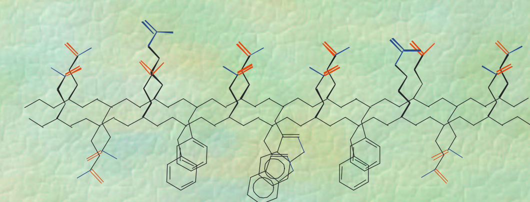
Peptide Self-Assembled Polymers

Sasha Semenov, Irena Nyrkova,
Dept. of Applied Mathematics
Amalia Aggelli, Mark Bell, Neville Boden, Peter Mawer
SOMS Centre
Sheena Radford
School of Biology
Tom McLeish, Alastair Smith
Polymer IRC, Dept. of Physics and Astronomy
University of Leeds
Geoge Fytas, Dimitris Vlassopoulos
FORTH, Herklion

Questions

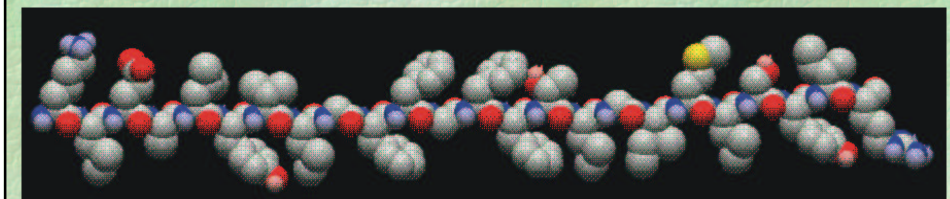


- Why and when do peptides self-assemble?
- What is a good coarse-grained model for the energies of interaction?
- What limits fibre/bundle diameters?
- What are the slow kinetics?
- Do they constitute and example of tightly entangled stiff polymers?
- …..

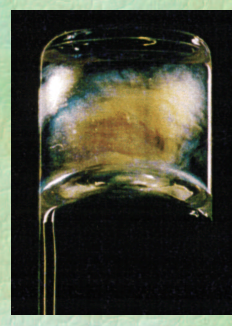
Peptide 1: K24 - organic solvent

Lys-Leu-Glu-Ala-Leu-Tyr-Val-Leu-Gly-Phe-Phe-Gly-Phe-Phe- Thr-Leu-Gly-Ile-Met-Leu-Ser-Tyr-Ile-Arg

\- + +



did this at only 1% in water



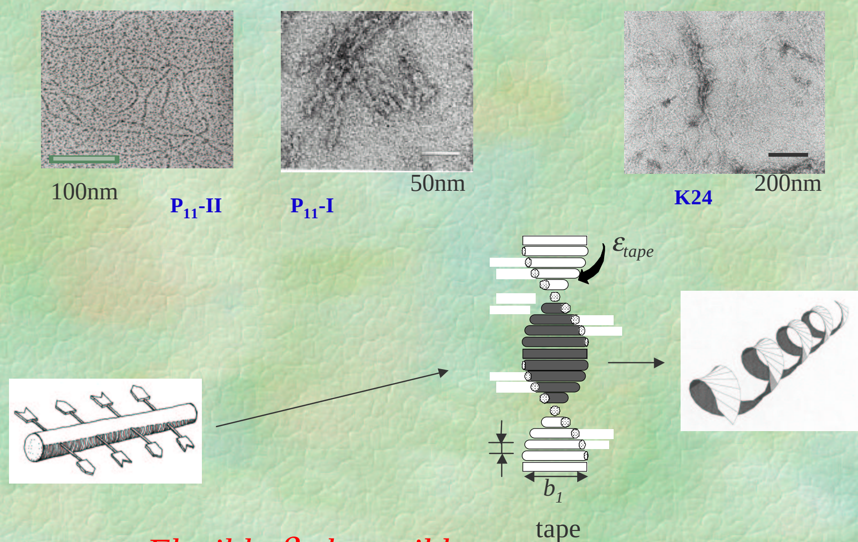
Peptides 2 and 3: P_{11}-I and P_{11}-II ; aqueous

I CH 3 CO-Gln- Gln-Arg-Phe-Gln-Trp-Gln-Phe-Glu-Gln-Gln-NH 2

… the same plus a hydrophobic side..

