

# PDEs on Complex Domains in Cell Biology

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Optimal Control for Evolutionary PDEs and Related Topics

Palazzone, Cortona

$\Gamma(t)$  denotes a moving curved hypersurface - an  $n$ -dimensional hypersurface in  $\mathbb{R}^{n+1}$ .

$\Omega(t)$  may denote a moving *bulk* domain in  $\mathbb{R}^{n+1}$  with boundary  $\Gamma(t)$ .

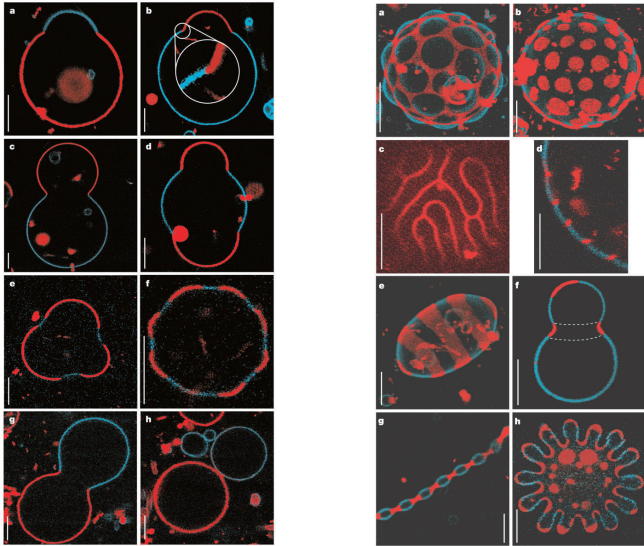
We may view  $\Omega(t)$  as a flat  $n + 1$ -dimensional hypersurface in  $\mathbb{R}^{n+2}$ .

## Boundary value problems

- **Interface problems** in which  $\Gamma$  separates two domains in which bulk PDEs hold
- **Unknown (free/moving) boundary problems (interfaces)** in which  $\Gamma$  is to be determined
- Energetic unknown surfaces/interfaces; **Geometric PDEs**  $\Gamma$  is determined by geometric quantities
- Coupling equations for and on a surface to equations in the bulk
- PDEs on a stationary or evolving surface
- **Interface/free boundary** on an evolving surface



## Challenges:- Morphology: Biomembranes



Giant unilamellar vesicles *Imaging coexisting fluid domains in biomembrane models coupling curvature and line tension* Baumgart, Hess, and Webb *Nature*. 425, pg 821 (2003)

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- Cells **polarise** forming a front and rear.
- Motion driven by **protrusion** of pseudopods at the front and **retraction** of the rear.
- Changes in direction via biased generation of pseudopods. New pseudopods generated by **splitting** of existing pseudopods.

Motion of Dictyostelium cells, King and Insall  
2009

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Dictyostelium

- Mathematical modelling

Here developments in large scale computing, analysis and numerical analysis allow more ambitious models!

- Formulation of PDEs In our context

- Parametric
- Implicit
- Diffuse interface/Phase field
- Unfitted finite element method UNFEM

- Analysis: each formulation may require its own version of the analysis

- Development of numerical methods: each method depends on formulation

- Analysis of discretisation, Analysis of solvers

- Implementation

- Data Assimilation

- Simulation + Parameter identification + Prediction + Control

**Goal:** Develop a robust modelling and computational framework for investigating cell motility.

In work with Stinner, Venkataraman, Croft, Ladds, Weston we consider models with the ingredients:-

- Mechanics: Geometric evolution equation for the motion of the cell boundary.
- Biochemistry: Surface PDEs (reaction diffusion equations) on the cell boundary account for gradient sensing and polarisation.

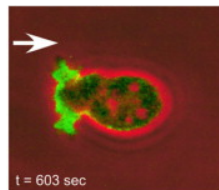
Approaches similar to ours:

- Geometric evolution law coupled to bulk PDEs [Hecht, Skoge, Charest, Ben-Jacob, Firtel, Loomis, Levine, and Rappel, 2011; Ziebert, Swaminathan, and Aranson, 2011].
- Geometric evolution law coupled to surface PDEs [Neilson, Mackenzie, Webb, and Insall, 2011].

