



A Becker-Döring type model for oscillatory aggregation kinetics in prion dynamics

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joint work with

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Journal of Theoretical Biology, **480** (2019) pp. 241–261.

Prions

Prion is derived from **proteinaceous infectious particle**.

The **prion phenomenon** involves

**self-propagation of a biological information
through the transfer of structural information**

from a misfolded/infectious protein in a prion-state to the same protein in a non-prion state.

Prion cause various diseases: Creutzfeld-Jacob, ...

Prion-like mechanisms are associated to Alzheimer, Parkinson and Huntington diseases.

Prions

Monomeric prion protein (PrPC) is converted into misfolded aggregating conformers (PrPSc).

PrPSc assemblies have the ability to self-replicate and self-organise (mechanism unknown).

Phenotype differences are assigned to structural differences in PrPSc assemblies.

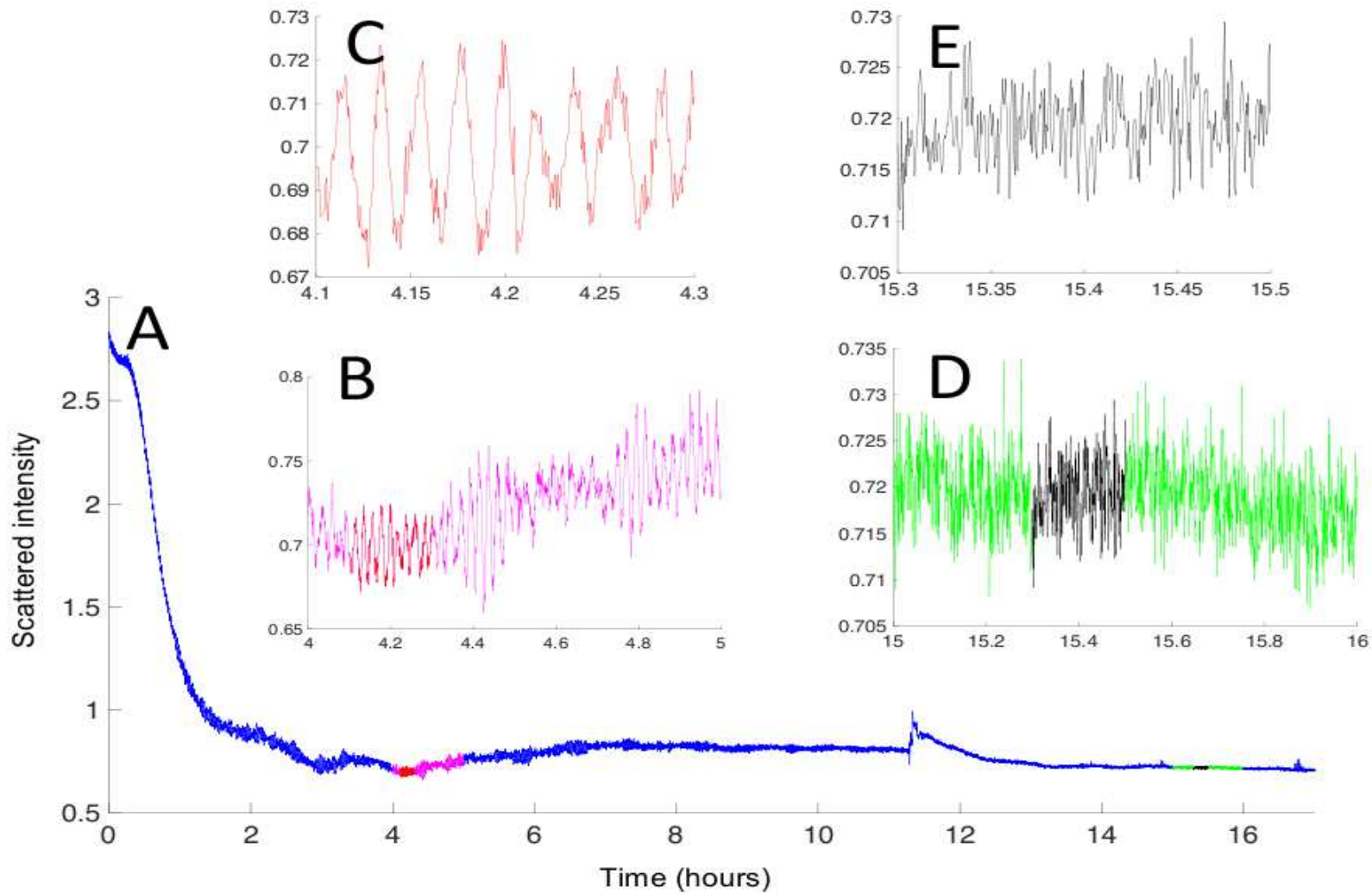
Experiments using Static Light Scattering (SLS) in the lab of Human Rezaei studied the depolymerisation kinetics of recombinant PrP amyloid fibrils.

⇒ surprising, transient oscillations!

The Challenge



Time evolution of the second moment of PrP polymers



Coagulation-fragmentation models

The **Formation** and the **Break-up** of **Clusters/Polymers** in

Physics aerosols, raindrops, smoke, sprays

Chemistry monomers/polymers

Astronomy formation of galaxies

Biology hematology, animal grouping

Coagulation-Fragmentation Models



Macroscopic viewpoint

The **Formation** and the **Break-up** of Clusters/Polymers



assume particles fully described by **mass/size** $y \in Y$.

full/realistic models can quickly get very difficult

Discrete coagulation-fragmentation models



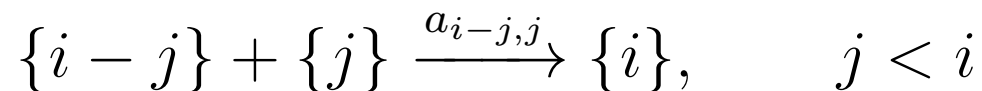
The Smoluchowski coagulation equation [1916/17]

discrete polymer size/mass $i \in \mathbb{N}$, density $c_i(t) \geq 0$, $c = (c_i)$

