

Modeling and simulation: Examples in Biology

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2 Propagation of biological impulses

Understanding wave propagation in discrete excitable media is challenging because of poorly understood phenomena associated with spatial discreteness. The study of the transmission of nerve impulses along myelinated axons and muscle contraction are paradigmatic examples. This section is taken from [1, 2, 3, 4, 7].

2.1 Myelinated nerves

Myelinated nerve fibers, such as the motor axons of vertebrates, are covered almost everywhere by a thick insulating coat of myelin. Only a fraction of the active membrane is exposed, at small active nodes called Ranvier nodes. The myelinated axons of motor nerves can be very long, and contain hundreds or thousands of nodes. The wave activity jumps from one node to the next one giving rise to “saltatory” propagation of impulses. Saltatory conduction on myelinated nerve models has two important features. One is the possibility of increasing the speed of the nerve impulse while decreasing the diameter of the nerve fiber. The other is propagation failure when the myelin coat is damaged, which causes diseases such as multiple sclerosis.

2.1.1 Hodgkin-Huxley equations for myelinated axons

A myelinated nerve is a sequence of exposed Ranvier nodes separated by regions covered with myelin sheaths. Myelin is considered to be a perfect insulator. Then, the nerve axon can be represented by an equivalent circuit where C and R represent lumped resistance and capacitance. V_k , I_k and $I_{ion}(k)$ represent the membrane potential, internodal current and ionic current at the k -th node. Applying Kirchoff’s laws to the circuit yields:

$$V_{k-1} - V_k = RI_k, \quad I_k - I_{k+1} = C \frac{dV_k}{dt} + I_{ion}(k)$$

Adopting at each node the Hodgkin-Huxley expression for the ion current, we obtain the discrete Hodgkin-Huxley model for a myelinated axon:

$$\begin{aligned} C \frac{dV_k}{dt} + I_{ion}(V_k, M_k, N_k, H_k) &= \\ \bar{D}(V_{k+1} - 2V_k + V_{k-1}), & \\ \frac{dM_k}{dt} &= \bar{\lambda}_M \bar{\Lambda}_M(V_k)(M_\infty(V_k) - M_k), \\ \frac{dN_k}{dt} &= \bar{\lambda}_N \bar{\Lambda}_N(V_k)(N_\infty(V_k) - N_k), \\ \frac{dH_k}{dt} &= \bar{\lambda}_H \bar{\Lambda}_H(V_k)(H_\infty(V_k) - H_k), \end{aligned}$$

where the index k designs the k -th node of the fiber. Here, V_k is the deviation from rest of the membrane potential, N_k is the potassium activation, M_k is the sodium activation and H_k the sodium inactivation. The ion current is given by:

$$\begin{aligned} I_{ion}(V, M, N, H) &= \bar{g}_{Na} M^3 H (V - \bar{V}_{Na,R}) \\ &+ \bar{g}_L (V - \bar{V}_{L,R}) + \bar{g}_K N^4 (V - \bar{V}_{K,R}). \end{aligned}$$

The fraction of open K^+ channels is computed as N_k^4 . The fraction of open Na^+ channels is approximated by $M_k^3 H_k$. The parameters have the following interpretation. \bar{g}_{Na} and \bar{g}_K are the maximum conductance values for Na^+ and K^+ pathways, respectively. \bar{g}_L is a constant leakage conductance. The corresponding equilibrium potentials are \bar{V}_{Na} , \bar{V}_K and \bar{V}_L , respectively. Then, $\bar{V}_{Na,R} = \bar{V}_{Na} - \bar{V}_R$, $\bar{V}_{K,R} = \bar{V}_K - \bar{V}_R$ and $\bar{V}_{L,R} = \bar{V}_L - \bar{V}_R$, where \bar{V}_R is the resting potential. C is the membrane capacitance. The coefficient $\bar{D} =$

$\frac{1}{L(r_i+r_e)} = \frac{1}{R}$, where L is the length of the myelin sheath between nodes and r_i, r_e the resistances per unit length of intracellular and extra-cellular media.

This model is adequate for the long axons of peripheral myelinated nerves. Numerical simulations representing the propagation of nerve impulses are presented in [3], where an asymptotic construction of pulse like solutions is also given. Nerve impulse propagation is shown to fail when the leading front of the pulse is pinned [1], which happens when the myelin sheath deteriorates (multiple sclerosis) or in the presence of drugs, see simulations in [3].