We developed computational tools based on surface finite elements [Dziuk, 2008; Dziuk and Elliott, 2007] for simulation and proposed an approach to parameter identification.

## Biochemistry: Surface PDE- Motivation

Reactions that lead to cell polarisation (possibly not only) take place on the plasma membrane, or in the cortex close to the membrane.



Assuming they may be effectively modelled as taking place on the surface  
 $\rightsquigarrow$  on the evolving cell membrane postulate a

Surface reaction-diffusion (-advection) system

F-actin labelled with a fluorescent marker  
[Dalous, Burghardt, Müller-Taubenberger, Bruckert, Gerisch, and Bretschneider, 2008].

$$\partial_{\mathbf{V}}^{\bullet} \mathbf{a} + \mathbf{a} \nabla_{\Gamma} \cdot \mathbf{V} = \mathbf{D} \Delta_{\Gamma} \mathbf{a} + \mathbf{g}(\mathbf{a}) \quad \text{on } \Gamma(t), t > 0,$$

for surface quantities  $\mathbf{a} = (a_1, \dots, a_N)^T : \Gamma \rightarrow \mathbb{R}^N$ .

Where

- $\nabla_{\Gamma(t)} a_i = \nabla a_i - \nabla a_i \cdot \boldsymbol{\nu} \boldsymbol{\nu}$  is the surface gradient of  $a_i$ .
- $\Delta_{\Gamma(t)} a_i = \nabla_{\Gamma(t)} \cdot \nabla_{\Gamma(t)} a_i$  is the surface Laplacian of  $a_i$ .
- $\partial_{\mathbf{V}}^{\bullet} a_i = \partial_t a_i + \mathbf{V} \cdot \nabla a_i$  is the material derivative of  $a_i$  w.r.t the velocity field  $\mathbf{V}$ .

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Spreading Neutrophil Cell [Bretschneider, Du, Elliott, Ranner, Stinner 2016]

$$\begin{aligned} \mathcal{J}_{sharp}(\mathbf{c}) = & \frac{1}{2} \sum_{i=1}^{n_s} \left( w_i \left( \int_{\Gamma(t^i)} |d_{\Gamma_h(t^i)}(\mathbf{x})| d\mathbf{x} + \int_{\Gamma_h(t^i)} |d_{\Gamma(t^i)}(\hat{\mathbf{x}})| d\hat{\mathbf{x}} \right)^2 \right. \\ & \left. + w_{i+n_s} \left( \int_{\Gamma(t^i)} \left| \mathbf{a}(\mathbf{x}, t^i) - \hat{\mathbf{a}}(\hat{\mathbf{x}}_{cp}(\mathbf{x}, t^i), t^i) \right| d\mathbf{x} + \int_{\Gamma_h(t^i)} \left| \hat{\mathbf{a}}(\hat{\mathbf{x}}, t^i) - \mathbf{a}(\mathbf{x}_{cp}(\hat{\mathbf{x}}, t^i), t^i) \right| d\hat{\mathbf{x}} \right)^2 \right) \end{aligned} \quad (0.1)$$

$$\mathcal{J}_{pf,\epsilon}(\mathbf{c}) = \frac{1}{2} \sum_{i=1}^{n_s} \left( w_i \left\| \hat{\phi}_\epsilon - \phi_\epsilon \right\|_{L_2(\Omega(t^i))}^2 + w_{i+n_s} \left\| \hat{\mathbf{a}}_\epsilon - \mathbf{a}_\epsilon \right\|_{L_2(\Omega(t^i))}^2 \right). \quad (0.2)$$

## Problem (Identification problem)

Given observations  $(\Gamma_h(t^i), \hat{\mathbf{a}}(\mathbf{x}, t^i))$ ,  $\mathbf{x} \in \Gamma_h(t^i)$ ,  $i = 0, \dots, n_s$ , find parameters  $\mathbf{c}^* \in \mathcal{U}_{ad}$ , such that with  $(\Gamma^0, \mathbf{a}^0)$  defined by  $(\Gamma_h(t^0), \hat{\mathbf{a}}(\mathbf{x}, t^0))$ ,  $\mathbf{x} \in \Gamma_h(t^0)$  and  $(\Gamma(t), \mathbf{a}(\mathbf{x}, t))$ ,  $\mathbf{x} \in \Gamma(t)$ ,  $t \in (0, T]$  solutions of the forward problem,  $\mathbf{c}^*$  solves the minimisation problem

