Acupunture, Modeling, and Simulation

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Outline

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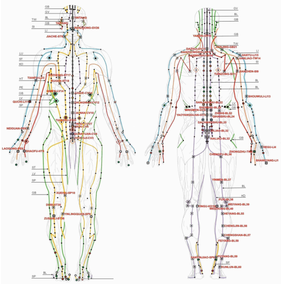
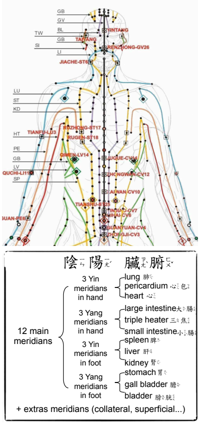
Acupuncture



http://en.wikipedia.org/wiki/Meridian_(Chinese_medicine)

- Acupuncture (針) and moxibustion (灸) are two minimally invasive procedures of traditional Chinese medicine.
- Applications include
  - alternative treatment to chemotherapy,
  - analgesic treatment,
  - depression and anxiety treatment,
  - alcohol and tobacco withdrawal treatment,
  - gastrointestinal disorder treatment,
  - skin condition treatment.

Foundation of traditional Chinese medicine (Cheng, 1987)



- Needles can be used to stimulate specific points on the body, namely acupoints (*xuè*, 穴), distributed along the meridians and collaterals.
- The meridians and collaterals (*jīng luò*, 經絡) are pathways along which the *qì*, blood, and body fluids flow.
- *Qì*, blood, and body fluids are the three fundamental material foundations for the physiological functions of the *zàng-fŭ* (臟腑) organs, tissues, and meridians.
- Meridians are connected to the *zàng fŭ* organs internally and extend over the body externally to form a network linking tissues and organs into a whole.
- The complex relationships of *qì*, blood, and body fluids manifest in physiology and are important in determining the treatment to adopt.
- Balance of the *yīn* (陰) and *yáng* (陽) is achieve by removing blocks in the flow of *qì* (氣) at acupoints.
- Proper manipulation leads to the *dé qì* (得氣) sensation.

Acupuncture framework

- There is a great demand for explanations regarding the basic concepts such as *qì*, meridians, and acupoints.
- Anatomical and physiological natures of acupoints and meridians are not yet fully understood.

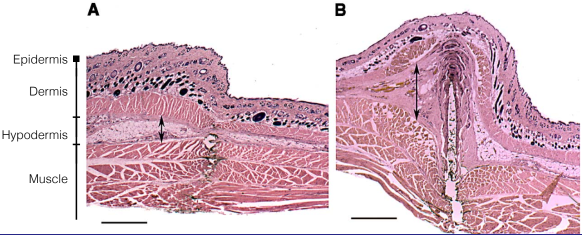
The absence of complete scientific background of the acupuncture biochemical mechanisms has motivated us to carry out modeling and numerical simulation of both macroscopic and microscopic aspects of the acupuncture process.

Motivation

Creation of a biologically relevant mathematical acupuncture model.

External stimuli

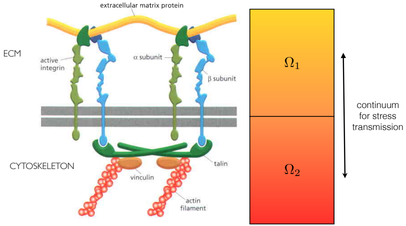
An acupuncture needle was inserted with no rotation (A) or unilateral rotation (B). (Bar = 1 mm)



Hypodermis main constituents (Iatridis et al., 2003)

- connective loose tissue,
- extracellular matrix : mesh-like medium (sparse collagen and elastic fibers immersed in a gel of glycoproteins and proteoglycans) that can bear gelification or fluidization,
- scattered cells : mastocytes, macrophages, fibroblasts, lymphocytes, adipocytes,
- high density of blood and lymphatic vessels and nerves terminals,
- high concentration of ions.

Signal development



Mechanotransduction

- refers to the various mechanisms by which cells convert mechanical stimuli into biochemical activity,
- results from stress transmission to the plasma membrane by the strained extracellular matrix.