2.1.2 FitzHugh-Hodgkin-Huxley equations

More biological detail can be included by adding an equation for the membrane potential $V(x, t)$ across the myelin sheath in the internodes:

$$c \frac{\partial V}{\partial T} = \frac{1}{r_i + r_e} \frac{\partial^2 V}{\partial x^2} - \frac{V}{r}, \quad x \in (x_k, x_{k+1}), t > 0$$

$$V(x_k, t) = V_k(t), \quad V(x_{k+1}, t) = V_{k+1}(t)$$

coupled with the system for M_k, N_k, H_k and:

$$C \frac{dV_k}{dT} + I_{ion}(V_k, M_k, N_k, H_k) = I_k(t)$$

$$I_k(t) = \frac{1}{r_i + r_e} \left[\frac{\partial V}{\partial x}(x_k^+, t) - \frac{\partial V}{\partial x}(x_k^-, t) \right]$$

In this way, myelinated nerve fibers can be described by a linear diffusion equation which is periodically loaded by the active nodes. This model produces a good quantitative approximation of the conduction velocity for toad axons. Numerical simulations of the sensitivity to different parameters (diameter, nodal area...) produce results in agreement with experiments. The discrete Hodgkin-Huxley model is recovered by assuming that the axial currents along the myelin sheath $\frac{\partial V}{\partial x}(x, t)$ are constant in each internode. Then, $\frac{\partial V}{\partial x}(x, t) = \frac{V_{k+1}(t) - V_k(t)}{L}$ in $[x_k, x_{k+1}]$ with $L = x_{k+1} - x_k$. As a result, $I_k(t) = \frac{1}{L(r_i+r_e)}(V_{k+1} - V_k + V_{k-1})$. This approximation is reasonable in view of the numerical solutions constructed in [7].

2.1.3 FitzHugh-Nagumo equations

The discrete Fitz Hugh-Nagumo system is a simplification of the Hodgkin-Huxley model for myelinated nerves useful to gain qualitative understanding of the mathematical clues of successful pulse propagation and propagation failure [1, 2]:

$$\frac{du_k}{dt} = d(u_{k+1} - 2u_k + u_{k-1}) + f(u_k) - v_k,$$

$$\frac{dv_k}{dt} = \epsilon(u_k - Bv_k),$$

$k = 0, \pm 1, \dots$. Here u_k and v_k are the membrane potential and the recovery variable (which acts as an outward ion current) at the k th excitable membrane site (node of Ranvier). The cubic source term $f(u_k)$ is an ionic current, and the discrete diffusive term is proportional to the difference in internodal currents through a given site. The constant B is selected so that the source terms in the FHN system are $O(1)$ for u_k and v_k of order 1, that the only stationary uniform solution is $u_k = 0 = v_k$, and that the FHN system has excitable dynamics. The constant $\epsilon > 0$ is the ratio between the characteristic time scales of both variables. We assume $\epsilon \ll 1$, that is, fast excitation and slow recovery.

2.2 Muscle contraction

Similar models are used to describe the contraction and recovery of muscle fibers. The Morris-Lecar model is given by

$$\begin{aligned}\frac{dv_k}{dt} &= D(v_{k+1} - 2v_k + v_{k-1}) + f(v_k, w_k) - 2I, \\ \frac{dw_k}{dt} &= \lambda \cosh\left(\frac{v_k - V_3}{2V_4}\right) \left[1 + \tanh\left(\frac{v_k - V_3}{V_4}\right) - 2w_k\right],\end{aligned}$$

where the index k denotes the k -th site and:

$$f(v, w) = 2w(v - V_K) + 2g_L(v - V_L) + g_{Ca} \left[1 + \tanh\left(\frac{v - V_1}{V_2}\right)\right] (v - 1).$$

v_k is the ratio of membrane potential to a reference potential and w_k is the fraction of open K^+ channels. The time scale is $\frac{\bar{g}_K}{2C_m}$, \bar{g}_K being the K^+ conductance and C_m the membrane capacitance.

This system is a reduced version of the full Morris-Lecar model, which involves one more fast variable m_k . It exhibits a rich dynamical behavior depending on its stationary solutions. There are two possibilities. If there is a unique stable constant solution, the system displays excitable dynamics. When it happens to be unstable, the system develops self-oscillations and displays synchronization phenomena [4].

3 Modular protein behavior

Tissue elasticity in living organisms results from the extension and recoil of proteins fastened to rigid structures that move under force. Polyproteins or modular proteins, such as titin that plays an important role in muscle contraction, ubiquitin and other relevant proteins, comprise a number of repeated single protein domains joined by short peptide linkers. A simple version of tissue elasticity appears in most single-molecule experiments, like atomic force microscopy (AFM), in which a biomolecule is chained to rigid platforms whose motion is controlled. Force-clamp and length-clamp experiments provide information on the protein structure, and can be interpreted by means of simple mathematical models. This section is taken from [9, 12, 13, 15].

In real experiments, the tip of the cantilever can attach the polyprotein at any point. Therefore, the number N of protein monomers exposed to force varies between one and the total number of monomers. Let the monomer positions be x_j , $j = 1, \dots, N$. The relative extensions of the monomers are $u_j = x_{j+1} - x_j$, $j = 1, \dots, N$ and external forces $\pm F$ applied to the ends of the monomer chain produce a potential $-F \sum_{j=0}^N u_j = Fx_0 - Fx_{N+1}$. Thus these forces on the chain ends yield an equal effective external force F on each of the extensions u_j . The free energy of the j th monomer is $V(u_j; \delta_j)$, where $V(u; \delta)$ is a double-well potential whose minima correspond to the folded (enthalpic) and unfolded (entropic) states. The parameter δ can vary from monomer to monomer. The monomers are connected to their next neighbors by harmonic springs (the linkers) and they undergo Brownian motion in the liquid in which they are immersed. We assume that their inertia can be neglected and therefore that their dynamics is overdamped. The resulting model is as follows [15]:

$$\begin{aligned} \gamma_j \dot{u}_j &= F - V'(u_j; \delta_j) - k_{j+1}(u_j - u_{j+1}) - k_j(u_j - u_{j-1}) + \sqrt{2k_B T \gamma_j} \xi_j(t), \\ \langle \xi_j(t) \rangle &= 0, \quad \langle \xi_j(t) \xi_l(t') \rangle = \delta_{jl} \delta(t - t'), \quad j = 1, \dots, N. \end{aligned}$$

