Centro de Ciencias Pedro Pascual
Benasque
24 August–4 September 2009

Looking for a Mathematical Model of Elctroporation

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August 26, 2009

Joint work with:

- Frédéric de Gournay (Université de Versailles Saint-Quentin, France)
- Lluis Mir (CNRS, Institut Gustave Roussy, Villejuif, France)
- Clair Poignard (INRIA, Bordeaux, France)

Today's talk

On Cells and Membranes
What is electroporation?
Mathematical questions
The Schwan model
A molecular dynamics approach
A model for the membrane

On Cells and Membranes

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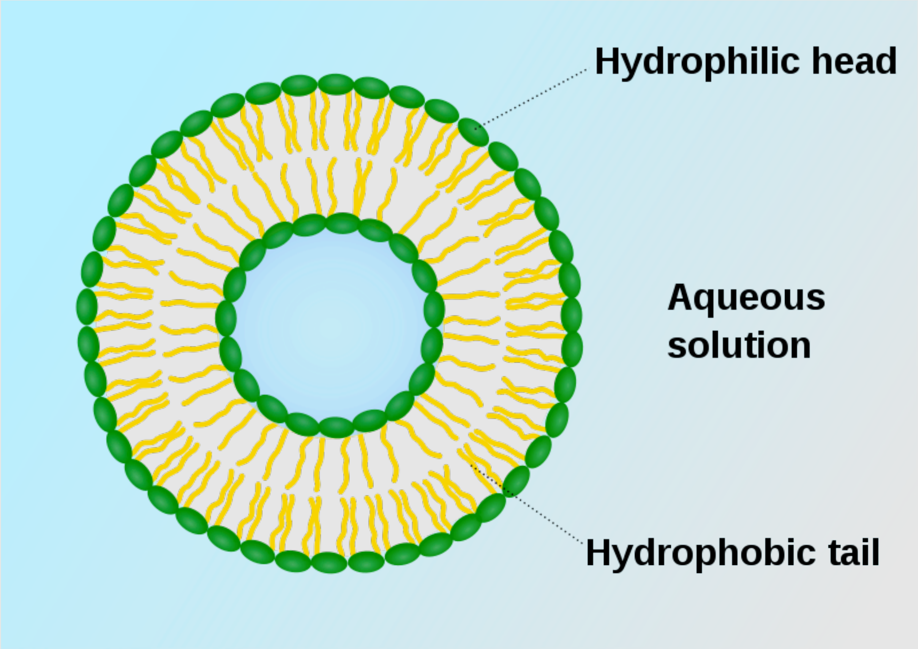
  here the green head + the yellow tail represent a phospholipid



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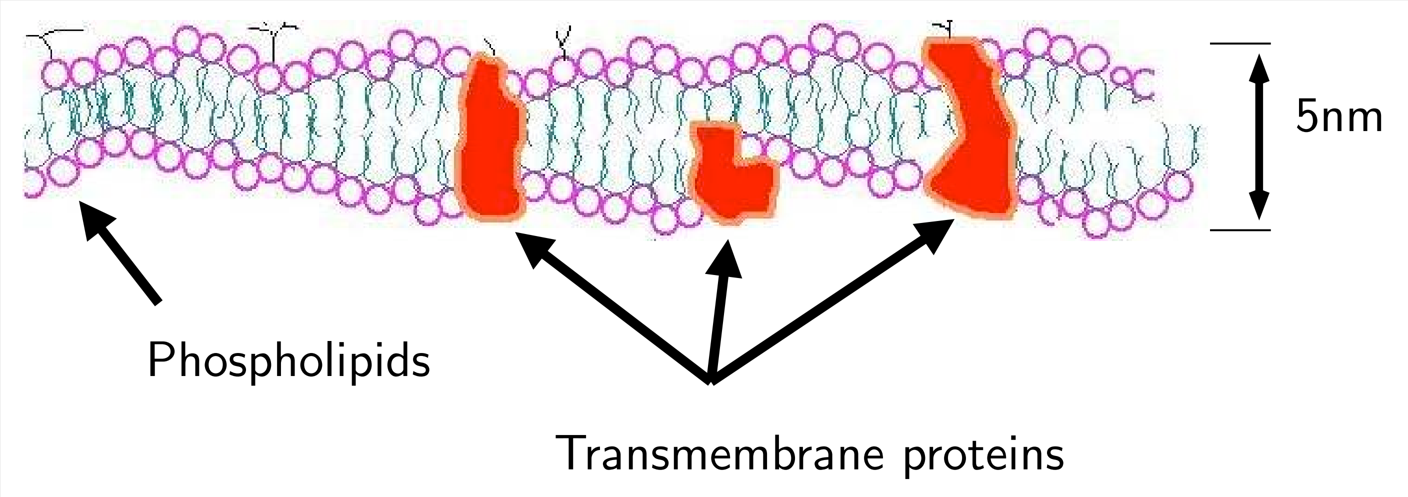