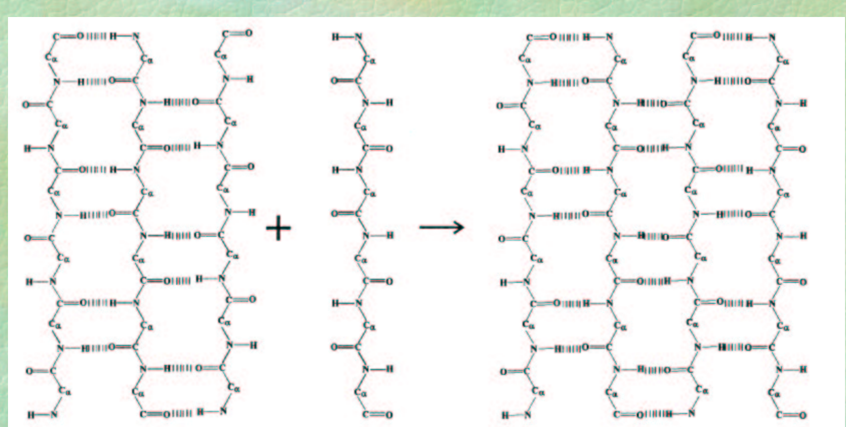
II CH 3 CO-Gln- Gln-Arg-Phe-Gln-Trp-Gln-Phe-Glu-Gln-Gln-NH 2

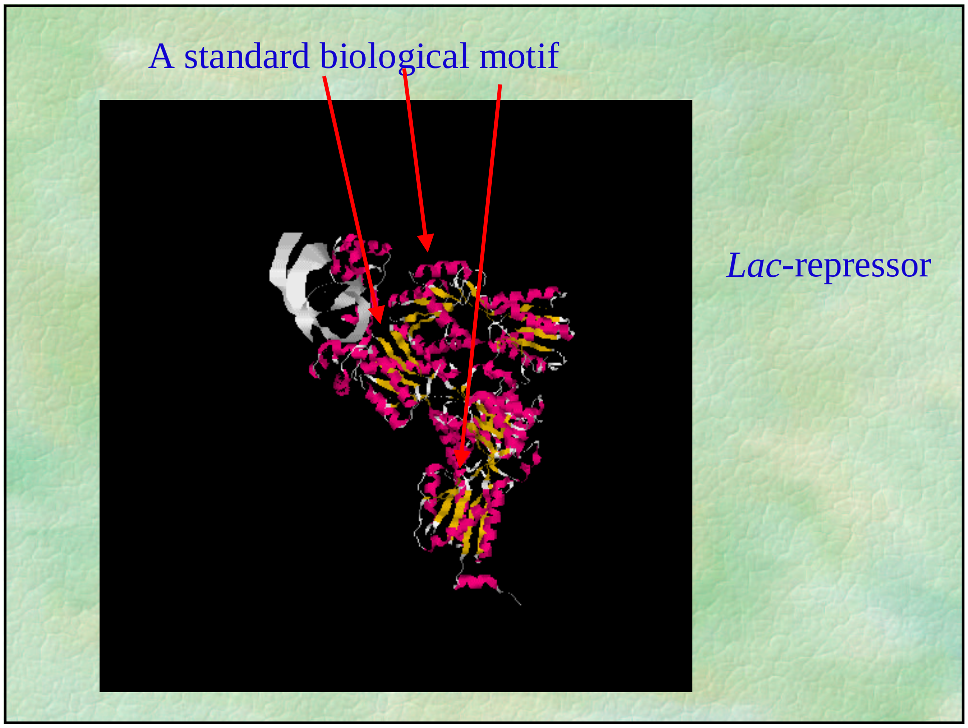
They must have formed polymers...

