"ωφελέειν, εἰ μη βλάπτειν"

'benefit and do not harm'

National & Kapodistrian University of Athens

The complexity of the liposomal membrane as an obstacle for producing nanosimilars. Biophysical and thermodynamic consideration

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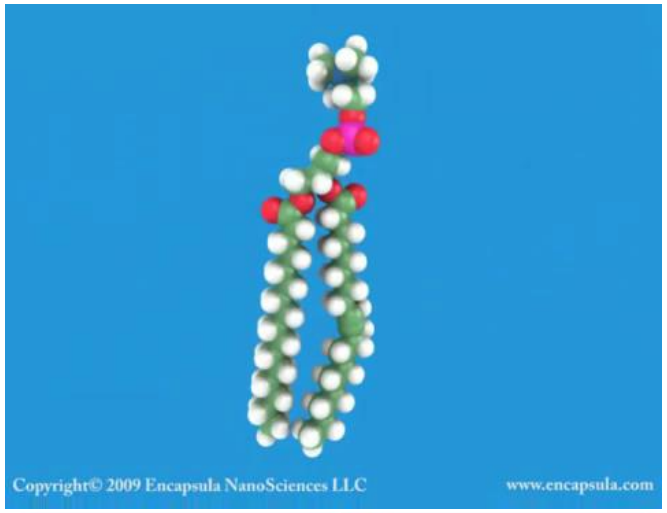
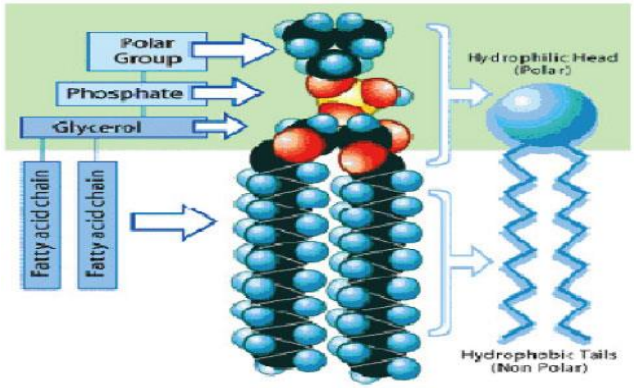
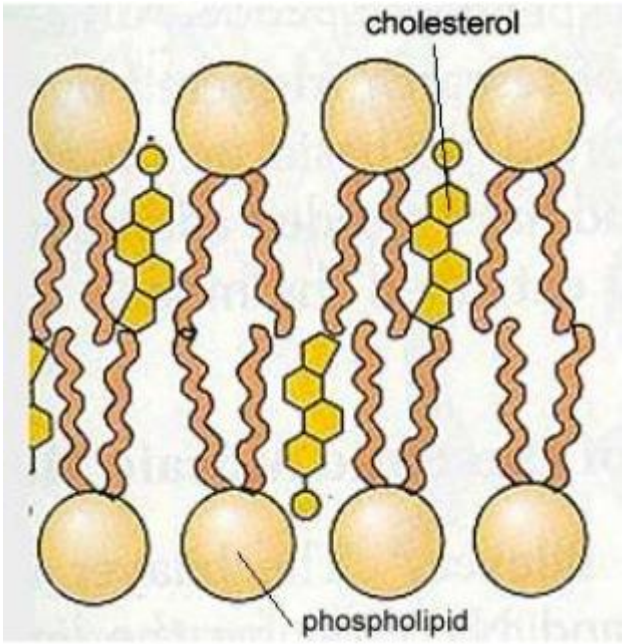
Phospholipids are the basic molecules from which lipidic bilayers consist







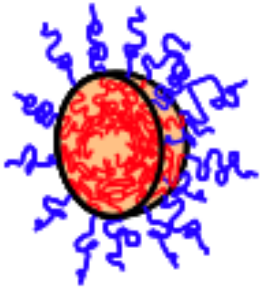
Cholesterol is a fundamental biomolecule that affects the lyotropism of liquid crystalline state of matter of lipidic bilayer. The lyotropic effect is a concentration dependent phenomenon

WHICH IS THE DRIVING FORCE FOR PRODUCING LIPID BILAYERS ?

SELF – ASSEMBLY

WHAT IS SELF – ASSEMBLY ?

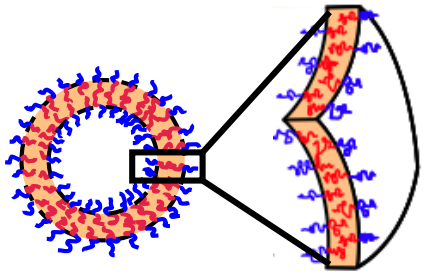
Self-assembly of bio structures



- "Self-assembly" is not synonymous with "formation." (Whitesiedes and Grzybowski, 2002).

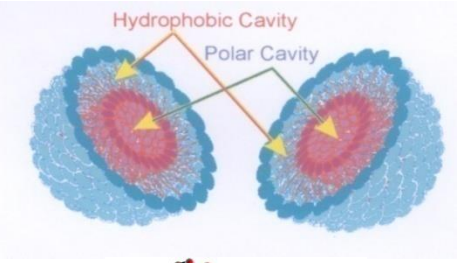
- **Self – assembly is the procedure by which individual compounds that contain enough information, can build an organized structure.**

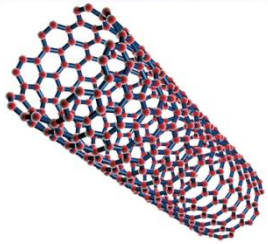
- The self-assembly process of amphiphilic molecules is of fundamental interest and is important in many applications,, nanomaterial synthesis, drug delivery, pharmaceutical formulation, and other dispersant technologies.



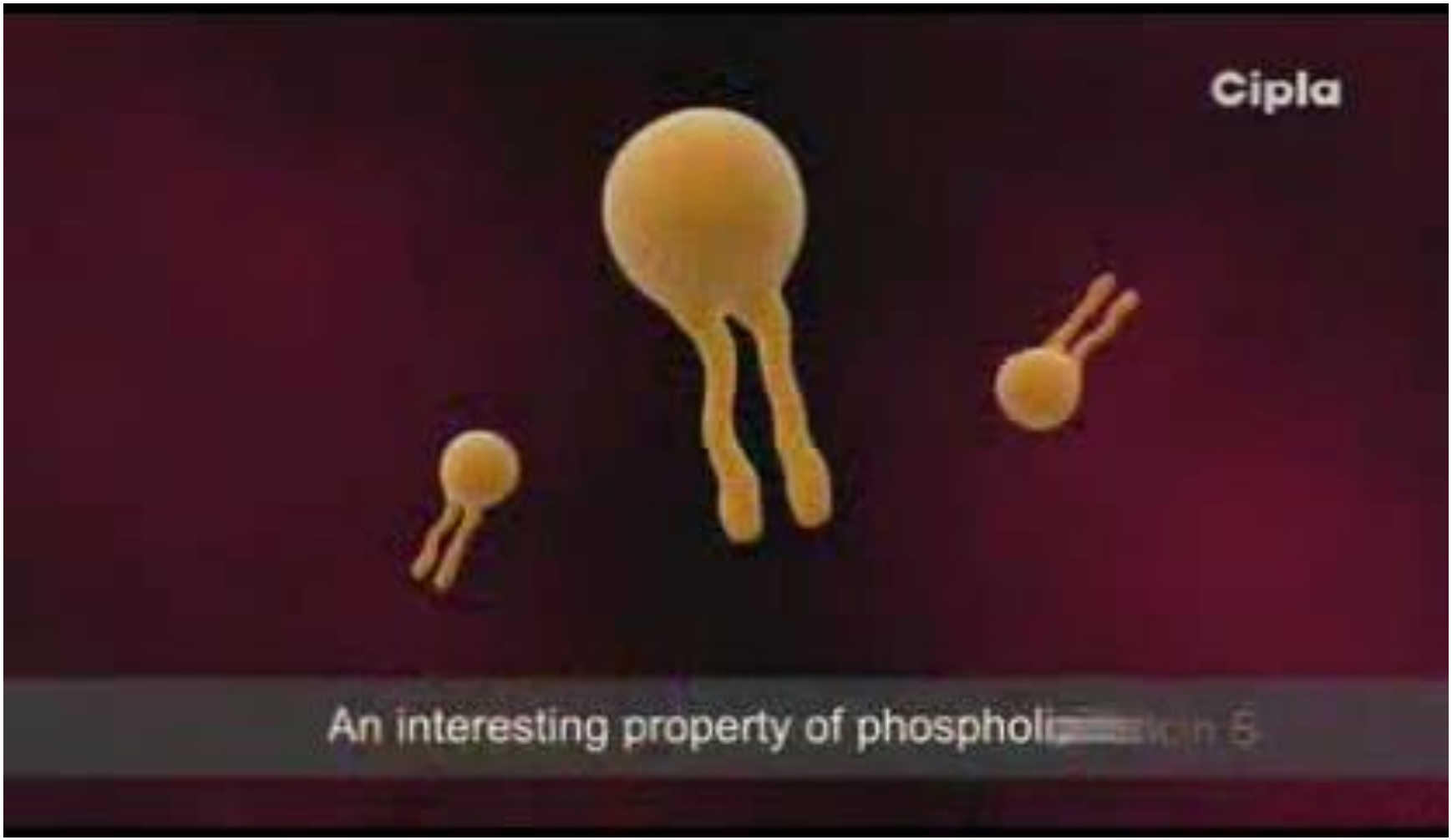
Particles can self-assemble as a result of their intermolecular forces. As systems look to minimize their free energy, self-assembly is one option for the system to achieve its lowest free energy thermodynamically

This *in situ* approach needs bio-organization process that '*promotes thermodynamic criteria governing phase transitions that are the mechanistic basis for their 'smartness'. There are no logic algorithms on board, no decision –making or rationalizing framework and no intellectual capacities*. [Ref. *Int. J. of Pharmaceutics* 454 , 521-524, 2013 by D. Grainger].