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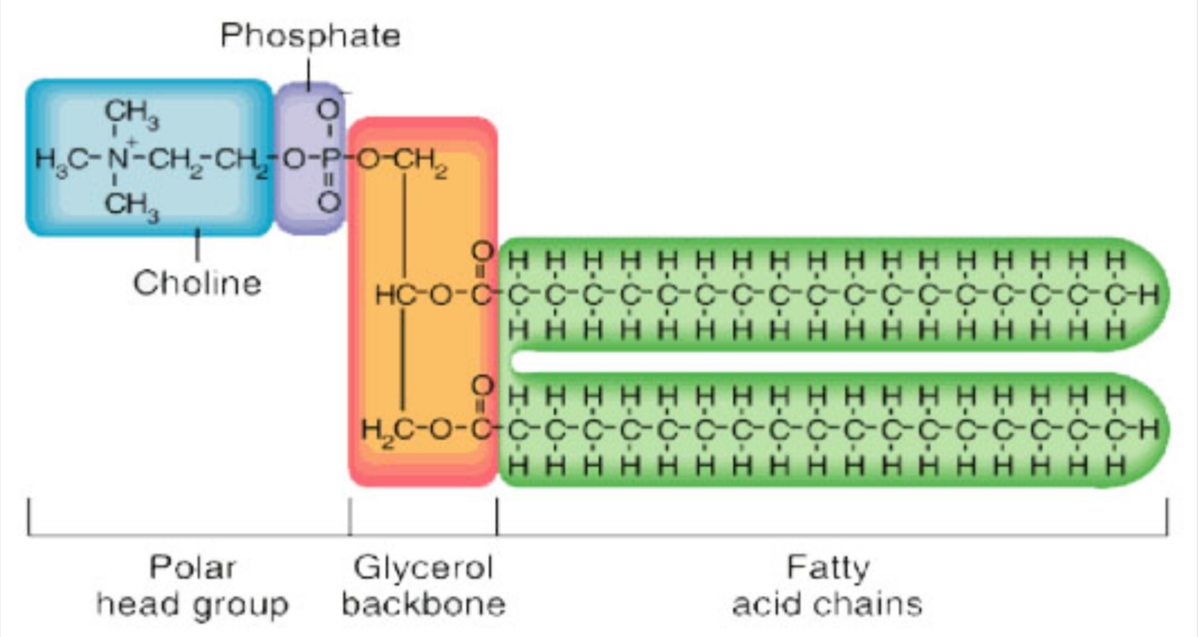
- Relative sizes are as follows:
  - Cell's diameter $\sim$ 5 000 nm
  - Membrane thickness $\sim$ 5 nm
  - Distance between two cells $\sim$ 100 nm
  - Distance between two phospholipids $\sim$ 1 nm
  - A molecule of water $\sim$ 0.1 nm

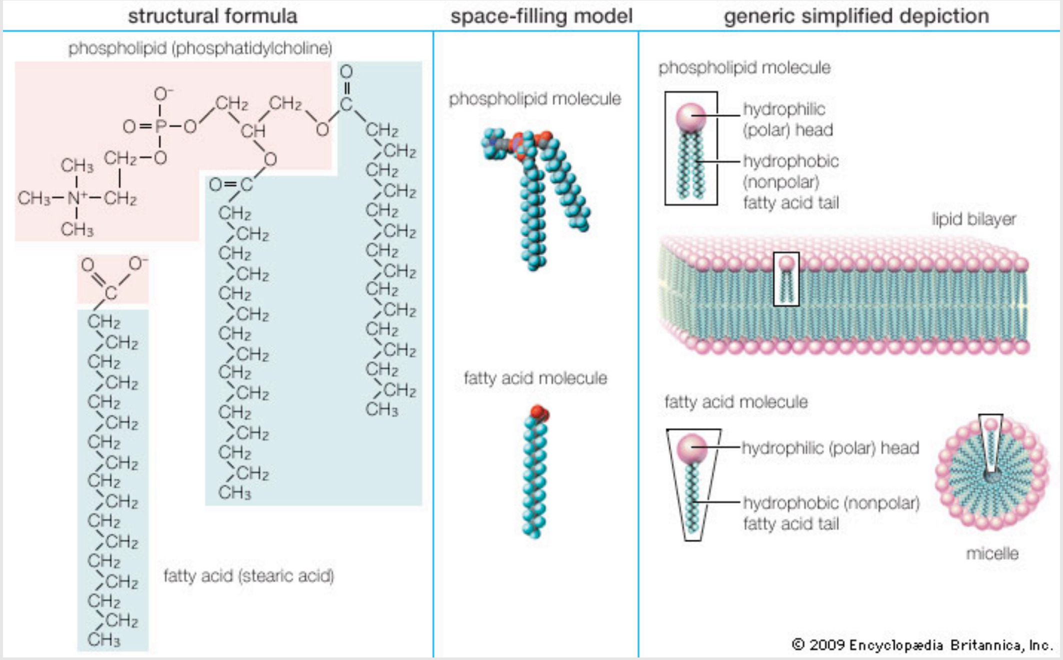
On Cells and Membranes

A typical example of a phospholipid is
image from
`http://www.uic.edu/classes/bios/bios100/lecturesf04am/lect08.htm`



