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

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joint work with

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Introduction

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.

Introduction

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).

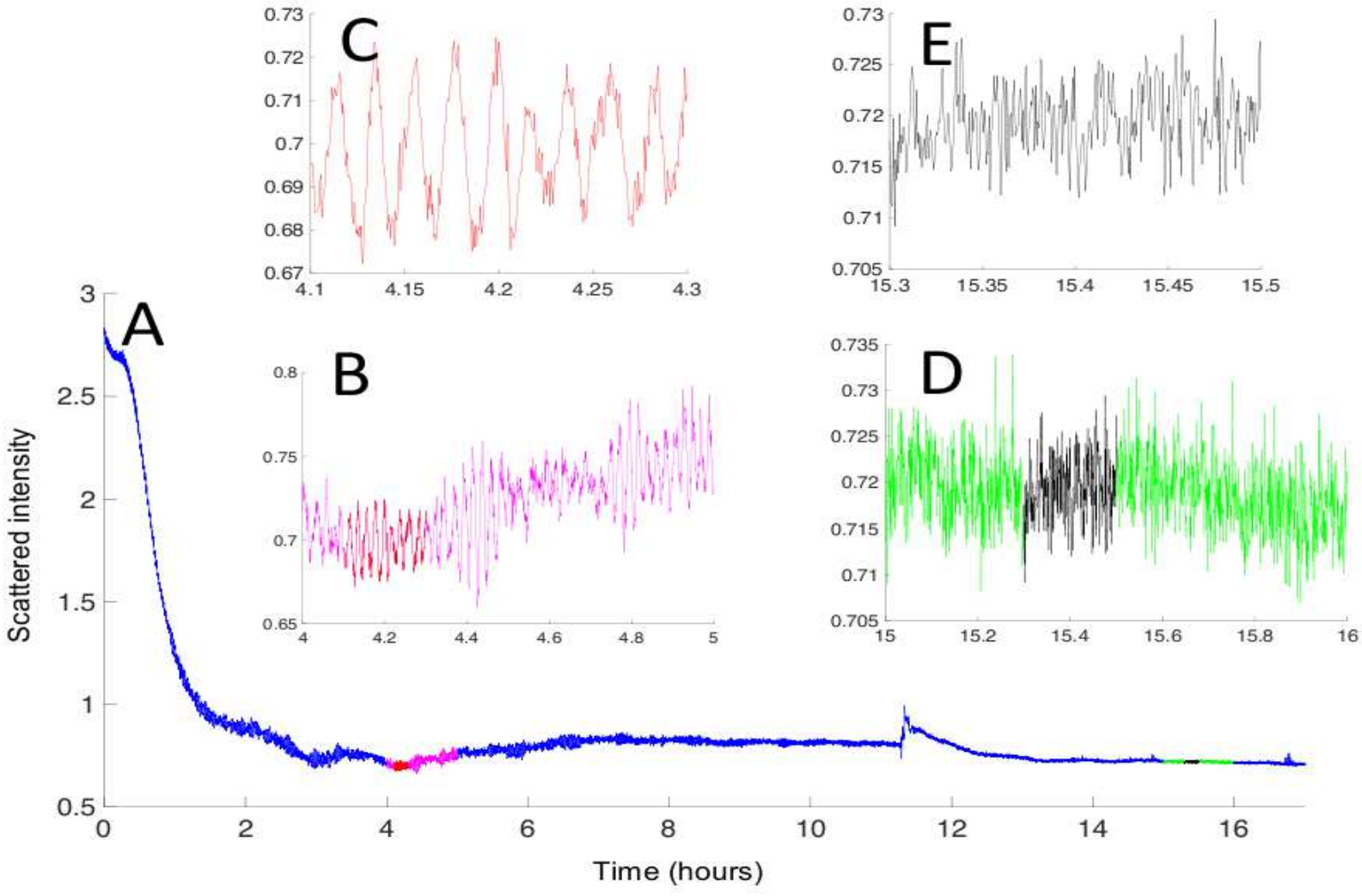
Phenotype differences are assigned to structural differences in PrPSc assemblies.