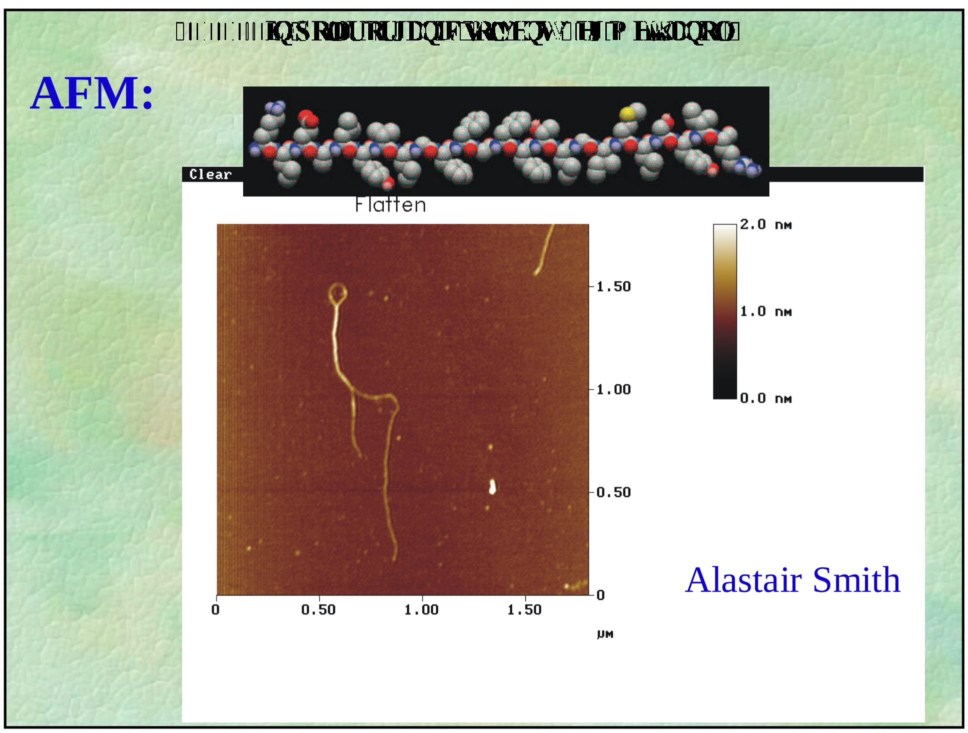


Flexible β-sheet ribbons

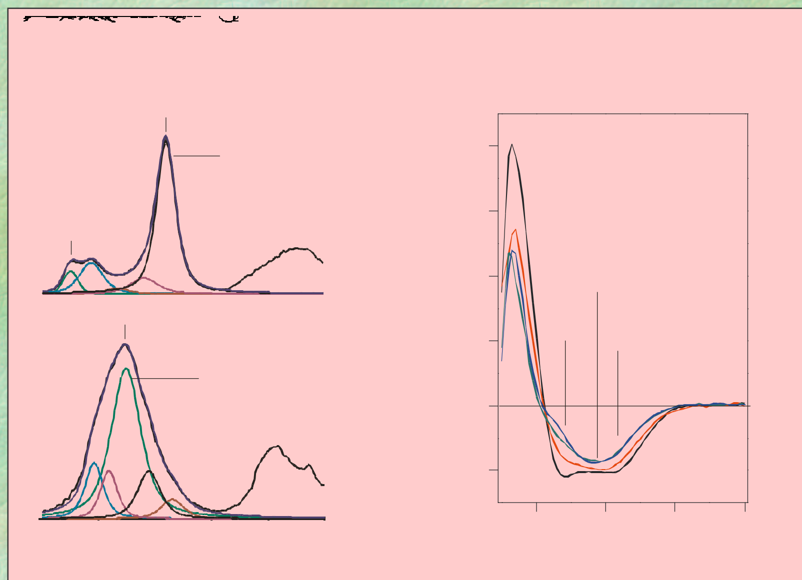
Hydrogen bonding modified by electrostatics




A standard biological motif
Lac-repressor


AFM:
Clear
Flatten
2.0 nm
1.0 nm
0.0 nm
1.50
1.00
0.50
0
0
0.50
1.00
1.50
µm
Alastair Smith

Check with spectroscopy



Surely an example of 1-d self-assembly:

$$\frac{F}{k_B T} = \sum_m N_m \ln\left(\frac{N_m v_0}{eV}\right) + \sum_m N_m \varepsilon_m$$