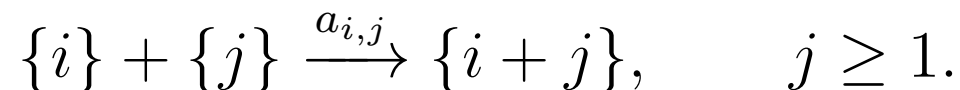
$$\begin{aligned}d_t c_i(t) &= Q_{coag}(c, c) + Q_{frag}(c) \\ &= Q_1(c, c) - Q_2(c, c) + Q_3(c) - Q_4(c)\end{aligned}$$

Binary coagulation:

$Q_1(c, c)$: gain of particles of size i



$Q_2(c, c)$: loss of particles of size i



Discrete coagulation-fragmentation models



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Fragmentation:

$Q_3(c)$: gain of particles of size i

$$\{i + j\} \xrightarrow{B_{i+j}\beta_{i+j,i}} \{i\} + \{j\}, \quad j > 1$$

$Q_4(c)$: loss of particles of size i

$$\{i\} \xrightarrow{B_i} \text{all pairs } \{i - j\} + \{j\} \quad \text{with } j < i.$$

Discrete coagulation-fragmentation equation

Discrete in size coagulation-fragmentation models

$$\partial_t c_i = Q_{i,coag}(c, c) + Q_{i,frag}(c), \quad i \in \mathbb{N},$$

$$Q_{i,coag} = \frac{1}{2} \sum_{j=1}^{i-1} a_{i-j,j} c_{i-j} c_j - \sum_{j=1}^{\infty} a_{i,j} c_i c_j,$$

$$Q_{i,frag} = \sum_{j=1}^{\infty} B_{i+j} \beta_{i+j,i} c_{i+j} - B_i c_i.$$

Coagulation-fragmentation coefficients

$$a_{i,j} = a_{j,i} \geq 0, \quad \beta_{i,j} \geq 0, \quad (i, j \in \mathbb{N}),$$

$$B_1 = 0, \quad B_i \geq 0, \quad (i \in \mathbb{N}),$$

$$(\text{mass conservation}) \quad i = \sum_{j=1}^{i-1} j \beta_{i,j}, \quad (i \in \mathbb{N}, i \geq 2).$$

Weak formulation, conservation of mass

Test-sequence φ_i ,

$$\sum_{i=1}^{\infty} \varphi_i Q_{i,coal} = \frac{1}{2} \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} a_{i,j} c_i c_j (\varphi_{i+j} - \varphi_i - \varphi_j),$$

$$\sum_{i=1}^{\infty} \varphi_i Q_{i,frag} = - \sum_{i=2}^{\infty} B_i c_i \left(\varphi_i - \sum_{j=1}^{i-1} \beta_{i,j} \varphi_j \right).$$

Conservation of total mass or **gelation**

$$\rho(t) = \sum_{i=1}^{\infty} i c_i(t) \leq \sum_{i=1}^{\infty} i c_i^0 = \rho^0.$$

The Becker-Döring model



Interaction between monomers and polymers

The Becker-Döring model only considers (de-)polymerisation with **monomers/clusters-of-size-one**.

System of a **monomer-equation** and **polymer-equations**:

$$\begin{cases} d_t c_1 = -J_1(c) - \sum_{i=1}^{\infty} J_i(c), \\ d_t c_i = J_{i-1}(c) - J_i(c), \quad i \geq 2 \end{cases}$$

where $J_i(c) = a_i c_1 c_i - b_{i+1} c_{i+1}$ ^a

The Becker-Döring model is **detailed balanced!**

^a $a_1 = a_{1,2}/2$, $b_2 = b_{1,1}/2$, and $a_i = a_{i,1}$, $b_i + 1 = b_{i,1}$, $i \geq 2$

Coagulation-Fragmentation models



Detailed balance condition : **continuous and discrete**

non-negative **equilibrium** $E(y) \in L_1^1(Y) := L^1(Y, (1 + y)dy)$:

$$a(y, y')E(y)E(y') = b(y, y')E(y + y'), \quad (y, y') \in Y \times Y$$

This equation is also satisfied by all

$$E_z(y) = E(y) z^y, \quad y \in Y, \quad \text{for } z \geq 0$$

but E_z **not necessarily** in $L_1^1(Y)$. Thus,

$$z_s := \sup\{z \geq 0 : E_z \in L_1^1(Y)\} \in [1, \infty]$$

$$\rho_s := M_1(E_{z_s}(y)) \in [0, \infty].$$

ρ_s is called the **saturation mass**

Entropy and detailed balance

Entropy functional: $H(f|E) = \int_Y f \left(\ln\left(\frac{f}{E}\right) - 1 \right) dy$

H-Theorem $f' = f(y')$, $f'' = f(y + y')$

$$\frac{d}{dt} H(f|E) = -\frac{1}{2} D(f),$$

$$D(f) = \int_Y \int_Y (a f f' - b f'') (\ln(a f f') - \ln(b f'')) dy dy'$$

Dissipation $D(f) = 0$ vanishes only for equilibria,

$$f(t, y) \xrightarrow{t \rightarrow \infty} E_z(y), \quad \begin{cases} z : M_1(E_z) = M_1(f_0) & M_1(f_0) \leq z_s \\ z_s & M_1(f_0) > z_s \end{cases}$$

