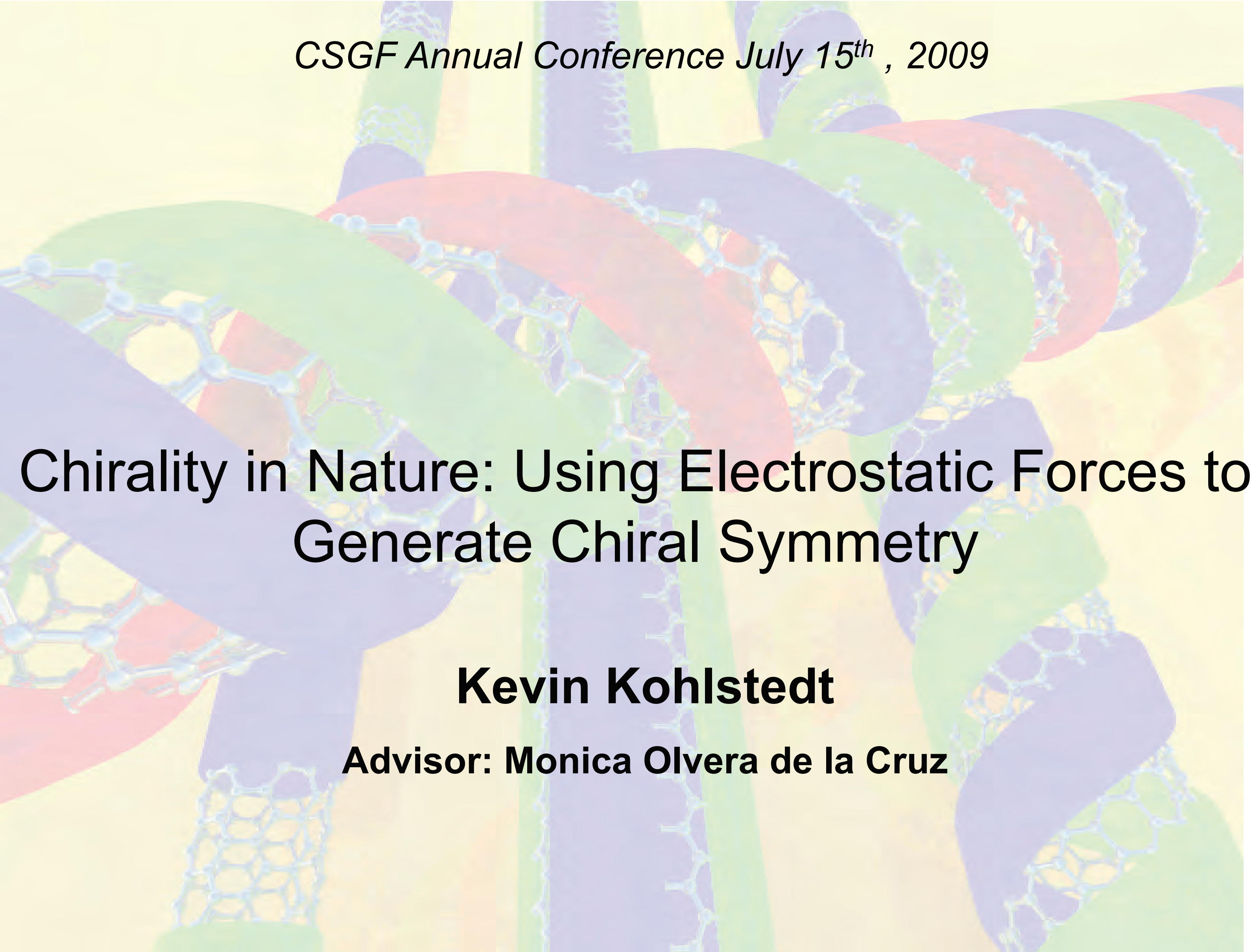


CSGF Annual Conference July 15th , 2009

Chirality in Nature: Using Electrostatic Forces to Generate Chiral Symmetry

Kevin Kohlstedt

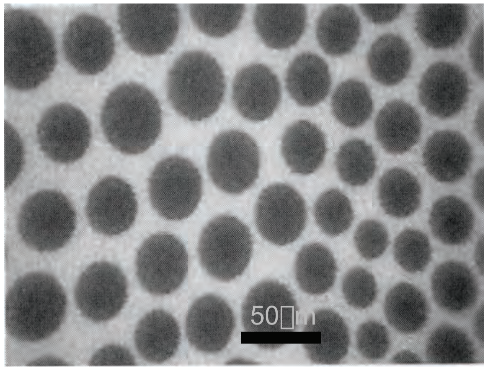
Advisor: Monica Olvera de la Cruz

Outline

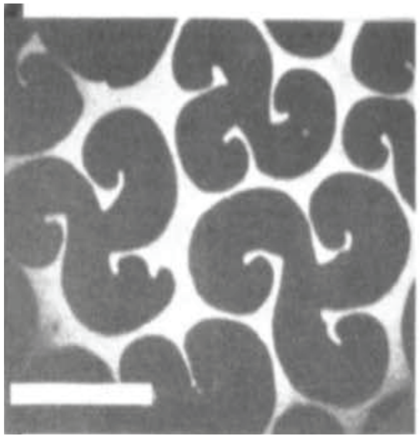
- Self-assembled charged surfaces that show patterns
  - Periodic domains
  - Chiral domains
- The property of chirality
  - Chirality in Nature
  - Self-assembled filaments and their relation to chirality
- The role electrostatics play in chiral structures
  - Model: the lamellar charge patterning of filaments
  - Investigate the details of electrostatic interactions on cylindrical surfaces
  - Experimental comparisons
- Other types of electrostatic patterns
  - Ionic lattices wrapped around filaments

Ordered Microphases

- Periodic phases
  - Lamellar and hexagonal arrangements
  - Electrostatics lead to long-range order
  - Theoretical description consists of Flory-Huggins and electrostatic repulsion [Andelman et al, 1987 JCP]
- Asymmetric domains
  - Chiral domains
    - L-, R- enantiomers translate to chiral domains
  - Topology directed anisotropy
    - Curved surfaces e.g. fibers, spontaneously curved membranes
- Can we go to smaller length scales?



Zasadzinski et al, *Biophys. J.*, **72** (1997)

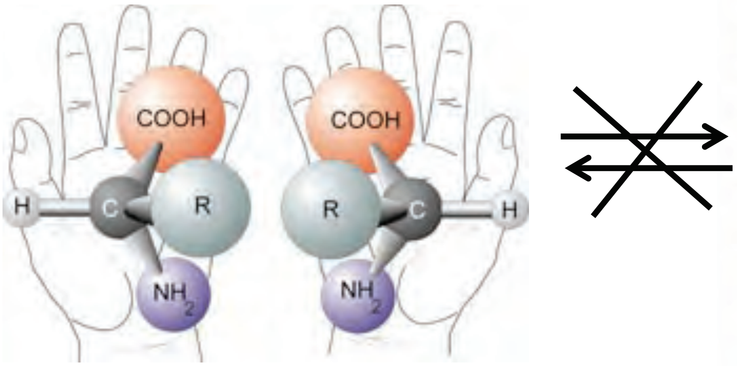


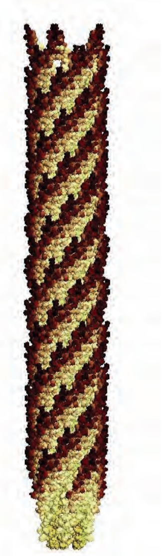
McConnell et al, *Nature,* **310** (1984)

Chirality in Nature

- Chirality is handedness
  - Not able to superimpose

- Examples
  - Universal: Elementary particles can have handedness
    - Chiral fermions and gauge fields
  - Mathematics: Mirror plane symmetry/Improper rotations
  - Molecular connectivity
    - Chiral centers
    - Chiral conformations



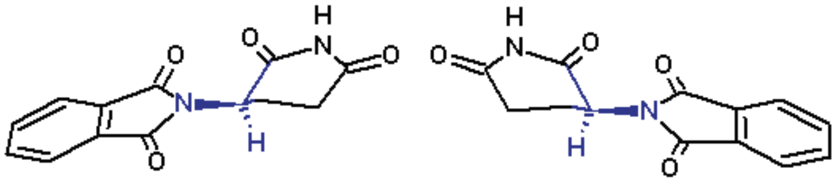


Pdb *f1 bacteriophage*

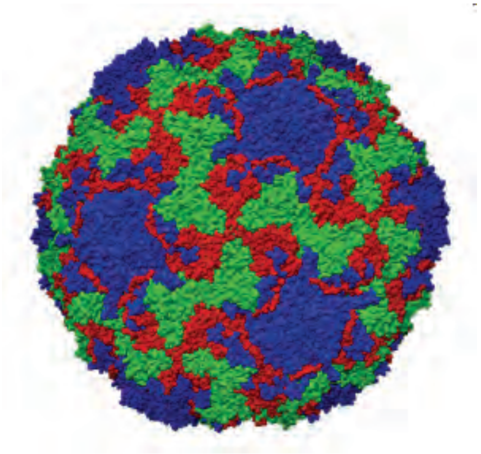
Chiralities: Configurational vs Conformational

- The arrangement of atoms in covalently bonded molecules can ha chiral centers
  - Left and right handed molecules can have very different chemistry
  - Dimensionality is also important in defining chirality– see the work of the Ratner/Szleifer Groups

- Conformational chirality is not determined by the chirality of composite molecules, but by their packing
  - Governed by non-bonded intermolecular forces



L-, S- Thalidomide

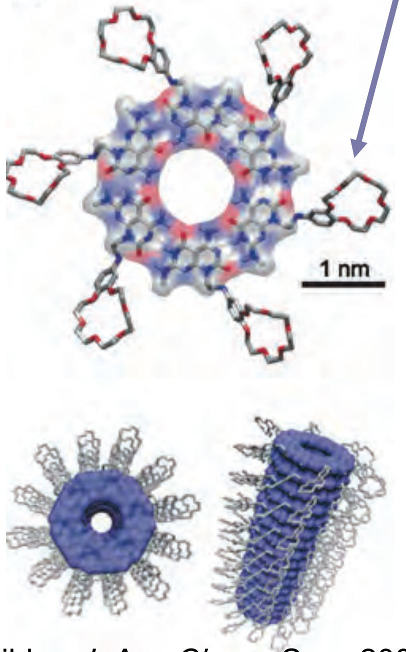


Human rhino virus
16derisilab.ucsf.edu

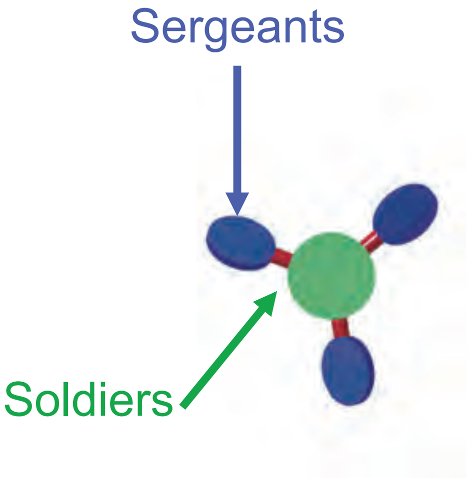
Controlling Chirality

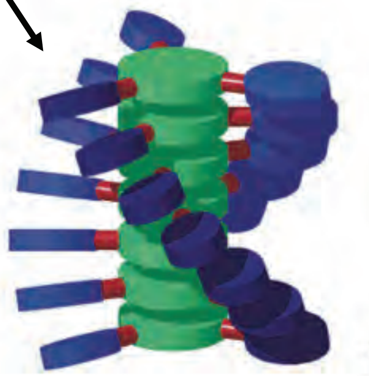
- Chiral amplification strategies
  - Chiral seeding i.e. small chiral perturbation
  - “Sergeants and Soldiers” technique
  - Chiral promoter

E. W. Meijer, *Nature*, 2000, **407**, 167.



A. E. Ribbe, *J. Am. Chem. Soc.*, 2002, **124**, 11064



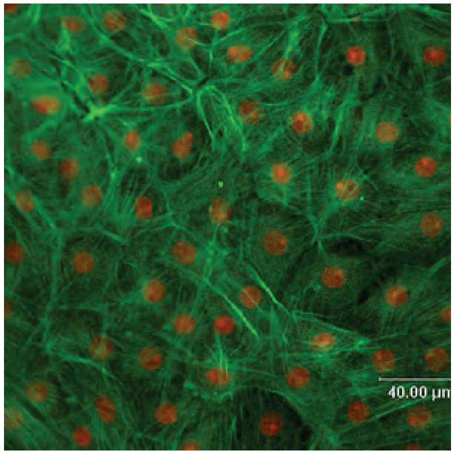


E. W. Meijer, *J. Am. Chem. Soc.*, 2002, **124**, 14759.

Conformational Chirality in Biology

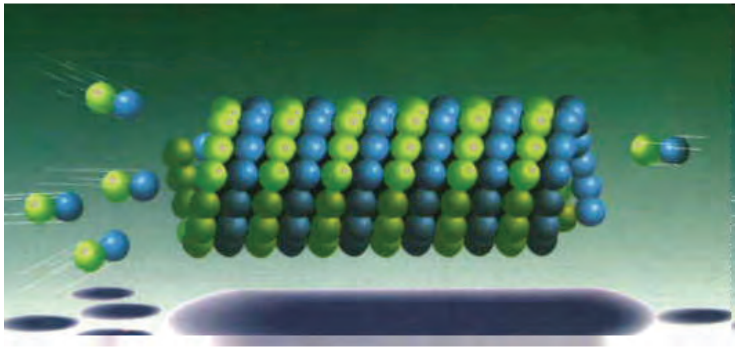
- Many self-assembled aggregates in Biology present chiral arrangements
    - Viruses, microfilaments, DNA
- What forces give rise to chirality?