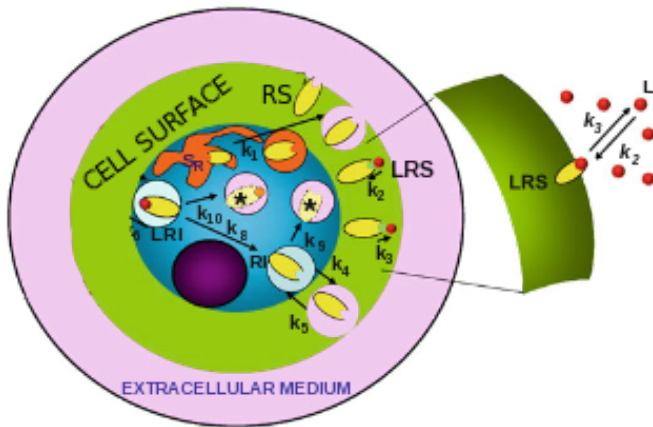
$$\min_{\mathbf{c} \in \mathcal{U}_{ad}} \mathcal{J}(\mathbf{c}), \quad \text{with } \mathcal{J}(\cdot) \text{ given by (0.1) or (0.2)}. \quad (0.3)$$



- Receptor-ligand interactions and the associated cascades of activation of signalling molecules, so called signalling cascades, are the primary mechanism by which cells sense and respond to their environment.
- Such processes therefore constitute a fundamental part of many basic phenomena in cell biology such as proliferation, motility, the maintenance of structure or form, adhesion, cellular signalling, etc..
- Due to the complexity of the biochemistry involved in in vivo signalling networks, an integrated approach combining theoretical studies with experimental and modelling efforts appears necessary.

# A ligand-receptor model

Joint work with Tom Ranner (Leeds, England) and Chandrashekar Venkataraman (St Andrews, Scotland)



- An exterior ( $\Omega(t)$ ) concentration of ligand ( $L$ ).
- The ligand concentration reacts at the surface ( $\Gamma(t)$ ) with receptors ( $RS$ ) to form ligand receptor complexes ( $LRS$ ).
- The receptors and ligand-receptor complexes can also be reversibly internalised.

- We focus on understanding a mathematical reduction of theoretical models for receptor-ligand dynamics in cell biology.
- The reaction under consideration is between mobile receptors that reside on the cell surface with ligands present in the **ECM** extra-cellular medium (the bulk region surrounding the cell).
- We assume a single species of mobile surface (cell membrane) resident receptor whose concentration (surface density) is denoted by  $c_r$  and a single species of bulk resident diffusible ligand whose concentration (bulk concentration) is denoted by  $c_L$ .
- The receptor and ligand react reversibly on the surface to form a (surface resident mobile) receptor-ligand complex, whose concentration is denoted by  $c_{rl}$ .
- The kinetic constants  $k_{\text{on}}$  and  $k_{\text{off}}$  represent the forward and reverse reaction rates.

Denoting by  $\Gamma$  the cell surface and by  $\Omega$  the extra-cellular medium with outer boundary  $\partial_0\Omega$  we have in mind models of the following form.

$$\left\{ \begin{array}{ll} \partial_t c_L - D_L \Delta c_L = 0 & \text{in } \Omega \times (0, T] \\ D_L \nabla c_L \cdot \boldsymbol{\nu} = -k_{\text{on}} c_L c_r + k_{\text{off}} c_{rl} & \text{on } \Gamma \times (0, T] \\ c_L = c_D \text{ or } D_L \nabla c_L \cdot \boldsymbol{\nu}_\Omega = 0 & \text{on } \partial_0\Omega \times (0, T] \\ \partial_t c_r - D_r \Delta_\Gamma c_r = -k_{\text{on}} c_L c_r + k_{\text{off}} c_{rl} & \text{on } \Gamma \times (0, T] \\ \partial_t c_{rl} - D_{rl} \Delta_\Gamma c_{rl} = k_{\text{on}} c_L c_r - k_{\text{off}} c_{rl} & \text{on } \Gamma \times (0, T], \end{array} \right.$$

