Kinetic Model of Prion Aggregate Growth

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1. Prions and prion-related diseases (very brief)
2. Kinetic model of aggregate formation
3. Comparison with experiments
4. Some consequences

Prions and prion-related diseases

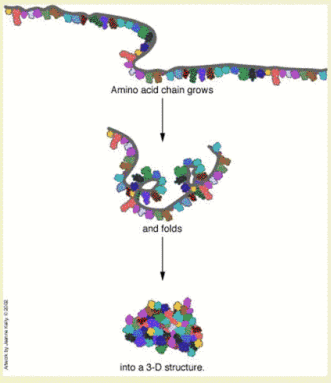
Prion = proteinaceous infectious particles

S.B. Prusiner, Nobel prize 1997 Medicine

„For his discovery of Prions - a new biological principle of infection"

What is an infectious protein?

Infection was attributed to viruses, bacteria which replicate by copying their genetic material.



Natural uninfectious Prion protein is found in cells of normal animals its function is unclear → PrP^{C}

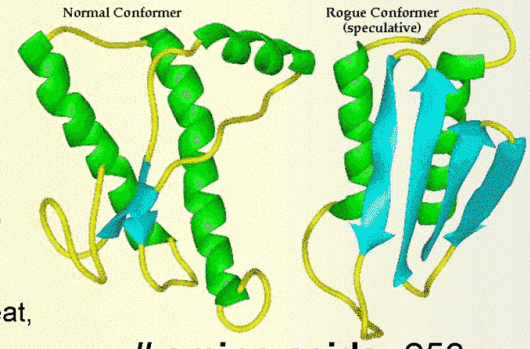
infectious protein is folded into a different shape very stable → PrP^{SC}

Prions and prion-related diseases

PrP^C

3% β-pleated
42% α-helical

structurally weak,
-easily soluble
-easily digested
by proteases, heat,
etc.



 # amino acids: 253

PrP^{SC}

43% β-pleated
30% α-helical

very stable,
-insoluble in all but
strongest solvents
-highly resistant to
digestion by proteases
-resists formaldehyde,
ethylene oxide, UV,
temperature,…

no detectable immune
response

self-replicating = prions multiply by converting PrP^C into PrP^{SC} by changing their conformation

PrP^{SC} + PrP^C → PrP^{SC} PrP^{SC}

no genetic material/nucleic acids needed for reproduction

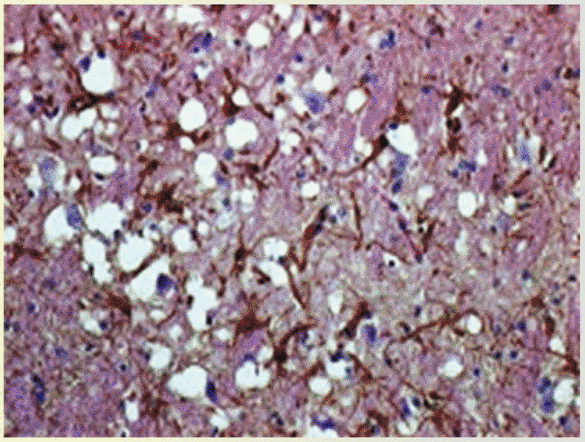
Prions and prion-related diseases

Formation of aggregates

PrP^{SC} + PrP^C → PrP^{SC} PrP^{SC}

…..

PrP^{SC} PrP^{SC} PrP^{SC} PrP^{SC} PrP^{SC} PrP^{SC}



Scrapie

Prions and prion-related diseases

most prominent: BSE = bovine spongiform encephalopathies

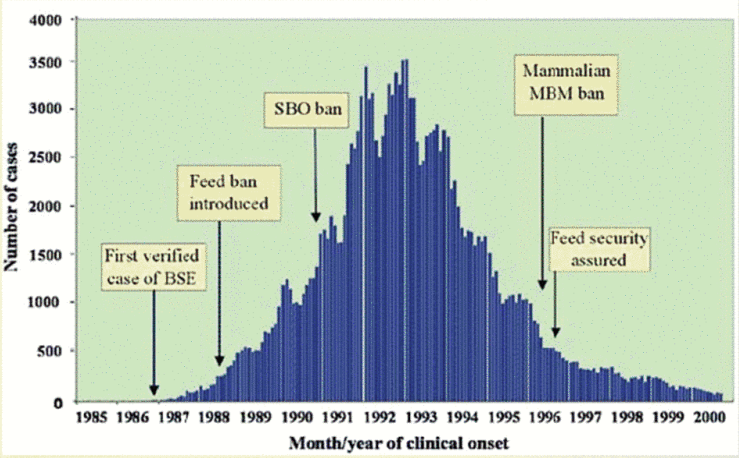
bovine = affects cattle
spongiform = sponge like
encephalon = brain
pathos = disease

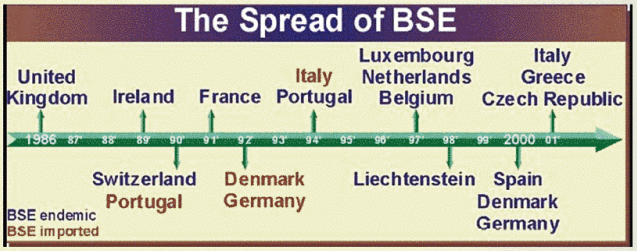
TSE = transmissable spongiform encephalopathies

-Prion fibers (fibrils) accumulate in the nerve cells and presumably cause the disease
-CWD in elk/deer
-TME in mink,…
-in humans:
+ CJD Creutzfeld 1920 / Jacob 1921/23 (spontaneous, medical treatment)
+ Kuru 1920 (Papua - New Guinea)
+ FFI Fatal Familial Insomnia
+ Gerstmann-Sträußler-Scheinker Syndrome 1936 (genetic disorder)