On Cells and Membranes

The abstract of all this is depicted here:
image from
`http://www.britannica.com/EBchecked/topic/457489/phospholipid`



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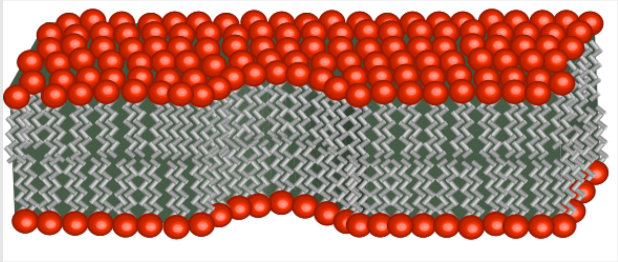

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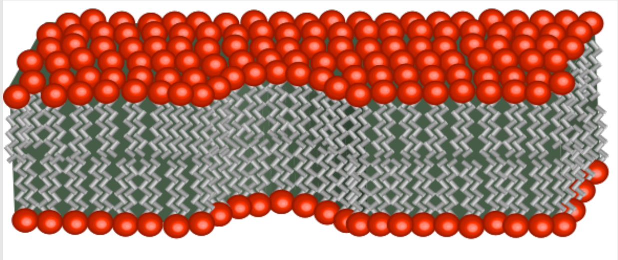
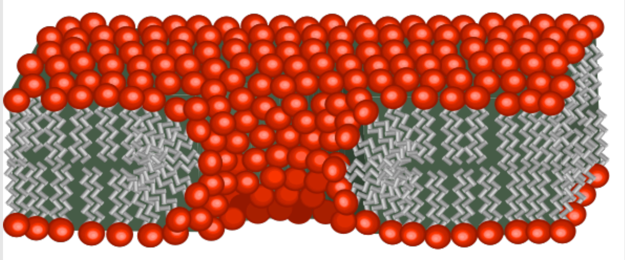
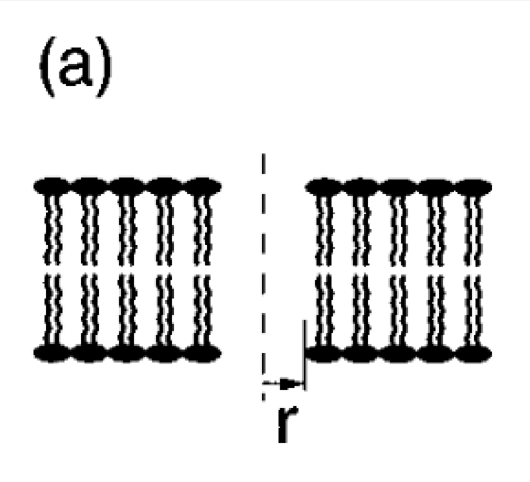


After an electric field (here parallel to the tails) is imposed a pore appears

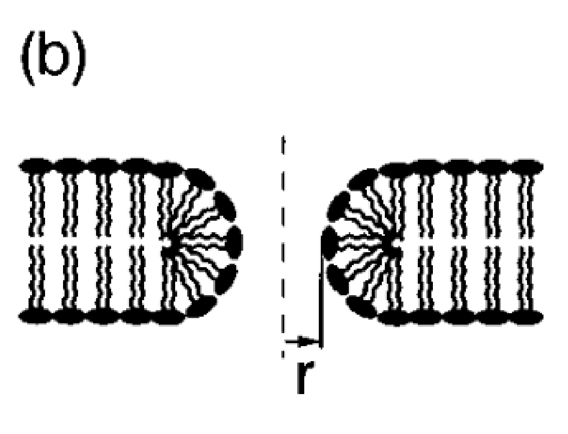


What is electroporation?