Here $V'(u; \delta) = dV(u; \delta)/du$, $k_j = k$ for $j = 1, \dots, N + 1$. As explained before, the force F provided by the AFM affects the effective potential of all monomers between the AFM tip and the platform equally. There are two possible experimental settings: (i) The force F is kept constant (force-clamp experiments); (ii) the total extension of the chain is controlled and kept constant or increased at a uniform rate (force-extension experiments). In case (ii), $F(t)$ is a new unknown that should be calculated. The boundary conditions for this chain are

$$u_0 = 0, \quad u_N = 0.$$

We assume that the monomers at x_1 and x_N rigidly follow the platform and the AFM tip so that $u_0 = u_N = 0$. For case (ii) we need to add the constraint that the total length of the monomer chain, L , be kept constant so that the following new equation holds:

$$\sum_{j=1}^N u_j = x_{N+1} - x_0 = L.$$

In force-extension experiments, $L = \mu t + \nu$, with a positive μ .

3.1 Folding and unfolding

In a typical force-clamp experiment, the force is first raised, kept at a large value until all domains become unfolded and then abruptly lowered to a smaller value. Immediately after the force increment, abrupt or stepwise unfolding of the polyprotein follows. On the other hand, after the force is lowered, refolding is similar for single module proteins and for homopolyproteins; the folding events do not show traces of sequential folding for polyproteins.

Assuming infinitely rigid springs connect the protein to AFM cantilever and platform, $u_0 = u_1$, $u_{N+1} = u_N$. At zero external force and temperature T , we use the effective potential:

$$V(u) = U_0 \left[\left(1 - e^{-2b(u-R_c)/R_c} \right)^2 - 1 \right] + \frac{k_B T L_c}{4P} \left(\frac{1}{1 - \frac{u}{L_c}} - 1 - \frac{u}{L_c} + \frac{2u^2}{L_c^2} \right).$$

It is a cubic, with three zeros, three of which are stable. Given F , the smallest $u^{(1)}(F)$ and largest $u^{(3)}(F)$ zeros represent the folded and unfolded state for each module. Folding and unfolding phenomena can be explained qualitatively and quantitatively in terms of pinning and depinning of fronts in this system [?].

3.2 Force-extension curves

As the polyprotein is pulled, one or more modules unfold at a typical force that measures its mechanical stability. It should be stressed that the unraveling of a domain is a stochastic event and may occur in a certain range of forces. These *length-clamp* experiments deliver a sawtooth force-extension curve (FEC). Similar curves are obtained by stretching nucleic acids and other biomolecules. When the force extension curve is swept at a finite rate, stochastic jumps between folded and unfolded states may be observed, and the unfolding force increases with the extension rate.

Studying stationary solutions of the model proposed above [12], we have a global constraint in the minimization procedure leading to the equilibrium values of the extensions. As a consequence, the force-extension curve has multiple branches in a certain range of forces. The stability of these branches is governed by the free energy: there are a series of first-order phase transitions at certain values of the total length, in which the free energy itself is continuous but its first derivative, the force, has a finite jump. This behavior is completely similar to the one observed in real experiments with biomolecules like proteins, and other complex systems. The effect of noise and unequal monomer presence are studied in detail in [15].

A simpler model of an oscillator coupled to Ising spins that undergo Glauber dynamics [8] in contact with a thermal bath could explain qualitatively many features of the force-extension curves measured in experiments with biomolecules [9]. DNA force-extension curves correspond to cycling at different rates the curves of the spin-oscillator first-order phase transition with the force as a control parameter. However, the spin-oscillator model is too simple to account for the sawtooth pattern observed in length-controlled experiments.

4 Biofilm spread

Biofilms are bacterial aggregates attached to wet surfaces and encased in a self-produced polymeric matrix. This makes them hard to eliminate. At hospitals, they are a major cause of hospital acquired infections. In industry, biofilm induced damage in materials causes substantial losses. On the other side, they are elementary cell aggregates which grow to develop patterns, providing a simple toy system for models of tissue development.

When spreading in flows, biofilms elongate with the current forming threads. The shape of the thread adapts to geometrical constraints, seeking to minimize adequate energies. Its time evolution until an equilibrium shape is reached can be described by discrete rod models. We tackle here two different experimental frameworks: biofilms in networks of cylindrical tubes and biofilms in channel flows. In the latter case, hybrid models combining cellular automata descriptions of cell activity and continuous descriptions of macroscopic fields for chemicals and flows reproduce a rich variety of patterns. Whereas biofilms in flows tend to form filamentary structures, biofilms spreading on agar/air interfaces adopt wrinkled shapes. Hybrid models incorporating elastic fields are also successful reproducing wrinkle formation processes. This section is taken from [11, 14, 16, 17].