together with suitable (bounded, non-negative) initial conditions. For the outer boundary condition we take either a Dirichlet or a Neumann boundary condition. The Dirichlet boundary condition, with  $c_D > 0$  a positive constant, arises due under the modelling assumption that the background concentration of ligands sufficiently far away from the cell is uniform. Alternatively, the Neumann boundary condition arises from assuming zero flux across  $\partial_0\Omega$ .

This can be formulated for moving cells: work in progress with Amal Alphonse and Joana Terra.

Let  $\Gamma$  be a smooth, compact closed  $n$ -dimensional hypersurface contained in a domain  $D \subset \mathbb{R}^{n+1}$ ,  $n = 1, 2$ . The surface  $\Gamma$  separates the domain  $D$  into an interior domain  $I$  and an exterior domain  $\Omega$ . We will denote by  $\partial_0\Omega$  the outer boundary of  $\Omega$ , i.e. the boundary  $\partial D$ . We will assume that this boundary is Lipschitz. We consider the following problem: Find  $u: \Omega \times [0, T] \rightarrow \mathbb{R}$  and  $w: \Gamma \times [0, T] \rightarrow \mathbb{R}$  such that

$$\delta_\Omega \partial_t u - \Delta u = 0 \quad \text{in } \Omega \quad (0.4a)$$

$$\nabla u \cdot \boldsymbol{\nu} = -\frac{1}{\delta_k} u w \quad \text{on } \Gamma \quad (0.4b)$$

$$u = u_D \text{ or } \nabla u \cdot \boldsymbol{\nu}_\Omega = 0 \quad \text{on } \partial_0\Omega \quad (0.4c)$$

$$\partial_t w - \delta_\Gamma \Delta_\Gamma w = \nabla u \cdot \boldsymbol{\nu} \quad \text{on } \Gamma \quad (0.4d)$$

$$u(\cdot, 0) = u^0(\cdot) \quad \text{in } \Omega \quad (0.4e)$$

$$w(\cdot, 0) = w^0(\cdot) \quad \text{on } \Gamma, \quad (0.4f)$$

where  $\delta_\Omega, \delta_\Gamma, \delta_k > 0$  and the initial data are bounded, nonnegative functions, i.e.,  $u^0 \in L_\infty(\Omega)$ ,  $w^0 \in L_\infty(\Gamma)$  and  $u^0, w^0 \geq 0$ . In the above  $\Delta_\Gamma$  denotes the Laplace-Beltrami operator on the surface  $\Gamma$  and  $\Delta$  the usual Cartesian Laplacian in  $\mathbb{R}^{n+1}$ . We will use either Dirichlet or Neumann boundary conditions on  $\partial_0\Omega$ . For the Dirichlet case, we assume that the Dirichlet boundary data  $u_D$  is a positive constant.

- **Signalling** Hynes (1992), Bongrand (1999), Locksley, Killeen, Leonardo (2001)
- **Parameter size** Glynn, Steward (1977) Friguier, Chafotte, Djavadi-Ohanian, Goldberg (1985)
- **Receptor, Ligand models** Garcia-Penarrubia, Galvez, Galvez (2013)
- **Turing models and signaling**  
Levine, Rappel (2005) Ratz, Roeger (2012, 2014) Madzvamuse, Chung, Venkataraman (2015)

- **Fast reaction limits**

Evans (1980), Bothe and Pierre (2001,2012)

Hilhorst, Van Der Hout Peletier (1996), Hilhorst, Iida, Mimura, Ninomiya (2001), Hilhorst, Mimura, Schaetzle (2003)

- **Elliptic and parabolic equations with nonlinear dynamic boundary conditions**

Athanasopoulos, Caffarelli (2010)

Vazquez, Vitillaro (2008,2009,2011)

- **Elliptic equations with surface free boundary problems**

Aitchison, Elliott, Ockendon (1983), Elliott, Friedman (1985), Colli, Kenmochi (1987)