As a matter of fact, one may have two kinds of « pores »



Hydrophobic pore



Hydrophilic pore

But in fact it is not known whether there is a « permeabilization » process or creation of pores…

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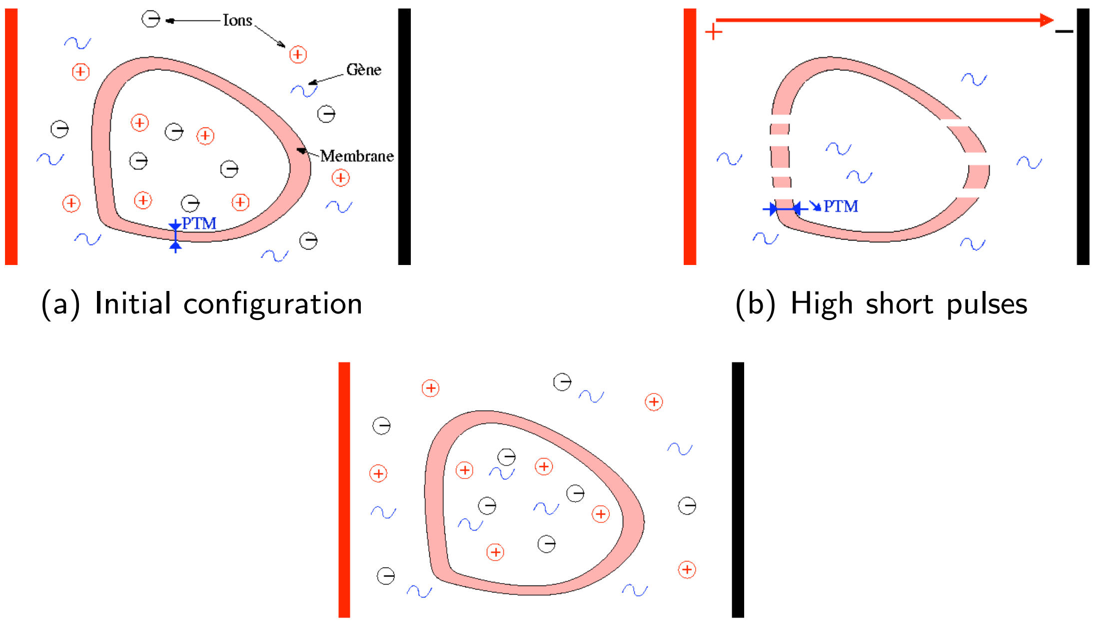
- Based on this, a new treatment of cancer tumors has been set up by Lluis Mir, Damjian Miklavčič and their colleagues: the electrochemotherapy
- A drug, such as bleomycin , is injected to the patient, locally or intravenous, while around the tumor a highly intense electric field is imposed

What is electroporation?

