A Systems Approach to Biology

MCB 195

Lecture 1
Thursday, 3 Feb 2005

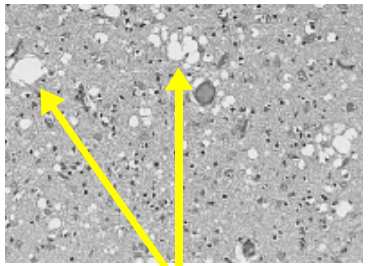
Jeremy Gunawardena

PRIONS

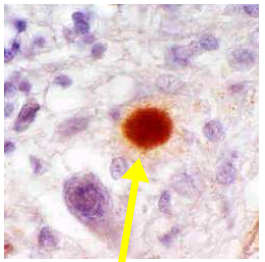
Transmissible spongiform encephalopathies (TSEs)

sporadic, genetic AND infectious

Human	CJD	dementia
	Kuru	ataxia
	GSS	ataxia
	FFI	sleep deficit
	vCJD	emotional instability
Bovine	BSE	
Sheep	scrapie	
Deer/Elk	CWD	



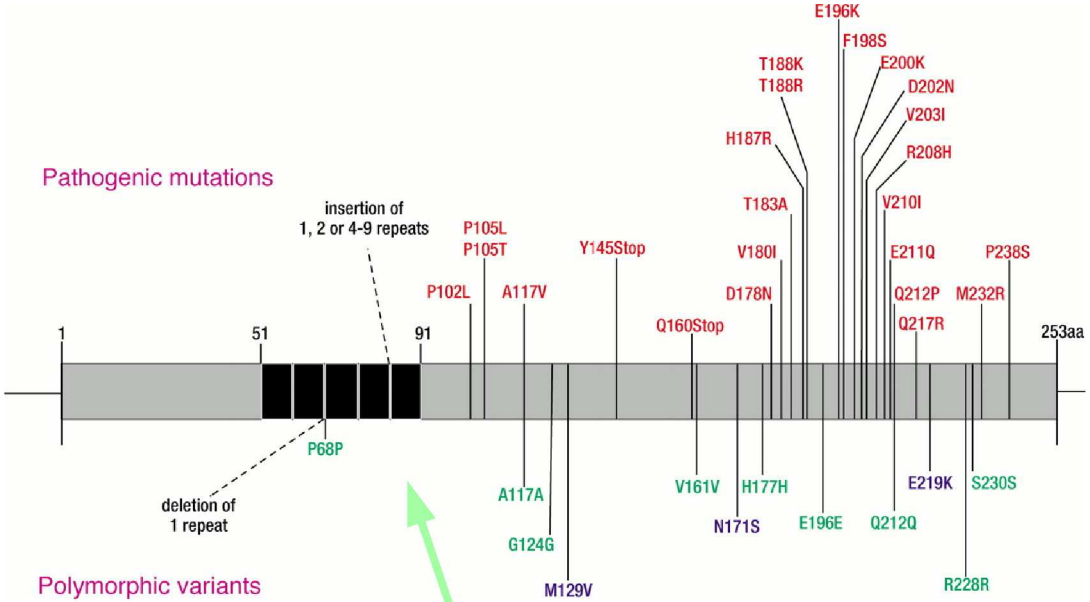
vacuoles

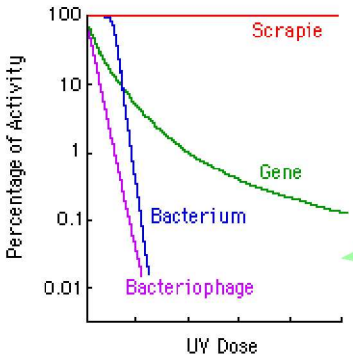


amyloid plaques

known since 17C, endemic worldwide

Colorado wildlife advisory: *"avoid consuming brain, spinal cord, eyes, spleen tonsils, pancreas, lymph nodes ... "*





1. familial variants map to the prp locus on chromosome 20
2. fibrils highly enriched for PrP
3. extremely resistant to nucleic acid inactivation

How can a protein be infectious?

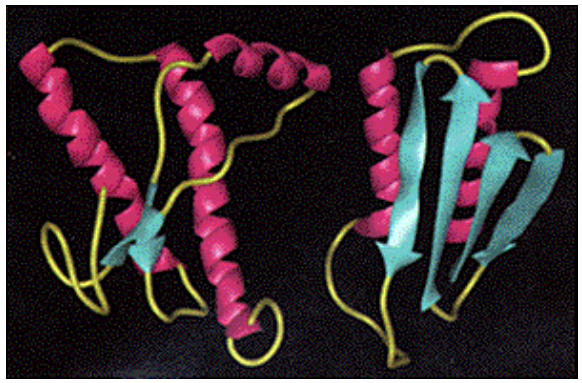
How can a protein be infectious?