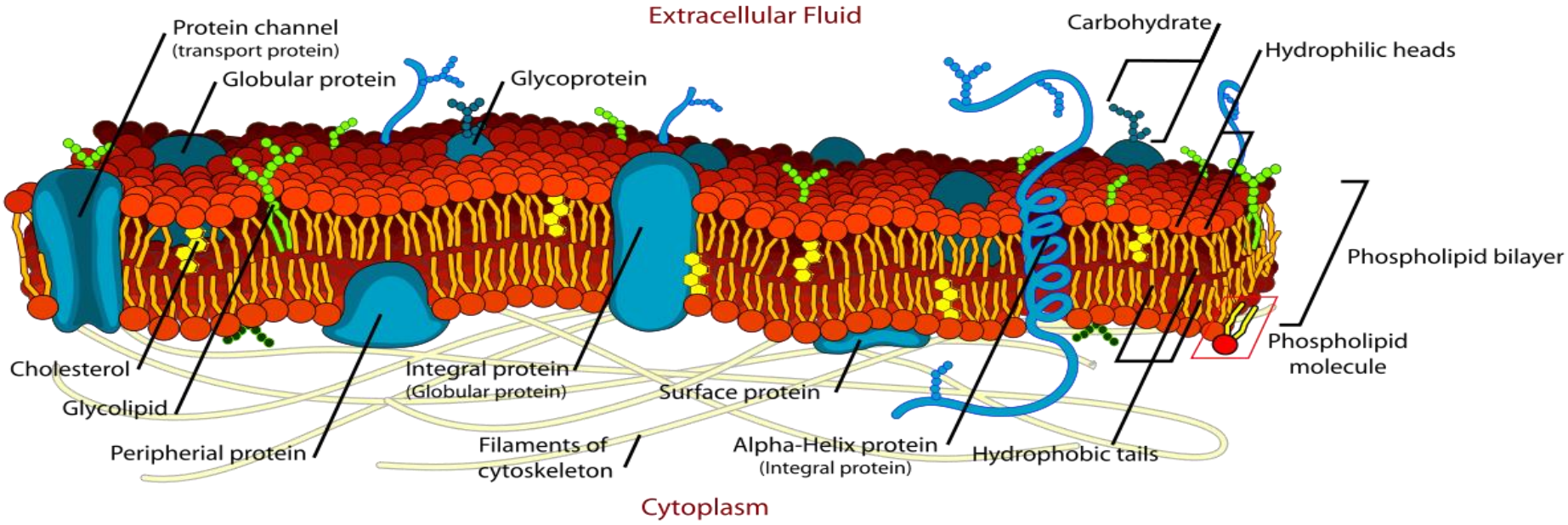


SELF ASSEMBLY PROCESS OF PHOSPHOLIPIDS FOR PRODUCING PHOSPHOLIPID BILAYERS.



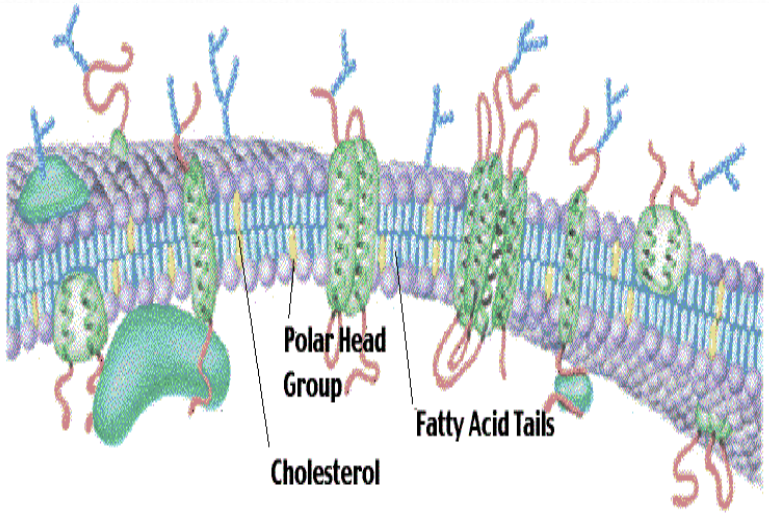
THE SELF ASSEMBLY PROCESS IS BASED ON THE PHYSICOCHEMICAL CHARACTERISTICS OF THE INITIAL BIOMATERIALS

CELL MEMBRANE

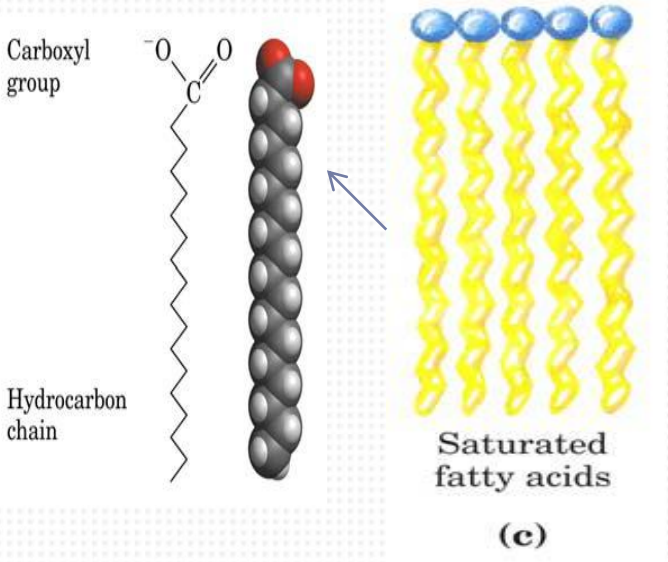


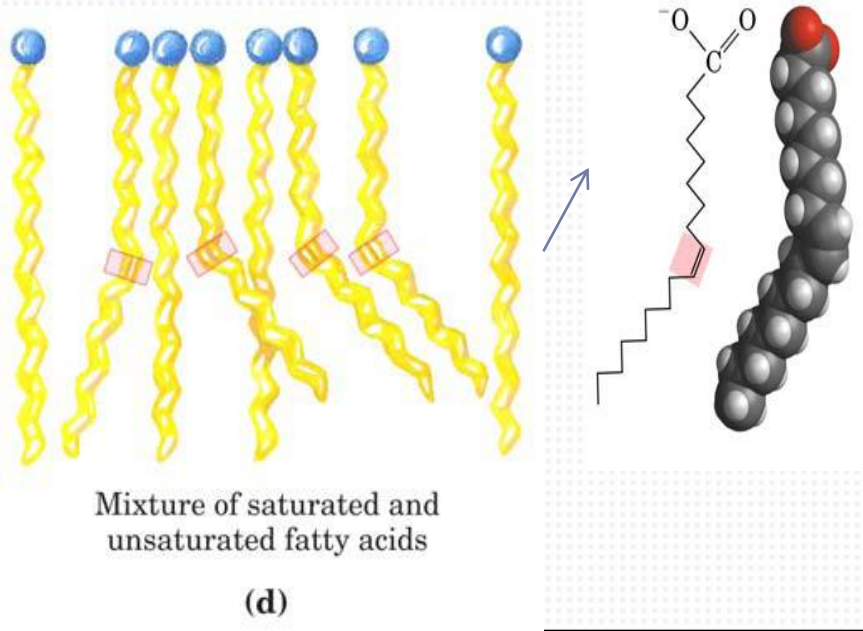
Plasma membrane lipid composition by weight percent of mammalian red blood cells						
	species					
lipid	pig	human	cat	rabbit	horse	rat
cholesterol	26.8	26.0	26.8	28.9	24.5	24.7
phosphatidylcholine	13.9	17.5	18.7	22.3	22.0	31.8
sphingomyelin	15.8	16.0	16.0	12.5	7.0	8.6
phosphatidylethanolamine	17.7	16.6	13.6	21.0	12.6	14.4
phosphatidylserine	10.6	7.9	8.1	8.0	9.4	7.2
phosphatidylinositol	1.1	1.2	4.5	1.0	0.2	2.3
phosphatidic acid	0.2	0.6	0.5	1.0	0.2	0.2
lysophosphatidylcholine	0.5	0.9	0.2	0.2	0.9	2.6
glycosphingolipids	13.4	11.0	11.9	5.3	23.5	8.3
Source: From Thomas E. Andreoli et al., *Membrane Physiology* , 2nd ed. (1987), Table I, chapter 27.						

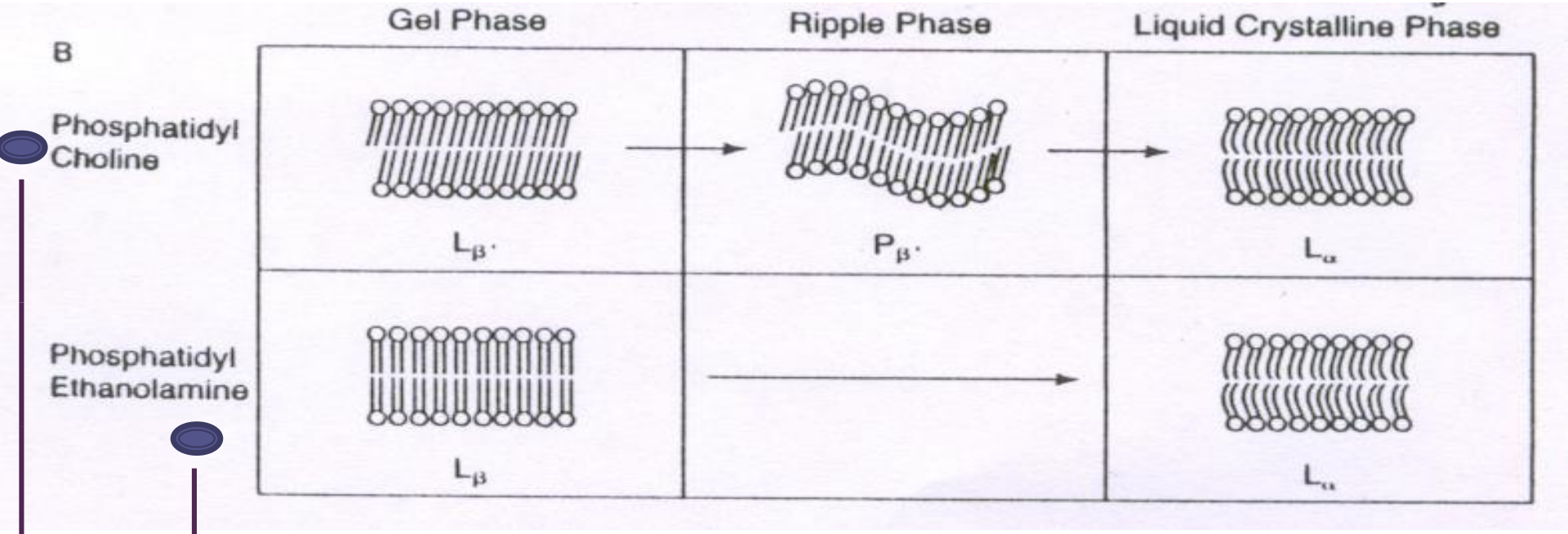
artificial Phospholipidic Membranes FORMING Bilayer CAN MIMIC THE FUNCTIONALITY OF Biomembranes AND MIMIC THEIR BEHAVIOUR.