with $$\sum_m N_m m = N$$

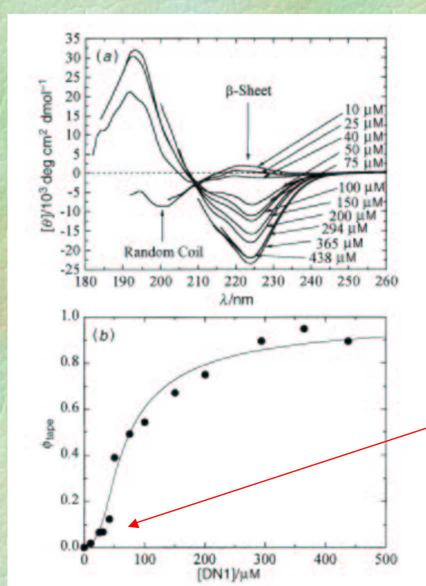
So we need a model for

Famous example: wormlike micelles

$$\varepsilon_m = 2\varepsilon_{cap}$$

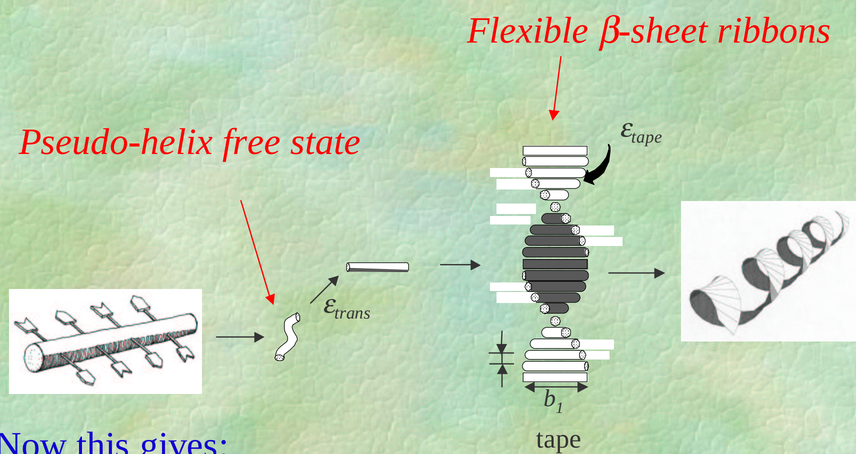
$$\Rightarrow \langle m \rangle = c^{1/2} e^{\varepsilon_{cap}}$$

But the Spectroscopic self-assembly curves are S-shaped:



Not ~ $c^{1/2}$!

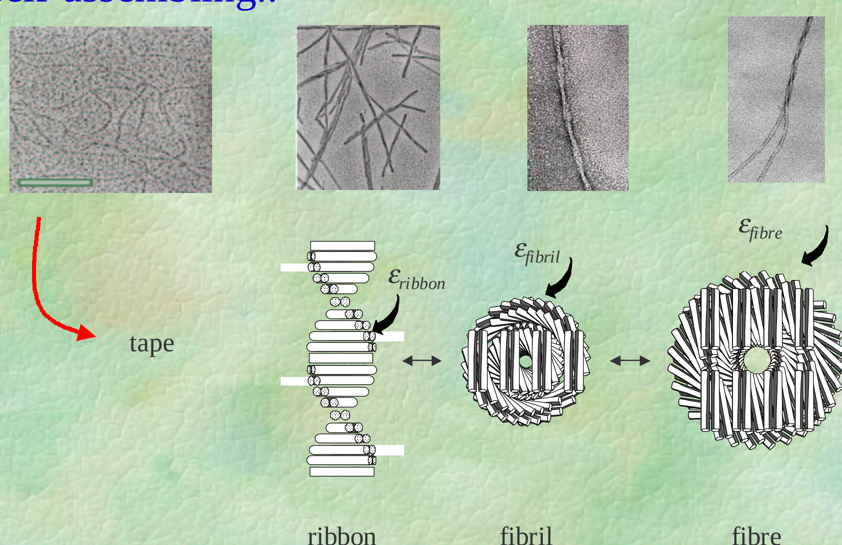
So modify the picture with a transition state...



Now this gives:

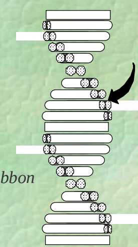
$$\langle m_{tape} \rangle = \left(\frac{c - c^*_{tape}}{c^*_{tape}} \right)^{1/2} e^{\varepsilon_{trans}/2} \quad \text{with} \quad c^*_{tape} \cong e^{-\varepsilon_{tape} + \varepsilon_{trans}}$$

With increased concentration they go on self-assembling..



So that, *e.g.*

$$\langle m_{ribbon} \rangle = \left(\frac{c - c^*_{ribbon}}{c^*_{ribbon}} \right)^{1/2} e^{(\varepsilon_{trans} + \varepsilon_{tape})/2}$$