No sustained oscillatory behaviour possible

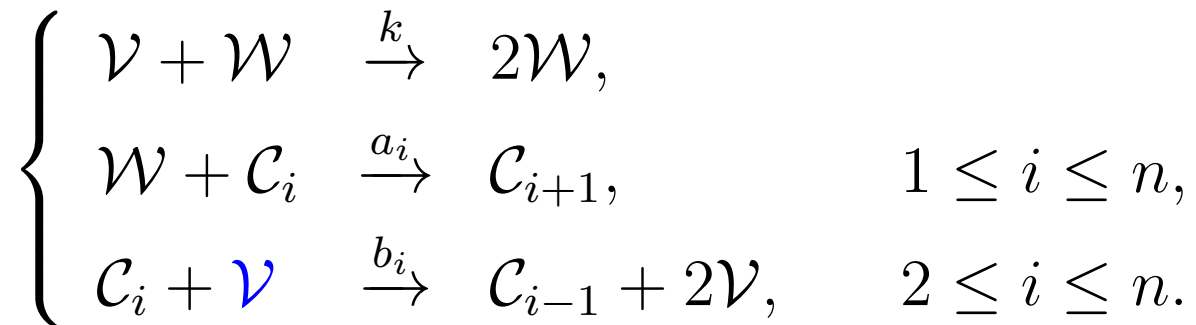
A bi-monomeric, nonlinear Becker-Döring model

\mathcal{V} monomeric species

\mathcal{W} conformer species (assumed monomeric for simplicity)

\mathcal{C}_i polymers built from i monomers

\mathcal{C}_1 **smallest size of "active" polymers** (one for simplicity)



k reaction rate constant for the monomer/conformer.

a_i and b_i polymerisation/depolymerisation coefficients.

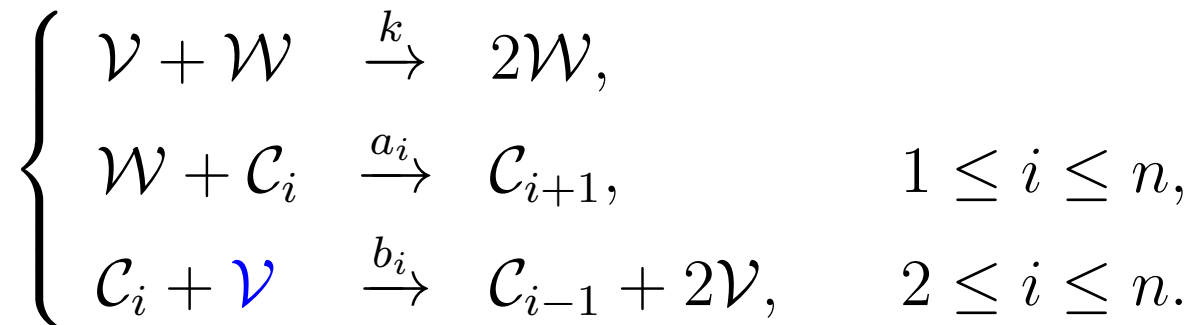
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Key modifications compared to Becker-Döring:

- two monomeric species
- monomer induced **nonlinear depolymerisation**

Equations and formal properties



A bi-monomeric, nonlinear Becker-Döring model

Define with $J_0 = J_n = 0$, $n \in \mathbb{N}$ or $J_0 = 0$, $n = \infty$

$$J_i(t) = a_i w(t)c_i(t) - b_{i+1} v(t)c_{i+1}(t), \quad 1 \leq i \leq n - 1.$$

$$\begin{cases} \frac{dv}{dt} = -kvw + v \sum_{i=2}^n b_i c_i, & v(0) = v^0, \\ \frac{dw}{dt} = -w \sum_{i=1}^{n-1} a_i c_i + kvw, & w(0) = w^0, \\ \frac{dc_i}{dt} = J_{i-1} - J_i, & c_i(0) = c_i^0, \quad 1 \leq i \leq n. \end{cases}$$

Two conservation laws

- Total number of polymers: $P_0 := \sum_{i=1}^n c_i(t)$
- Total mass: $M_{tot} := v(t) + w(t) + \sum_{i=1}^n i c_i(t)$

The two polymer model $n = 2$

The simplest model for $n = 2$

$$\begin{cases} \frac{dv}{dt} = v [-kw + c_2], \\ \frac{dw}{dt} = w [kv - c_1], \end{cases} \quad \begin{cases} \frac{dc_1}{dt} = -wc_1 + vc_2, \\ \frac{dc_2}{dt} = wc_1 - vc_2, \end{cases}$$

transforms upon using the two conservation laws into a **generalised Lotka-Volterra system** for v and w

$$\begin{cases} \frac{dv}{dt} = v [M - (k + 1)w - v], \\ \frac{dw}{dt} = w [(M - P_0) + (k - 1)v - w]. \end{cases}$$

with $M = M_{tot} - P_0$.

The two polymer model $n = 2$

Simplest model for $n = 2$

$$\begin{cases} \frac{dv}{dt} = v [M - (k + 1)w - v], \\ \frac{dw}{dt} = w [(M - P_0) + (k - 1)v - w]. \end{cases}$$

Boundary equilibria $(\bar{v}, \bar{w}) = (M, 0)$ and $(\bar{v}, \bar{w}) = (0, M - P_0)$
(in case $M \geq P_0$).

Positive equilibrium $(v_\infty, w_\infty) > 0$ provided $P_0 \in \left(\frac{kM}{1+k}, kM\right)$

$$v_\infty := \frac{P_0}{k} \left(1 + \frac{1}{k}\right) - \frac{M}{k}, \quad w_\infty := \frac{M}{k} - \frac{P_0}{k^2}.$$

Rescaling two polymer model

Equilibrium (v_∞, w_∞) is of order $\varepsilon := 1/k$.