F-Actin filaments



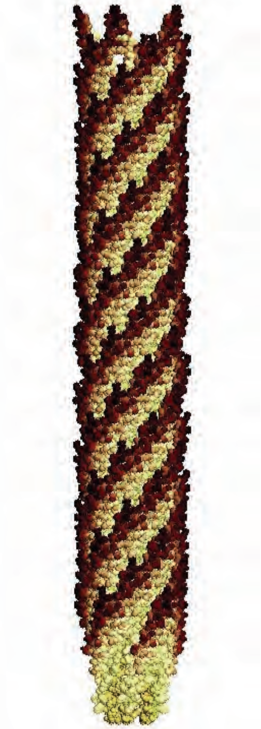
Baehr *et al. Cerebrospinal Fluid Research* 2006

Microtubule elongation



python.rice.edu

Ff f1 bacteriophage



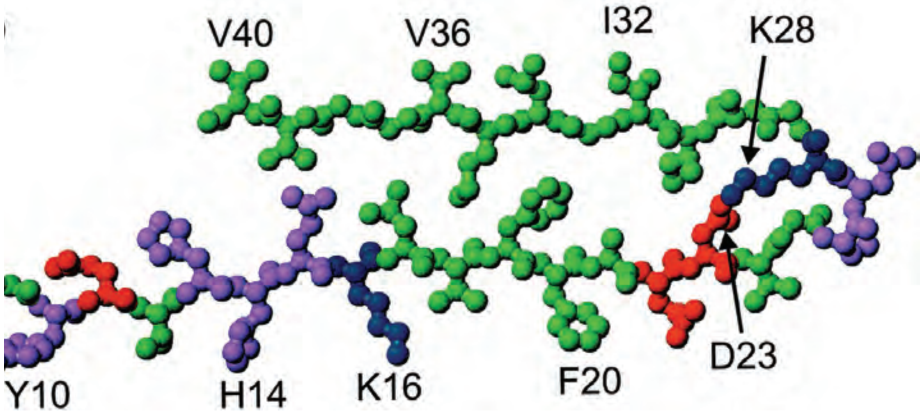
Pdb virus.wisconsin.edu

Forces in Self-Assembled Nanofibers

- While hydrophobic confinement anchors the fiber structure
- Electrostatic interactions are important for the finer structural elements such as quaternary structure and chirality

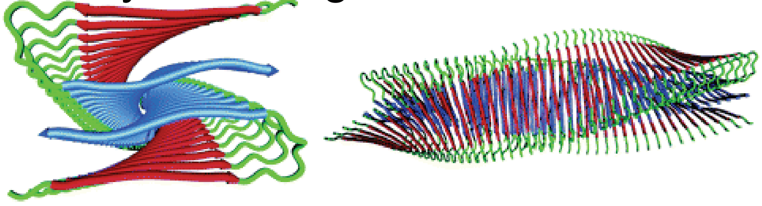
z-type amyloid fibril

Kohlstedt et al, *Biophys. J.* 94 (2008)



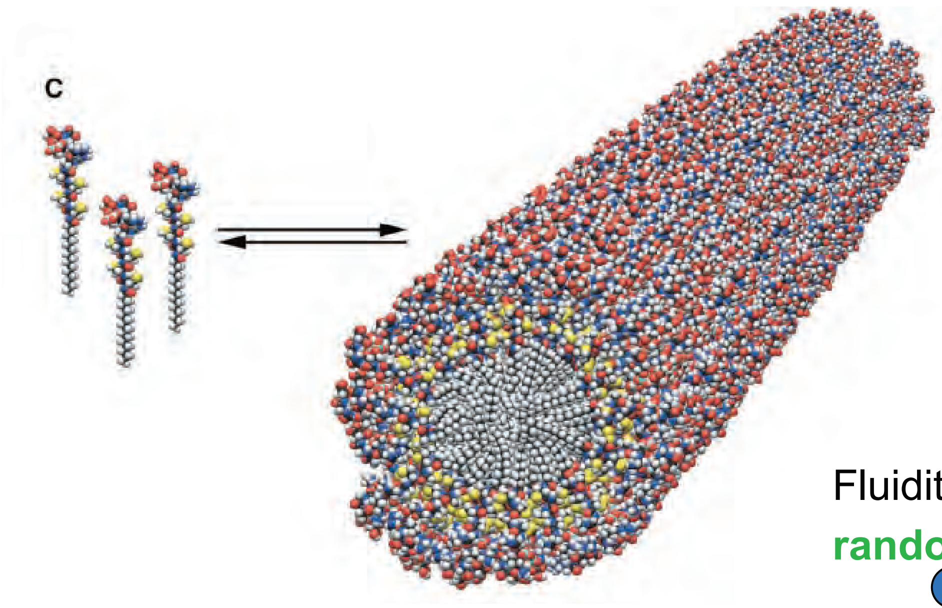
Petkova A. T. et.al. *PNAS* 2002;99:16742

Can helical twist be controlled by salt bridge formations?



Tycko, *Biochemistry* **2006,** 45, 498-512.

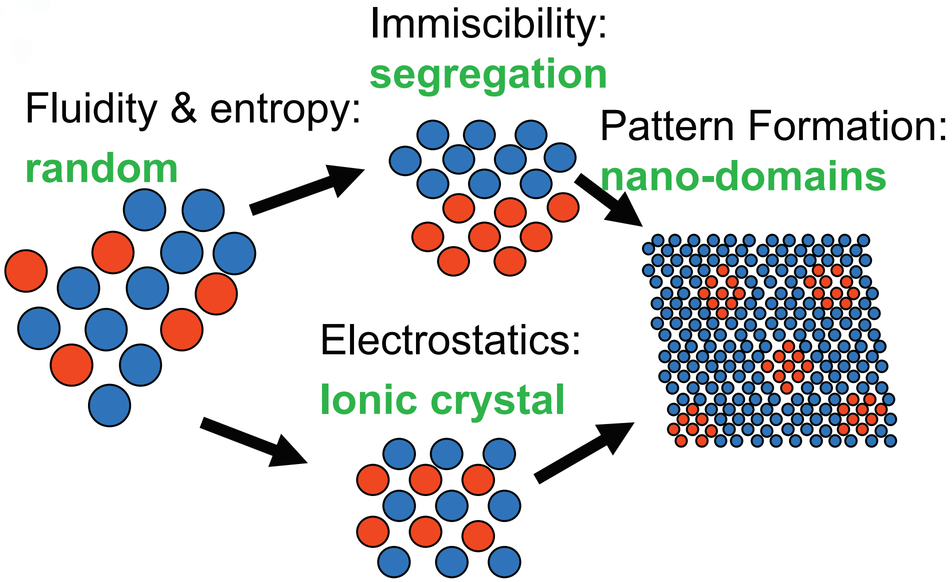
Self-Assembled Peptide Amphiphiles



Hartgerink, Stupp, et al. *Science* 2001

Lateral heterogeneities are possible due to charge interactions

- Surface patterning due to competition of short and long range forces such as steric/van der Waals and Electrostatics


Fluidity & entropy: **random**

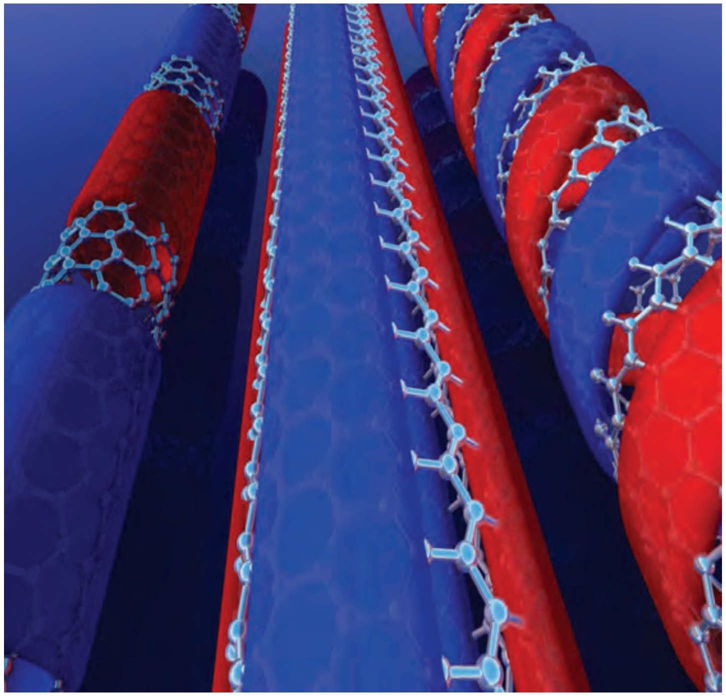
Immiscibility: **segregation**

Electrostatics: **Ionic crystal**

Pattern Formation: **nano-domains**

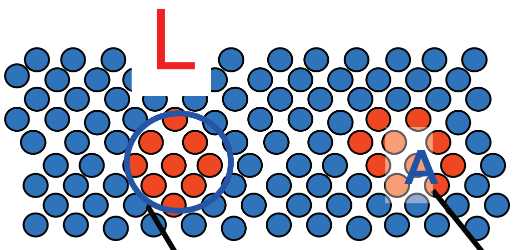
Lamellar Patterning of Charged Nanofibers

- One-dimensional case: lamellar domains on fiber surface
  - Three possible periodic phases: stacked rings, vertically striped, and helical
- Examples:
  - DNA wrapped carbon nanotubes
  - Filamentous viruses
  - Actin filaments
  - Peptide amphiphile fibers



KL Kohlstedt, et al *Soft Matter* 2009

Model: Free energy of a unit cell



$$\frac{F}{N_{cell}} = \frac{1}{N_{cell}}\left(s_1 \gamma L + s_2 \frac{\sigma^2 A^2}{\varepsilon L}\right)$$

$N_{cell} >> 1$

Two competing length scales

$L_0 = \sqrt{\frac{\varepsilon \gamma}{\sigma^2}}$ Pattern size that minimizes F

- s_1 and s_2 are geometrical parameters
  - ☐ s_1 = actual interface / characteristic length
  - ☐ s_2 = screened electrostatic potential over entire surface

κ^{-1} Yukawa-type screening length

N_{cell} = # of charges in cell

F = free energy

A = area of domain

L = unit length

γ = line tension

σ = charge density

ε = dielectric constant

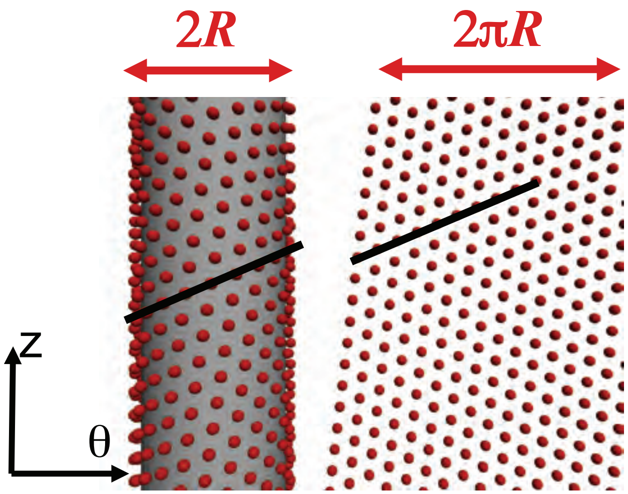
Screened Coulomb interactions on a cylinder

Potential independent of pattern!

$$V(z,\theta,R) = \frac{e^{-\kappa d}}{d}$$

$$d = \sqrt{z^2 + 4R^2 \sin^2\left(\frac{\theta}{2}\right)}$$

$$\longrightarrow$$



Full Coulomb potential
on cylinder (Fourier space)

$$\hat{V}\left(\vec{Q}\right) = 4\pi R\, I_m\left(R\sqrt{\kappa^2 + \left|\vec{Q}\right|^2}\right) K_m\left(R\sqrt{\kappa^2 + \left|\vec{Q}\right|^2}\right)$$

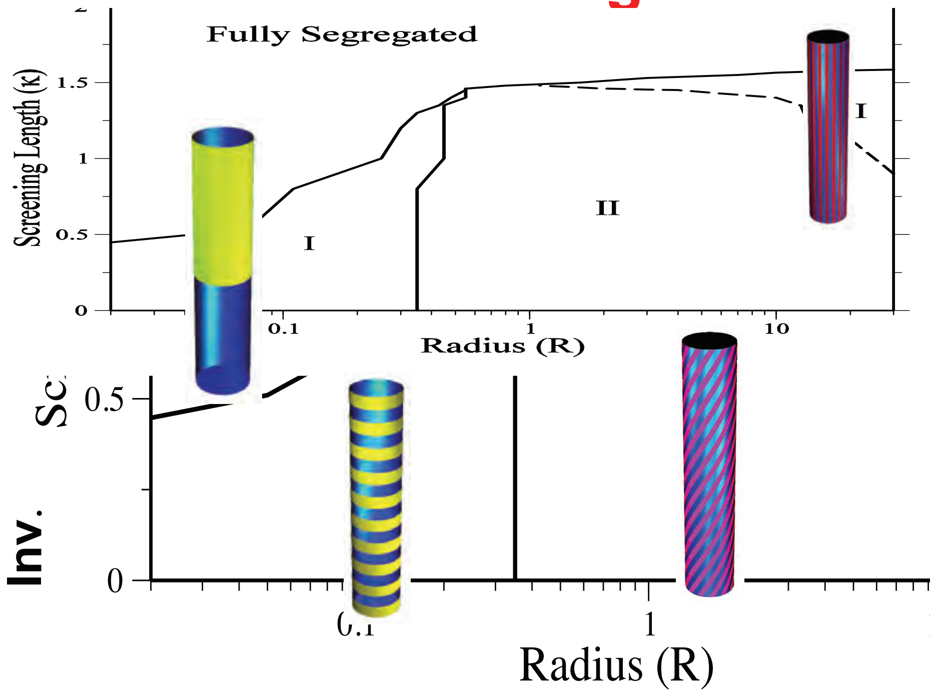
Large-R
Asymptotic Expansion

$$\hat{V}\left(\vec{Q}\right) \sim \frac{2\pi}{\sqrt{\left|\vec{Q}\right|^2 + \kappa^2}} - \frac{\pi}{4} \frac{\left(4\left|\vec{Q}\right|^2 - 5Q_z^2 - \kappa^2\right)\left(Q_z^2 + \kappa^2\right)}{\left(\left|\vec{Q}\right|^2 + \kappa^2\right)^{\frac{7}{2}}} \frac{1}{R^2} + O\left[\frac{1}{R^4}\right]$$

