On a computational framework of studying needle cell interaction in acupuncture manipulation - a preliminary study

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（許文翰）

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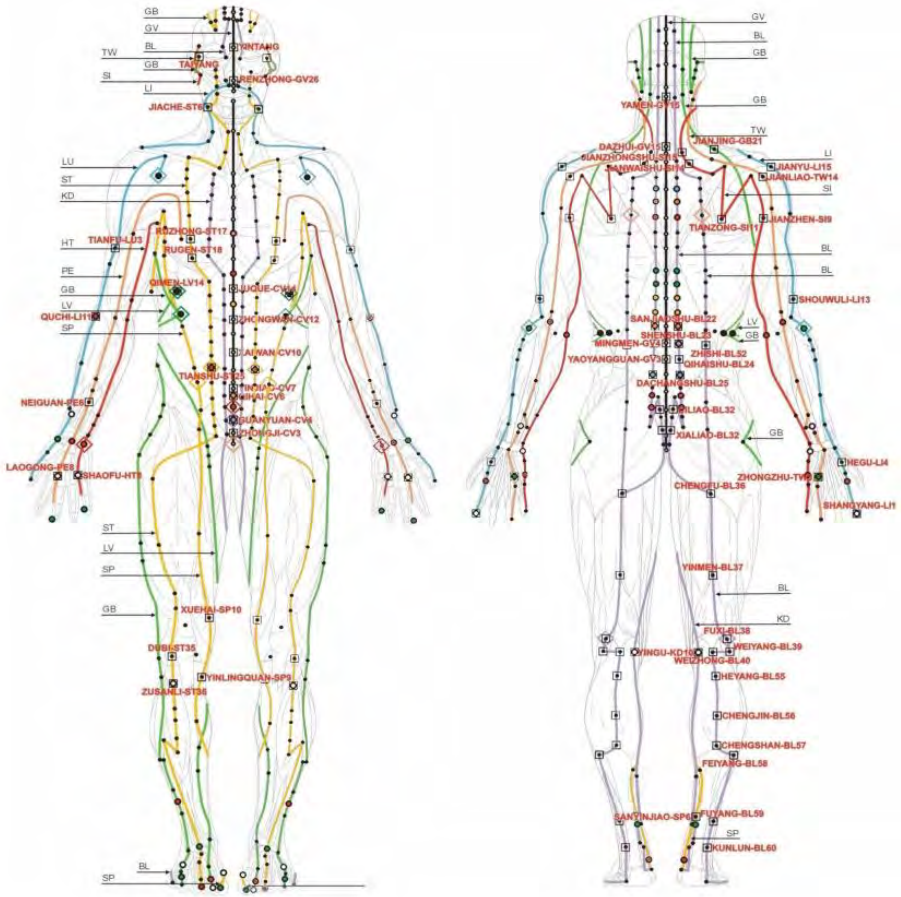
Contents

1. Introduction on Chinese medicine
2. Motivation and objectives
3. Description of the framework of needle – mastocyte studies
    1. Needle / mastocyte interaction
    2. Transport of Ca^{2+} through ion channel of a mastocyte
    3. Mastocyte degranulation through exocytosis
    4. Mastocyte chemotactic recruitment

Introduction on Chinese medicine



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

Stimulation of acupoints via hair-thin needles or moxa stick in order to restore the balance between Yin (陰) and Yang (陽) energies by removing blockages in the flow of Qi (氣).

Introduction on Chinese medicine

1. Applications
   - Anesthesia (麻醉): appropriate + quick postoperative recovery + low cost health system (to be promoted)
     Brain: a wonderful chemical processor (natural analgesia (無痛覺) & anesthesia).
   - Pains treatment
     - Gastrointestinal (腸胃) disorders.
     - Musculoskeletal (骨關節) disorders.
     - Skin condition.
2. Modes of operation
   - signaling via nervous impulses
   - signaling via endocrine (內分泌的) messengers conveyed by blood flow. They must cross bloodbrain barrier (BBB) or more permeable capillary networks in neuroendocrine (神經內分泌) nuclei.

Introduction on Chinese medicine

- 4 main techniques that can be combined for treatment use

Acupuncture

Development of a **local mechanical stress** field by needle motions (lifting–thrusting cycle or rotation) at acupoints or applying finger pressure at the acupoint (mechanotransduction) ;

Moxibustion

Development of a **local temperature field** by directly applying a heating moxa (mugwort herb) stick on the skin or indirectly by applying this stick ot the acupuncture needle 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) ;

Laseracupuncture

Stimulation of **photosensitive GPCRs** by laser light at acupoints in the absence of physical effects (phototransduction).

Introduction on Chinese medicine

Primary players

Mastocyte

- are present in large density in the hypodermis (皮下組織),
- contains granules storing chemical mediators,
- release granule content within minutes for intra-, auto-, juxta-, para-, and endocrine signaling.

Neural terminals

(i) Capillaries

high density

(ii) Ions

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

Introduction on Chinese medicine

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 (充血) in a given local brain region (attractor for endocrine messengers) ;
- neurotransmission using endocannabinoids (大麻), antalgics, etc.

Capillaries

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

Introduction on Chinese medicine

Adjoining and remote targets

Heart

- increases the blood flow rate

Brain

- receives afferent (向心的) signaling

Introduction on Chinese medicine

Basic transducers

- Mastocyte stimulation by a physical process opens calcium ion channel;
- Cytosolic Ca^{2+} causes granule transport to the cell surface and liberation of its content

activated ion channel O(ms)
$[Ca^{2+}]_i$ O(s)

1. Mechanosensitive Ca^{2+} channel
2. Thermosensitive Ca^{2+} channel
3. Voltage-gated Ca^{2+} channel
4. Ca^{2+} channel coupled with photosensitive GPCRs

Summary of events in acupuncture manipulation

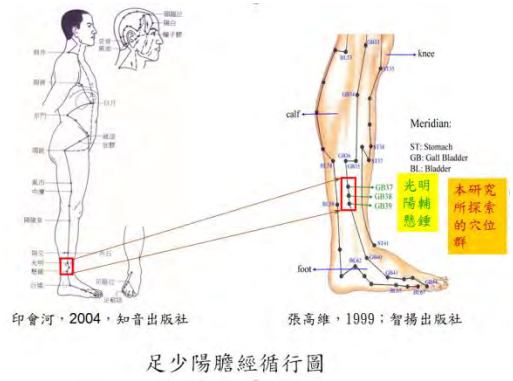
- generation of a local stress field.
- mechano-, thermo-, electro-, photo- transduction.
- Ca^{2+} entry via ion channels.
- granule exocytosis (substance release).
- triggering of action potential (early, quick response).
- chemotaxis (mastocytes from regional pools and blood).
- degranulation of newly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

Summary of the previous study on Chinese medicines

1. Acupuncture (針)

(A) Macroscopic aspect – Development of an **electro-osmotic** model for simulating chi-blood interaction.

1. 中國針灸, 27, 589-593, 2007.
2. J. of Accord Integrative medicine, 4(2), 97-107, 2008.
3. Int. J. for Numerical Methods in Fluid, 56, 739-751,2008.



足少陽膽經循行圖

(1)動量守恒方程式

$$\frac{\partial \mathbf{V}}{\partial t} + \mathbf{V}\cdot\nabla\mathbf{V} = -\nabla P + \frac{1}{Re}\nabla^2\mathbf{V} + \alpha\,\psi\,\nabla\phi$$

Electrokinetic force due to electric double layer formation next to the no-slip surface

(2)質量守恒方程式

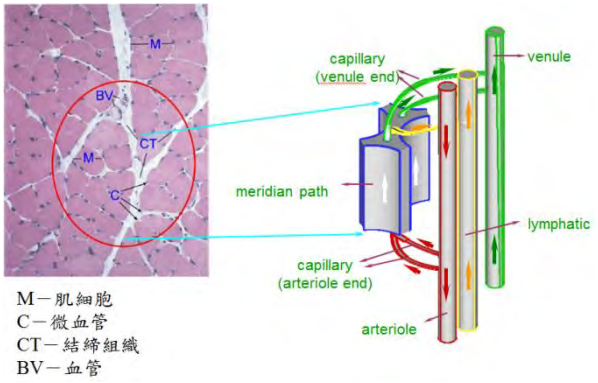
$$\nabla\cdot\mathbf{V} = 0$$

(3)描述電雙邊之Helmholtz方程式

$$\nabla^2\psi = \kappa^2\psi$$

(4)描述外加電場之Laplace方程式

$$\nabla^2\phi = 0$$



M－肌細胞
C－微血管
CT－結締組織
BV－血管

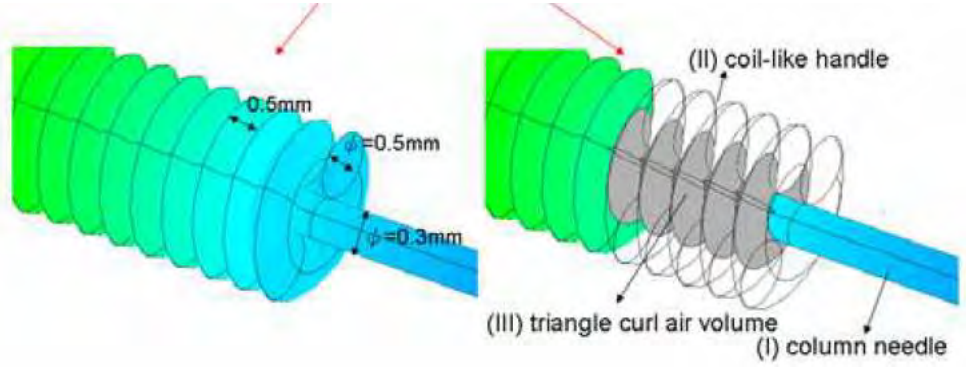
(B) Microscopic aspect – Under current investigation.

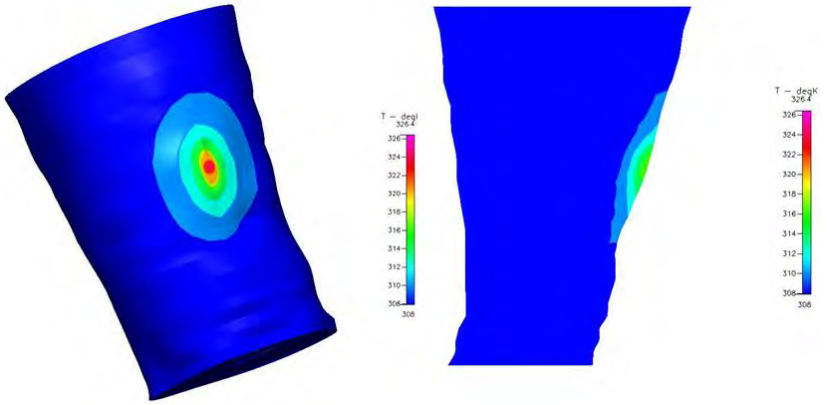
Summary of the previous study on Chinese medicines

2. Moxibustion (灸)

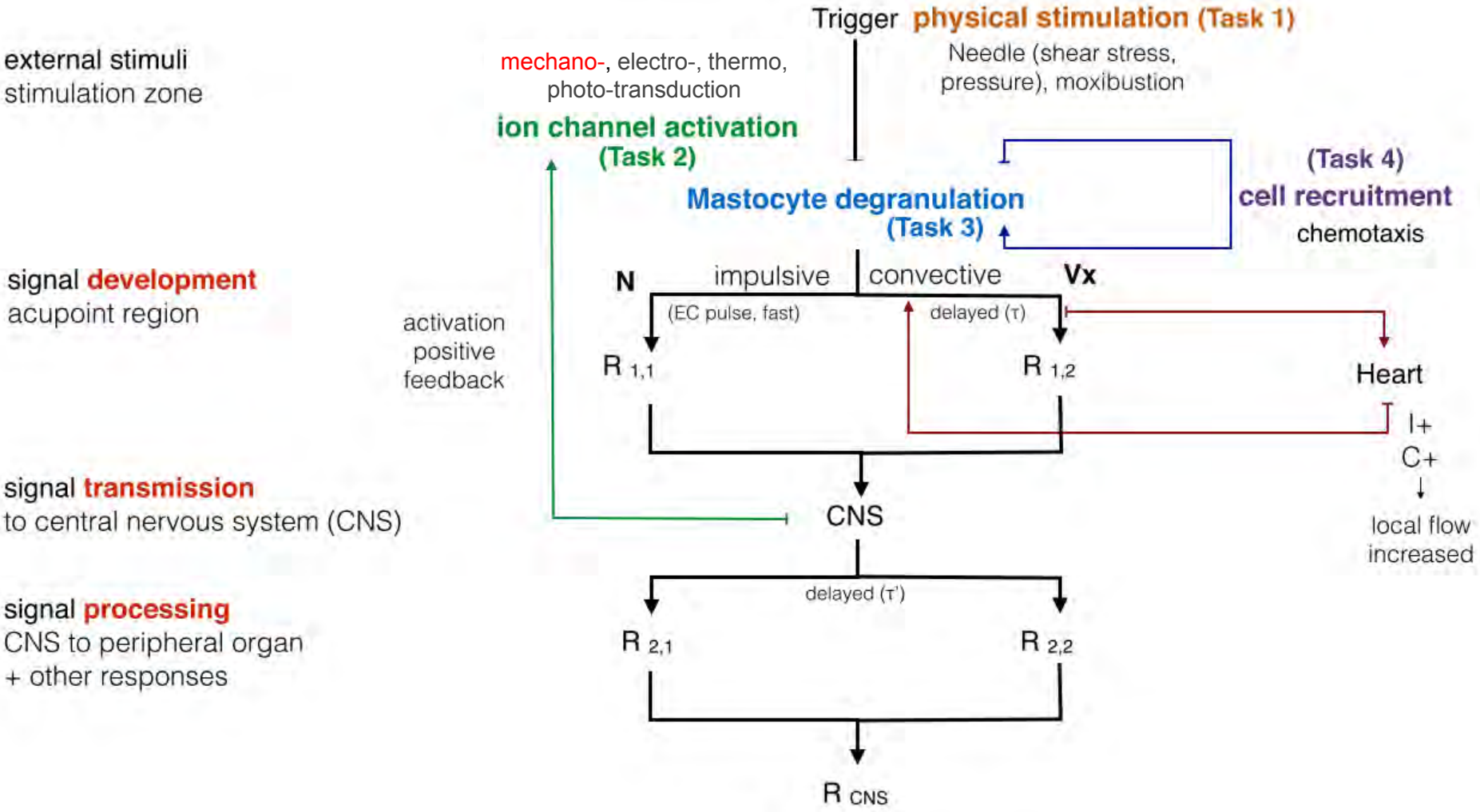
Development of a conjugate heat transfer model for simulating blood flow subject to a heated moxa

1. Acupuncture and Electro-Therapeutics Research, 33(3-4), 169-178, 2008.
2. Int. J. of Heat and Mass Transfer, 63, 141-149, 2013.

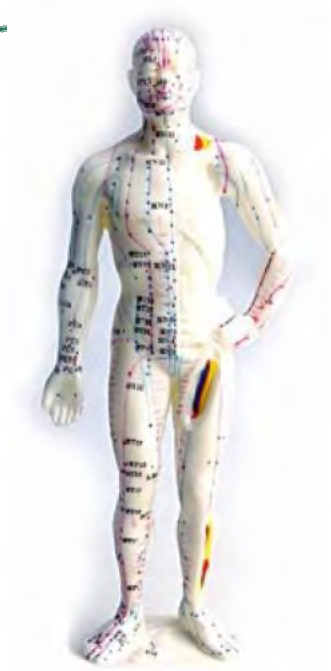


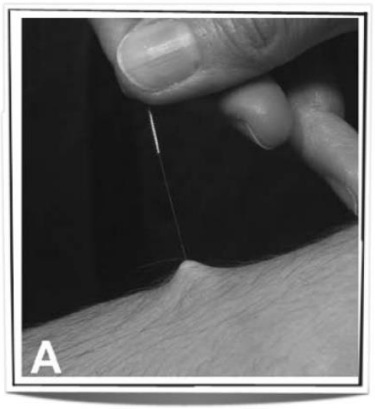


Framework


external stimuli
stimulation zone
signal development
acupoint region
signal transmission
to central nervous system (CNS)
signal processing
CNS to peripheral organ
+ other responses
Trigger physical stimulation (Task 1)
Needle (shear stress, pressure), moxibustion
mechano-, electro-, thermo, photo-transduction
ion channel activation (Task 2)
(Task 4)
cell recruitment
chemotaxis
Mastocyte degranulation (Task 3)
N
impulsive
convective
Vx
(EC pulse, fast)
delayed (τ)
activation positive feedback
R 1,1
R 1,2
Heart
I+
C+
local flow increased
CNS
delayed (τ')
R 2,1
R 2,2
R CNS

Motivation and objectives





Source: Langevin, 2010

- During traditional acupuncture, a needle is inserted in the skin and it interacts with the hypodermis (Langevin et al., 2001, 2002) ;
- The stress created can be perceived by the **mechanosensitive** proteins on the surface of the cells (Langevin, Churchill, and Cipolla, 2001) ;
- Interstitial (空隙的) fluid shear stress can induce mastocyte degranulation via increment of cytosolic Ca^{2+} concentration (Wei et al., 2012; Yao, Li, and Ding, 2012) ;
- Mastocyte degranulation can lead to a cascade of biochemical reactions that are linked with acupuncture effects (Fung, 2009; Zhang et al., 2008) ;
- Accumulation of mastocyte near the acupoint has been observed upon stimulation (Mingfu et al., 2013) .