The process of electroporation is assumed to be as follows



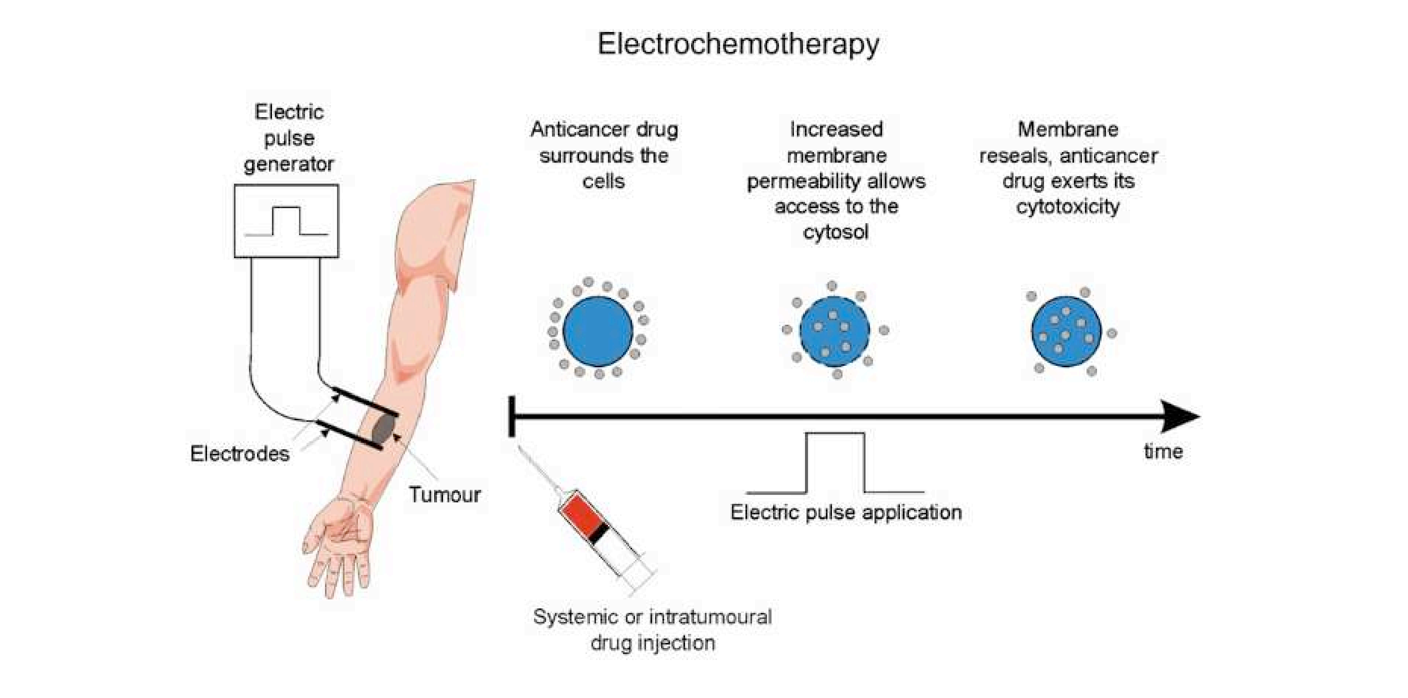
(a) Initial configuration

(b) High short pulses

(c) Interruption of the pulses

What is electroporation?

Principle of electrochemotherapy (according to D. Miklavčič)



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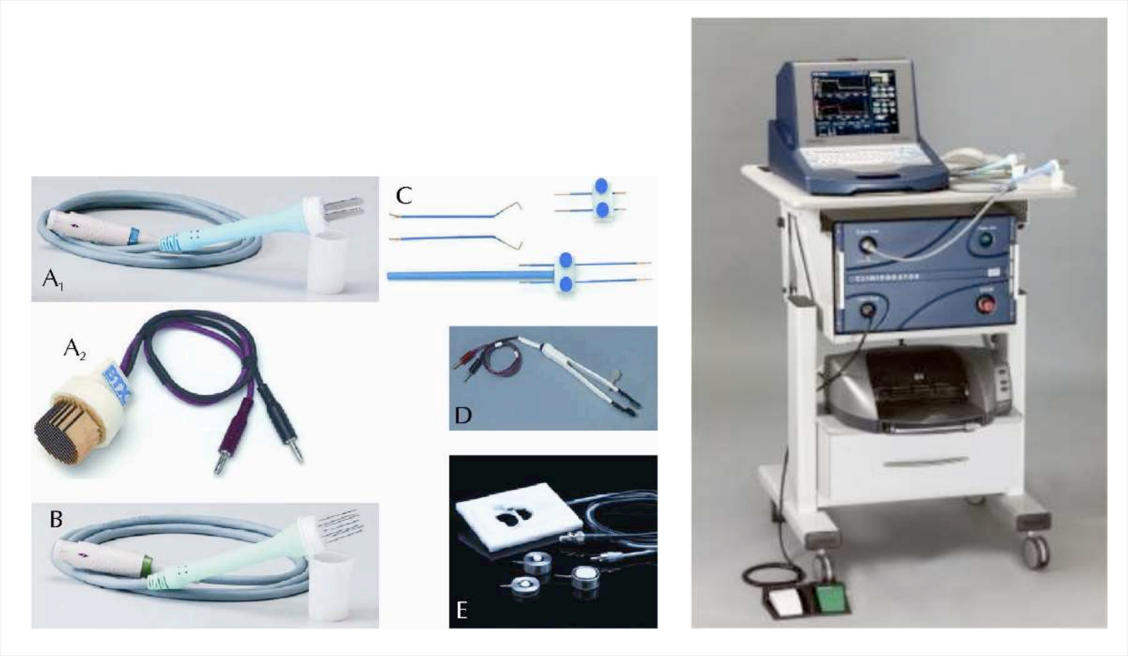
The typical apparatus used, according to Lluis Mir, is as follows



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- The treatment of a tumor is local and thus has much less side effects
- The patient has to undergo a lesser number of treatment

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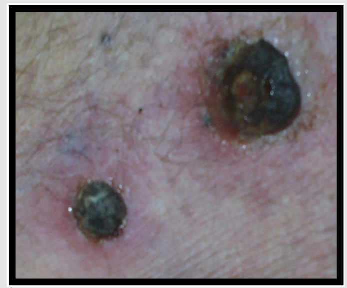
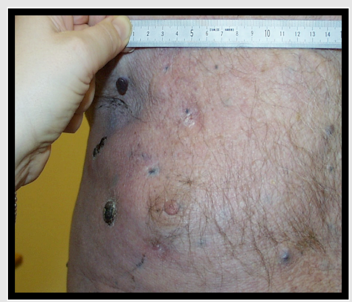
Before treatment



After 5 days

After 2 weeks



After 8 weeks

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- Deep tumors cannot yet be treated
- Due to the high intensity of the electric field (in the range of 5–25 kV/cm) some patients cannot undergo the treatment (pacemakers, anticoagulant therapy)
- The process of the electroporation is not well understood, thus the dosage may not be well calibrated