~750,000 cattle entered food products during BSE epidemic in GB

Prions and prion-related diseases





SBO = specified bovine offals ban

MBM = meat and bone meal ban

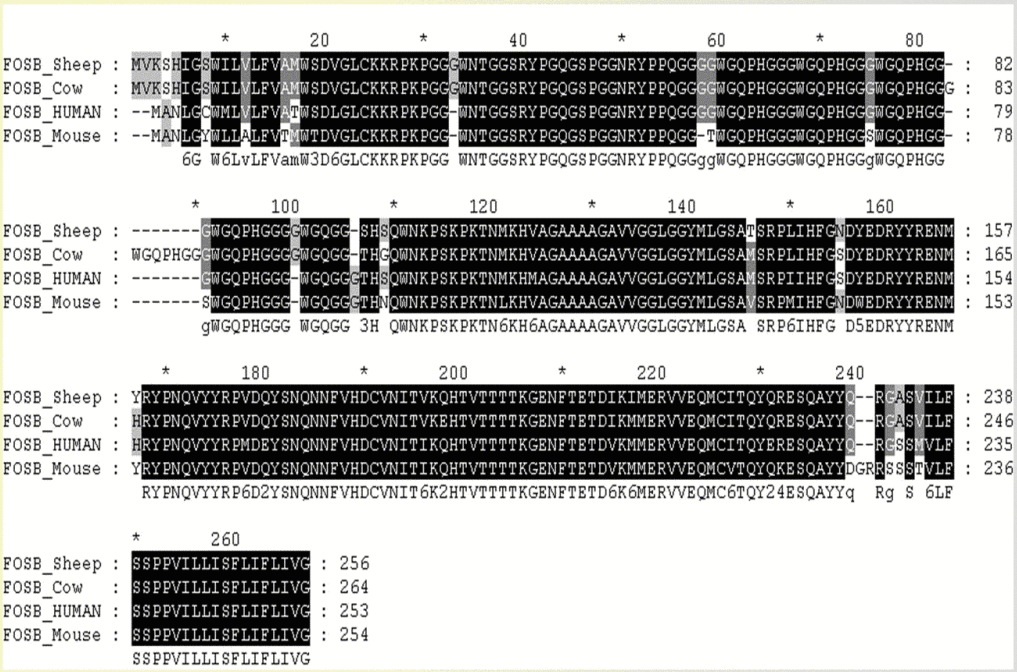
1986 - first in UK

1993 – 100,000 in UK

~750,000 cattle entered food products during BSE epidemic in GB

Prions and prion-related diseases

Comparison of human, cow, sheep and mouse prion protein sequence



2. Kinetic model of aggregate formation - nucleated polymerization

Most important assumption: PrPsc-polymers are essentially one-dimensional structures

1. variable number of PrPc-monomers: $x(t)$ (1)

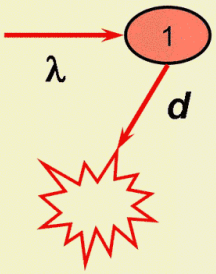
2. variable number of PrPsc-polymers of size *i*: $y_i(t)$ polymer of size *i*
   polymers grow at both ends at constant rate
   $y_i \to y_i - 1 \qquad y_{i+1} \to y_{i+1} + 1$

3. polymers of size *i* break at each position at the same rate,
   $y_i \to y_i - 1 \qquad y_j \to y_j + 1 \qquad y_{i-j} \to y_{i-j} + 1$

4. polymers below a certain size *n* are unstable
   $y_i \to y_i - 1 \qquad x \to x + i$ if $i<n$

2. Kinetic model of aggregate formation

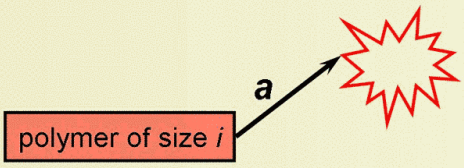
Masel, Jansen, Nowak,
Biophys. Chem.'99

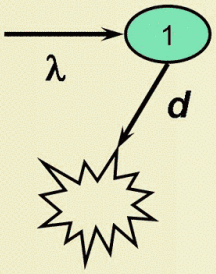


$$\frac{dx}{dt} = \lambda - dx$$

PrPc-monomers are generated at constant rate λ and degraded metabolically at rate *d*

2. Kinetic model of aggregate formation



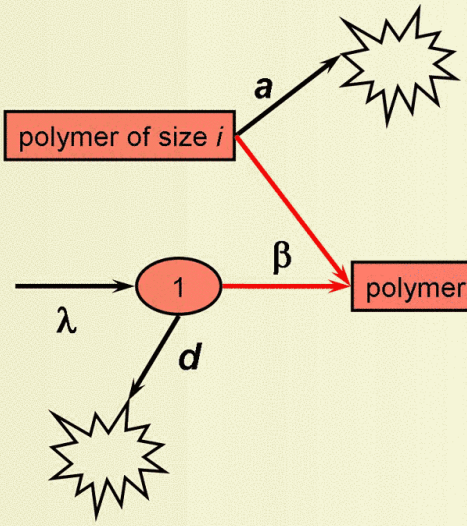


$$\frac{dx}{dt} = \lambda - dx$$

$$\frac{dy_i}{dt} = -ay_i$$

PrPsc-polymers are degraded at conatent rate *a*, independently of their size

2. Kinetic model of aggregate formation

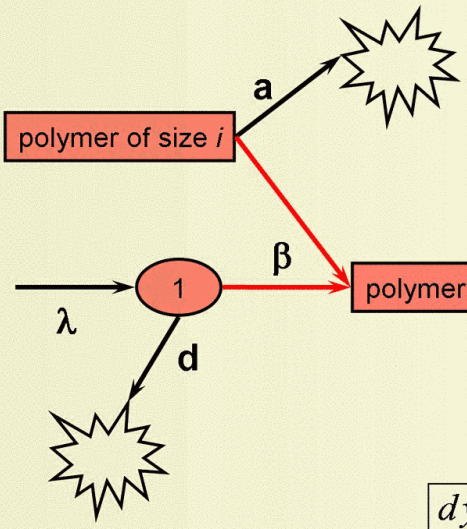


$$\frac{dx}{dt} = \lambda - dx$$

$$\frac{dy_i}{dt} = -ay_i$$

each PrPsc-polymer grows at rate β (*i*>*n*-1)