Objectives

1. Needle - mastocyte interaction
   - Needle implantation, generation of local stress field
   - Interstitium considered as a porous medium
   - Flow/structure interaction (Brinkman model)
2. Ion channel gating
   - Ca^{2+} transport
   - PNP - NS differential equation model
3. Mastocyte degranulation
   - granule exocytosis triggered by Ca^{2+} entry
   - release of chemoattractants, nerve messengers, cardiovascular stimulants
   - flow-structure interaction (NS equations)

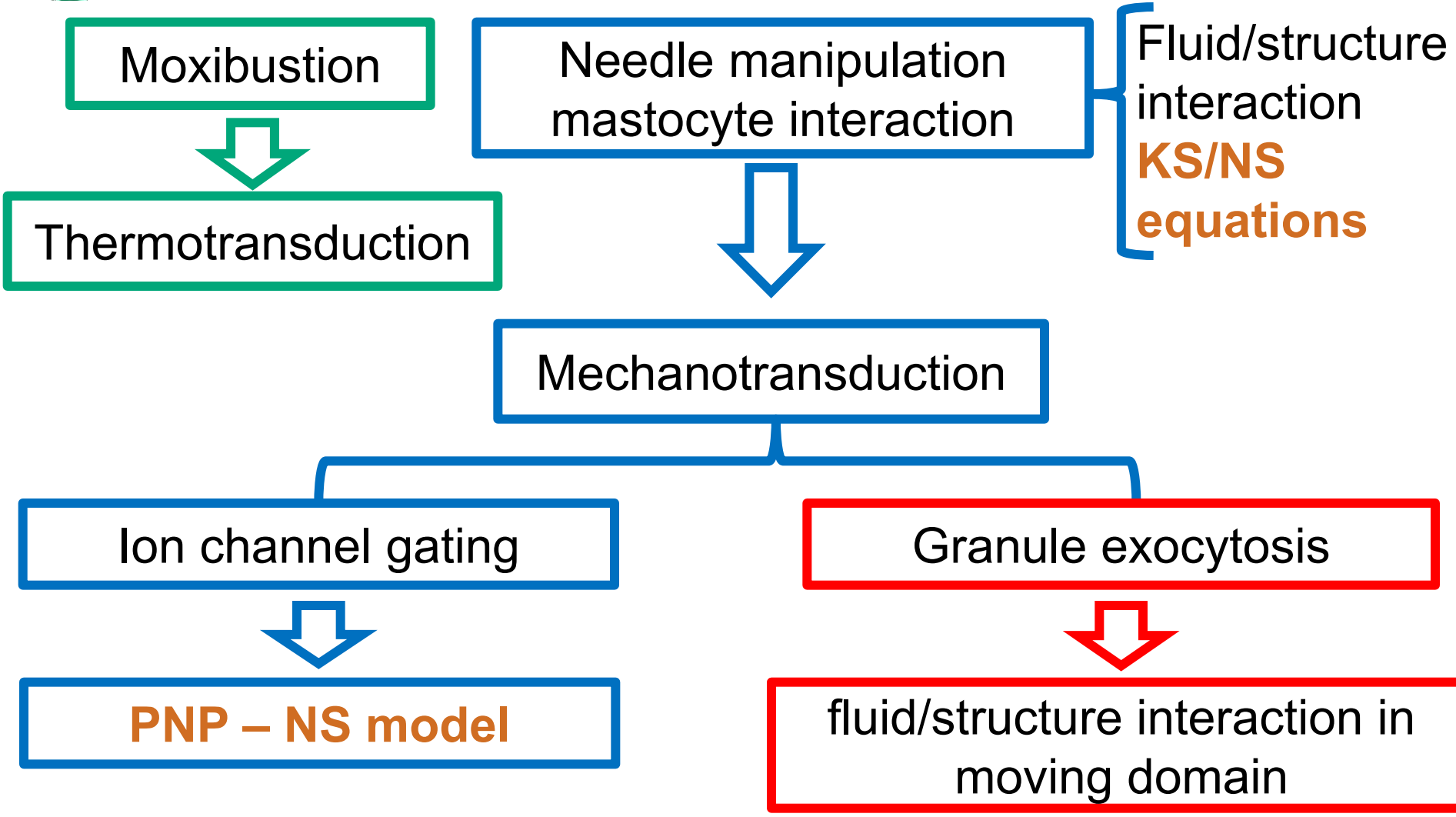
Objectives

4. Mastocyte recruitment
   - chemotaxis (Keller-Segel differential model)
   - forced local stress field
   - release of chemoattractants, nerve messengers, cardiovascular stimulants

The objectives of our work are

- predict the physical stresses on mast cells during acupuncture needling,
- understand the calcium entry phenomenon after stimulation of ion channels,
- investigate the granule exocytosis mechanism leading to the release of chemical mediators
- demonstrate the role of mastocyte recruitment

Summary


Moxibustion
Thermotransduction
Needle manipulation
mastocyte interaction
Fluid/structure
interaction
KS/NS
equations
Mechanotransduction
Ion channel gating
PNP – NS model
Granule exocytosis
fluid/structure interaction in
moving domain

Task # 1 – Needle / mastocyte interaction

by Yannick Deleuze

1-1 Introduction

1-2 Mathematical model

- Brinkman equations

1-3 Numerical model

- FreeFem++

1-4 Numerical results

Introduction

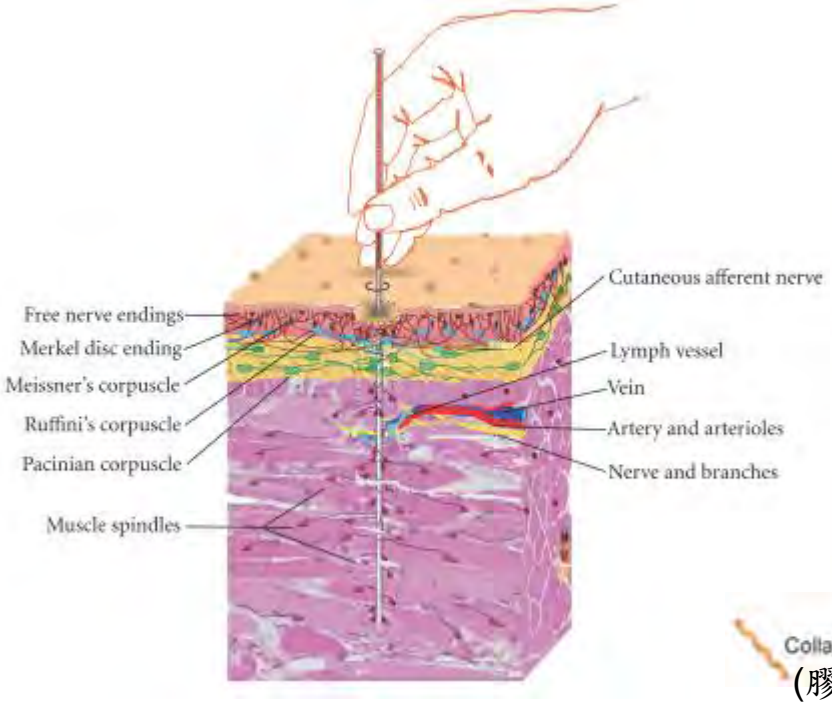


Figure: Needle in the hypodernis
[Source: Zhang & al., 2012]

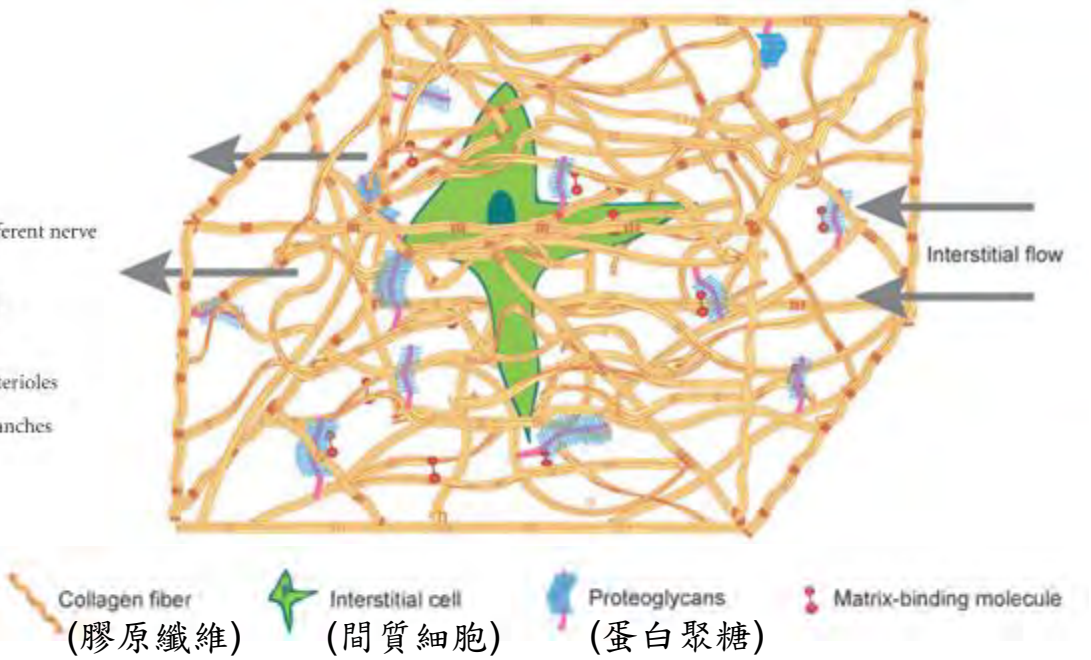


Figure: Cell embedded in the extracellular matrix (ECM) composed of collagen and elastic fibers, ground substance, and proteoglycans [Source: Alberts, 2007]

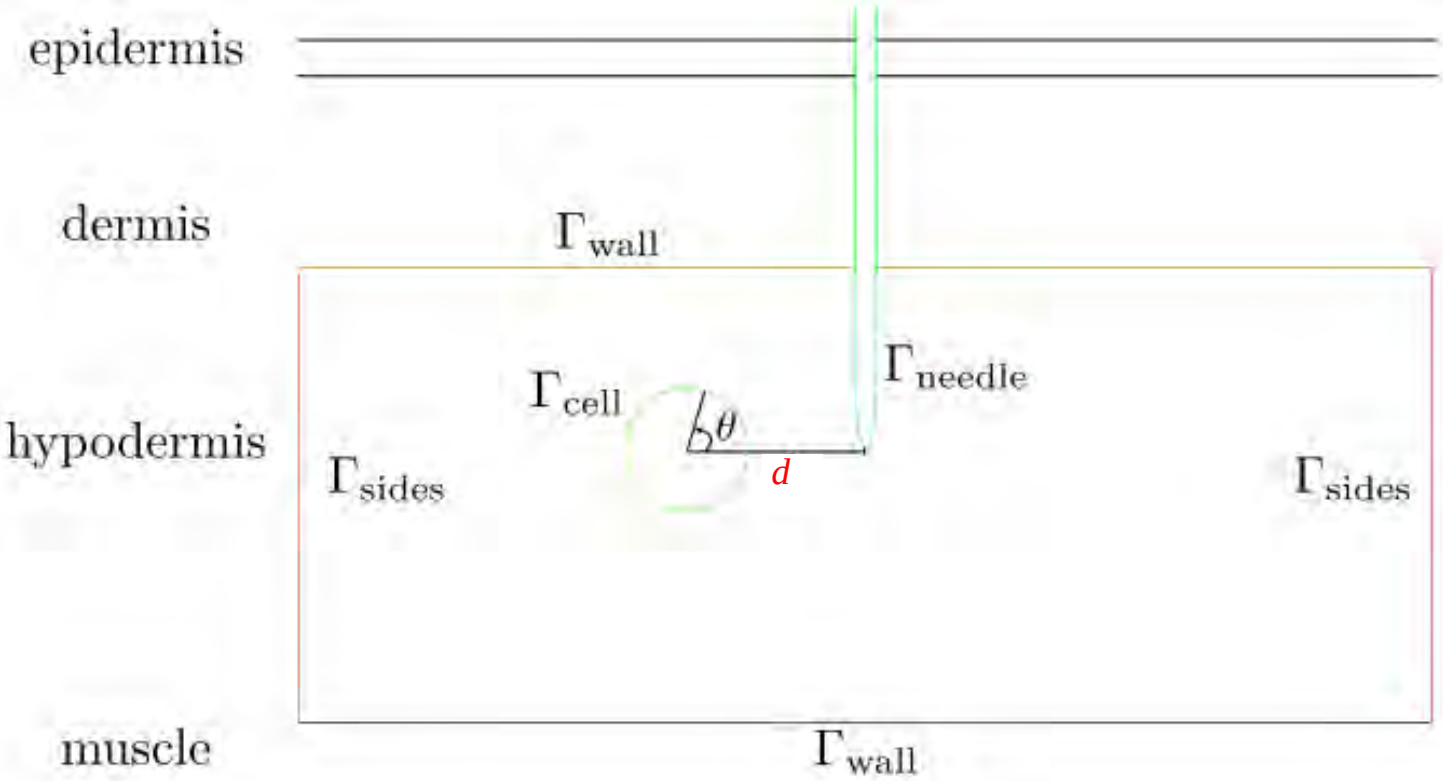
- The ECM (細胞外基質) of loose connective tissue contains relatively sparse fibers.
- The interstitial fluid (water + ions + small molecules = plasma - large molecules) interacts with the ground substance (expansion of a dense network of proteoglycans due to water) to form a gel-like medium.

Problem description

Needle implantation model

Transient regime: generation of a local stress field (needle implantation)

- component: fluid-filled fibrous material subjected to high stress;
- mathematical setting: incompressible convective Brinkman equations;



Incompressible convective Brinkman equations

$$\frac{1}{\alpha_f}\frac{\partial \mathbf{u}}{\partial t}+\frac{1}{\alpha_f}\mathbf{u}\cdot\nabla\left(\frac{\mathbf{u}}{\alpha_f}\right)-\frac{1}{\mathrm{Re}}\nabla^2\mathbf{u}+\frac{1}{\alpha_f}\nabla(\alpha_f p)=-\frac{1}{\mathrm{DaRe}}\mathbf{u} \qquad \text{in } \Omega$$

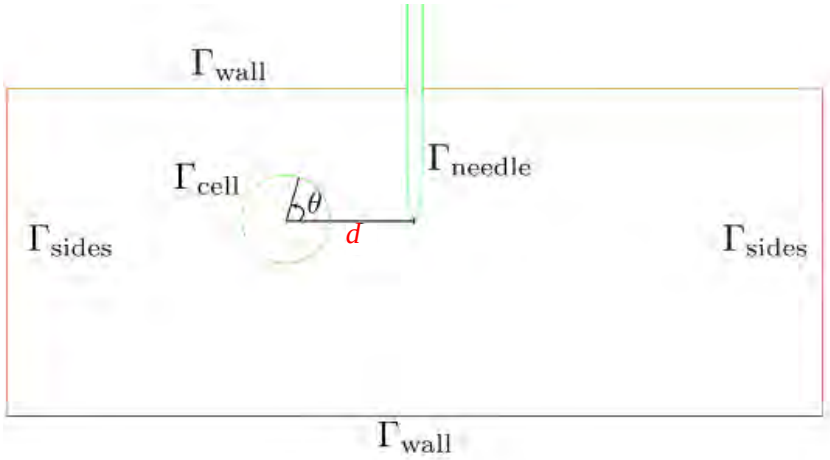
$$\nabla\cdot\mathbf{u}=0$$

$$\mathbf{u}=0 \qquad \text{on } \Gamma_{\text{wall}},$$

$$\mathbf{u}=\mathbf{g} \qquad \text{on } \Gamma_{\text{needle}},$$

$$-\frac{1}{\mathrm{Re}}\nabla\mathbf{u}\cdot\mathbf{n}+p\mathbf{n}=0 \qquad \text{on } \Gamma_{\text{sides}}.$$

where the fluid fractional volume α_f is considered as a space-dependent parameter.



FreeFem++

The governing equations are solved using the finite element software FreeFem++.

The code programs the discrete equations derived from the finite element weak formulation for the problem using a characteristic/Galerkin model to stabilize the convection terms.

A general ALE method used to construct the mapping, or equivalently the domain velocity a (ALE velocity or grid velocity), consists of solving the Laplace equation [Decoene A. & Maury B. Moving meshes with FreeFem++. 2013]

- FreeFrem++ : http://www.freefem.org/ff++/index.htm
- **TWSIAM Activity Group FreeFem++** : http://homepage.ntu.edu.tw/~twhsheu/twsiamff++/freefem.html

Variational formulation

Let us consider the product space

$$V\varphi = \left\{(\mathbf{w}, q) \in [H^1(\Omega)]^2 \times L^2(\Omega), \mathbf{w} = \varphi \text{ on } \Gamma_{\text{needle}}, \mathbf{w} = 0 \text{ on } \Gamma_{\text{wall}}\right\}, \forall \varphi \in H^{1/2}(\Gamma_{\text{needle}})$$

If α_f is constant, the numerical scheme is

$$\int_\Omega \frac{\mathbf{u}^{n+1} - \mathbf{u}^n \circ X^n(\mathbf{x})}{\Delta t} \cdot \mathbf{w}\, d\mathbf{x} + \int_\Omega \nu \nabla \mathbf{u}^{n+1} \cdot \nabla \mathbf{w}\, d\mathbf{x} - \int_\Omega \alpha_f p^{n+1} \nabla \cdot \mathbf{w}\, d\mathbf{x} = -\int_\Omega \alpha_f \nu_D \mathbf{u}^{n+1} \cdot \mathbf{w}\, d\mathbf{x}, \quad (1)$$

$$\int_\Omega \nabla \cdot \mathbf{u}^{n+1} q\, d\mathbf{x} + \int_\Omega \varepsilon p^{n+1} q\, d\mathbf{x} = 0, \quad (2)$$

for all $(\mathbf{w}, q) \in V_0$ and where we consider the approximation

$$X^n = \mathbf{x} - (\mathbf{u}^n(\mathbf{x}) - \mathbf{a}^n(\mathbf{x}))\,\Delta t$$

P2/P1 mixed formulation; characteristic/Galerkin; Euler scheme

(In the above $\nu = \frac{1}{\text{Re}}$ and $\nu_D = \frac{1}{\text{DaRe}}$.)

