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Description of adhering with saturation using boundary conditions of hysteresis type☆

N.D. Botkin[a,*], K.-H. Hoffmann[a], A.M. Meirmanov[b], V.N. Starovoitov[a]

[a] *Center of Advanced European Studies and Research (caesar), Ludwig-Erhard-Allee 2, 53175 Bonn, Germany*
[b] *Ugra Research Institute of Information Technologies, Mira street 153, Hanty-Mansiisk, 628011 Russian Federation*

Abstract

The problem considered in this paper is related to the development of biosensors which serve for the quantitative detection of proteins in solutions. An important part of such sensors is a wet cell, say a tiny box, filled with water into which a solution containing a protein to be detected is injected. Special molecules called aptamers are immobilized on the bottom of the wet cell. The aptamers can selectively bind the desired protein from the solution. The change of the surface mass loading can be analyzed using acoustic waves propagating along the aptamer layer. Thus, the concentration of the protein in the solution can be estimated. In this paper, a model describing the propagation of the protein in the wet cell and its adherence to the aptamer is proposed. It is assumed for simplicity that the propagation of the injected protein is governed by a diffusion equation. The central point of the model is a boundary condition of hysteresis type posed on the bottom of the wet cell. This condition provides the monotone growth with saturation of the surface concentration of the deposited protein. The monotonicity reflects non-detachment of already adhered protein molecules, whereas the saturation corresponds to the exhaustion of free aptamer molecules. We prove the existence and the uniqueness of solutions to this problem, study their regularity, and perform numerical simulations that clarify their behavior.

Keywords: Biosensors; Diffusion with adherence; Boundary hysteresis operators

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[*] Corresponding author.
E-mail address: botkin@caesar.de (N.D. Botkin).

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1. Mathematical model and main result

Let $\Omega = (0, 1)^3$ be the open unit cube in $\mathbb{R}^3$ (the wet cell), and $\partial\Omega$ the boundary of Ω. Let $\Gamma = \{\boldsymbol{x} \in \partial\Omega | x_3 = 0\}$ be the part of $\partial\Omega$ occupied by the aptamer. Note that the thickness of the aptamer layer is negligibly small ($\approx 4 \times 10^{-9}$ m).

The mathematical formulation is as follows:

$$\boldsymbol{x} \in \Omega, \quad t \in [0, T] : \; u_t = \Delta u, \tag{1}$$

$$t = 0 : \; u = u^0, \quad \eta = \eta^0, \tag{2}$$

$$\partial\Omega\backslash\Gamma : \; \frac{\partial u}{\partial \nu} = 0, \tag{3}$$

$$\Gamma : \; \eta_t = -\frac{\partial u}{\partial \nu}, \quad \eta = \mathscr{A}(\gamma_0 u). \tag{4}$$

Here, u is the protein volume fracture scaled to avoid very small typical physical values ($\approx 10^{-8}$) so that u can be greater than one; η is the surface concentration of the adhered protein on Γ (this variable assumes values between 0 and 1); $\gamma_0 : H^1(\Omega) \to H^{1/2}(\Gamma)$ is the trace operator; and $\mathscr{A}$ is a hysteresis operator defined by the relation

$$\mathscr{A}(v)(t) = \operatorname{ess\,sup}\{H(v(\tau)) : \; \tau \leqslant t\},$$

where the function H is defined as is shown in Fig. 1a, The action of the operator $\mathscr{A}$ is shown schematically in Fig. 1b.

Remark. We omit the symbol γ_0 whenever this does not lead to confusion.

Denote $\Omega_T = \Omega \times [0, T]$ and $\Gamma_T = \Gamma \times [0, T]$. Let d$s$ be the two-dimensional Lebesgue measure.

Definition 1.1. A pair of functions u, η such that

$$u \in H^1(\Omega_T), \quad u|_{t=0} = u^0, \quad \eta \in L^\infty(\Gamma_T), \quad \eta_t \in L^2(\Gamma_T)$$

is a generalized solution to Problem (1)–(4) if

$$\eta(\boldsymbol{x}, t) = \mathscr{A}(u(\boldsymbol{x}, \cdot))(t)$$

for almost all $(\boldsymbol{x}, t) \in \Gamma_T$, and the integral identity

$$\int_0^T \int_\Omega (u_t \psi + \nabla u \cdot \nabla \psi)\, \mathrm{d}\boldsymbol{x}\, \mathrm{d}t - \int_0^T \int_\Gamma \eta \psi_t \, \mathrm{d}s\, \mathrm{d}t + \int_\Gamma \eta^0 \psi^0 \, \mathrm{d}s = 0$$

holds for every smooth function ψ with $\psi|_{t=T} = 0$. Here $\psi^0 = \psi|_{t=0}$ and $\eta^0 = \eta|_{t=0}$.

