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Chapter 7

Topological Shooting of Solutions for Fickian Diffusion into Core-Shell Geometry

T. G. de Jong and A. E. Sterk

Abstract King et al. (2019) introduced a model for Fickian diffusion into core-shell geometry. The purpose of this model is to study diffusion of oxygen through protective shells encapsulating pancreatic Langerhan islets. These core-shells are of interest for the preparation of artificial pancreas to treat diabetes. In this paper we prove the existence of viable core-shell solutions for King's model using a topological shooting method. The governing equations of the diffusion model can be reduced to a 2-dimensional non-autonomous first order ordinary differential equation. Solutions which correspond to viable core-shell diffusion are required to satisfy global constraints and boundary conditions in both the core and the encapsulating shell. These boundary conditions each give rise to one free parameter. We call solutions satisfying the core boundary condition core solutions. We identify two parameter spaces corresponding to core solution families. The viable core-shell solutions are on the boundary of these two core solution families. Using analytically obtained bounds we apply the intermediate value theorem to prove the existence of core-shell solutions. In addition, we obtain rigorous approximations for the boundary conditions of the viable diffusion core-shell solution.

7.1 Introduction

Type 1 diabetes is a chronic disease that is characterized by the autoimmune system destroying the insulin producing pancreatic langerhan islets. Treatment requires monitoring and maintaining insulin levels. Insulin has to be entered externally into

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the body by means of injections or an insulin pump. Transplantation of pancreatic Langerhan islets might provide a new medical solution for type 1 diabetes patients. The transplanted islets need to be protected from the host immune system while being able to absorb nutrients and secrete insulin. Encapsulation by an alginate membrane seems promising since alginates can be fabricated to selectively diffuse or block certain molecules [7]. In addition, alginates are relatively inert when exposed to mammalian cells [1].

King et al. [9] proposed a mathematical model for Fickian diffusion into core-shell geometry. Specifically, their model describes the diffusion of oxygen through protective shells encapsulating a core of donor cells with the aim of avoiding hypoxia within the core. These core-shells are of interest for the preparation of an artificial pancreas to treat type 1 diabetes. The governing equations of the diffusion model are separated into a core and a shell. Under the assumption of radial symmetry, both diffusion models are described by a 2-dimensional system of 1st-order ODEs. Viable solutions of this model are solutions for which the oxygen levels within the core are above the hypoxia threshold. The existence of such solutions was shown by King et al. using non-rigorous numerics. In addition, their results suggest that these solutions are meagre in the phase space.

The aim of this paper is to prove rigorous results for the diffusion model of King et al. For biologically realistic parameter values taken from [2, 3, 10] we prove that there exists a solution which corresponds to viable diffusion of oxygen in the core-shell. More specifically, the boundary conditions imposed by the model gives rise to one free parameter on each boundary. We call solutions satisfying the core boundary condition core solutions. A topological shooting method is used to shoot these core solutions to the boundary conditions of the shell. For general theory on topological shooting we refer to [8] and for examples of topological shooting we refer to [5, 12]. Furthermore, a non-rigorous approximation of the viable solution is computed numerically to check our rigorous work.

7.2 Model

We briefly review the reaction-diffusion transport model of King et al. [9]. The core-shell is comprised of a core which consists of pancreatic Langerhan islets and a shell which consists of an protective alginate membrane. Based on experimental observations it is assumed that the islets and alginate encapsulation shape are described by a radial variable, see Fig. 7.1.

Assuming Fickian diffusion and Michaelis-Menten consumption a PDE can be derived for the concentration within the core and shell. The assumption that the concentration is described by a radially symmetric steady state solution reduces the concentration equations to an ODE. In [9] the equations are derived for the dimensionless variables. The dimensionless independent radial variable is denoted by ρ . The dependent variables are given by the dimensionless oxygen concentration

Fig. 7.1 Core-shell geometry. The donor cells are represented by the core and the protective alginate is represented by the shell. The core and shell are assumed to be spherical with outer-radius R_1 and R_2 , respectively

for the interior and exterior which are denoted by χ_i and χ_e , respectively. Following [9] the resulting differential equations are

$$\begin{aligned} \frac{2}{\rho} \chi_i' + \chi_i'' - \frac{\nu \chi_i}{\kappa + \chi_i} &= 0, \text{ for } 0 < \rho < \rho_1, \\ \frac{2}{\rho} \chi_e' + \chi_e'' &= 0, \text{ for } \rho_1 < \rho < 1, \end{aligned} \quad (7.1)$$