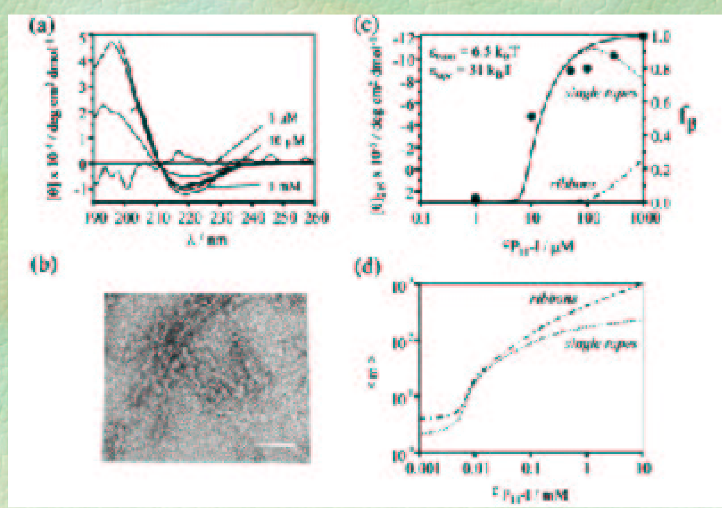
ε_{ribbon}

ribbon

with

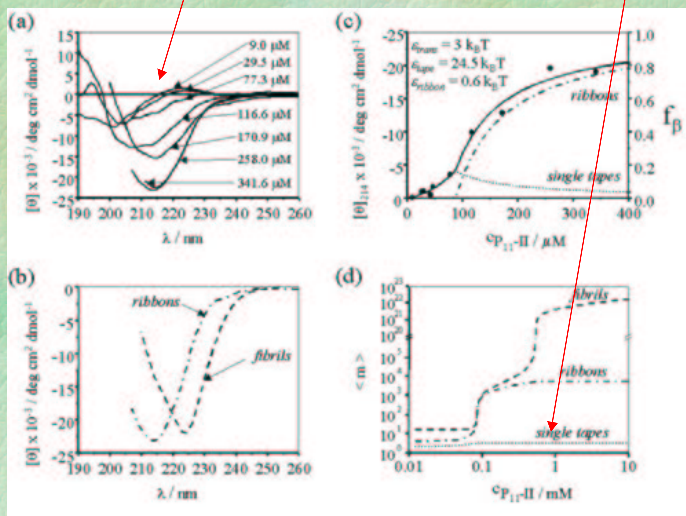
$$c^*_{ribbon} \cong c^*_{tape} + \varepsilon^{-2}_{ribbon} e^{-\varepsilon_{tape}}$$

P$_{11}$-I looks like curly tapes

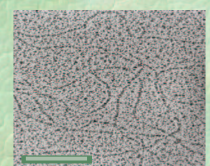


P_{11}-II must be ribbons, then fibrils

- No isochroic point
- Single tapes too short



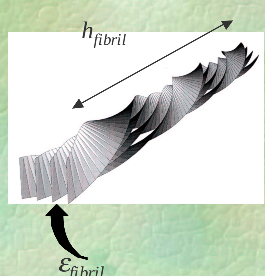
- Persistence l_p~500nm



But what stabilises the fibrils?

$$\varepsilon_{elast} = \frac{1}{2} k_{bend} (\nu - \nu_0)^2 + \frac{1}{2} k_{twist} (\theta - \theta_0)^2$$