Rescaling

$$v \rightarrow \frac{v}{k} = \varepsilon v, \quad \text{and} \quad w \rightarrow \frac{w}{k} = \varepsilon w,$$

Rescaled equilibrium values

$$v_\infty = P_0 (1 + \varepsilon) - M, \quad \text{and} \quad w_\infty = M - \varepsilon P_0,$$

Rescaled two polymer system

$$\begin{cases} \frac{dv}{dt} = v [w_\infty - w] - \varepsilon v [v - v_\infty + w - w_\infty], \\ \frac{dw}{dt} = w [v - v_\infty] - \varepsilon w [v - v_\infty + w - w_\infty]. \end{cases}$$

Limiting $\varepsilon = 0$ Hamiltonian system

The case $\varepsilon = 0$ constitutes a classical Lotka-Volterra system

$$\begin{cases} \frac{dv_0}{dt} = v_0 [w_\infty - w_0] = v_0 w_0 \left(-\frac{\partial H}{\partial w_0} \right), \\ \frac{dw_0}{dt} = w_0 [v_0 - v_\infty] = w_0 v_0 \left(\frac{\partial H}{\partial v_0} \right), \end{cases}$$

which is defined by and conserves the **Hamiltonian**

$$H(v, w) = v - v_\infty \ln v + w - w_\infty \ln w$$

$$\frac{d}{dt} H(v_0(t), w_0(t)) = \frac{\partial H}{\partial v} \frac{dv_0}{dt} + \frac{\partial H}{\partial w} \frac{dw_0}{dt} = 0.$$

Any **positive** equilibrium $(v_\infty, w_\infty) > 0$ is the **unique minimiser** of the associated **convex Hamiltonian**.

Exponential convergence to positive equilibrium

Theorem: Let $P_0 \in \left(\frac{kM}{1+k}, kM\right) \Rightarrow$ positive equilibrium (v_∞, w_∞)

Then, the Hamiltonian is a **convex Lyapunov functional** with

$$\frac{d}{dt}H(v(t), w(t)) = -\varepsilon [(v - v_\infty) + (w - w_\infty)]^2.$$

Moreover, for ε sufficiently small, every solution $(v(t), w(t))$ subject to positive initial data $(v_0, w_0) > 0$ satisfies

$$|v - v_\infty|^2 + |w - w_\infty|^2 \leq C (H^0 - H_\infty) e^{-\varepsilon r t}.$$

The rate r and constant C depend only on the initial Hamiltonian value $H^0 := H(v^0, w^0)$ and (v_∞, w_∞) .

Entropy method

Proof: Entropy method for

$$\frac{d}{dt}H(v(t), w(t)) = -\varepsilon p(v, w)^2.$$

Aim for **entropy estimate**

$$\dot{H} \leq -\varepsilon C(H(v, w) - H(v_\infty, w_\infty)).$$

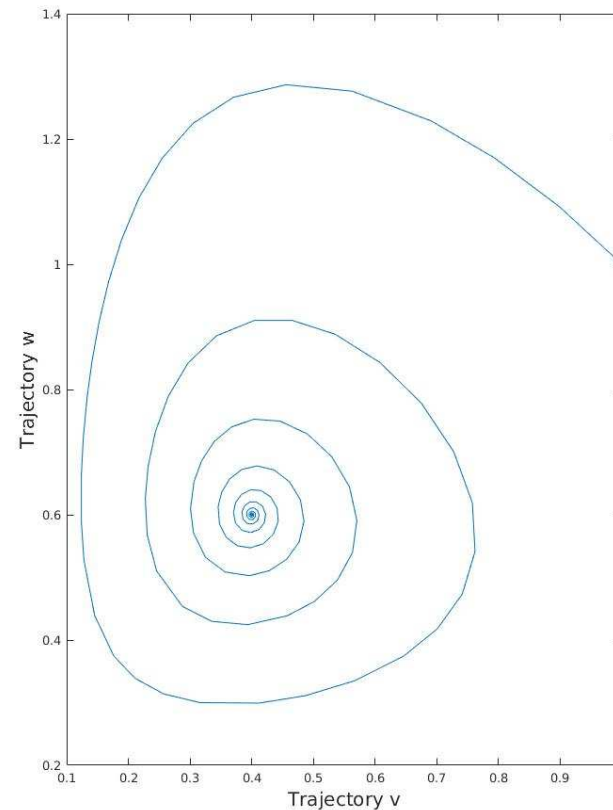
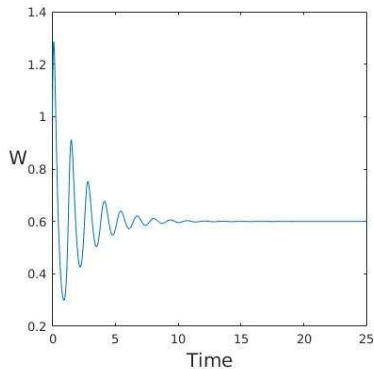
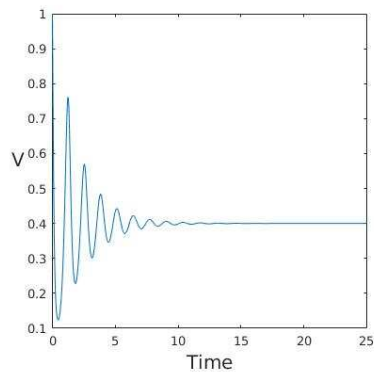
Difficulty due to a degenerate line in (v, w) -phase space:

$$p = 0 \quad \iff \quad w - w_\infty = -(v - v_\infty).$$

Workaround: Show that trajectories cross an area containing $p = 0$ in finite time with finite, positive speed.