4.1 Biofilms in tubes

Consider the typical flow circuits used in medical systems. Injecting bacteria of the *Pseudomonas* genus inside, tubes fill with helical biofilms which wrap around the walls [16]. Vortical motion drive bacteria to the walls creating biofilm nucleation sites. The biofilm then elongates following the streamlines until it undergoes a helical instability.

Discrete rod models describe the process. The filament is discretized using a sequence of nodes \mathbf{x}^i along the filament γ , plus a reference system at each one (the material frame) that measures the twist. This frame is obtained at each location twisting the Bishop frame (a fixed untwisted frame) a certain angle θ^i . The dynamics of the discrete filament is then governed by equations for the angles θ^i , and for the node positions \mathbf{x}^i .

The equations for the angles follow from energy arguments. When the undeformed configuration of the filament is straight and its elastic response is isotropic, the elastic energy due to torsion and bending takes the form:

$$E = \sum_{i=1}^n \beta \frac{(\theta^i - \theta^{i-1})^2}{\bar{\ell}^i} + \sum_{i=1}^n \frac{\alpha}{2\bar{\ell}^i} \sum_{j=i-1}^i \|\mathbf{w}_i^j - \bar{\mathbf{w}}_i^j\|^2,$$

where α and β are the bending and torsion moduli, respectively. $\bar{\ell}^i$ is the length of the segments $\bar{\mathbf{e}}^i = \bar{\mathbf{x}}^{i+1} - \bar{\mathbf{x}}^i$ in a reference undeformed configuration $\{\bar{\mathbf{x}}^0, \bar{\mathbf{x}}^1, \dots, \bar{\mathbf{x}}^{n+1}\}$. The vectors $\mathbf{w}_i^j, \bar{\mathbf{w}}_i^j, j = i - 1, i$, are material curvatures in the deformed and undeformed configurations, respectively. The material frame

is updated in a quasistatic way. Imposing

$$\frac{\partial E}{\partial \theta^i} = 0,$$

for all segments i not fixed by a boundary condition, this system of equations determines the angle configuration that minimizes the energy of the thread. Clamped ends are accounted for assigning the material frame for $i = 0$, $i = n$. No boundary condition corresponds to a stress free end.

We keep track of the filament position displacing the nodes according to Newton's second law:

$$\mathbf{M} \frac{d^2 \mathbf{x}}{dt^2} = - \frac{dE}{d\mathbf{x}} + \mathbf{f},$$

where \mathbf{f} represents the external forces and $-\frac{dE}{d\mathbf{x}}$ the elastic forces. \mathbf{M} is the mass matrix, we set $\mathbf{M} = m\mathbf{I}$. Biofilm filaments live inside tubes of a certain shape. A simple way to incorporate this restriction and reproduce helical instabilities in tubes is a penalty method [16].

4.2 Biofilms in channels

Discrete rod models also allow us to reproduce the dynamics of filaments in corner flows, for instance. The dynamics of biofilm layers covering channel walls, instead, is more appropriately described by means on hybrid models coupling continuous descriptions of flow and chemical fields with cellular automata models of cell activity [11, 17].

Cellular automata provide a simple strategy allowing for an easy transfer of information into macroscopic models. The film is divided in tiles, each of them of the size of a cell. We have to decide for each cell whether it is dead or deactivated, it moves, it detaches or it divides creating a newborn cell that displaces the rest. That is done resorting to probabilities that depend on the relevant concentrations. This approach allows us to use the same grid of tiles to discretize the equations for the concentrations and the displacements.

The fluid surrounding the biofilm is governed by the incompressible Navier-Stokes equations:

$$\begin{aligned} \rho \mathbf{u}_t - \mu \Delta \mathbf{u} + \mathbf{u} \cdot \nabla \mathbf{u} + \nabla p &= 0, & \mathbf{x} \in \Omega_f, t > 0 \\ \operatorname{div} \mathbf{u} &= 0, & \mathbf{x} \in \Omega_f, t > 0 \end{aligned}$$

where $\mathbf{u}(\mathbf{x}, t)$ is the velocity and $p(\mathbf{x}, t)$ the pressure. ρ and μ stand for the density and viscosity of the fluid. The non-slip condition on the velocity holds at the biofilm/fluid interface Γ .

Biomass tiles \mathcal{C} located on the surface of the biofilm detach due to shear forces exerted by the flow [17]

$$P_e(\mathcal{C}) = \frac{1}{1 + \frac{\gamma}{\tau(\mathcal{C})}} = \frac{\tau(\mathcal{C})}{\tau(\mathcal{C}) + \gamma}.$$

γ is a measure of the biofilm cohesion. $\tau(\mathcal{C})$ measures the shear force felt by cell \mathcal{C} . The probability for biomass motion in the x directions is defined as:

$$P_x(\mathcal{C}) = \frac{1}{1 + \frac{\gamma}{|F_x(\mathcal{C})|}} = \frac{|F_x(\mathcal{C})|}{|F_x(\mathcal{C})| + \gamma}.$$

F_x is the force exerted by the flow in the x direction (on cell walls normal to the x direction) weighted with a geometrical factor accounting for neighbor protection. Similar expressions are used in the y and z directions.

