{\partial M_{\sigma,i-1,\ell}}{\partial \rho'_{dcs,0}} \\
\frac{\partial}{\partial \rho'_{dcs,0}} \left[\mathcal{F}^{\varepsilon,n}_{\sigma,i+1/2}\right] &= \sum_{\ell=1}^{4} \lambda_\ell \left[\frac{\partial F_{\sigma,\ell,i+1/2}}{\partial M_{\sigma,-1,\ell}} \frac{\partial M_{\sigma,i-1,\ell}}{\partial \rho'_{dcs,,1}} + \frac{\partial F_{\sigma,\ell,i+1/2}}{\partial M_{\sigma,0,\ell}} \frac{\partial M_{\sigma,i,\ell}}{\partial \rho'_{dcs,,0}}\right] \\
\frac{\partial}{\partial \rho'_{dcsi,1}} \left[\mathcal{F}^{\varepsilon,n}_{\sigma,i+1/2}\right] &= \sum_{\ell=1}^{4} \lambda_\ell \left[\frac{\partial F_{\sigma,\ell,i+1/2}}{\partial M_{\sigma,0,\ell}} \frac{\partial M_{\sigma,i,\ell}}{\partial \rho'_{dcs,,1}} + \frac{\partial F_{\sigma,\ell,i+1/2}}{\partial M_{\sigma,1,\ell}} \frac{\partial M_{\sigma,i+1,\ell}}{\partial \rho'_{dcs,,0}}\right] \\
\frac{\partial}{\partial \rho'_{dcs,2}} \left[\mathcal{F}^{\varepsilon,n}_{\sigma,i+1/2}\right] &= \sum_{\ell=1}^{4} \lambda_\ell \frac{\partial F_{\sigma,\ell,i+1/2}}{\partial M_{\sigma,1,\ell}} \frac{\partial M_{\sigma,i+1,\ell}}{\partial \rho'_{dcs,,1}}
\end{aligned}$$

for $\sigma = sc, pc$. Then, we can replace these derivatives of the flux directly on (3.13).

To calculate these derivatives it is necessary to specify the calculation of the derivative of the flux with respect to the Maxwellian ones, as well as the derivatives of the Maxwellian ones with respect to the distribution of cells. Below we detail these two levels of derivatives.

A.3. **Derivative of the flux respect of the maxwellian distrubutions.** For $\ell = 1, 2$ we consider a second order limiter flux with Lax-Wendroff scheme, that is

$$\begin{aligned} \lambda_1 F_1(M_{-1}, M_0, M_1) &= \lambda F_1(M_{-1}, M_0, M_1) \\ &= \lambda M_0 + \frac{\lambda}{2}\varphi(M_{-1}, M_0, M_1)\left(1 - \lambda\frac{\delta t}{\delta z}\right)(M_1 - M_0) \\ \lambda_2 F_2(M_{-1}, M_0, M_1) &= -\lambda F_2(M_{-1}, M_0, M_1) \\ &= -\lambda M_1 + \frac{\lambda}{2}\varphi(M_{-1}, M_0, M_1)\left(1 - \lambda\frac{\delta t}{\delta z}\right)(M_1 - M_0). \end{aligned}$$

On the other hand, the flux for $\ell = 3, 4$ are given by monotone 5-points schemes such that $F_3(M_{-1}, M_0, M_1) = F_4(M_1, M_0, M_{-1}))$, and taking the sample particular case of [**?**], we have:

$$\begin{aligned} F_1(M_{-1}, M_0, M_1) &= M_0 + \frac{1}{2}\varphi(M_{-1}, M_0, M_1)\left(1 - \lambda\frac{\delta t}{\delta z}\right)(M_1 - M_0) \\ F_2(M_{-1}, M_0, M_1) &= M_1 - \frac{1}{2}\varphi(M_{-1}, M_0, M_1)\left(1 - \lambda\frac{\delta t}{\delta z}\right)(M_1 - M_0) \\ F_3(M_{-1}, M_0, M_1) &= M_0 + b_0(M_1 - M_0) \\ F_4(M_{-1}, M_0, M_1) &= M_1 - b_0(M_1 - M_0) \end{aligned}$$