where $\rho_1 = \frac{R_1}{R_2}$ with R_1, R_2 as given in Fig. 7.1, ν and κ are positive (dimensionless) parameters for Michaelis-Menten consumption and the prime denotes the derivative with respect to ρ . The boundary conditions are given by

$$\begin{aligned} \lim_{\rho \rightarrow 0} \chi_i(\rho) &= a > 0, & \lim_{\rho \rightarrow 0} \chi_i'(\rho) &= 0, & \lim_{\rho \rightarrow 1} \chi_e(\rho) &= 1, \\ \lim_{\rho \rightarrow \rho_1} \chi_i(\rho) &= \lim_{\rho \rightarrow \rho_1} \chi_e(\rho), & \eta \lim_{\rho \rightarrow \rho_1} \chi_i'(\rho) &= \lim_{\rho \rightarrow \rho_1} \chi_e'(\rho), \end{aligned} \quad (7.2)$$

where a is a free parameter and η is the diffusion coefficient quotient of the interior divided by the exterior. Oxygen deprivation of the cells inside the core occurs if χ_i is below or equal to $\chi_* := 4.1 \times 10^{-3}$. In addition, χ_i cannot exceed the dimensionless concentration at the shell's external boundary. Consequently, we obtain the following global condition:

$$\chi_* < \chi_i(\rho) < 1 \quad \forall \rho \in (0, \rho_1). \quad (7.3)$$

The aim of this paper is to prove that given parameters the ν, κ, η , and ρ_1 there exists a solution of the boundary value problem (7.1), (7.2) satisfying (7.3).

Definition 7.2.1 (*Viable core-shell solution*) A solution pair (χ_i, χ_e) of the ODE (7.1) is called a viable core-shell solution if it satisfies boundary conditions (7.2) and global condition (7.3).

In [9] viable core-shell solutions are computed numerically.

7.3 Main Theorem

Our main result concerns the existence of core-shell solutions for biologically realistic parameters:

Theorem 7.3.1 (Existence viable core-shell solution) *For $\rho_1 = 1/2$, $\eta = 22/13$, $\nu = 9$, $\kappa = 5 \cdot 10^{-3}$ the ODE (7.1) has a viable core-shell solution (χ_i, χ_e) as given by Definition 7.2.1. Furthermore, χ_i satisfies*

$$\lim_{\rho \rightarrow 0} \chi_i(\rho) \in \left[\frac{39}{100}, \frac{42}{100} \right], \quad \lim_{\rho \rightarrow \rho_1} \chi_i(\rho) \in \left[\frac{312}{425}, \frac{159}{200} \right].$$

Appendix provides the experimental support for the parameter values in Theorem 7.3.1.

In the remainder of this section Theorem 7.3.1 will be proven. We first reduce the governing equations (7.1) and define a dynamical system with a reduced phase space. Then, we define and prove the existence of so-called core solutions. These core solutions will be used to shoot the viable core-shell solution, Definition 7.2.1. Finally, we formulate the shooting method and give analytical bounds on core solutions which will allow for the implementation of the shooting method.

7.3.1 Reduction Governing Equations

The solution χ_e in (7.1) with boundary condition $\lim_{\rho \rightarrow 1} \chi_e(\rho) = 1$ from (7.2) can be solved analytically:

$$\chi_e(\rho) = 1 - b + \frac{b}{\rho}, \quad (7.4)$$

where b is a free parameter. Note that Definition 7.2.1 imposes a condition on the sign of b :

Proposition 7.3.1 *If (χ_i, χ_e) is a viable core-shell solution as given by Definition 7.2.1, then $b < 0$ in (7.4).*

Proof Observe that $\lim_{\rho \rightarrow \rho_1} \chi_i(\rho) = \lim_{\rho \rightarrow \rho_1} \chi_e(\rho)$ in (7.2) and the upper bound in (7.3) can only be satisfied if $b < 0$. $\square$

The boundary value problem corresponding to (7.1) and (7.2) can be reformulated as a boundary value problem involving only the variable χ_i . For notational convenience denote χ_i by x . In preparation of the dynamical systems analysis we formulate the differential equations corresponding to x given in (7.1) as the first order ODE

$$\begin{aligned} x' &= y, \\ y' &= \frac{\nu x}{\kappa + x} - \frac{2}{\rho} y, \end{aligned} \quad (7.5)$$

with phase space given by

$$M_0 = \{(x, y) \in \mathbb{R}_{>0} \times \mathbb{R}\}.$$

In the reduced setting the boundary conditions (7.2) take the form

$$\lim_{\rho \rightarrow 0} x(\rho) = a > 0, \quad \lim_{\rho \rightarrow 0} y(\rho) = 0, \quad (7.6)$$

$$x(\rho_1) = 1 + \frac{b(1 - \rho_1)}{\rho_1}, \quad y(\rho_1) = -\frac{b\eta}{\rho_1^2}. \quad (7.7)$$

The boundary condition (7.7) was obtained by substituting (7.4) into (7.2). The boundary conditions (7.6), (7.7) give the free parameters a and b .