The concentrations of nutrients and oxygen inside the region containing the biofilm and the boundary layer are governed by:

$$\begin{aligned} -D_s \Delta^2 c_s &= k_2 \frac{c_s}{c_s + K_s} \frac{c_o}{c_o + K_o}, \\ -D_o \Delta^2 c_o &= \omega k_2 \frac{c_s}{c_s + K_s} \frac{c_o}{c_o + K_o}, \end{aligned}$$

with zero flux conditions at the substratum. One of them will act as limiting concentration c_l , that is, the concentration that limits biofilm growth. The cells will divide with probability:

$$P_d(\mathcal{C}) = \frac{c_l(\mathcal{C})}{c_l(\mathcal{C}) + K_l},$$

where c_l denotes the limiting concentration and K_l its saturation coefficient in the Monod law. Whenever neighboring grid tiles are empty, the daughter cell is placed in any of the empty tiles with equal probability. Otherwise, the new cell will shift one of the neighbors. The cell offering the minimal mechanical resistance is chosen [11].

This kind of hybrid models allows us to reproduce a variety of patterns, such as ripples, mounds and streamers, as well as erosion and fragment detachment, on channels of different geometry and roughness [11, 17].

4.3 Biofilms on surfaces

We can reproduce wrinkle branching in an expanding biofilm resorting to Föppl-Von Karman descriptions of the interface biofilm/agar:

$$\begin{aligned} \frac{\partial \xi}{\partial t} &= \frac{1 - 2\nu_v}{2(1 - \nu_v)} \frac{h_v}{\eta_v} \left[D(-\Delta^2 \xi + \Delta C_M) + h \frac{\partial}{\partial x_\beta} \left(\sigma_{\alpha, \beta}(\mathbf{u}) \frac{\partial \xi}{\partial x_\alpha} \right) \right] - \frac{\mu_v}{\eta_v} \xi, \\ \frac{\partial \mathbf{u}}{\partial t} &= \frac{h_v h}{\eta_v} \nabla \cdot \sigma(\mathbf{u}) - \frac{\mu_v}{\eta_v} \mathbf{u}, \end{aligned}$$

where h_v is the thickness of the viscoelastic substratum and μ_v , ν_v , η_v its rubbery modulus, Poisson ratio, and viscosity, respectively. The bending stiffness is $D = \frac{Eh^3}{12(1-\nu^2)}$, where E and ν represent the Young and Poisson moduli of the biofilm, whereas h is the film thickness. ξ stands for the out of plane displacement and \mathbf{u} the in plane displacement. α and β stand for x, y and summation

over repeated indices is intended. Stresses σ and strains ε are defined in terms of in-plane displacements $\mathbf{u} = (u_x, u_y)$:

$$\varepsilon_{\alpha,\beta} = \frac{1}{2} \left(\frac{\partial u_\alpha}{\partial x_\beta} + \frac{\partial u_\beta}{\partial x_\alpha} + \frac{\partial \xi}{\partial x_\alpha} \frac{\partial \xi}{\partial x_\beta} \right) + \varepsilon_{\alpha,\beta}^0,$$

$$\sigma_{xx} = \frac{E}{1-\nu^2} (\varepsilon_{xx} + \nu \varepsilon_{yy}), \quad \sigma_{xy} = \frac{E}{1+\nu} \varepsilon_{xy}, \quad \sigma_{yy} = \frac{E}{1-\nu^2} (\varepsilon_{yy} + \nu \varepsilon_{xx}).$$

The residual strains $\varepsilon_{\alpha,\beta}^0$ are expressed in terms of the growth tensor as:

$$\varepsilon_{\alpha,\beta}^0 = -\frac{1}{2} (g_{\alpha\beta} + g_{\beta\alpha} + g_{z\alpha} g_{z\beta}),$$

and should be computed from cellular activity.

Using a cellular automata description of cell activity, we can calculate growth tensors due to cell division, death, and water absorption processes, and estimate the residual stresses. Performing ensemble averages, the averaged stresses reproduce spatial variations reflecting cellular activity. Filtering the resulting fields using image processing techniques yields smooth approximations with a clear spatial structure averaging just a few runs. These fields are smooth enough to be plugged in Von Karman's equations without causing numerical instability, allowing to reproduce behaviors that resemble observed patterns [14].

5 Angiogenesis

Angiogenesis is a process through which new blood vessels grow from pre-existing ones. Angiogenesis is vital for tissue development and repair. However, angiogenic disorders are often the cause of inflammatory and immune diseases. Moreover, angiogenesis is essential for the transition of benign tumors into malignant ones, and for subsequent tumor spread.