Interstitial pressure

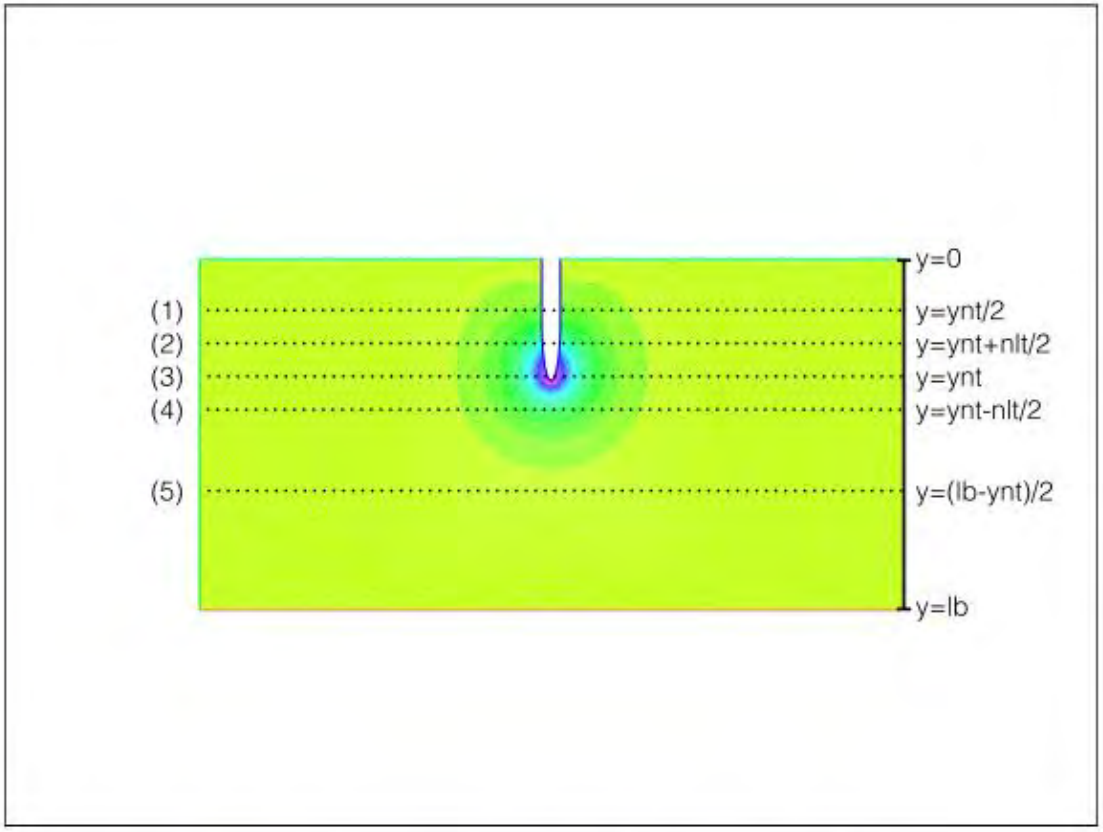


Figure: Pressure p at $t = 0.01 \times 40 = 0.40$

- ynt := inserted needle length;
- nlt := needle tip length;
- lb := height of the domain;

Interstitial pressure

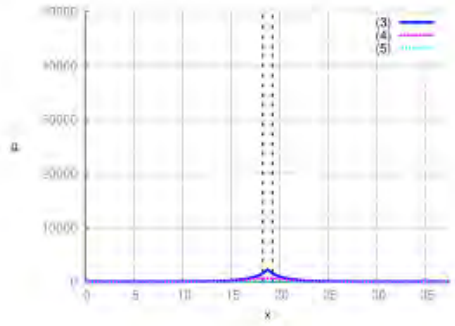


Figure: $t = 0.01$

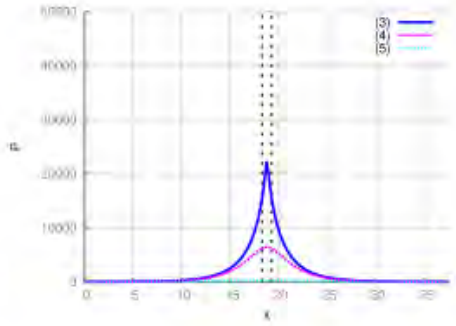


Figure: $t = 0.10$

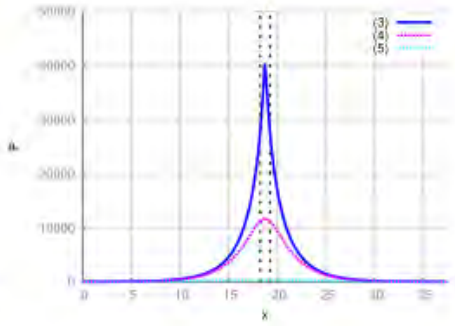


Figure: $t = 0.20$

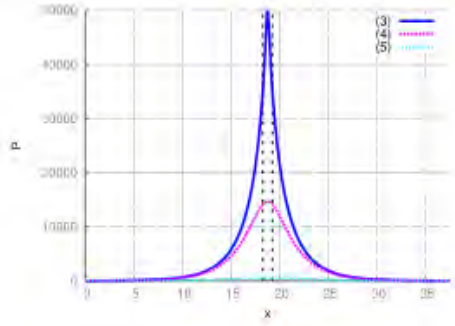


Figure: $t = 0.30$

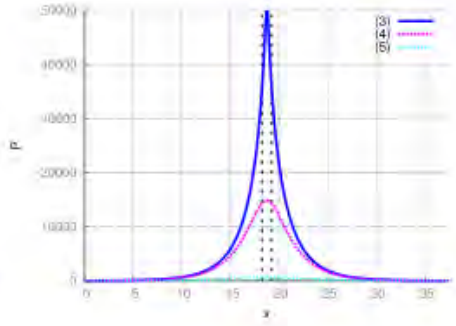


Figure: $t = 0.40$

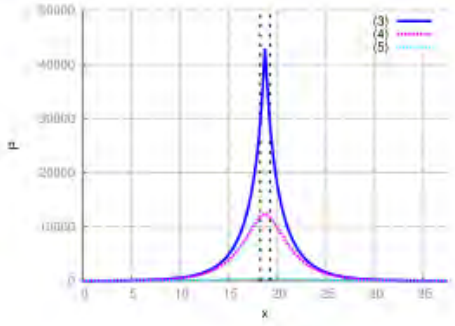
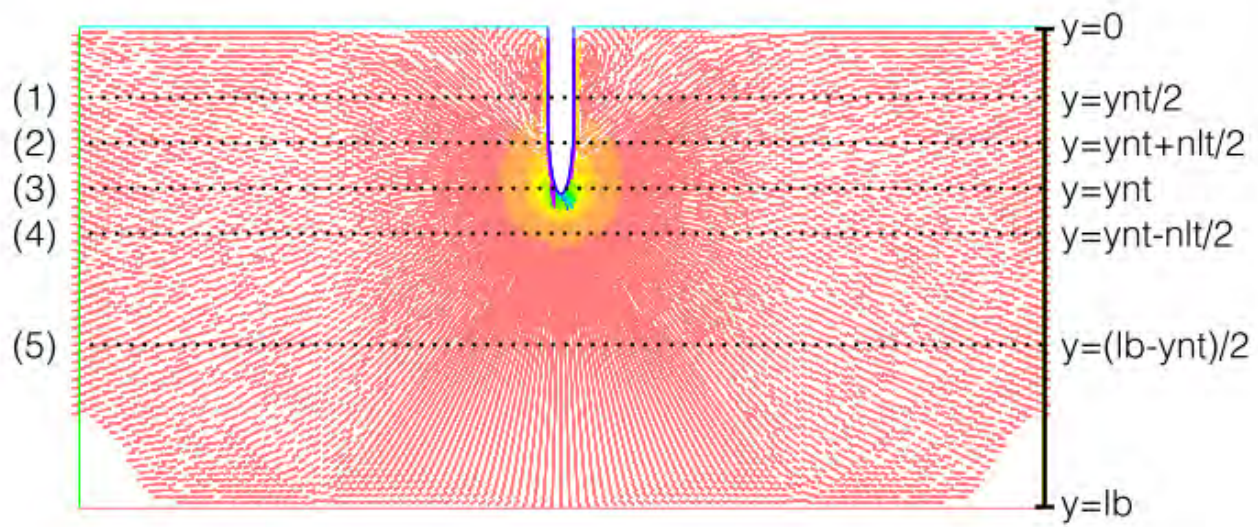


Figure: $t = 0.50$

Figure: Pressure p for $x \in [0, 37.5]$ under the needle, at (3) the needle tip $y = \mathrm{ynt}$, (4) half the height of the needle tip under the needle $y = \mathrm{ynt} - \mathrm{nlt}/2$, and (5) half the height between the needle tip and the bottom $y = (\mathrm{lb} - \mathrm{ynt})/2$. The lines in dots show the x-position of the needle.

Interstitial pressure



Velocity Magnitude

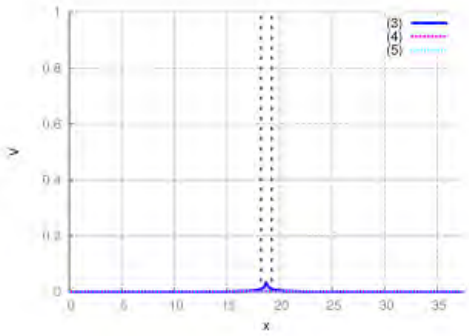


Figure: $t = 0.01$

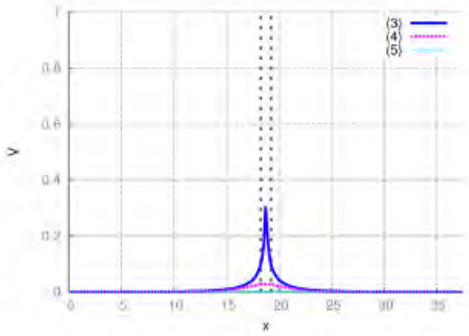


Figure: $t = 0.10$

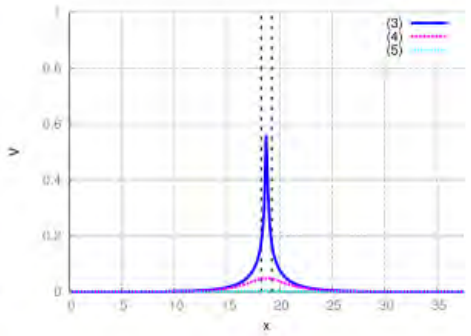


Figure: $t = 0.20$

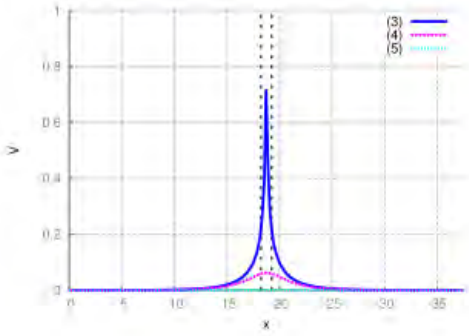


Figure: $t = 0.30$

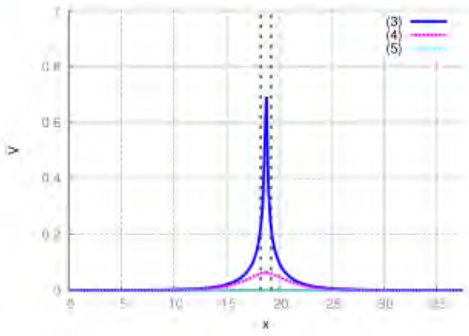


Figure: $t = 0.40$

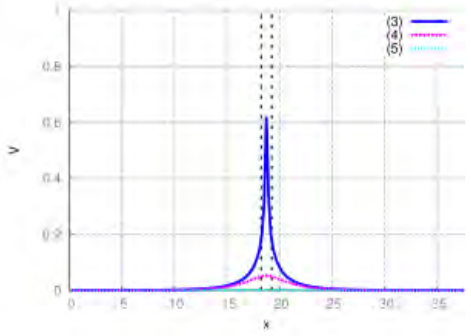


Figure: $t = 0.50$

Figure: Velocity magnitude $\mathrm{V} = |\mathbf{u}|_2$ for $x \in [0, 37.5]$ under the needle, at (3) the needle tip $y = \mathrm{ynt}$, (4) half the height of the needle tip under the needle $y = \mathrm{ynt} - \mathrm{nlt}/2$, and (5) half the height between the needle tip and the bottom $y = (\mathrm{lb} - \mathrm{ynt})/2$. The lines in dots show the x-position of the needle.

Needle motion with one cell

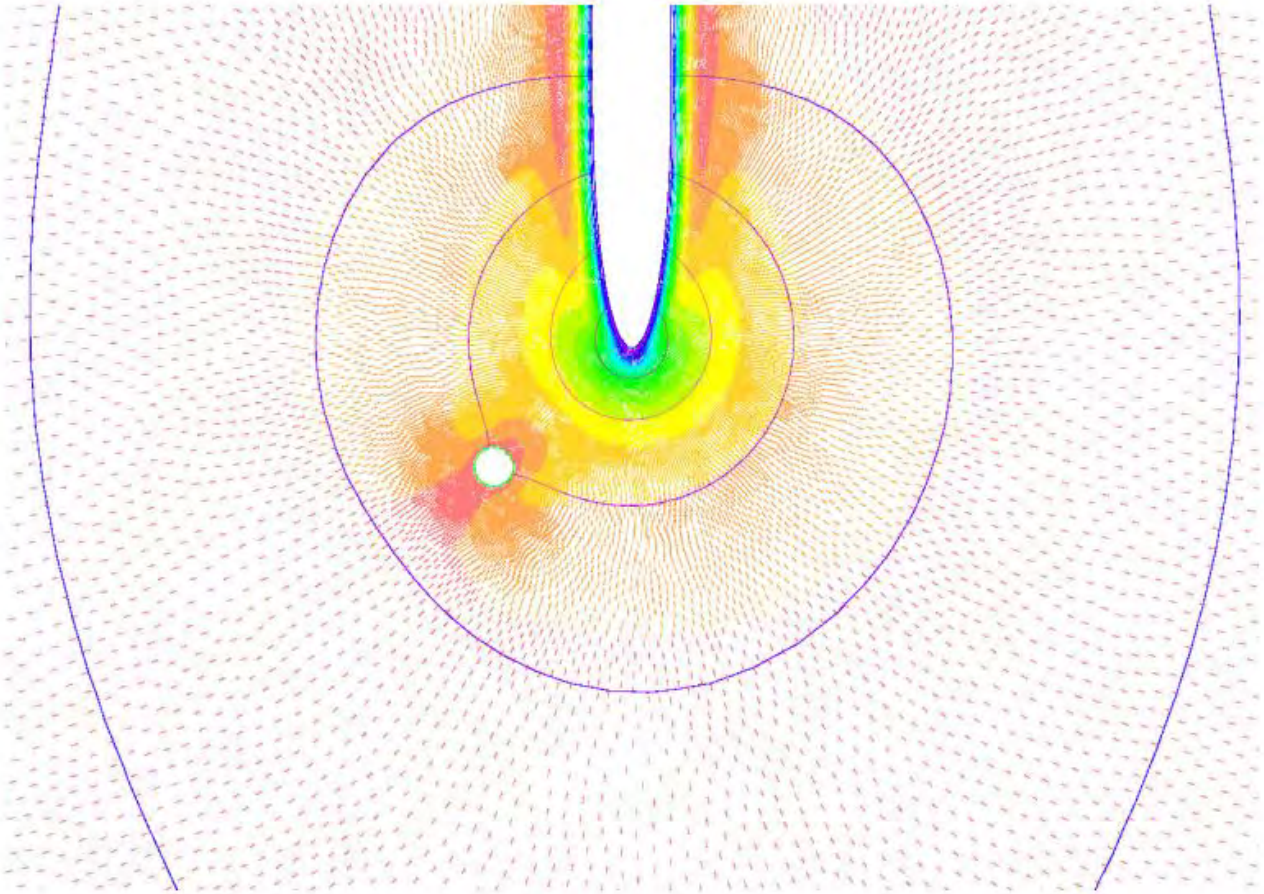


Figure: Pressure contours and velocity field computed in FreeFrem++ (Hecht, 2013)

Evolution of the pressure along the cell boundary

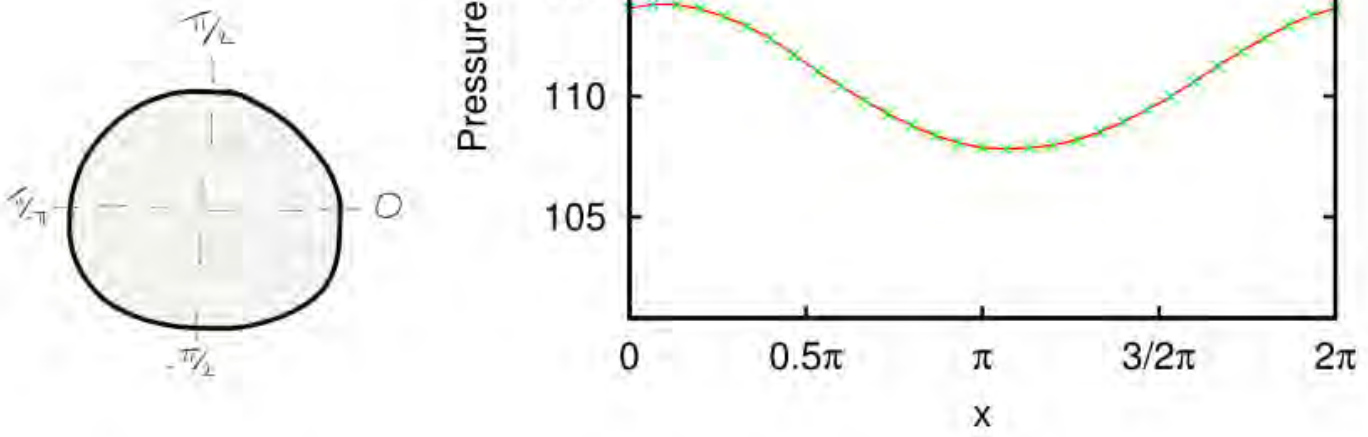


Figure: The predicted pressure along the cell surface. Pressure gradient observed along the cell surface.