Aitchison, Lacey, Shillor (1984), Caffarelli, Friedman (1985)

- **Hele-Shaw and Stefan problems**

Crowley (1979)

Elliott (1980), Elliott Janovsky (1981)

Duvaut (1973)

Rodrigues (1987)

## Theorem (Existence of a bounded, positive solutions )

Given bounded positive initial data  $u_0$  and  $w_0$ , there exists a solution pair  $(u, w)$  to (0.5). Furthermore, we have that in the case of Dirichlet data

$$\begin{aligned} 0 \leq u(x, t) &\leq \max(\|u_0\|_{L^\infty(\Omega)}, u_D) && \text{for a.e. } (x, t) \in \Omega \times (0, T) \\ 0 \leq w(x, t) &\leq \|w_0\|_{L^\infty(\Gamma)} && \text{for a.e. } (x, t) \in \Gamma \times (0, T), \end{aligned}$$

or in the case of Neumann data

$$\begin{aligned} 0 \leq u(x, t) &\leq \|u_0\|_{L^\infty(\Omega)} && \text{for a.e. } (x, t) \in \Omega \times (0, T) \\ 0 \leq w(x, t) &\leq \|w_0\|_{L^\infty(\Gamma)} && \text{for a.e. } (x, t) \in \Gamma \times (0, T). \end{aligned}$$



Find  $u: \Omega \times [0, T] \rightarrow \mathbb{R}$  and  $v: \Gamma \times [0, T] \rightarrow \mathbb{R}$  such that

$$\delta_\Omega \partial_t u - \Delta u = 0 \quad \text{in } \Omega \quad (0.5a)$$

$$\delta_k \nabla u \cdot \boldsymbol{\nu} = uv \quad \text{on } \Gamma \quad (0.5b)$$

$$u = u_D \text{ or } \nabla u \cdot \boldsymbol{\nu}_\Omega = 0 \quad \text{on } \partial_0 \Omega \quad (0.5c)$$

$$\partial_t v - \delta_\Gamma \Delta_\Gamma v + \nabla u \cdot \boldsymbol{\nu} = 0 \quad \text{on } \Gamma \quad (0.5d)$$

$$u(\cdot, 0) = u^0(\cdot) \quad \text{in } \Omega \quad (0.5e)$$

$$v(\cdot, 0) = v^0(\cdot) \quad \text{on } \Gamma, \quad (0.5f)$$

where  $\delta_\Omega, \delta_\Gamma, \delta_k > 0$  and the initial data are bounded functions, i.e.,  $u^0 \in L_\infty(\Omega)$ ,  $v^0 \in L_\infty(\Gamma)$  and  $u^0, -v^0 \geq 0$ .

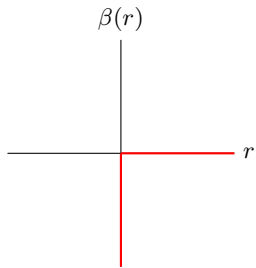
Find  $\bar{u}: \Omega \times (0, T) \rightarrow \mathbb{R}^+$ ,  $\bar{v}: \Gamma \times (0, T) \rightarrow \mathbb{R}^-$  such that

$$\begin{cases} \delta_\Omega \partial_t \bar{u} - \Delta \bar{u} = 0 & \text{in } \Omega \times (0, T) \\ \nabla \bar{u} \cdot \boldsymbol{\nu} + \partial_t \bar{v} - \delta_\Gamma \Delta_\Gamma \bar{v} = 0 \quad \text{and} \quad \bar{v} \in \beta(\bar{u}) & \text{on } \Gamma \times (0, T) \\ \bar{u} = u_D \quad \text{or} \quad \nabla \bar{u} \cdot \boldsymbol{\nu}_\Omega = 0 & \text{on } \partial_0 \Omega \times (0, T) \\ \bar{u}(\cdot, 0) = u^0(\cdot) \geq 0 & \text{in } \Omega \\ \bar{v}(\cdot, 0) = -w^0(\cdot) \leq 0 & \text{on } \Gamma. \end{cases}$$

Here  $\beta: \mathbb{R} \rightarrow \{0, 1\}^\mathbb{R}$  is the set valued function

$$\beta(r) = \begin{cases} \emptyset & \text{if } r < 0 \\ [-\infty, 0] & \text{if } r = 0 \\ \{0\} & \text{if } r > 0. \end{cases}$$

We consider this system as a parabolic equation with dynamic boundary conditions interpreted as a differential inclusion.