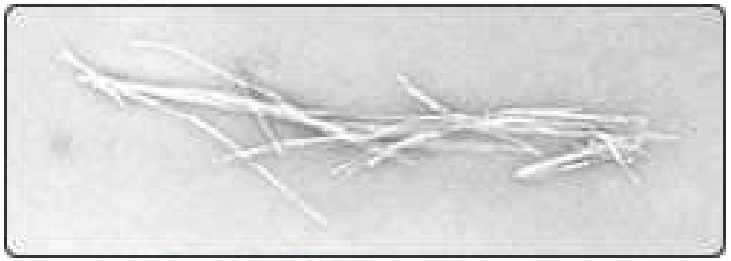
1. Auto-catalysis

J S Griffiths, “Self-replication and scrapie”, Nature **215**:1043-4, 1967

> *“there is no reason to fear that the existence of a protein agent would cause the whole theoretical structure of molecular biology to come tumbling down”*

F E Cohen et al, “Structural clues to prion replication”, Science **264**:530-1, 1994

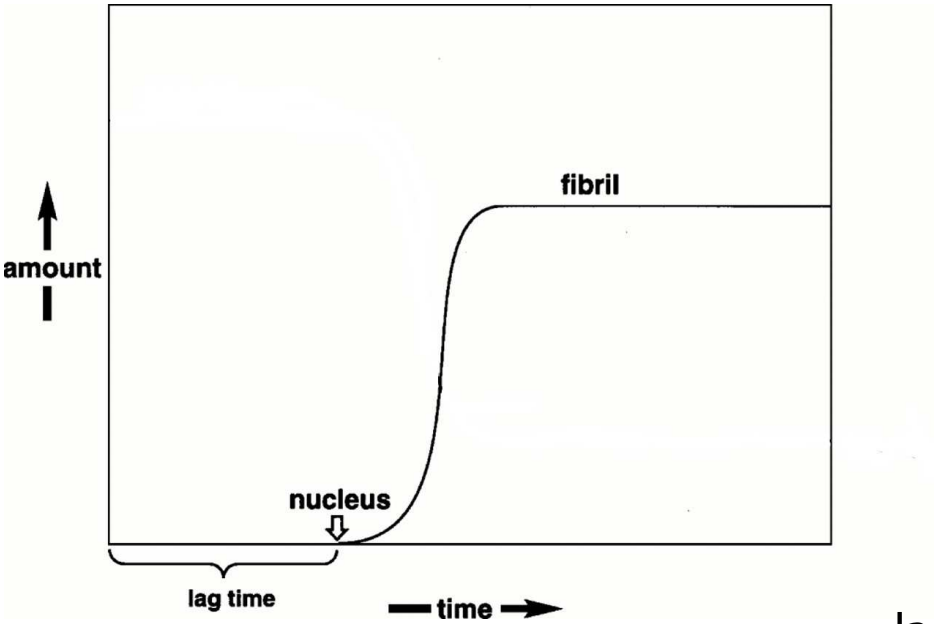




Electron Microscope Image of Amyloid Fibrils

$PrP^{C} \longleftrightarrow PrP^{SC}$

$PrP^{C} + PrP^{SC} \longrightarrow 2 \times PrP^{SC} \longrightarrow$ amyloid fibrils