2. Kinetic model of aggregate formation

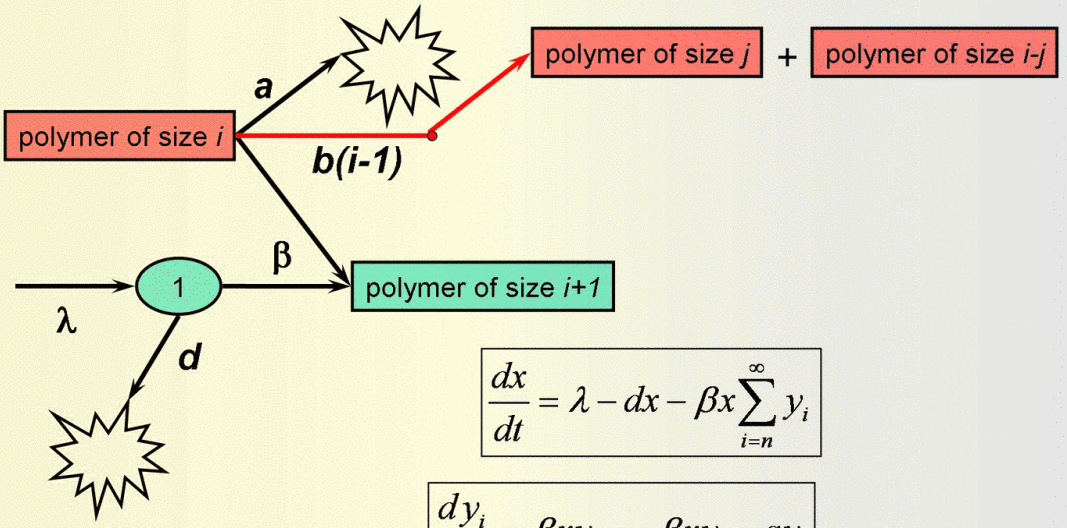


$$\frac{dx}{dt} = \lambda - dx - \beta x \sum_{i=n}^{\infty} y_i$$

$$\frac{dy_i}{dt} = \beta x y_{i-1} - \beta x y_i - a y_i$$

each PrPsc-polymer grows at rate β (*i*>*n*-1)

2. Kinetic model of aggregate formation



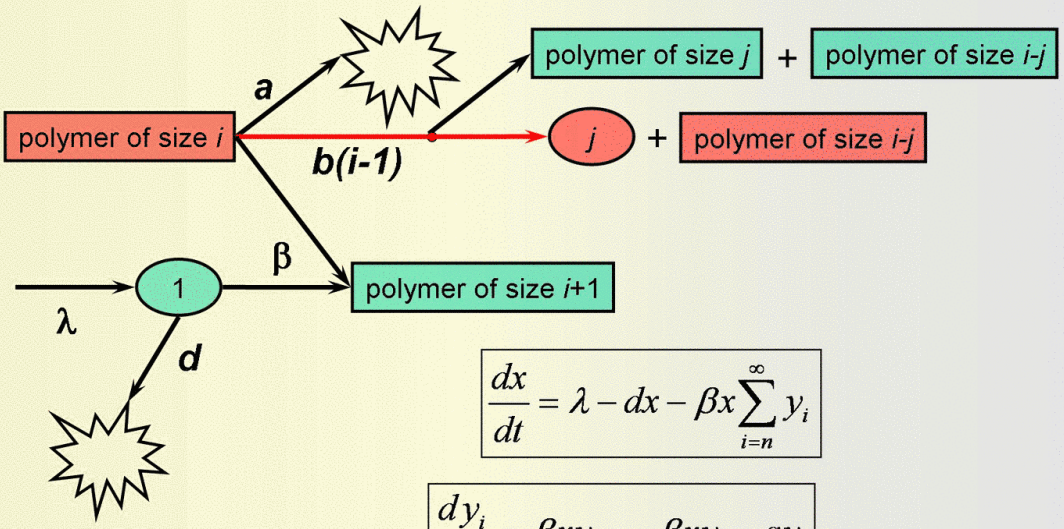
$$\frac{dx}{dt} = \lambda - dx - \beta x \sum_{i=n}^{\infty} y_i$$

$$\frac{dy_i}{dt} = \beta x y_{i-1} - \beta x y_i - a y_i$$

each PrPsc-polymer of size *i* breaks at each of its *i*-1 connections at the same rate *b*