Sketch of the function  $\beta$

Find  $\tilde{u}: \Omega \times (0, T) \rightarrow \mathbb{R}$  and  $\tilde{v}: \Gamma \times (0, T) \rightarrow \mathbb{R}$  such that

$$\begin{cases} \delta_\Omega \partial_t \tilde{u} - \Delta \tilde{u} = 0 & \text{in } \Omega \times (0, T) \\ \nabla \tilde{u} \cdot \boldsymbol{\nu} + \partial_t \tilde{v} = 0 & \text{on } \Gamma \times (0, T) \\ \tilde{v} \in \beta(\tilde{u}) & \text{on } \Gamma \times (0, T) \\ \tilde{u} = u_D \quad \text{or} \quad \nabla \tilde{u} \cdot \boldsymbol{\nu} = 0 & \text{on } \partial_0 \Omega \times (0, T) \\ \tilde{u}(\cdot, 0) = u_0(\cdot) \geq 0 & \text{on } \Omega \\ \tilde{v}(\cdot, 0) = -w_0(\cdot) \leq 0 & \text{on } \Gamma, \end{cases}$$

where  $\beta: \mathbb{R} \rightarrow \{0, 1\}^{\mathbb{R}}$  is the set valued function defined in (20).

# Elliptic limit problem with dynamic boundary condition ( $\delta_\Omega = \delta_\Gamma = \delta_k = 0$ )

Find  $\hat{u}: \Omega \times (0, T) \rightarrow \mathbb{R}$  and  $\hat{v}: \Gamma \times (0, T) \rightarrow \mathbb{R}$  such that

$$\begin{cases} -\Delta \hat{u} = 0 & \text{in } \Omega \times (0, T) \\ \nabla \hat{u} \cdot \boldsymbol{\nu} + \partial_t \hat{v} = 0 & \text{on } \Gamma \times (0, T) \\ \hat{v} \in \beta(\hat{u}) & \text{on } \Gamma \times (0, T) \\ \hat{u} = u_D & \text{on } \partial_0 \Omega \times (0, T) \\ \hat{u}(\cdot, 0) = u_0(\cdot) \geq 0 & \text{on } \Omega \\ \hat{v}(\cdot, 0) = -w_0(\cdot) \leq 0 & \text{on } \Gamma, \end{cases}$$

where  $\beta: \mathbb{R} \rightarrow \{0, 1\}^{\mathbb{R}}$  is the set valued function defined earlier.

Set

$$z(\cdot, t) = \int_0^t \hat{u}(\cdot, s) ds,$$

where  $u$  solves the elliptic dynamic BC problem with  $u_D = 1$  for simplicity. The pair  $(z, \hat{v})$  satisfy the following problem:-

For each  $t \in (0, T)$ , find  $z(t) \in H^1(\Omega)$  and  $\hat{v}(t) \in L^2(\Gamma)$  such that

$$\begin{aligned} -\Delta z &= 0 && \text{in } \Omega \\ \nabla z \cdot \boldsymbol{\nu} + \hat{v} &= v^0 \leq 0 && \text{on } \Gamma \\ \hat{v} &\in \beta(z) && \text{on } \Gamma \\ z &= t && \text{on } \partial_0 \Omega. \end{aligned}$$

**EVI:** find  $z \in K_t$  such that

$$\int_{\Omega} \nabla z \cdot \nabla(\eta - z) \geq \int_{\Gamma} v^0(\eta - z) \quad \forall \eta \in K_t.$$

$$K_t := \{f \in H_{e_t}^1(\Omega) | f \geq 0\}$$

**PVI** find  $z \in K_t$  such that

$$\int_{\Omega} \delta_{\Omega} \partial_t z \eta + \nabla z \cdot \nabla(\eta - z) \geq \int_{\Omega} \gamma u^0(\eta - z) + \int_{\Gamma} v^0(\eta - z) \quad \forall \eta \in K_t.$$

