

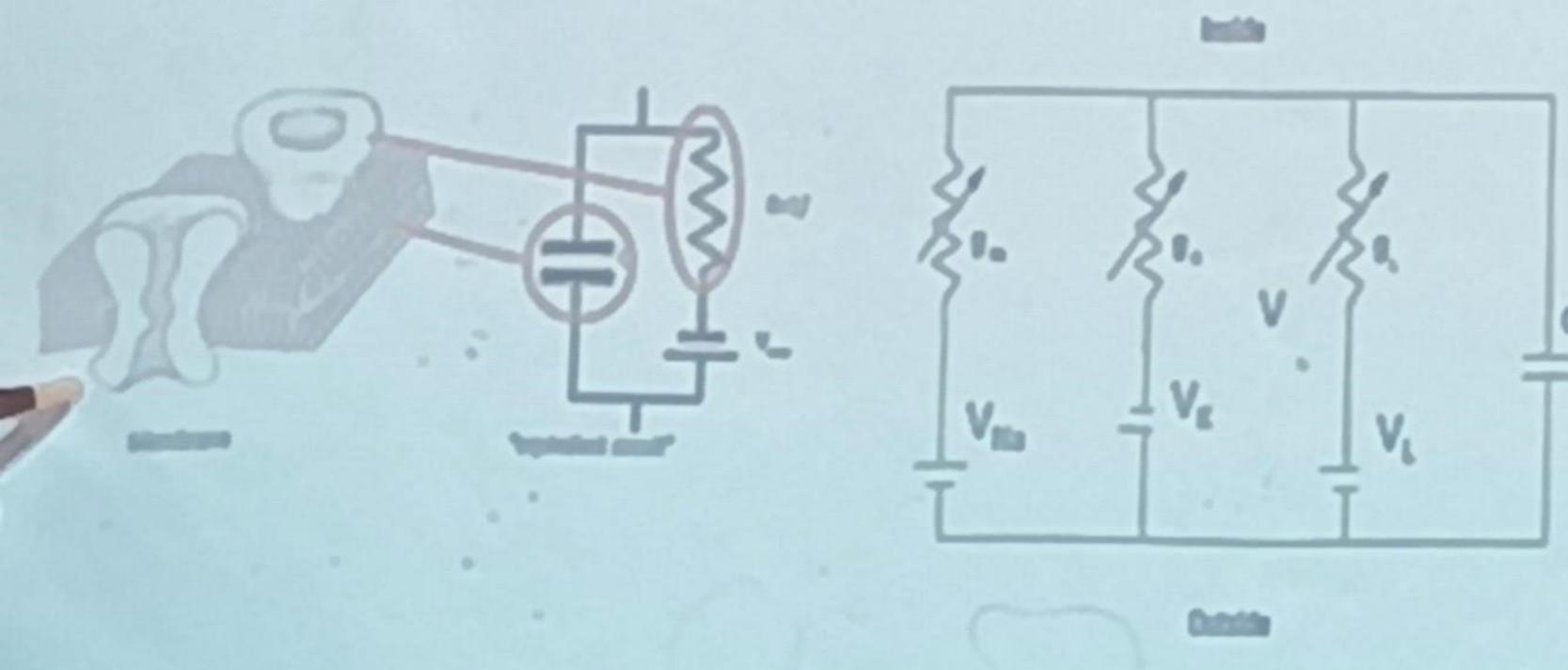
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Breakthrough of HH Model

- The breakthrough of Hodgkin and Huxley was that they succeeded to measure how the cell membrane voltage or current can be modeled and represented as electrical circuits

Full equations for electric circuit model

Recap



Hodgkin Huxley (HH) Model

$$I_{TOT} = I_K + I_{Na} + I_L \quad I_{Na}(V, t) = (V_{Na} - V)g_{Na}(V, t) \quad \text{Basic form of conductances:}$$

$$I_K(V, t) = (V_K - V)g_K(V, t) \quad g = g_{MAX} \cdot f(V, t)$$

$$I_{TOT} = \frac{dQ}{dt} = C \frac{dV}{dt}$$

$$I_L(V, t) = (V_L - V)g_L$$

f is the fraction of channels open,
which depends on V and t

$$I_{TOT} = C \frac{dV}{dt} = (V_K - V)g_K(V, t) + (V_{Na} - V)g_{Na}(V, t) + (V_L - V)g_L$$

Hodgkin Huxley Model

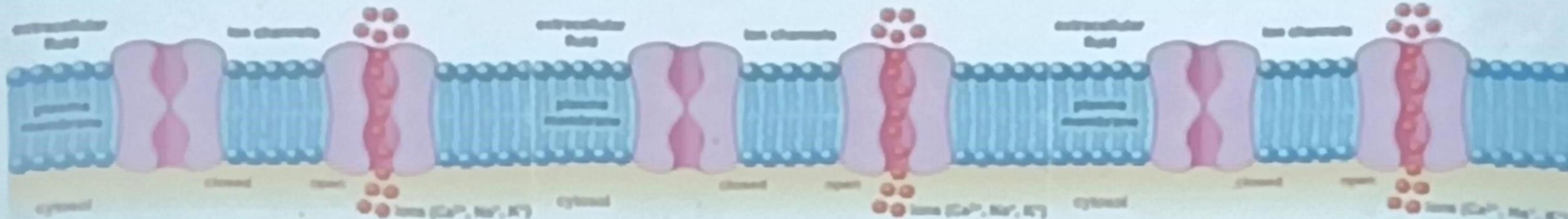
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- *Semi permeable membrane acts as a capacitor*
- Each channel type (Na^+ , K^+) is represented/characterized by a *resistor*.
- *Nernst potential* generated by differences in ion is represented by battery. E_L is leakage voltage for Cl^- and other ions
- Specific batteries since Nernst potential is different for each ion type.

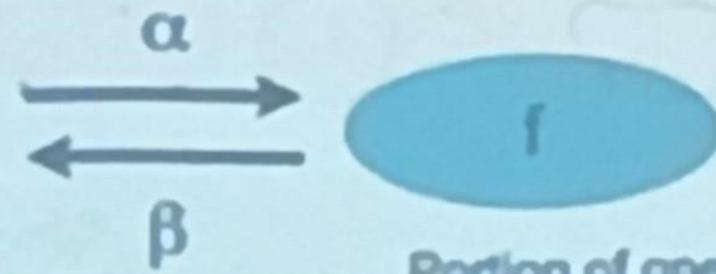
If input current $I(t)$ is injected into the neuron cell it charges the capacitor or leaks through the channels in cell membrane.

Key concept : gating variable

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Rate coefficients



$$\frac{df}{dt} = \alpha_f(1 - f) - \beta_f f$$

f = Gating variable

f : fraction of open channels
a.k.a. the gating variable
(depends on V and t)

α : rate at which closed channels open (depends on V)

β : rate at which open channels close (depends on V)

Note: The f gating variable will be called n , m and h for the three types of gating: K activation, Na activation, and Na inactivation

Hodgkin
Huxley (HH)
Model

Potassium current (activation)

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Maximum conductivity
with all gates open
($n = 1$)

We can write an expression for the conductivity of this ion as

$$g_K = \bar{g}_K n^4(V, t)$$

And then assume a simple first order kinetic behavior of the
gating variable n

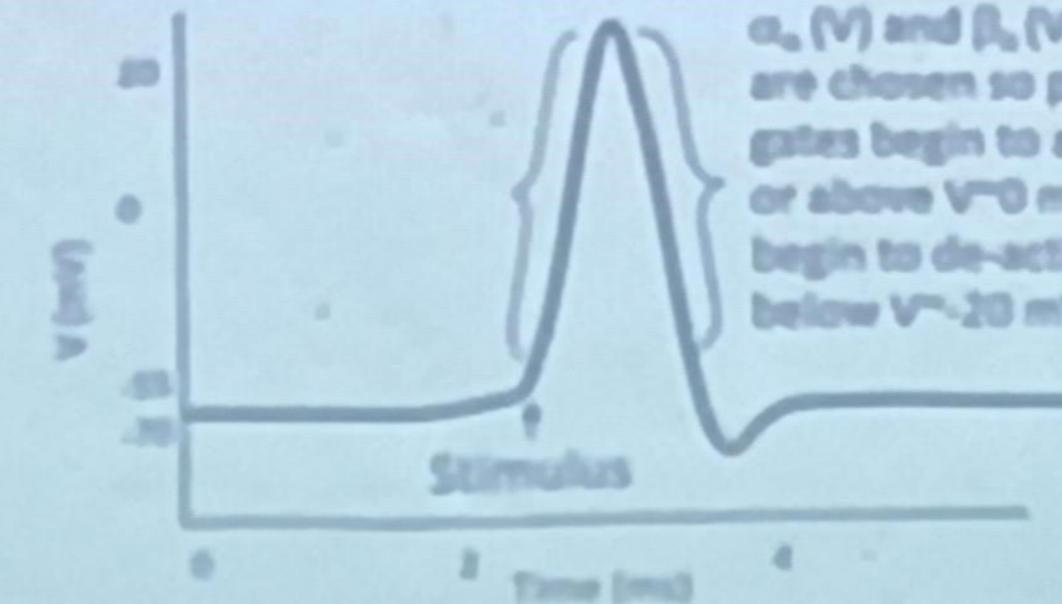
$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n$$