From here the partial derivative rules that interest us are given by

$$\begin{aligned} \frac{\partial}{\partial M_{-1}} F_1(M_{-1}, M_0, M_1) &= \mathcal{S}\frac{\partial}{\partial M_{-1}} w(M_{-1}, M_0, M_1) \\ \frac{\partial}{\partial M_{-1}} F_2(M_{-1}, M_0, M_1) &= -\mathcal{S}\frac{\partial}{\partial M_{-1}} w(M_{-1}, M_0, M_1) \\ \frac{\partial}{\partial M_{-1}} F_3(M_{-1}, M_0, M_1) &= \frac{\partial}{\partial M_{-1}} F_4(M_{-1}, M_0, M_1) \;=\; 0 \\ \frac{\partial}{\partial M_0} F_1(M_{-1}, M_0, M_1) &= 1 - \mathcal{M} + \mathcal{S}\frac{\partial}{\partial M_0} w(M_{-1}, M_0, M_1) \\ \frac{\partial}{\partial M_0} F_2(M_{-1}, M_0, M_1) &= \mathcal{M} - \mathcal{S}\frac{\partial}{\partial M_0} w(M_{-1}, M_0, M_1) \\ \frac{\partial}{\partial M_1} F_1(M_{-1}, M_0, M_1) &= \mathcal{M} + \mathcal{S}\frac{\partial}{\partial M_1} w(M_{-1}, M_0, M_1) \\ \frac{\partial}{\partial M_1} F_2(M_{-1}, M_0, M_1) &= 1 - \mathcal{M} - \mathcal{S}\frac{\partial}{\partial M_1} w(M_{-1}, M_0, M_1) \\ \frac{\partial}{\partial M_0} F_3(M_{-1}, M_0, M_1) &= \frac{\partial}{\partial M_1} F_4(M_{-1}, M_0, M_1) \;=\; 1 - b_0 \\ \frac{\partial}{\partial M_1} F_3(M_{-1}, M_0, M_1) &= \frac{\partial}{\partial M_0} F_4(M_{-1}, M_0, M_1) \;=\; b_0. \end{aligned}$$

where

$$\mathcal{S} = \frac{1}{2}\left(1-\lambda\frac{\delta t}{\delta z}\right)(M_1-M_0)\varphi'\circ w(M_{-1},M_0,M_1)$$
$$\mathcal{M} = \frac{1}{2}\left(1-\lambda\frac{\delta t}{\delta z}\right)\varphi\circ w(M_{-1},M_0,M_1),$$

$$\varphi'_{Superbee}(w)=\begin{cases}2 & \text{if } 0\leqslant w<1/2,\\ 1 & \text{if } 1\leqslant w<2,\\ 0 & \text{otherwise}\end{cases}, \qquad \varphi'_{VanLeer}(w)=\frac{2}{(1+w)^2}\text{Heaviside(w)},$$

and because $w=\dfrac{M_0-M_{-1}}{M_1-M_0}$

$$\frac{\partial w}{\partial M_{-1}}=-\frac{1}{M_1-M_0},\qquad \frac{\partial w}{\partial M_0}=\frac{M_1-M_{-1}}{(M_1-M_0)^2},\qquad \frac{\partial w}{\partial M_1}=-\frac{M_0-M_{-1}}{(M_1-M_0)^2}$$

A.4. **Derivative of the deep crypt secretory respect of his parameters.** The deep crypt secretory (dcs) probability density is given by [3]:

$$\rho_{dcs}(z)=(d(z-z_d)+1)\mathbb{1}_{[z_d-1/d,z_d]}(z)+\mathbb{1}_{]z_d,z_u[}(z)+(1+u(z-z_u))\mathbb{1}_{[z_u,z_u-1/u]}(z)$$

where $\mathbb{1}[a,b](z)=H(x-a)-H(x-b)$ is the characteristic function for the interval $[a,b]$. Thus, the derivative of ρ_{dcs} respect of his parameters are given by:

$$\frac{\partial}{\partial d}\rho_{dcs}=(z-z_d)\mathbb{1}_{[z_d-1/d,z_d]}(z) \qquad \frac{\partial}{\partial z_d}\rho_{dcs}=-d\mathbb{1}_{[z_d-1/d,z_d]}(z)$$
$$\frac{\partial}{\partial u}\rho_{dcs}=(z-z_u)\mathbb{1}_{[z_u,z_u-1/u]}(z) \qquad \frac{\partial}{\partial z_u}\rho_{dcs}=-u\mathbb{1}_{[z_d-1/d,z_d]}(z)$$

In the derivative of the cost function we need also to compute the derivative of ρ'_{dcs} respect of the same parameters, which are:

$$\frac{\partial}{\partial d}\rho'_{dcs}=\frac{1}{d}\delta(z-z_d-1/d)+\mathbb{1}_{[z_d-1/d,z_d]}(z) \qquad \frac{\partial}{\partial z_d}\rho_{dcs}=-d(\delta(z-z_d-1/d)-\delta(z-z_d))$$
$$\frac{\partial}{\partial u}\rho_{dcs}=-\frac{1}{u}\delta(z-z_u-1/u)+\mathbb{1}_{[z_u-1/u,z_u]}(z) \qquad \frac{\partial}{\partial z_u}\rho_{dcs}=-u(\delta(z-z_u)-\delta(z-z_u-1/u))$$

Université Paris-Saclay, INRAE, MaIAGE, 78350 Jouy-en-Josas, France
Université Paris-Saclay, Inria Saclay-Ile-de-France, 91120, Palaiseau, France
Email address: marie.haghebaert@inrae.fr

Université Paris-Saclay, INRAE, MaIAGE, 78350 Jouy-en-Josas, France
Université Paris-Saclay, Inria Saclay-Ile-de-France, 91120, Palaiseau, France
Email address: beatrice.laroche@inrae.fr

DIM & CI^{2}MA, Universidad de Concepción, Concepción, Chile
Email address: maursepu@udec.cl