Towards Understanding Multiple Sclerosis – A Biophysical Prospective

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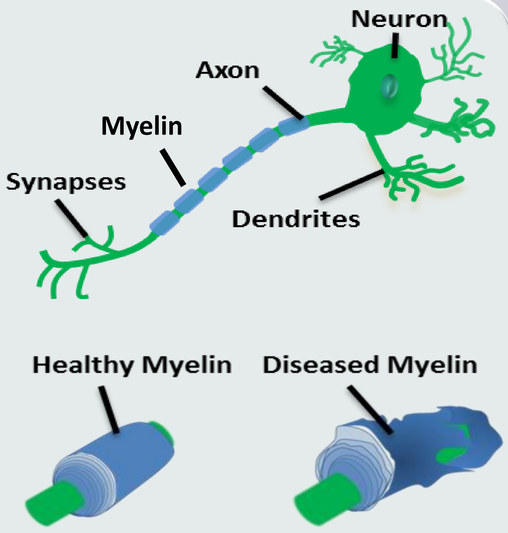
Introduction and motivation

- The nerve cells in the body are coated with a layer of insulation called myelin sheaths
- The myelin sheath is a tightly packed, multilayered lipid-protein complex wrapped around axons
- In multiple sclerosis (MS), the immune system mistakes the myelin for invading pathogen and attacks it
- The nerves essentially "short circuit," leading to versatile symptoms determined by the function of the affected neuron

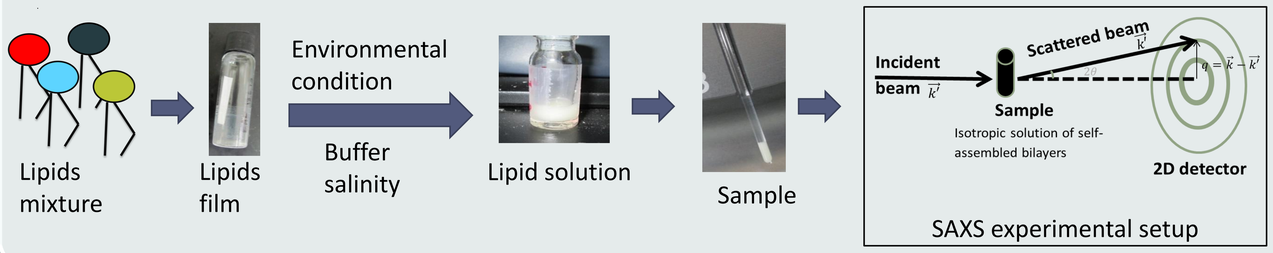


- **Using SAXS and cryo-TEM we characterize the healthy and diseased states myelin structures in order to study the phase transition conditions**
- **Main results: modification in the lipids-protein compositions and the environmental conditions can result in pathological structural phase transition**

Sample preparation

- Samples prepared with lipid composition mimicking that of healthy and diseased states (table)
- Lipids films were suspended in different buffers containing varying ion-types and salt concentrations
- Temperature was changed during the experiments

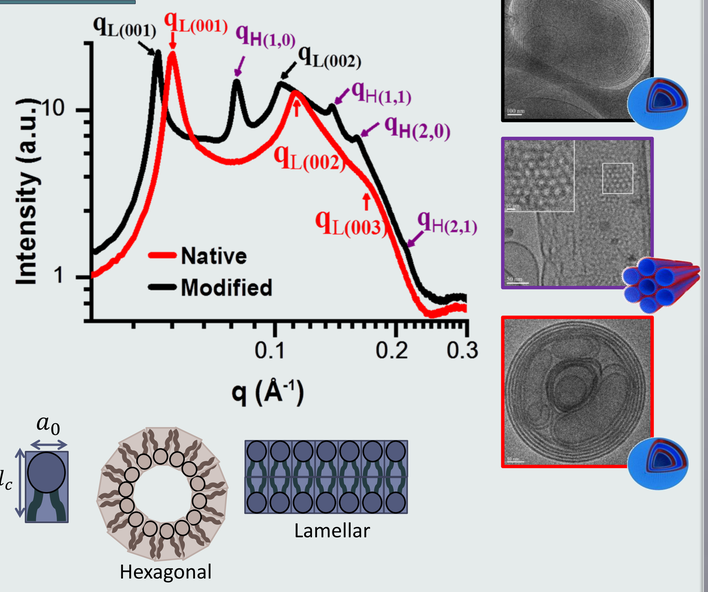
Lipid	Healthy	EAE
PS-	7.0	7.4
SM±	6.2	2.2
PE±	29.0	32.9
PC±	25.9	20.1
CHOL	31.6	37.4