Shear stress with respect to the distance from the needle

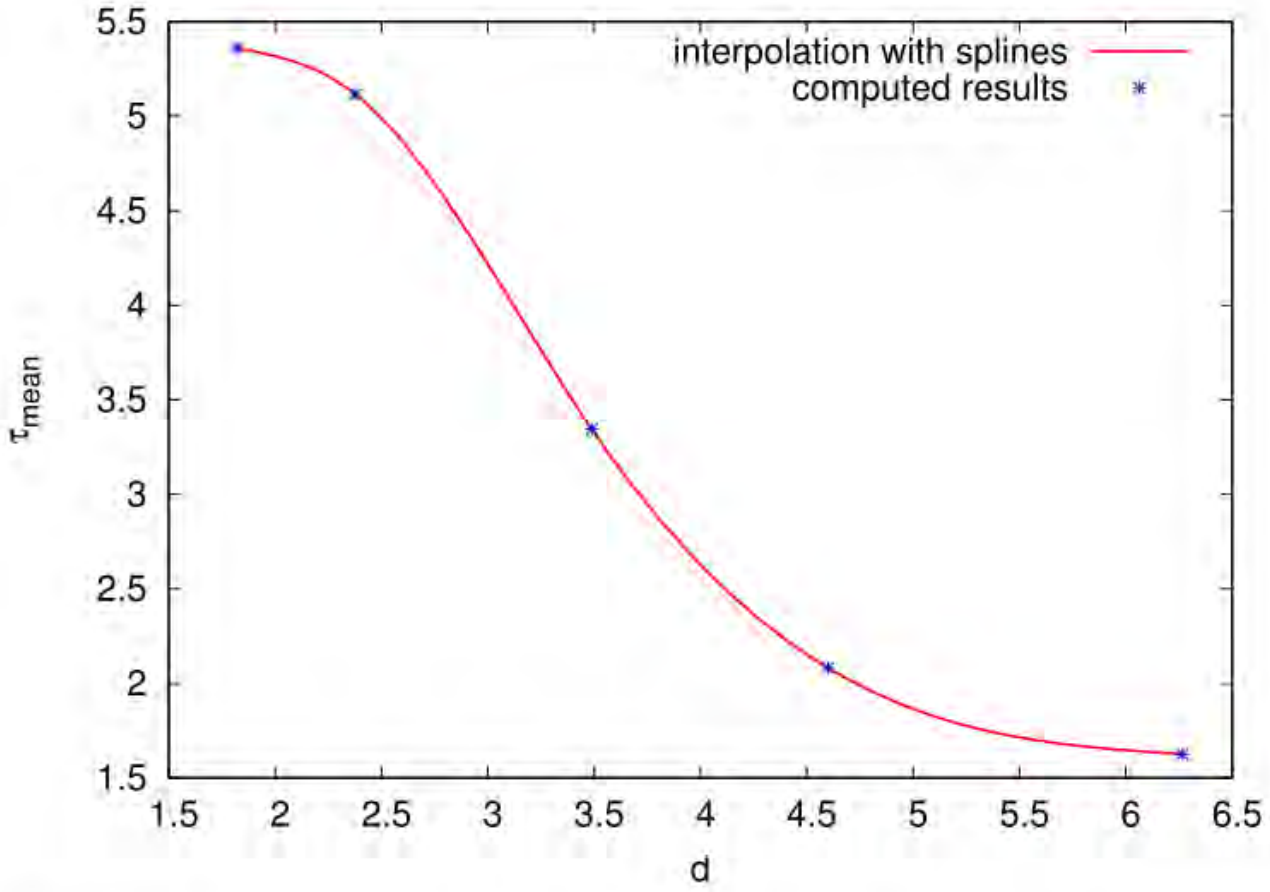


Figure: The predicted mean shear stress τ_{mean} on the cell surface with respect to the distance d measured from the needle. A higher shear stress is expected to be observed at a location close to the needle.

Concluding remarks on task # 1

- Insertion of a needle produces a local mechanical stimulation in the environment;
- pressure/shear stress induced by the flow can affect the cell activity (mechanotransduction).

Task # 2 – transport of Ca^{2+} through ion channel of a mastocyte by 薛向成

2-1 Introduction

- The metabolism (代謝)
- The mechanism and different types of ion channel
- The function of ion channel

2-2 Mathematical model

2-3 Numerical model

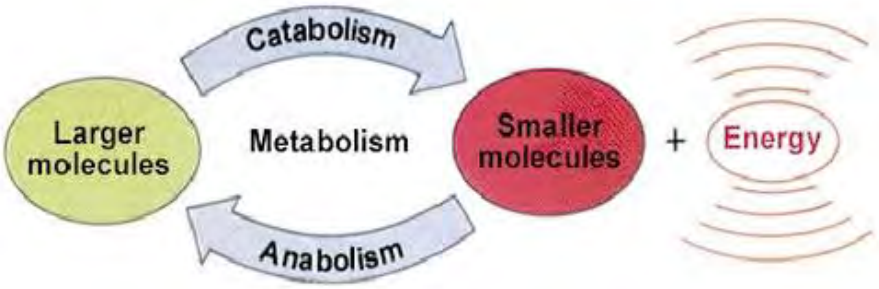
- The combined compact difference scheme
- Fourth order accurate Laplace operator

2-4 Problem setting

2-5 Numerical results

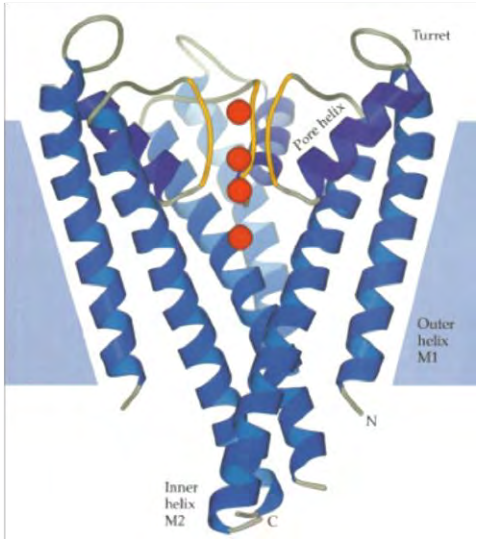
Introduction

1. Metabolism
   - (分解代謝) Catabolism
   - Anabolism (合成代謝)

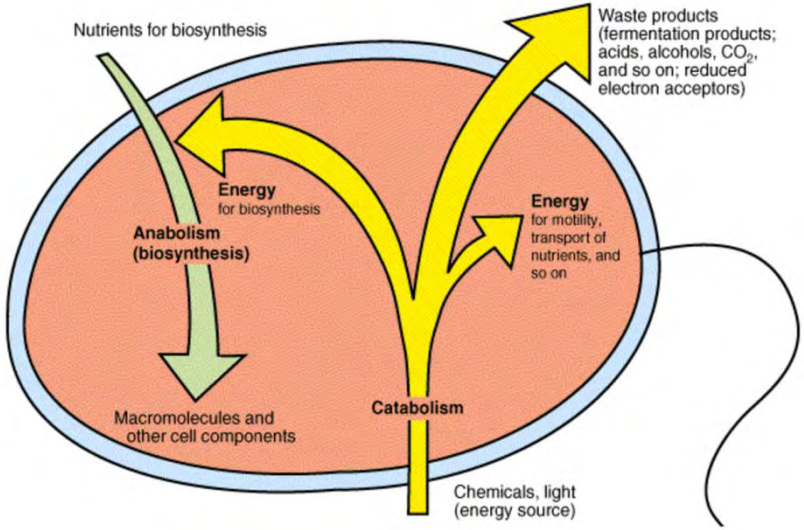


2. The substances in the cell are always water-soluble (可溶的): ions, carbohydrate (碳水化合物), etc.

3. Ion channels are macromolecules embed in cell membranes that form a pore to let ions pass through.



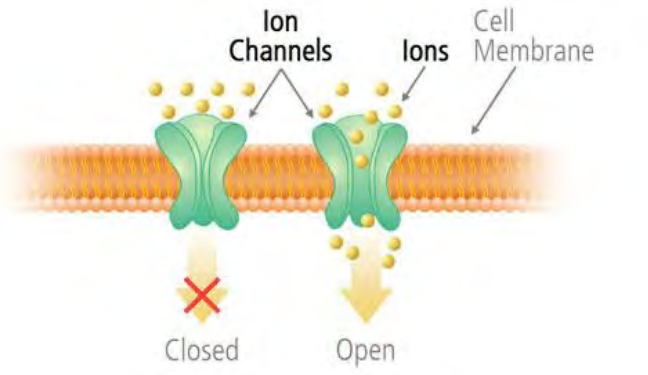
Microbial (微生物的) Nutrition
Cell metabolism (生物合成)



References : Hille B., Ion Channels of Excitable Membranes; http://www.expertsmind.com/topic/microbiology/nutrition-and-metabolism-92630.aspx; http://www.myfirstbrain.com/student_view.aspx?ID=35501

Introduction

- Gating: mechanism of opening and closing to respond to cell signaling.
- Selectivity: ion channel possess selective filters so that only one specie pass through the channel.

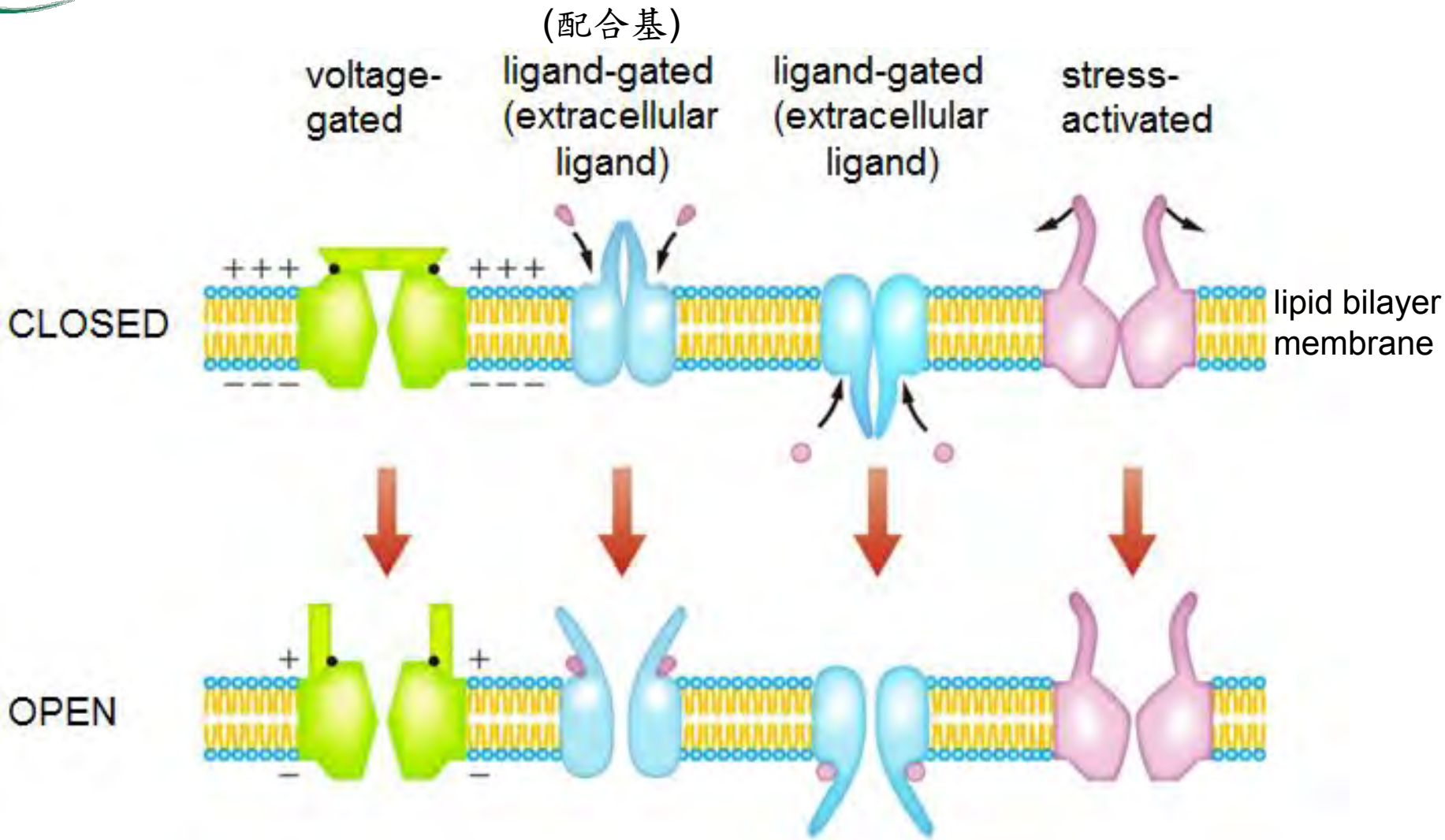


There are three types of ion channel

1. Voltage sensitive → Open or close by the potential change on membrane, like K^+、Na^+、Ca^{2+}、Cl^-
2. Chemical gated → Open or close by the combination of neurotransmitters and receptor molecule on the protein
3. Mechanosensitive → Open or close by the stress change on the surface of membrane

Reference : http://www.neusentis.com/IonChannels.php

Introduction



Reference : http://why276.weebly.com/38626233763689036947.html

Introduction

Main functions of ion channel

1. Ca^{2+} channels permit entry of Ca^{2+} in the cell to trigger a series of physiological reaction such as muscle contraction, glandular secretion (腺分泌的), or vesicle exocytosis.

2. Facilitate (促進) diffusion of ions across biological membranes.

3. Maintain balance of electric potential on membrane.

4. Maintain normal volume (osmolality (滲透)) and functional integrity of the cell.

Mathematical model

Poisson – Nernst – Planck – Navier-Stokes equations

PNP

1. $\nabla^2\phi = 0$ ~ Externally applied electrical potential (Laplace equation)

2. $\nabla^2\psi = -\frac{(\kappa H)^2}{2}(n_+ - n_-)$ ~ Electrical potential in EDL (Poisson equation)

3. $\frac{\partial n_+}{\partial t} + \nabla\cdot(n_+\underline{u}) - \frac{1}{Sc\,\mathrm{Re}}\nabla^2 n_+ - \frac{1}{Sc\,\mathrm{Re}}\nabla\cdot\left[n_+\nabla(\phi+\psi)\right] = 0$ ~ The Nernst-Planck Eq of cation

4. $\frac{\partial n_-}{\partial t} + \nabla\cdot(n_-\underline{u}) - \frac{1}{Sc\,\mathrm{Re}}\nabla^2 n_- + \frac{1}{Sc\,\mathrm{Re}}\nabla\cdot\left[n_-\nabla(\phi+\psi)\right] = 0$ ~ The Nernst-Planck Eq of anion

NS

5. $\nabla\cdot\underline{u} = 0$ ~ Continuity equation

6. $\frac{\partial \underline{u}}{\partial t} + \underline{u}\cdot\nabla\underline{u} = -\nabla p + \frac{1}{\mathrm{Re}}\nabla^2\underline{u} + Gx(n_- - n_+)\nabla(\phi+\psi)$ ~ Momentum equation

Numerical model

- Combined compact difference scheme

1. The scheme, which accommodates a better dispersion relation for the convective terms in the transport equation, is proposed to enhance the convective stability of the convection-diffusion equation by virtue of the increased dispersive accuracy.
2. The dispersion-relation-preserving compact scheme has been rigorously developed within the three stencil point framework through the dispersion and dissipation analyses.

- The scalar transport equation for a field variable ϕ :

$$a\frac{\partial \phi}{\partial x}+b\frac{\partial \phi}{\partial y}-k\left(\frac{\partial^2 \phi}{\partial x^2}+\frac{\partial^2 \phi}{\partial y^2}\right)=f$$

k : diffusion coefficient

a : constant velocity along x direction

b : constant velocity along y direction

f : source term

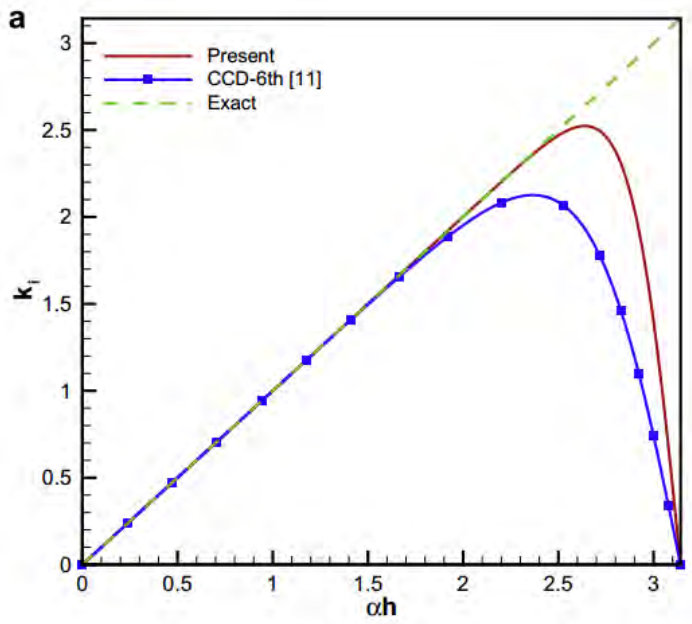
Both of the first-order and second-order spatial derivative terms are approximated at the uniform grid size $\Delta x=\Delta y=h$.