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

$\Rightarrow$ 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, rainsdrops, 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 $c_i(t) \geq 0, \quad c = (c_i)$

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

Binary coagulation:

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

$$\{i-j\} + \{j\} \xrightarrow{a_{i-j,j}} \{i\}, \qquad j < i$$

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

$$\{i\} + \{j\} \xrightarrow{a_{i,j}} \{i+j\}, \qquad j \geq 1.$$

Discrete coagulation-fragmentation models

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Fragmentation:

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

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

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

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

Discrete coagulation-fragmentation equation

Discrete in size coagulation-fragmentation models

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

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

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

Coagulation-fragmentation coefficients

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

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

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

Discrete coagulation-fragmentation models

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:

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

where $J_i(c) = a_i\, c_1\, c_i - b_{i+1}\, c_{i+1}$ [a]

The Becker-Döring model is detailed balanced!

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[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 $E(y) \in L_1^1(Y) := L^1(Y, (1+y)dy)$:

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

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

Coagulation-Fragmentation models

Entropy and detailed balance

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

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

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

$$D(f) = \int_Y \int_Y (aff' - bf'')(\ln(aff') - \ln(bf'')) \, dy dy'$$

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

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

No sustained oscillatory behaviour possible

Modelling

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)

$$\begin{cases} \mathcal{V} + \mathcal{W} & \xrightarrow{k} & 2\mathcal{W}, & \\ \mathcal{W} + \mathcal{C}_i & \xrightarrow{a_i} & \mathcal{C}_{i+1}, & 1 \le i \le n, \\ \mathcal{C}_i + \mathcal{V} & \xrightarrow{b_i} & \mathcal{C}_{i-1} + 2\mathcal{V}, & 2 \le i \le n. \end{cases}$$

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 $J_0 = 0$, $n = \infty$

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

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

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 $n = 2$

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

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

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

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

The two polymer model $n = 2$

Simplest model for $n = 2$

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

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 $P_0 \in \left(\frac{kM}{1+k}, kM\right)$

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

Rescaling two polymer model

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

Rescaling

$$v \to \frac{v}{k} = \varepsilon v, \qquad \text{and} \qquad w \to \frac{w}{k} = \varepsilon w,$$

Rescaled equilibrium values

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

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

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

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

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

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

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

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:

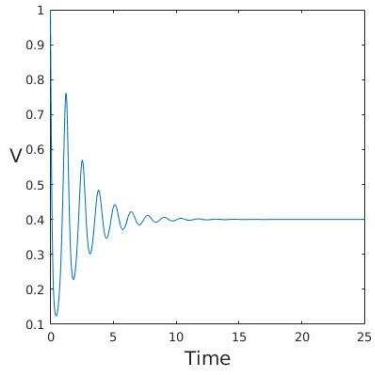
$$p = 0 \quad \Longleftrightarrow \quad w - w_\infty = -(v - v_\infty).$$

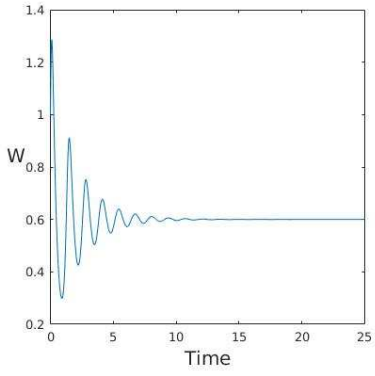
Workaround: Show that trajectories cross an area containing $p = 0$ in finite time with finite, positive speed.