Motivation

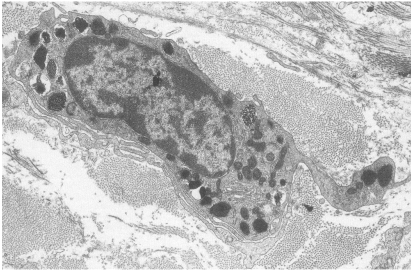
Computation of the stress field affecting the cell membrane.

Signal development

Mastocyte (肥大細胞)

Immunocyte that

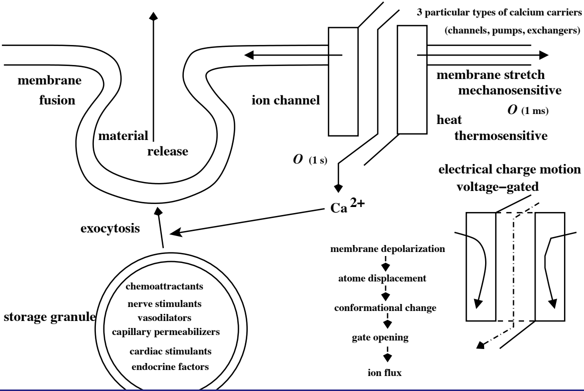
- is found in large quantity in connective tissue,
- contains granules storing chemical mediators,
- releases granule content within minutes,
- resynthesizes its content upon release.



Signal development

Cell responses to a physical field

- Mastocyte stimulation by a physical process opens calcium ion channel.
- Cytosolic Ca^{2+} causes granule transport to the membrane and release of its content.



Signal development

Operation mode

- 4 main techniques that can be combined

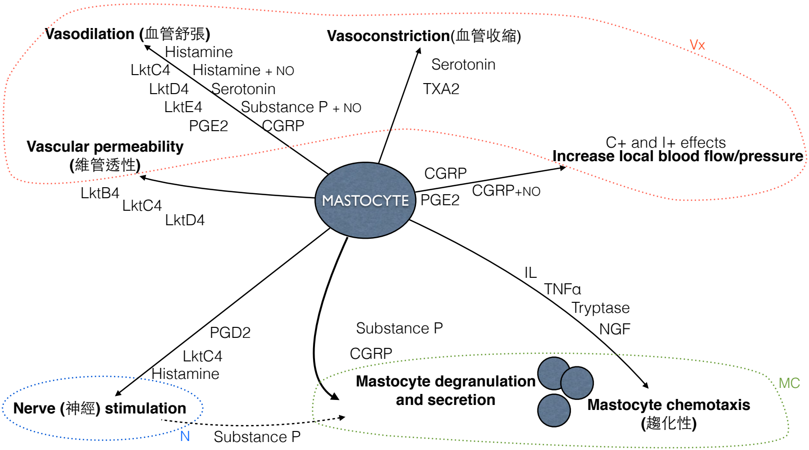
  acupuncture development of a local mechanical stress field by needle motions (lifting–thrusting cycle or rotation)or applying finger pressure at the acupoint (mechanotransduction),

  moxibustion development of a local temperature field by directly or indirectly applying a heating moxa (mugwort herb) at acupoints (thermotransduction),

  electroacupuncture development of a local electrical field by applying a small electric current between a pair of acupuncture needles at acupoints (electrotransduction),

  laser acupuncture stimulation of photosensitive GPCRs by laser light at acupoints (phototransduction).

Signal development



Signal development

Acupoint - Primary actors

Mastocytes
- are present in large density in the hypodermis,
- contain granules storing chemical mediators,
- release granule content within minutes for intra-, auto-, juxta-, para-, and endocrine signaling.

Neural terminals high density

Capillaries high density

Ions high concentrations (K^{+}, Ca^{2+}, Fe^{2+}, Mn^{2+}, Zn^{2+}, PO_4^{3-}).