A kinetic integrodifferential system is able to reproduce some aspects of the development of the stochastic vessel network. The evolution of the density of blood vessel tips p in response to the concentration of tumor angiogenic factor released by cells c is described by the following set of equations:

$$\begin{aligned} \frac{\partial}{\partial t} p(\mathbf{x}, \mathbf{v}, t) &= \alpha(c(\mathbf{x}, t)) \delta_{\mathbf{v}_0}(\mathbf{v}) p(\mathbf{x}, \mathbf{v}, t) - \gamma p(\mathbf{x}, \mathbf{v}, t) \int_0^t ds \int d\mathbf{v}' p(\mathbf{x}, \mathbf{v}', s) \\ &\quad - \mathbf{v} \cdot \nabla_{\mathbf{x}} p(\mathbf{x}, \mathbf{v}, t) + \beta \operatorname{div}_{\mathbf{v}}(\mathbf{v} p(\mathbf{x}, \mathbf{v}, t)) + \\ &\quad - \operatorname{div}_{\mathbf{v}} [\mathbf{F}(c(\mathbf{x}, t))] p(\mathbf{x}, \mathbf{v}, t) + \sigma \Delta_{\mathbf{v}} p(\mathbf{x}, \mathbf{v}, t), \\ \frac{\partial}{\partial t} c(\mathbf{x}, t) &= d \Delta_{\mathbf{x}} c(\mathbf{x}, t) - \eta c(\mathbf{x}, t) j(\mathbf{x}, t), \\ p(\mathbf{x}, \mathbf{v}, 0) &= p_0(\mathbf{x}, \mathbf{v}), \quad c(\mathbf{x}, 0) = c_0(\mathbf{x}), \end{aligned}$$

where

$$\alpha(c) = \alpha_1 \frac{\frac{c}{c_R}}{1 + \frac{c}{c_R}}, \quad \mathbf{F}(c) = \frac{d_1}{(1 + \gamma_1 c)^{q_1}} \nabla_{\mathbf{x}} c,$$

$$j(\mathbf{x}, t) = \int_{\mathbb{R}^N} \frac{|\mathbf{v}|}{1 + e^{|\mathbf{v} - \mathbf{v}_0 \chi|^2 / \sigma_v^2}} p(\mathbf{x}, \mathbf{v}, t) d\mathbf{v}, \quad \rho(\mathbf{x}, t) = \int_{\mathbb{R}^N} p(\mathbf{x}, \mathbf{v}, t) d\mathbf{v},$$

for $\mathbf{x} \in \Omega \subset \mathbb{R}^N$, $\mathbf{v} \in \mathbb{R}^N$, $N = 2, 3$, $t \in [0, \infty)$. The constants β , σ , γ , d , η , α_1 , c_R , d_1 , γ_1 , q_1 are positive. The parameter $\chi \gg 1$ (typically $\chi > 10$) whereas $\sigma_v^2 \ll 1$. $\delta_{\mathbf{v}_0}$ is a Dirac measure supported at a point \mathbf{v}_0 . \mathbf{v}_0 is a typical sprouting velocity for the tips. The source term $\alpha(c)\delta_{\mathbf{v}_0} p$ represents creation of new tips due to vessel tip branching. Tip vessel death when a tip encounters another vessel (anastomosis) is described by the integral sink $-\gamma p \int_0^t \rho(p)$. The Fokker-Planck operator expresses blood vessel extension. The chemotactic force $\mathbf{F}(c)$ is taken to depend on the flux of blood vessel tips through j to represent that consumption of tumor angiogenic factor is mostly due to the additional endothelial cells that produce vessel extensions. The velocity cut-off through the Fermi-Dirac distribution in the definition of j reflects the fact that cell velocities are limited, and small [20]. Solutions in the whole space for this model and simplified diffusion versions are constructed in [19, 20].

The general form of the boundary conditions in dimension $N = 2, 3$, is as follows [21]. We impose Neumann boundary conditions for c :

$$\frac{\partial c}{\partial r}(\mathbf{x}, t) = c_{r_0}(\mathbf{x}, t) < 0, \quad \mathbf{x} \in S_{r_0}, \quad \frac{\partial c}{\partial r}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in S_{r_1}, \quad t \in [0, T],$$

where c_{r_0} represents the influx of tumor angiogenic factor coming from the inner core of the tumor. S_{r_0} and S_{r_1} are spheres of radius r_0 and r_1 , respectively. Since diffusion is absent in the \mathbf{x} variable, the transport operator forces boundary conditions of the form:

$$p^-(\mathbf{x}, \mathbf{v}, t) = g(\mathbf{x}, \mathbf{v}, t) \quad \text{on } \Sigma_T^-.$$