Four activation gates
result in fourth power
for gating variable n

(same as previous slide,
with f now called n)



Potassium gate
protein with
4 identical
subunits in a
ring shape (leading
to the 4th power of n ,
as all gates must be
open for ion to pass)



$\alpha_n(V)$ and $\beta_n(V)$
are chosen so potassium
gates begin to activate at
or above $V=0$ mV and
begin to de-activate at or
below $V=-20$ mV

Hodgkin Huxley (HH) Model

Sodium current (inactivation)

Inactivation corresponds to value $h=0$, giving $g_{Na} = 0$

$$g_{Na}(V, t)$$

$$g_{Na} = \bar{g}_{Na} m^3(V, t) h V_{in}(t)$$

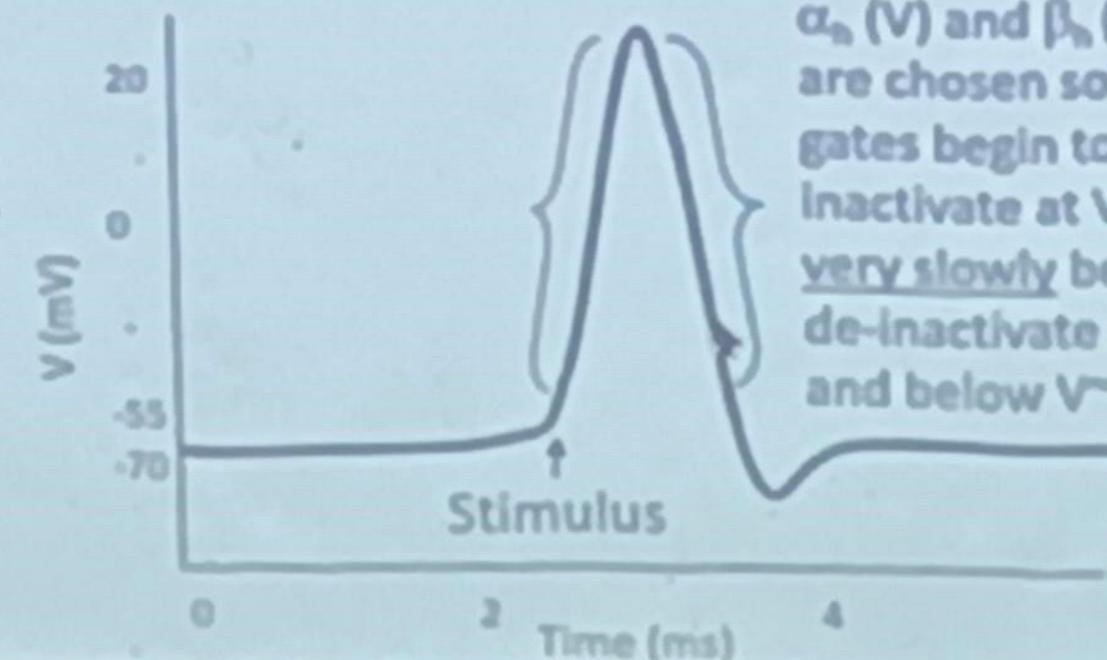
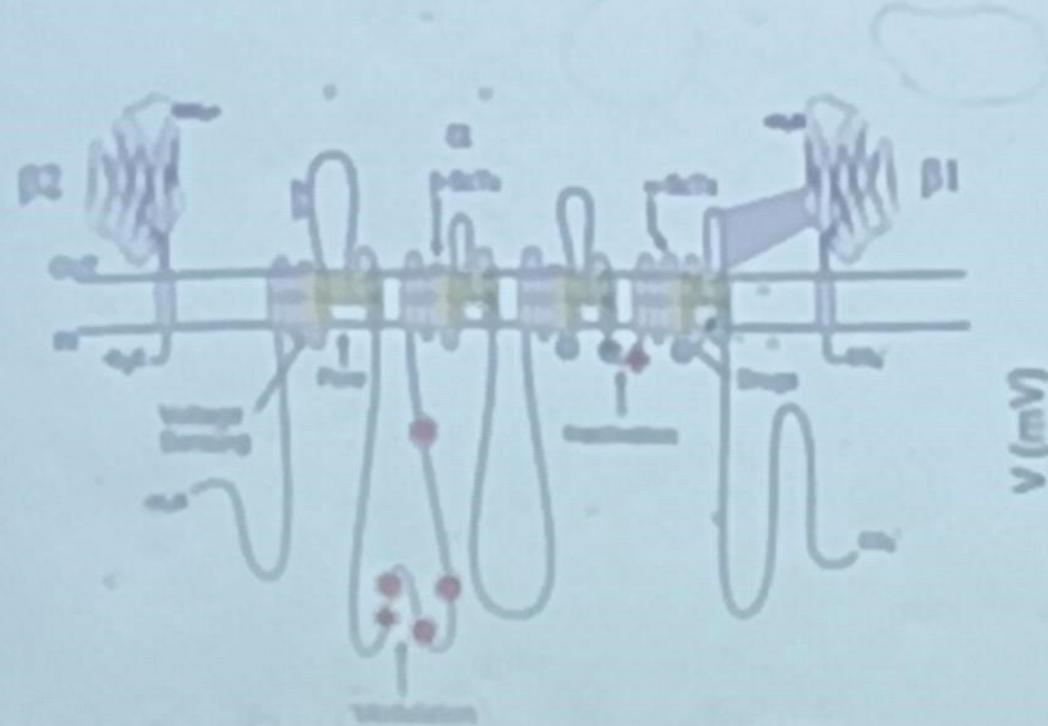
for which we write a similar ordinary differential equation

$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h$$

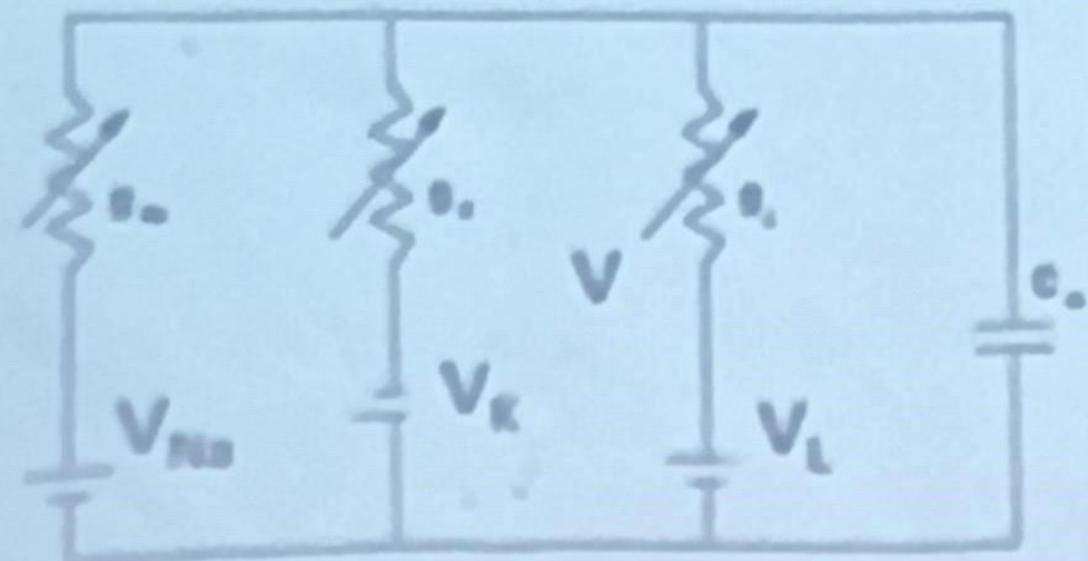
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Hodgkin Huxley (HH) Model

One Inactivation gate results in first power for gating variable h



$\alpha_h(V)$ and $\beta_h(V)$ are chosen so that sodium gates begin to slowly inactivate at $V \sim -20 and very slowly begin to de-inactivate at and below $V \sim -40$$



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Entire Hodgkin Huxley (HH) Model

$$I_{TOT} = C \frac{dV}{dt} = (V_K - V)g_K(V,t) + (V_{Na} - V)g_{Na}(V,t) + (V_L - V)g_L$$

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$

The three α and β functions are chosen so that the channel gates open at the observed membrane potentials and with the appropriate speed for a particular type of neuron

$$g_K(V,t) = \bar{g}_K (n(V,t))^4$$

$$g_{Na}(V,t) = \bar{g}_{Na} (m(V,t))^3 h(V,t)$$

$$g_L = \bar{g}_L$$

Parameters $C, V_K, V_{Na}, V_L, \bar{g}_K, \bar{g}_{Na}, \bar{g}_L$
are derived from experimental measurements

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Applications of Hodgkin Huxley Model

- Mathematical modeling can reveal mechanisms of nerve impulse propagation long before they can be observed directly.
- Framework for studying and analyzing ion channel kinetics.