If (x, χ_e) is a viable core-shell solution then $(x, y) = (x, x')$ is a solution of (7.5) satisfying (7.6), (7.7) and

$$\chi_* < x(\rho) < 1, \quad \forall \rho \in (0, \rho_1). \quad (7.8)$$

Hence, our analysis will be restricted to (7.5). For notational convenience we will denote a solution (x, y) of (7.5) by $\mathbf{x}$. We introduce an equivalent definition for Definition 7.2.1.

Definition 7.3.1 (*Reduced core-shell solution*) A solution $\mathbf{x}$ of (7.5) is called a reduced core-shell solution if it satisfies boundary conditions (7.6), (7.7) and global condition (7.8).

7.3.2 Reduced Phase Space

We will consider (7.5) with phase space

$$M = \{(x, y) \in \mathbb{R}_{>0} \times \mathbb{R}_{>0}\} \subset M_0. \quad (7.9)$$

In Sect. 7.3.4 we will show that the reduced core-shell solution, Definition 7.3.1, exists in M . From an analysis perspective it is easier to work in M since solution curves in M cannot change sign. In addition, we have that:

Lemma 7.3.1 *Let $\mathbf{x}$ be a solution of (7.5) satisfying $\mathbf{x}(\rho_0) \in M$ with $\rho_0 > 0$. Then $\mathbf{x}(\rho) \in M$ for all $\rho \in (\rho_0, \infty)$.*

Proof Let $\rho_s > \rho_0$ be arbitrary. For any C^2 -function $x : [\rho_0, \rho_s] \rightarrow \mathbb{R}$ we define its defect as

$$Px = x'' - f(\rho, x, x') \quad \text{where} \quad f(\rho, x, x') = \frac{vx}{\kappa + x} - \frac{2}{\rho}x'.$$

Note that f is increasing in x and locally Lipschitz in both x and x' .

Assume that $\mathbf{x} = (x, y)$ is a solution of (7.5) such that $x(\rho_0) > 0$ and $x'(\rho_0) = y(\rho_0) > 0$. Define the linear function

$$w(\rho) = \varepsilon(\rho - \rho_0) + x(\rho_0),$$

where

$$0 < \varepsilon \leq \min \left\{ x'(\rho_0), \frac{\rho_0}{2} \cdot \frac{vx(\rho_0)}{\kappa + x(\rho_0)} \right\}.$$

Then, for $\rho \in [\rho_0, \rho_s]$ we have that

$$f(\rho, w, w') \geq \frac{vw(\rho_0)}{\kappa + w(\rho_0)} - \frac{2\varepsilon}{\rho_0} \geq 0.$$

In conclusion, we have the following inequalities:

$$w(\rho_0) \leq x(\rho_0), \quad w'(\rho_0) \leq x'(\rho_0), \quad Pw \leq 0 = Px \quad \forall \rho \in [\rho_0, \rho_s].$$

The Comparison Theorem [14, Theorem 11.XVI] implies that

$$x(\rho) \geq w(\rho) > 0 \quad \text{and} \quad y(\rho) = x'(\rho) \geq w'(\rho) = \varepsilon > 0 \quad \forall \rho \in [\rho_0, \rho_s].$$

This shows that $\mathbf{x}(\rho) \in M$ for all $\rho \in [\rho_0, \rho_s]$. Since $\rho_s > \rho_0$ is arbitrary, the proof is complete. $\square$

7.3.3 Core Solutions

We will apply topological shooting to solutions that satisfy the local conditions corresponding to $\rho \rightarrow 0$ in (7.6). Consequently, we introduce:

Definition 7.3.2 (*Core solution*) A solution $\mathbf{x}$ of (7.5) is called a core solution if it satisfies (7.6). A core solution $\mathbf{x} = (x, y)$ satisfying $\lim_{\rho \rightarrow 0} x(\rho) = a > 0$ is denoted by $\mathbf{x}_a$.

We will show that the range of $\mathbf{x}_a$ corresponds to an invariant manifold. Observe that the vector field corresponding to (7.6) is not defined for $\rho \rightarrow 0$. We will introduce

variables such that the new governing equations are autonomous and have equilibria corresponding to the limits in (7.6).