case a) both parts are not smaller than *n*

2. Kinetic model of aggregate formation



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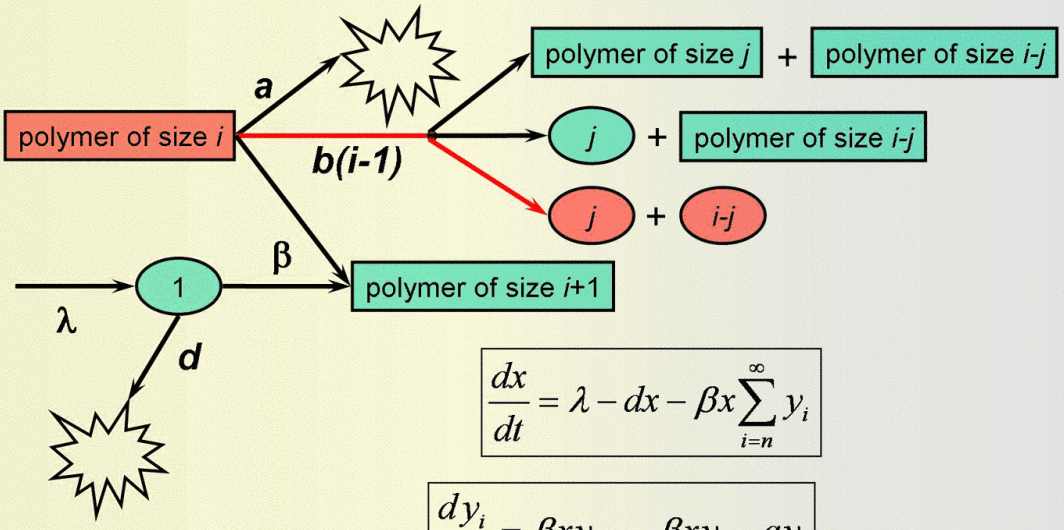
each PrPsc-polymer of size *i* breaks at each of its *i*-1 connections at the same rate *b*

case b) one of the parts is smaller than *n*

2. Kinetic model of aggregate formation



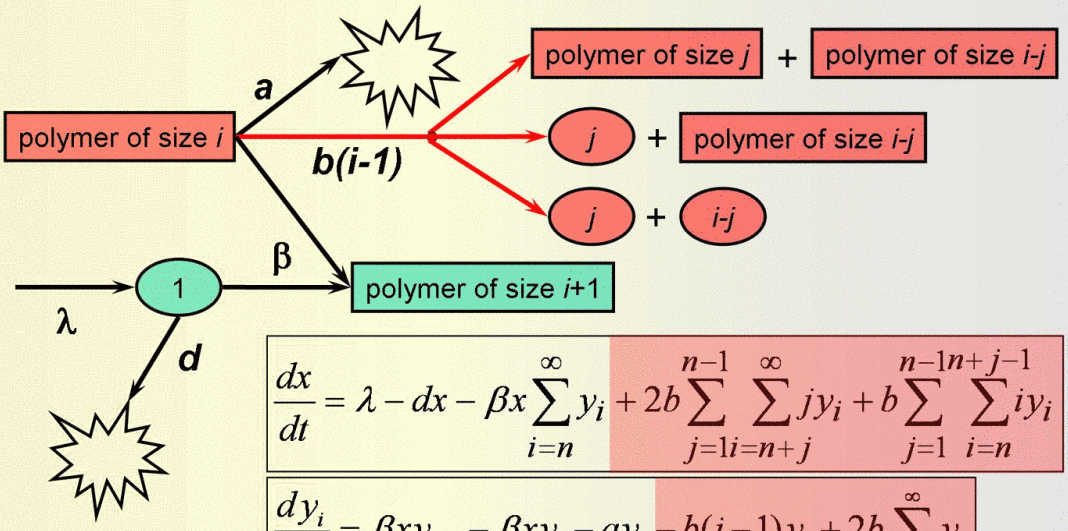
$$\frac{dx}{dt} = \lambda - dx - \beta x \sum_{i=n}^{\infty} y_i$$

$$\frac{dy_i}{dt} = \beta x y_{i-1} - \beta x y_i - a y_i$$

each PrPsc-polymer of size *i* breaks at each of its *i*-1 connections at the same rate *b*

case c) both parts are smaller than *n*

2. Kinetic model of aggregate formation



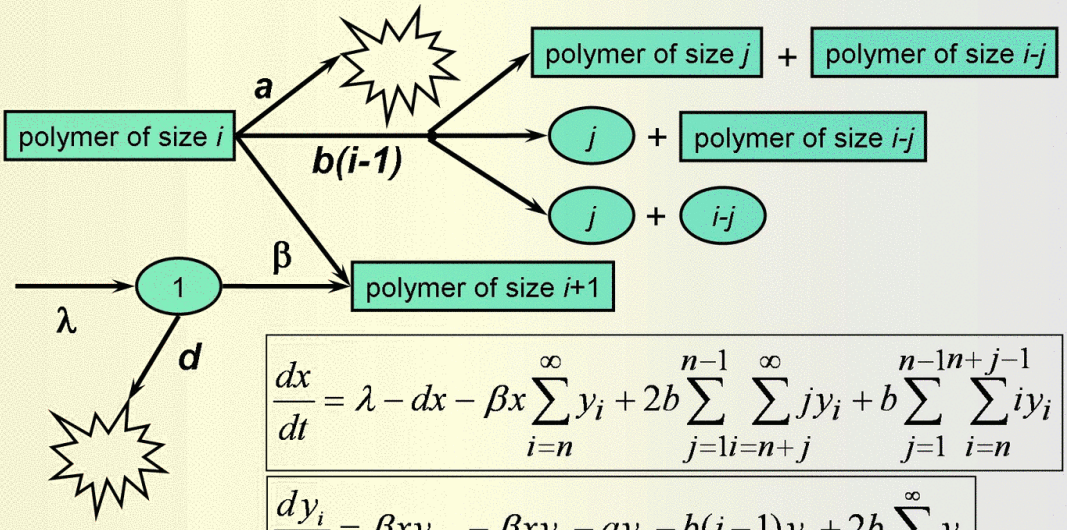
$$\frac{dx}{dt} = \lambda - dx - \beta x \sum_{i=n}^{\infty} y_i + 2b \sum_{j=1}^{n-1} \sum_{i=n+j}^{\infty} j y_i + b \sum_{j=1}^{n-1} \sum_{i=n}^{n+j-1} i y_i$$

$$\frac{dy_i}{dt} = \beta x y_{i-1} - \beta x y_i - a y_i - b(i-1) y_i + 2b \sum_{j=i+1}^{\infty} y_i$$

each PrPsc-polymer of size *i* breaks at each of its *i*-1 connections at the same rate *b*

cases a,b,c)