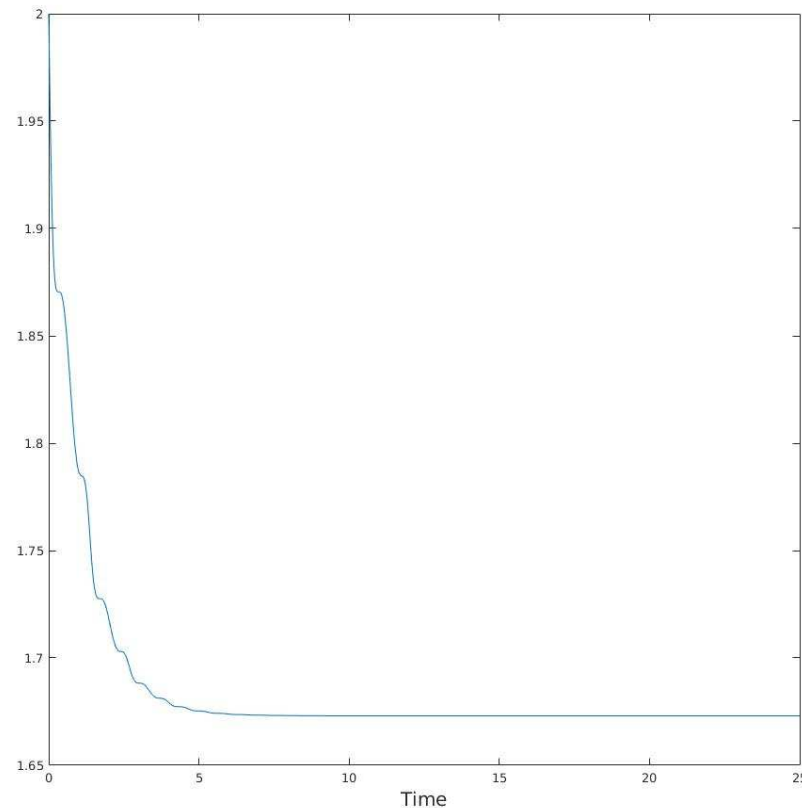
Oscillatory mechanism of two polymer model

Trajectories of the monomeric concentrations v and w for the two-polymer model for $k = 10$, $a = b = 1$ and $\frac{kM}{1+k} < P_0 < kM$.



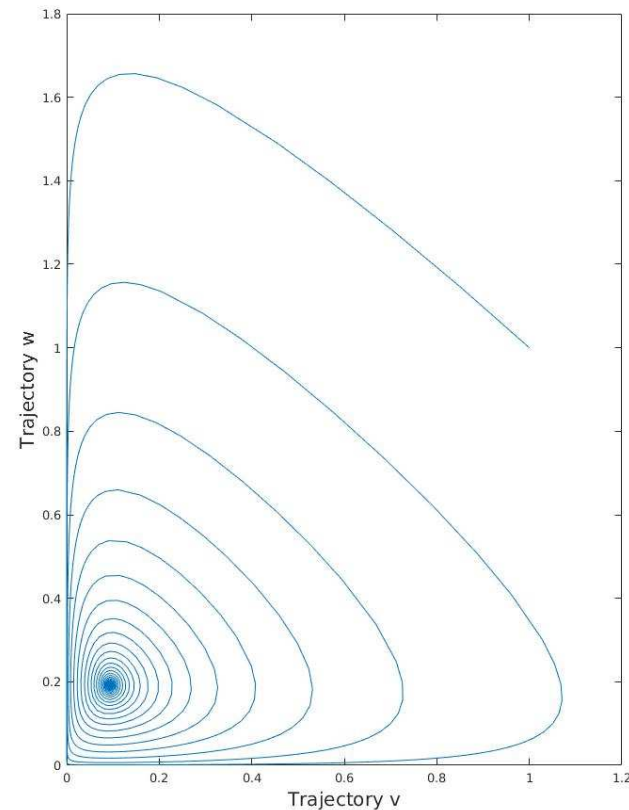
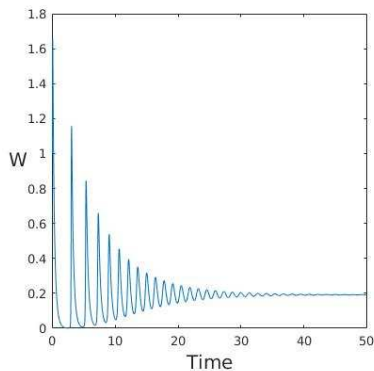
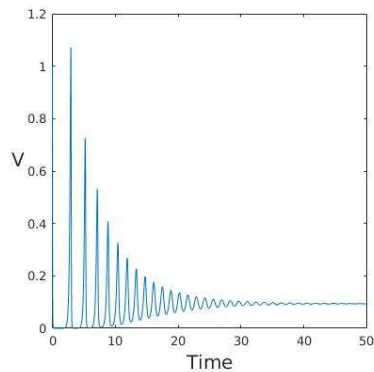
Oscillatory mechanism of two polymer model

Monotone decay of the Lyapunov functional for the two-polymer model for $k = 10$, $a = b = 1$ and $\frac{kM}{1+k} < P_0 < kM$



Oscillatory mechanism of two polymer model

Trajectories of the monomeric concentrations v and w for the two-polymer model for $k = 35$, $a = b = 1$ and $\frac{kM}{1+k} < P_0 < kM$.



Fast transient oscillations

Corollary: For $v = v_0 + \varepsilon v_1 + O(\varepsilon^2)$ and $w = w_0 + \varepsilon w_1 + O(\varepsilon^2)$, we find a **regular perturbation** of the zero order **T -periodic Lotka-Volterra solutions** $(v_0(t), w_0(t))$. The first order terms $(v_1(t), w_1(t))$ satisfy the non-autonomous, inhomogeneous system

$$\begin{pmatrix} \dot{v}_1 \\ \dot{w}_1 \end{pmatrix} = \begin{pmatrix} w_\infty - w_0 & -v_0 \\ w_0 & v_0 - v_\infty \end{pmatrix} \cdot \begin{pmatrix} v_1 \\ w_1 \end{pmatrix} - \begin{pmatrix} v_0(v_\infty - v_0 + w_\infty - w_0) \\ w_0(v_\infty - v_0 + w_\infty - w_0) \end{pmatrix}$$