7.3.3.1 Change of Variables

Define the new independent variable t by setting $\rho = e^t$ so that the limit $\rho \rightarrow 0$ corresponds to the limit $t \rightarrow -\infty$. Denote by the sup-dot the derivative with respect to t . If $\hat{x}(t) = x(e^t)$, $\hat{y}(t) = e^t y(e^t)$, then

$$\begin{aligned}\dot{\hat{x}}(t) &= e^t y(e^t) \\ &= \hat{y}(t), \\ \dot{\hat{y}}(t) &= e^t y(e^t) + e^{2t} y'(e^t) \\ &= -\hat{y} + \frac{v\hat{x}e^{2t}}{\kappa + \hat{x}}.\end{aligned}$$

We introduce the variable $\hat{z} = e^{2t}$. Hence, the first order ODE (7.5) can be written as an autonomous system:

$$\begin{aligned}\dot{\hat{x}} &= \hat{y}, \\ \dot{\hat{y}} &= -\hat{y} + \frac{v\hat{x}\hat{z}}{\kappa + \hat{x}}, \\ \dot{\hat{z}} &= 2\hat{z}.\end{aligned}\tag{7.10}$$

It follows from (7.6), (7.7) and M in (7.9) that the new phase space becomes

$$N := \{(\hat{x}, \hat{y}, \hat{z}) \in \mathbb{R}_{>0} \times \mathbb{R}_{>0} \times (0, e^{2\rho_1})\}.$$

7.3.3.2 Formulation in Terms of Unstable Manifolds

Observe that the limit in (7.6) corresponds to

$$\lim_{t \rightarrow -\infty} (\hat{x}, \hat{y}, \hat{z})(t) = (a, 0, 0).$$

We have that $q(a) := (a, 0, 0) \notin N$. Therefore, we consider the closure of N as phase space which will be denoted by $\bar{N}$. The Jacobian matrix of (7.10) evaluated at $q(a)$ has eigenvalues $\lambda_1 = 0$, $\lambda_2 = -1$, and $\lambda_3 = 2$. The eigenvector corresponding to λ_1 and λ_3 will be of importance:

$$\mathbf{v}_1 = (1, 0, 0)^T, \quad \mathbf{v}_3 = \left(\frac{av}{6(a + \kappa)}, \frac{av}{3(a + \kappa)}, 1 \right)^T. \tag{7.11}$$

Denote the unstable, stable and center manifold corresponding to $q(a)$ by $W^u(q(a))$, $W^s(q(a))$ and $W^c(q(a))$. The invariant manifolds $W^u(q(a))$, $W^s(q(a))$, $W^c(q(a))$ are one dimensional. Denote by $\mathcal{W}^c$ the union of all center manifolds.

Lemma 7.3.2 *We have that $\mathcal{W}^c = \{(\hat{x}, 0, 0) : \hat{x} > 0\}$.*

Proof Observe that $W^c(q(a))$ in the $\hat{z}$ -direction is 0 since otherwise $W^c(q(a))$ would exhibit dynamics corresponding to $W^u(q(a))$. Then, $W^c(q(a))$ must also equal zero in the $\hat{y}$ -direction since otherwise $W^c(q(a))$ would exhibit dynamics corresponding to the stable manifold $W^s(q(a))$. Hence, we have that $W^c(q(a)) \subset \{(\hat{x}, 0, 0) \in \mathbb{R}^3 : \hat{x} > 0\}$. Consequently, we obtain that $\mathcal{W}^c = \{(\hat{x}, 0, 0) \in \mathbb{R}^3 : \hat{x} > 0\}$. $\square$

The invariant manifold $W^u(q(a))$ will be used to construct core solutions. We define $\Psi : N \rightarrow M \times \mathbb{R}_{>0}$ given by

$$\Psi(\hat{x}, \hat{y}, \hat{z}) = \left((\hat{x}, \hat{y}/\sqrt{\hat{z}}, \sqrt{\hat{z}}) \right).$$

Lemma 7.3.3 *There exists a local unstable manifold $W_{\text{loc}}^u(q(a))$ such that $W_{\text{loc}}^u(q(a)) \cap N$ is non-empty and connected.*

Proof The components of $\mathbf{v}_3$ have the same sign. Hence, any $W_{\text{loc}}^u(q(a))$ intersects N . It follows from the smoothness of $W_{\text{loc}}^u(q(a))$ at $q(a)$ that sufficiently close to $q(a)$ the manifold $W_{\text{loc}}^u(q(a))$ is connected. $\square$

Take $W_{\text{loc}}^u(q(a))$ as in Lemma 7.3.3. Denote the invariant manifold generated from $W_{\text{loc}}^u(q(a)) \cap N$ using the forward flow by $W_+^u(q(a))$.