Hodgkin and Huxley, Journal of Physiology, 1952

Ion channels-related diseases

Neuronal disorders like Epilepsy, Depression, Alzheimer's disease, Parkinson's disease, Schizophrenia, etc, etc may result from dysfunction of voltage-gated sodium, potassium and calcium channels



MODEL MEMBRANE -LIPOSOMES

- a. Lipids connection to Liposomes**
- b. Introduction to Liposomes**
- c. Formation of Liposomes**
 - i. Bangham Method**
 - ii. Sonification**

Acknowledgment: Aggregated Lecture from lot of resources
(Textbook/Journal Papers/Youtube lectures)

Liposome: classification, preparation, and applications

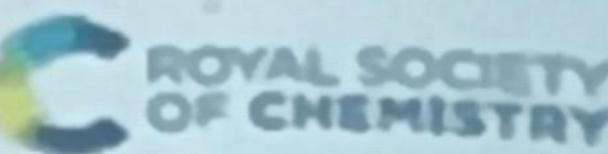
Nanoscale
Horizons

REVIEW

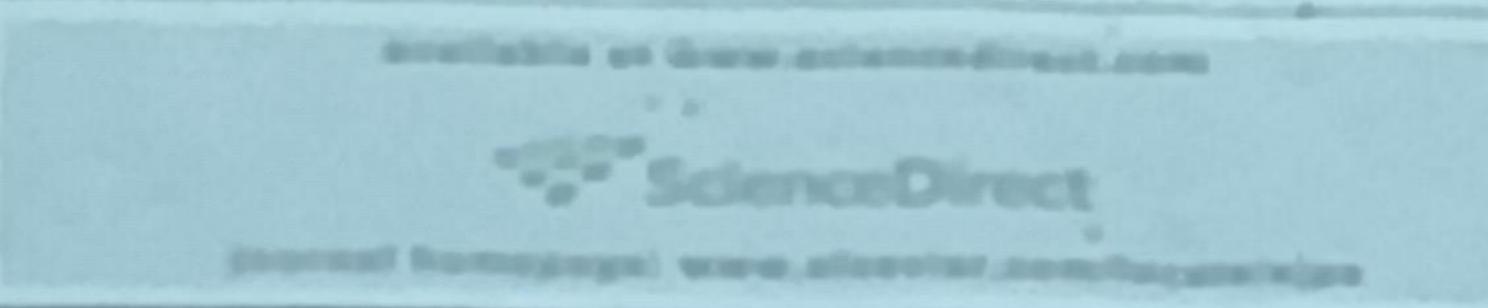


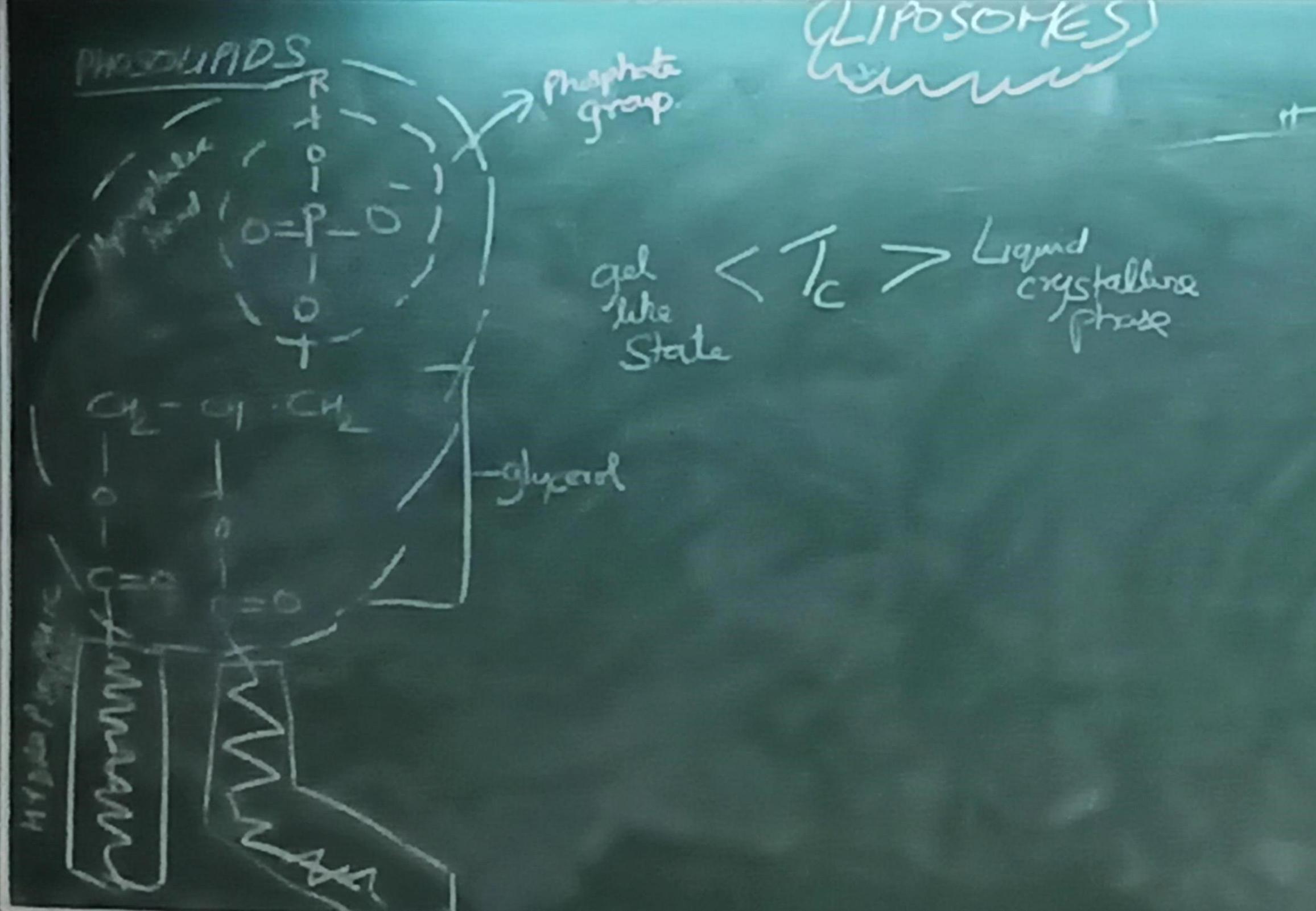
Targeted liposomal drug delivery: a nanoscience
and biophysical perspective

Wei Li^a, Erika M. Castro-Santos^b and Junshan Lin^{a,c}



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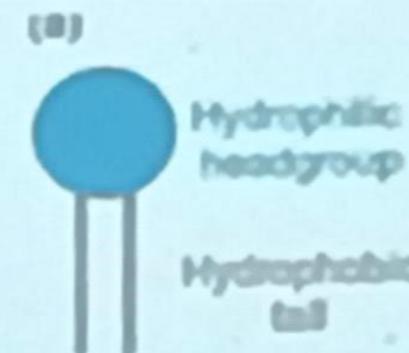
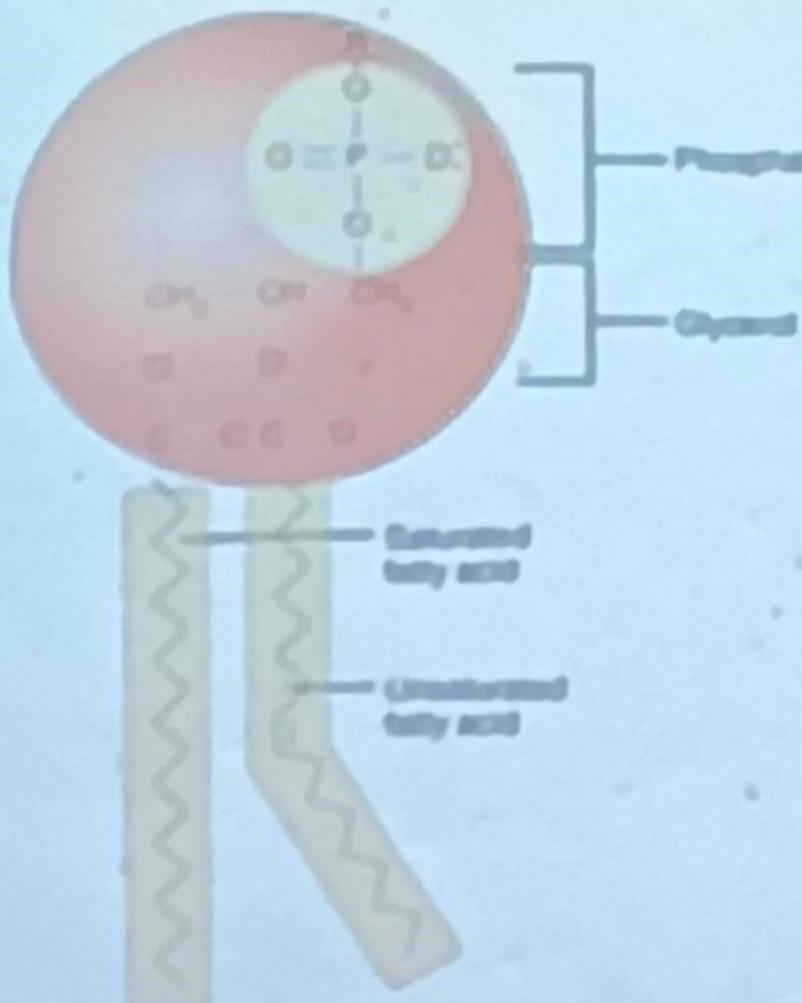




Introduction to Lipids

Schematic illustration of (a) a lipid.