Numerical model

The three-point compact difference scheme for the first derivative and second derivative terms are as follows.

$$a_1 \left.\frac{\partial \phi}{\partial x}\right|_{i-1} + \left.\frac{\partial \phi}{\partial x}\right|_{i} = \frac{1}{h}\left(c_1\phi_{i-1} + c_2\phi_i + c_3\phi_{i+1}\right) - h\left(b_1 \left.\frac{\partial^2 \phi}{\partial x^2}\right|_{i-1} + b_2 \left.\frac{\partial^2 \phi}{\partial x^2}\right|_{i} + b_3 \left.\frac{\partial^2 \phi}{\partial x^2}\right|_{i+1} \right)$$

$$\overline{b}_1 \left.\frac{\partial^2 \phi}{\partial x^2}\right|_{i-1} + \left.\frac{\partial^2 \phi}{\partial x^2}\right|_{i} + \overline{b}_3 \left.\frac{\partial^2 \phi}{\partial x^2}\right|_{i+1} = \frac{1}{h^2}\left(\overline{c}_1\phi_{i-1} + \overline{c}_2\phi_i + \overline{c}_3\phi_{i+1}\right) - \frac{1}{h}\left(\overline{a}_1 \left.\frac{\partial \phi}{\partial x}\right|_{i-1} + \overline{a}_2 \left.\frac{\partial \phi}{\partial x}\right|_{i} + \overline{a}_3 \left.\frac{\partial \phi}{\partial x}\right|_{i+1} \right)$$



Reference : P.H. Chiu , Tony W.H. Sheu , On the development of a dispersion-relation-preserving dual-compact upwind scheme for convection-diffusion equation , Journal of Computational Physics 228 (2009) 3640-3655

Numerical model - Fourth order accuracy for the Laplace operator

Poisson equation : $\phi_{xx} + \phi_{yy} = f(x, y)$

Discrete the equation

$$\delta_x^2 \phi_{ij} + \delta_y^2 \phi_{ij} - \tau_{ij} = f_{ij} \quad \text{where} \quad \tau_{ij} = \left\lfloor \frac{\partial^4 \phi}{\partial x^4} + \frac{\partial^4 \phi}{\partial y^4} \right\rfloor_{ij} \frac{h^2}{12} + \left\lfloor \frac{\partial^6 \phi}{\partial x^6} + \frac{\partial^6 \phi}{\partial y^6} \right\rfloor_{ij} \frac{h^4}{360} + O(h^6)$$

$$\begin{cases} \dfrac{\partial^4 \phi}{\partial x^4} = \dfrac{\partial^2 f}{\partial x^2} - \dfrac{\partial^4 \phi}{\partial x^2 \partial y^2} \\ \dfrac{\partial^4 \phi}{\partial y^4} = \dfrac{\partial^2 f}{\partial y^2} - \dfrac{\partial^4 \phi}{\partial x^2 \partial y^2} \end{cases}$$

$$\tau_{ij} = \left\lfloor \frac{\partial^2 f}{\partial x^2} - 2\frac{\partial^4 \phi}{\partial x^2 \partial y^2} + \frac{\partial^2 f}{\partial y^2} \right\rfloor_{ij} \frac{h^2}{12} + \left\lfloor \frac{\partial^6 \phi}{\partial x^6} + \frac{\partial^6 \phi}{\partial y^6} \right\rfloor_{ij} \frac{h^4}{360} + O(h^6)$$

Numerical model - Fourth order accuracy for the Laplace operator

Approximation of the term $\left.\frac{\partial^4\phi}{\partial x^2\partial y^2}\right|_{ij}$

$$\left.\frac{\partial^4\phi}{\partial x^2\partial y^2}\right|_{ij} = \delta_x^2\delta_y^2\phi_{ij} - \left[\left(\frac{\partial^6\phi}{\partial x^4\partial y^2} + \frac{\partial^6\phi}{\partial x^2\partial y^4}\right)\right]_{ij}\frac{h^2}{12} + O(h^4)$$

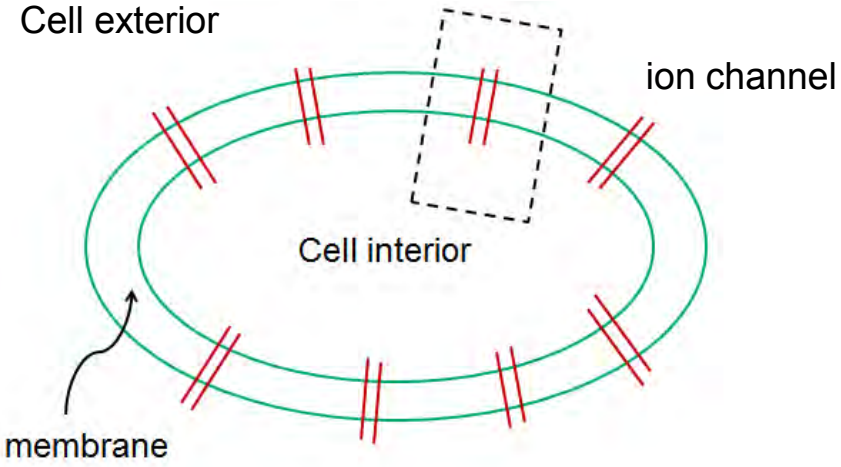
$$\delta_x^2\delta_y^2\phi_{ij} = \frac{1}{h^4}\left[4\phi_{ij} - 2(\phi_{i-1,j} + \phi_{i+1,j} + \phi_{i,j-1} + \phi_{i,j+1}) + \phi_{i-1,j-1} + \phi_{i+1,j-1} + \phi_{i+1,j+1} + \phi_{i-1,j+1}\right]$$

We can derive the high-order compact difference scheme of order fourth

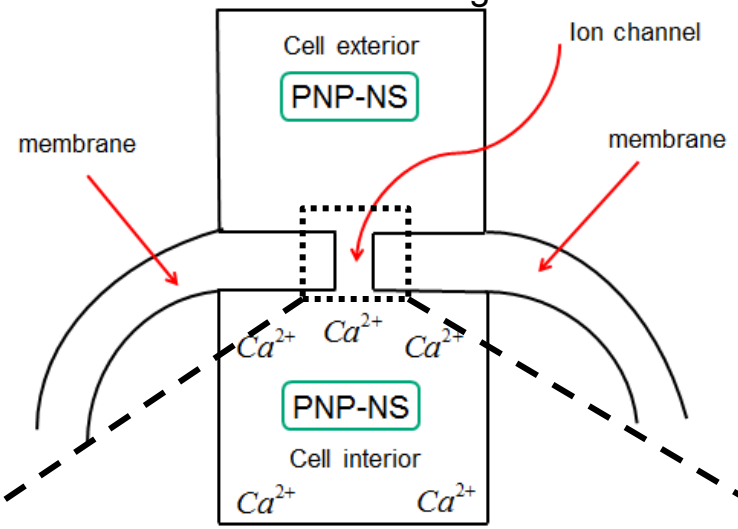
$$\delta_x^2\phi_{ij} + \delta_y^2\phi_{ij} + \frac{h^2}{6}\delta_x^2\delta_y^2\phi_{ij} - \tau_{ij} = f_{ij} + \frac{h^2}{12}(\delta_x^2 f_{ij} + \delta_y^2 f_{ij}) \qquad \text{(HOC-4)}$$

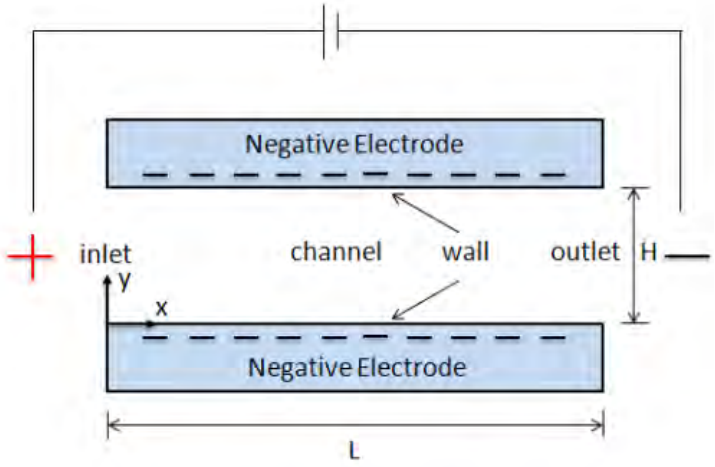
Reference : Akil J. Harfash Huda A. Jalob, Sixth and Fourth Order Compact Finite Difference Schemes for Two and Three Dimension Poisson Equation with Two Methods to derive These Schemes, Department of Mathematics, College of Science, University of Basrah Vol.24(2),1-20, 2006

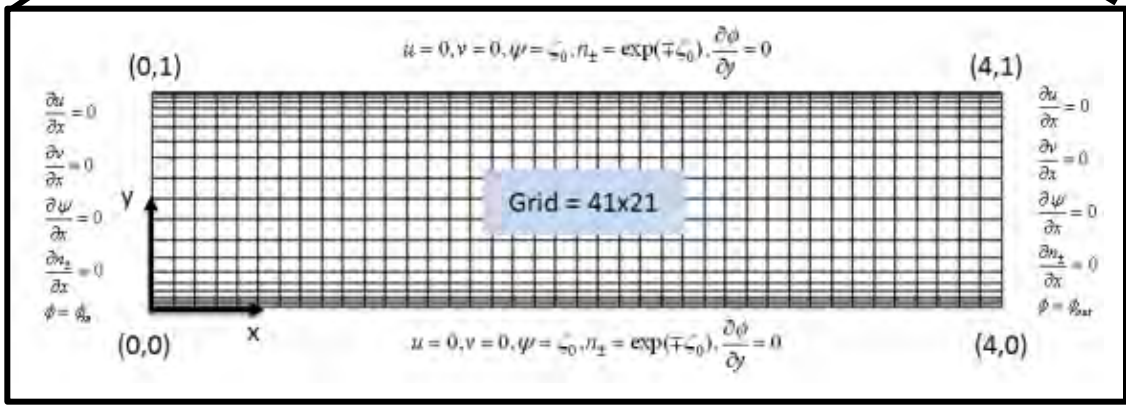
Problem setting



Working physical domain
under current investigation







Numerical result

- Verification of the proposed numerical model for solving the PNP-NS equations

The exact solutions of ϕ , ψ , n_+ , n_- , u , v and p are as follow

$$\phi = \frac{-2}{(1+x)^2+(1+y)^2}$$

$$\varphi = \frac{-2}{(1+x)^2+(1+y)^2}$$

$$n_+ = \frac{-2(1+y)}{(1+x)^2+(1+y)^2}$$

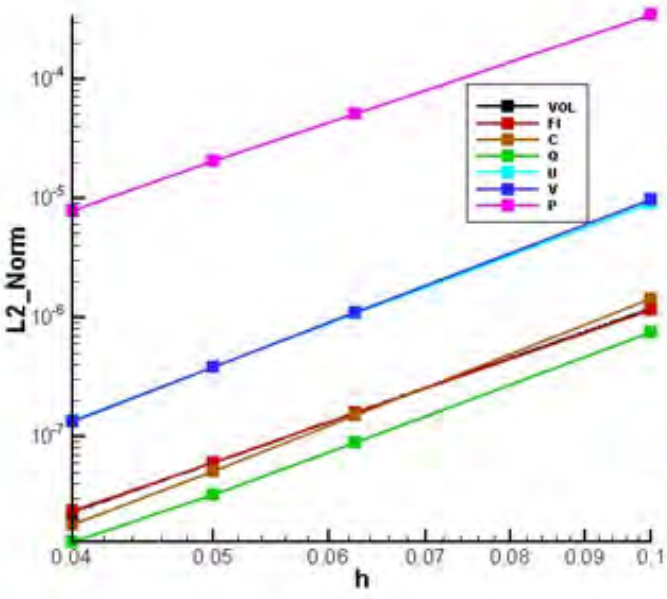
$$n_- = \frac{-2(1+y)}{(1+x)^2+(1+y)^2}$$

$$u = \frac{-2(1+y)}{(1+x)^2+(1+y)^2}$$

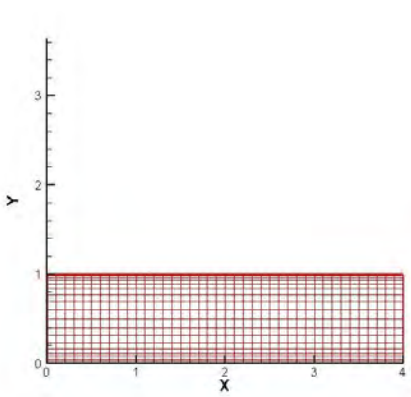
$$v = \frac{2(1+x)}{(1+x)^2+(1+y)^2}$$

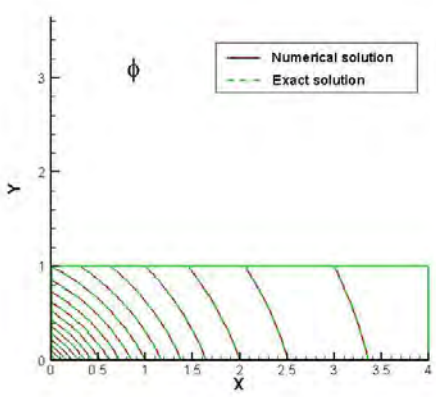
$$p = \frac{-2}{(1+x)^2+(1+y)^2}$$

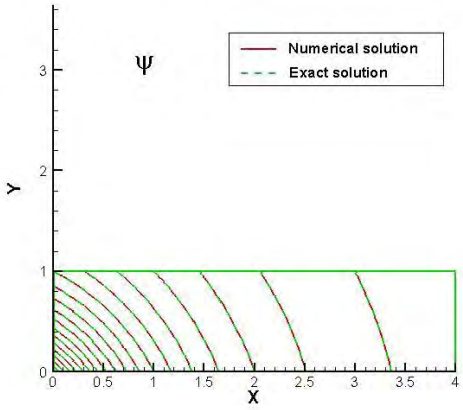
	Rate of convergence
ϕ (VOL)	4.29810
ψ (FI)	4.25269
n_- (C)	4.77800
n_+ (Q)	4.43243
u	4.57656
v	4.66774
p	4.10885

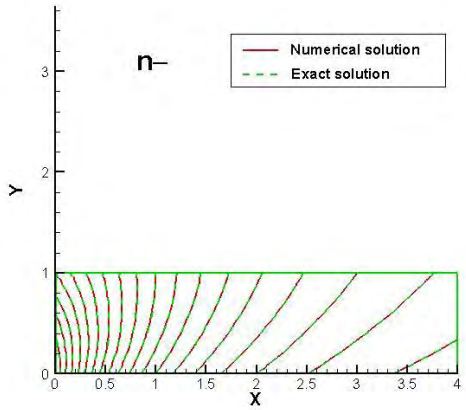


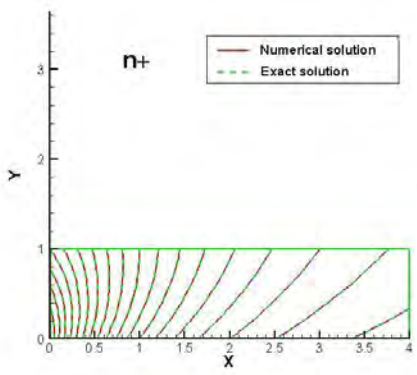
Numerical result

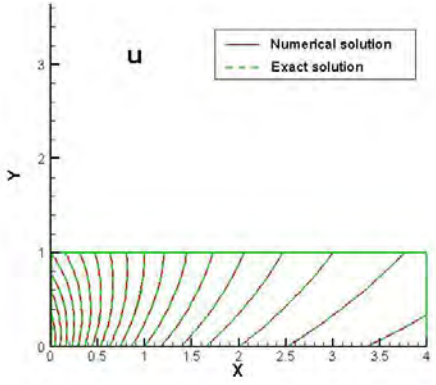


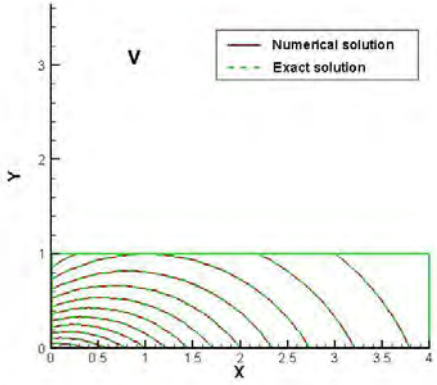


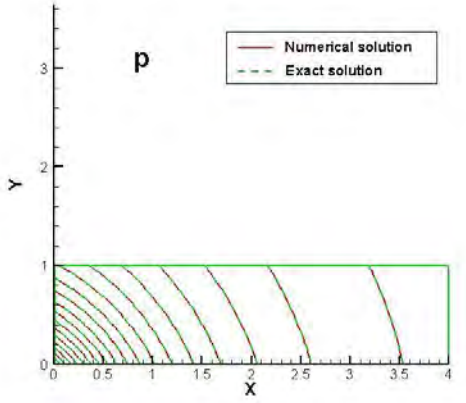












Concluding remarks on task # 2

- The proposed numerical scheme is verified by the predicted spatial rate of convergence (src) based on the predicted L^2-error norms for the exact solutions of seven variables.