Lemma 7.3.4 *$W_+^u(q(a))$ is non-empty and connected. Furthermore, we have that $W_+^u(q(a)) \subset N$.*

Proof From Lemma 7.3.2 it follows that $W_+^u(q(a))$ is non-empty. From Lemma 7.3.1 and Lemma 7.3.2 it follows that $W_+^u(q(a))$ is connected. The manifold $W_+^u(q(a))$ is generated from $W_{\text{loc}}^u(q(a)) \cap N$. Hence, using Lemma 7.3.1 we get that $W_+^u(q(a)) \subset N$. $\square$

Theorem 7.3.2 *$\{(\mathbf{x}(\rho), \rho) : \rho \in (0, \rho_1)\} = \Psi(W_+^u(q(a)))$ if and only if $\mathbf{x} = \mathbf{x}_a$ is a core solution as given in Definition 7.3.2.*

Proof ($\Rightarrow$) Observe that we only need to prove that $\mathbf{x} = (x, y)$ satisfies (7.6). It follows from Lemma 7.3.4 that $W_+^u(q(a))$ is a non-empty, connected invariant manifold. Hence, there exists a solution $(\hat{x}, \hat{y}, \hat{z})$ with range $W_+^u(q(a))$. Observe that $\lim_{\rho \rightarrow 0} x(\rho) = \lim_{t \rightarrow -\infty} \hat{x}(t) = 0$. We have that

$$\lim_{\rho \rightarrow 0} y(\rho) = \lim_{t \rightarrow 0} \frac{\hat{y}(t)}{\sqrt{\hat{z}(t)}}.$$

From $\mathbf{v}_3$ it follows that $\frac{av}{3(a+\kappa)}\hat{y}(t) \sim \hat{z}(t)$ for $t \ll 1$. Hence, we have that

$$\lim_{t \rightarrow 0} \frac{\hat{y}(t)}{\sqrt{\hat{z}(t)}} = 0.$$

($\Leftarrow$) Since $\mathbf{x}$ is a core solution and since $t \rightarrow -\infty$ is equivalent to $\rho \rightarrow 0$ one of the following must be true:

- (i) $\Psi(W_{\text{loc}}^c(q(a)) \cap N) \subset \{(\mathbf{x}(\rho), \rho) : \rho \in (0, \rho_1)\}$,
- (ii) $\Psi(W_{\text{loc}}^u(q(a)) \cap N) \subset \{(\mathbf{x}(\rho), \rho) : \rho \in (0, \rho_1)\}$.

From Lemma 7.3.2 it follows that (i) is not true. Hence, (ii) is true. The global version of $W_{\text{loc}}^u(q(a)) \cap N$ is given by $W_+^u(q(a))$. From Lemma 7.3.4 we get that $W_+^u(q(a)) \subset N$. Consequently, we obtain that $\{(\mathbf{x}(\rho), \rho) : \rho \in (0, \rho_1)\} = \Psi(W_+^u(q(a)))$. $\square$

Denote by $\mathcal{W}^{cu}$ the center unstable manifold induced by $\mathcal{W}^c$.

Lemma 7.3.5 *There exists a smooth map $f : \mathbb{R}_{>0} \times [0, e^{2\rho_1}) \rightarrow \mathbb{R}^2$ satisfying $(f(a, 0), 0) = q(a)$ and such that*

$$\mathcal{W}^{cu} = \{(f(a, z), z) \in \overline{N} : (a, z) \in \mathbb{R}_{>0} \times [0, e^{2\rho_1})\}.$$

Proof To avoid working with clopen sets we first extend the phase space for (7.10) to $\hat{N} := \{(\hat{x}, \hat{y}, \hat{z}) \in \mathbb{R}_{>0} \times \mathbb{R} \times (-e^{2\rho_1}, e^{2\rho_1})\}$. We will show that:

Claim: There exists a neighbourhood $U \subset \mathbb{R}^3$ of $q(a)$, a neighbourhood $V \subset \mathbb{R}^2$ of $(a, 0)$, and a smooth $f_{\text{loc}} : V \rightarrow \mathbb{R}^2$ satisfying

$$\begin{aligned} \mathcal{W}^{cu} \cap U &= \{(f_{\text{loc}}(a, z), z) \in \hat{N} : (a, z) \in V\}, \\ (f_{\text{loc}}(a, 0), 0) &= q(a) \quad \forall (a, 0) \in V. \end{aligned}$$