2. Kinetic model of aggregate formation



$$\frac{dx}{dt} = \lambda - dx - \beta x \sum_{i=n}^{\infty} y_i + 2b \sum_{j=1}^{n-1} \sum_{i=n+j}^{\infty} j y_i + b \sum_{j=1}^{n-1} \sum_{i=n}^{n+j-1} i y_i$$

$$\frac{dy_i}{dt} = \beta x y_{i-1} - \beta x y_i - a y_i - b(i-1) y_i + 2b \sum_{j=i+1}^{\infty} y_i$$

Thus, the kinetics of the system is complete

2. Kinetic model of aggregate formation

$$\frac{dx}{dt} = \lambda - dx - \beta x \sum_{i=n}^{\infty} y_i + 2b \sum_{j=1}^{n-1} \sum_{i=n+j}^{\infty} j y_i + b \sum_{j=1}^{n-1} \sum_{i=n}^{n+j-1} i y_i$$

monomers

$$\frac{dy_i}{dt} = \beta x y_{i-1} - \beta x y_i - a y_i - b(i-1) y_i + 2b \sum_{j=i+1}^{\infty} y_i$$

polymers of size *i*

further interesting quantities:

$y = \sum_{i=n}^{\infty} y_i$ total number of polymers

$z = \sum_{i=n}^{\infty} i y_i$ total number of monomers, contained in all polymers
= mass of PrPsc material

These quantities are measurable!
Need the corresponding kinetic equations.

2. Kinetic model of aggregate formation

$$\frac{dx}{dt} = \lambda - dx - \beta x \sum_{i=n}^{\infty} y_i + 2b \sum_{j=1}^{n-1} \sum_{i=n+j}^{\infty} j y_i + b \sum_{j=1}^{n-1} \sum_{i=n}^{n+j-1} i y_i$$

monomers

$$\frac{dy_i}{dt} = \beta x y_{i-1} - \beta x y_i - a y_i - b(i-1) y_i + 2b \sum_{j=i+1}^{\infty} y_i$$

polymers of size *i*

$$y = \sum_{i=n}^{\infty} y_i$$

$$z = \sum_{i=n}^{\infty} i y_i$$

$$\frac{dx}{dt} = \lambda - dx - \beta x y + n(n-1) b y$$

$$\frac{dy}{dt} = -ay + bz + (1-2n) b y$$

$$\frac{dz}{dt} = -\beta x y - az - bn(n-1) y$$

closed set of coupled differential equations

2a. Constant concentration of monomers

assumption: $x(t) = x_0 = const.$ is regulated by some external process

$$\frac{dy}{dt} = -ay + bz + (1-2n) b y$$

$$\frac{dz}{dt} = -\beta x_0 y - az - bn(n-1) y$$

only solution: exponential growth

$$y(t) = C_1 \exp(r_1 t) + C_2 \exp(r_2 t)$$

$$z(t) = D_1 \exp(r_1 t) + D_2 \exp(r_2 t)$$

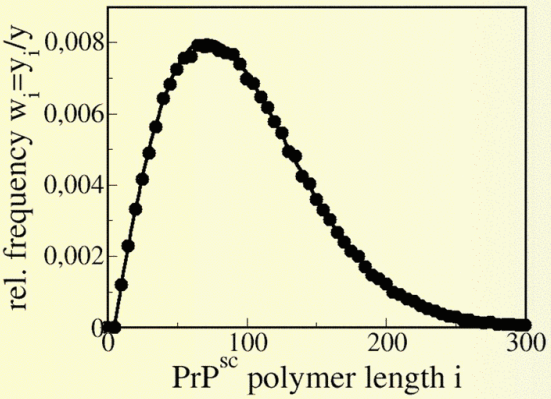
stationary characteristics: polymer size distribution

dynamical characteristics: temporal evolution of the average size

➔ scenarios after an infection

2a. Constant concentration of monomers

polymer size distribution



full analytic solution:

$$w_i = \frac{q_i - q_{i+1}}{q_n}$$

$$q_k = (k+\nu_0)\exp\left(-\nu_2(k+\nu_0)^2/2\right)$$

$$\nu_0 = (a + r_1 + b)/b$$

$$\nu_2 = b/\beta x_0$$

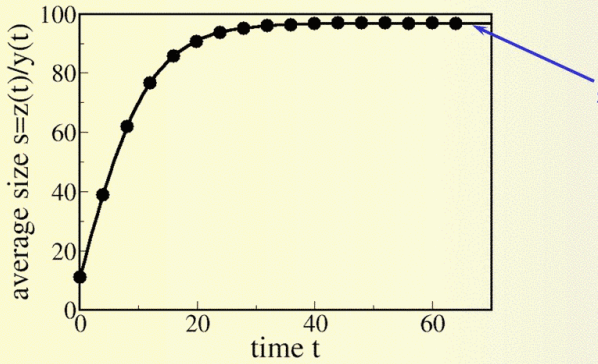
$$r_1 = -a - bn + \frac{b}{2} + \frac{1}{2}\sqrt{b^2 + 4b\beta x_0}$$

details: Pöschel, Brilliantov, Frömmel, Biophys. J. 85, 3460 (2003)