The Differences in fatty acid acyl chain of phospholipids explain differences in fluidity of lipid bilayers while the *tans–gauche* conformational transitions are affect biophysical properties and their thermodynamics

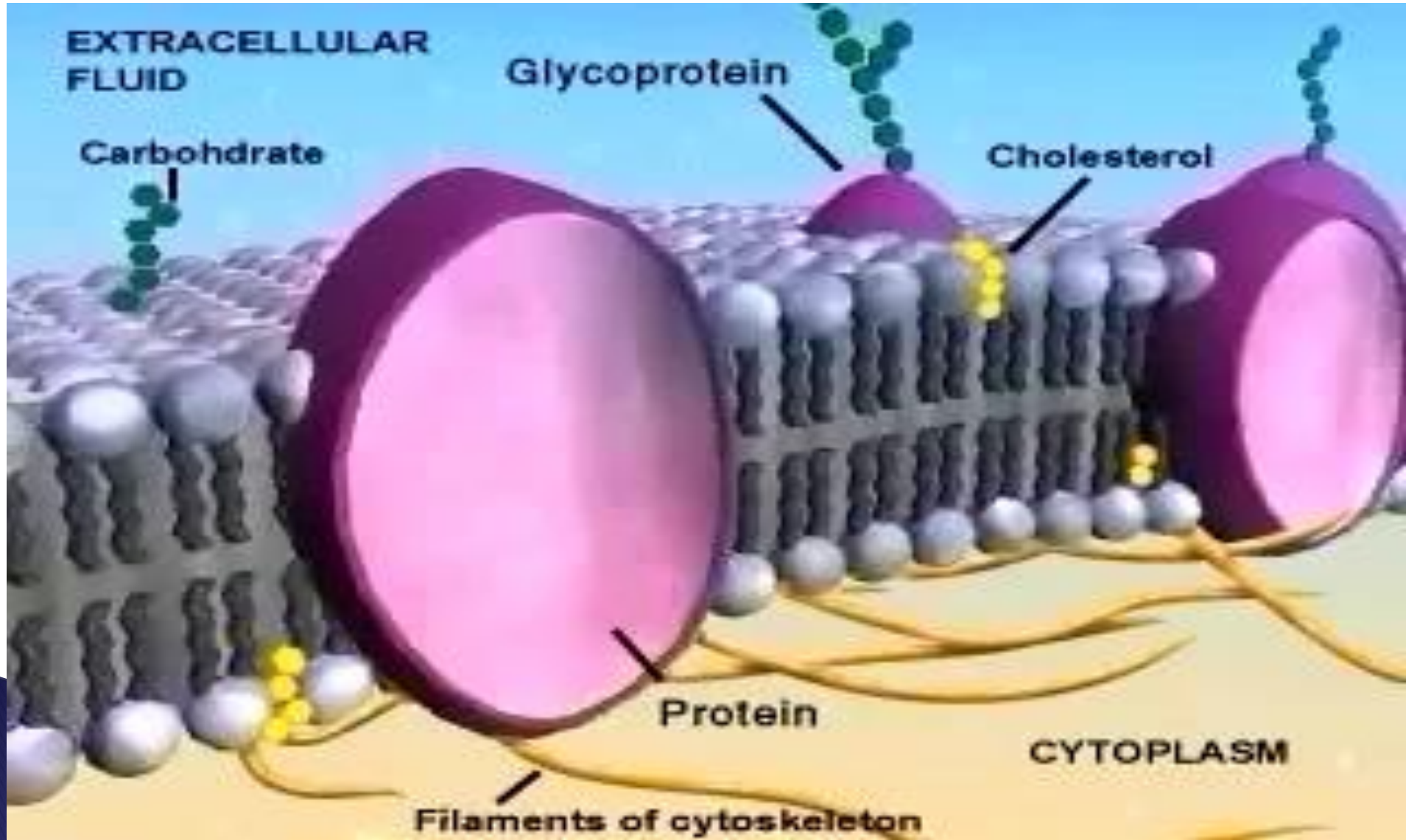






Changes in the lipid composition result in different self assembly process , organization and consequently in a different functionality of the bio system

Nature promotes complex systems as 'living systems' . This concept promotes plethora of **metastable phases** and *clustering effects* which are processes of high quality (i.e signalling transduction) that take place within the lipid bilayers of cell membranes. (Ref. Binder eta al., Angew. Chem. Ind. Ed. , 42, 5802-27, 2003)

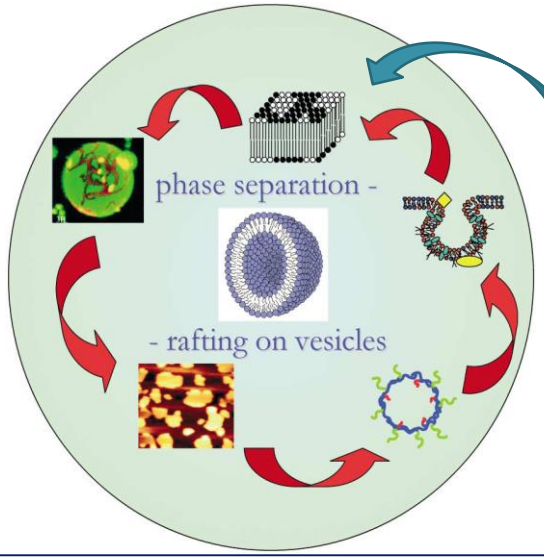


Metastable phases play an important role in the behavior of lipid membranes. Topics touched upon include the experimental detection of domains, their composition, domain induction, properties of rafts (a special form of domain), and **the relationship of metastable phases to human diseases**.

The metastable phases, can cause biophysical and thermodynamic abnormalities that could be defined as ' ***biophysical disease factors***'

'Pharmaceutical Nanotechnology. Funtamentals and practical applications',
by
Costas Demetzos

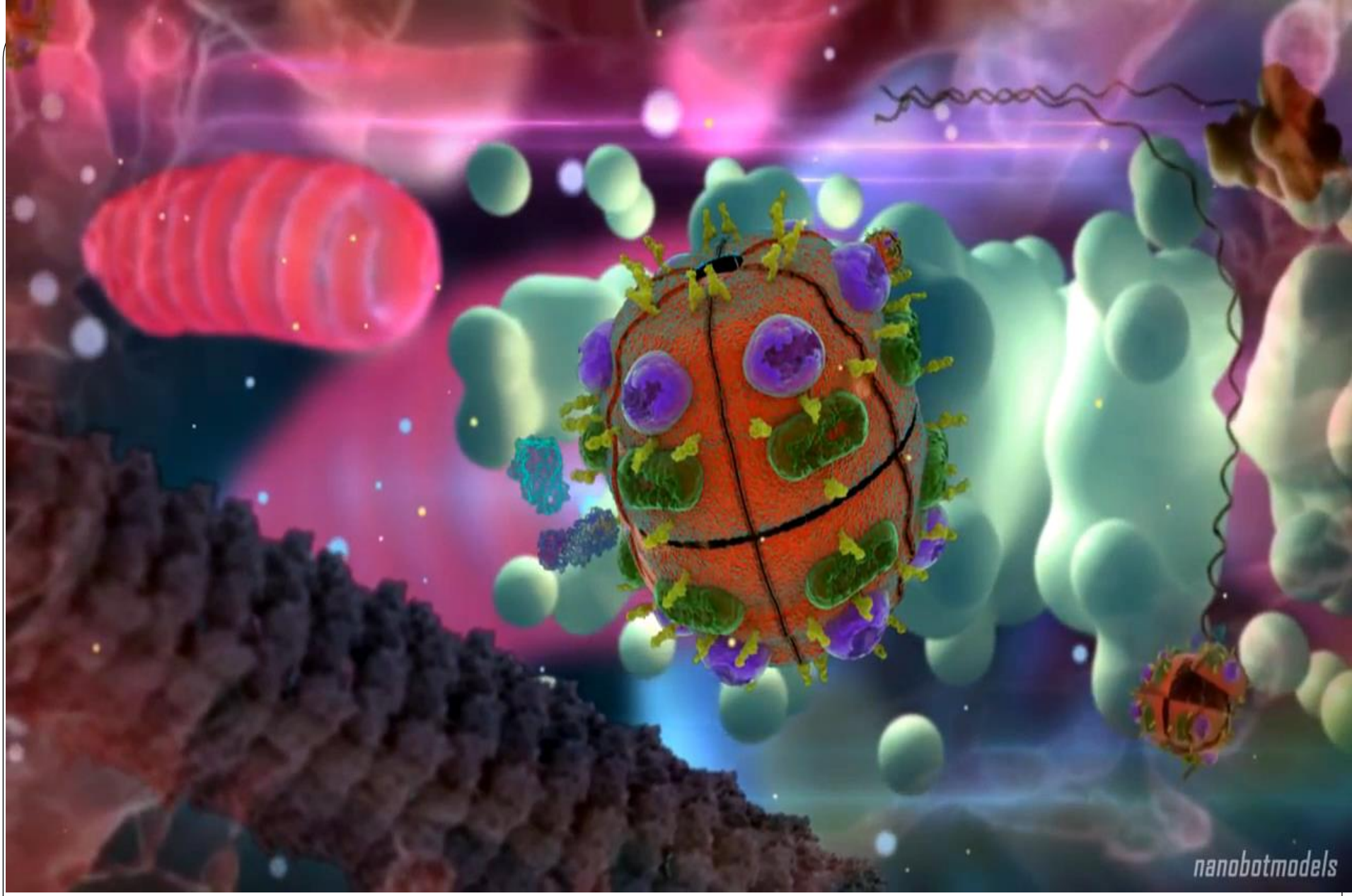
Springer, 2016



Domains and Rafts in Lipid Membranes
by
Wolfgang H. Binder,*
Veronique Barragan,
and Fredric M. Menger