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- Understand how to go from one cell to a cluster of cells making up a tumor
- Set up a model for electroporation so that the electrochemotherapy can be coupled with models in which the growth of tumors can be predicted
- Once an affordable model is set up, and the « direct » problem is solved, study the « inverse » problem

The Schwan model

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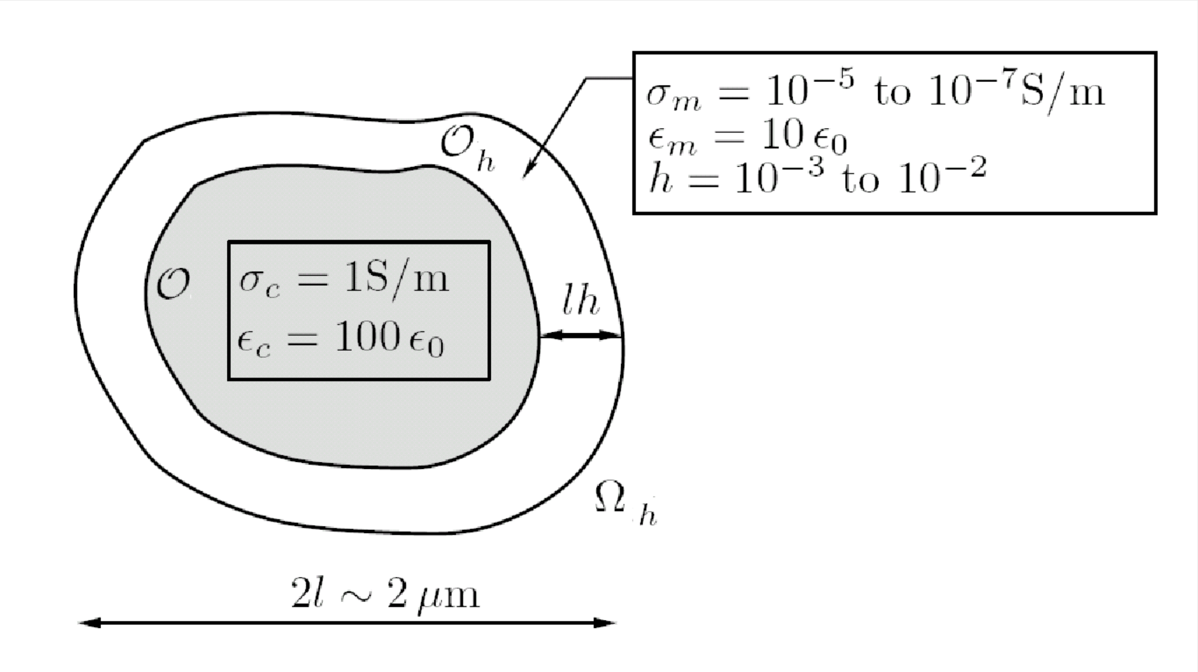

The Schwan model

- the electric potential v satisfies a time dependent quasistatic equation

$$(1) \qquad \begin{cases} \dfrac{\partial}{\partial t}\mathrm{div}(\varepsilon\nabla v) + \mathrm{div}(\sigma\nabla v) &= 0 \qquad \text{in } (0,\infty)\times\Omega \\ v(0,x) &= 0 \qquad \text{in } \Omega. \\ v(t,x) &= v_{\mathrm{imp}} \quad \text{on } (0,\infty)\times\partial\Omega \end{cases}$$

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- or a quasi-static equation in time harmonic regime: setting $\tilde{\varepsilon} := \varepsilon + \mathrm{i}\sigma/\omega$, v satisfies

(2)
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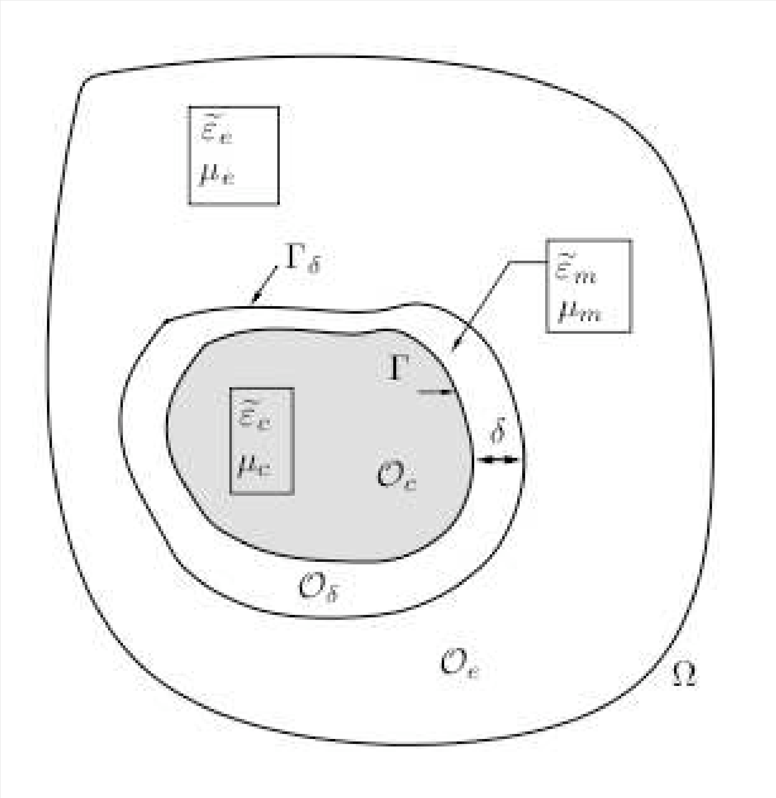
The Schwan model