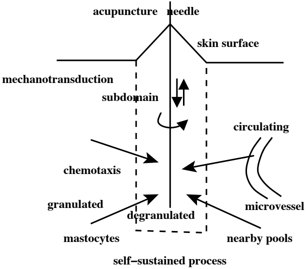
Signal development

Mastocyte chemotactic recruitment acupoints

Self-sustained process that enables continuous secretion of messengers by arrivals of new mastocyte pools from nearby capillaries and regional mastocyte populations

Chemotaxis of circulating and tissular mastocytes

1. transmigration of circulating mastocytes (across blood vessel walls, i.e., exit from blood),
2. migration of loaded (granulated) mastocytes across a region of low-amplitude mechanical stress [threshold ℓ]),
3. migration across a region of triggering mechanical stress and unloading (degranulation) [0—ℓ].



Signal transmission

Adjoining and remote targets

Nerve terminals
- immediate triggering (O[1 s–1mn]) of fast, short-lived action potentials, but sustained action due to cell recruitment,
- hyperemia in a given local brain region (attractor for endocrine messengers),
- neurotransmission using endocannabinoids, antalgics, etc.

Capillaries
- increase in permeability (enhanced transport),
- blood and lymph convection of endocrine messengers to the brain,
- delayed, slower, but sustained (because of cell recruitment),

Heart increase in blood flow rate.

Brain wanted afferent signaling.

Model of the chemotactic response of mastocytes to a physical stress

Motivation : Creation of a biologically relevant mathematical acupuncture model.

1. Conception an acupuncture framework for mathematical modeling :
   - identification involved biological and physical processes,
   - selection of major involved biological, physical, and chemical variables.

Summary of events

- generation of a local stress field
- mechano-, thermo-, electro-, photo- transduction
- Ca^{2+} entry via ion channels
- granule exocytosis (substance release)
- triggering of action potential (early, quick response)
- chemotaxis (mastocytes from regional pools and blood)
- degranulation of newly arrived mastocytes at acupoints (autosustained process)
- local elevation of vascular permeability (enhanced endocrine signaling)
- vasodilation with increased blood flow (cardiac effect)
- delayed, permanent endocrine signaling to central nervous system (preferential distribution in hyperemic region)

Model of the chemotactic response of mastocytes to a physical stress

Motivation : Creation of a biologically relevant mathematical acupuncture model.

2 Conception of a mathematical model of the chemotactic response of mastocytes to a physical stress

Hypothesis A self-sustained process is created via recruitment of the circulating mastocytes and excitation of regional pools of mastocytes.

Method

- chemotaxis PDE model of the Keller-Segel type with a local forcing term, release of chemoattractants, nerve messengers, and cardiovascular stimulants by the mastocytes,
- mathematical analysis of a reduced PDE model of the nonlinear degenerate parabolic type,
- model equations solved with the finite element method.

Results The numerical study infers the theoretical results and the observed blow-up interpreted as a hyper reactivity at the acupoint where a large quantity of mastocytes are present. Permanent signaling can be provided by chemotaxis and continuous recruitment of mastocytes.

Mechanobiological model of the stress field affecting the cell membrane

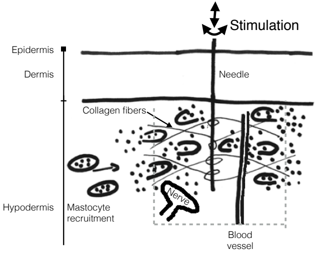
Motivation : Computation of the stress field affecting the cell membrane.

3 Conception of a biomechanical model of the interstitial fluid flow driven by a needle motion (moving domain)

Hypothesis Mechanical stimuli sensed by cells is local and acute at acupoint.

Method Convective incompressible Brinkman equations solved with an arbitrary Lagrangian–Eulerian (ALE) finite element scheme.

Results Numerical prediction of fluid pressure and shear stress field that can be sensed by local pools of mastocytes.