The sets $\Sigma_T^\pm = (0, T) \times \Gamma^\pm$, where $\Gamma^\pm = \{(\mathbf{x}, \mathbf{v}) \in \partial\Omega \times \mathbb{R} \mid \pm \mathbf{v} \cdot \mathbf{n}(\mathbf{x}) > 0\}$, $\mathbf{n}(\mathbf{x})$ being the outward unit normal onto the boundary $\partial\Omega$. We denote by p^+ and p^- the traces of p on Σ_T^+ and Σ_T^- , respectively. In our geometry, the boundary conditions for p are defined using the magnitudes that can actually be measured: the marginal tip density $\rho = \int p d\mathbf{v}$ in the inner boundary and the flux of blood vessels $\mathbf{j} = \int \mathbf{v} p d\mathbf{v}$ in the outer boundary. Using coordinates $\mathbf{x} = r\boldsymbol{\theta}$, with $r = |\mathbf{x}|$, $\boldsymbol{\theta} \in S_{N-1}$, and $\mathbf{v} = v_r \boldsymbol{\phi}$, with $v_r = |\mathbf{v}|$, $\boldsymbol{\phi} \in S_{N-1}$, the boundary conditions on Σ_T^- read:

$$p^-(r_0, \boldsymbol{\theta}, v_r, \boldsymbol{\phi}, t) = \frac{e^{-\frac{\beta}{\sigma} |\mathbf{v} - \mathbf{v}_0|^2}}{\mathcal{I}_0} \left[\rho(r_0, \boldsymbol{\theta}, t) - \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} \mid \tilde{\mathbf{v}} \cdot \mathbf{n} > 0\}} d\tilde{\boldsymbol{\phi}} p^+(r_0, \boldsymbol{\theta}, \tilde{v}_r, \tilde{\boldsymbol{\phi}}, t) \right],$$

$$p^-(r_1, \boldsymbol{\theta}, v_r, \boldsymbol{\phi}, t) = \frac{e^{-\frac{\beta}{\sigma} |\mathbf{v} - \mathbf{v}_0|^2}}{\mathcal{I}_1} \left[-j_0 - \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\boldsymbol{\phi}} \in S_{N-1} \mid \tilde{\mathbf{v}} \cdot \mathbf{n} > 0\}} d\tilde{\boldsymbol{\phi}} p^+(r_1, \boldsymbol{\theta}, \tilde{v}_r, \tilde{\boldsymbol{\phi}}, t) f_1(\mathbf{v}) \right],$$

where p^+ and p^- denote the traces of the solution p on Σ_T^+ and Σ_T^- , respectively, and

$$\mathcal{I}_0 = \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\phi} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\phi} e^{-\frac{\beta}{\sigma} |\tilde{\mathbf{v}} - \mathbf{v}_0|^2}, \quad \mathcal{I}_1 = \int_0^\infty d\tilde{v}_r \tilde{v}_r^{N-1} \int_{\{\tilde{\phi} \in S_{N-1} | \tilde{\mathbf{v}} \cdot \mathbf{n} < 0\}} d\tilde{\phi} e^{-\frac{\beta}{\sigma} |\tilde{\mathbf{v}} - \mathbf{v}_0|^2} f_1(\tilde{\mathbf{v}}).$$

The remaining functions are defined as:

$$f_1(\mathbf{v}) = \mathbf{v} \cdot \mathbf{n} \left[1 + e^{|\mathbf{v} - \mathbf{v}_0|^2 / \sigma_v^2} \right]^{-1},$$

$$j_0(\boldsymbol{\theta}, t) = v_0 \alpha(c(r_1, \boldsymbol{\theta}, t)) p(r_1, \boldsymbol{\theta}, v_0, \mathbf{w}_0, t),$$

for the fixed velocity $\mathbf{v}_0 = (v_0, \mathbf{w}_0)$, $v_0 > 0$, $\mathbf{w}_0 \in \mathbb{R}^{N-1}$.

6 Imaging of biological structures

In many situations we need to extract information on the inner structure of a medium from external indirect observations. Technology has provided many tools for different purposes: magnetic resonance, tomography, ultrasound, radar, seismic imaging... All of them are based on emitting some kind of wave which interacts with the medium under study, and is then measured at a set of receptors. Knowing the data recorded at the receptors and the emitted waves, we wish to reconstruct the internal geometry and/or material properties of the medium. We consider here two particular imaging set-ups of biological relevance: electrical impedance tomography and holography. This section is taken from [10, 18].

6.1 Electrical impedance tomography

The impedance imaging problem consists in producing an image of the electromagnetic properties of a medium by applying electric currents to its exterior surface and measuring voltages on it. The range of medical applications is wide, because different tissues have different electromagnetic properties. For example, we can think of monitoring for lung problems (embolies, clots, accumulation of fluids) or blood flow (internal bleeding, heart function), screening for breast cancer, determining the boundary between dead and living cells, detecting temperature changes in hyperthermia treatments...

We want to reconstruct the admittivity γ inside Ω from measurements on the boundary. If we assume that Ω contains a number of inclusions $\Omega_{i,j}$, the admittivity γ is a piecewise function in Ω with discontinuities at the boundaries of the inclusions. We set $\Omega_i = \cup_{j=1}^d \Omega_{i,j}$ with $\Omega_{i,j}$ open connected bounded sets satisfying $\bar{\Omega}_{i,l} \cap \bar{\Omega}_{i,j} = \emptyset$ for $l \neq j$. The admittivity in the matrix $\Omega_e = \Omega \setminus \bar{\Omega}_i$ is γ_e . We define γ_i in Ω_i as $\gamma_i = \gamma_{i,j}$ in $\Omega_{i,j}$. To simplify, we assume γ_e to be known. To identify the inclusions from the recorded data, we can solve the optimization problem [10]

$$J(\Omega_i, \gamma_i) = \frac{1}{2} \int_{\partial\Omega} |u - V_{meas}|^2 dl$$

where u solves

$$\begin{cases} \nabla \cdot \gamma_e \nabla u = 0 & \text{in } \Omega_e, & \nabla \cdot \gamma_i \nabla u = 0 & \text{in } \Omega_i, \\ u^- - u^+ = 0 & \text{on } \partial\Omega_i, & \gamma_i \partial_{\mathbf{n}} u^- - \gamma_e \partial_{\mathbf{n}} u^+ = 0 & \text{on } \partial\Omega_i, \\ \gamma_e \partial_{\mathbf{n}} u = j & \text{on } \partial\Omega. \end{cases}$$