The main result of this paper is the following theorem.

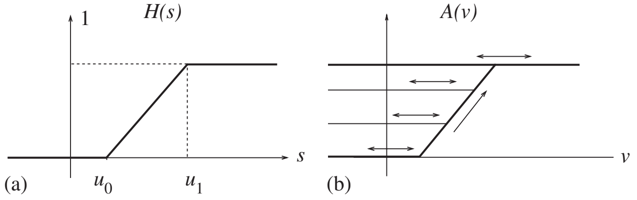

Fig. 1. Schematic representation of the operator $\mathscr{A}$.

Theorem 1.1. *Let* $u^0 \in H^1(\Omega) \cap L^\infty(\Omega)$, $u^0 \geqslant 0$, *and* η^0 *be a measurable function such that* $\eta^0(\boldsymbol{x}) = H(u^0(\boldsymbol{x}))$ *for* $\boldsymbol{x} \in \Gamma$. *Then there exists a unique generalized solution to Problem* (1)–(4) *such that*

$$u_t, \quad \Delta u \in L^2(\Omega_T), \quad u_x \in L^\infty(0, T; L^2(\Omega)),$$

$$0 \leqslant u \leqslant \|u^0\|_{L^\infty(\Omega)}, \quad \eta_t \in L^2(\Gamma_T), \quad \eta \in H^{1/2}(\Gamma_T).$$

Remark. The condition $\eta^0 = H(u^0)$ is not important and can be omitted. Nevertheless, this relation simplifies mathematical calculations.

Bibliographical remark. Problems with hysteresis were considered in numerous publications. We refer to the books [1–3,5] for surveys in this theory. The common feature of the investigations cited is that the regularizing term $\varepsilon\,\partial u/\partial t$ is being added to the boundary condition (4) to improve the regularity of $u|_\Gamma$ with respect to t. Thus, the boundary condition on Γ is as follows:

$$\varepsilon \frac{\partial u}{\partial t} + \eta_t = -\frac{\partial u}{\partial \nu}, \quad \eta = \mathscr{A}(u).$$

A technique proposed in this paper allows us to handle the singular case, $\varepsilon = 0$.

2. Sketch of the proof of the main result

The proof of Theorem 1.1 is rather complicated technically and cannot be reproduced within a short paper. The aim of this section is to present new ideas that enable us to extend conventional results.

2.1. Proof of the existence

Use the following implicit time discretization scheme to approximate Problem (1)–(4). Fix arbitrary $N \in \mathbb{N}$ and set $\tau = T/N$. Consider the following problem for u^n, $n \in \{1, 2, \ldots, N\}$:

$$u^n - u^{n-1} = \tau \Delta u^n, \quad \boldsymbol{x} \in \Omega, \tag{5}$$

$$\eta^n - \eta^{n-1} = -\tau \frac{\partial u^n}{\partial \nu}, \quad \boldsymbol{x} \in \Gamma, \tag{6}$$

$$\frac{\partial u^n}{\partial \nu} = 0, \quad \boldsymbol{x} \in \partial\Omega \backslash \Gamma, \tag{7}$$

where

$$\eta^n(\boldsymbol{x}) = \max_{k \in \{0,1,\dots,n\}} H(u^k(\boldsymbol{x})), \quad \boldsymbol{x} \in \Gamma. \tag{8}$$

Denote

$$\zeta^n(\boldsymbol{x}) = \max_{k \in \{0,1,\dots,n\}} H(u^k(\boldsymbol{x})), \quad \boldsymbol{x} \in \Omega. \tag{9}$$

It is obvious that $\eta^n = \gamma_0 \zeta^n$.

For every $N \in \mathbb{N}$, let $u_N(\boldsymbol{x}, t)$, $\eta_N(\boldsymbol{x}, t)$, and $\zeta_N(\boldsymbol{x}, t)$ be piecewise linear time interpolations of $\{u^n(\boldsymbol{x})\}$, $\{\eta^n(\boldsymbol{x})\}$, and $\{\zeta^n(\boldsymbol{x})\}$, respectively. Remember that the piecewise linear interpolation of $\{u^n(\boldsymbol{x})\}$ is defined as follows:

$$u_N(\boldsymbol{x}, t) = u^n(\boldsymbol{x}) \left(1 - n + \frac{t}{\tau}\right) + u^{n-1}(\boldsymbol{x}) \left(n - \frac{t}{\tau}\right), \quad \text{if } t \in [(n-1)\tau, n\tau].$$