Outline

Data & hypotheses

- Relatively high density of resting mastocytes at acupoints;
- 2 mastocyte states according to localization w.r.t. acupoint: granulated and degranulated;
- Quasi-instantaneous release of chemical mediators upon stimulation (mechanotransduction & calcium influx);
- release of chemoattractants, nerve messengers, and endocrine messengers;
- delayed regeneration of granules content,
- negligible convection in the matrix

Variables

For $x \in \Omega$ bounded and $t \in \mathbb{R}^+$:

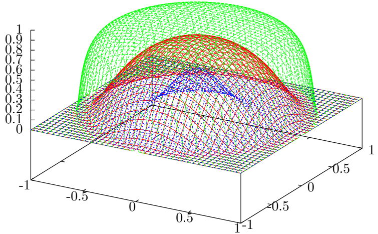
- $n_g(t, x)$: density of granulated mastocytes
- $n_d(t, x)$: density of degranulated mastocytes
- $c(t, x)$: concentration of chemoattractant
- $s_n(t, x)$: concentration of nerve stimulant
- $s_e(t, x)$: concentration of endocrine stimulant

Model (Deleuze, 2013; Thiriet, Deleuze, and Sheu, 2015)

$$\begin{aligned}
\frac{\partial n_g}{\partial t} - \mathcal{D}_m \nabla^2 n_g + \nabla.(\mathrm{S}\, n_g \nabla c) &= -\mathrm{A}\Phi n_g + k_r n_d, \quad t > 0, x \in \Omega \\
\frac{\partial c}{\partial t} - \mathcal{D}_c \nabla^2 c &= \kappa_c \mathrm{A}\Phi n_g - \delta_c c, \\
\frac{\partial n_d}{\partial t} - \mathcal{D}_m \nabla^2 n_d &= \mathrm{A}\Phi n_g - k_r n_d, \\
\frac{\partial s_n}{\partial t} - \mathcal{D}_n \nabla^2 s_n &= \kappa_n \mathrm{A}\Phi n_g - \delta_n s_n, \\
\frac{\partial s_e}{\partial t} - \mathcal{D}_e \nabla^2 s_e &= \kappa_e \mathrm{A}\Phi n_g - \delta_e s_e.
\end{aligned} \tag{1}$$

- $\Phi(x)$: magnitude of mechanical stress;
- $\mathcal{D}_{m/c/n/e}$: diffusivity (mastocyte/chemoattractant/nervous messenger/endocrine mediator) $[\mathrm{L}^2\mathrm{T}^{-1}]$;
- A: activation rate $[\mathrm{T}^{-1}]$;
- k_r: regeneration rate of degranulated mastocytes $[\mathrm{T}^{-1}]$;
- S: mastocyte sensitivity to chemoattractant (index that measures chemoattractant power, i.e., migration distance par unit concentration and unit time $[\mathrm{L}^4\mathrm{mol}^{-1}\mathrm{T}^{-1}]$);
- $\kappa_{c,e,n}$: release quantity coefficient [mol];
- $\delta_{c,e,n}$: degradation rate $[\mathrm{T}^{-1}]$.

Physical stress Φ



Φ is C^∞ compactly supported function from $\mathbb{R}^2$ to $[0,1]$

$$\Phi(x) \leq 1, \forall x \in \mathbb{R}^2,$$

$$\Phi(x) = 0, \forall x \in \mathbb{R}^2, |x| \geq \ell.$$

ℓ denote the subdomain close to the needle ($|x| < \ell$) where physical constraint magnitude is high enough.

Spatial distribution of the cell population (Perthame, 2007)

Definition : total number of cells

$$m_0(t) := \int_{\mathbb{R}^2} n(t,x)dx;$$

Definition : second x moment

$$m_2(t) := \int_{\mathbb{R}^2} \frac{|x|^2}{2} n(t,x)dx.$$

Blow-up condition in the case of a sole state for mastocytes

$$\begin{aligned} \partial_t n - \nabla^2 n + \nabla.(S\, n \nabla c) &= -A\Phi n; & (2)\\ -\nabla^2 c &= \kappa_c A \Phi n; & (3)\\ n|_{t=0} &= n^0 \geq 0. & (4)\\ t > 0; \quad \mathbf{x} \in \mathbb{R}^2. \end{aligned}$$

Theorem (Deleuze, 2013)

In $\mathbb{R}^2$, let $p > 1$ and assume that $n^0 \in L^1_+(\mathbb{R}^2, (1+|x|^2)dx)$.