Angewandte Chemie

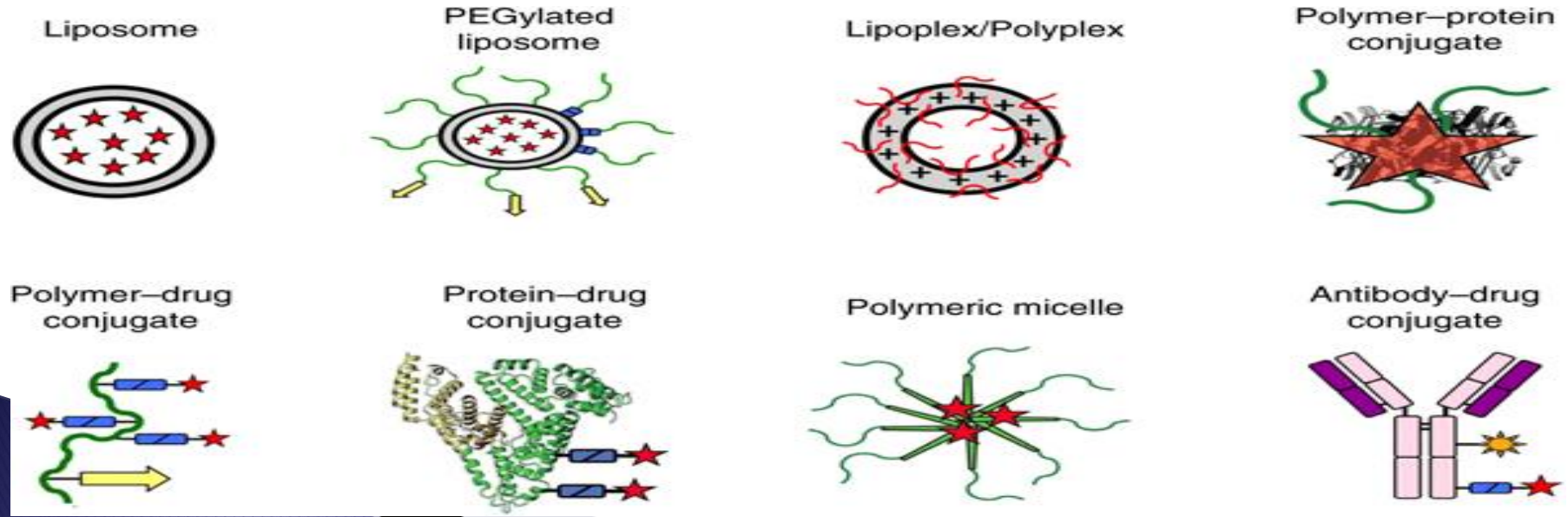
Future progress in biology …continuing to address membrane structures, dynamics and functions where domains and 'rafts' (i.e. metastable phases), play a key role**. Even now it can be assumed that new strategies for fighting viral infections, lipid storage disease, cancer ….will arise through the understanding of 'rafts (i.e. metastable phases)**


nanobotmodels

THE QUESTIONS THAT HAVE BEEN RAISED ARE :

IS THE COMPLEXITY AND THE METASTABILITY EFFECT OF ARTIFICIAL CELL MEMBRANES THE BARRIER FOR THEIR REPRODUCIBILITY ?

Meaning, **do the non-equilibrium and quantum effects** that are related with the bio- and thermo -behaviour of the lipid bilayers of artificial cell membrane nanoprlatforms **play an important role in the production identical or statistically similar copies of the prototypes ??**



Summing up

The metastable phases and the meta-equilibrium (from the thermodynamic point of view) status of self assembled structures are considered as being responsible for their physicochemical and biophysical fingerprint that affect their interfacial phenomena and behaviour.

By mimicking biological functions and by ‘reproducing’ the metastable phases of living cells by constructing artificial bio-systems at nano-dimension (i.e. liposomes) we can create ‘smart’ bio-nanosystems that are able to mimic living cell membranes and can be used for drug delivery.

NANOSIMILARS

"ωφελέειν, εἰ μη βλάπτειν"

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Nanosimilars are considered as new medicinal outcomes combining the generic drug and the nanocarrier which could be classified as an innovative excipient giving floor to the regulatory agencies for discussions and to promote a new regulatory environment for their approval.

The similarity could be studied based on the pharmacological activity of the bioactive substances (generic drug) and of the physicochemical, biophysical and thermodynamic properties of the innovative excipient with self-assembled properties

Demetzos C (2015) Biophysics and Thermodynamics: the scientific blocks of bio-inspired drug delivery nano systems. AAPS PharmSciTEch 16(3):491-495.

Demetzos C., Pippa N. , 2015. Fractal geometry as a new approach for proving the nanosimilarity. Int. J. Pharm. 483:1-5.

EMA has Reflection Papers (RP) on this subject

Specific Reflection Papers

- ❑ Nanosimilar iron medicinal products (EMA/CHMP/SWP/100094/2011)
- ❑Coated nanomedicine products (EMA/325027/2013)
- ❑Nanosimilar liposomal product (EMA/CHMP/806058/2009/Rev.02)

Draft Specific Reflection Papers

These papers are under public consultation with a view to developing guidelines for specific nanosimilar products

- ❑Block copolymer micelle medicinal products (EMA/CHMP/13099/2013)
- ❑Nanosimilar intravenous iron-based nano-colloidal products (EMA/CHMP/SWP/620008/2012)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 March 2011
EMA/CHMP/SWP/100094/2011
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2013
EMA/325027/2013
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products

What we need …

We need specific tools that can meet the requirements for characterizing nanoparticulete medicines and to control the manufacturing process for their development.

Determination of the physicochemical functionality of nanomedicines is related to their surface characteristics.

size, size distribution, ζ-potential, shape, **surface properties**,

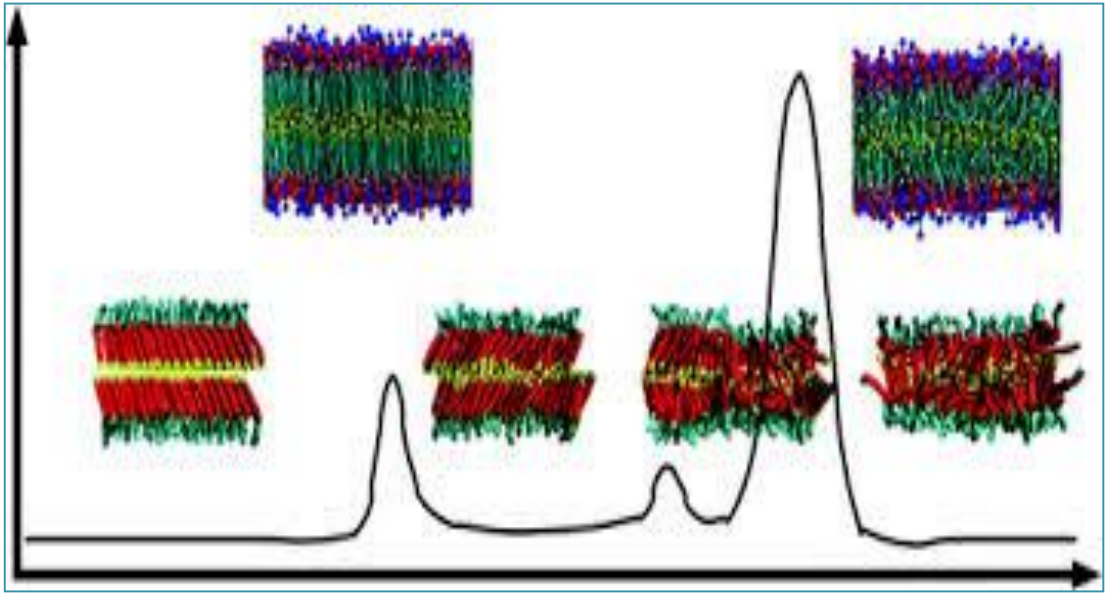
more

Studies of their metastable phases behaviour and tools by which we can identify the metastability process in order to develop nanosimilar medicines

- The need for sensitive and accurate **analytical methods** to identify and quantify the nanomedicine is considered as essential for its quality in part and as final product

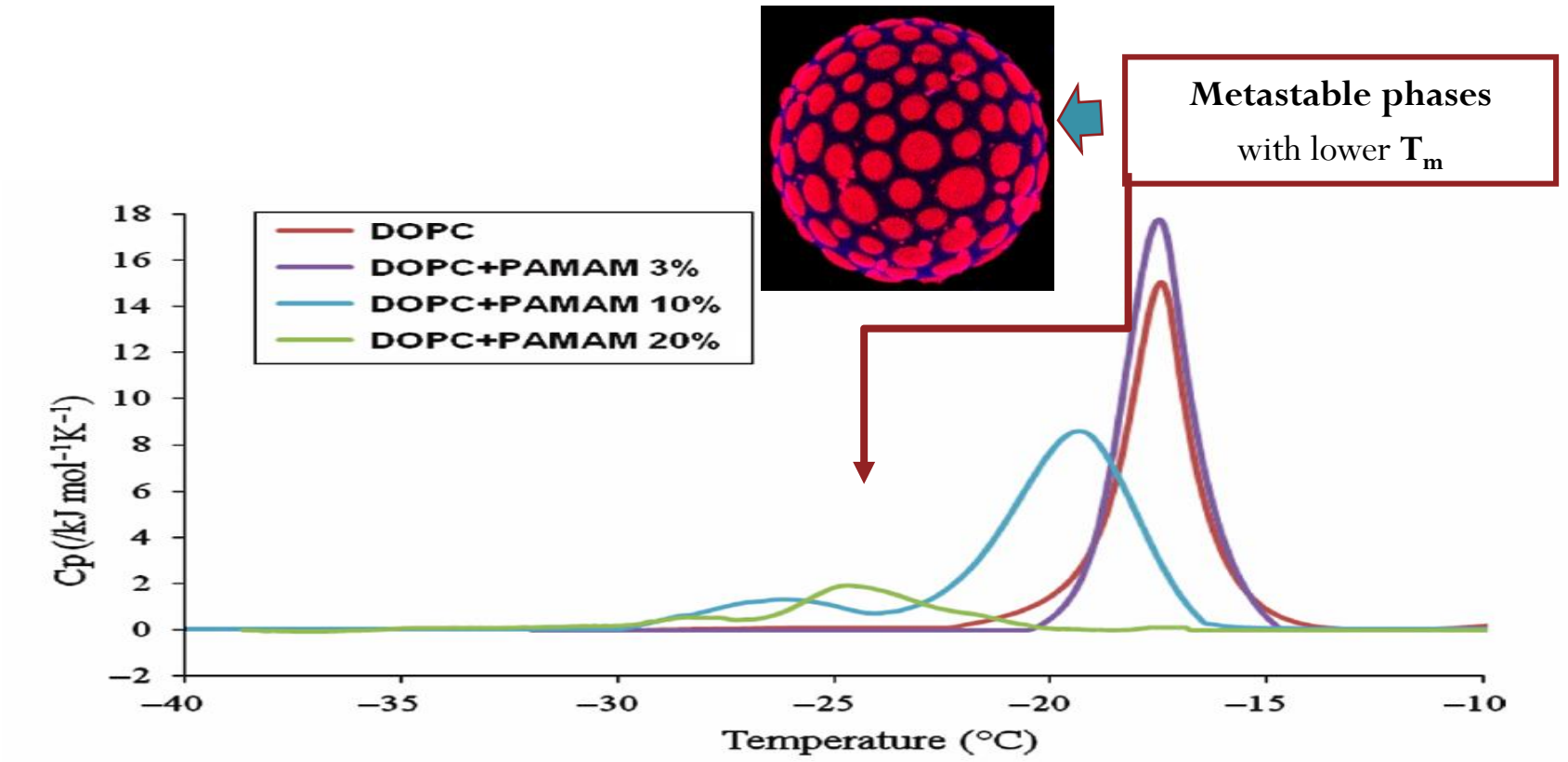
Thermodynamics is the fundamental scientific element that could efficiently be used for studying and analyzing the behavior of artificial biological membranes that could be correlated with biological networks and create scientific platforms for the system therapeutics concept.