Lamellar patterns on cylinders: Chiral phase

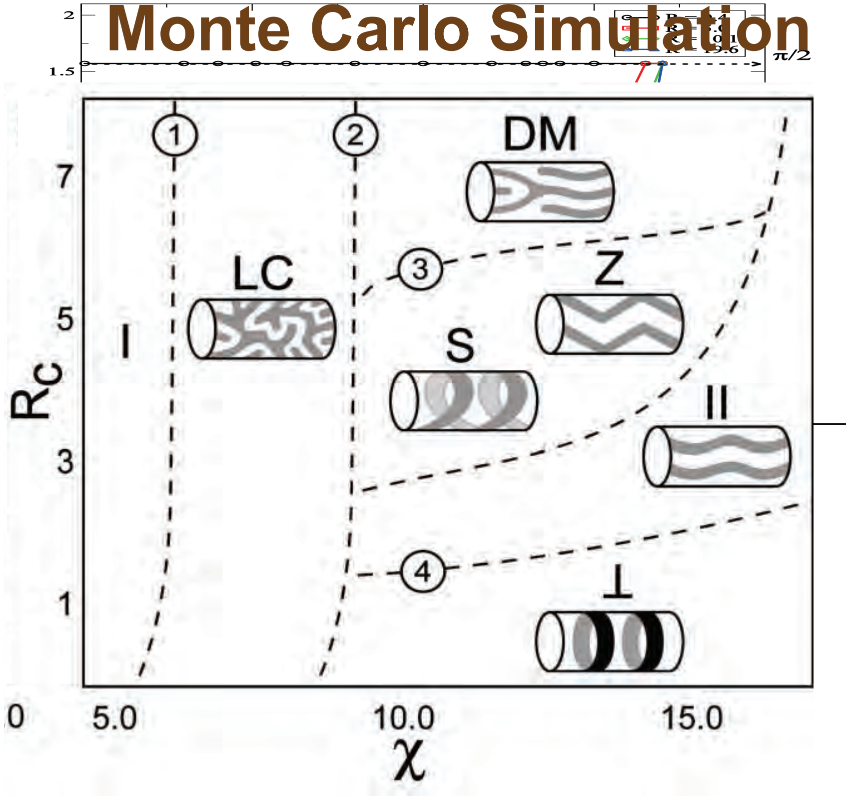
- **Phase diagram** ⟶ **Numerical Methods**
- **Features** κ^T θ^* ⟶ **Analytical Methods**

Phase Diagram



KL Kohlstedt, et al - Phys Rev Lett, 2007

Monte Carlo Simulation



YS Velichko, MO de la Cruz - Phys Rev E, 2005

Not breaking chiral symmetry with Electrostatics

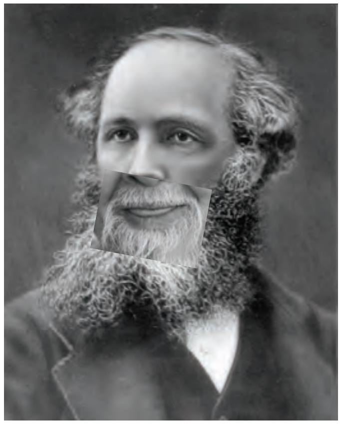
- Maxwell's equation are indeed still invariant under charge conjugation, parity, and time inversion!

$$\nabla \cdot \mathbf{D} = 4\pi \rho_f$$

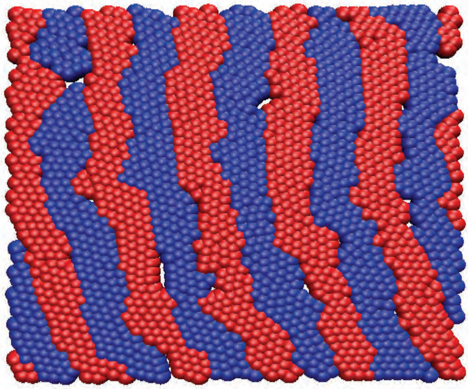
$$\nabla \cdot \mathbf{B} = 0$$

$$\nabla \times \mathbf{E} = -\frac{1}{c}\frac{\partial \mathbf{B}}{\partial t}$$

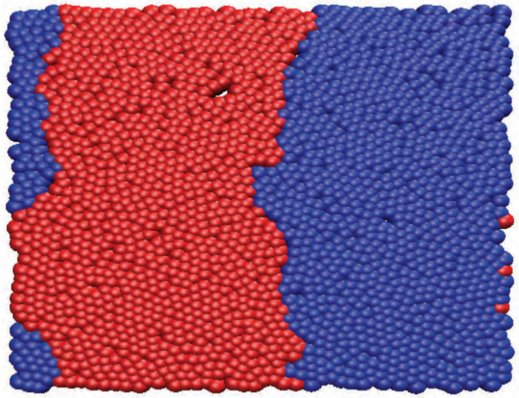
$$\nabla \times \mathbf{H} = \frac{1}{c}\frac{\partial \mathbf{D}}{\partial t} + \frac{4\pi}{c}\mathbf{J}_f$$

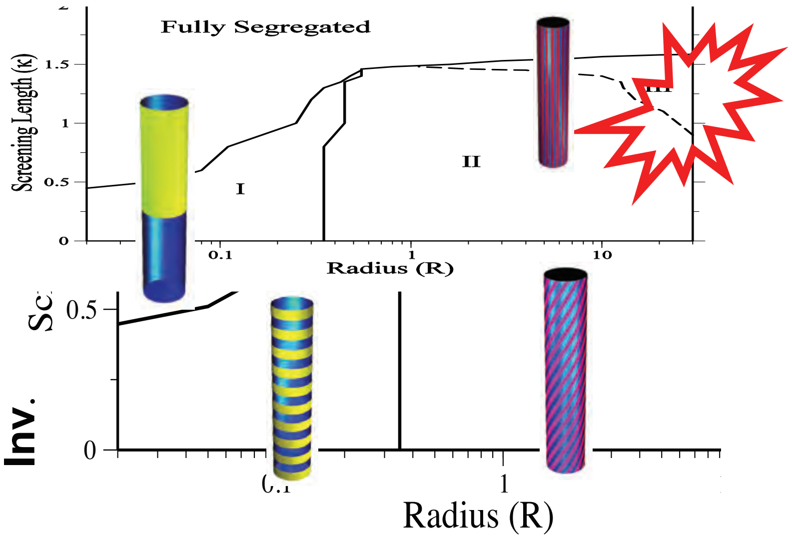


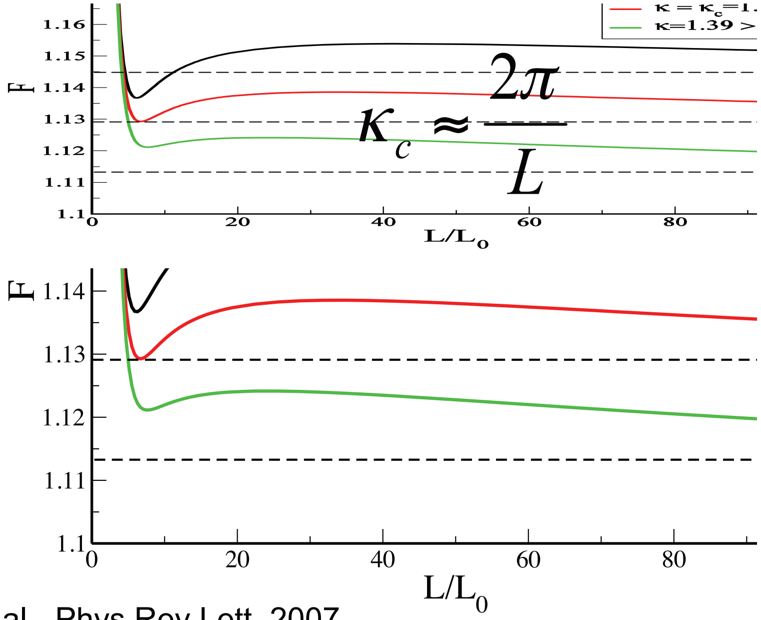
Salt-induced Melting Transition



[S. Loverde et al., *JCP*]







$$\kappa_c \approx \frac{2\pi}{L}$$

KL Kohlstedt, et al - Phys Rev Lett, 2007

Fixed pattern separation

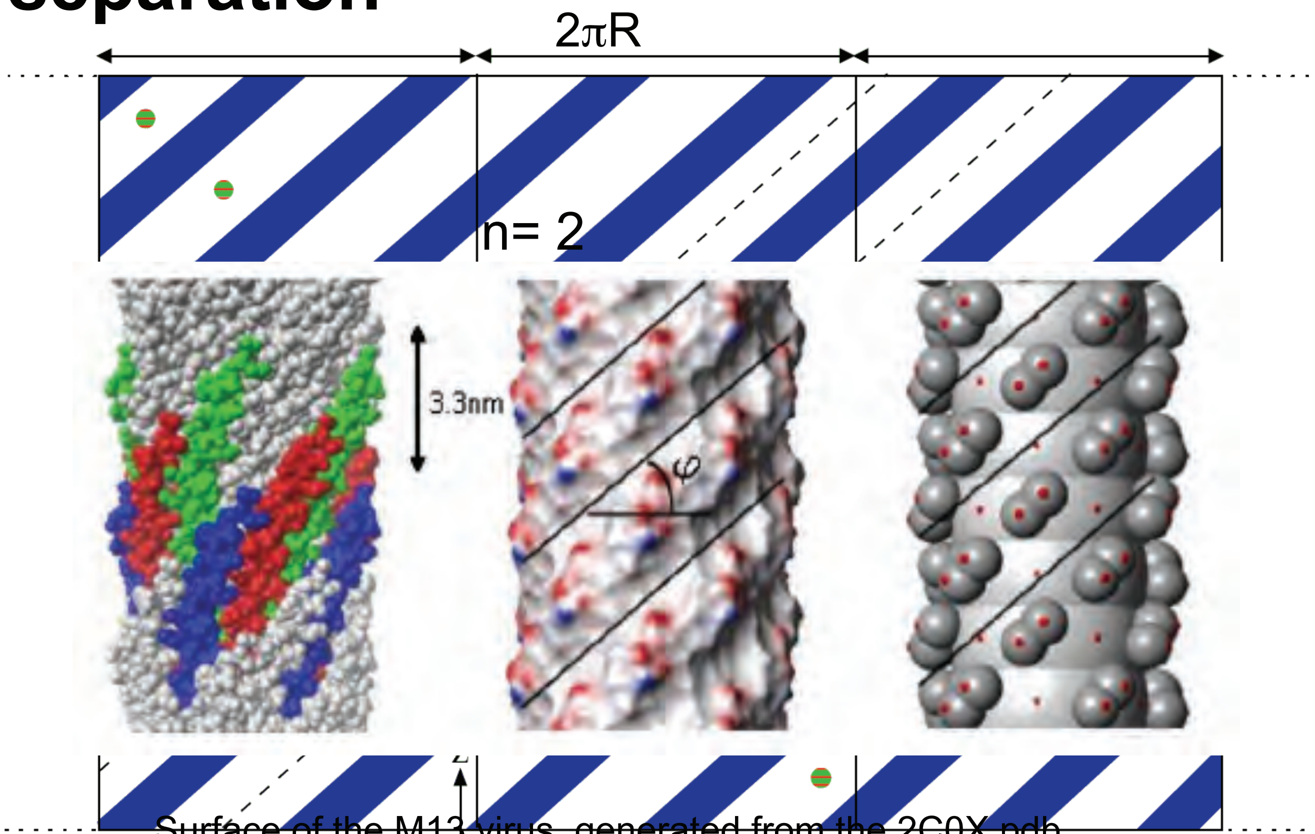
- Focus on behavior of electrostatics through fixed charge distance
- Absorbed charged molecules on surface of cylinder

n: The number of lamellae per pitch

θ: The pitch angle

L: the charge separation distance

R: The cylinder radius

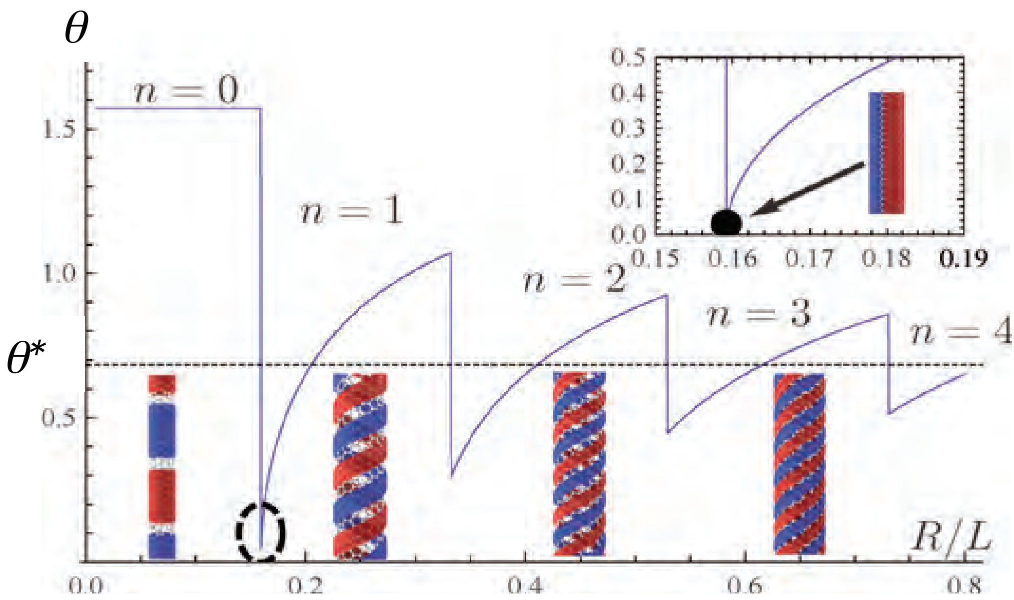


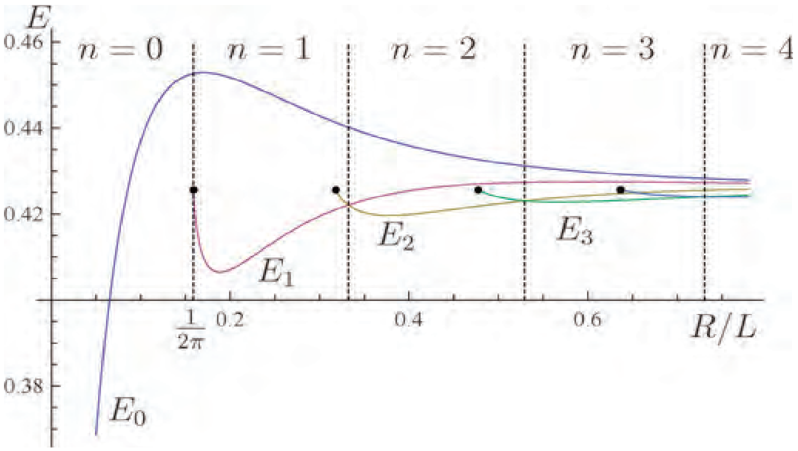
Surface of the M13 virus, generated from the 2C0X.pdb capsid protein structure [Tombolato et al. PRL **96,** 258302 (2006)]

Pitch angle is controlled by number of helical wrappings

The relation $2\pi R \cos \theta = n L$ constrains the free energy.