- The different subdomains involved are as follows:



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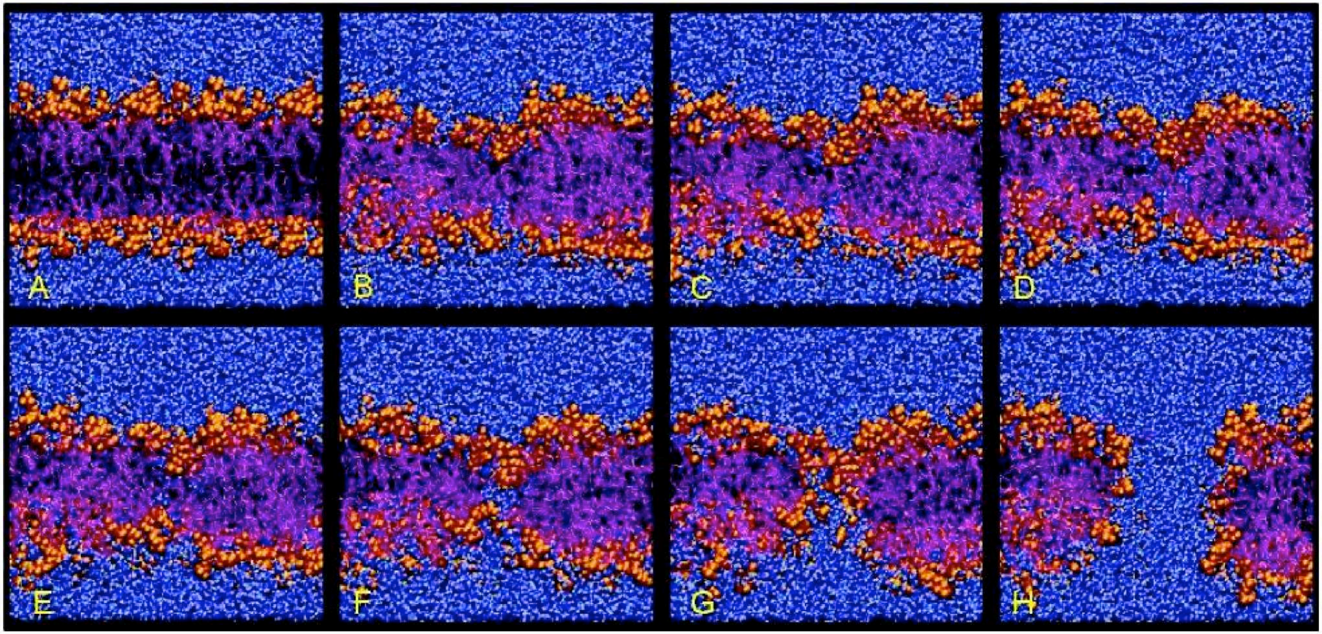
- …and one solves numerically these equations…