- Our future work is to simulate 3D ion transport through channels on membrane bridging the cell interior and cell exterior with the goal of better understanding physical behavior.

Task # 3 – Mastocyte degranulation (脫顆粒) through exocytosis (胞吐作用) by 楊燿宇

3-1 Introduction

3-2 Mathematical model

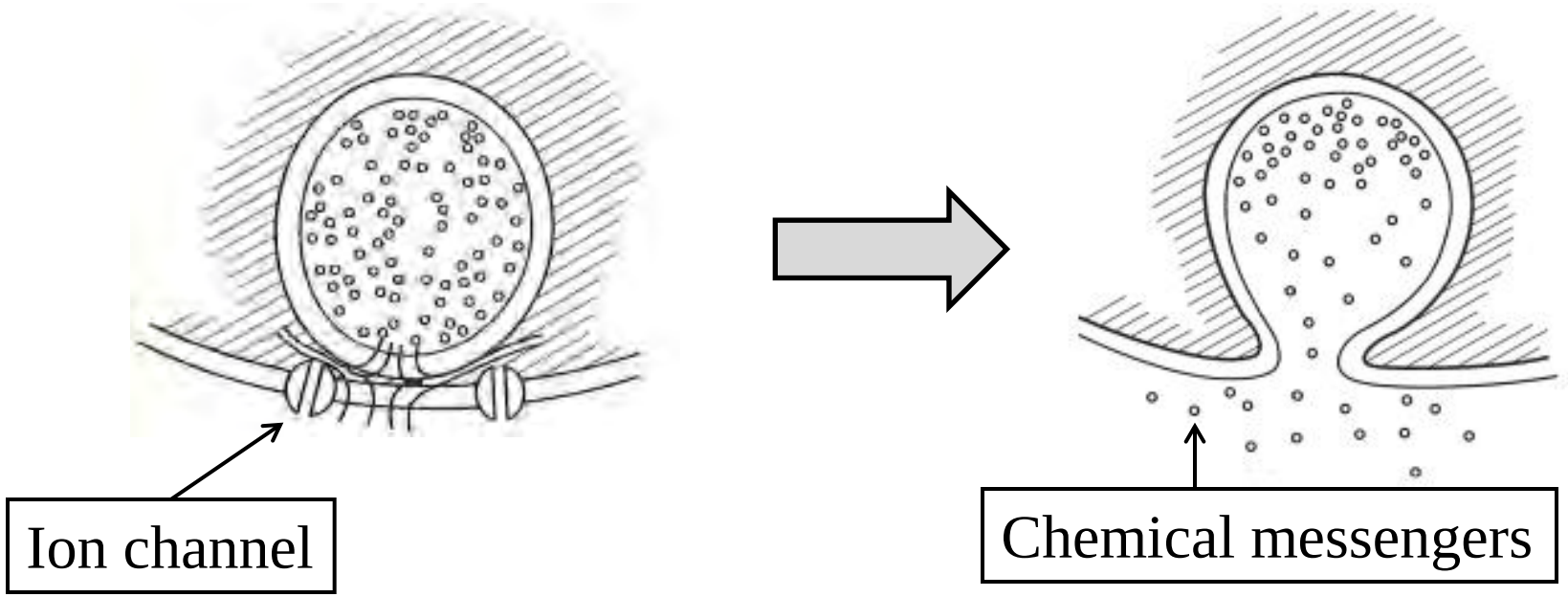
3-4 Numerical model

3-5 Problem setting

3-6 Numerical results

Introduction

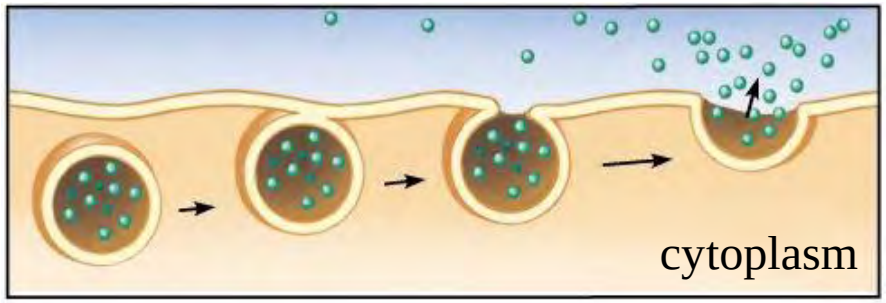
Exocytosis process

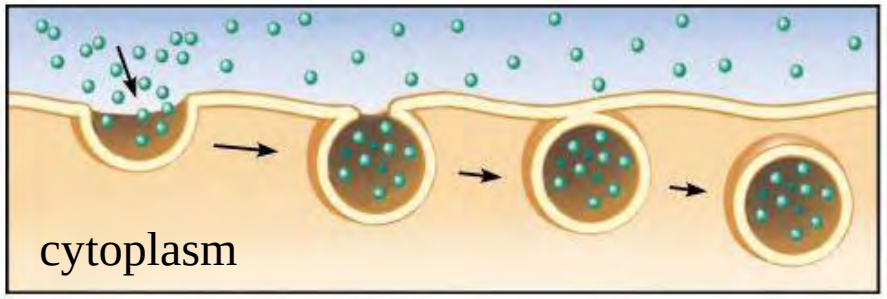


Reference : Hille B., Ion Channels of Excitable Membranes

Introduction

- Exocytosis corresponds to the expulsion of vesicle content (e.g. chemical messengers, neurotransmitters, nutrients, waste, enzymes, etc.) out of the cell, a process reverse to endocytosis (胞噬作用) where the cell absorbs or swallows cell debris, germ or virus into the cytoplasm (細胞內).





http://www.kscience.co.uk/as/module1/endocytosis.htm

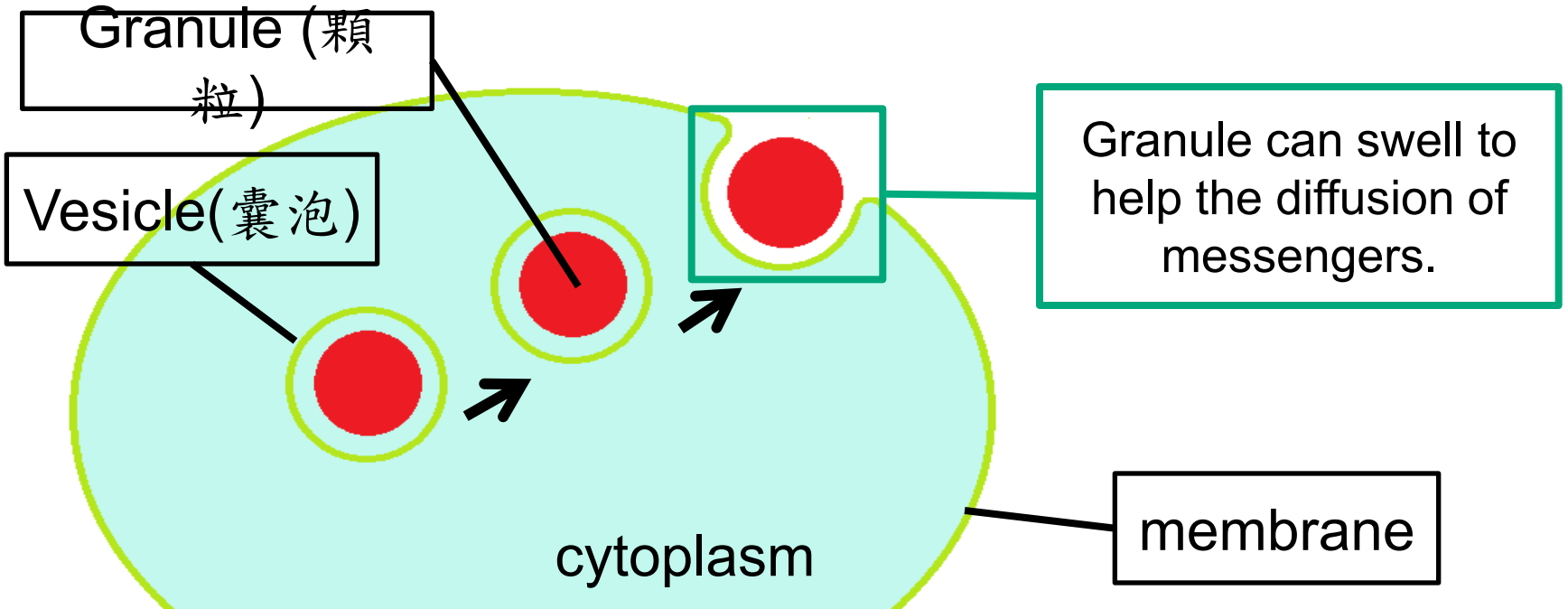
Exocytosis

Endocytosis

Introduction

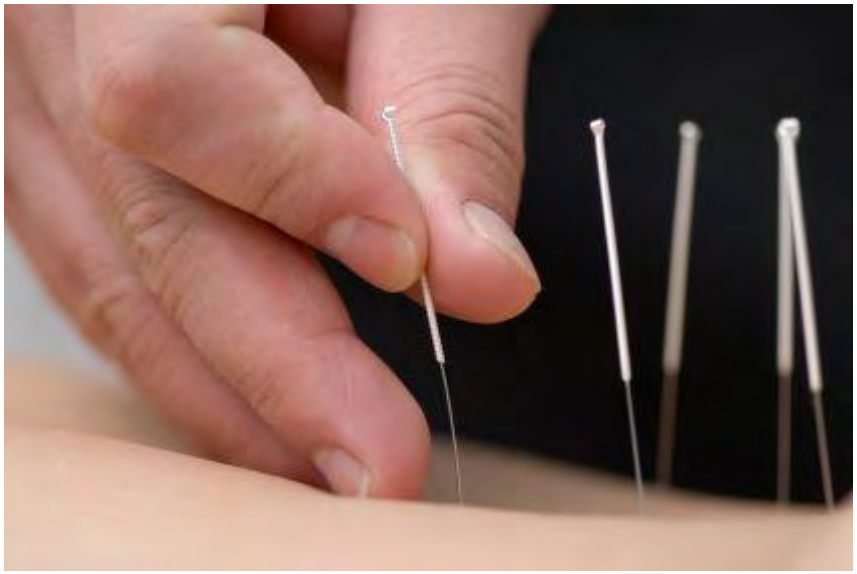
The granules form a network of proteins embedding a high quantity of chemical messengers and ionic species.

Degranulation (exocytosis of a granule) occurs when the cell is excited (Ca^{2+} entry).



Introduction

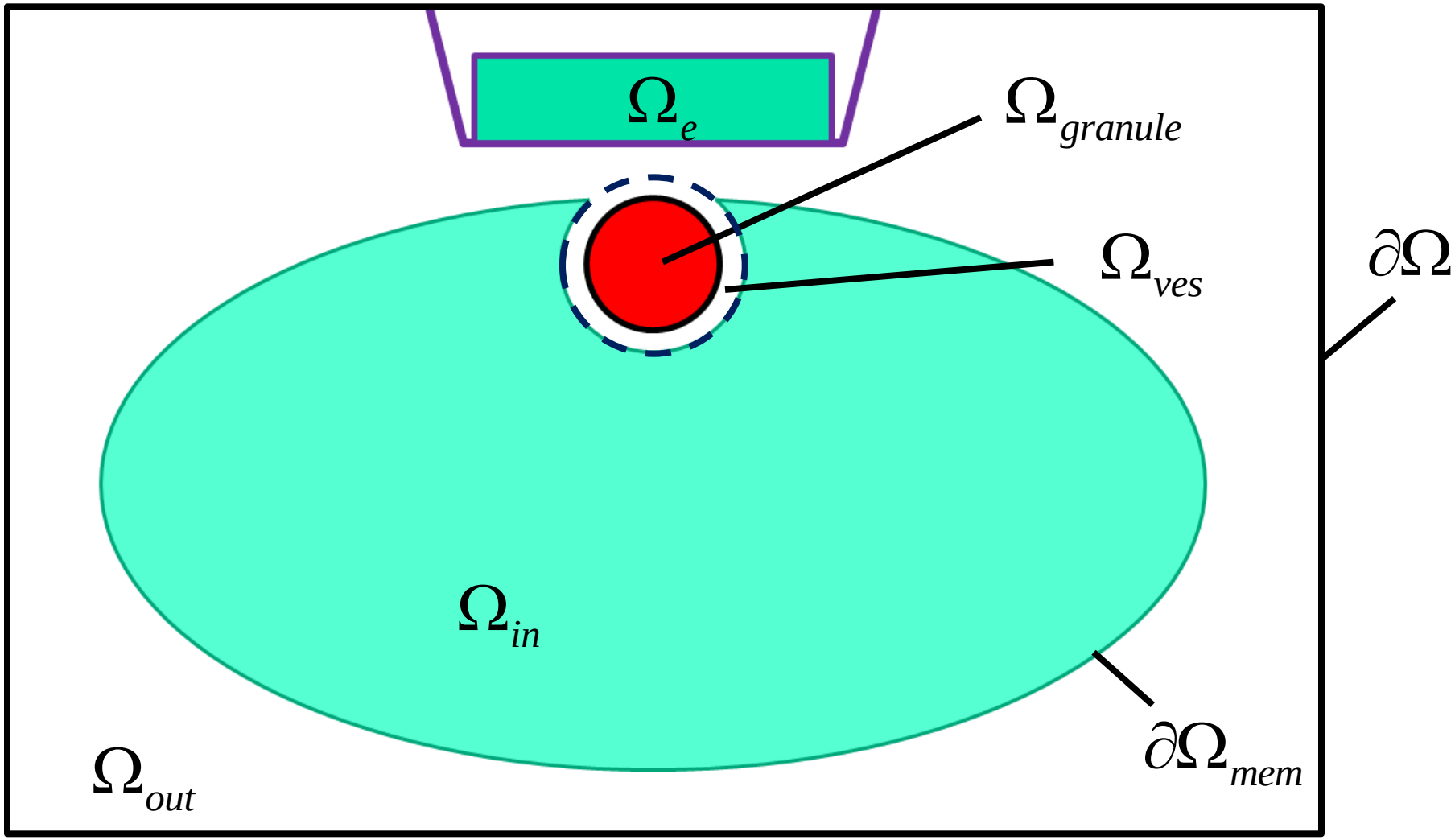
- Reasons leading to degranulation:
  - Temperature field (e.g. moxibustion) ;
  - Physical stress (e.g. acupuncture needle) ;
  - Chemical messengers (e.g. allergies, neural stimulant).



http://shanghanbing.h.baike.com/article-151553.html

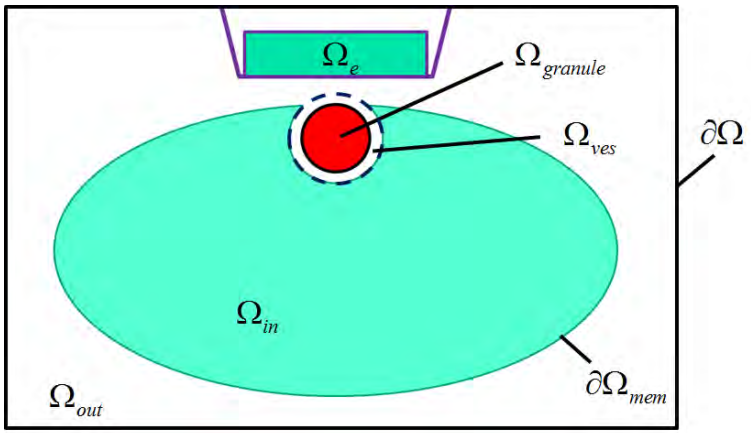
http://www.fffffw.com/2012/tcm_1221/8679.html

Mathematical model



Introduction

- $\partial\Omega$: boundary of whole domain
- Ω_e : domain of electrode (added to measure the release of chemical messengers)
- $\Omega_{granule}$: domain of granule
- Ω_{ves} : domain of vesicle
- Ω_{in} : domain of cell interior
- Ω_{out} : domain of cell exterior
- $\partial\Omega_{mem}$: boundary of membrane



Mathematical model

- Equations for the fluid (Stokes) :

$$\begin{cases} \nabla p - \mu \nabla^2 \vec{u} = 0 \\ \nabla \cdot \vec{u} = 0 \end{cases}$$

- Equation for the evolution of messenger concentration :

$$\frac{\partial c}{\partial t} + \nabla \cdot (c\vec{u}) - D\nabla^2 c = 0$$

p : pressure

μ : viscosity of fluid

$\vec{u}$: fluid velocity

c : concentration

$\vec{v}$: velocity which affect concentration

D : diffusivity

Mathematical model

- Boundary condition

Fluid :

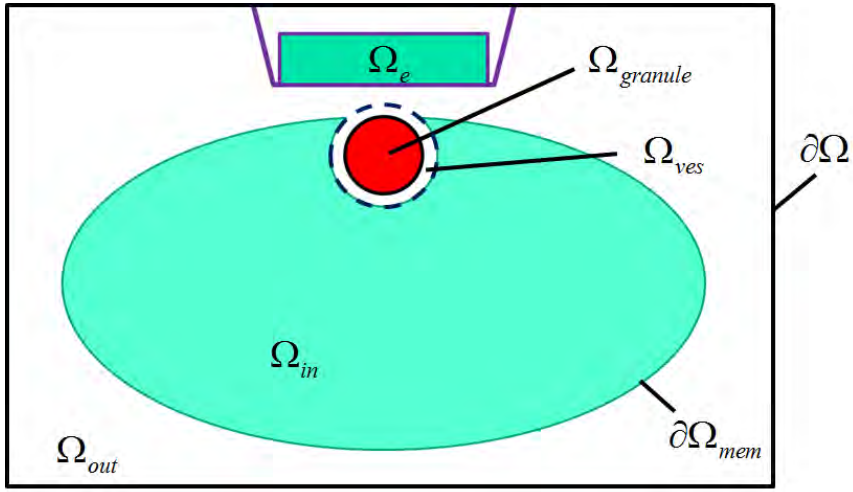
$$\vec{u} = \begin{cases} u_{mem} & \text{on } \partial\Omega_{mem} \\ 0 & \text{on } \partial\Omega_e \end{cases}$$

$$\nabla\vec{u}\cdot\vec{n} = 0 \quad \text{on } \partial\Omega$$

Concentration :

$$c = \begin{cases} 0 & \text{on } \partial\Omega_e \\ 0 & \text{on } \partial\Omega \end{cases}$$

$$\nabla c\cdot\vec{n} = 0 \quad \text{on } \partial\Omega$$

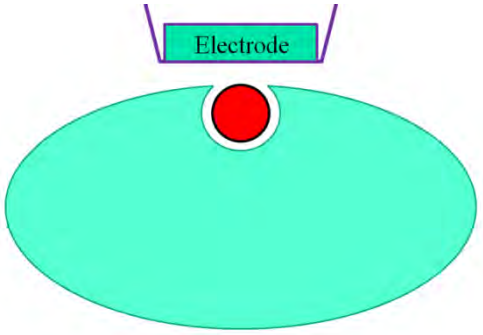


Problem setting

- Goal : To simulate the process of degranulation

- Assumptions

  - Case 1 :
    1. a granule matrix is considered in the vesicle;
    2. swelling of the granule;
    3. cell membrane remains fixed.