- If the initial total number of cells is small enough, there exists a solution to (2)-(4) in $L^p(\mathbb{R}^2, dx)$ for all times.
- Let $[0, T^*)$ be the maximal interval of existence. Then, if the initial number of cells is large enough and the second momentum is small enough, the solution of (2)-(4) blows-up as $t \to T^*$.

Interpretation from the mathematical analysis

Blow-up corresponds to the significant recruitment of mastocytes at the treated acupoint. The theorem gives the conditions for the effectiveness of acupuncture :

- the initial number of mastocytes is large enough and
- the initial dispersion of the population of cells is small enough.

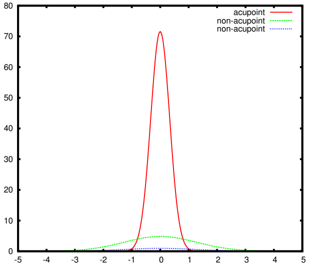


Figure: Red : acupoint ($m_0(0) = 50$, $m_2(0) = 11.12$); green : non-acupoint ($m_0(0) = 50$, $m_2(0) = 165.19$). Blue : non-acupoint ($m_0(0) = 10$).

Acupoint vs non-acupoint

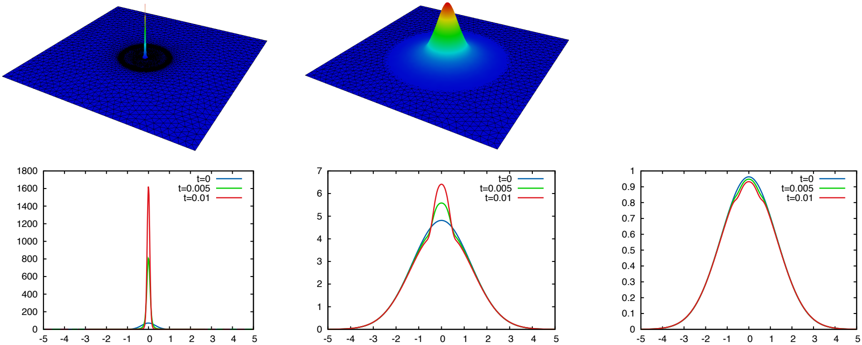
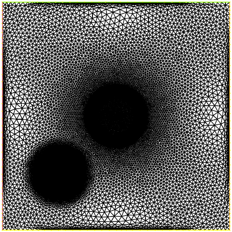
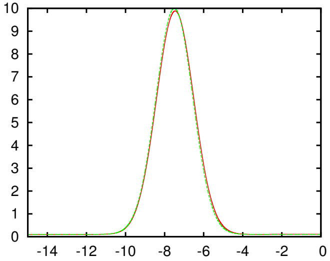
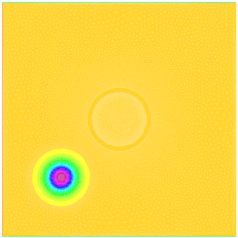


Figure: Dynamics of the density of granulated mastocytes. (left) Acupoint : $m_0(0) = 50.00$, $m_2(0) = 11.12$; (middle) Non-acupoints : $m_0(0) = 50.00$, $m_2(0) = 165.19$; (left) Non-Acupoint : $m_0(0)0 = 10.00$.

Needling outside an acupoint







Discussion

Results

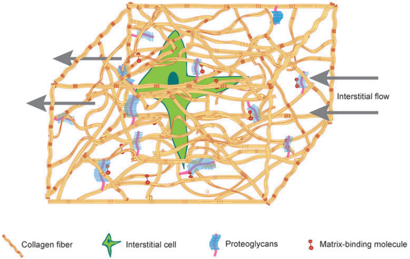
- Proposed model can help gain a better understanding of the role of chemotactic recruitment of mastocytes in response to physical stimuli.
- The mathematical analysis of a simplified model can a mechanism for blow-up in the chemotactic mechanism during acupuncture.
- Expected numerical blow-up solution (success of treatment) is obtained depending on the initial mastocyte distribution (acupoint/non-acupoint), and on the proper needle location.