Liquid crystalline phases of phospholipids



Ref. Koynova R., Caffrey M., Phases and phase transition of the phosphatidylocholines, Biochim. Biophys. Acta 1376, 91-145, 1998

Chimeric Liposomes Incorporating Bioactive Compounds and Biomaterials – (PAMAM Dendrimer). Lyotropism and Metastable phases are predominant.



DSC thermograms of DOPC lipid bilayers in the presence of increasing concentrations of PAMAM dendrimer. **(Adapted from *J NanosciNanotechnol,* 2011 11, 3764-3772. A New Chimeric Drug Delivery Nano System (chi-aDDnS) Composed of PAMAM G 3.5 Dendrimer and Liposomes as Doxorubicin's Carrier. Gardikis, K; Fessas, D; Signorelli, M; Dimas, K; Tsimplouli, C; Ionov, M; Demetzos, C.)**

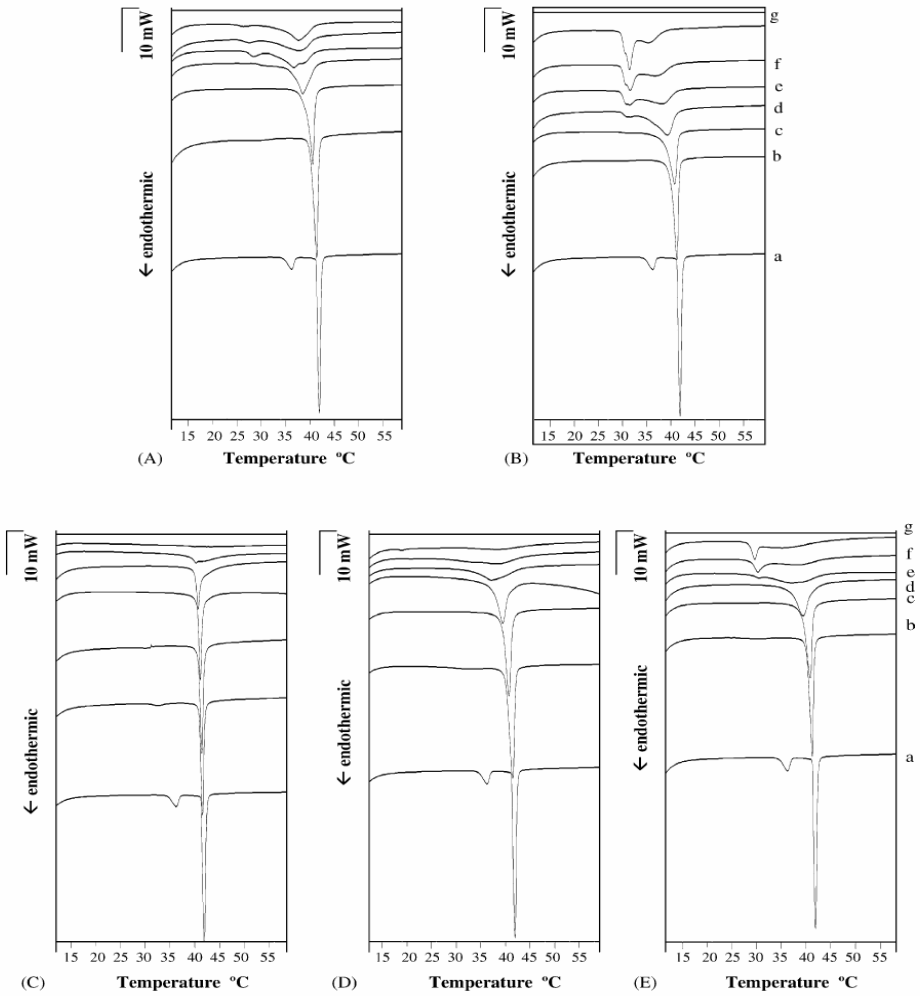
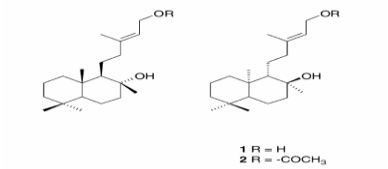


Fig. 2. DSC thermograms of fully hydrated bilayers of DPPC with varying amounts (a, 0 mol%; b, 2.5 mol%; c, 5 mol%; d, 10 mol%; e, 15 mol%; f, 20 mol%; g, 30 mol%) of compound **1** (A), compound **2** (B), cholesterol (C), equimolar mixture of cholesterol and compound **1** (D) and equimolar mixture of cholesterol and compound **2** (E).

Table 1
Calorimetric parameters

Sample (x = mol%)	T_{onset} (°C)	S.D.	T_m (°C)	S.D.	$T_{1/2}$ (°C)	S.D.	ΔH (kJ/mol)	S.D.
DPPC	41.28	0.16	41.67	0.15	41.96	0.17	35.48	1.14
DPPC/cholesterol (x=2.5)	40.72	0.01	41.31	0.02	41.24	0.01	32.79	0.08
DPPC/cholesterol (x=5)	40.57	0.01	41.15	0.01	41.09	0.01	30.87	0.02
DPPC/cholesterol (x=10)	40.35	0.01	40.84	0.00	40.86	0.01	27.56	0.13
DPPC/cholesterol (x=15)	39.87	0.00	40.49	0.00	40.90	0.00	22.24	0.24
DPPC/cholesterol (x=20)	38.64	0.03	40.18	0.03	41.55	0.02	21.10	0.14
DPPC/cholesterol (x=30)	38.83	0.89	41.20	0.02	44.48	0.43	17.21	1.51
DPPC/**1** (x=2.5)	40.02	0.01	41.07	0.02	40.86	0.01	38.64	0.06
DPPC/**1** (x=5)	38.96	0.04	40.39	0.00	39.98	0.01	39.28	0.10
DPPC/**1** (x=10)	35.77	0.12	38.38	0.02	38.05	0.01	38.56	0.17
DPPC/**1** (x=15)	32.45	0.18	36.52	0.09	36.20	0.05	38.74	0.20
DPPC/**1** (x=20)	31.03	0.31	37.69	0.11	36.37	0.19	35.83	0.09
DPPC/**1** (x=30)	33.61	0.04	37.50	0.06	36.76	0.02	37.52	0.66
DPPC/Chol/**1** (x=1.25+1.25)	39.91	0.02	41.21	0.04	40.95	0.01	37.04	0.10
DPPC/Chol/**1** (x=2.5+2.5)	39.22	0.02	40.47	0.01	40.27	0.01	35.98	0.11
DPPC/Chol/**1** (x=5+5)	37.31	0.03	39.27	0.03	39.06	0.02	28.88	0.23
DPPC/Chol/**1** (x=7.5+7.5)	32.84	0.10	37.07	0.12	37.52	0.04	29.84	0.12
DPPC/Chol/**1** (x=10+10)	28.75	0.22	38.54	0.14	36.49	0.03	25.21	0.15
DPPC/Chol/**1** (x=15+15)	31.71	0.49	38.58	0.09	38.52	0.18	11.06	0.33
DPPC/**2** (x=2.5)	39.76	0.01	40.99	0.02	40.71	0.00	39.81	0.17
DPPC/**2** (x=5)	38.64	0.08	40.60	0.05	39.99	0.05	38.88	0.21
DPPC/**2** (x=10)	34.33	0.24	39.19	0.08	37.76	0.06	39.14	0.29
DPPC/**2** (x=15)	29.68	0.26	31.39	0.06	35.45	0.09	40.19	0.22
DPPC/**2** (x=20)	29.55	0.01	31.45	0.07	33.65	0.11	40.57	0.09
DPPC/**2** (x=30)	29.83	0.23	31.31	0.02	32.17	0.02	39.82	0.04
DPPC/Chol/**2** (x=1.25+1.25)	40.04	0.01	40.96	0.00	40.79	0.00	32.71	0.01
DPPC/Chol/**2** (x=2.5+2.5)	39.08	0.03	40.63	0.03	40.29	0.02	35,41	0.24
DPPC/Chol/**2** (x=5+5)	36.63	0.05	39.25	0.05	38.98	0.02	32.91	0.10
DPPC/Chol/**2** (x=7.5+7.5)	30.21	0.31	36.85	0.20	36.82	0.04	30.80	0.22
DPPC/Chol/**2** (x=10+10)	28.63	0.07	30.14	0.04	35.11	0.03	29.96	0.12
DPPC/Chol/**2** (x=15+15)	28.27	0.10	29.56	0.04	34.48	0.04	26.72	0.29

T_{onset}, temperature at which the thermal effect starts; T_m, temperature at which heat capacity (ΔC_p) at constant pressure, is maximum; $T_{1/2}$, temperature at which the transition is half completed; ΔH, transition enthalpy normalised per mole of DPPC; **1**, labd-13(E)-ene-8α,15-diol; **2**, derivative labd-13(E)-ene-8α-ol-15-yl-acetate.