distribution completely determined by the rates, n, and x_0

2a. Constant concentration of monomers

evolution of the average size of the polymers $s(t) = z(t)/y(t)$

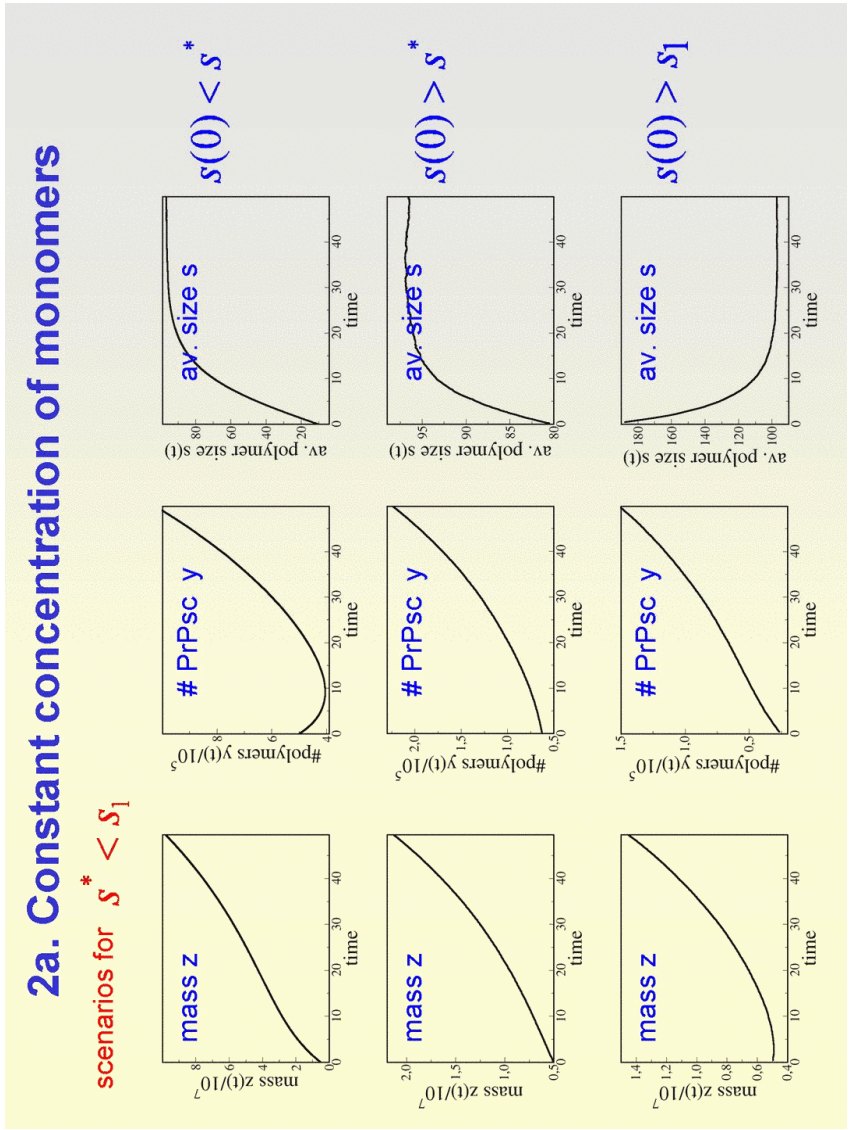


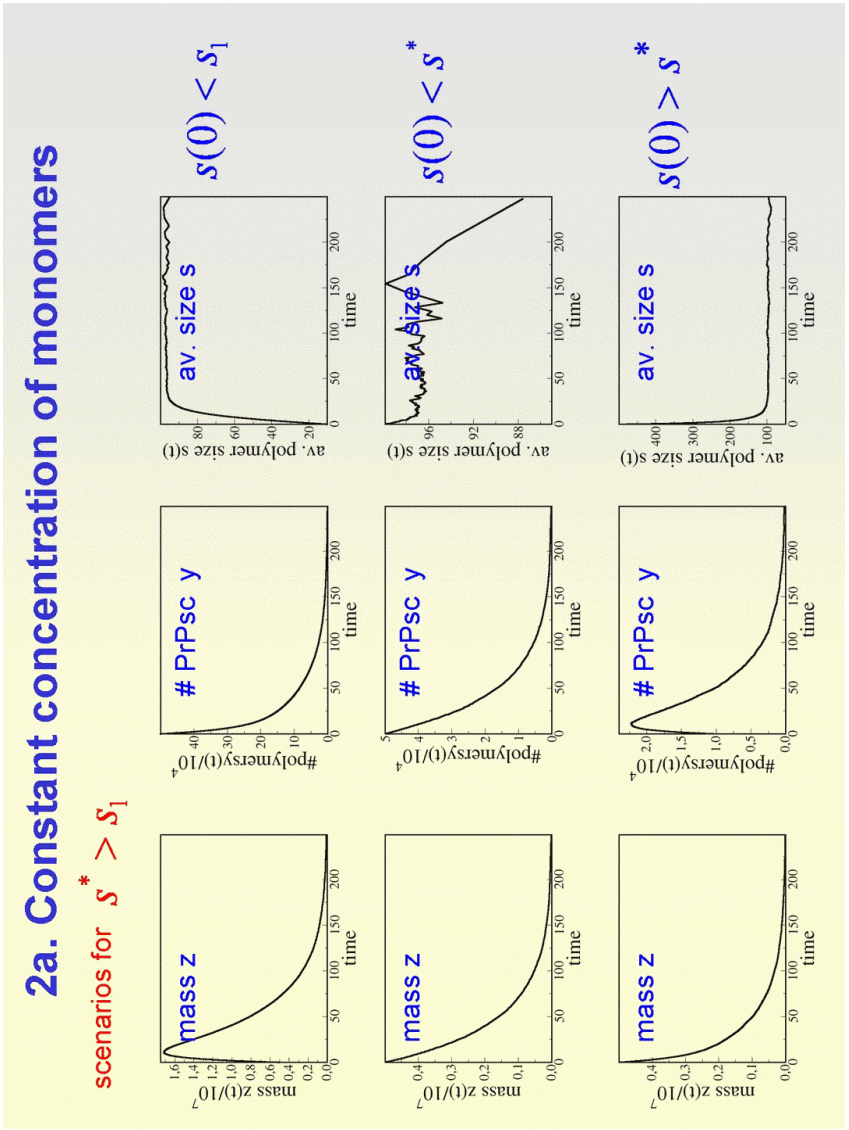
$$s_1 = n - \frac{1}{2} + \sqrt{\frac{\beta x_0}{b} + \frac{1}{4}}$$