Limitations

- The blow-up solution is already a limitation of the proposed model that corresponds to an over-simplification of the biology.
- The lack of experimental data.

Outline

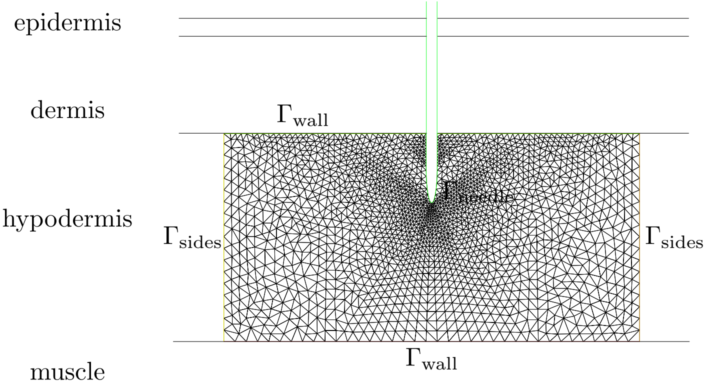
Subcutaneous loose connective tissue



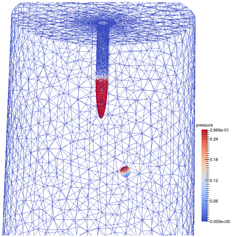
[Alberts, B. Molecular biology of the cell, 2007]

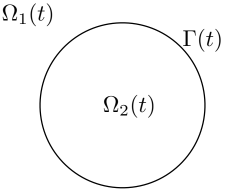
- Extracellular matrix : mesh-like medium (sparse collagen and elastic fibers immersed in a gel of glycoproteins and proteoglycans) that can bear gelification or fluidization,
- The interstitial fluid (IF) (water + ions + small molecules = plasma - large molecules : Stokes flow) interacts with the ground substance (expansion of a dense network of proteoglycans due to water) to form a gel-like medium.

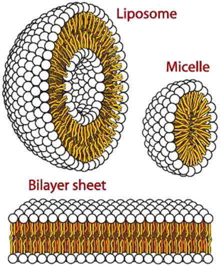
Computational domain



Computational domain







Merlet, Benoît. "A Highly Anisotropic Nonlinear Elasticity Model for Vesicles" (2015)

Incompressible convective Brinkman model (Deleuze, Thiriet, and Sheu, 2015)

The extracellular and intracellular can be modeled by a incompressible viscous fluid in porous medium and thus modeled by the incompressible convective Brinkman equation.
The fluid-structure interaction problems investigated are solved with the finite element method and the ALE approach. The membrane is considered as a viscoelastic structure such that the evolution of its displacement $\mathbf{d}$ is given by

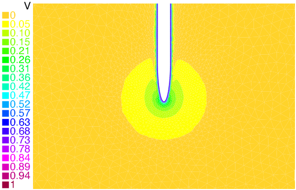
$$\rho_s \frac{\partial^2 \mathbf{d}}{\partial t^2} - \sigma \frac{\partial^2 \mathbf{d}}{\partial x^2} - K \frac{\partial^2}{\partial x^2}\frac{\partial \mathbf{d}}{\partial t} = \sum_i \mathbf{T}_{\mathbf{FL_i}} \quad \text{in } \Gamma \times (0, T) \tag{5}$$

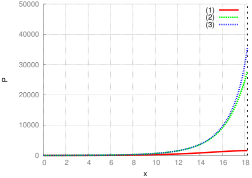
The intra- and extracellular flow velocities and pressure are given by the convective Brinkman equations stated as follows

$$\begin{aligned} \frac{1}{\alpha_i}\frac{\partial \mathbf{u_i}}{\partial t} + \frac{1}{\alpha_i}\mathbf{u_i} \cdot \boldsymbol{\nabla}\left(\frac{\mathbf{u_i}}{\alpha_i}\right) - \frac{1}{\mathrm{Re}_i}\nabla^2 \mathbf{u_i} + \frac{1}{\alpha_i}\boldsymbol{\nabla}(\alpha_i p_i) = \frac{-1}{\mathrm{Da}_i \mathrm{Re}_i}\mathbf{u_i} \quad & \text{in } \Omega_i \times (0, T), \\ \boldsymbol{\nabla} \cdot \mathbf{u_i} = 0 \quad & \text{in } \Omega_i \times (0, T) \end{aligned} \tag{6}$$