From the claim it follows that the parametrization exists in a local neighbourhood of $q(a)$. The local parametrization can be extended using transitivity of the flow and the property that solutions of the system (7.10) satisfying $\hat{z} \neq 0$ can be smoothly parametrized in the $\hat{z}$ -variable. Which proves the lemma. To show the claim observe that the tangent space of $\mathcal{W}^{cu}(q(a))$ at $q(a)$ is $\text{span}(\mathbf{v}_1, \mathbf{v}_3)$. The $\hat{x}$ -component of $\mathbf{v}_1$ is non-zero and the $\hat{z}$ -component of $\mathbf{v}_3$ is non-zero. Hence, using the implicit function theorem the claim follows. $\square$

Corollary 7.3.1 *For all $a \in \mathbb{R}_{>0}$ there exists a unique core solution $\mathbf{x}_a$ specified by Definition 7.3.2. In addition, the map $G : a \mapsto \mathbf{x}_a$ is continuous in a .*

Proof Uniqueness of $\mathbf{x}_a$ follows from Theorem 7.3.2. Consider $\mathcal{W}^{cu} \cap N$ foliated by solutions curves, applying the transformation Ψ and using Lemma 7.3.5 gives that the map $G : a \mapsto \mathbf{x}_a$ is continuous in a . $\square$

7.3.4 Shooting Method

We consider a closed connected $U \subset M$. We use the boundary conditions at $\rho = \rho_1$ given by (7.7) to divide U into three subsets given by

$$\begin{aligned} A(U) &:= \left\{ (x, y) \in U : x < 1 - \frac{y\rho_1(1 - \rho_1)}{\eta} \right\}, \\ B(U) &:= \left\{ (x, y) \in U : x > 1 - \frac{y\rho_1(1 - \rho_1)}{\eta} \right\}, \\ X(U) &:= U \setminus (A(U) \cup B(U)). \end{aligned} \quad (7.12)$$

We then arrive at the shooting lemma:

Lemma 7.3.6 *Let $\mathbf{x}_a = (x_a, y_a)$ be a core solution as given by Definition 7.3.2. If there exist $a_1, a_2 \in [\chi_*, 1]$ with $a_1 < a_2$, $U \subset M$ such that*

$$\mathbf{x}_{a_1}(\rho_1) \in A(U), \quad \mathbf{x}_{a_2}(\rho_1) \in B(U), \quad (7.13)$$

$$\mathbf{x}_a(\rho_1) \in U, \quad (7.14)$$

then there exists an $a_ \in (a_1, a_2)$ such that $\mathbf{x}_{a_*}(\rho_1) \in X(U)$ and $\mathbf{x}_{a_*}$ is a reduced core-shell solution as specified by Definition 7.3.1.*

The conditions in Lemma 7.3.6 are visualised in Fig. 7.2. In the next section Lemma 7.3.6 will be applied by computing explicit bounds on a domain.

Proof Theorem 7.3.2 implies that $G : a \mapsto \mathbf{x}_a$ is continuous. Hence, it follows from applying the intermediate value theorem and using (7.13), (7.14) that there exists an

Fig. 7.2 Conditions of Lemma 7.3.6 for an example set. U is given by the rectangle which is subdivided into: $A(U)$, white area, $B(U)$, dark grey, and $X(U)$, light grey line. In addition, we have continued $X(U)$ beyond U with a dashed line to show the intersection points with axes. Observe that the core solutions $\mathbf{x}_a$ with $a \in [a_1, a_2]$ satisfy the conditions (7.13), (7.14) of Lemma 7.3.6

$a_* \in (\chi_*, 1)$ such that $\mathbf{x}_{a_*}(\rho_1) \in X(U)$. Then, $\mathbf{x}_{a_*}$ satisfies the boundary condition (7.7). Observe that $\lim_{\rho \rightarrow 0} x_a(\rho) \geq \chi_*$ for all $a \in (a_1, a_2)$. Since $\mathbf{x}_{a_*}(\rho_1) \in X(U)$, it follows that $x_{a_*}(\rho_1) < 1$. Then, using the increasing monotonicity on x_a from Lemma 7.3.1 it follows that $\mathbf{x}_{a_*}$ satisfies the global condition (7.8). Consequently, $\mathbf{x}_{a_*}$ is a reduced core-shell solution. $\square$

We will compute analytical bounds on $\mathbf{x}_a = (x_a, y_a)$. For the parameters of Theorem 7.3.1 these bounds allow us to apply Lemma 7.3.6. We define

$$\mathcal{B}(a, \rho) := \left\{ (x, y) \in \mathbb{R}^2 : \frac{va\rho^2}{6(\kappa + a)} \leq x - a \leq \frac{v\rho^2}{6}, \frac{va\rho}{3(\kappa + a)} \leq y \leq \frac{v\rho}{3} \right\}.$$