The pitch angle tends towards the analytical predictions θ^* as the fiber radii increases or R >> L





The free energy as a function of the radius shows how the interlaced minima prefer helical arrangements at n > 0.

$$\theta^* = \cos^{-1}\left(\sqrt{3/5}\right) \approx 38^{o}$$

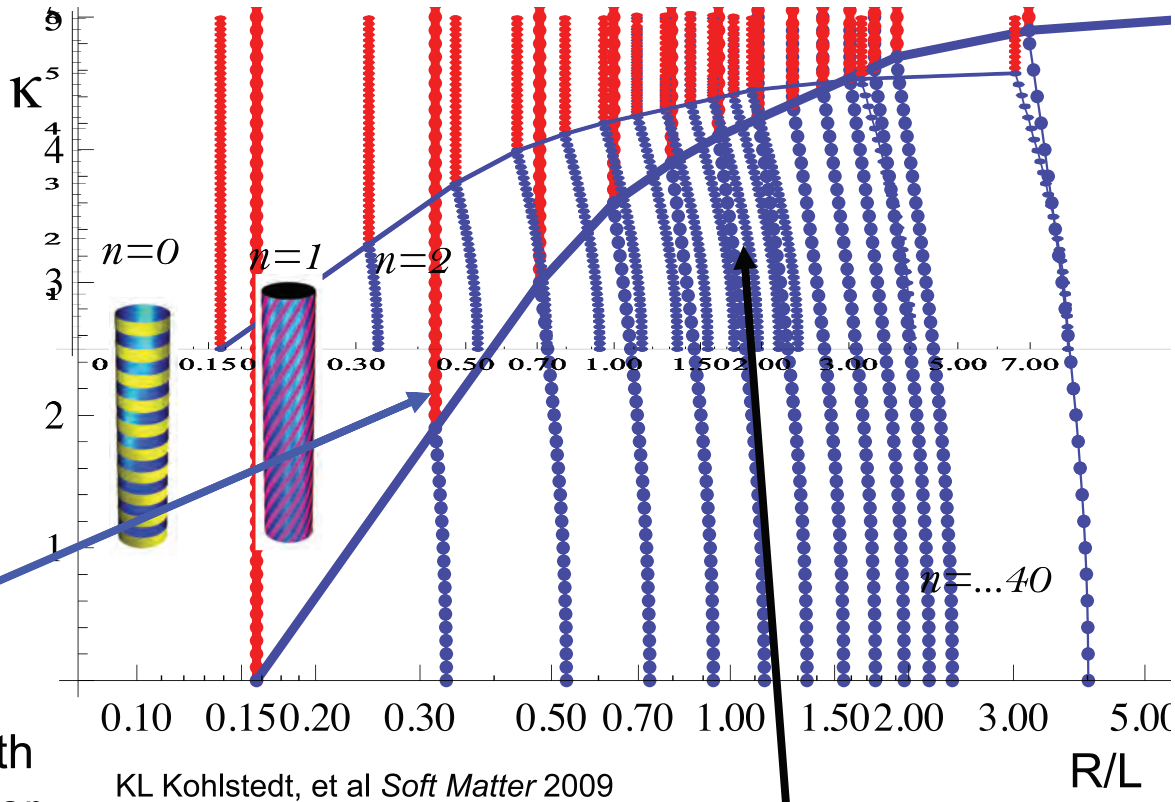
Fine Structure Phase Diagram

Features:

Understand the structure inside the chiral phase

Separate types of wrappings i.e. ds-DNA vs ss-DNA

“Chiral envelope”



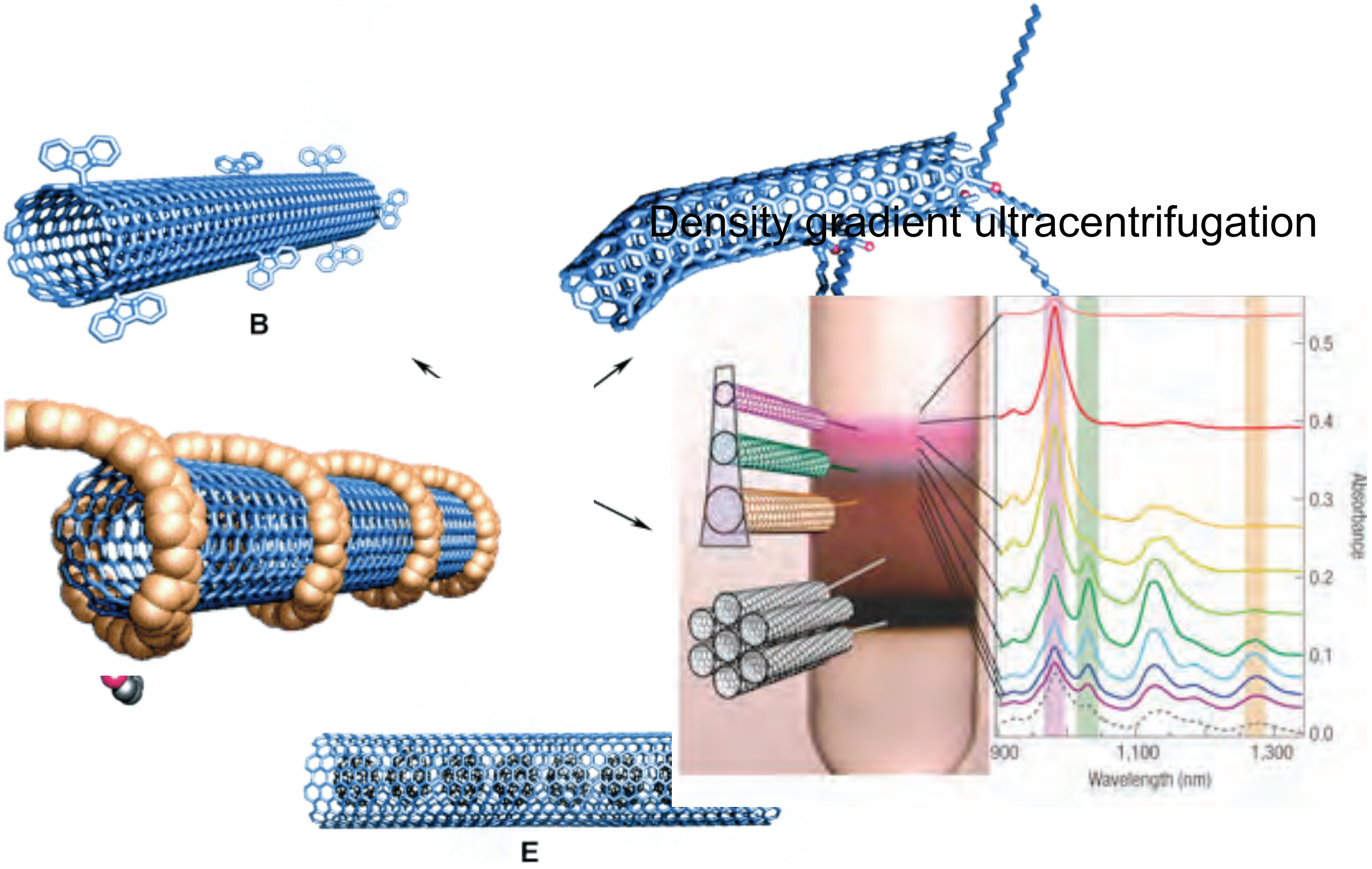
KL Kohlstedt, et al *Soft Matter* 2009

An increasing screening length leads to smaller pitch angles or

κ↑ leads to θ↓

Origin of vertical stripes or Phase III

Applications: Carbon Nanotubes Hybridized ss-DNA

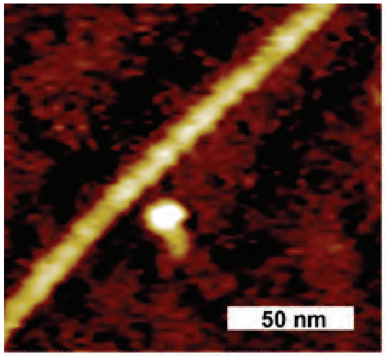


Density gradient ultracentrifugation

Hersam, Nature Nanotechnology 3, (2008)

Predictions: Carbon Nanotubes Hybridized ss-DNA

- ss-DNA with 120 bp has a measured pitch of ~14nm

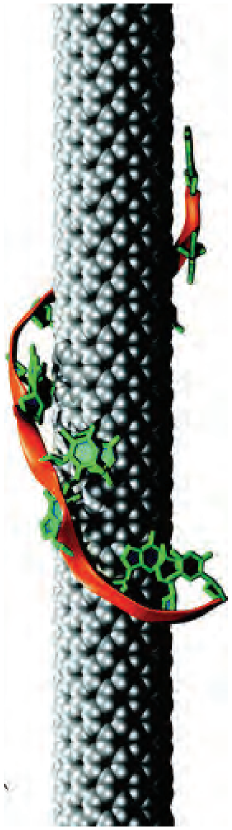


Campbell J. Am. Chem. Soc.,
130 (32), 2008.

- Our model is consistent with P≈15nm

- Atomistic simulation reveals different mechanism with much smaller pitches P<10nm

- Electrostatics play vital role in backbone conformations



Klein, Nano Lett., **8** (1), 2008

Predictions: M13 fibrous virus

- Five-fold surface symmetry: Fibrillar virus

Input into our model:

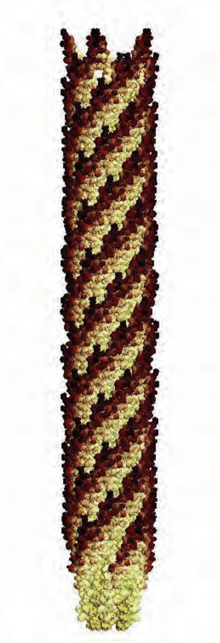
$R=3.3$ nm

$L=3.2$ nm

The model predicts:

$n=5$

$\theta=38.8^{o}$



Pdb virus.wisconsin.edu

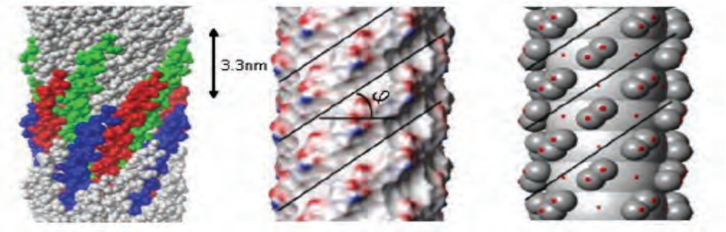
Nanotube measurements from X-Ray scattering

$R=3.3$ nm

$L=3.23$ nm

$n=5$

$\theta=36.7^{o}$

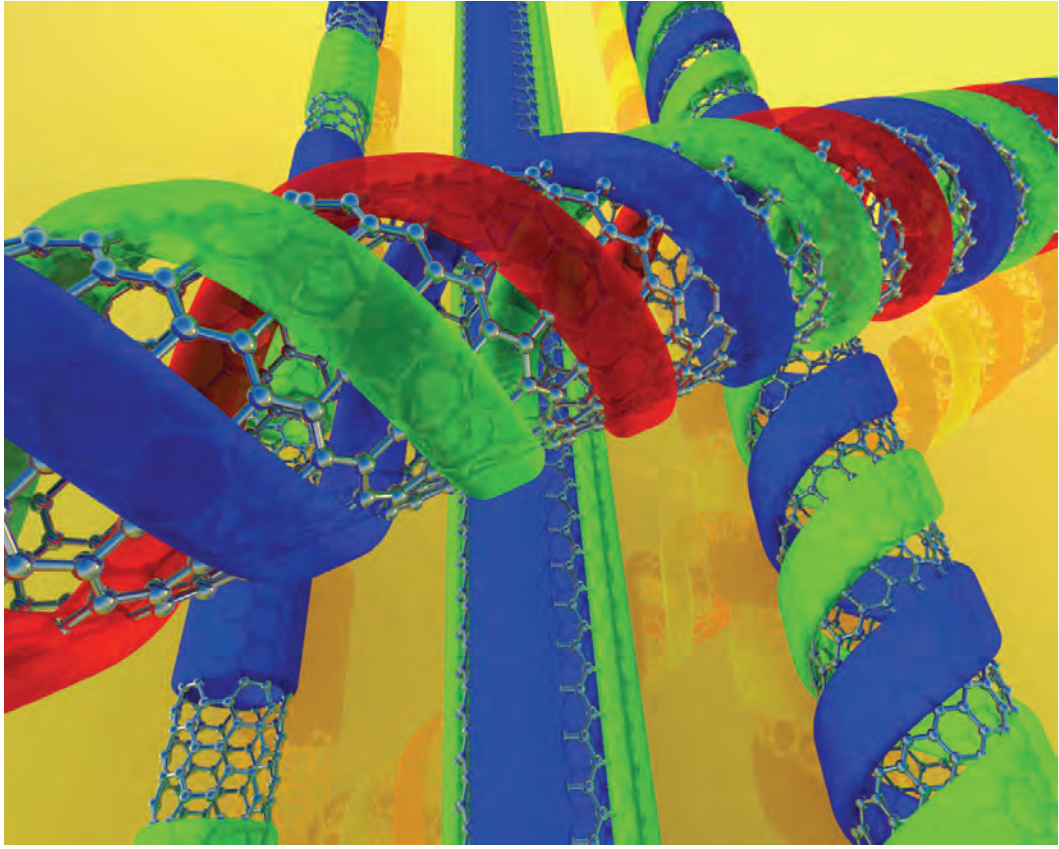


Tombolato et al. PRL **96,** 258302 (2006)

Using just electrostatic interactions one can predict basic surface properties!

A Closer Look at the Chiral Phase

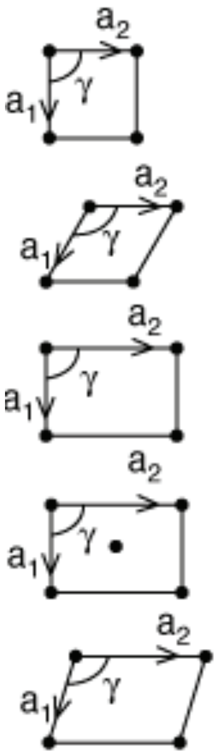
- How does the pitch angle change as the strength of the electrostatics and size of filament changes?