The unit normal \mathbf{n} points outside Ω_e but inside Ω_i and u^- and u^+ denote the limit values of u on $\partial\Omega_i$ from outside and inside Ω_i , respectively. Topological derivative methods allow us to approximate solutions of the inverse problem for such incident waves [10]. Instead of electromagnetic signals, other methods monitor temperature recordings to locate unhealthy tissue. One can invert similar problems by topological methods using thermal waves [5, 6].

6.2 Holography

Digital in-line holography is a promising tool for high speed three dimensional (3D) imaging of live cells and soft matter. It can achieve high temporal (microseconds) and spatial (nanometers) resolution while avoiding the usage of toxic stains and fluorescent markers. Holograms are two-dimensional (2D) light interference patterns that contain information about the 3D positions and optical properties of an object or set of objects.

When the emitted light beams are time harmonic, that is, $\mathcal{E}_{\text{inc}}(\mathbf{x}, t) = \text{Re}[e^{-i\omega t} \mathbf{E}_{\text{inc}}(\mathbf{x})]$, the resulting wave fields also happen to be time harmonic $\mathcal{E}_{\Omega, \kappa}(\mathbf{x}, t) = \text{Re}[e^{-i\omega t} \mathbf{E}_{\Omega, \kappa}(\mathbf{x})]$ and the complex amplitude $\mathbf{E}_{\Omega, \kappa}(\mathbf{x})$ satisfies a stationary version of the time dependent Maxwell equations, the so-called forward problem:

$$\begin{aligned} \mathbf{curl} \left(\frac{1}{\mu_e} \mathbf{curl} \mathbf{E} \right) - \frac{\kappa_e^2}{\mu_e} \mathbf{E} &= 0 & \text{in } \mathbb{R}^3 \setminus \overline{\Omega}, \\ \mathbf{curl} \left(\frac{1}{\mu_i} \mathbf{curl} \mathbf{E} \right) - \frac{\kappa_i^2}{\mu_i} \mathbf{E} &= 0 & \text{in } \Omega, \\ \hat{\mathbf{n}} \times \mathbf{E}^- &= \hat{\mathbf{n}} \times \mathbf{E}^+, & \text{on } \partial\Omega, \\ \frac{1}{\mu_i} \hat{\mathbf{n}} \times \mathbf{curl} \mathbf{E}^- &= \frac{1}{\mu_e} \hat{\mathbf{n}} \times \mathbf{curl} \mathbf{E}^+, & \text{on } \partial\Omega, \\ \lim_{|\mathbf{x}| \rightarrow \infty} |\mathbf{x}| \left| \mathbf{curl} (\mathbf{E} - \mathbf{E}_{\text{inc}}) \times \frac{\mathbf{x}}{|\mathbf{x}|} - i\kappa_e (\mathbf{E} - \mathbf{E}_{\text{inc}}) \right| &= 0, \end{aligned}$$

where $\mu_i, \varepsilon_i, \kappa_i$ and $\mu_e, \varepsilon_e, \kappa_e$ are the permeabilities, permittivities and wavenumbers $\kappa^2 = \omega^2 \varepsilon \mu$ of the objects and the ambient medium, respectively. In biological media, $\mu_i \sim \mu_e \sim \mu_0$, μ_0 being the vacuum permeability [?]. The signs + and - denote the values from outside and inside Ω . The vector $\hat{\mathbf{n}}$ represents the outer normal vector.

The imaging problem becomes [18] finding objects Ω such that the equation:

$$\mathbf{I}_{\text{meas}}(\mathbf{x}_j) = |\mathbf{E}_{\Omega}(\mathbf{x}_j)|^2, \quad j = 1, \dots, N,$$

is satisfied. Alternatively, we can reformulate this equation as a constrained

optimization problem: Find the global minimum Ω of

$$J(\mathbb{R}^3 \setminus \bar{\Omega}) = \frac{1}{2} \sum_{j=1}^N |\mathbf{I}_{\Omega}(\mathbf{x}_j) - \mathbf{I}_{\text{meas}}(\mathbf{x}_j)|^2.$$

Here, $\mathbf{I}_{\Omega} = |\mathbf{E}_{\Omega}|^2$ and \mathbf{E}_{Ω} is the solution of the dimensionless forward system. Ω is the design variable in this optimization problem. The stationary Maxwell system is the constraint. The true objects are a global minimum at which the cost functional vanishes. We can tackle this problem by topological derivative techniques [18].

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