A typical lipid molecule contains a hydrophilic headgroup and two hydrophobic tails (Fig. 1a). The charge of lipids and their chemical properties can be varied by changing the headgroup, while the hydrophobic tails mainly govern the packing in membranes.

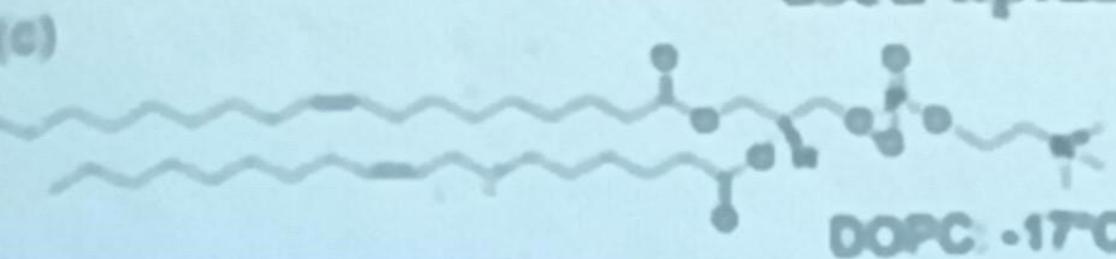


The tail structures can be changed rendering different phase transition temperatures (T_c). T_c is an important parameter that governs the fluidity of lipid bilayers. Above T_c , lipid tails have gauche conformation and can diffuse more freely, and the membrane exist in a liquid crystalline phase.²⁰ Below T_c , lipid tails are extended and diffuse slowly, and the membrane is in a gel-like state.

- *Phospholipids are a special group of lipids containing phosphate.*
- *Lipids in general are hydrophobic, also called non-polar. However, the phosphate group in phospholipids is hydrophilic, also called polar.*

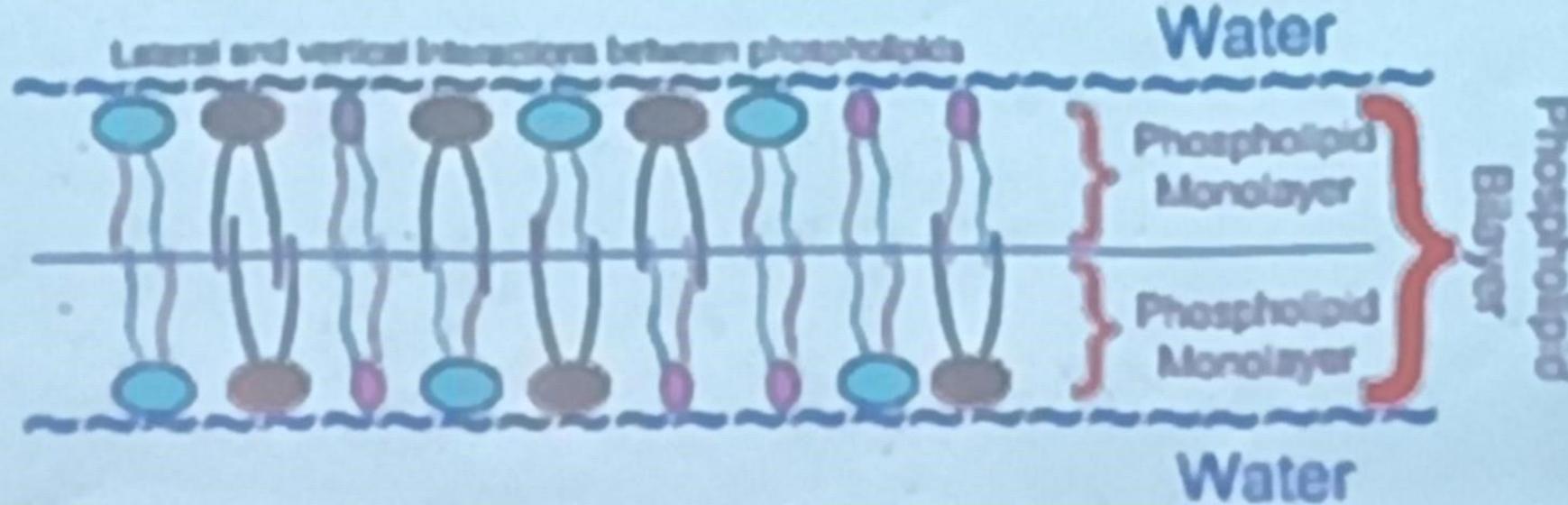
PhosphoLipid Bilayer (Example)

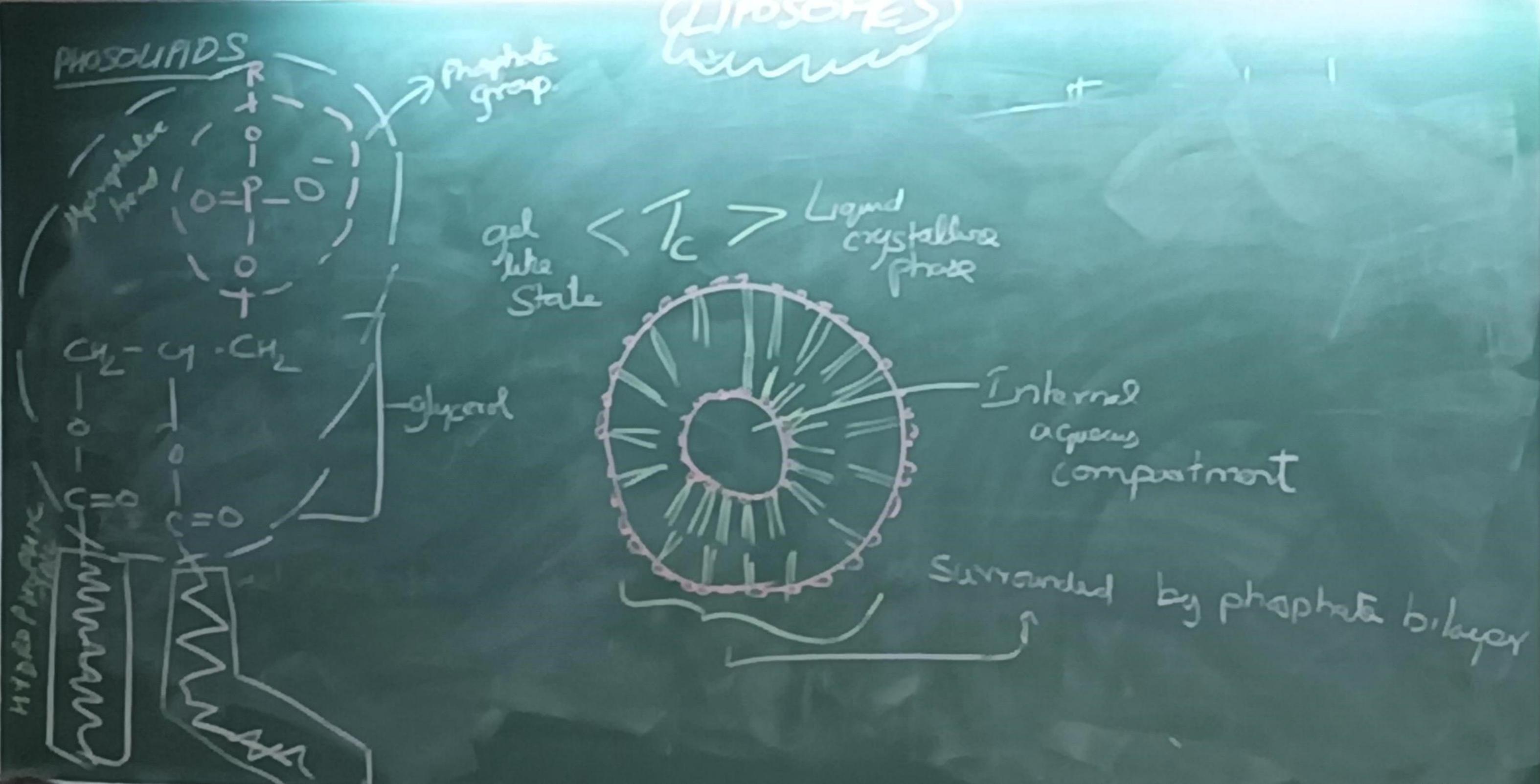
A vast number of lipids are found in nature and more are available via chemical synthesis. A few commonly used lipids are listed in Fig. 1.