Lemma 7.3.7 *We have that $\mathbf{x}_a(\rho) \in \mathcal{B}(a, \rho)$.*

Proof Consider the term $\frac{x_a}{\kappa + x_a}$, using Lemma 7.3.1 we obtain an under bound for $\frac{x_a}{\kappa + x_a}$ and using the positivity of x_a and κ we obtain an upper bound:

$$\frac{a}{\kappa + a} \leq \frac{x_a}{\kappa + x_a} \leq 1. \quad (7.15)$$

From the y -equation in (7.5) it follows that

$$(y_a \rho^2)' = \frac{vx_a \rho^2}{\kappa + x_a}. \quad (7.16)$$

Applying the bounds (7.15) to (7.16) we obtain the bounds:

$$\frac{va\rho}{3(\kappa + a)} \leq y_a \leq \frac{v\rho}{3}. \quad (7.17)$$

From the x -equation in (7.5) and using (7.17) we obtain:

$$\frac{va\rho^2}{6(\kappa + a)} \leq x_a - a \leq \frac{v\rho^2}{6}. \quad (7.18)$$

$\square$

Proof (Theorem 7.3.1) To apply Lemma 7.3.6 we will show the following:

Claim. Given the parameters of Theorem 7.3.1 there exist $a_1, a_2 \in [\chi_*, 1]$ such that

$$\chi_* < x \quad \forall (x, y) \in U. \quad (7.19)$$

$$\mathcal{B}(a_1, 1/2) \subset A(U), \quad \mathcal{B}(a_2, 1/2) \subset B(U), \quad (7.20)$$

$$\mathcal{B}(a, 1/2) \subset U, \quad \forall a \in [a_1, a_2], \quad (7.21)$$

It follows from Lemma 7.3.7 that the Claim proves Theorem 7.3.1. We continue with a proof of the claim. Take $a_1 = \frac{39}{100}$, $a_2 = \frac{42}{100}$ and $U = \left[\frac{312}{425}, \frac{159}{200} \right] \times \left[\frac{117}{170}, \frac{3}{4} \right]$. By choice

of U we have that (7.19) is satisfied. The property (7.20) follows directly from the definition of $\mathcal{B}$. Finally, (7.21) can be shown by applying $\mathcal{B}$ on $[a_1, a_2] \times [1/2, 1/2]$ and using interval arithmetic to obtain bounds on the resulting domain. For readers unfamiliar with interval arithmetic we refer to [13]. $\square$

7.4 Numerical Validation

The numerically computed viable core-shell solution corresponding to Theorem 7.3.1 is displayed in Fig. 7.3. Recall $A(U)$, $B(U)$, $X(U)$ defined in (7.12) and visualized in Fig. 7.2. Shooting core solutions, Definition 7.3.2, we approximated $a \in X(U)$ by using that a is on the boundary of $A(U)$ and $B(U)$. This gives the χ_i -solution. The numerical method is similar to those applied in [6, 8]. The connecting χ_e -solution was computed using (7.4).

The numerical solution satisfies $\lim_{\rho \rightarrow 0} \chi_i(\rho) \approx 0.4087 \in [\frac{39}{100}, \frac{42}{100}]$ and $\lim_{\rho \rightarrow 1/2} \chi_i(\rho) \approx 0.7802 \in [\frac{312}{425}, \frac{159}{200}]$ which is in accordance with the bounds in Theorem 7.3.1.

7.5 Conclusion

In this paper we considered a mathematical model for Fickian diffusion into core-shell geometry proposed by King et al. [9]. In particular, we proved the existence of a solution which corresponds to viable diffusion of oxygen in the core-shell for biologically realistic parameters. The main ingredient of the proof is an implementation of a fully analytical topological shooting method.

Fig. 7.3 Numerically computed viable core-shell solution (χ_i, χ_e)

The analytically computed bounds from Lemma 7.3.7 give a good approximation of solutions for application of the shooting lemma, Lemma 7.3.6, since κ in Theorem 7.3.1 is relatively small compared to the bounds on $\lim_{\rho \rightarrow 0} \chi_i(\rho)$ in Theorem 7.3.1. For κ outside this regime rigorous numerics could be used to approximate core solutions for application of the shooting lemma.

The model by King et al. [9] only considers dynamics of the oxygen concentration inside the core-shell. Biologically, the consumption of glucose and production of insulin are important to obtain an accurate model for an artificial pancreas. Buchwald [4] presents a local glucose-and oxygen concentration-based insulin secretion model for pancreatic islets. The model by Buchwald could be considered in the core-shell setting. This new model would be an extension of the model by King et al. The governing equations will be higher dimensional and will have more parameters. Hence, we expect that this will lead to more complex dynamics. Both the analytical and numerical investigation of such a model is an interesting topic for future research.