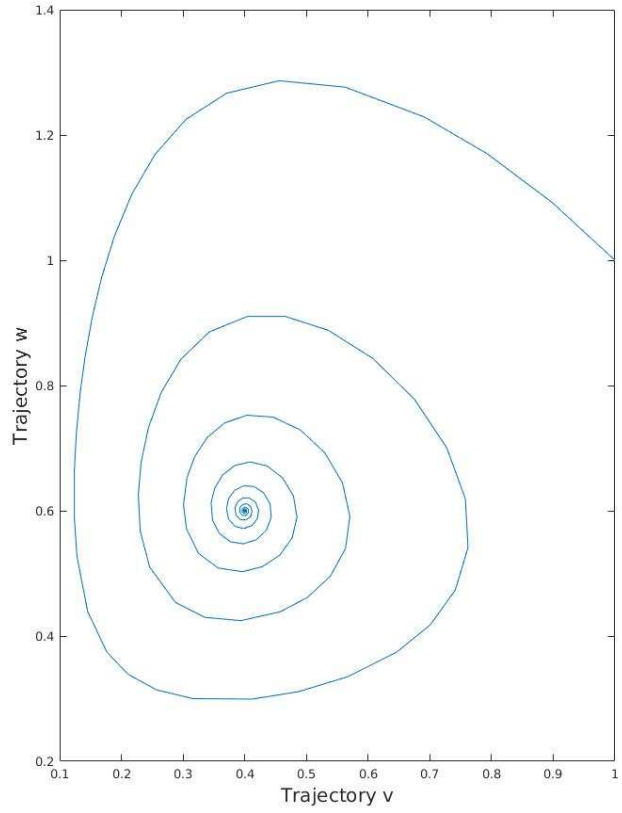
Numerics

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 $\frac{kM}{1+k} < P_0 < kM$.



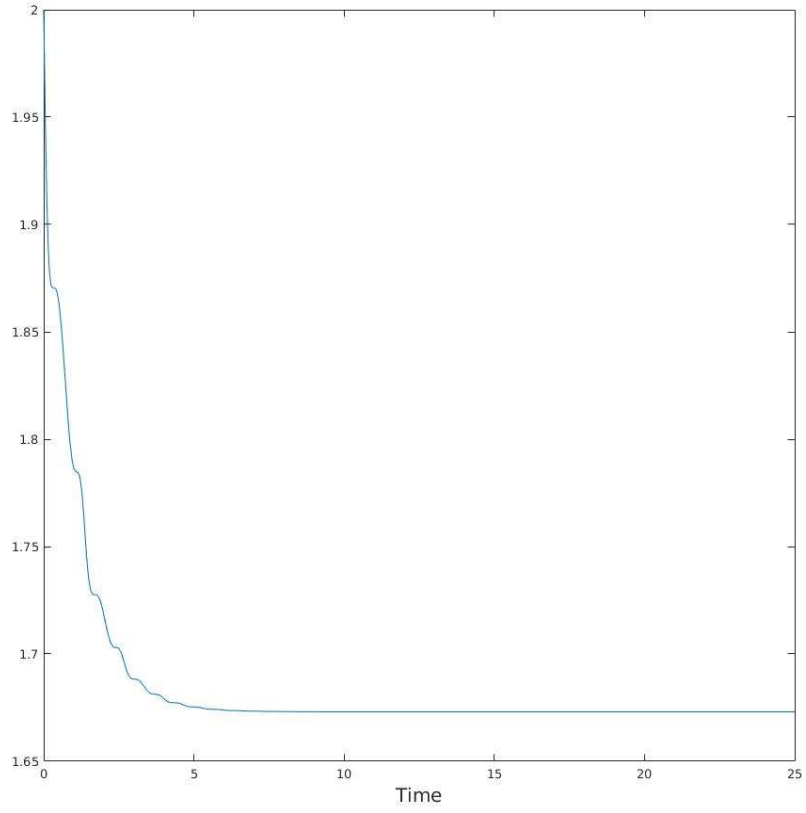




Numerics

Oscilatory mechanism of two polymer model

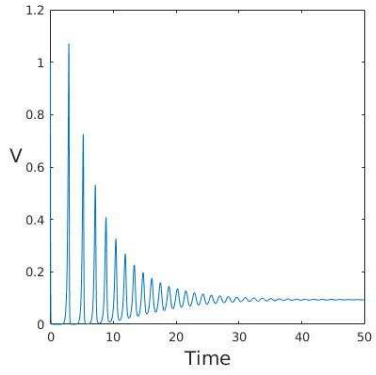
Monotone decay of the Lyapunov functional for the two-polymer model for $k = 10$, $a = b = 1$ and $\frac{kM}{1+k} < P_0 < kM$