G Vernizzi, KL Kohlstedt, MO de la Cruz (cover article) Soft Matter 2009

Other types of charge surfaces

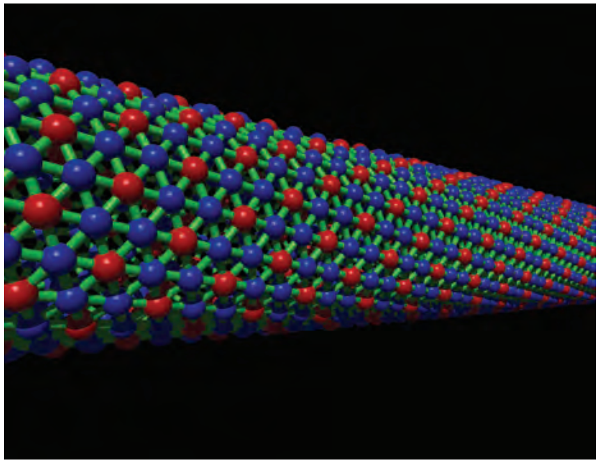
- Patterns on 2-D Bravais lattices

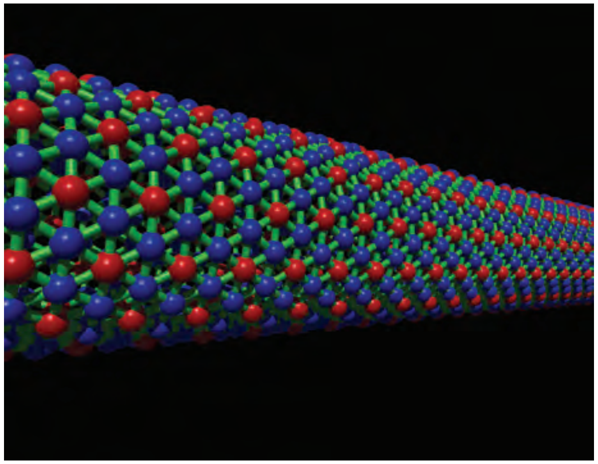


- Square
- Hexagonal
- Rectangular
- Centered Rectangular
- Oblique

Which one minimizes the electrostatic energy?

Chiral-
Hexagonal

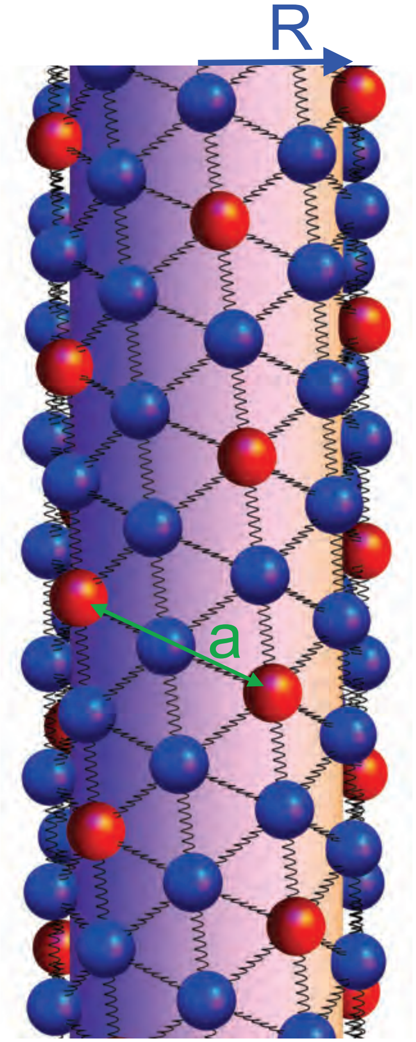




Achiral-
Hexagonal

Model for Curved Ionic Lattice

- **Description of the Model**
- Coulomb and elastic interactions on the clyinder: R(radius), a(lattice constant)
  - We use analytical and numerical methods to find minimum energy structures for different lattice configurations
- The model naturally interpolates between planar/cylindrical geometry and short/long range interactions



Kohlstedt et al, *Phys. Rev. E*, 2009 submission

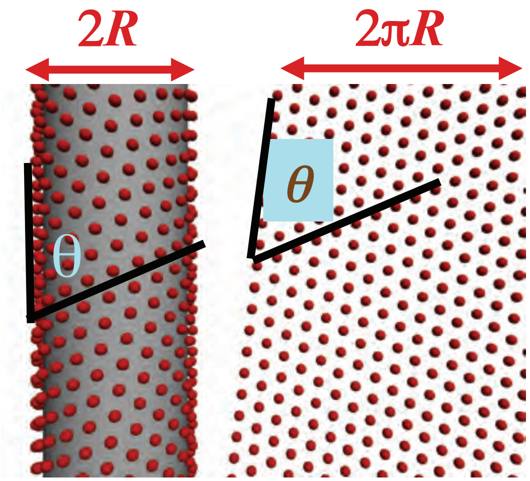
Ionic lattice on a cylinder

Mapping from cylinder to plane

$$V(z,\theta) = \frac{e^{-\kappa d}}{d}$$

$$d = \sqrt{z^2 + 4R^2 \sin^2\left(\frac{\theta}{2}\right)}$$

$$\longrightarrow$$



Full Coulomb potential
on cylinder (Ewald Sum)

$$E_c = \frac{1}{A_c}\sum_{Q} F\left(\vec{Q}, R\right)\left[\left(\sum_i \cos\left(\vec{b}_i.\vec{Q}\right)q_i\right)^2 + \left(\sum_j \sin\left(\vec{b}_j.\vec{Q}\right)q_j\right)^2\right]$$

$$-\frac{1}{\sqrt{\pi}}\sum_i q_i^2\eta + \frac{1}{\sqrt{\pi}}\sum_{i,j,\Lambda} q_i q_j \int_{\eta}^{\infty} dt\, e^{-t^2 D_{ij}^2}$$

$$F\left(\vec{Q}, R\right) = \pi R \int_0^1 dt \frac{e^{-at - \vec{Q}.\hat{z}/4\eta^2 t}}{t} I_\nu(at)$$

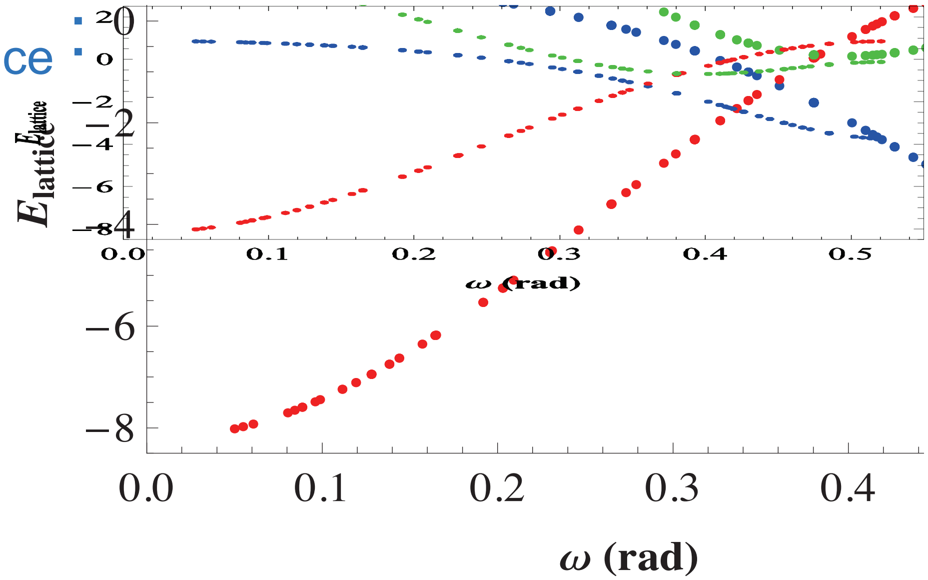
$a = 2\eta^2 R^2$; $q_{i,j}$ ≡ **charges in the cell;**

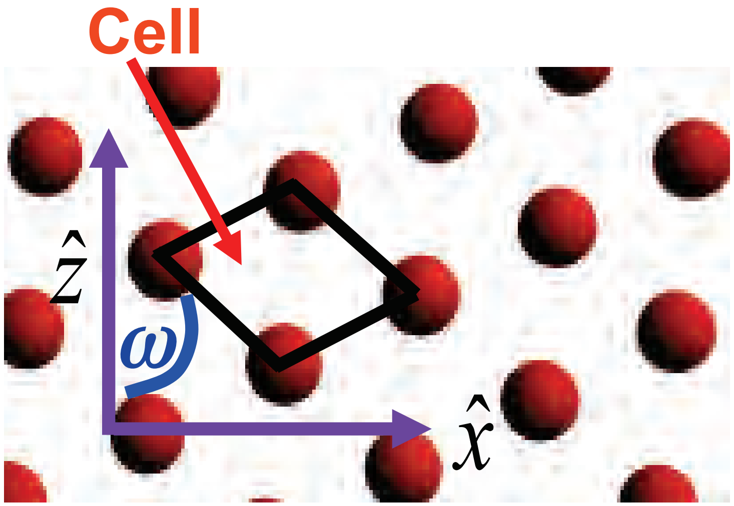
$b_{i,j}$ ≡ **basis vectors of charges in the cell;**

A_c ≡ **Area of cell;** D_{ij} ≡ **charge distance**

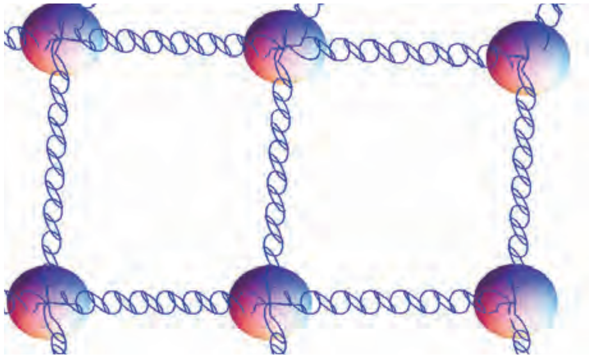
Ionic lattice prefers to be symmetric

- Competing terms in $E_{lattice}$:
  - Electrostatic Term





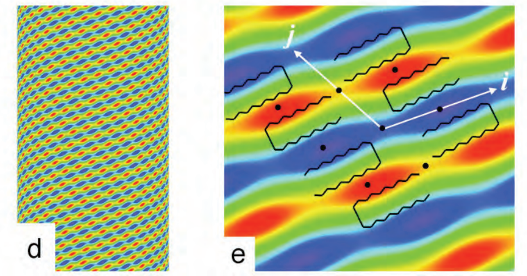
  - Elastic Term

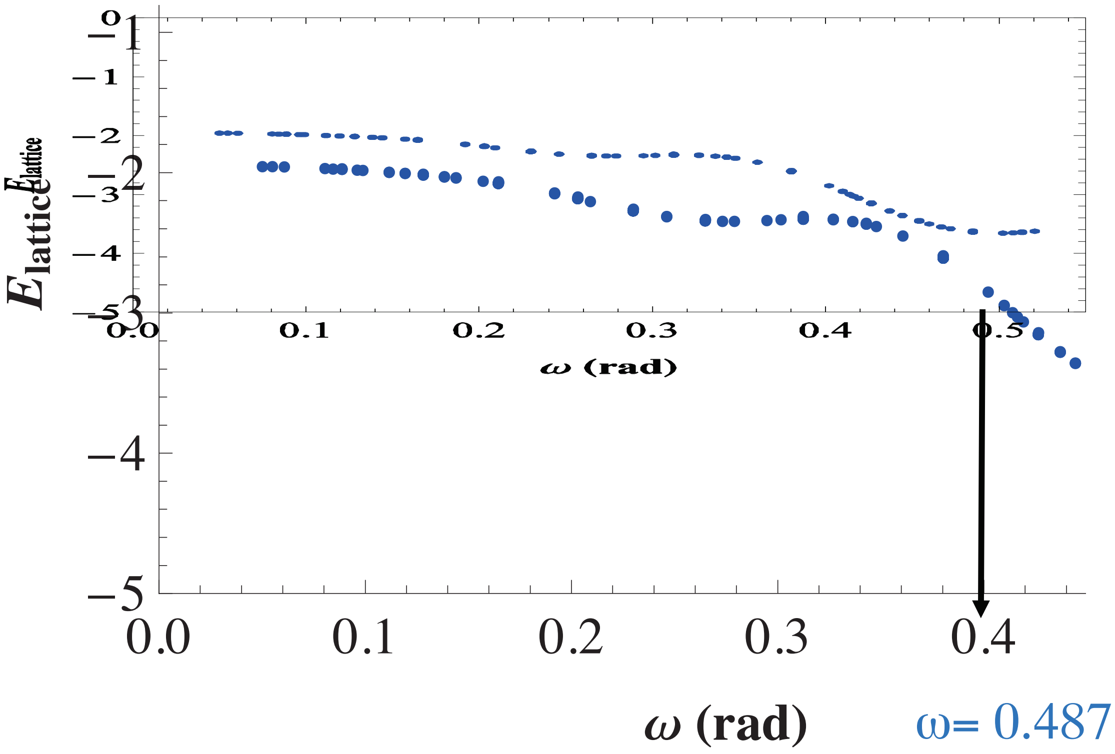


- Calculate Energy per cell
  - Minimize over ω

Chirality dependent on lattice structure

- Ionic ratio of 3:1 breaks triangular lattice symmetry
- Transitions from achiral step lattice to chiral lattice with angle $\omega = 0.487$