  - Case 2 :
    1. no granule in the vesicle;
    2. membrane movement.

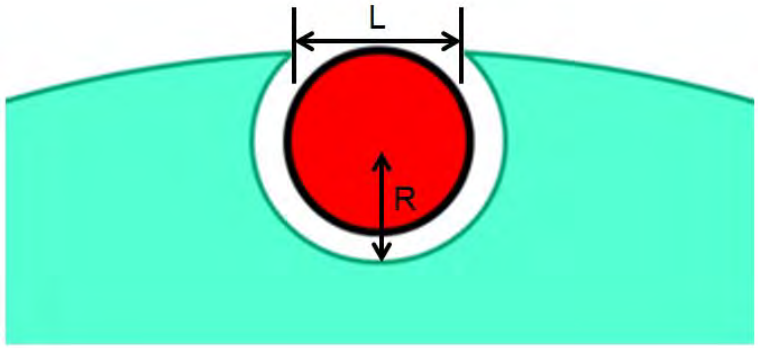
Problem setting

Case 1

D (diffusivity) :

D = 1 in $\Omega_{granule}$

D = 30, 300, 3000 in Ω_{out}

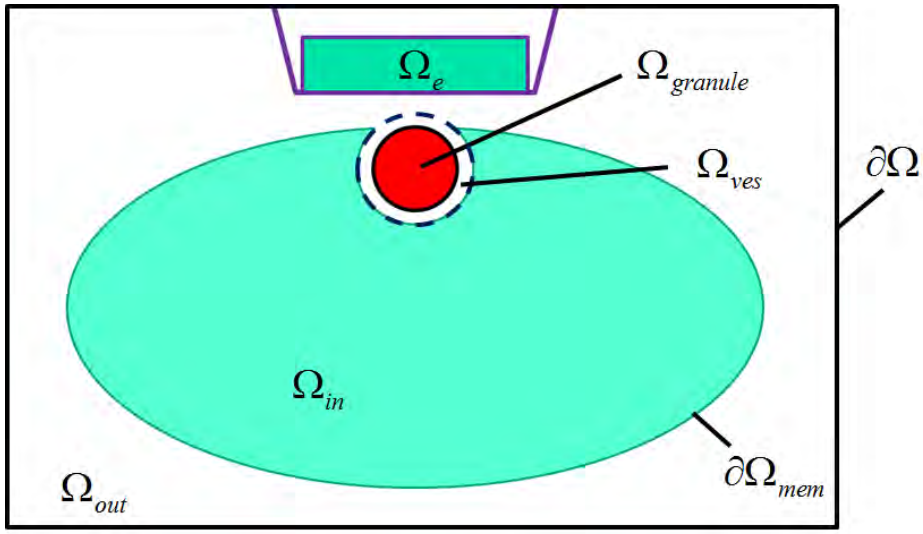


S = L/R (Pore size) :

S = 0.235, 0.741, 1.55, 2

Dt (time step) :

Dt = 0.001



Mathematical model

Case 1 **Granule swelling equation**

$$\frac{\partial \vec{d}}{\partial t} = \frac{K + \eta/3}{f} \nabla(\nabla \cdot \vec{d}) + \frac{\eta}{f} \nabla^2 \vec{d} \quad , \vec{d} = (d_1, d_2)$$

$$\text{I.C.} : \begin{cases} d_1(x, t=0) = \dfrac{d_r(r,0)}{r} x \\ d_2(x, t=0) = \dfrac{d_r(r,0)}{r} y \end{cases} \quad ; \text{ B.C.} : \frac{\partial \vec{d}}{\partial n} = 0$$

where

$$d_r(r,0) = \frac{\pi_0 r}{3K} \quad , r = \sqrt{x^2 + y^2}$$

$\vec{d}$: displacement vector

a : final radius

K : bulk modulus of elasticity

η : shear modulus

f : coefficient of friction

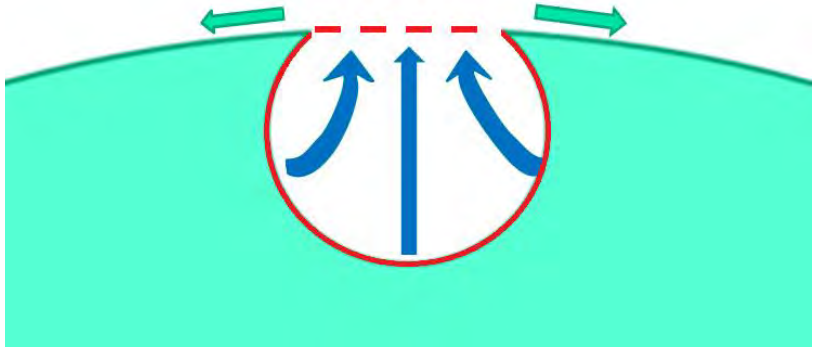
π_0 : coefficient of swelling or shrink.

T. Tanaka and D. J. Fillmore. Kinetics of swelling of gels, J. Chem. Phys. 70, 1214-1218 (1979)

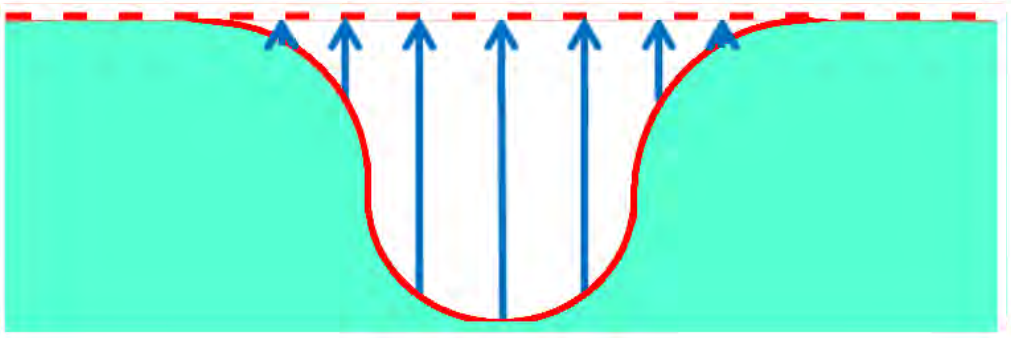
Problem setting

Case 2 **Membrane movement**

Motion governed by the exocytosis mechanism



Motion along the vertical direction



Simplification

Problem setting

Case 2 **Parametric description of the motion**

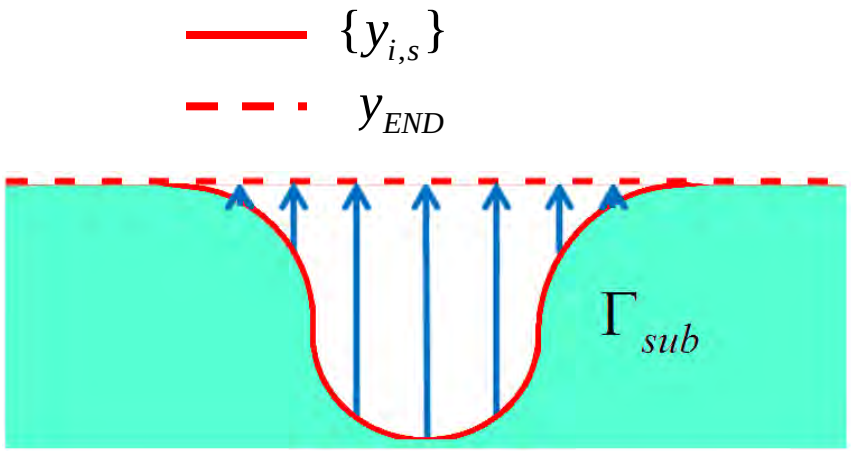
$$y_i^{n+1} = \begin{cases} y_i^n + \Delta d \times (y_{END} - y_{i,s}) & , y^n < y_{END} \\ y_i^n & , y^n \geq y_{END} \end{cases}$$

where $\forall \Delta d \in \mathbb{R}^+ \ , \forall y_i^n \in y_i \ , \forall i \in \mathbb{N} \ , \forall n \in \mathbb{N} \cup \{0\}$

$$v_{\Gamma_{sub}} = \frac{y^{n+1} - y^n}{\Delta t} = \Delta d \times (y_{END} - y_{i,s})$$

$v_{\Gamma_{sub}}$ is the velocity on Γ_{sub}

(Γ_{sub} is subdomain of $\partial\Omega_{mem}$, red soild line)



Problem setting

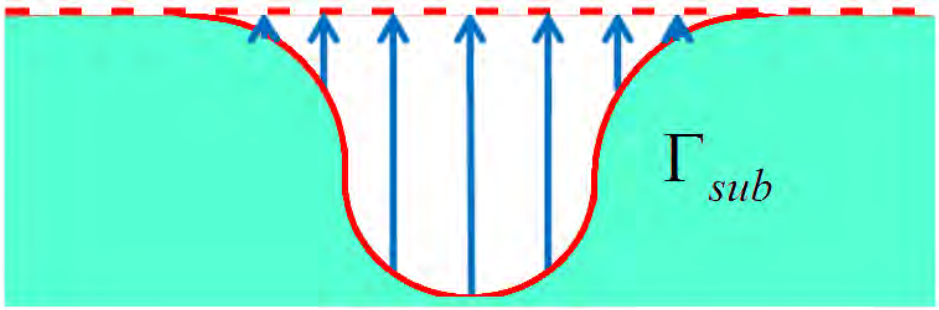
Case 2

velocity :

$v_{\Gamma_{sub}}$ = 0, 342, 427, 570, 855

Dt (time step) :

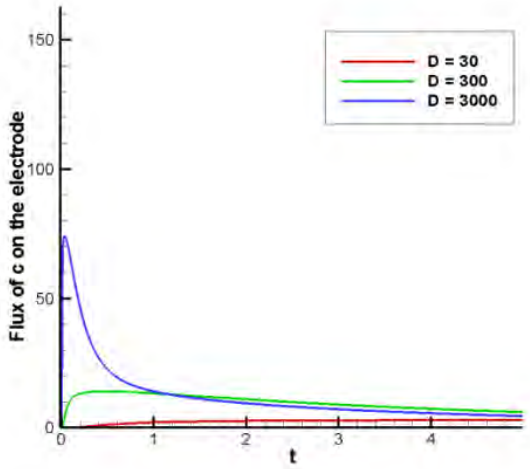
Dt = 0.001



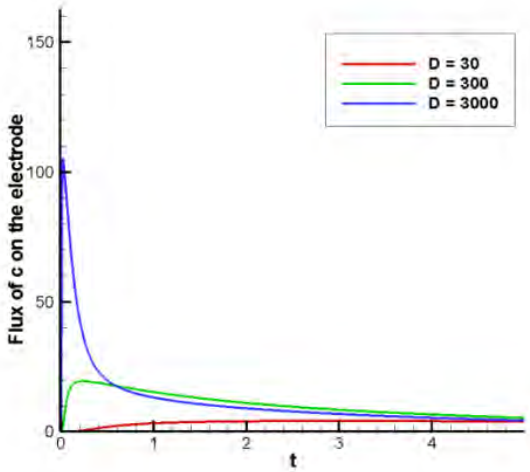
Numerical results

Case 1

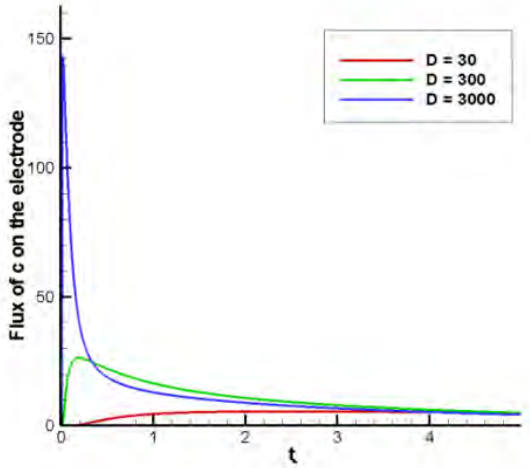
Flux of **c** across $\partial\Omega_e$ with respect to **S**



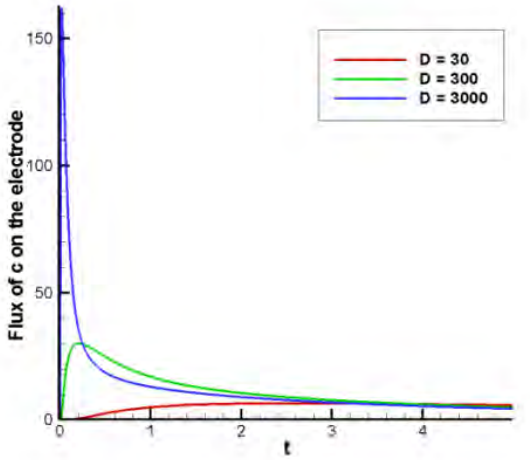
S = 0.235



S = 0.741



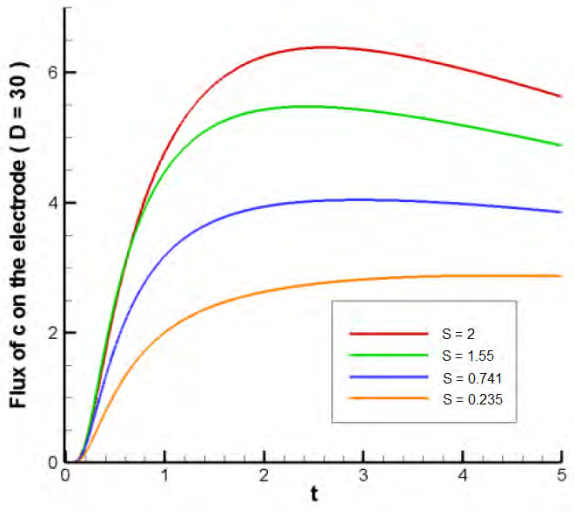
S = 1.55



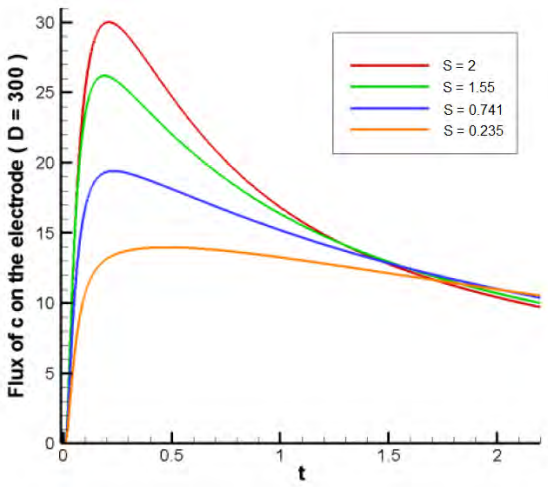
S = 2

Numerical results

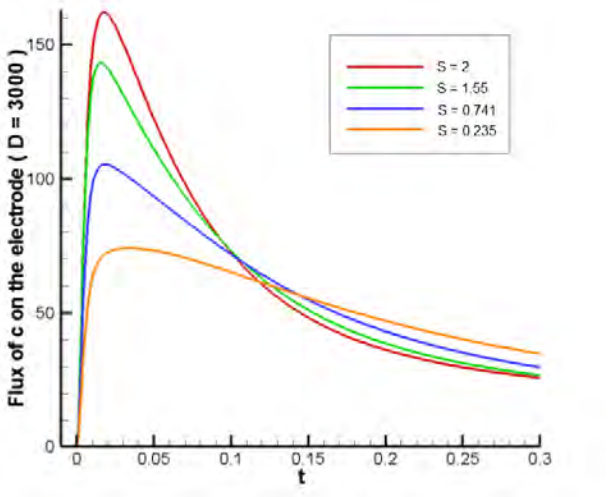
Case 1 Flux of **c** across $\partial\Omega_e$ with respect to $\mathbf{D}$.