## Connections with the (steady) one-phase Stefan and Hele-Shaw problems

We denote by  $A^0 : H^{1/2}(\Gamma) \rightarrow H^{-1/2}(\Gamma)$  the so called Dirichlet-to-Neumann (DtN) map defined as follows, for  $\phi \in H^1(\Omega)$

$$\int_{\Gamma} A^0 \phi \eta = \int_{\Gamma} \nabla \phi \cdot \nu \eta \quad \forall \eta \in H_{e_0}^1(\Omega).$$

Thus we may write the elliptic VI find  $z \in K_t$  s.t,

$$\int_{\Gamma} A^0 z (\eta - z) \geq \int_{\Gamma} v^0 (\eta - z) \quad \forall \eta \in K_t.$$

We may also introduce in a similar fashion the (DtN) map  $A^{\delta\Omega}$  associated with the bulk parabolic equation.

Finally, we note that the half-Laplacian  $(-\Delta_{\Gamma})^{1/2}$  of a function on  $\Gamma$  may be defined through the DtN map of the harmonic extension of the function. We may relate two of these limit problems to the classical Hele-Shaw and steady one phase Stefan problems by replacing the usual Laplacian  $(-\Delta)$  (or Laplace-Beltrami in the case of a surface) by the (DtN) map.

Thus we conclude that our elliptic variational inequalities are “simply” a one-phase Stefan or Hele-Shaw problem on the surface  $\Gamma$  in which the differential operator is the half-laplacian.

## Degenerate parabolic equations

*Fast reaction limit* ( $\delta_k = 0$ )

Find  $\bar{u} \in L^2(0, T; H^{1/2}(\Gamma))$  and  $\bar{v} \in L^2(0, T; H^1(\Gamma))$  with  $\partial_t \bar{v} \in L^2(0, T; H^{-1}(\Gamma))$  such that

$$\begin{aligned}\partial_t \bar{v} + \delta_\Gamma L \bar{v} + A^{\delta_\Omega} \bar{u} + U_D^\nu + U_I^\nu &= 0 && \text{in } L^2(0, T; H^{-1}(\Gamma)) \\ \bar{v} &\in \beta(\bar{u}) && \text{on } \Gamma \times (0, T) \\ \bar{u}(\cdot, 0) &= u^0 && \text{in } \Omega.\end{aligned}$$

*Parabolic equation with dynamic boundary condition* ( $\delta_k = \delta_\Gamma = 0$ )

Find  $\tilde{u} \in L^2(0, T; H^{1/2}(\Gamma))$  and  $\tilde{v} \in L^2(0, T; L^2(\Gamma))$  with  $\partial_t \tilde{v} \in L^2(0, T; H^{-1/2}(\Gamma))$  such that

$$\begin{aligned}\partial_t \tilde{v} + A^{\delta_\Omega} \tilde{u} + U_D^\nu + U_I^\nu &= 0 && \text{in } L^2(0, T; H^{-1/2}(\Gamma)) \\ \tilde{v} &\in \beta(\tilde{u}) && \text{on } \Gamma \times (0, T) \\ \tilde{v}(\cdot, 0) &= v^0 && \text{in } \Omega.\end{aligned}$$

*Elliptic equation with dynamic boundary condition* ( $\delta_k = \delta_\Gamma = \delta_\Omega = 0$ ) Find

$\hat{u} \in L^2(0, T; H^{1/2}(\Gamma))$  and  $\hat{v} \in L^2(0, T; L^2(\Gamma))$  with  $\partial_t \hat{v} \in L^2(0, T; H^{-1/2}(\Gamma))$  such that

$$\begin{aligned}\partial_t \hat{v} + A^0 \hat{u} + U_D^\nu &= 0 && \text{in } L^2(0, T; H^{-1/2}(\Gamma)) \\ \hat{v} &\in \beta(\hat{u}) && \text{on } \Gamma \times (0, T) \\ \hat{v}(\cdot, 0) &= v^0 && \text{in } \Omega.\end{aligned}$$



Bye Bye!

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