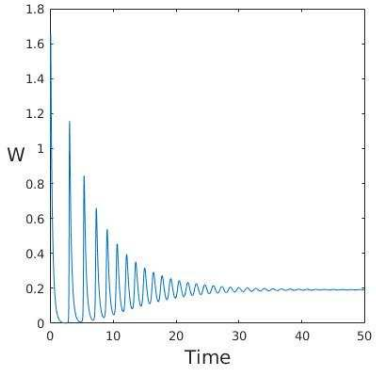


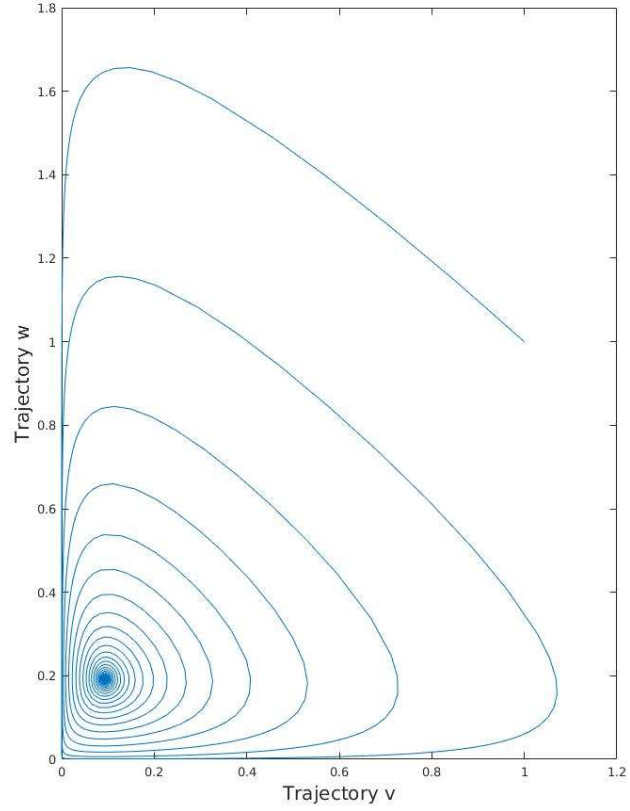
Numerics

Oscilatory 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 $(v_1(t), w_1(t))$ satisfiy the non-autonomous, inhomogeneous system