A molecular dynamics approach

For instance here is what one may see, according to D.P. Tieleman



A model for the membrane

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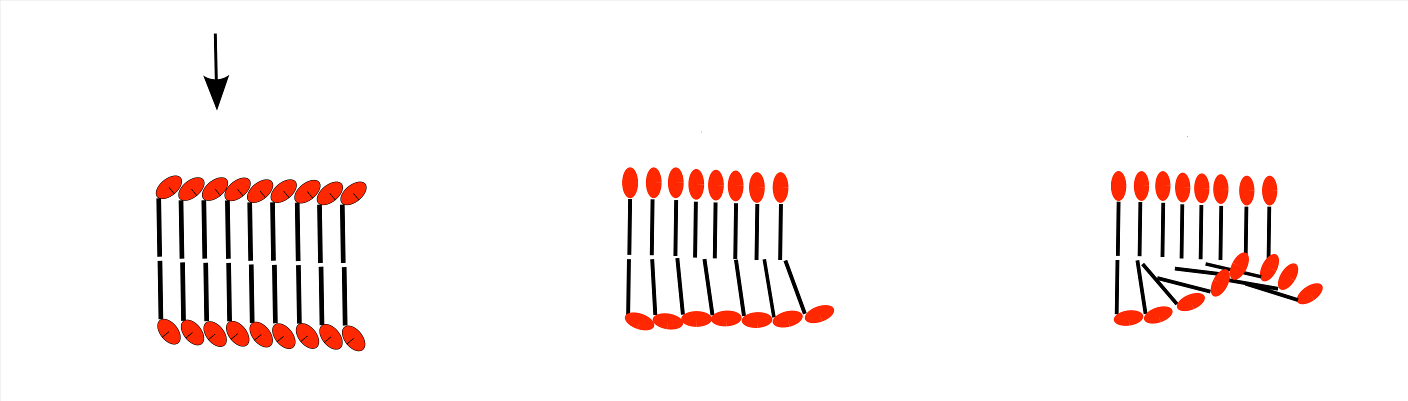
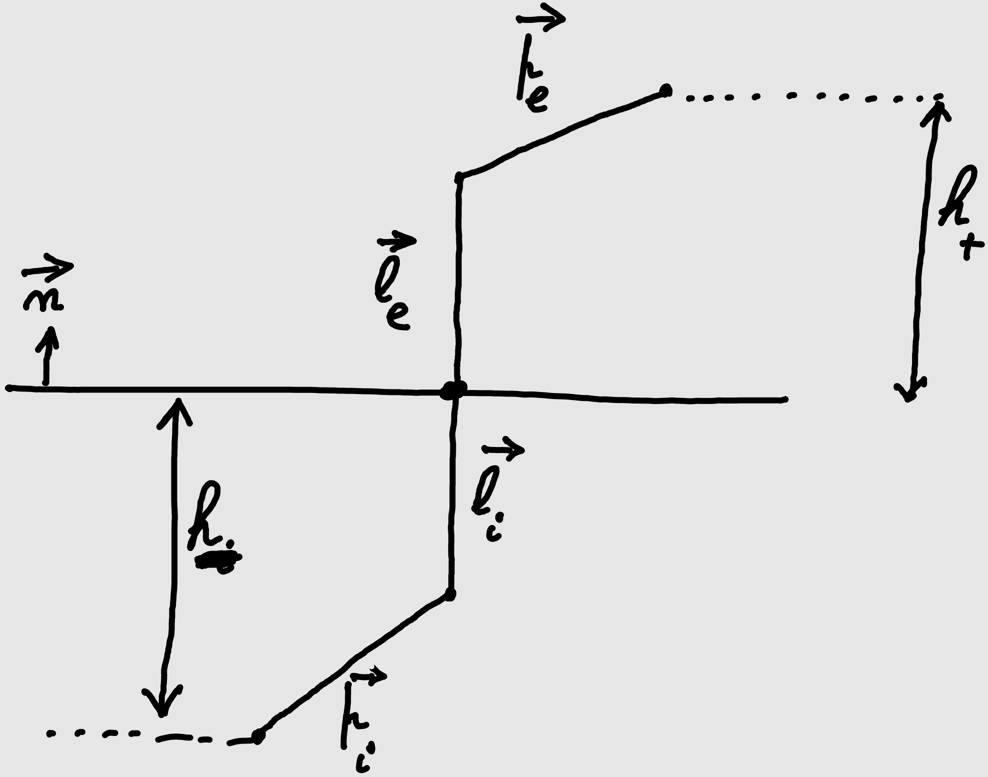
However one may conjecture that as a matter of fact, what happens is something like



That is first the dipoles (heads) get oriented and then there is a partial collapse of the phospholipids. There is no « pore », but rather a sharp decrease of the thickness, which is enough for the passage of molecules.

A model for the membrane



A model for the membrane

- We denote by $\mathbf{n}$ the normal to the mean surface of the membrane, and by $h_\pm$ the height of the dipole above or below this surface

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- The dipoles $p_\pm$ tend to rotate when submitted to an electric field.
- We assume that they satisfy a Landau-Lifschitz-Gilbert equation, namely:

$$\begin{cases} \dfrac{\partial p_\pm}{\partial t} &= \alpha_1 p_\pm \times (\nabla v_{\Gamma_\pm} + G_\pm) - \alpha_2 p_\pm \times \dfrac{\partial p_\pm}{\partial t} \\ p_\pm(0) &= c_\pm G_\pm \end{cases}$$

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- The boundary conditions are

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where v_c^0 is a potential obtained by an asypmtotic analysis, making the thickness δ tend to zero. See the **domain**.

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- Existence and uniqueness of the solution is established by reducing the system to a new system written on Γ (using Steklov-Poincaré operators).
- Numerical simulations made by Frédéric de Gournay show that there is « permeabilization » in some spots, this behavior is not symmetric, and the membrane returns to its initial position once the electric field is turned off.