The Geometry and Dynamics of the Bilayer Membrane-Vesicle Fusion Event in Animal Cells – An Invitation

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Based on joint ongoing work with
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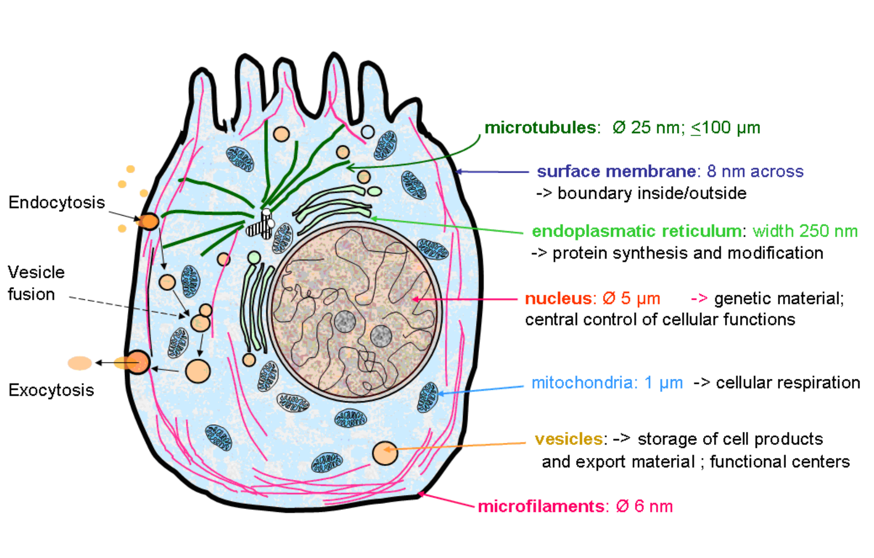
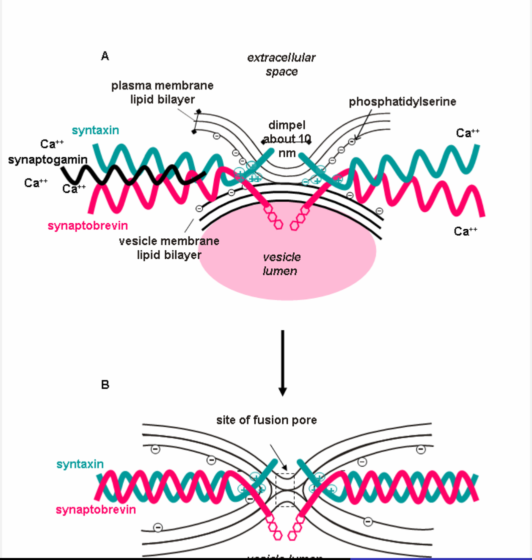
Outline

1. Phenomenology
   - Vesicular Traffic
   - Electromagnetic Quantities
2. The Model
   - Goals
   - Free Boundary Route
   - Reservations
3. References

Selected structures and functions of an animal cell

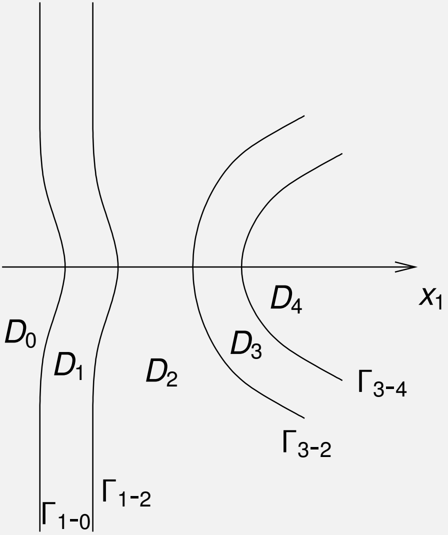


Bilayer membrane fusion



Clearly separated regions

- D_0 Amorphous outside cell neighbourhood
- D_1 Plasma membrane, $\partial D_1 = \Gamma_{1-0} \cup \Gamma_{1-2}$
- D_2 Cytosol
- D_3 Vesicle membrane, $\partial D_3 = \Gamma_{3-2} \cup \Gamma_{3-4}$
- D_4 Vesicle lumen
- $\{M_j\}$ *Ca* storage organelles to be activated
- N Cell nucleus



Electrical charges, electric space field, electrical potential

Q Charges; charge density $q := Q/V$; V volume

- Positive electrical charges on bilayer lipid membrane outsides $\Gamma_{1-0} \cup \Gamma_{3-2}$
- Negative electrical charges on bilayer lipid membrane insides $\Gamma_{1-2} \cup \Gamma_{3-4}$