The structure of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC)

- Due to their amphiphilic nature, phospholipids have the ability to spontaneously form bilayer membranes. This is why phospholipids are major constituents of eukaryotic cell membranes.

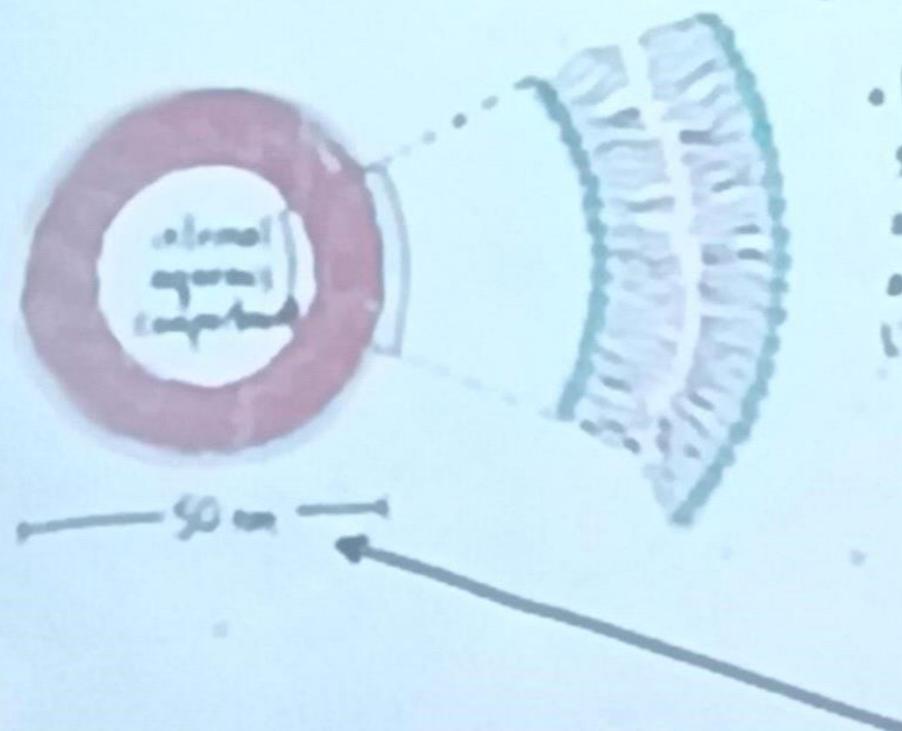




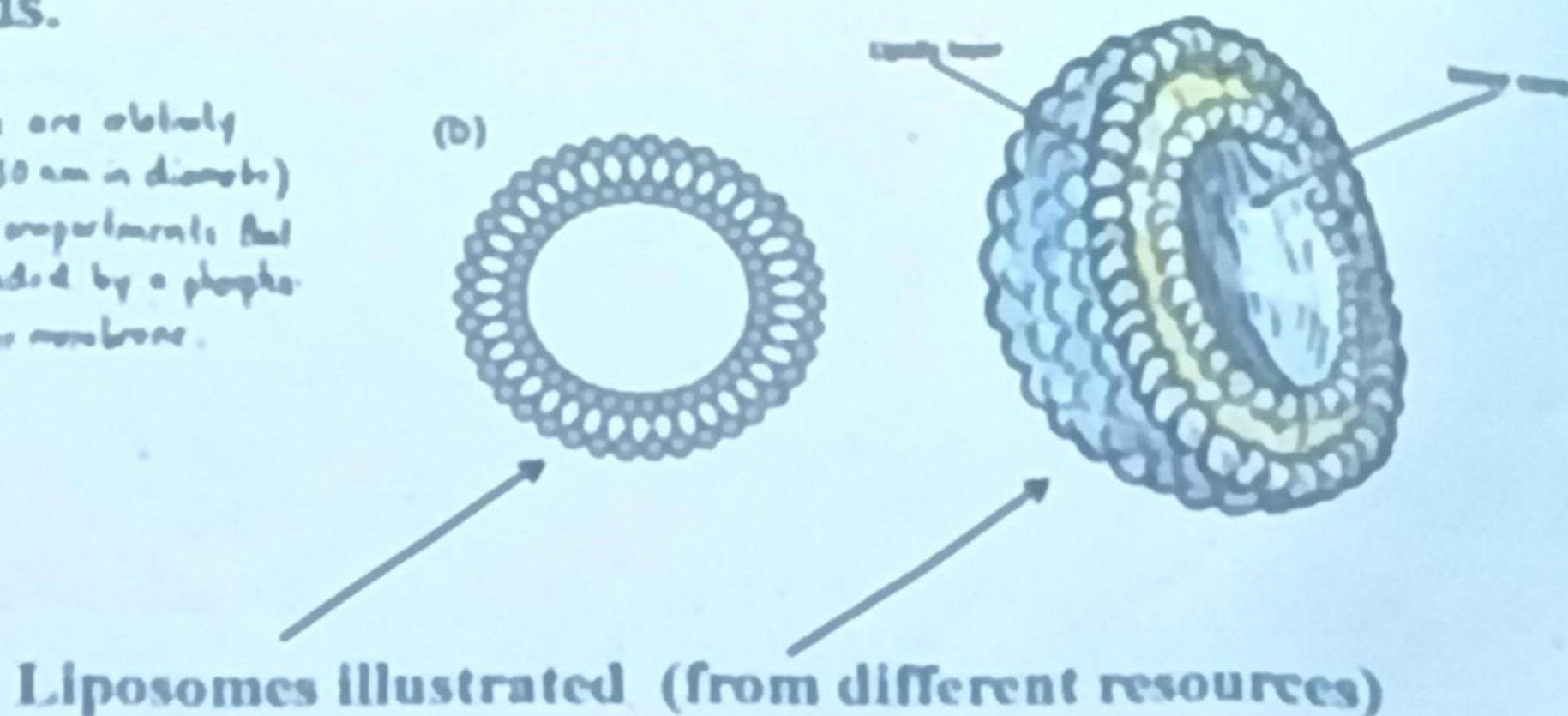
Lipids Connection to Liposomes

In addition, we can use the propensity of phospholipids to form membranes to create special structures called liposomes (also called lipid vesicles).

Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural non-toxic phospholipids.