Key experimental results – compositions

Lipid composition

- Native (healthy) lipid composition → lamellar stacks (L_α)
- Modified (diseased) lipid composition → structural instability towards inverted hexagonal phase (H_{II})
- Inverted hexagonal phase is induced by high content of lipids with large packing parameter $\rho = V/a_0 l_c$

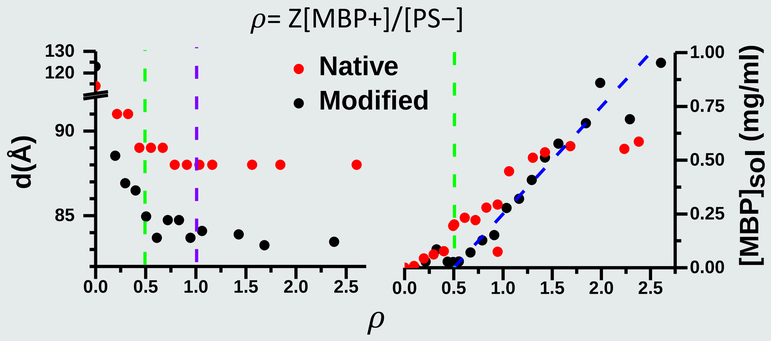


Lipid-protein composition

- Membrane compaction
- Native lipid composition → in-plane lateral myelin basic protein (MBP) dimers network
- Modified lipid composition → abolish hexagonal phase and no MBP network formation

Charge ratio

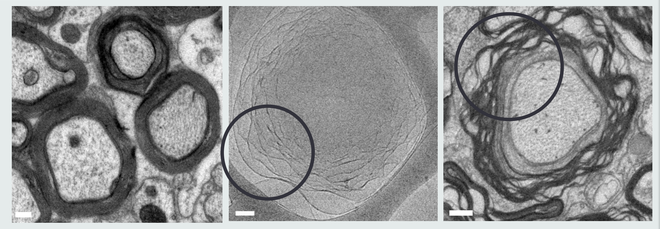
- MBP intake is correlated with membrane compaction
- Condensation persists only up to a fraction of complete charge neutrality, suggesting that other intermolecular forces must be taken into account like MBP-MBP and specific lipid-MBP interactions

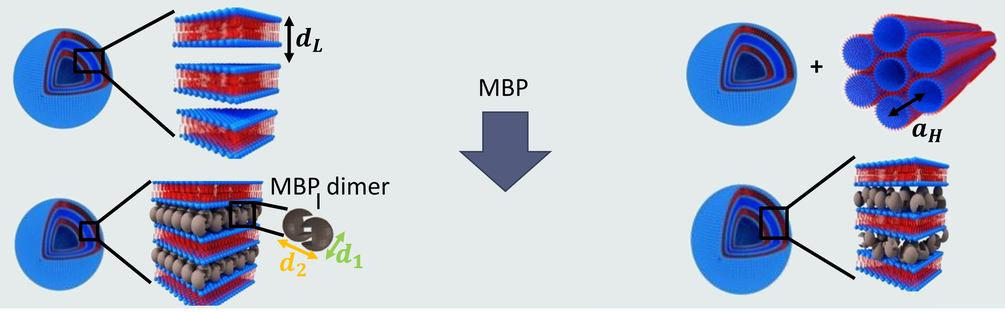


Synchrotron experiments performed at: MAX IV LABORATORY, diamond, SOLEIL SYNCHROTRON, DESY