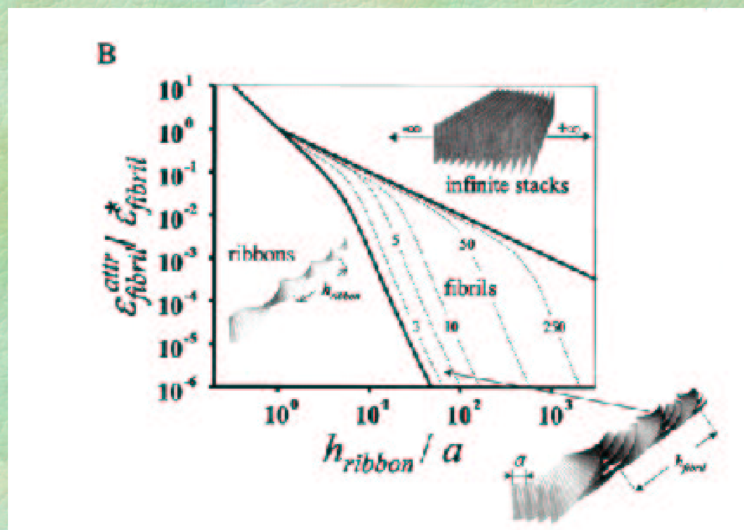
Twist-Stack Model



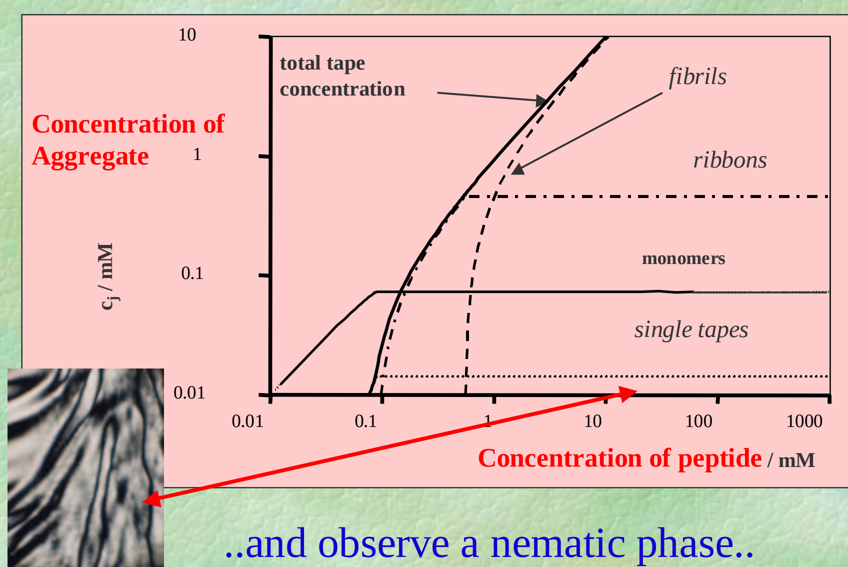
$$\nu = \gamma^2 \frac{\rho}{(1+\gamma^2\rho^2)}; \quad \theta = \gamma \frac{1}{(1+\gamma^2\rho^2)}$$

$$\varepsilon_{fibril} = \frac{p-1}{2p} \varepsilon_{fibril}^{attr} - \varepsilon_{elast}^{fibril}$$

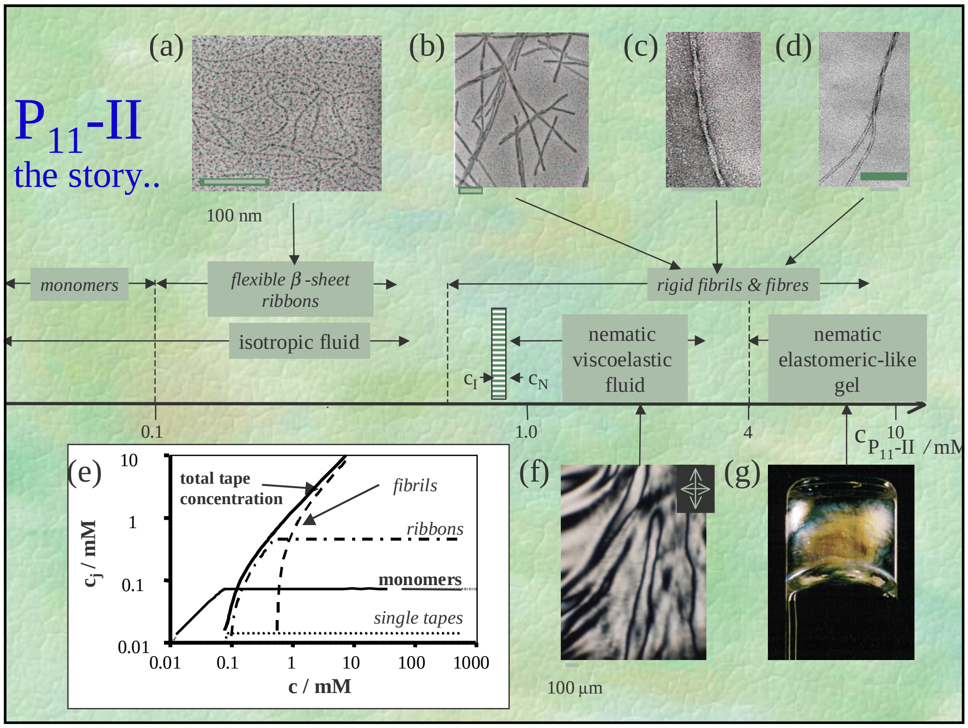
A structural phase diagram:



We can predict their formation quantitatively..



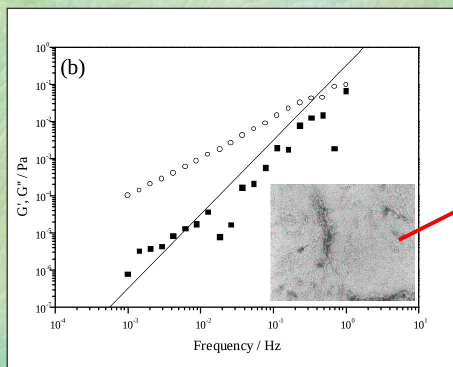
..and observe a nematic phase..