Adopting conventional techniques to the problem under consideration yields the existence of limiting functions

$$u = \lim_{N \to \infty} u_N, \quad \eta = \lim_{N \to \infty} \eta_N \quad \text{and} \quad \zeta = \lim_{N \to \infty} \zeta_N$$

that possess the following regularities:

$$\begin{aligned} &u \in H^1(0, T; L^2(\Omega)) \cap L^\infty(0, T; H^1(\Omega)), \quad \Delta u \in L^2(\Omega_T), \\ &\zeta \in H^1(0, T; L^2(\Omega)) \cap L^\infty(0, T; H^1(\Omega)), \\ &\eta \in H^1(0, T; L^2(\Gamma)) \cap L^\infty(0, T; H^{1/2}(\Gamma)), \end{aligned}$$

and satisfy the equations:

$$\frac{\partial u}{\partial t} = \Delta u \quad \text{in } L^2(\Omega_T), \tag{10}$$

$$\frac{\partial \eta}{\partial t} = -\frac{\partial u}{\partial \nu} \quad \text{in } L^2(0, T; H^{-1/2}(\Gamma)), \tag{11}$$

$$\frac{\partial u}{\partial \nu} = 0 \quad \text{in } L^2(0, T; H^{-1/2}(\partial\Omega \backslash \Gamma)), \tag{12}$$

$$\eta = \gamma_0 \zeta \quad \text{in } L^\infty(0, T; H^{1/2}(\Gamma)). \tag{13}$$

Moreover,

$$\zeta(\boldsymbol{x}, t) = \mathscr{A}(u(\boldsymbol{x}, \cdot))(t) \quad \text{for almost all } (\boldsymbol{x}, t) \in \Omega_T. \tag{14}$$

In view of Eqs. (13) and (14), it remains to prove only that

$$\gamma_0 \mathscr{A}(u)(t) = \mathscr{A}(\gamma_0 u)(t) \quad \text{for almost all } t \in [0, T]. \tag{15}$$

The next lemma states the continuity of u in domains separated from the hyperplain $t = 0$. The assertion of the lemma follows (not quite immediately) from Theorem 1.7 of [4].

Lemma 2.1. *For every $\delta > 0$, there exists $\alpha \in (0, 1)$ such that $u \in C^{\alpha,\alpha/2}(\overline{Q})$, where Q is an arbitrary domain such that $Q \subset \Omega_T \cap \{(\boldsymbol{x}, t) : t > \delta\}$.*

For every $\delta > 0$, introduce the following operator

$$\mathscr{A}_\delta(v)(t) = \begin{cases} 0 & t < \delta, \\ \operatorname*{ess\,sup}\limits_{\delta \leqslant s \leqslant t} H(v(s)) & t \geqslant \delta, \end{cases}$$

defined for functions $v \in L^\infty(0, T)$. Since u is continuous in $\overline{\Omega} \times [\delta, T]$, the following is true:

$$\gamma_0 \mathscr{A}_\delta(u)(t) = \mathscr{A}_\delta(\gamma_0 u)(t) \quad \text{for all } t \in [0, T]. \tag{16}$$

Note that $\mathscr{A}(v)(t) = \|v\|_{L^\infty(0,t)}$ for any nonnegative function $v \in L^\infty(0, T)$, and $\mathscr{A}_\delta(v)(t) = \|\chi_\delta v\|_{L^\infty(0,t)}$, where $\chi_\delta : \mathbb{R} \to \{0, 1\}$ is the characteristic function of the interval (δ, T). It is clear that $\mathscr{A}(v)(t) \geqslant \mathscr{A}_\delta(v)(t)$. On the other hand, $\mathscr{A}(v)(t) \leqslant \liminf_{\delta\to 0} \mathscr{A}_\delta (v)(t)$ due to the $*$ weak semi-continuity of the norm in L^∞. The two last inequalities provide

$$\mathscr{A}(v)(t) = \lim_{\delta\to 0} \mathscr{A}_\delta(v)(t)$$

for almost all $t \in [0, T]$ and for every nonnegative function $v \in L^\infty(0, T)$. Passage to the limit in Eq. (16) as $\delta \to 0$ yields Eq. (15), which proves the solvability of Problem (1)–(4).