Correlation with *in vivo* experiments

- *S*imilar behavior of enhanced spontaneous curvature and membrane undulations



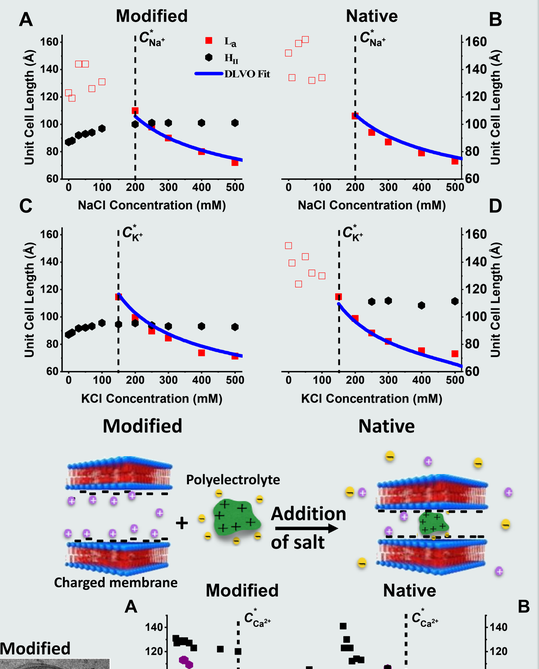


Key experimental results – environmental conditions

- Although the environmental conditions are highly regulated *in vivo,* local alterations may still occur
- **Environmental conditions such as temperature and buffer salinity induce the same pathological phase transition as the lipid composition**
- **These phase transitions are ion specific and have different critical points depending on the lipids compositions**

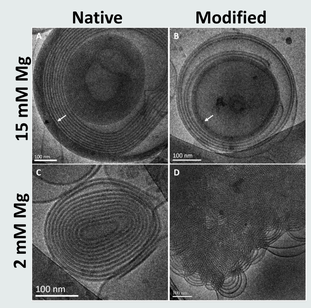
Monovalent ions

- Native (healthy) lipid compositions → L_α unit cell length decreases
- Modified (diseased) lipid compositions → coexistence of L_α and H_{II} phases, L_α unit cell length decreases while H_{II} unit cell length increases
- DLVO theory fittings → Hamaker constant $A = 2.2 \cdot 10^{-20}$J
- Different distribution of the charged lipids
- Ion-type specific → different C*



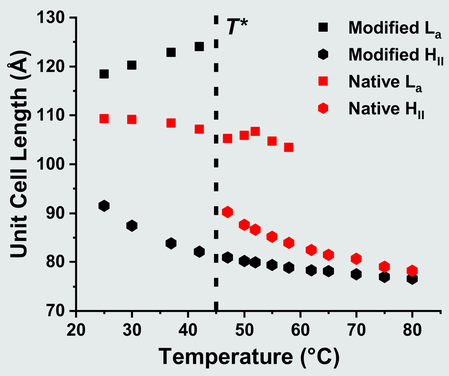
Divalent ions

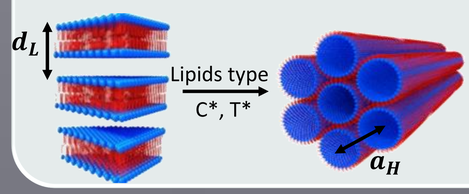
- Membrane compaction
- Ion-type specific → different C*: $C^*_{Mg} > C^*_{Ca} > C^*_{Zn}$
- New dense lamellar phase



Temperature

- Above T* native lipid composition → mixed L_α + H_{II}
- Above T* modified lipid composition → L_α





Specific environmental conditions and lipid compositions (healthy/diseased) result in drastic structural reorganization and instabilities. These instabilities originate from phase transition from healthy lamellar membranes to inverted hexagonal phase. These results highlight that local environmental conditions are critical for myelin function, and should be considered as alternative routes for early pathology and as a mean to avoid the initiation of demyelination.

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