$$\frac{dy}{dt} = b(s - s^*)y \quad \text{mit} \quad s^* = (2n-1) + a/b$$

→Depending on the initial average size of the polymers, and, thus, of the (regulated) monomer concentration, x_0 , there are different scenarios

complete cure if $s_1 < s^*$, i.e. $x_0 < x^*$ with $x^* = \frac{b}{\beta}\left(n + \frac{a}{b}\right)\left(n - 1 + \frac{a}{b}\right)$

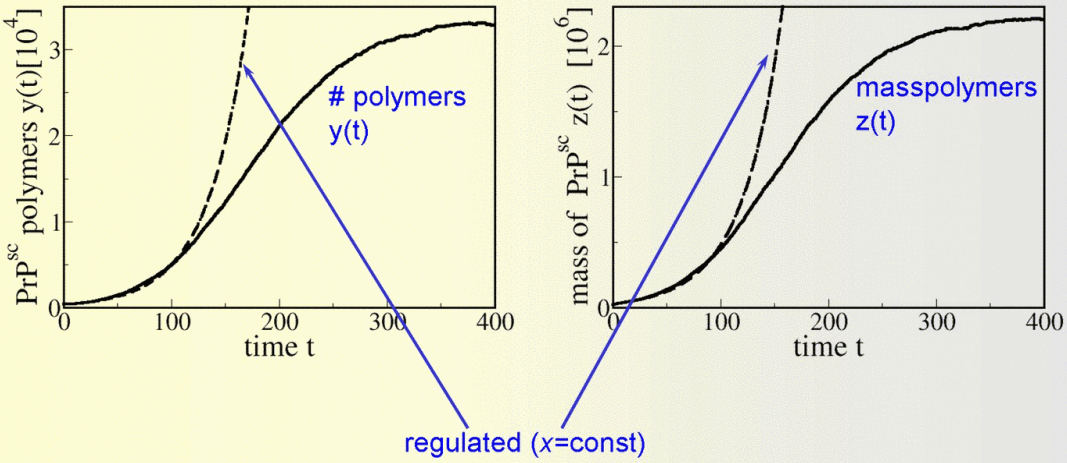

2a. Constant concentration of monomers
scenarios for $s^* < s_1$
$s(0) < s^*$
$s(0) > s^*$
$s(0) > s_1$
av. size s
PrPsc y
mass z
av. polymer size s(t)
#polymers y(t)/10^5
mass z(t)/10^7
time


2a. Constant concentration of monomers
scenarios for $s^* > s_1$
$s(0) < s_1$
$s(0) < s^*$
$s(0) > s^*$
av. size s
PrPsc y
mass z
av. polymer size s(t)
#polymersy(t)/10^4
mass z(t)/10^7
time

2b. Variable concentration of monomers

release the constraint $x(t) = x_0 = const.$ (no external regulation)

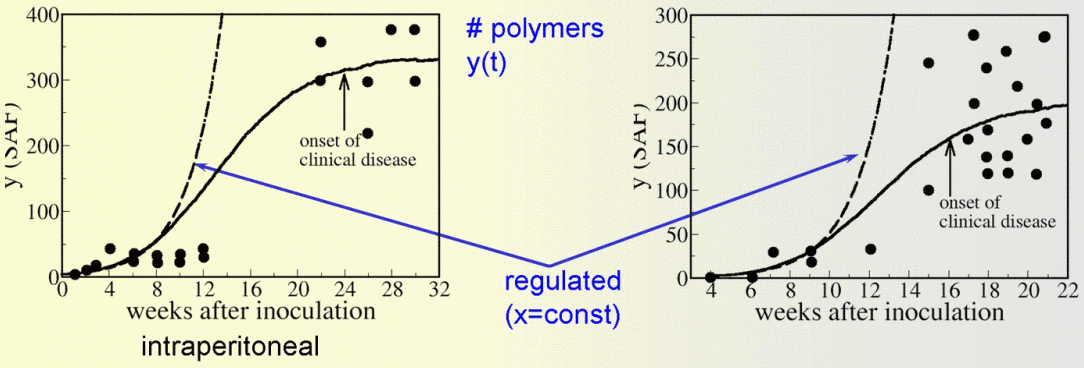
polymers y(t) and total mass z(t)



3. Comparison with experiments

if onset of clinical disease during exponential growth → no discrimination
(Beekes et al.'96, Taylor et al.'00, Kimberlin & Walker'86,…)

Model can be verified, if clinical disease occurs during the saturation:
Rubenstein et al'91: intracerebrale + intraperitonale infection of SAF in mice;
aggregates measured by negative-stain microscopy



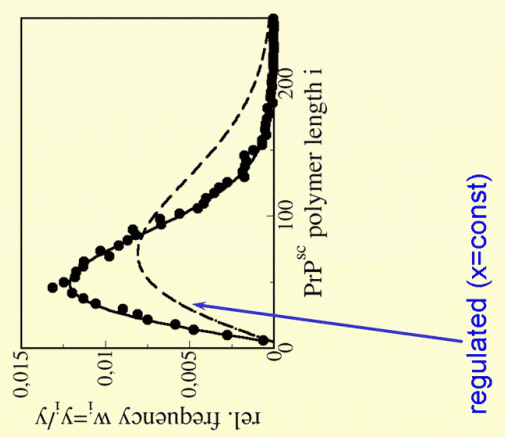
→ Complete (unregulated) model supported by experiments

Exponential fit? → doubling periode of 25 days.
Our fit: initial doubling periode T=2.6 days (Beekes et al.'96, Taylor et al.'00,..)