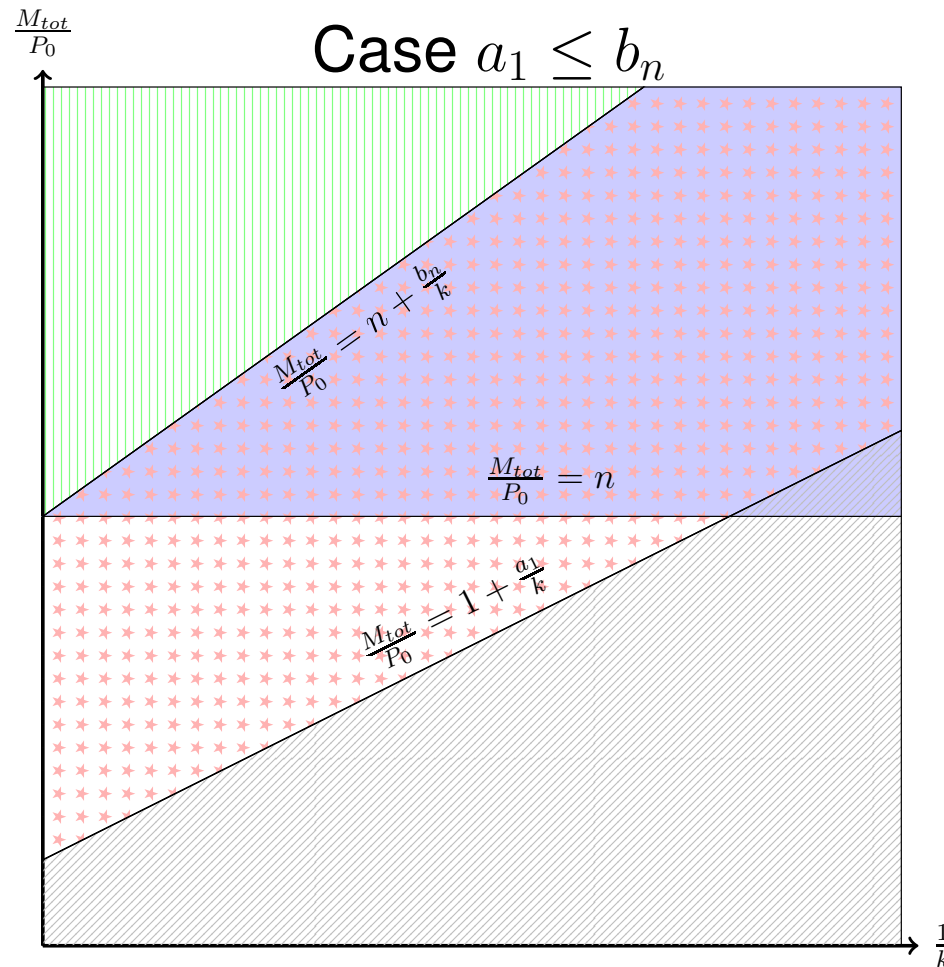
The solutions $(v(t), w(t))$ deviate $O(\varepsilon)$ far from the T -periodic $(v_0(t), w_0(t))$ on a time interval of size $O(T)$ and undergo $O(1/\varepsilon)$ many oscillations before converging to (v_∞, w_∞) .

The finite $n \in \mathbb{N}$ $2nBD$ model



Stationary state analysis

Stability regions of the SSs in $\frac{1}{k} - \frac{M_{tot}}{P_0}$ parametric space:

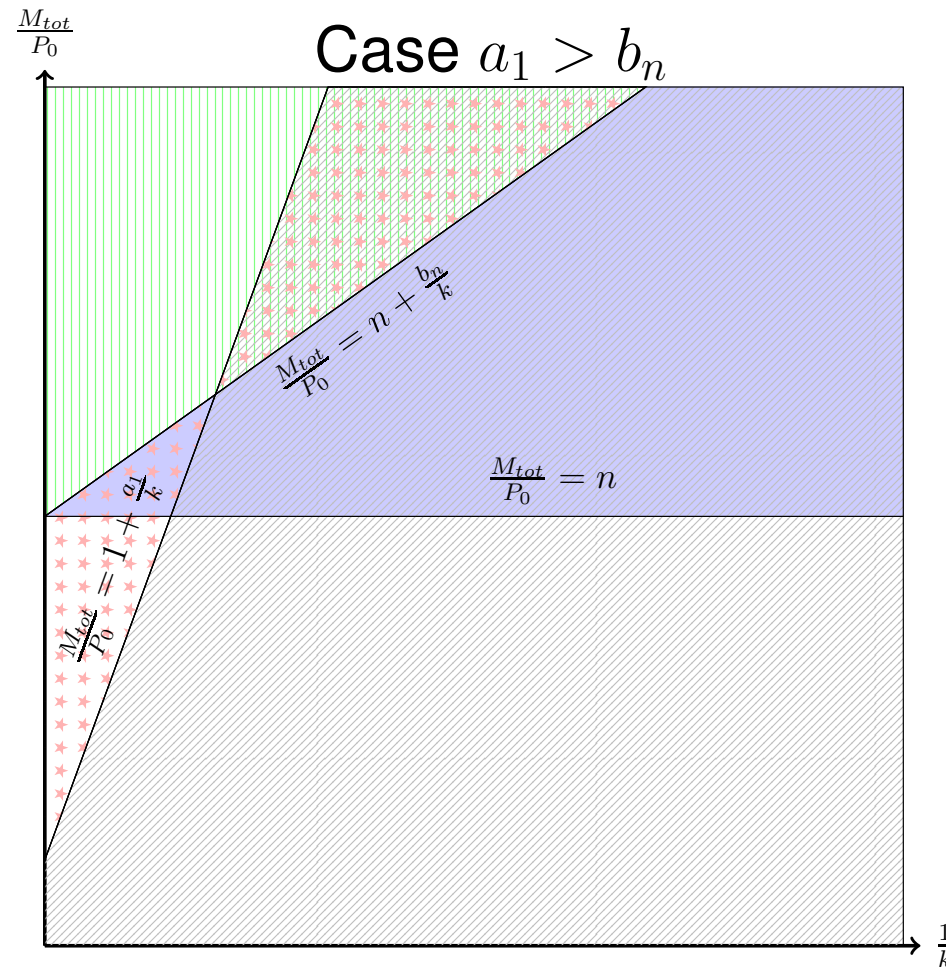


The finite $n \in \mathbb{N}$ $2nBD$ model



Stationary state analysis

Stability regions of the SSs in $\frac{1}{k} - \frac{M_{tot}}{P_0}$ parametric space:



The $n < \infty$ model



Biological Interpretation: Stationary state analysis

A key quantity is

$$\frac{M_{tot}}{P_0} = \frac{\sum i c_i}{P_0} + \frac{v + w}{P_0},$$

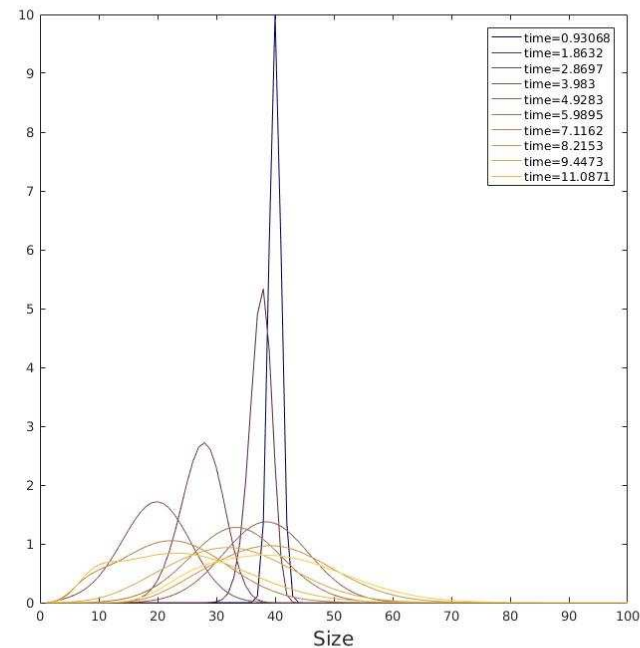
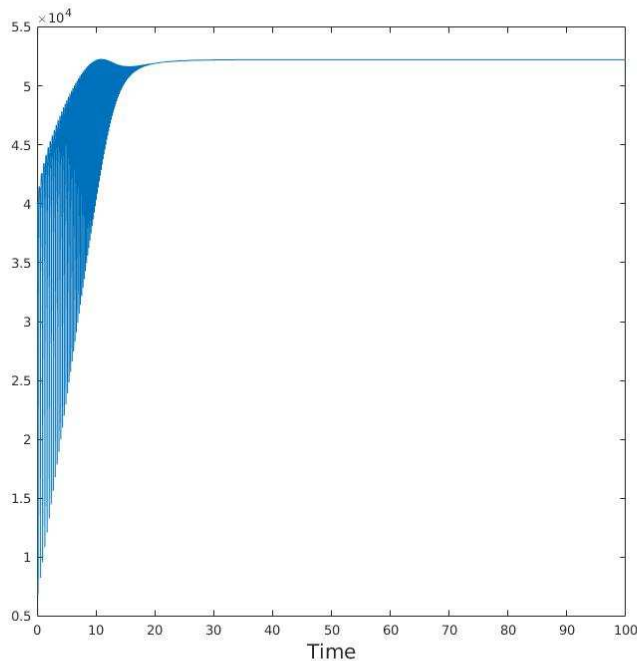
sum of **average polymer size** plus **monomer-polymer ratio**.

The biologically more realistic zone is $\frac{M_{tot}}{P_0} < n$.

Then, there is either **one positive steady state** (conjecture to be stable) or a stable boundary equilibrium with **extinct conformer species** $w = 0$.

Oscillatory mechanism of two polymer model

Convergence to positive SS and evolution of the size distribution (right images). The parameters are $n = 100$, $k = 1.1$, $a = 1.5$, $b = 2$ and $1 + \frac{a}{k} < \frac{M_{tot}}{P_0} < n + \frac{b}{k}$.



The $n = \infty$ model



The constant coefficient case $a_i = a, b_i = b$

A strictly positive steady state $(\bar{v}, \bar{w}, \bar{c}_{i \geq 1})$ is given by

$$\bar{v} = \frac{a}{k}P_0, \quad \bar{w} = \gamma \frac{b}{k}P_0, \quad \bar{c}_1 = (1 - \gamma)P_0, \quad \bar{c}_{i \geq 2} = \gamma^{i-1}(1 - \gamma)P_0,$$

where $\gamma = \frac{1}{2} \left(-\frac{a}{b} + \frac{kM_{tot}}{bP_0} + 1 - \sqrt{\left(\frac{a}{b} - \frac{kM_{tot}}{bP_0} + 1 \right)^2 + \frac{4k}{b}} \right)$.