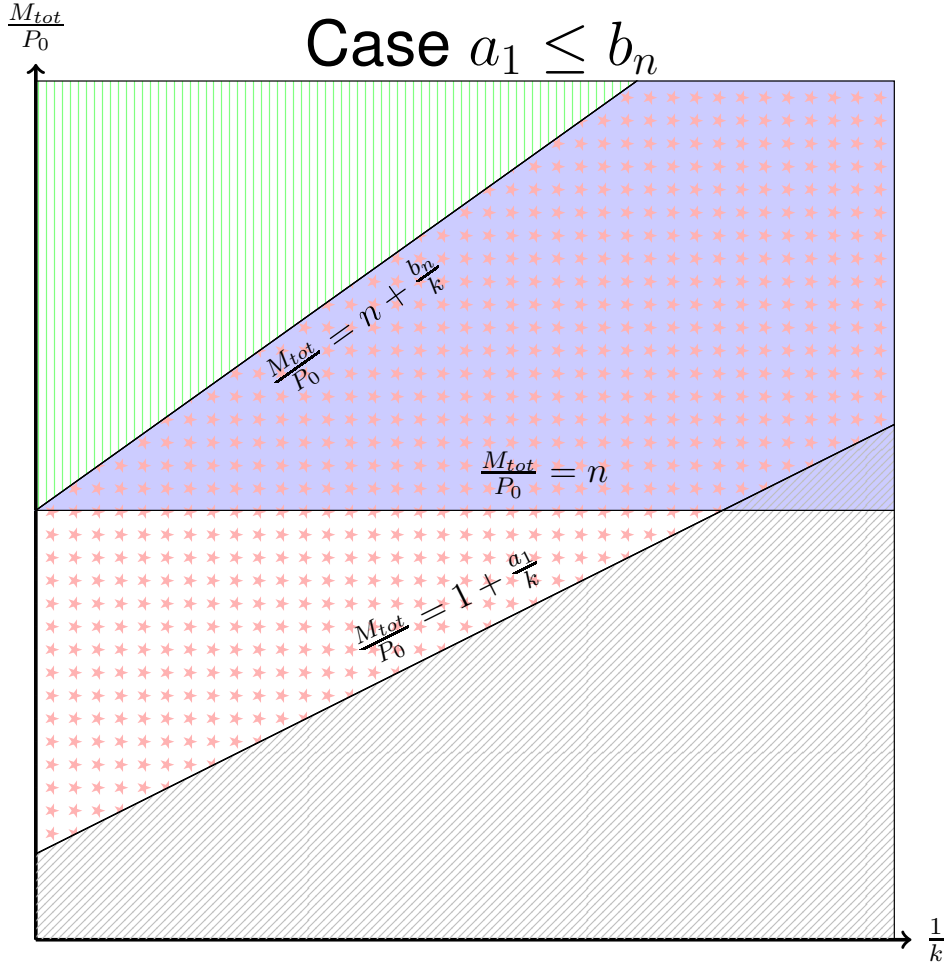
$$\begin{pmatrix} \dot{v}_1 \\ \dot{w}_1 \end{pmatrix} = \begin{pmatrix} w_\infty - w_0 & -v_0 \\ w_0 & v_0 - v_\infty \end{pmatrix} \cdot \begin{pmatrix} v_1 \\ w_1 \end{pmatrix} - \begin{pmatrix} v_0(v_\infty - v_0 + w_\infty - w_0) \\ w_0(v_\infty - v_0 + w_\infty - w_0) \end{pmatrix}$$

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:



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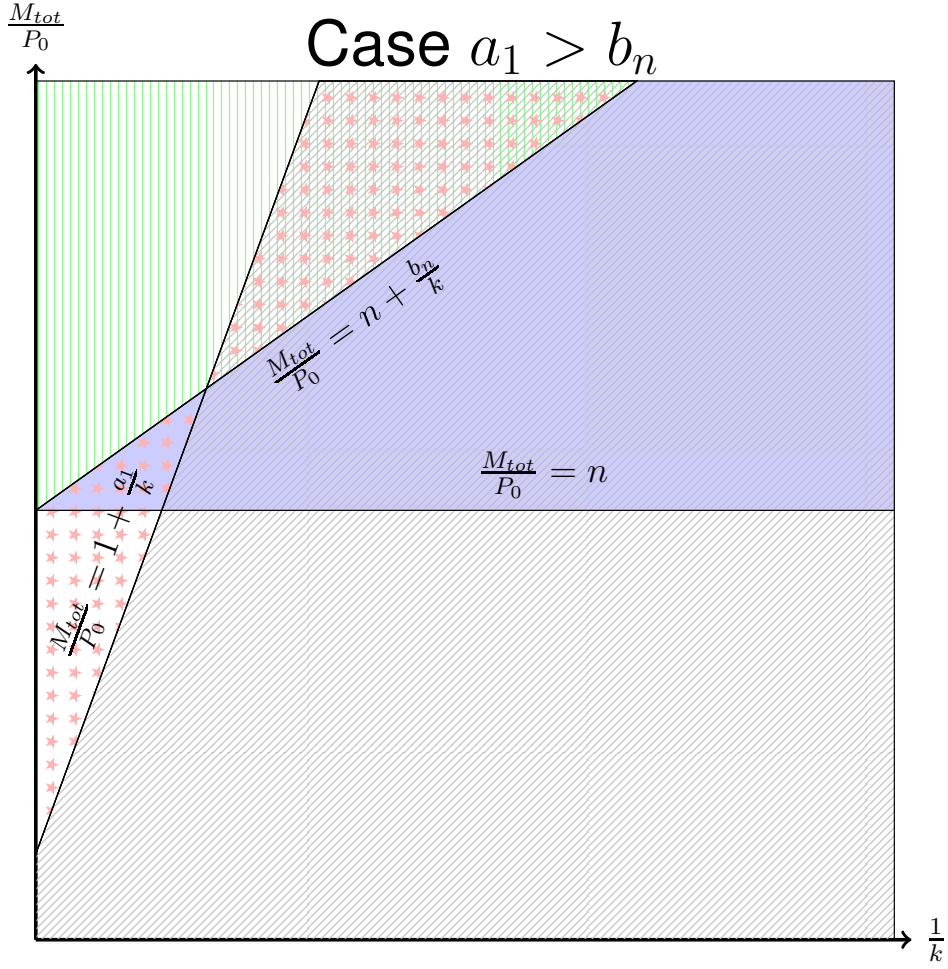