2.2. Uniqueness of solutions

Denote

$$H_e(s) = \begin{cases} 0 & s < 0, \\ [0, 1] & s = 0, \\ 1 & s > 0, \end{cases} \qquad H_e^m(s) = \begin{cases} 0 & s < 0, \\ ms & 0 \leqslant s \leqslant 1/m, \\ 1 & s > 1/m. \end{cases}$$

Let $\{u_k, \eta_k\}$, $k = 1, 2$, be two solutions of Problem (1)–(4). Denote $\tilde{u} = u_1 - u_2$, $\tilde{\eta} = \eta_1 - \eta_2$. Due to the Hilpert inequality (see [5, III.2])

$$\frac{\mathrm{d}\tilde{\eta}^+(\boldsymbol{x}, \cdot)}{\mathrm{d}t} \leqslant \frac{\mathrm{d}\tilde{\eta}(\boldsymbol{x}, \cdot)}{\mathrm{d}t} q(\boldsymbol{x}, \cdot) \quad \text{a.e. in } (0, T) \tag{17}$$

for almost all $\boldsymbol{x} \in \Gamma$ and for every measurable function $q(\boldsymbol{x}, \cdot) \in H_e(\tilde{u}(\boldsymbol{x}, \cdot))$. Multiply (1) by $q_m(\boldsymbol{x}, t) = H_e^m(\tilde{u}(\boldsymbol{x}, t))$ to obtain the inequality

$$\int_\Omega \nabla\tilde{u} \cdot \nabla q_m \, \mathrm{d}\boldsymbol{x} = \int_\Omega (H_e^m)'(\tilde{u}) |\nabla\tilde{u}|^2 \, \mathrm{d}\boldsymbol{x} \geqslant 0.$$

This implies

$$\int_{\Omega} \frac{\partial \tilde{u}}{\partial t}\, H_e^m(\tilde{u})\, \mathrm{d}\boldsymbol{x} + \int_{\Gamma} \frac{\partial \tilde{\eta}}{\partial t}\, H_e^m(\tilde{u})\, \mathrm{d}s \leqslant 0 \quad \text{a.e. in } (0, T).$$

Passage to the limit as $m \to 0$ yields

$$\int_{\Omega} \frac{\partial \tilde{u}^+}{\partial t}\, \mathrm{d}\boldsymbol{x} + \int_{\Gamma} \frac{\partial \tilde{\eta}}{\partial t}\, q\, \mathrm{d}s \leqslant 0 \quad \text{a.e. in } (0, T),$$

where $q \in H_e(\tilde{u})$ is a function such that $H_e^m(\tilde{u}) \to q$, as $m \to 0$, almost everywhere in Γ_T. Therefore, inequality Eq. (17) implies

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\int_{\Omega} \tilde{u}^+\, \mathrm{d}\boldsymbol{x} + \int_{\Gamma} \tilde{\eta}^+\, \mathrm{d}s\right) \leqslant 0.$$

This means that $\tilde{u}^+ = 0$ and $\tilde{\eta}^+ = 0$. Interchanging indices 1 and 2 in the definition of $\tilde{u}$ and $\tilde{\eta}$, we conclude that $\tilde{u} = 0$ and $\tilde{\eta} = 0$. The theorem is proved.

3. Numerical simulation

Let $u_0 = 0$ and $u_1 = 0.1$ in the definition of the function H. The initial concentration u_0 is of the form

$$u_0(x_1, x_2, x_3) = \begin{cases} 13 & \text{if } (x_1 - 0.3)^2 + (x_2 - 0.3)^2 + (x_3 - 0.4)^2 < 0.2^2, \\ 12 & \text{if } (x_1 - 0.7)^2 + (x_2 - 0.7)^2 + (x_3 - 0.3)^2 < 0.2^2, \\ 0 & \text{otherwise.} \end{cases}$$

Numerical simulations show the following behavior of the model. The concentration $u|_\Gamma$ grows first and then goes down because the protein is being spread out over the volume. The surface concentration η grows monotonically and achieves saturation. Fig. 2 shows a snapshot of the process at the time instant when η achieves its saturation value equal to one. Remember that $u|_\Gamma$ and η are defined on Γ which is the bottom of the wet cell Ω.

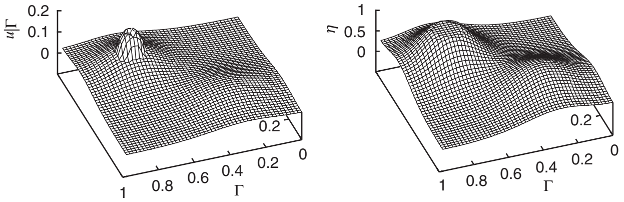

Fig. 2. Snapshots of the concentration $u|_\Gamma$ (to the left) and the surface concentration η (to the right). The growth of $u|_\Gamma$ is very quick in the region where η achieves its saturation value because the flux towards Γ stops in this region.

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