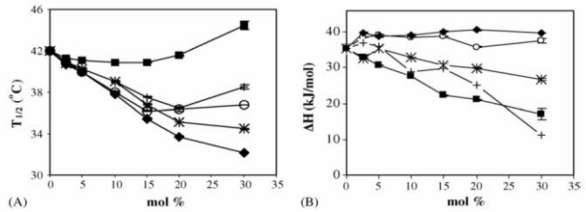
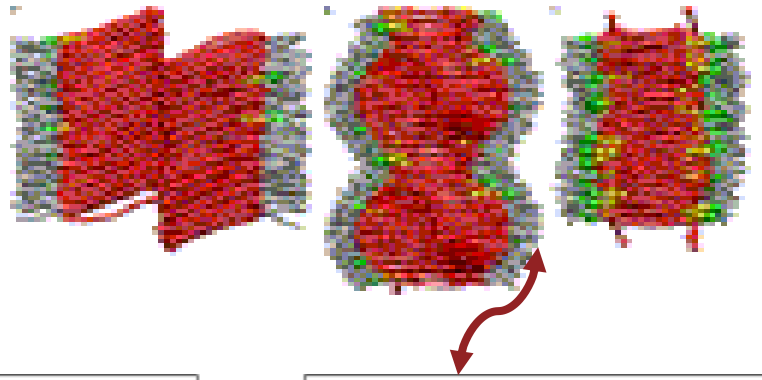


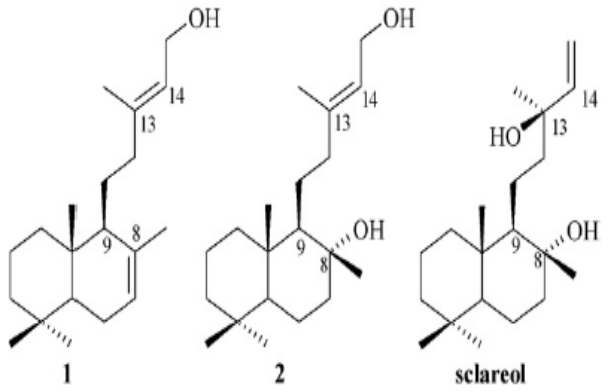
Fig. 3. $T_{1/2}$ (°C) and ΔH (J/mol DPPC) values of DPPC bilayers vs. concentrations of compound **1** (○), **2** (♦), cholesterol (■), equimolar mixture of cholesterol/**1** (+) and equimolar mixture of cholesterol/**2** (✱).

DSC thermograms of fully hydrated bilayers of DPPC with varying amounts (a: 0 mol%, b: 2.5 mol%, c: 5 mol%, d: 10 mol%, e: 15 mol%, f: 20 mol%, g: 30 mol%) of compound 1 (A), compound 2 (B), cholesterol (C), equimolar mixture of cholesterol and compound 1 (D) and equimolar mixture of cholesterol and compound 2 (E). (Adapted with permission from Elsevier, from *Chem Phys Lipids,* 2005 138, 1-11. Labdane-type diterpenes: thermal effects on phospholipid bilayers, incorporation into liposomes and biological activity. Matsingou, C; Hatziantoniou, S; Georgopoulos, A; Dimas, K; Terzis, A; Demetzos, C.)

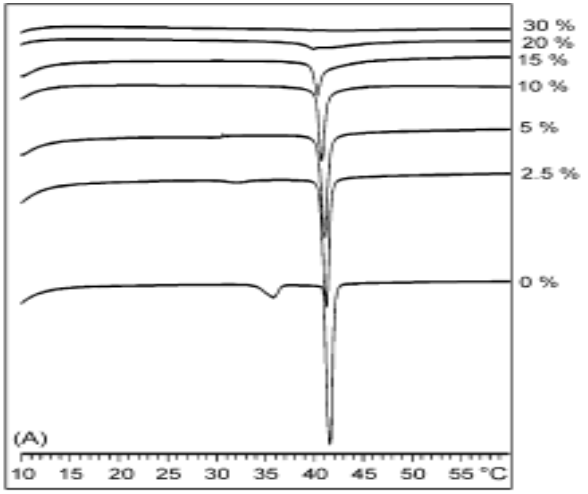
Interdigitated phase in DPPC fully hydrated bilayers incorporating bioactive molecules

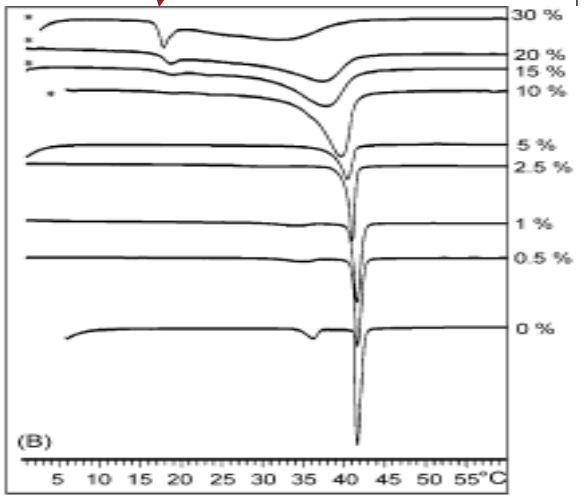


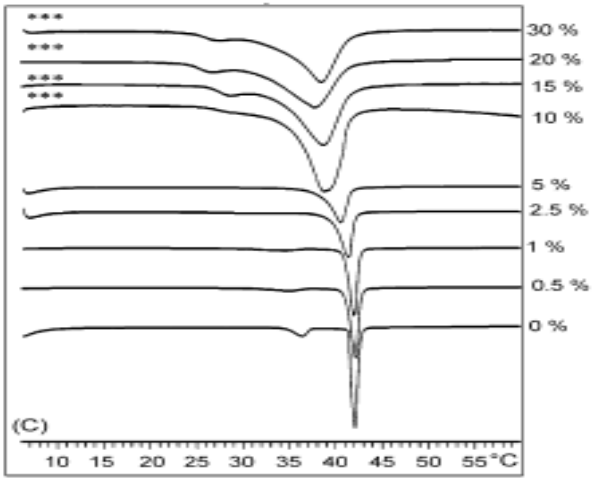
Interdigitated phases are a portion of metastability concept and affect the biophysical and thermodynamic profile of liposomal nanomedicines

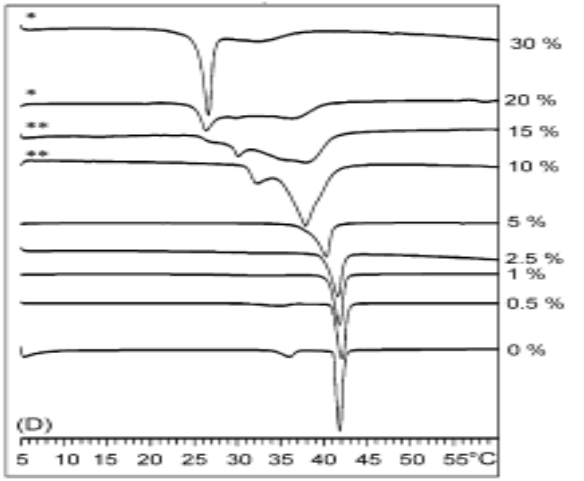


Structures of labd-7,13-dien-15-ol (**1**), labd-13-ene-8α,15-diol (**2**) and labd-14-ene-8,13-diol (sclareol).









Metastable Phases of Vinblastine incorporating into DPPC lipid bilayers and into liposomes

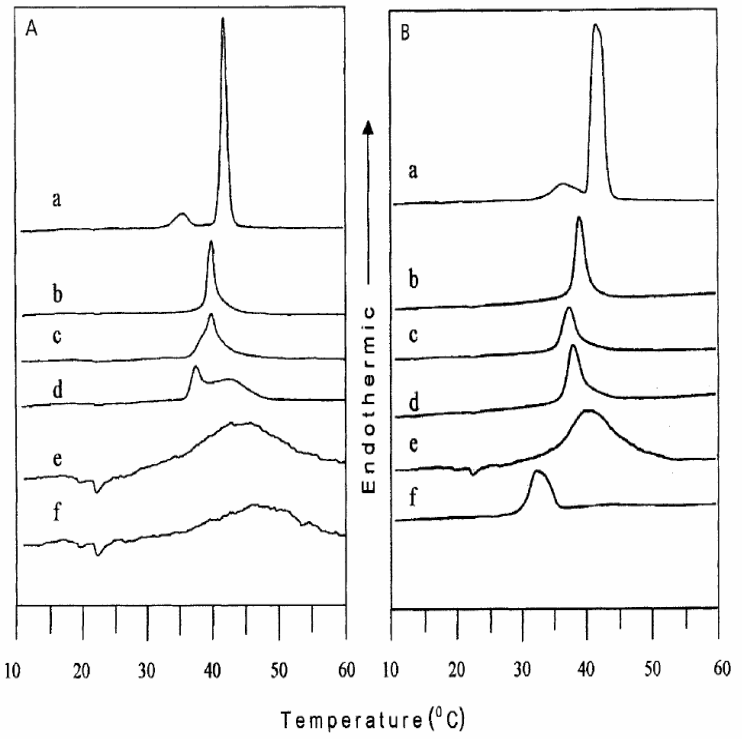
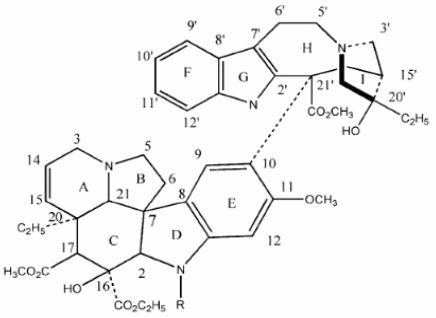


Figure 4 A. DSC calorimetry scan of: DPPC (a); DPPC–cholesterol (x = 0.10) (b); DPPC+cholesterol (x = 0.10)+vinblastine (x = 0.045) (c); DPPC+cholesterol (x = 0.10)+vinblastine (x = 0.17) (d); DPPC–cholesterol (x = 0.30) (e); and DPPC–cholesterol (x = 0.30) +vinblastine (x = 0.17) (f). B. DSC calorimetry scan of: DPPG (a); DPPG–cholesterol (x = 0.10) (b); DPPG+cholesterol (x = 0.10)+vinblastine (x = 0.045) (c); DPPG+cholesterol (x = 0.10)+vinblastine (x = 0.17) (d); DPPG-cholesterol (x = 0.30) (e); and DPPG–cholesterol (x = 0.30)+vinblastine (x = 0.17) (f). x represents molar ratio.