D=30



D=300

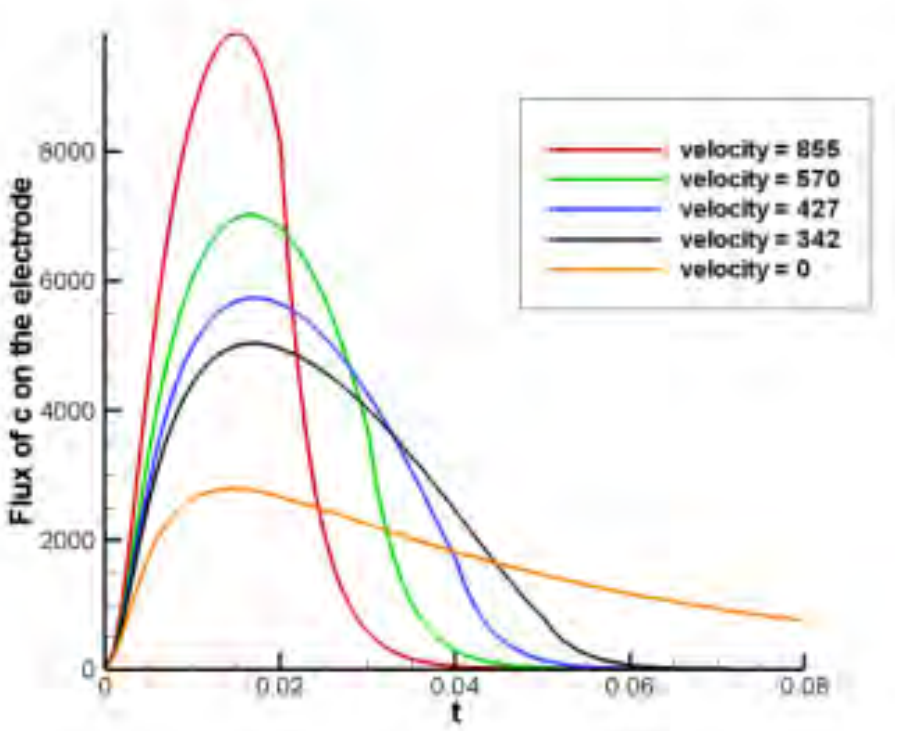


D=3000

Numerical results

Case 2

Flux of **c** across $\partial\Omega_e$ with respect to the velocity $v_{\Gamma_{sub}}$



Concluding remarks on task # 3

- The flux of concentration of chemical messenger across the electrode is proportional to the pore size and the diffusivity in Case 1 and membrane velocity in Case 2.

- Future work :

  To construct a physically more relevant model membrane movement.

Task # 4 – Mastocyte chemotactic recruitment by Yannick Deleuze and Marc Thiriet

4-1 Introduction

4-2 Mathematical model

4-3 Numerical analysis

4-4 Numerical results

Introduction

Data & hypotheses

- Relatively high density of resting mastocytes at acupoints;
- Two mastocyte states according to the 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.

Model (Deleuze, Thiriet, 2013)

$$\frac{\partial n_g}{\partial t} - \mathcal{D}_m \nabla^2 n_g + \nabla.(S\, n_g \nabla c) = -A\Phi n_g + k_r n_d, \qquad t > 0, x \in \Omega$$

$$\frac{\partial c}{\partial t} - \mathcal{D}_c \nabla^2 c = \kappa_c A\Phi n_g - \delta_c c,$$

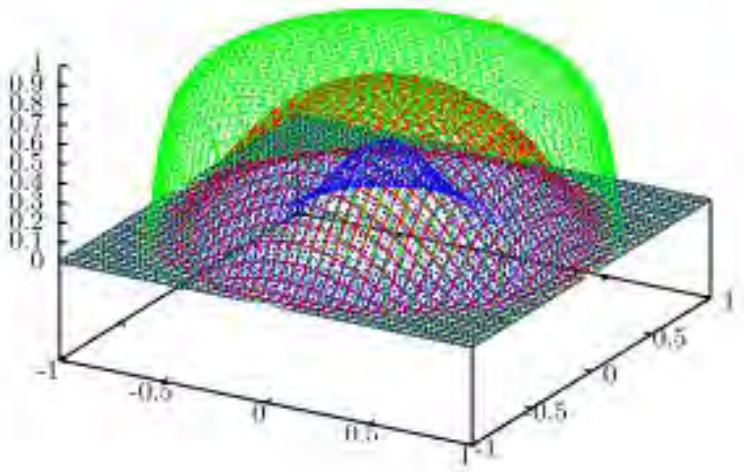
$$\frac{\partial n_d}{\partial t} - \mathcal{D}_m \nabla^2 n_d = A\Phi n_g - k_r n_d,$$

$$\frac{\partial s_n}{\partial t} - \mathcal{D}_{s_n} \nabla^2 s_n = \kappa_n A\Phi n_g - \delta_{s_n} s_n,$$

$$\frac{\partial s_e}{\partial t} - \mathcal{D}_{s_e} \nabla^2 s_e = \kappa_e A\Phi n_g - \delta_{s_e} s_e.$$

- $\Phi(x)$: magnitude of mechanical stress $\rightarrow 0 \leq \Phi(x) \leq 1\ (0 \leq x \leq \ell)$;
- $\mathcal{D}_{m/c/n/e}$: diffusion coefficient (mastocyte/chemoattractant/nervous messenger/endocrine mediator) $[L^2T^{-1}]$;
- A: activation rate $[T^{-1}]$;
- R: regeneration rate of degranulated masotocytes $[T^{-1}]$;
- S: mastocyte sensitivity to chemoattractant (index that measures chemoattractant power, i.e., migration distance par unit concentration and unit time $[L^4 mol^{-1} T^{-1}]$);
- $\kappa_{c,e,n}$: release quantity coefficient [mol].

Physical stress Φ



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

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

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

Mathematical result

$$\partial_t n - \nabla^2 n + \nabla.(S\, n \nabla c) = -A\Phi n; \quad (1)$$

$$-\nabla^2 c = \kappa_c A \Phi n; \quad (2)$$

$$n|_{t=0} = n^0 \geq 0. \quad (3)$$

$$t > 0; \quad \mathbf{x} \in \mathbb{R}^2.$$

Theorem (Deleuze Y. , C. R. Acad. Sci. Paris, Ser. I, 2013)

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

- If the initial number of cells is small enough, there exists a solution to (1)-(3) in $L^p(R^2, dx)$ 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 (1)-(3) blows-up as $t \to T^*$.

Mathematical result

The explosion of the solution at the critical point corresponds to the amplification of the response of the immune system at the needling point. We want the blow-up to occur to show the effectiveness of acupuncture needling.
Blow-up of the mastocyte density occurs if :
(i) The initial number of mastocytes is large enough
(ii) The dispersion of the population of cells is small enough

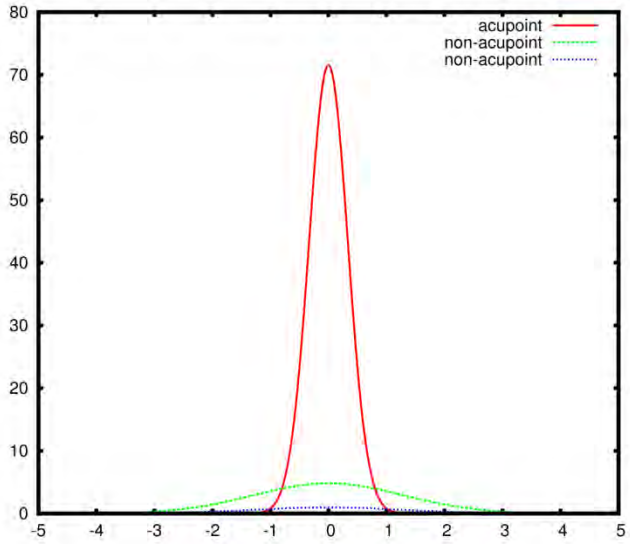


Figure: Initial mastocyte Gaussian distribution at an acupoint (concentrated distribution in red) ; non-acupoint (dispersed distribution in green) with the same cell number ; and non-acupoint (in blue) with a lower cell number.

Acupoint

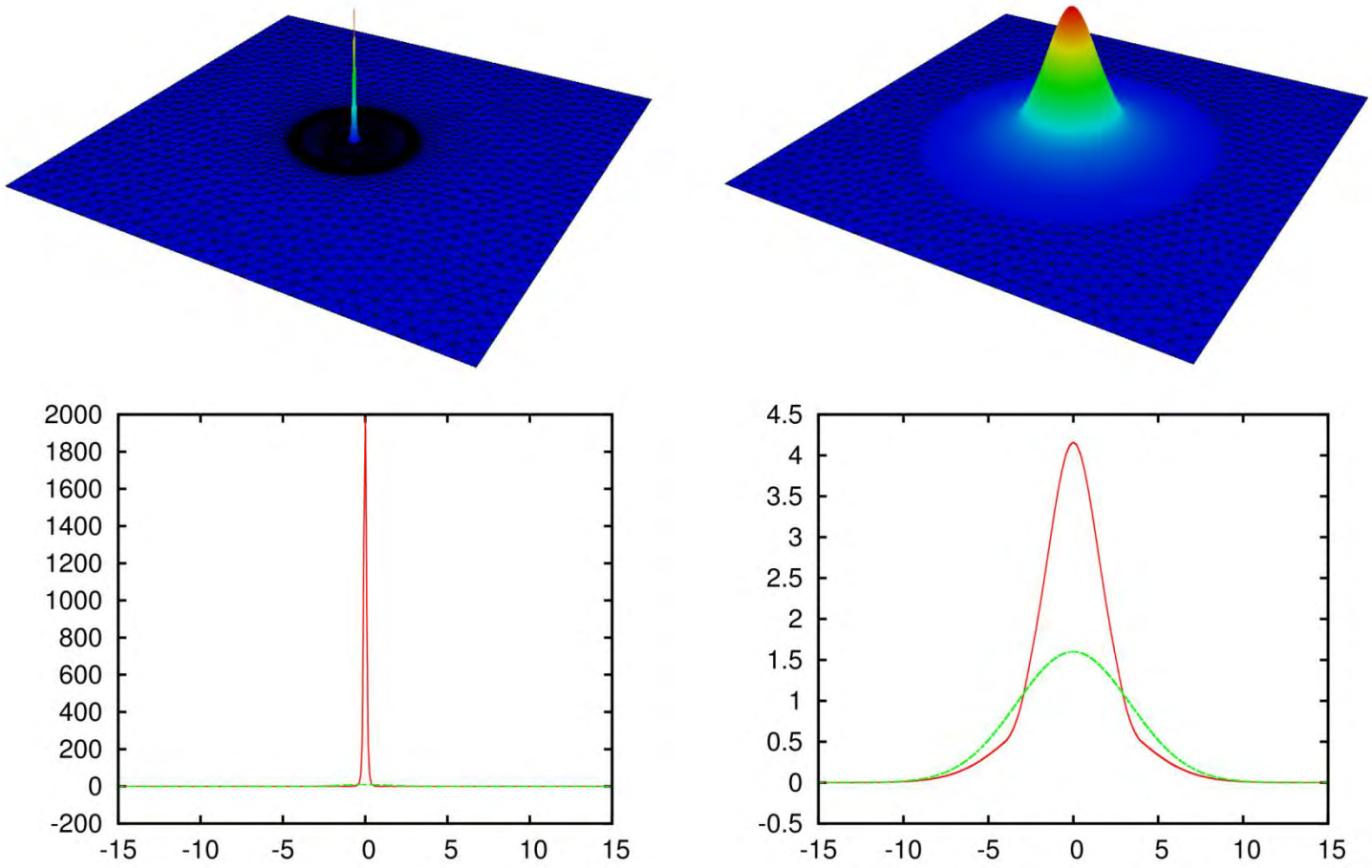
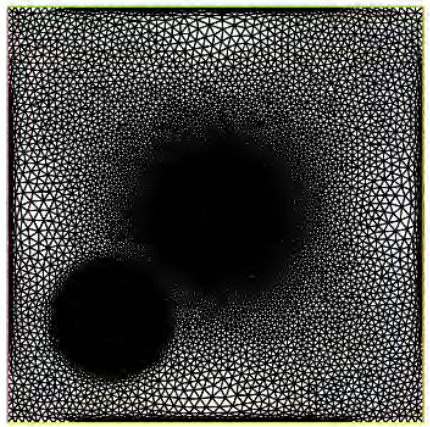


Figure: Initial (green) and final (red) distribution of mastocytes at acupoint (**left**) and in a non-acupoint mastocyte pool. The blow-up solution is only expected to occur at acupoint Computed in FreeFrem++ (Hecht, 2013)..

Acupoint



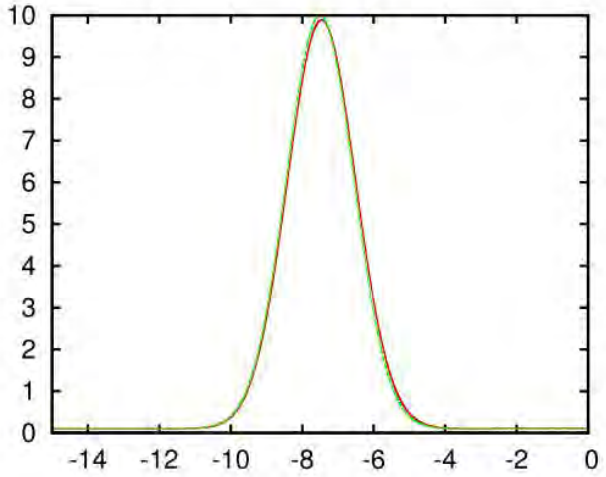


Figure: Needling outside an acupoint. Mesh with refinements in the needle region (top left) and mastocyte pool (bottom left). Absence of significant change in cell population distribution (top right). Computed in FreeFrem++ (Hecht, 2013).

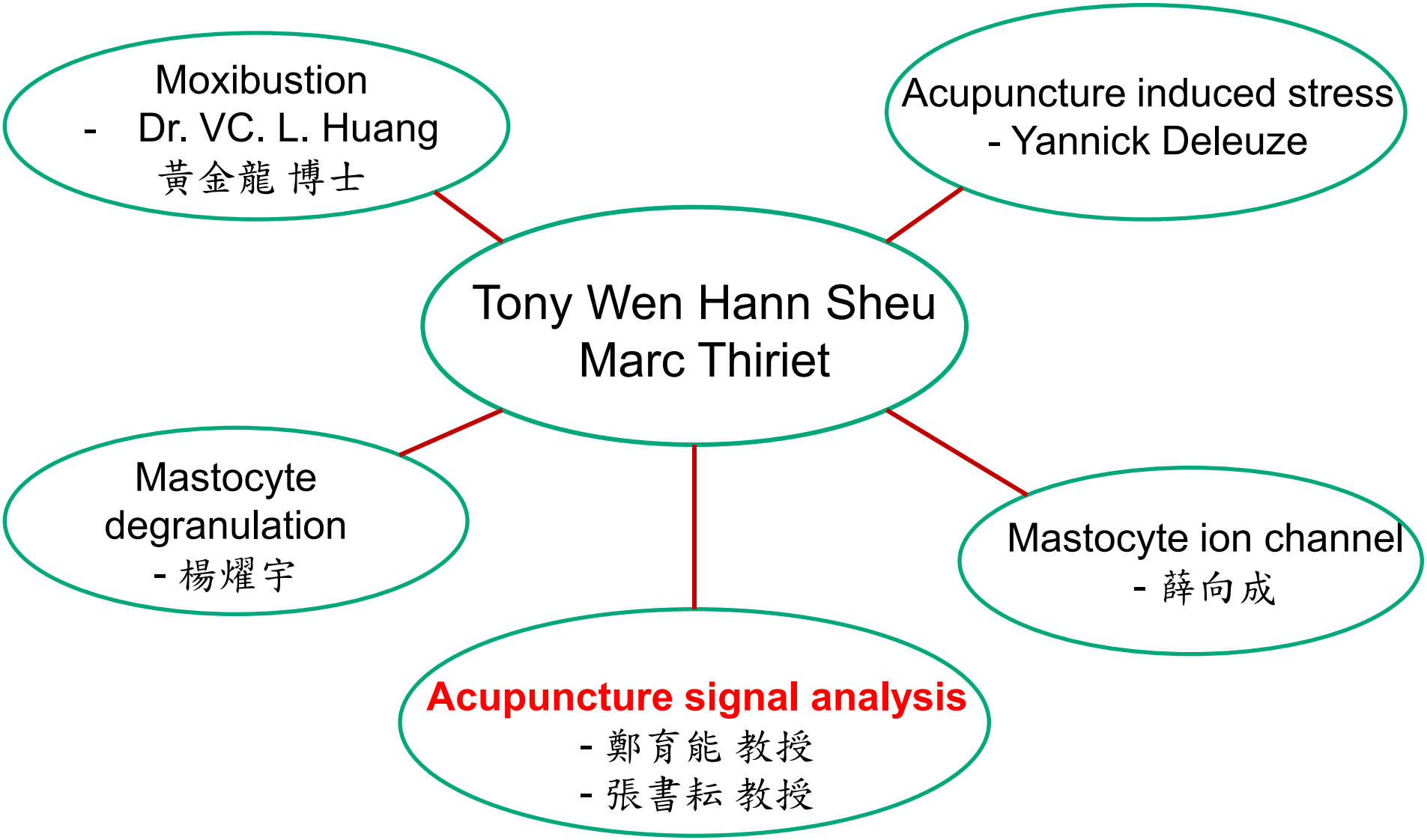
Concluding remarks and perspectives on task # 4

- Stimulation and recruitment of mastocytes at acupoints can sustain physiological response.

The current study motivates us

- to consider more realistic model
- to complete the mathematical analysis,
- to complete the model with experimental data,
- to discuss our results with acupuncture expert and practitioner.

Tony's team in conducting Chinese medicine study



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