$\alpha_i = \frac{\text{fluid volume}}{\text{total volume}}$: fluid volume fraction (effective porosity),

Simulated velocity and pressure profiles





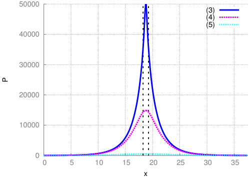
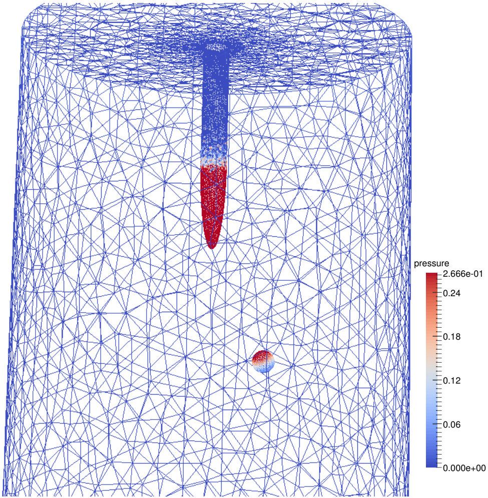


Figure: The lines in dots show the x-position of the needle. $\mathrm{Re} = 0.208$, $\mathrm{Da} = 3.48 \times 10^{-05}$, $\alpha_f = 0.6$ (Swartz and Fleury, 2007).

Simulated velocity and pressure profiles with an interstitial cell



Simulated mean shear stress on the cell surface

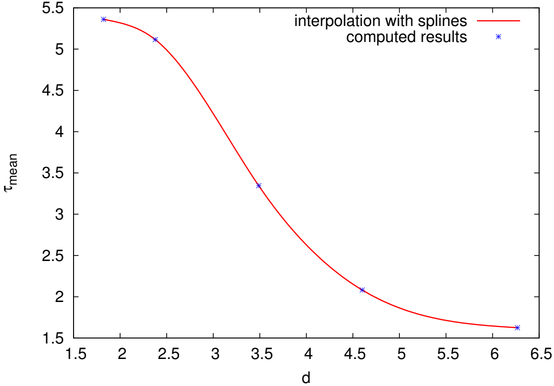


Figure: The simulated mean shear stress τ_{mean} on the cell surface with respect to the distance d measured from the needle. A higher shear stress is expected to be observed at a location close to the needle.

Discussion

Results

- The proposed model for the interstitial flow is able to describe the shear stress and pressure on a given cell.
- High local fluid pressure and shear stress on cells are most likely to appear near the needling region.

Limitations

- The fractional fluid volume and Darcy permeability only describe the macroscopic property of the fiber matrix.
- The proposed method does not allow the rotation of the needle to be taken into account.

Acupuncture framework

1. Needle - mastocyte interaction (In progress)
   - needle implantation, generation of local stress field
   - interstitium considered as a porous medium
   - Flow/structure interaction (Brinkman model)
2. Ion channel gating (In progress)
   - Ca^{2+} entry
   - PNP - NS model
3. Mastocyte degranulation (In progress)
   - granule exocytosis
   - release of chemoattractants, nerve messengers, cardiovascular stimulants
   - flow-structure interaction (elasticity and NS equations)
4. Mastocyte recruitment (In progress)
   - chemotaxis (KS model)
   - forced local stress field
   - release of chemoattractants, nerve messengers, cardiovascular stimulants
   - interaction with interstitial fluid (coupled Stokes/KS model)
5. Signal transmission to brain (To be investigated)

Thank you for your attention.

Yannick Deleuze

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Pôle Modélisation et Simulation

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