VINBLASTINE

Table 1 Values of pretransition temperature ($T_{pretrans}$), half-width temperature ($T_{m2}^{\downarrow}$), peak temperature ($T_{m2}^{\downarrow}$), peak temperature (T_m) and enthalpy change (ΔH) of phospholipid bilayers without and with vinblastine and phospholipid-cholesterol without or with vinblastine.

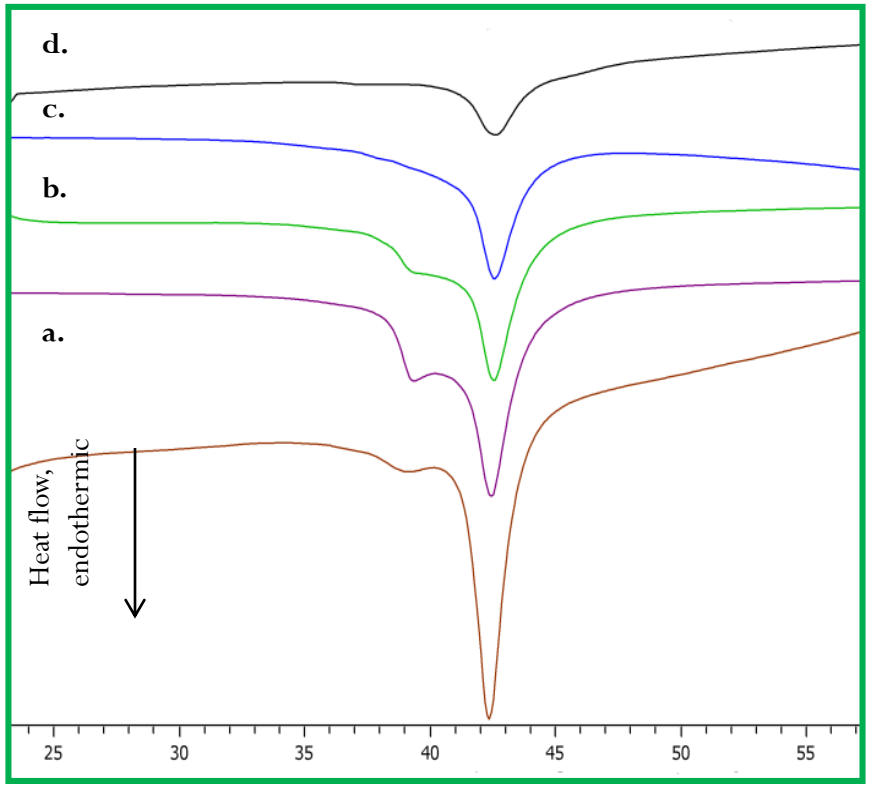
Samples	$T_{pretrans}$	T_m (°C)	$T_{m2}^{\downarrow}$ (°C)	ΔH (cal g^{-1})
DPPC	34.8	41.2	2.8	1.11±0.04
			1.0	9.96±0.08
DPPC+cholesterol (x = 0.10)		39.5	1.1	6.65±0.44
DPPC+cholesterol+vinblastine (x = 0.045)		38.9	3.0	8.11±0.56
DPPC+cholesterol+vinblastine (x = 0.17)		36.2	7.5	8.31±0.32
DPPC+cholesterol (x = 0.3)		41.7	16	3.02±0.15
DPPC+cholesterol+vinblastine (x = 0.17)		44.9	17.5	1.69±0.26
DPPG	36.3	40.7	5.0	1.08±0.02
			2.25	10.74±0.04
DPPG+cholesterol (x = 0.10)		38.0	1.9	7.97±0.50
DPPG+cholesterol+vinblastine (x = 0.045)		35.9	2.5	5.54±0.24
DPPG+cholesterol+vinblastine (x = 0.17)		36.7	2.5	7.48±0.27
DPPG+cholesterol (x = 0.30)		39.2	8.5	4.53±0.13
DPPG+cholesterol+vinblastine (x = 0.17)		31.8	4.0	4.88±0.04

Marqibo , liposomal vincristine 2012 approved FDA, lymphoblastic leukemia (Orphan Drug approval process)

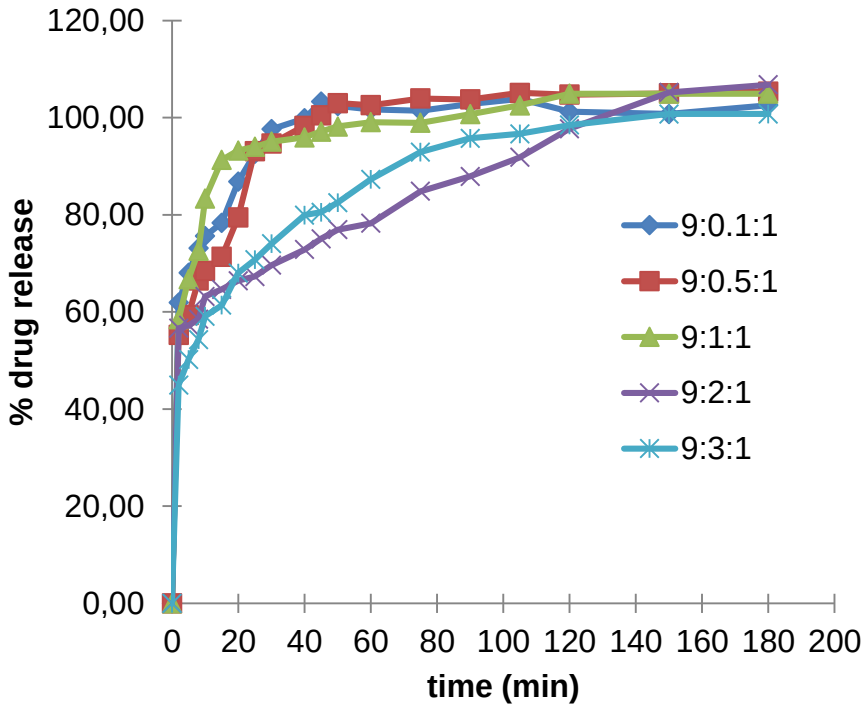
C. Demetzos, D. Angelopoulou, A. Kolocouris, I. Daliani, and T. Mavromoustakos (2001) Structure Elucidation, Conformational Analysis and Thermal Effects on Membrane Bilayers of an Antimicrobial Myricetin Ether Derivative ; H. Maswadeh, C. Demetzos, K. Dimas, Y. L. Loukas, A. Georgopoulos, T. Mavromoustakos and G. Th. Papaioannou (2002) In-vitro cytotoxic/cytostatic activity of anionic liposomes containing vinblastine against leukaemic human cell lines

Correlation of the thermotropic behaviour of *chimeric* liposomal nanosystems incorporating drug with their release profile.

The *chimeric* liposomal nanosystems is composed of phospholipids (DPPC) and of a block co-polymer (MPOx). The lyotropic effect of the nanosystem (biophysical behaviour) is driven by the percentage composition of the polymeric guest

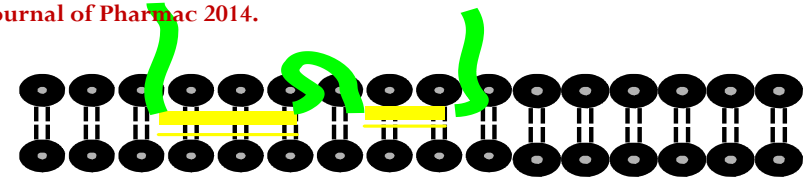


DSC heating scans of DPPC:MPOx **a.** 9:0 **b.** 9:0.1 **c.** 9:05 **d.** 9:1 and **e.** 9:3 molar ratio liposomes.



Ref. Pippa N., Dokumetzidis A., Pispas S., Demetzos C., et al. Intern. Journal of Pharmac 2014.

The cartoon represents the structural organization of the lipidic bilayer



The results from the DSC experiments based on calculated thermodynamic parameters could be used not only to select appropriate biomaterials for designing an effective and stable liposomal DDnS
could be used
to study the metastable phases of artificial phospholipid membrane bilayers

"*It takes a membrane to make sense out of disorder in biology. You have to be able to catch energy and hold it, storing precisely the needed amount and releasing it in measured shares*". So wrote Lewis Thomas in The Lives of Cells.

Metastable phases….play an important role in the behavior of lipid membranes.

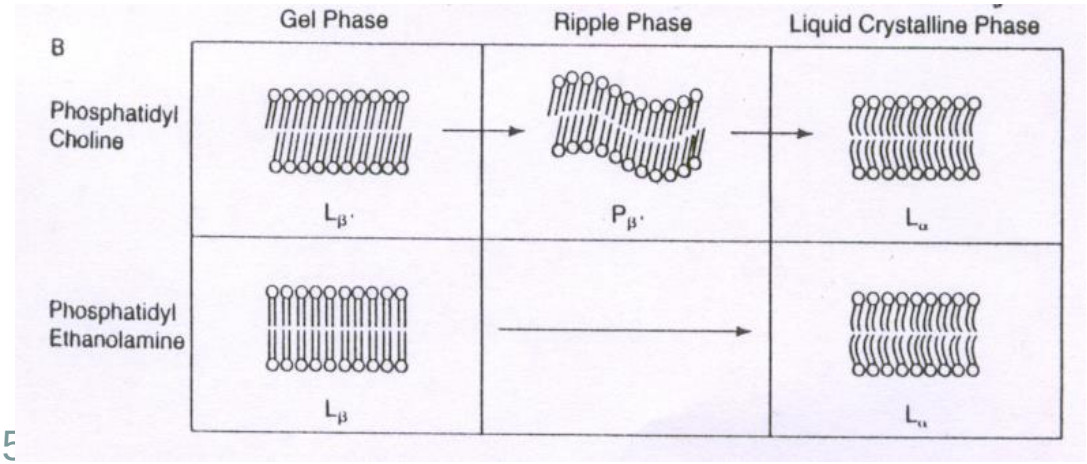
The metastable phases are responsible for the variability of bio systems' parameters that cause biophysical and thermodynamic 'abnormalities'. These abnormalities could be defined as '***biophysical disease factors***' as mentioned in the recent published monograph by Demetzos (Ref. Springer 2016) and is referred in the article entitled '*Domains and Rafts in lipid membranes*' published by W. H. Binder, V. Barragan, and F. M. Menger in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827.