The $n < \infty$ model

Biological Intepretation: Stationary state analysis

A key quantity is

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

sum of average polymer size plus momomer-polymer ratio.

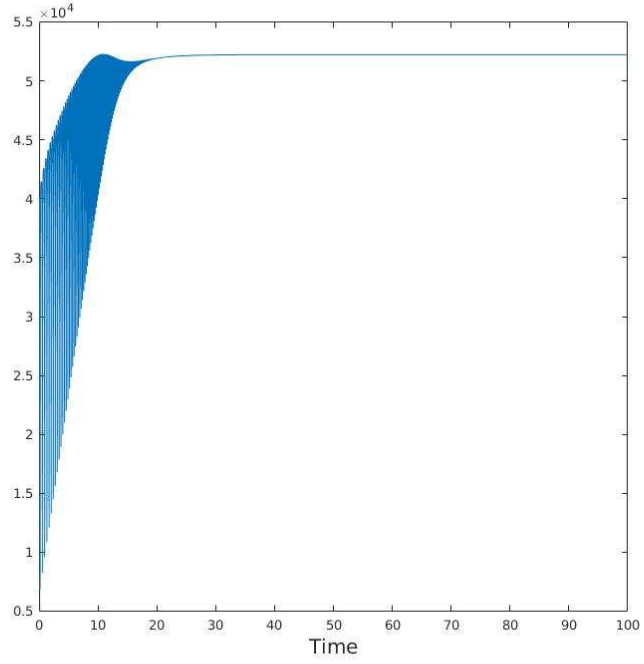
The biologically more realistic zone is $\frac{M_{tot}}{P_0} < n$.

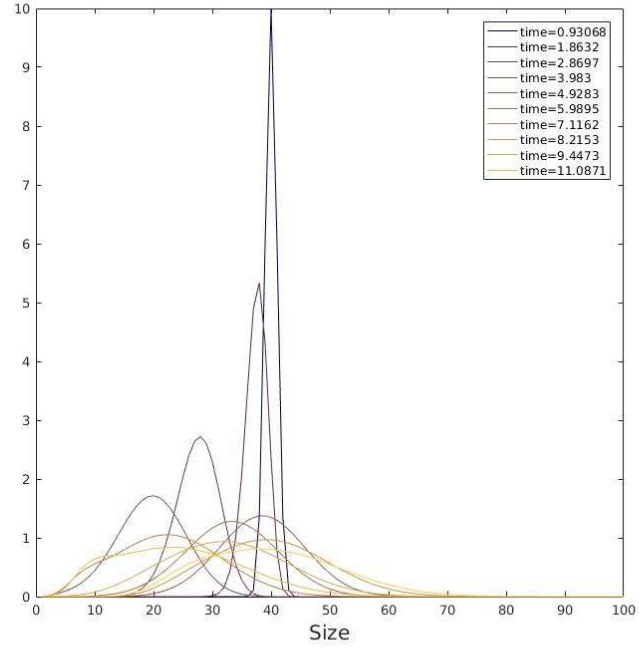
Then, there is either one positive steaty state (conjecture to be stable) or a stable boundary equilibrium with extinged conformer species $w = 0$.