$$\text{lag time} = \frac{1}{[\text{monomer}]^n}$$

Quantitative information from in-vitro studies

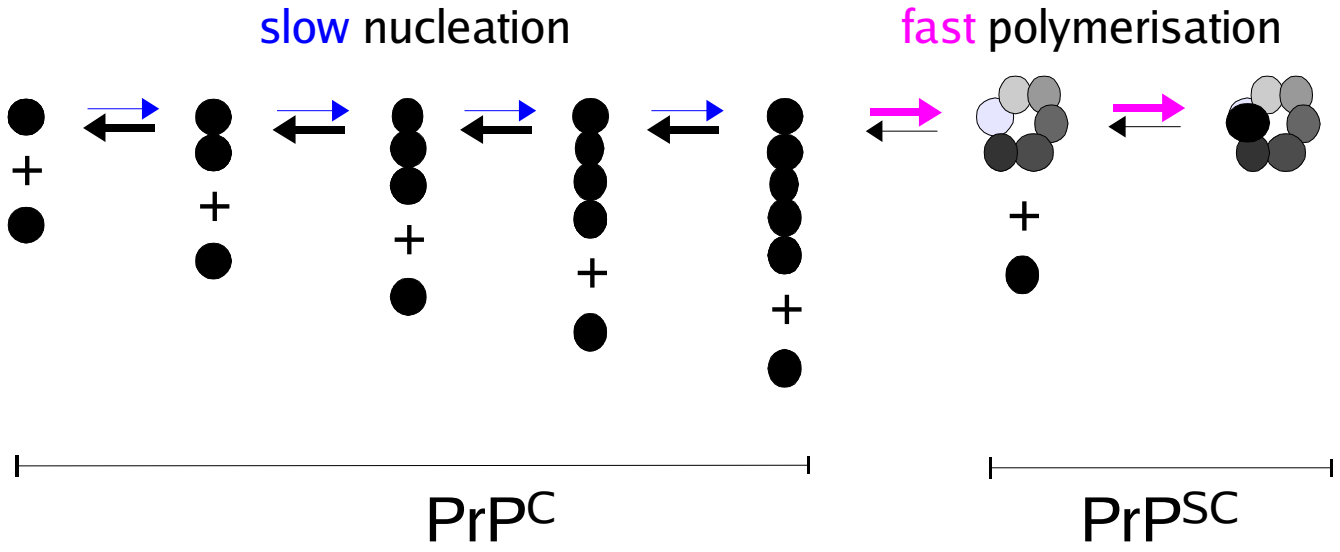
1. critical concentration threshold for fibril formation
2. lag time for fibril formation
3. lag time highly sensitive to monomer concentration
4. exponential growth after lag time
5. sigmoidal (S-shaped) growth curve

Hard to explain this with auto-catalysis

How can a protein be infectious?

2. Nucleated polymerisation

J D Harper & P T Lansbury, “Models of amyloid seeding in Alzheimer's disease and scrapie”, Annual Review of Biochemistry, **66**:385-407, 1997



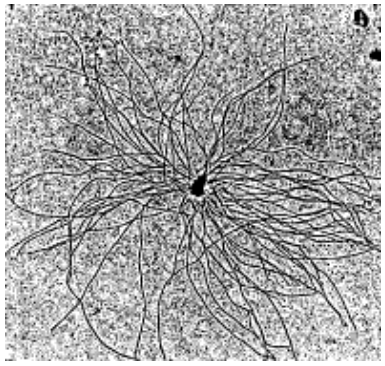
Protein polymerisation is a central mechanism

Disease

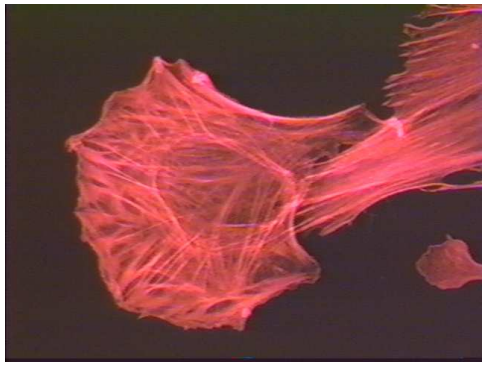
TSEs	PrP
Alzheimer's	Aβ
Parkinson's	α synuclein
Huntington's	huntingtin
Diabetes	IAPP
Sickle-cell anemia	hemoglobin