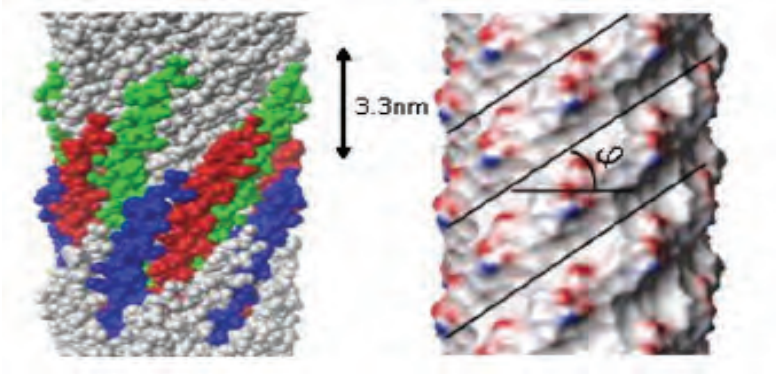


$\omega = 0.487$

Valery, Celine et al. (2003) Proc. Natl. Acad. Sci. USA 100, 10258-10262

Symmetric patterns are an idealized representation

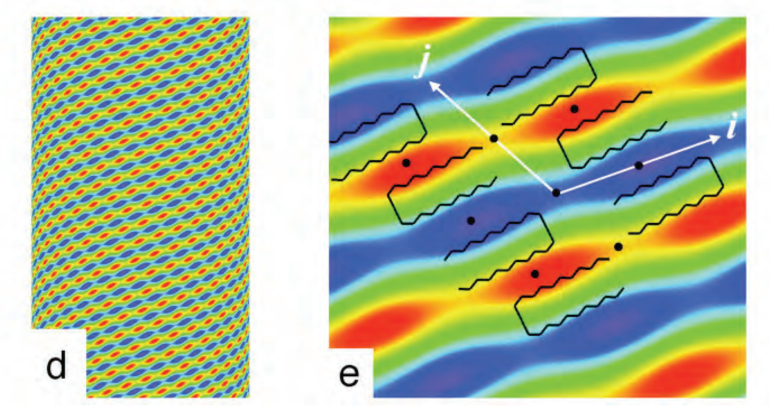
- Many assembled fibers that show regular surface patterns do *not* exactly have regular domains



Tombolato et al. PRL **96,** 258302 (2006)

Ex. Protein units that cover a *fd*-phage virion have a 5-fold screw axis that wraps around the DNA are stretched along the axis of the fiber shown by NMR and diffraction studies due to side chain interactions

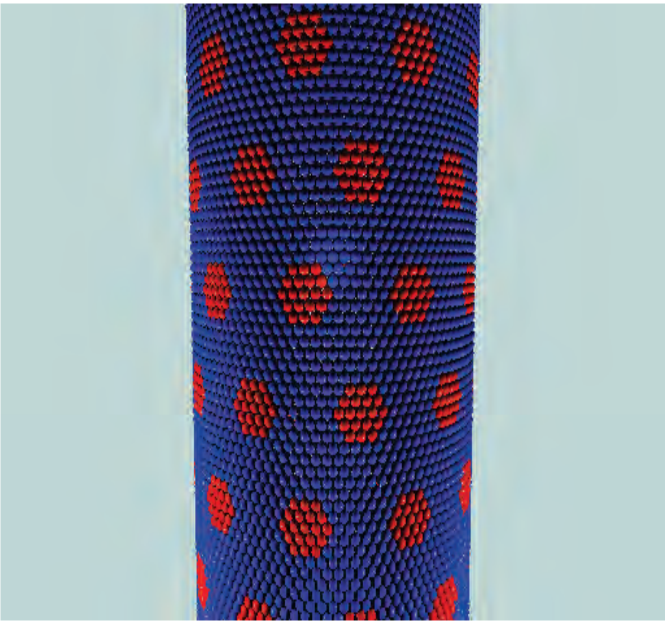
Ex. β-sheet forming octapeptides can assemble into nanotubes. Diffraction studies show an elliptical surface charge density between the hydrogen bonding peptides as they decorate the wall of the nanotube.



Valery, C., et al. (2003) *PNAS.* **100**, 10258-10262

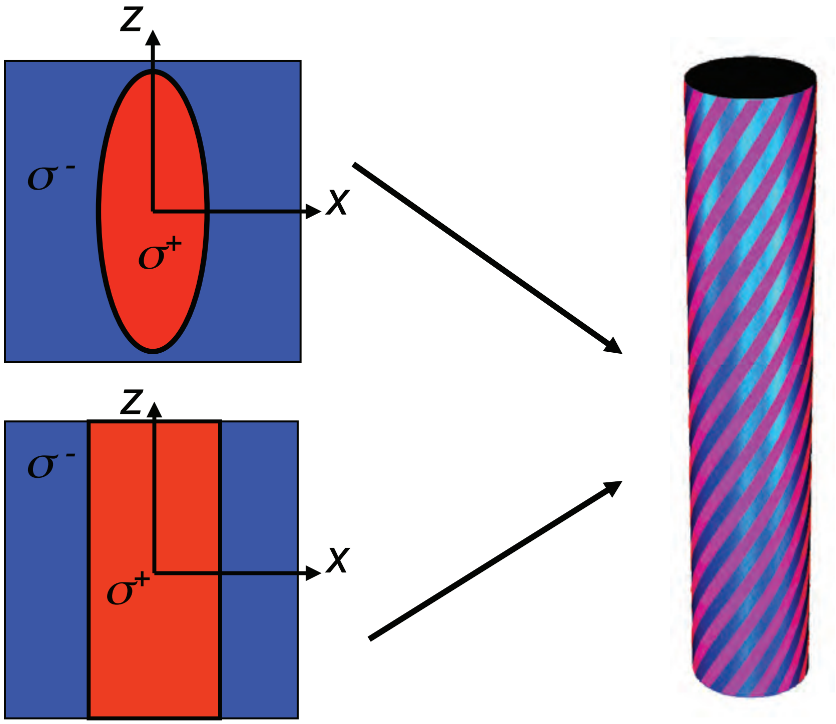
Asymmetric charged patterns leads to chiral symmetry: elliptical pattern study

- Circular patterns tiled around cylinders do not break chiral symmetry



- Hexagonally symmetric around a cylinder

- Elliptical patterns tiled around a cylinder have helical wrappings similar to lamellar patterns



KL Kohlstedt, et al - Phys Rev Lett, 2007

Conclusions

- Electrostatic interactions on a cylinder lead to helical (chiral) configurations for sufficiently large radii
  - A dominant chiral angle appears for ~ 1/r purely long-range interactions
  - Helical patterns melt via first-order phase transition
- Provides a mechanism to explain ubiquitous chiral symmetry seen in many biological systems
  - Phase diagram can predict experimentally measured structures
- Two-dimensional patterns are chiral when electrostatic interactions compete with neighboring elastic interactions
  - Discrete ionic lattice shows chiral families
  - Elliptical patterns show helical chiral angle at high eccentricities

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Earlier Work

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Granular Physics; Chaotic Systems

Igor Aranson

Theoretical Condensed Matter

Teresa Head-Gordon

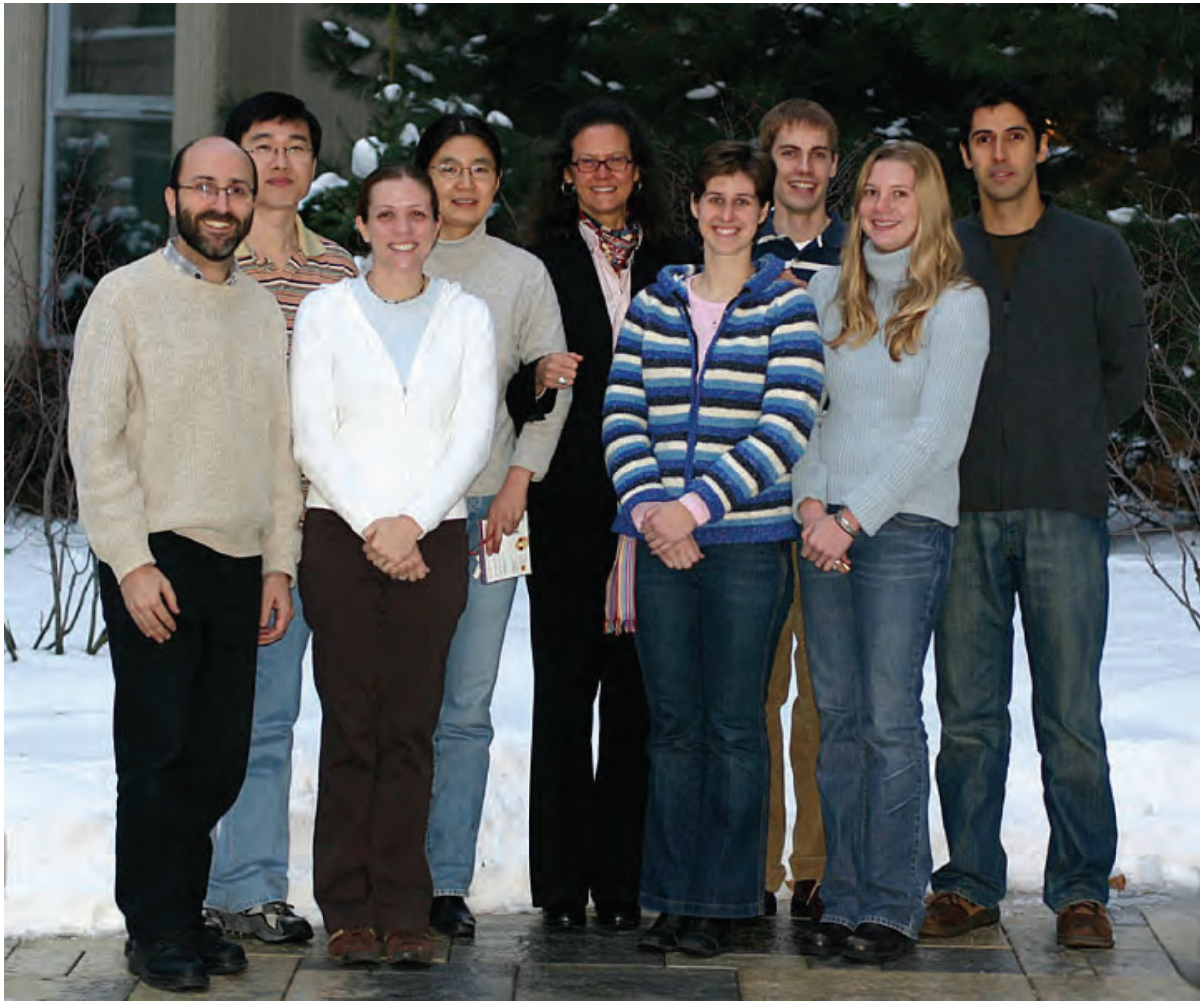
Computational Protein Dynamics;
Structure of Water

Monica Olvera de la Cruz

Statistical Mechanics of Charged
Systems

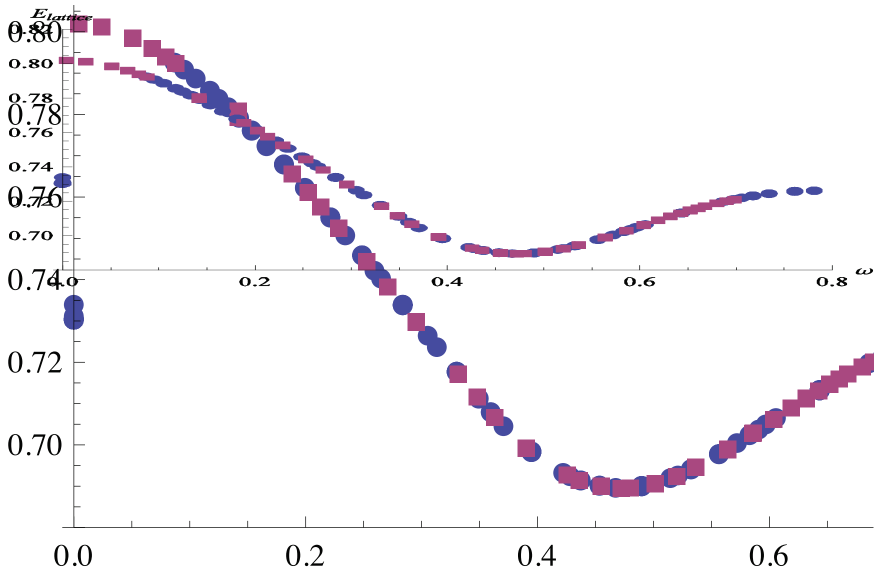
Current Work

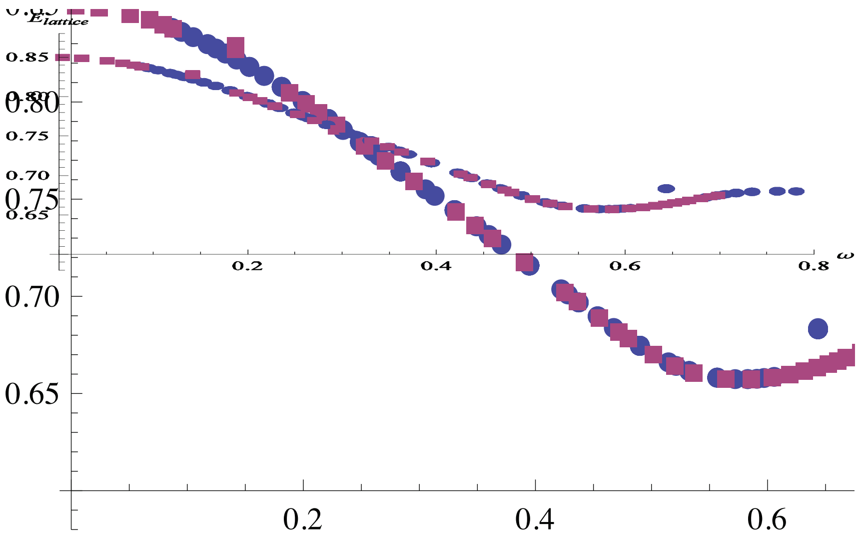
Thank You



Elliptical cell leads to helical phase

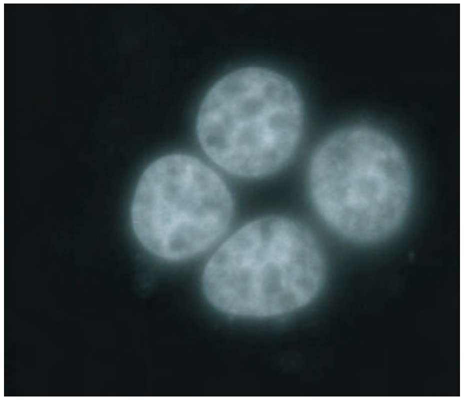
- Elliptical free energy vs pitch angle



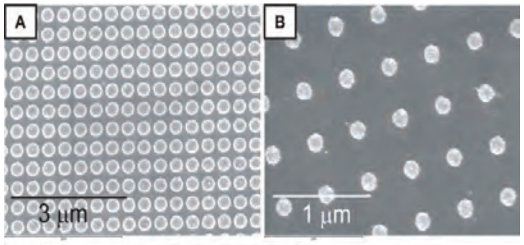


Self-assembled surfaces with segregated domains

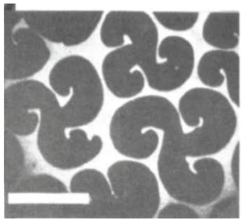
- Crystallography of model membranes reveals condensed domains on the surface
  - There is still much debate on their existence in cells
  - Mechanism is important to understand cell pathways
- Important in creating novel assays- a materials challenge
- Anisotropy leads to interesting domain morphologies
  - Electrostatics can amplify effects