Appendix: Parameters

We show that the parameters in Theorem 7.3.1 correspond to the parameters in an experimental setting. From the experimental results in [10] we observe that the following radii are viable: $R_1 = 135 \mu\text{m}$, $R_2 = 270 \mu\text{m}$. Consequently, we have that $\rho = R_1/R_2 = 1/2$. For the diffusion coefficient of the Langerhan islets we have that $D_i = 1.3 \cdot 10^{-9} \text{ m}^2/\text{s}$ [2] and for the diffusion coefficient of the alginate (in vivo, intraperitoneal) we have that $D_e = 2.2 \cdot 10^{-9} \text{ m}^2/\text{s}$ [11]. Hence, we obtain that $\eta = \frac{22}{13}$. The dimensionless Michaelis-Menten parameters are determined from

$$\nu = \frac{V_m R_2^2}{D_i C_2}, \quad \kappa = \frac{K_m}{C_2}, \quad (7.22)$$

with V_m the Michaelis-Menten maximum consumption rate, K_m the Michaelis constant and C_2 the ambient oxygen concentration. For a derivation of (7.22) see [9]. We consider the following parameters used by [3]: $V_m = 3.4 \cdot 10^{-2} \text{ mol}/\text{m}^3\text{s}$, $K_m = 1.0 \cdot 10^{-3} \text{ mol} \cdot \text{m}^{-3}$, $C_2 = 0.20 \text{ mol}/\text{m}^3$. Hence, we obtain that $\nu \approx 9$ and $\kappa = 5 \cdot 10^{-3}$.

References

1. Augst, A.D., Kong, H.J., Mooney, D.J.: Alginate hydrogels as biomaterials. *Macromol. Biosci.* **8**(6), 623–633 (2006)
2. Avgoustiniatos, E.S., Dionne, K.E., Wilson, D.F., Yarmush, M.L.: Measurements of the effective diffusion coefficient of oxygen in pancreatic islets. *Ind. Eng. Chem. Res.* **46**(19), 6157–6163 (2007)

3. Buchwald, P.: FEM-based oxygen consumption and cell viability models for avascular pancreatic islets. *Theor. Biol. Med. Model.* **6**(5) (2009)
4. Buchwald, P.: A local glucose-and oxygen concentration-based insulin secretion model for pancreatic islets. *Theor. Biol. Med. Model* **8**(20) (2011)
5. De Jong, T.G., Sterk, A.E., Broer, H.W.: Fungal tip growth arising through a codimension-1 bifurcation. *Int. J. Bifurc. Chaos* (2020)
6. De Jong, T.G., Sterk, A.E., Guo, F.: Numerical method to compute hypha tip growth for data driven validation. *IEEE Access* **7**, 53766–53776 (2019)
7. Goosen, M.F., O'Shea, G.M., Gharapetian, H.M., Chou, S., Sun, A.M.: Optimization of microencapsulation parameters: semipermeable microcapsules as a bioartificial pancreas. *Biotechnol. Bioeng.* **2**(27) (1985)
8. Hastings, S.P., McLeod, J.B.: *Classical Methods in Ordinary Differential Equations*. AMS, Rhode Island (2012)
9. King, C.C., Brown, A.A., Sargin, I., Bratlie, K.M., Beckman, S.P.: Modelling of reaction-diffusion transport into core-shell geometry. *J. Theor. Biol.* **260**, 204–208 (2019)
10. Ma, M., Chiu, A., Sahay, G., Doloff, J.C., Dholakia, N., Thakrar, R., Cohen, J., Vegas, A., Chen, D., Bratlie, K.M., Dang, T., York, R.L., Hollister-Lock, J., Weir, G.C., Anderson, D.G.: Core-shell hydrogel microcapsules for improved islets encapsulation. *Adv. Healthc. Mater.* **2**(5) (2013)
11. Najdahmadi, A., Lakey, J.: Diffusion coefficient of alginate microcapsules used in pancreatic islet transplantation, a method to cure type 1 diabetes. In: *Proceedings of SPIE* (2018)
12. Peletier, L.A., Troy, W.C.: A topological shooting method and the existence of kinks of the extended Fisher-Kolmogorov equation. *Topol. Methods Nonlinear Anal.* **6**(2), 331–355 (1995)
13. Tucker, W.: *Validated Numerics: A Short Introduction to Rigorous Computations*. Princeton University Press (2011)
14. Walter, W.: *Ordinary Differential Equations*. Springer (1998)