Normal physiology

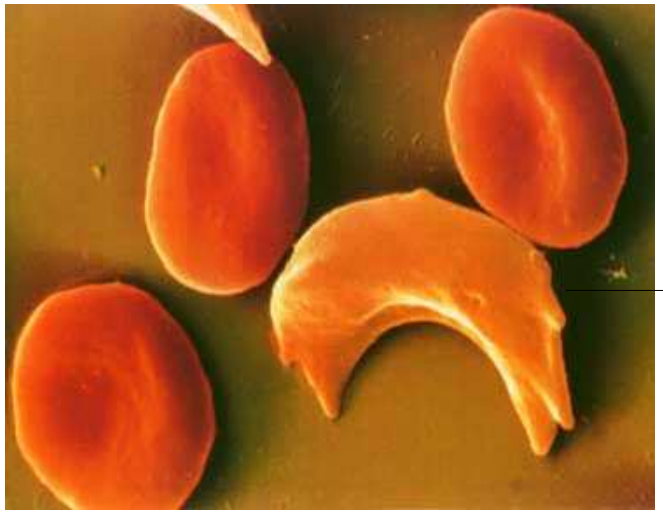
microtubules



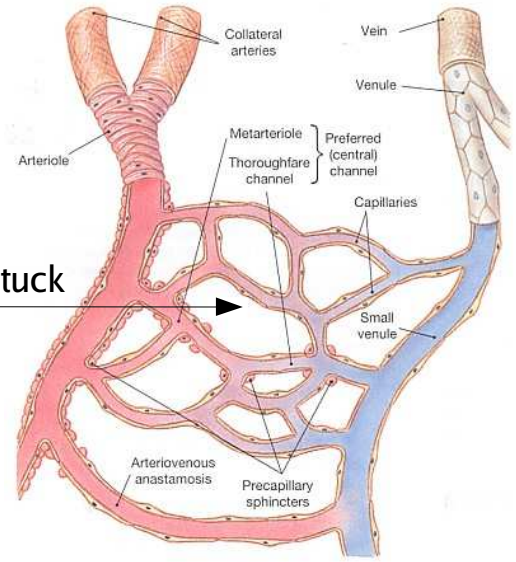
actin



Sickle cell anemia



sickled cells get stuck



sickling is caused by Glu -> Val mutation on β globin of hemoglobin $\alpha 2 \beta 2$

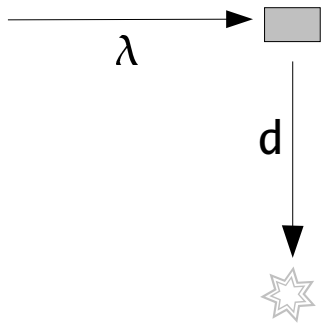
hydroxyurea treatment increases fetal hemoglobin $\alpha 2 \gamma 2$

effective concentration of $\alpha 2 \beta 2$ hemoglobin falls a little lag time increases a lot

more red blood cells esape the microcirculation before sickling

40% decrease in death rate for severe cases

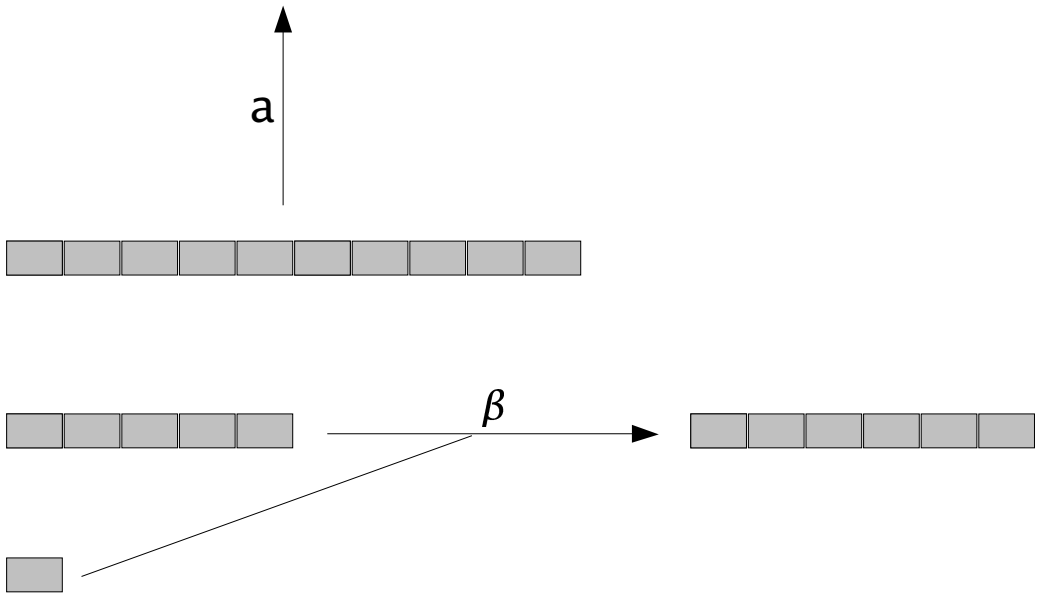
$$\text{lag time} = \frac{1}{[\text{monomer}]^n}$$



monomer rates

λ	production	(mols)(time)$^{-1}$		monomer
d	degradation	(time)$^{-1}$		degraded

J Masel, V Jansen & M Nowak, “Quantifying the kinetic parameters of prion replication” Biophysical Chemistry **77**:139-152 1999



polymer rates

β	aggregation	$(\text{mols})^{-1}(\text{time})^{-1}$
a	clearance	$(\text{time})^{-1}$

polymer with 5 units

degraded