Kemmer *et al. BMC Genomics* 2006 **7**



Odom, et al NSEC Ann. Report 2008

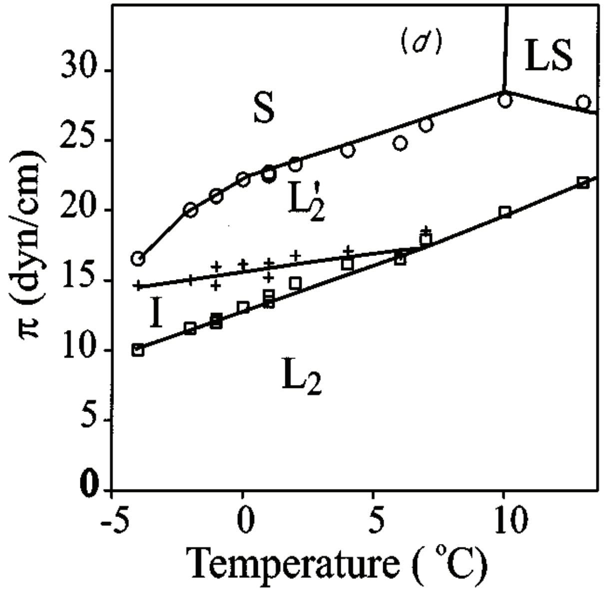


Weis et al, *Nature,* **310** (1984)

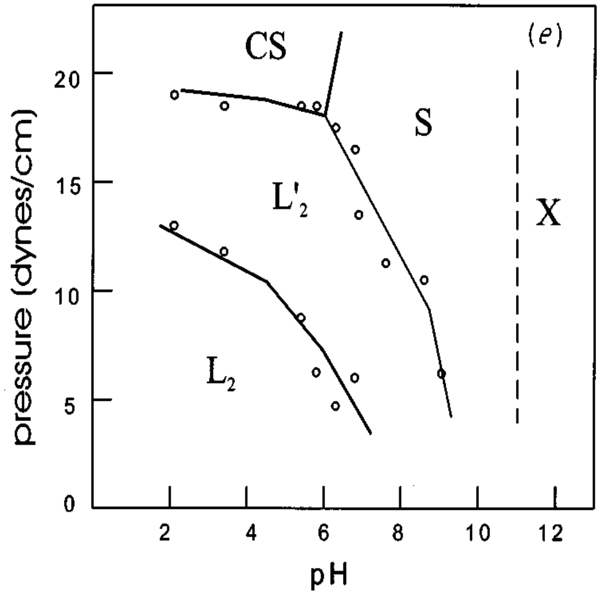
Langmuir Monolayers

Phase diagram of simple fatty acid (C21)

Ca^{2+} ions leads to ordering at lower pressures



Durbin et al, *JCP*, **106** (1997)



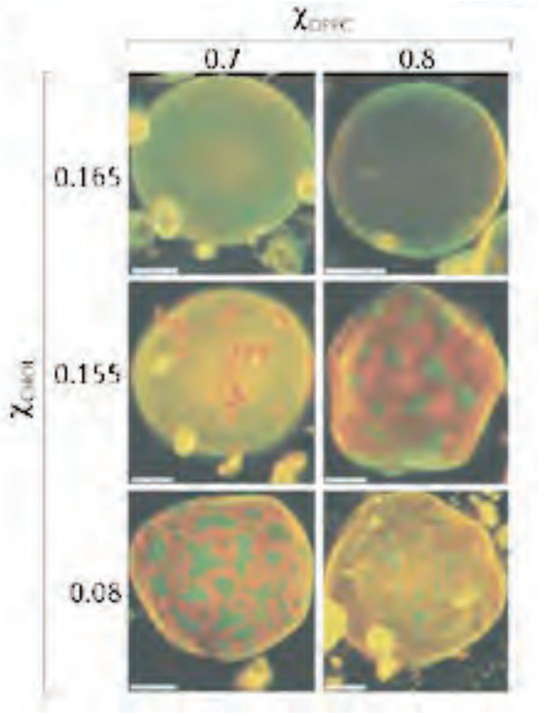
Shih et al, *JCP*, **96** (1992)

-At higher pH the acid head group charges are more exposed leading stronger repulsions

-Ion correlations can further amplify ordering (esp. multivalent Ca^{2+})

Lipid rafts- nanopatterns in biology?

- Lateral heterogeneities of transmembrane proteins are known to occur on cell membranes
- The ordering and density of the surrounding lipids is still not known
  - Probing techniques have not sufficiently advanced to elucidate the lateral arrangements
- A vigorous computational and theoretical effort has incorporated many of the complexities in the multi-component cell wall

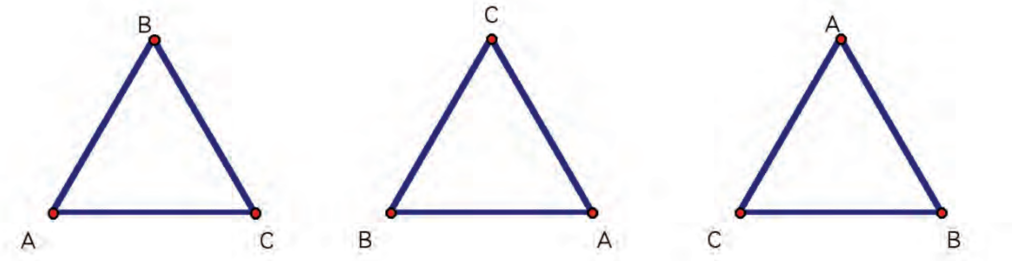


Hancock *Nature Reviews* **7**, (2006)

Group theory definition of chiral object

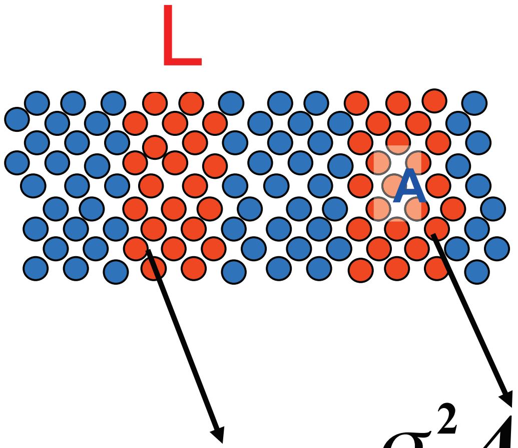
- Group theory provides a useful definition of a chiral object
  - A object is chiral iff it has no improper rotations
  - An improper rotation is defined as a two-part operation that includes a proper rotation Z_k and a refection across a plane perpendicular to the axis of the proper rotation
  - The group is designated by S_k where *k* are the number of rotations

Z_3 Group



3 Proper Rotations

Free Energy of a unit cell: lamellar case



$$F = s_1 \gamma L + s_2 \frac{\sigma^2 A^2}{\varepsilon L}$$

F = free energy per cell

A = area of domain

L = unit length

γ = line tension

σ = charge density

ε = dielectric constant

- s_1 and s_2 for lamellar case
  - $s_1 = 2$
  - $s_2 = \frac{1}{2}\sum_{\Lambda}\int_{cell} d\xi \int_{cell} d\eta\, \sigma(\xi)\sigma(\Lambda+\eta)V(\Lambda+\eta-\xi)$

Group theory of the phase diagram

- The phase diagram be described the following subgroups

The classification of the symmetry groups on a charged fiber

Subgroups

SO(2) $\oplus$ R (homogenously charged surface)

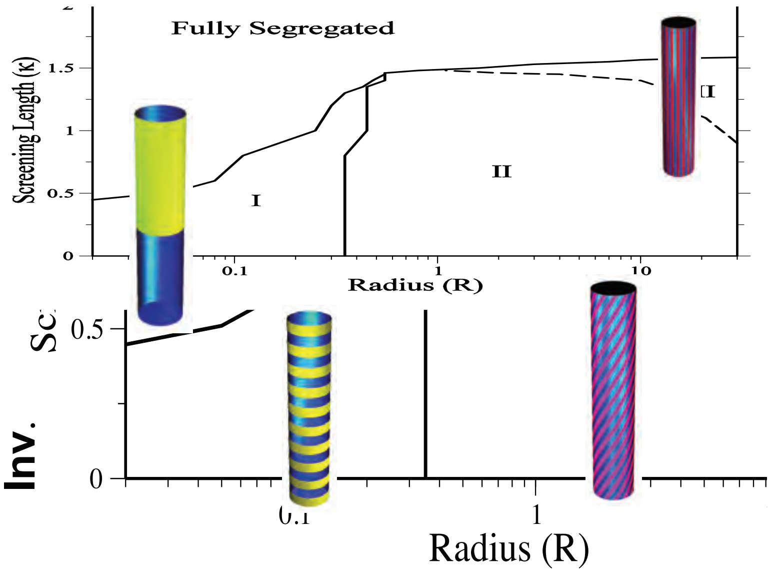
SO(2) (continuous rotational symmetry) **F.S**

SO(2) $\oplus$ Z (continuous rotations translated) **I**

$Z_k \oplus$ R (discrete rotations with translations) **III**

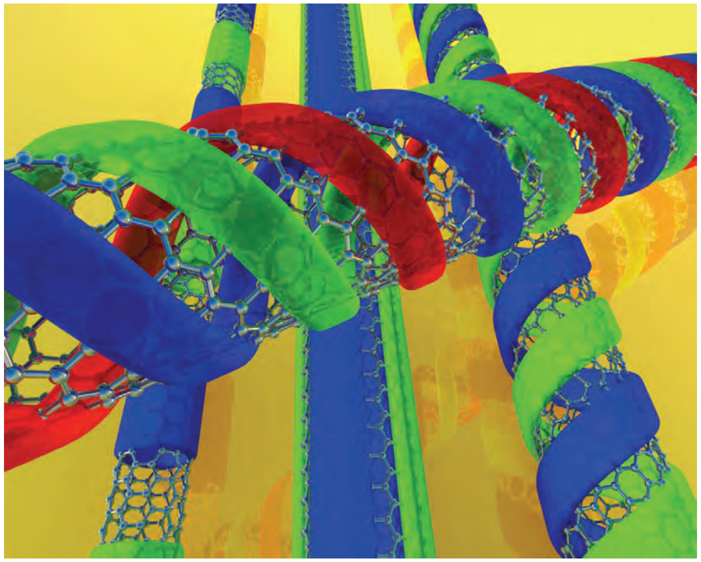
$Z_k \oplus$ L (discrete rotations with 180^o twist) **II**

$Z_k \oplus L_{\pi/k}$ (discrete rotations with π/k twist)

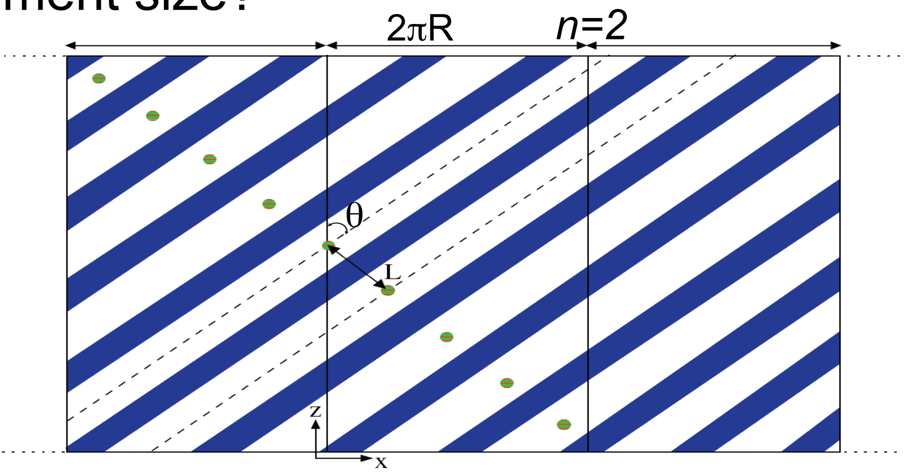


A closer look at the chiral helical phase on charged filaments

- How does the pitch angle of charged helices change as a function of the Coulomb strength and filament size?



G Vernizzi, KL Kohlstedt, MO de la Cruz (cover article) Soft Matter 2009

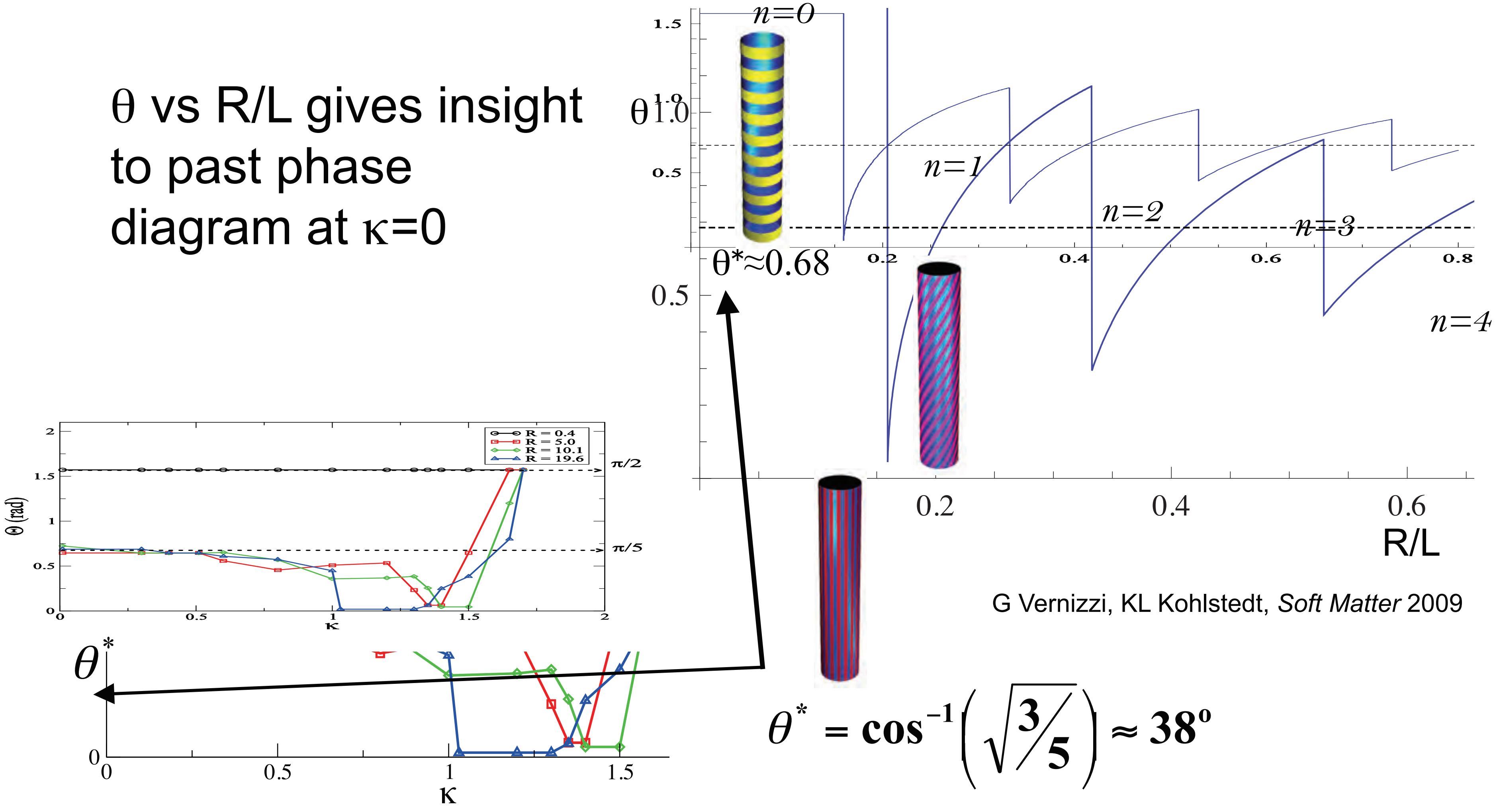


Using a model of any *n* number of charged lamellar stripes with a periodicity *L* wrapped around a cylinder, we show how the helices can be tuned by changing the Coulomb interaction