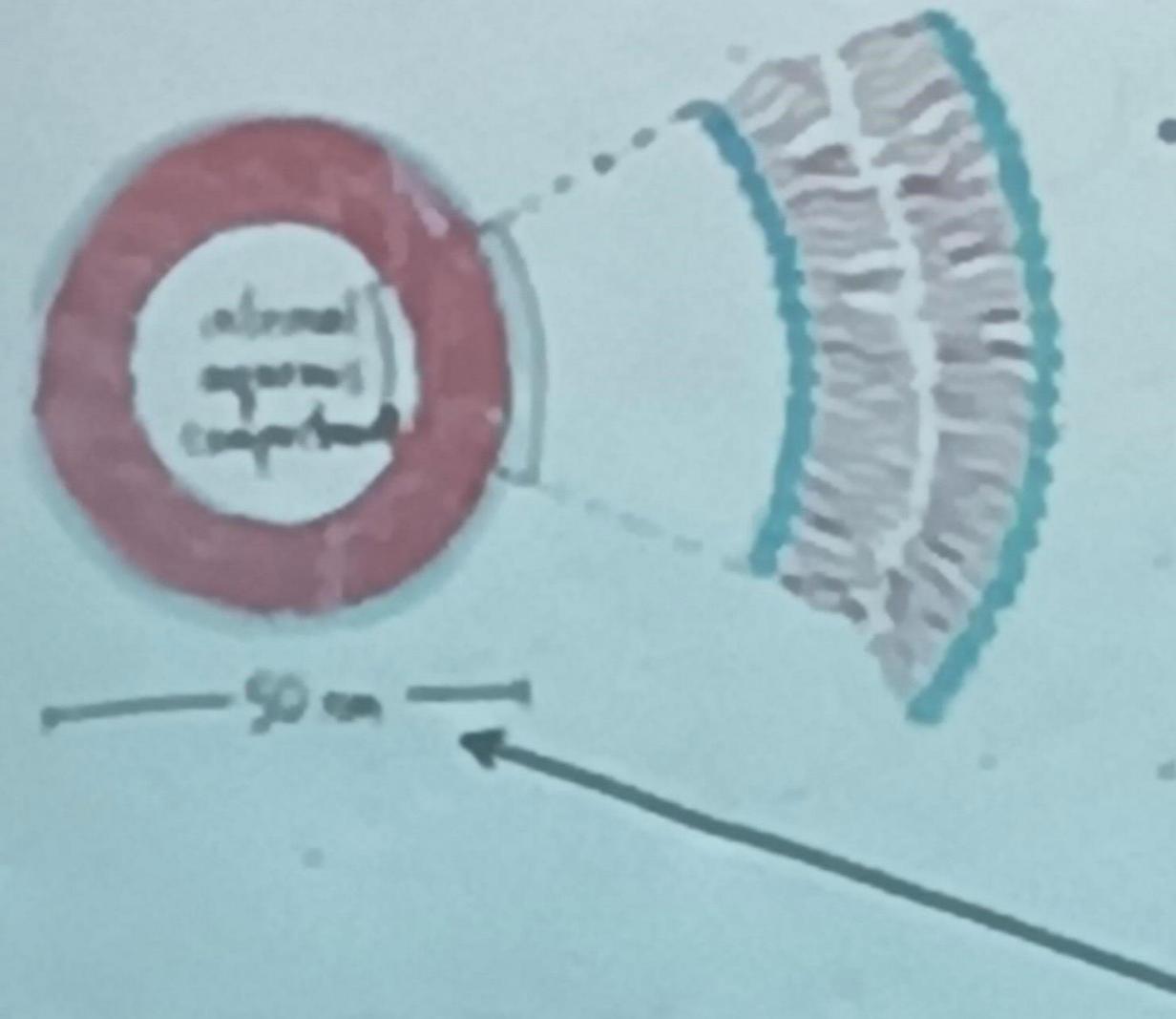


- Liposomes are relatively small (~50 nm in diameter) aqueous compartments that are surrounded by a phospholipid bilayer membrane.



Liposomes illustrated. (from different resources)

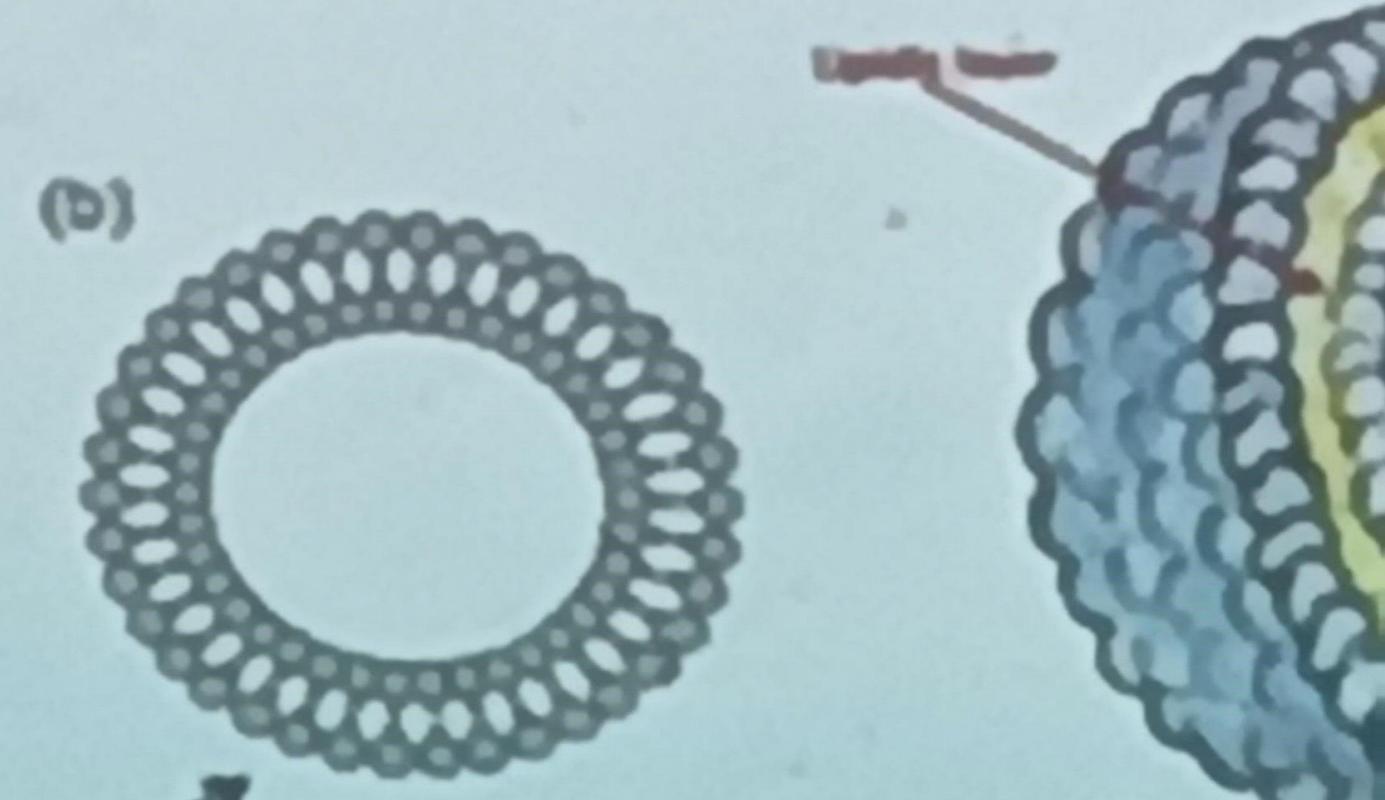
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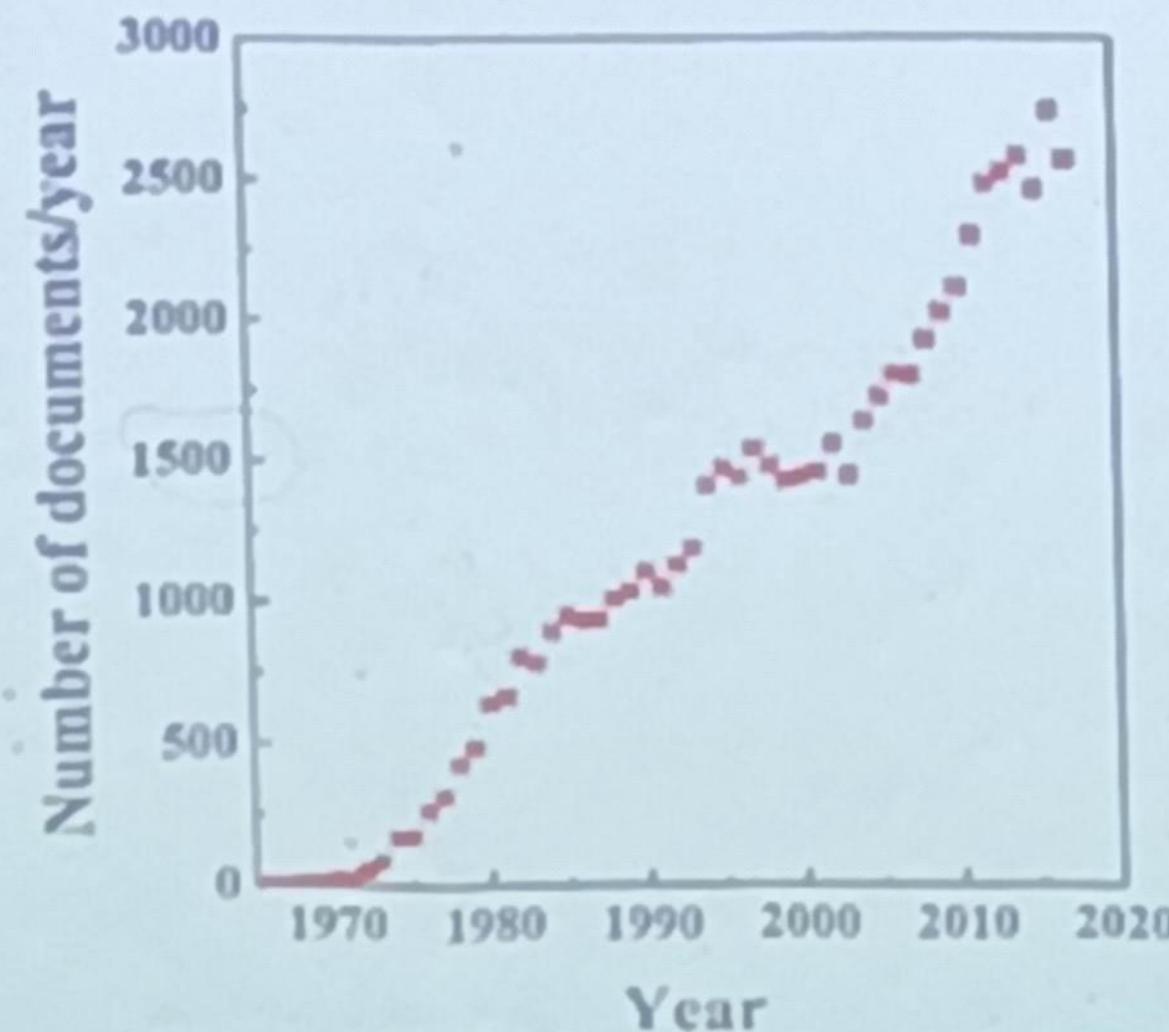
- Liposomes are relatively small (~50 nm in diameter) aqueous compartments that are surrounded by a phospholipid bilayer membrane.