4. Some consequences (full model)

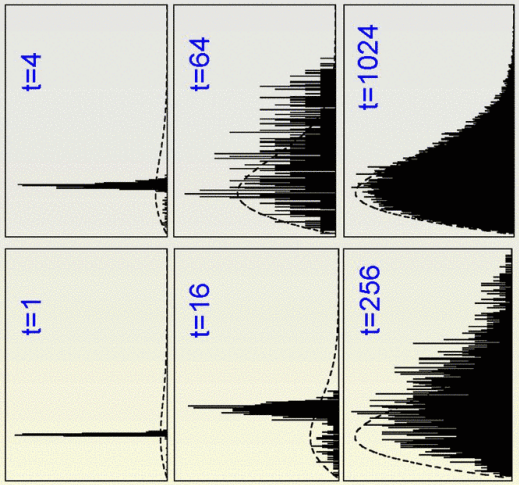
(no assumption $x(t) = x_0 = const.$ unregulated)

size distribution of polymers



regulated (x=const)

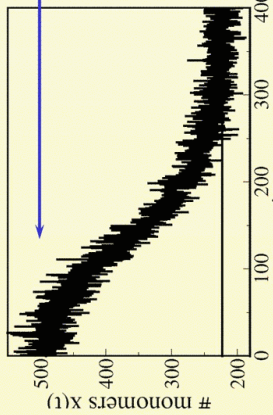
evolution of size distribution



4. Some consequences (full model)

evolution of the monomer concentration

regulated value



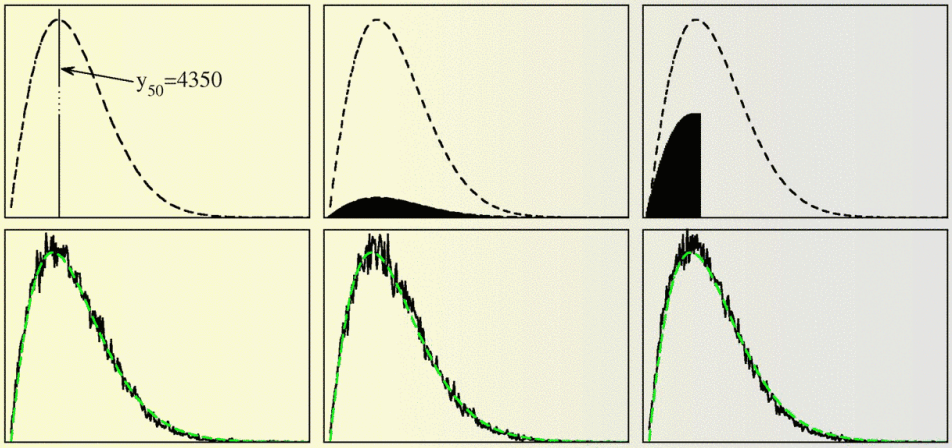
evolution of average polymer size s=z(t)/y(t)

diagnosis ?

4. Some consequences – filtering

size distribution for different initial conditions (equal total mass)

delta shaped | natural | filtered



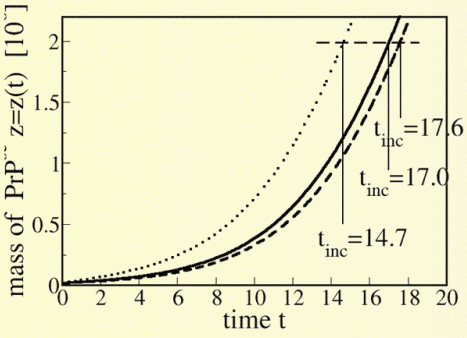
total mass = 2,000,000

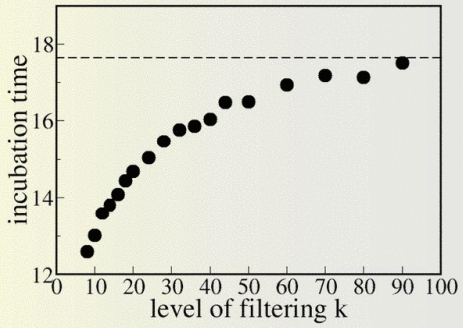
After short time the shape of the distributions converge to the same value.

The total masses of PrPsc, z(t), are very different!

4. Some consequences – filtering

total mass of PrPsc for different level of filtering (same inhitial mass)





➔ Incubation periode is significantly determined by filtering.

Infected mice fell ill as soon as there was a certain amount of PrPsc in their brain, independently of the incubation time and inoculation dose
(Manson et al.'94, Büelen et a;.'94)

→ define incubation period as the time when a certain amount PrPsc is produced (here 2,000,000).

5. Sumary

- complete mathematical model for the kinetics of aggregate formation, based on the modell by Masel et al.'99
- regulated monomer-concentration $x(t) = x_0 = const.$
  → exponential growth or exponential decay
- unregulated monomer-concentration (full model)
  → saturation (experimentally confirmed)
- aggregate size distribution for both cases →diagnosis ?
  experiments ???
- Effect of filtering on the incubation periode
  → for constant total mass of inoculated PrPsc, the incubation periode may vary by the factot 5 for different levels of filtering
  → possible implications for experimental treatment (e.g. ultrasonic treatment)

details: Pöschel, Brilliantov, Frömmel,
Biophys. J. 85, 3460 (2003)
Biophys. J. 87, 729 (2004)