- The pitch angle is modified by the number of commensurate helices, the pitch goes towards theoretical limit $\theta^* = \cos^{-1}\left(\sqrt{3/5}\right) \approx 38^{\circ}$

Fine structure of lamellar patterns

θ vs R/L gives insight to past phase diagram at κ=0



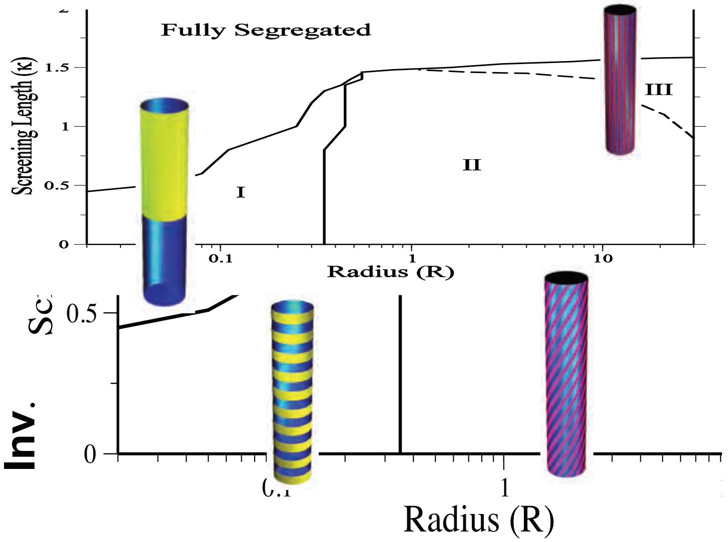
G Vernizzi, KL Kohlstedt, *Soft Matter* 2009

$$\theta^* = \cos^{-1}\left(\sqrt{3/5}\right) \approx 38^{\mathrm{o}}$$

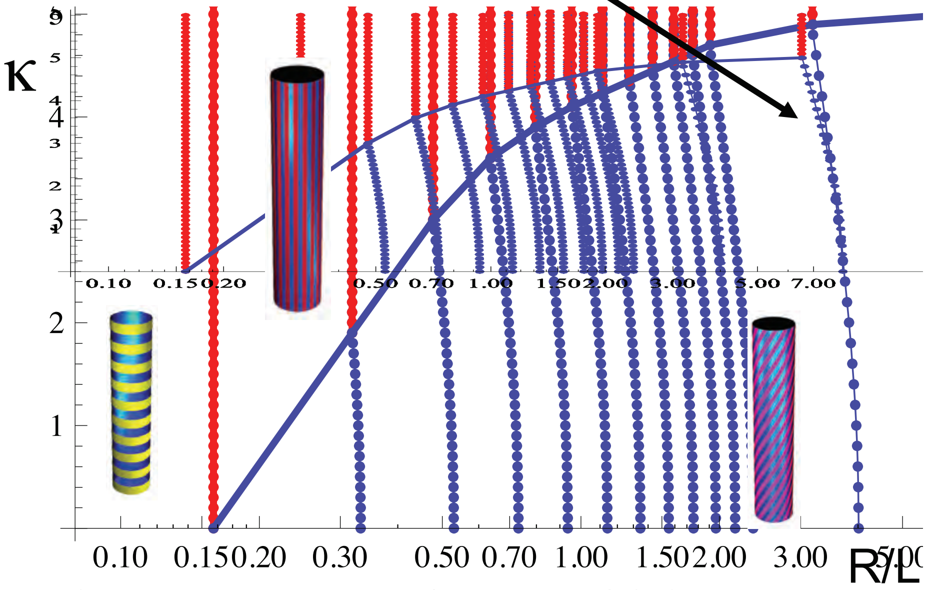
KL Kohlstedt, et al - Phys Rev Lett, 2007

Comparing Phase Diagrams

- Chiral phase merges into striped phase by bounding line
- From expansion $R >> L$ $\kappa_0 L = 2\left(\frac{2}{3}\right)^{1/2}\pi \approx 5.2$
- Recover features!

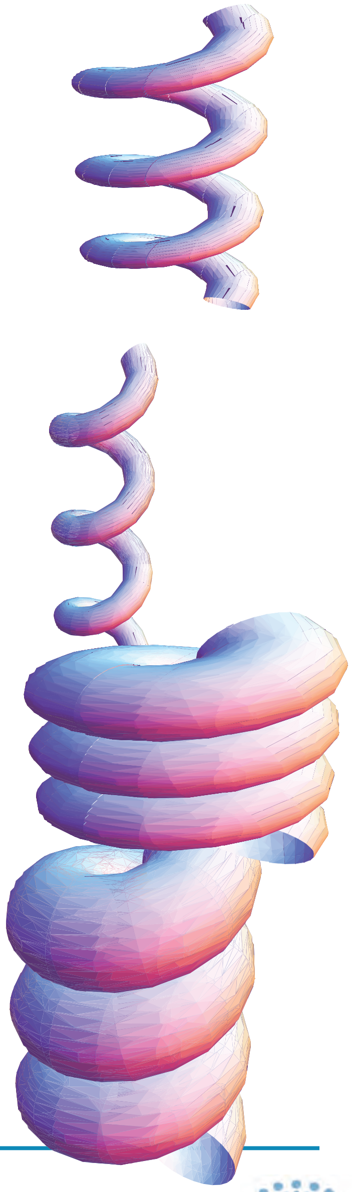


KL Kohlstedt, et al - Phys Rev Lett, 2007



G Vernizzi, KL Kohlstedt, (cover article) Soft Matter 2009

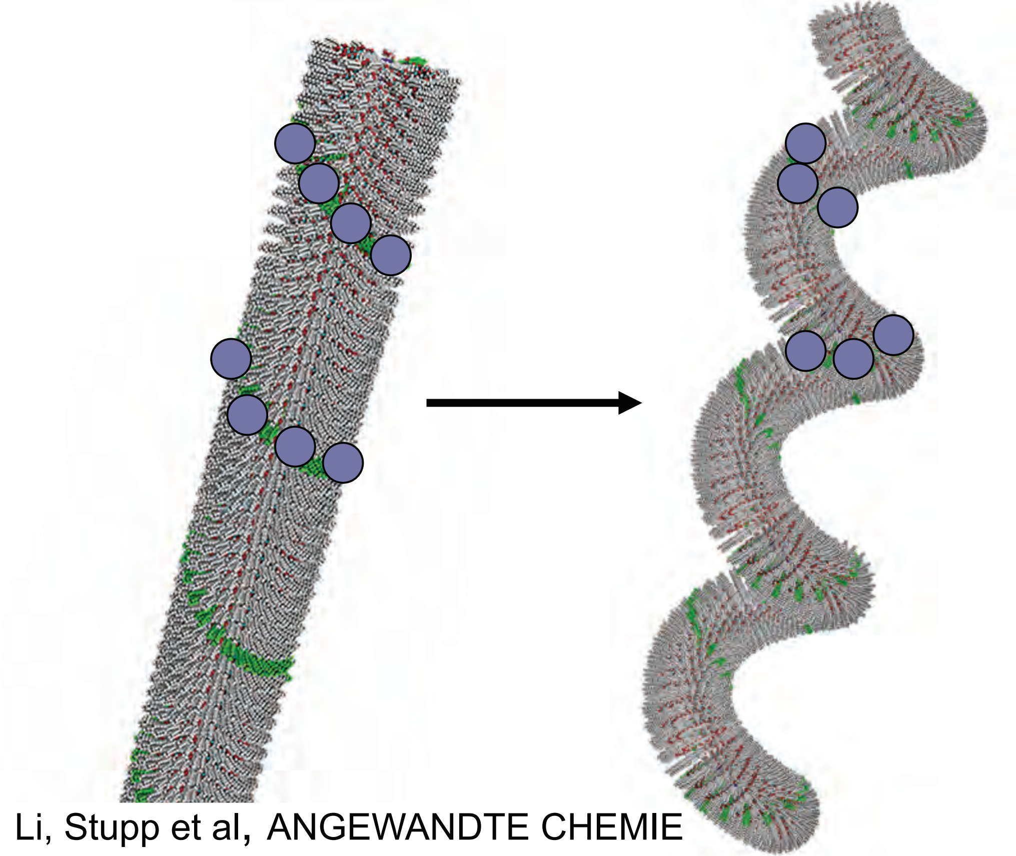
Coiled Cylinder Mapping



- Can coiled cylinder be mapped into the periodic plane?
  - Maybe! Spring is translationally invariant along the axis, but not along inner tube
- Parametrization of coiled fiber must be independent of starting position when calculating distance between two points
  - Elliptic functions might be applicable
- Mapping allows calculation of long-range forces in Fourier space possible so calculations are tractable

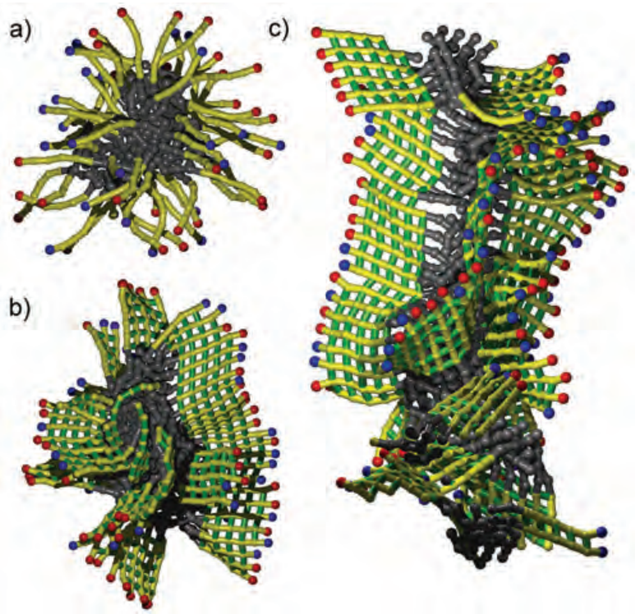
Future plans: Supercoiling Transition

Simulation of coil transition can be modeled using MD through the addition of bulky groups on the surface



Li, Stupp et al, ANGEWANDTE CHEMIE

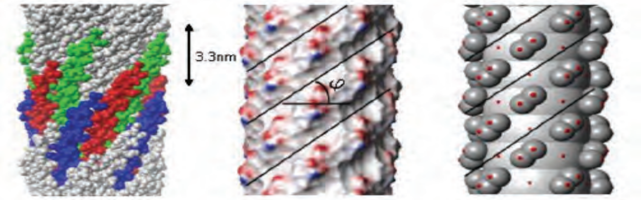
MD simulations to show β-sheet fibril aggregation



Courtesy of Y. Velichko

Future Work

- Study the electrostatic-induced nanopatterning on cylinders with a screening length to see if elasticity is enough to prevent macroscopic segregation of ionic lattice. In particular, the issue of chiral symmetry breaking by electrostatic interactions will be addressed.
- Perform numerical simulations for studying the effects of electrostatics on the elastic properties of nano-crystalline ionic domains over fluid membranes. This is relevant for understanding and controlling the buckling of nano-vesicles into polyhedral shapes.
- Extend our results to the case of nanoparticles grafted with charged polymers. We would like to show how electrostatic interactions can control the shape fluctuations and packing properties of charged polymers end-grafted on nanoparticles: we aim to characterize and quantify, by computer numerical simulations, how multivalence can be induced.



Surface of the M13 virus, generated from the 2C0X.pdb capsid protein structure [Tombolato et al. PRL **96,** 258302 (2006)]

Chiral domains

- Chiral lipids have been shown to form triskelion shapes of like chirality
- Electrostatic interactions between the lipid head groups has been shown to amplify the chirality
- It is still unclear what the mechanism is for the transfer of chiral centers of molecules to larger complex chiral shapes

Weis, *Nature,* **310** (1984)

Conclusions

- Self-assembled finite sized domains are important in many materials especially in biological materials
    - ❑ Lipid membranes are an important biological material that are thought to possess nanoscale domains
    - ❑ Experimental protocol for "ordered" fluid domains at the nanoscale is still lacking
    - ❑ Many lipid molecules are charged and electrostatic interactions tends to order molecules
- Low-dimensional self-assembled molecules provide unique opportunity to study nanopatterning
    - ❑ Many filamentous aggregates in the body interact with the cell membrane
    - ❑ Furthermore many show chiral domains on their surfaces
- Group theory provides a rigorous method to classify the symmetry of the patterns on low-dimensional assemblies

Model: Screened Electrostatics and Immiscibility

- Continuum model used to show what type patterns are possible
- Description based on phenomena of two component charged molecules co-assembled into cylindrical fibers
    - ☐ Constrained by charge electroneutrality and pattern commensurability conditions
    - ☐ T → 0 limit
- Planar to cylindrical topologies