Liposomes Illustrated (from different re-

(b)



Liposomes Significance (Publications)



Liposomes Significance

Liposomes: From Bangham to Supercritical Fluids

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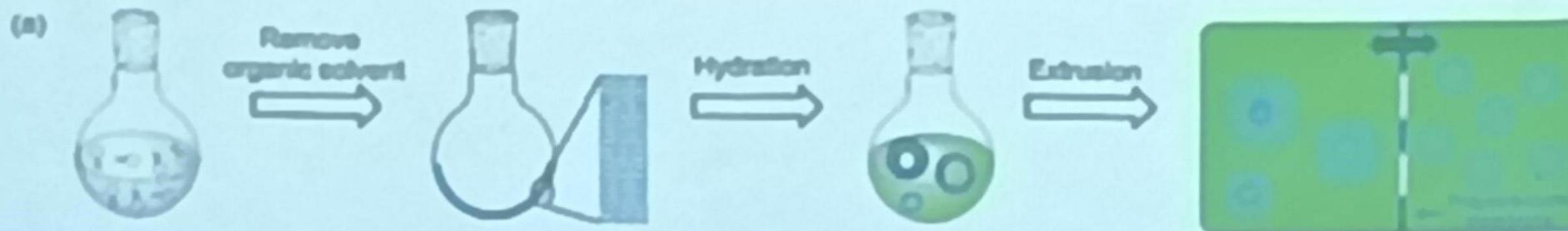
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Abstract: Liposomes are spherical vesicles made up of an aqueous core surrounded by phospholipids. These delivery systems (DS) are largely employed as drug carriers in several industrial fields, such as pharmaceutical and nutraceutical fields. The aim of this short review is to provide a fast overview on

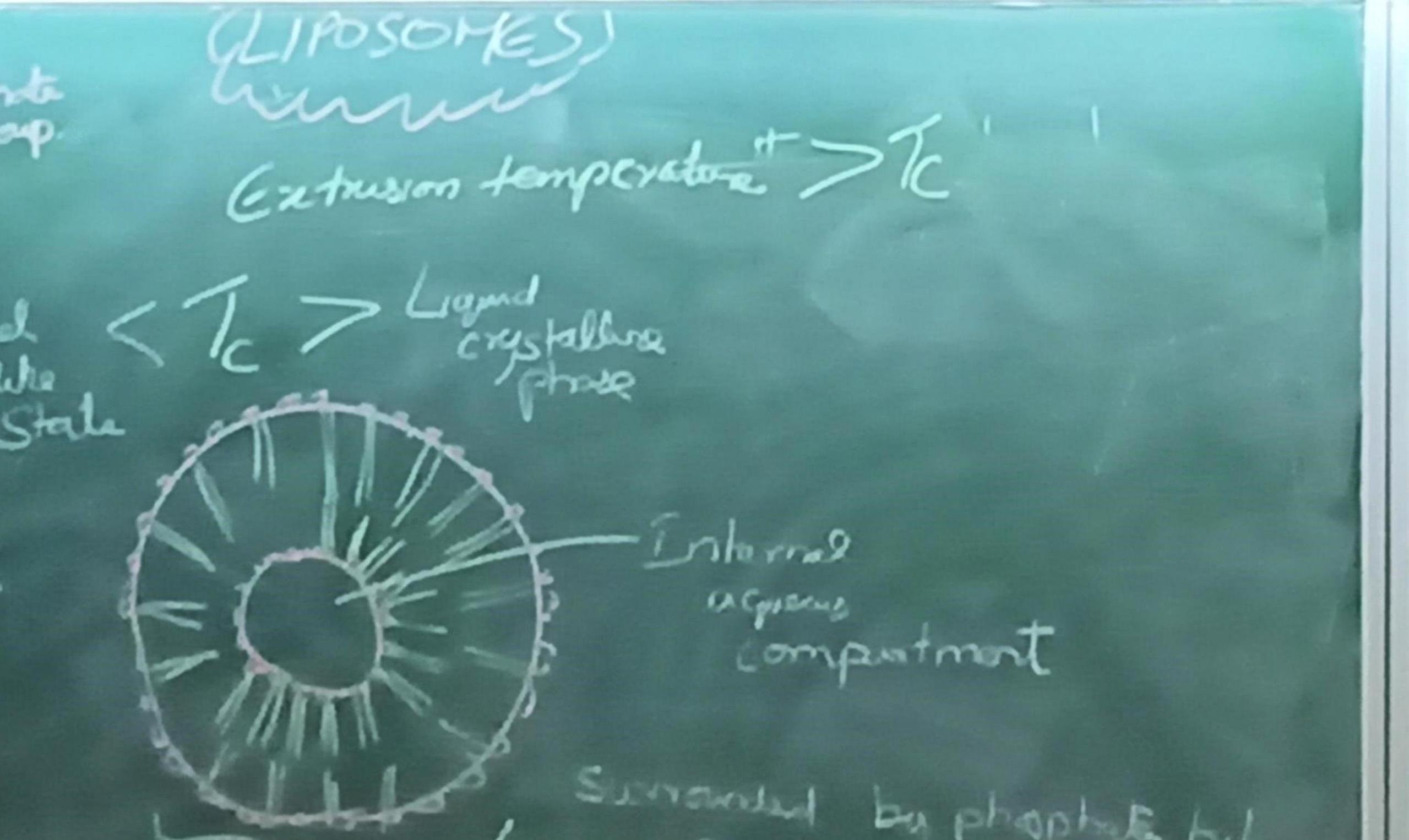
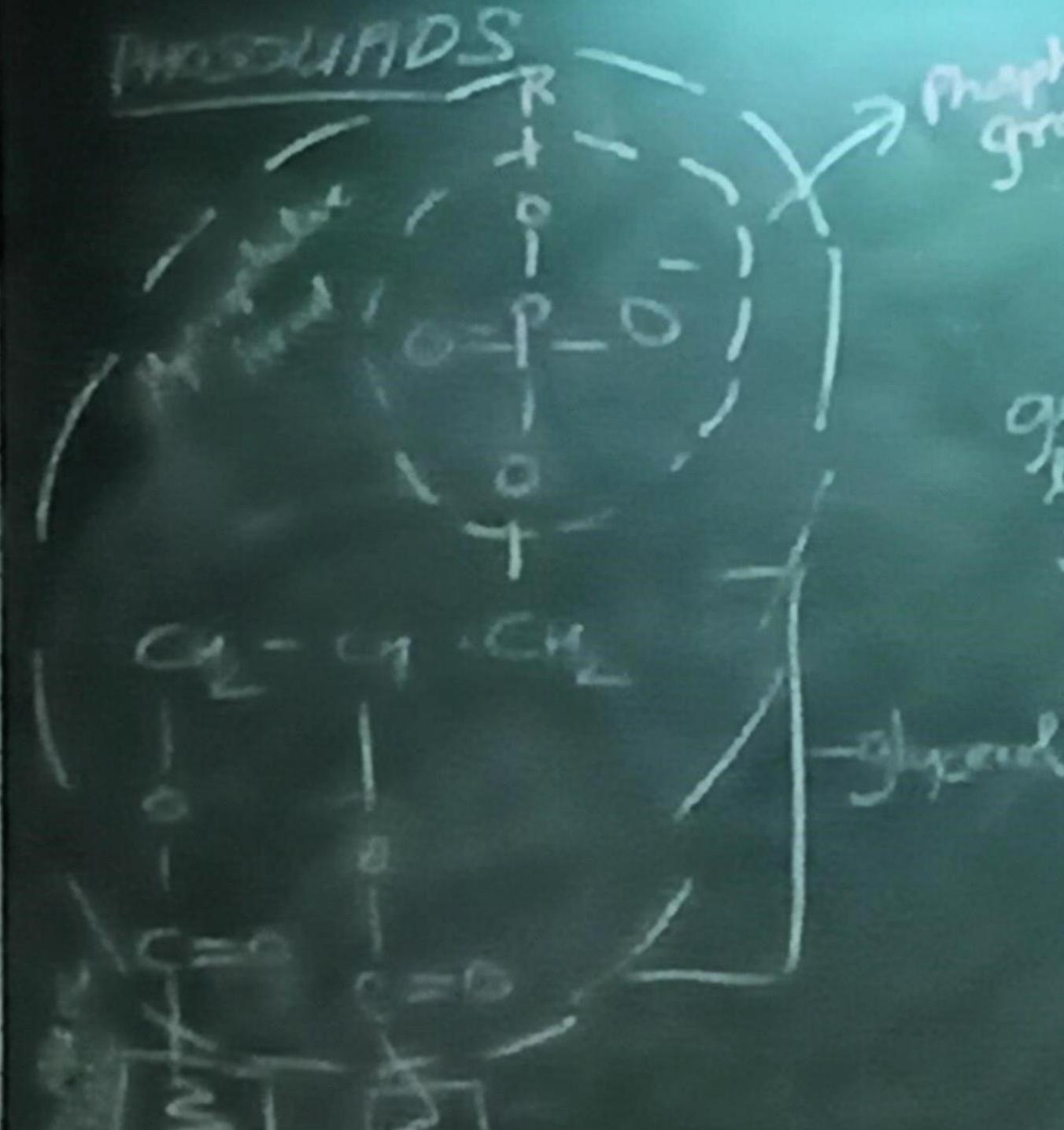
Several drug delivery systems (DDS) have been developed for the treatment of human illnesses [1], such as polymeric and lipidic particles [2], hydrogels [3], emulsions [4], membranes [5], microspheres [6], dendrimers [7] and other molecular complexes. The development of these novel drug formulations