Parameter Summary

	Peptide P_{11}-I β-Tapes	Ribbons	Fibrils	β-Tapes	Ribbons	Fibrils
c_{cr} / µM	8*	1,000*	c > 25,000*	< 90*	90*	700 ± 200*
ε_{trans}		6.5 ± 1.5			3 ± 1	
ε_{tape}	31.0 ± 1.5			24.5 ± 1.0		
ε_{ribbon}		$(3.5 \pm 1.5)10^{-3}$			0.6 ± 0.3	
ε_{fibril}			$< 10^{-3}$			$(2.0 \pm 0.3)10^{-4}$
Pitch h / nm	30 ± 15*	50 ± 20*			160 ± 40	160 ± 40*
Twist angle γ_0/°	3*	3*		1	1	1*
Bend angle γ_b/°	3*	0*			0*	0*
$\tilde{l}$ / µm	< 0.3*	0.6 ± 0.2*			1.0 ± 0.3*	20–70*
L / µm (c = 6 mM)	10^{-1}	$10^{-1} - 10^{0}$		10^{-3}	10^{0}	10^{17}
Properties of aq. solution	Isotropic fluid (c < 13 mM) Nematic fluid / gel (c >13 mM)			Isotropic fluid (c < 0.9 mM) Nematic fluid ($c \approx$ 0.9 – 6 mM) Nematic gel (c > 6 mM)		

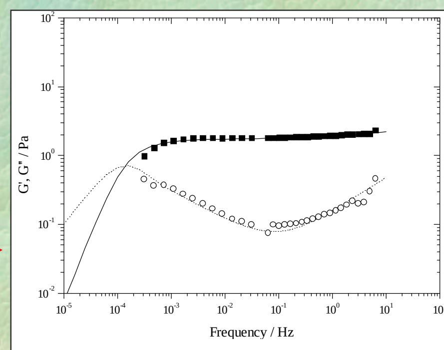
Dynamics and Rheology: K24 in 2chloroethanol



L_p~500nm

c=0.001

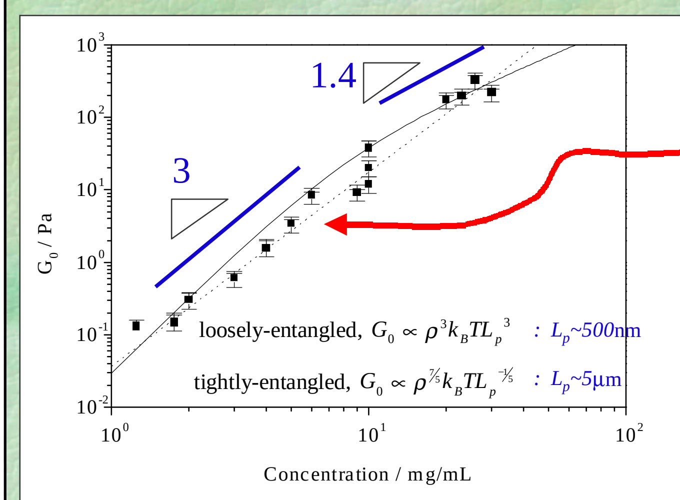
c=0.004



Plateau Modulus looks like stiff-entangled:

Estimate of L_e~100nm gives $G_{curve} \cong \frac{\rho k_B T}{L_e}$

$\cong 4Pa$



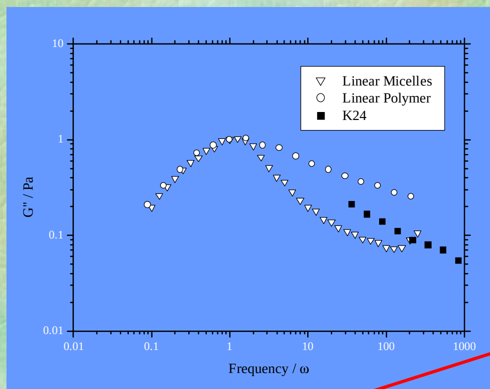
at

$\varphi = 5.10^{-3}$

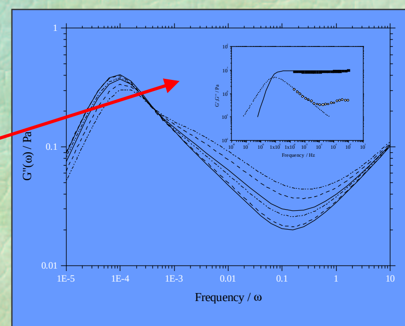
so

$\rho = 10^{14} m^{-2}$

Additional evidence from stiffness from DE-like spectrum

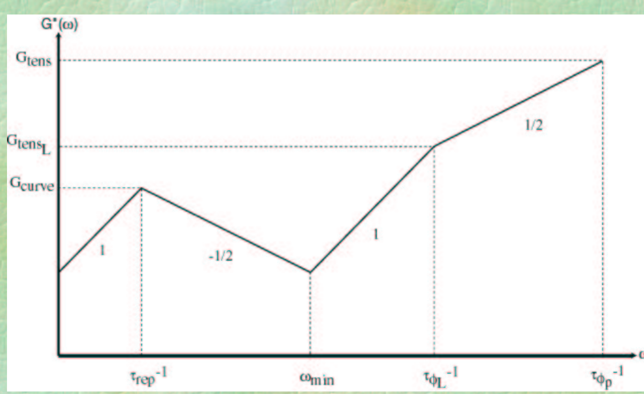


$$U_{eff}(s) = \left(B_{entropy} + B_{bend}\right)\left(\frac{s^2}{2}\right)$$



By fitting: $L_p/L_e \sim 10$

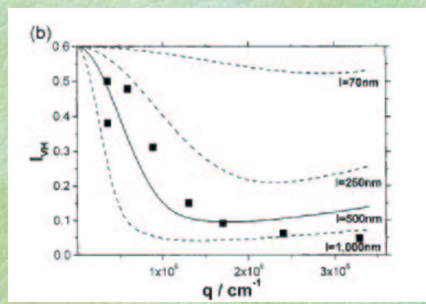
More from Morse, Maggs and more….



Useful relation: $\ln\left(\frac{\omega_{\min}}{\tau_d^{-1}}\right) = \frac{2}{3}\left[1 + \ln\left(\frac{L^2}{L_p L_e}\right)\right] \Rightarrow \frac{L}{L_e} \cong 250 \cong 100\mu$

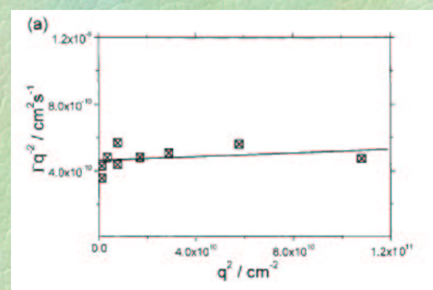
Depolarised Light Scattering

I_{VH}



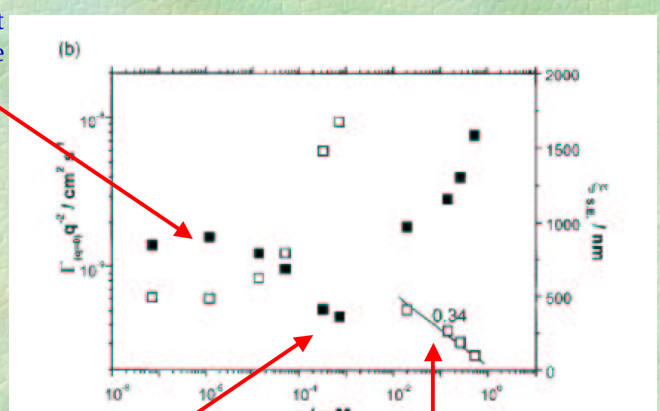
..looks like rods locally

… $D(q)\sim q^0$



Relaxation rate with concentration

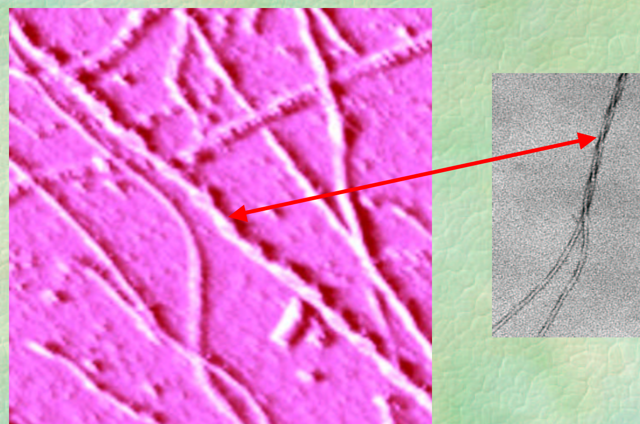
But *L* should only be at *most* 100nm down here



Strange slowing down

Anomalous semi-dilute exponent with *c*

Application: these structures resemble “amyloids”



C. Dobson and A. Hill (Oxford)

- Next step is to understand kinetics (months!)
- We may have a cleanish model system
- Physics may have more to say about biology when it goes Wrong!