Obtain **perturbation of predator-pray Lotka-Volterra system**

$$\begin{cases} \frac{dv}{dt} = -kvw + bv(P_0 - c_1), \\ \frac{dw}{dt} = -awP_0 + kvw, \\ \frac{dc_i}{dt} = J_{i-1} - J_i, \quad 1 \leq i. \end{cases}$$

The $n = \infty$ model



The linear coefficient case $a_i = ia$, and $b_{i+1} = ib$

A strictly positive steady state $(\bar{v}, \bar{w}, \bar{c}_{i \geq 1})$ is given by

$$\bar{v} = \frac{aP_0}{k(1-\gamma)}, \quad \bar{w} = \frac{b\gamma P_0}{k(1-\gamma)}, \quad \bar{c}_1 = (1-\gamma)P_0, \quad \bar{c}_{i \geq 2} = \gamma^{i-1}(1-\gamma)P_0,$$

and $\gamma = \frac{M_{tot}k - P_0(a+k)}{M_{tot}k + P_0b} \in (0, 1)$. Introducing $M_1 = M_{tot} - v - w$ yields for $P_0 \ll M_1$ a **perturbation of the Ivanova system**^a

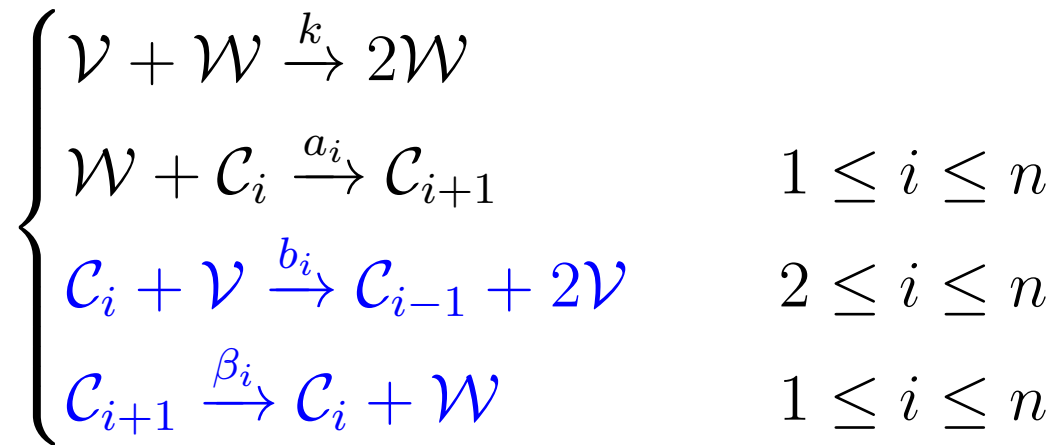
$$\begin{cases} \frac{dv}{dt} = -kvw + vb(M_1 - P_0), \\ \frac{dw}{dt} = -waM_1 + kvw, \\ \frac{dM_1}{dt} = waM_1 - vb(M_1 - P_0). \end{cases}$$

$${}^a \mathcal{V} + \mathcal{W} \xrightarrow{k} 2\mathcal{W}, \quad \mathcal{W} + \mathcal{M} \xrightarrow{a} 2\mathcal{M}, \quad \mathcal{M} + \mathcal{V} \xrightarrow{b} 2\mathcal{V},$$

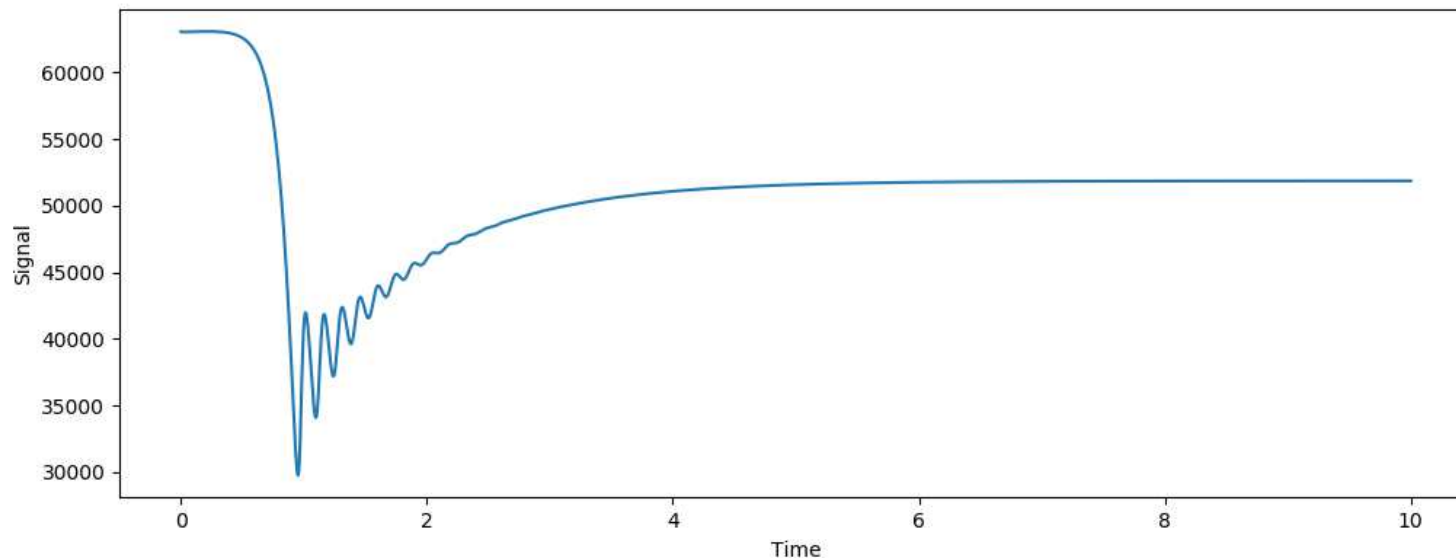
A hybrid bi-monomeric, Becker-Döring Model



Only small fraction of nonlinear depolymerisation



Simulation: $k = 0.3$, $a_i = 2$, $b_i = 0.1$, $\beta_i = 1.9$, $n = 50$.



Conclusions

- Biologist like the suggested mechanism
→ Experiments are needed to test/improve the model.
- Observed oscillatory behaviour should serves as hint towards unraveling the biological machinery.
- Two-polymer model can be solved completely and exemplifies an oscillatory mechanism for large k .
- The models with $n \geq 3$ feature related oscillations as *interaction of monomer species to polymer hierarchy*.
- Our model will needs extensions to explain non-oscillatory behaviour of experiments.

A bi-monomeric, nonlinear BD model



THANK YOU VERY MUCH!