Formation of Liposomes (Bangham Mtd)

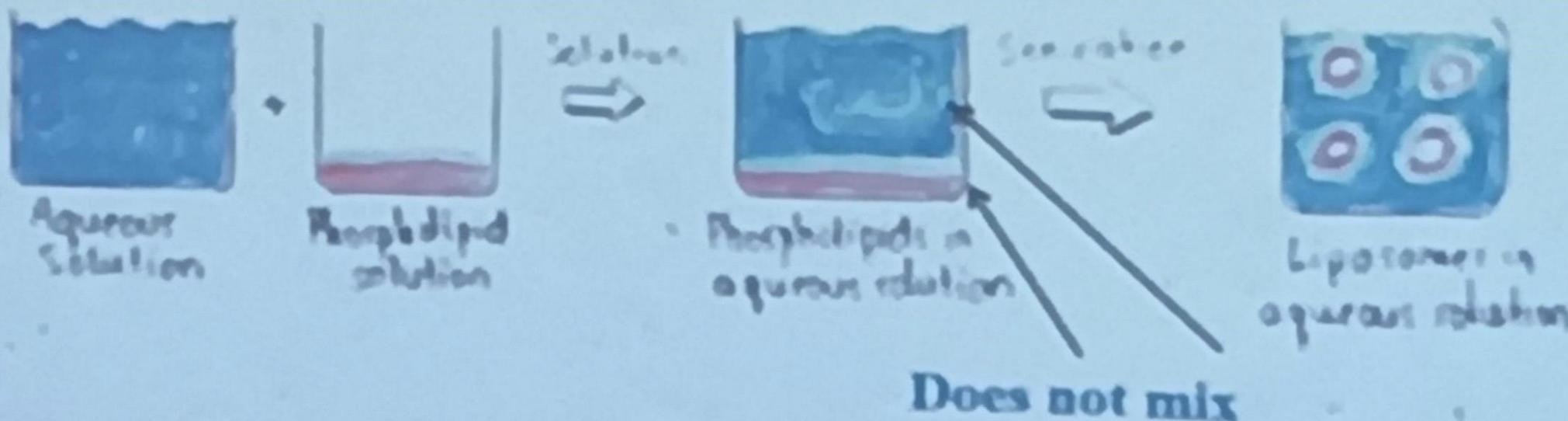


(a) Schematic illustration of liposome preparation via hydration of dried lipid films followed by extrusion.

The most common Bangham method involves the formation of a lipid film by evaporating the organic solvent used to dissolve lipids.⁵⁴ After hydration with an aqueous solution, multilamellar vesicles with a heterogeneous size distribution are formed. By extrusion through a polycarbonate membrane, small unilamellar vesicles (SUVs) with a narrow size distribution are obtained (Fig. 2a). The extrusion temperature needs to be higher than the T_c of the lipids. This method can produce liposomes from ~50 nm to ~200 nm. The larger the membrane pores, the more likely to form multilamellar vesicles.



Formation of Liposomes (Sonification)



Formation of Liposomes

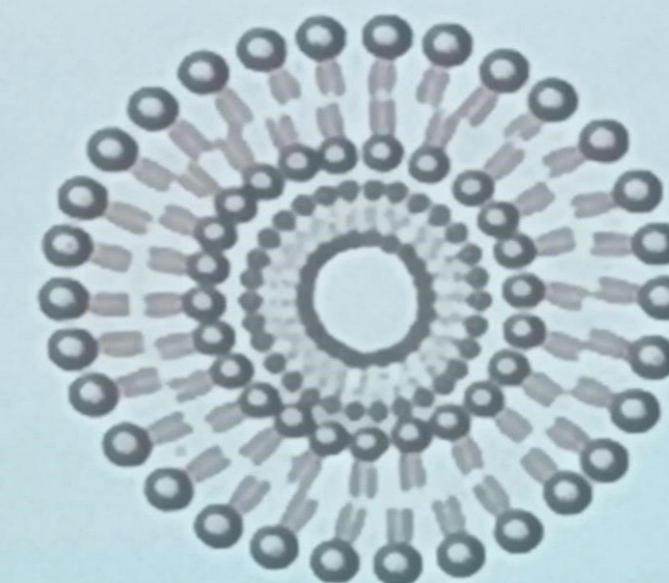
- Lipid vesicles can be formed by mixing a lipid solution into an aqueous solution and then sonicating the solution. Sonication involves bombarding the solution with sound waves. The energy carried by the sound waves disperse the lipids, allowing them to spontaneously aggregate into bilayer membranes (i.e. liposomes).

Classification of Liposomes

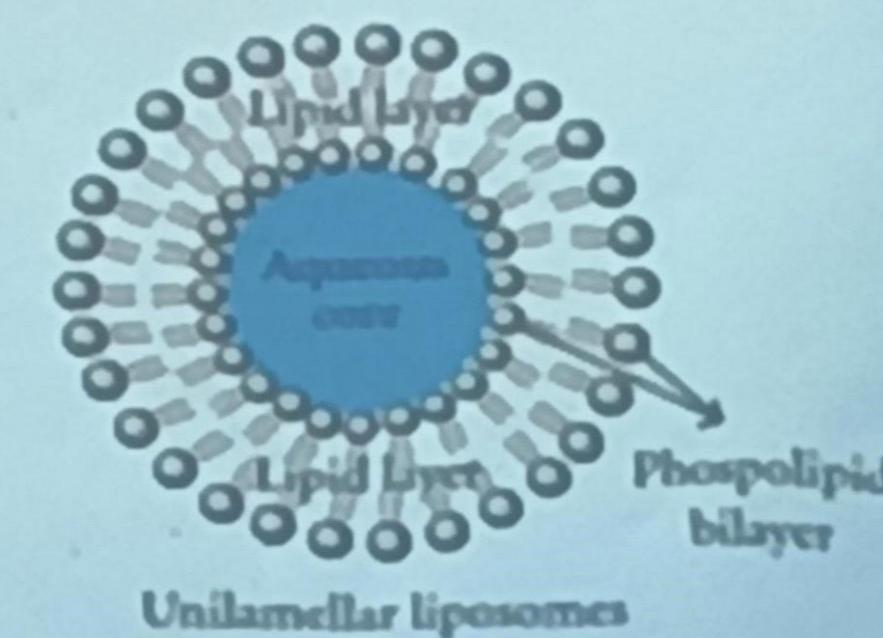
Classification of Liposomes

The **liposome size** can vary from very small ($0.025\text{ }\mu\text{m}$) to large ($2.5\text{ }\mu\text{m}$) vesicles. Moreover, liposomes may have

one or bilayer membranes. The **vesicle size** is an acute parameter in determining the circulation half-life of liposomes, and both size and number of bilayers affect the amount of drug encapsulation in the liposomes. On the **basis of their size and number of bilayers**, liposomes can also be classified into one of two categories: (1) multilamellar vesicles (MLV) and (2) unilamellar vesicles. Unilamellar vesicles can also be classified into two categories: (1) large unilamellar vesicles (LUV) and (2) small unilamellar vesicles (SUV) [16]. In unilamellar liposomes, the vesicle has a single phospholipid bilayer sphere enclosing the aqueous solution. In multilamellar liposomes, vesicles have an onion structure. Classically, several unilamellar vesicles will form on the inside of the other with smaller size, making a multilamellar structure of concentric phospholipid spheres separated by layers of water.



Multilamellar liposomes



Unilamellar liposomes