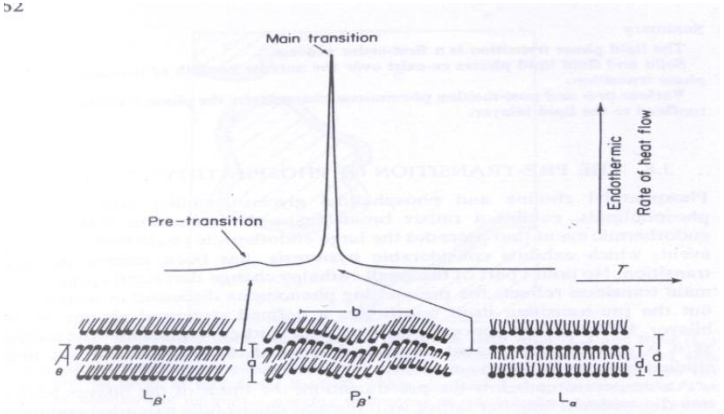
Ref. C. Demetzos 'Pharmaceutical Nanotechnology. Funtamentals and practical applications', Springer, 2016

Going a little further…..

Nano-Thermodynamics

Nanosystems such as liposomal systems are mostly nonequilibrium systems, with **dynamic structural characteristics** and their interactions with the environment being dominated by thermal fluctuations. Pressure in a nanosystem cannot be considered isotropic **Properties considered in classical thermodynamics as intensive at equilibrium, like internal energy, specific enthalpy, specific entropy, specific free Gibbs energy, are not intensive any more.** These are related to the fact that chemical potential (**μ**) for **nanophases depends on the size** (number of atoms) and for the microenviromental factors. **For example …a polymeric guest or drugs affect the microenviroment of lipidic bilayer and create phase separation and metastable phases.**





METASTABLE PHASES of liposomal membranes and of the living cells, are considered as an emerged field that should be studied based on nano-thermodynamics concept and on the **Tsallis' theory and Hills'** thermodynamics of small systems. The Tsallis' theory introduced the term '***entropic index q***'. ***q:*** describes the degree of non-extensivity of the system. A new kind of entropy, called non- extensive entropy, has been proposed in the literature

Thermal Transitions Metastable Phases and Tsallis' entropic index

- ❖Inetrfacial energy , must be taken into consideration
- ❖Fluctuation of thermodynamic variables should also be taken into consideration
- ❖In nanosystems properties such as *T* and *P* are not stable
- ❖Quantum effects for small systems may also become important

$$S_q(p_i) = \frac{k}{q-1}\left(1 - \sum_i p_i^q\right),$$

k is a positive constant, *pi* is the probability of the system at the quantum state *i* , ***q*** is the '*entropic index*''.

- ❖ **This equation can be applied in nano-non extensive systems while preserving the fundamental property of entropy in the Second Law of Thermodynamics.**

Entropy is considered to be an extensive property, i.e., that its value depends on the amount of material present.

- ❖ **Constantino Tsallis has proposed a nonextensive entropy *(Tsallis entropy) as an extension of the traditional Boltzmann–Gibbs entropy*.**

$$S = -k_B \sum_i p_i \ln p_i$$

The rationale behind the theory is that Gibbs-Boltzmann entropy leads to systems that have a strong dependence on initial conditions. In reality most materials behave quite independently of initial conditions.
Nonextensive entropy leads to nonextensive statistical mechanics, whose typical functions are power laws, instead of the traditional exponentials.

The concept was introduced in 1988 by Constantino Tsallis as a basis for generalizing the standard statistical mechanics, within Information Theory.

proposed by Claude E. Shannon in 1948 to find fundamental limits on signal processing and communication operations

Small scale systems and small numbers

Ref. '*What is life*' E. Schrodinger p. 30

- It is important to figure out the following statement

The non-equilibrium state is the driving force for the creation of functional self assemblies that statistically affect the functionality of small systems.

Natural laws driven by the statistical physics of small systems, produce 'quantum lifts' that influence the evolution process of macroscopic systems (i.e large systems) that are considered as in the equilibrium state

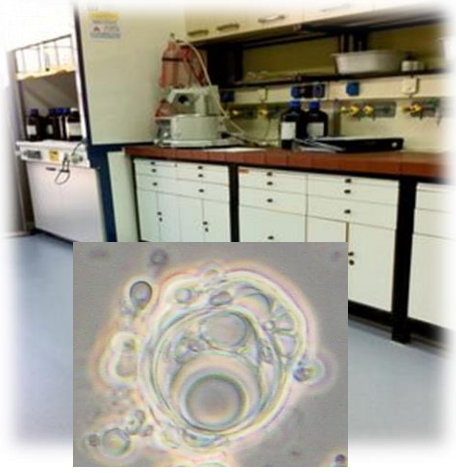
HOWEVER

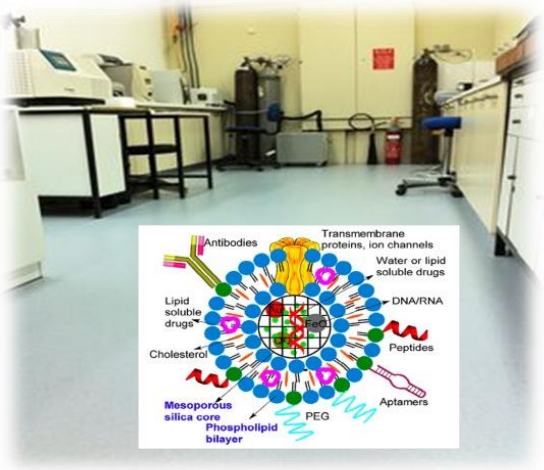
The Metastable phases of liposomal membranes could be considered as in the non-equilibrium state they behave as 'quantum lifts' and affect and influence the effectiveness of the whole liposomal product product.

By investigating their behaviour in a statistically point of view (quantum statistics approaches) we could be achieve the max effective rate regarding their functionality to their effectiveness.
This approach could be applied to new nanomedicinal and nanosimilars medicines as a new tool for their design and for the industrial development and scale –up processes.

Laboratory of Pharmaceutical Nanotechnology University of Athens, Greece

http://nanopharmlab.gr/index.php/en/





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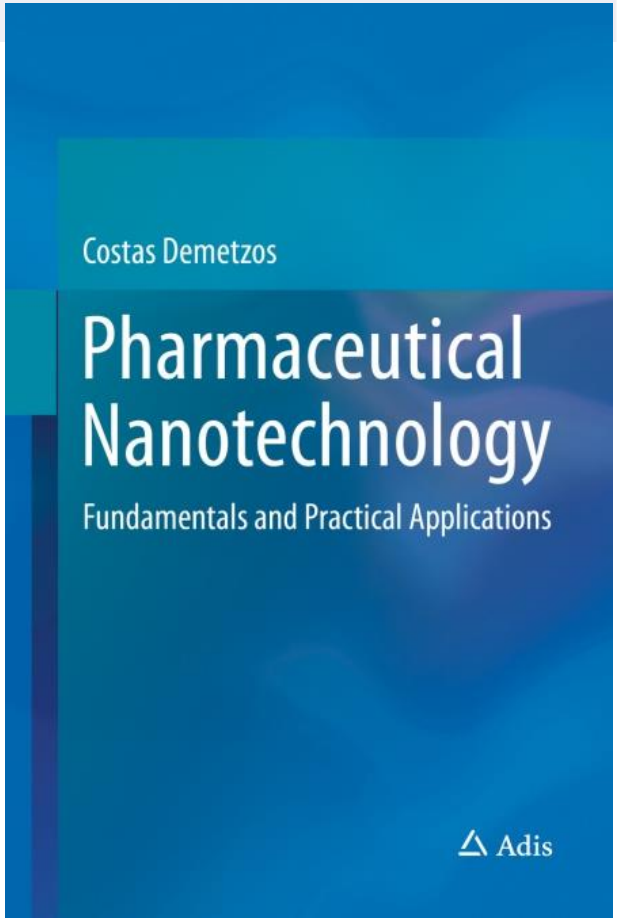

Biophysical Disease Factor

Προλογίζει
Gregory Gregoriadis, PhD, DSc
Professor Emeritus,
UCL School of Pharmacy London

(…) It has been therefore a great personal pleasure to write the Preface of the present book by Professor Costas Demetzos.
His monograph, 'Pharmaceutical Nanotechnology', is a unique publication (…)

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FINAL Conclusions

Metastable phases is an amazing research platform for studying the behavior of lyotropic liquid crystalline artificial bio- lipidic membranes

The behavior of bio-membranes as highly complex bio-systems, as well as of artificial lipidic membranes, leads to the formation of **metastable phases.**

- **In our point of view the metastable phases should be studied in depth.**
- **It is a challenge to promote investigations regarding, non-extensive entropic behaviour (entropy index *q*) - from a thermodynamic point of view- and also to promote new insights regarding the extension of Boltzmann-Gibbs entropy achieved by Tsallis – based on the complexity of artificial lipidic bio-membranes as drug delivery platforms.**
- **Nonextensive statistical mechanics fits very nicely to metastable structures of liposomal artificial membranes and this approach is absolutely associated with the fractal organization of the metastable phases.**
- **Nano-thermodynamics (Hill's and Tsalli's ideas) could be used as tools for studying the similarity of the prototype nanomedicines with nanosimilar medicines.**
- **This approach is complementary to our past proposal regarding the comparison of the morphology of nanosimilars to that of the prototype nanomedicine by using the fractal dimension.**

" (…) most of novel nanomaterials are 'art' rather than 'smart'. This because they generally are highly complex formulations, difficult to synthesize and scale –up in a controllable and reproducible manner (…)"

Ref. T. Lammers, Int. J. Pharmac., 454. 527-529, 2013

Ref. 1. Costas Demetzos *'Pharmaceutical Nanotechnology. Funtamendals and practical Applicatio*n', 2016, Springer
2. W. H. Binder, V. Barragan, and F. M. Menger in the Journal of *Angew. Chem. Ind. Ed*, 2003, 42, 5802-5827

This lecture is dedicated to the memory of my mentor
Prof. Dimitrios Papahadjopoulos
who introduced me to the liposomal and nanotechnology world during my sabbatical period at UCSF, USA

Vincent van Gogh
Branch of almond – tree in flowers, 1890

Thank you for your kind attention!