$\mathcal{E}_{\text{space}}$ Electric space field; vanishing at dimple tip in fusion pore

$\mathcal{D}_{\text{space}}$ Electric space field density; related to $\mathcal{E}_{\text{space}}$ by $\mathcal{D}_{\text{space}} = \varepsilon \mathcal{E}_{\text{space}}$ with $\varepsilon = \varepsilon_0 \varepsilon_r$ dielectric constant

u Electrical potential; related to $\mathcal{E}_{\text{space}}$ by $\operatorname{grad} u = \mathcal{E}_{\text{space}}$

- Vanishing on surface-like membranes D_1 and D_3
- Positive on D_0 close to Γ_{1-0} and on D_2 close to Γ_{3-2}
- Negative on D_2 close to Γ_{1-2} and on D_4 close to Γ_{3-4}

Magnetic field wave

Ca^{++} Oscillations, directed in space and time

$\mathcal{D}$ Alternating electrical field density of low frequency

$$f = \begin{cases} \sim 5\,\mathrm{Hz} & \text{for } \beta \text{ cells} \\ \sim 100\,\mathrm{Hz} & \text{for nerve cells} \end{cases}$$

$\mathcal{E}$ Corresponding electrical field

$\mathcal{H}$ Resulting magnetic field wave

$\mathcal{B}$ Corresponding magnetic flux density $\mathcal{B} = \mu_0 \mathcal{H}$, permeability μ_0, field amplitude $\widehat{\mathcal{B}}$

X_C Capacitive reactance $X_C := 1/(\omega C)$

- $\omega = 2\pi f$, C capacitance
- Recall $Z = R + iX_C$ complex impedance
- Vanishing on D_0 and D_2
- Forming the dimple implies decreasing X_C until X_C vanishes in the fusion pore

Aims of our mathematical modelling

Explanation Dimple making

- Hemifusion, fusion pore, flickering
- Apply physical (electro-magnetic) fundamental equations

Description Check parameters (influences, characteristic values)

- Energy needed for exocytosis / fusion event
- Field amplitude $\widehat{\mathcal{B}}$, frequency f
- Velocity v of field wave and characteristic time for event
- Number of involved Ca^{++} depots

Prediction Typical and atypical developments

- Explain deficiencies (stress, aging)
- Early diagnosis of metabolic diseases

Prescription Exocytosis pacemaker for diabetes 2 ?

Hypothetical feedback mechanism

1. Nucleus activates linear array of molecularly bound *Ca* storages
   - Through chosen vesicle, selecting the hemifusion area on plasma membrane
   - Signalling mechanism unknown
2. Superposition of locally distributed coordinated and oriented Ca^{++} activity
   - Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
   - To begin with, high X_C in D_1 and low $\widehat{\mathcal{B}}$
3. Transmembrane proteins become activated
4. Form change decreases X_C close to the emerging dimple
   - Magnetic field wave enters D_1 more easily
   - Increased current density (sharper bundling)
   - Increased Lorentz force balancing elastic forces
5. Hemifusion, branch point, short circuit, fusion pore

Two–phases problem

$\Omega \subset \mathbb{R}^3$ Specified domain

$\mathfrak{e}_1$ Unit inside normal vector

- Model the membrane dimple by a graph in the $\mathfrak{e}_1$ direction
- Consider $\{u = 0\} \supset D_1 \cap \Omega$; there grad $u \neq 0$ in general
- Focus on branch point where all three phases touch

Forces $\mathcal{F} = m\ddot{\mathfrak{h}} = \mathcal{F}_L + \mathcal{F}_M = \Lambda_+ \chi_{\{x_1>0\}}\mathfrak{e}_1 - \Lambda_- \chi_{\{x_1<0\}}\mathfrak{e}_1$

- $\mathcal{F}_L = q\mathcal{E}_{\text{space}} + q(\mathfrak{v} \times \mathcal{B}) - \gamma\mathfrak{v}$ Lorentz force
- $\mathcal{F}_M$ Elastic force

Equation $\Delta u = \frac{\lambda_+}{2}\chi_{\{u>0\}} - \frac{\lambda_-}{2}\chi_{\{u<0\}}$

- Minimizing energy losses

Character of our model?

Mathematical models are different:

- Ad-hoc models
  - Predictive power when tuned properly
  - No theoretical basis
- Theoretically based models
  - Strong explanatory power
  - In science: exceptional
- Metaphors
  - Imaginative power
  - Totally misleading when taken literally
  - Only applicable for excluding erroneous perceptions

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