Numerics

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

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

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

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

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

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

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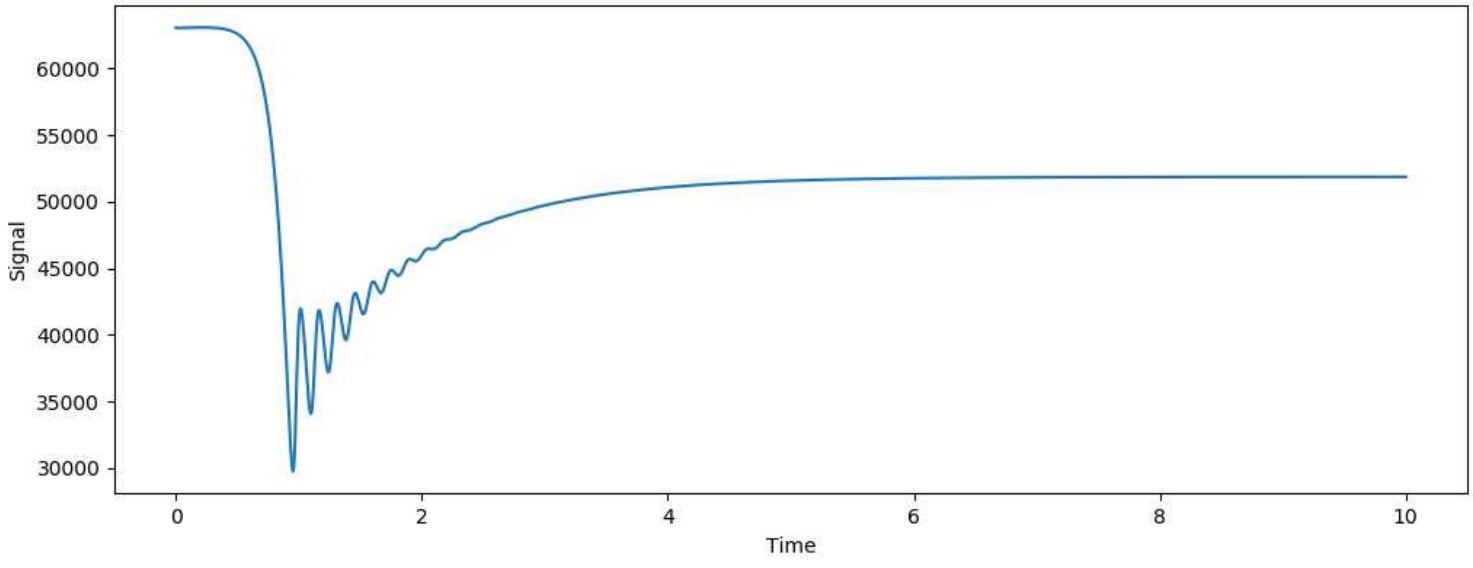
[a] $\mathcal{V} + \mathcal{W} \xrightarrow{k} 2\mathcal{W}, \qquad \mathcal{W} + \mathcal{M} \xrightarrow{a} 2\mathcal{M}, \qquad \mathcal{M} + \mathcal{V} \xrightarrow{b} 2\mathcal{V},$

A hybrid bi-monomeric, Becker-Döring Model

Only small fraction of nonlinear depolymerisation

$$\begin{cases} \mathcal{V} + \mathcal{W} \xrightarrow{k} 2\mathcal{W} & \\ \mathcal{W} + \mathcal{C}_i \xrightarrow{a_i} \mathcal{C}_{i+1} & 1 \le i \le n \\ \mathcal{C}_i + \mathcal{V} \xrightarrow{b_i} \mathcal{C}_{i-1} + 2\mathcal{V} & 2 \le i \le n \\ \mathcal{C}_{i+1} \xrightarrow{\beta_i} \mathcal{C}_i + \mathcal{W} & 1 \le i \le n \end{cases}$$

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



Conclusions

- Biologist like the suggested mechanism
  $\rightarrow$ 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 examplfies an oscillatory mechanism for large k.
- The models with $n \geq 3$ feature related oscillations as interaction of momomer species to polymer hierarachy.
- Our model will needs extensions to explain non-oscillatory behaviour of experiments.

A bi-monomeric, nonlinear BD model

THANK YOU VERY MUCH!