From Becker-Döring to oscillatory behaviour in prion dynamics

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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 aggregating conformer (PrPSc) in a prion-state to the same protein in a non-prion state (PrPC).

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

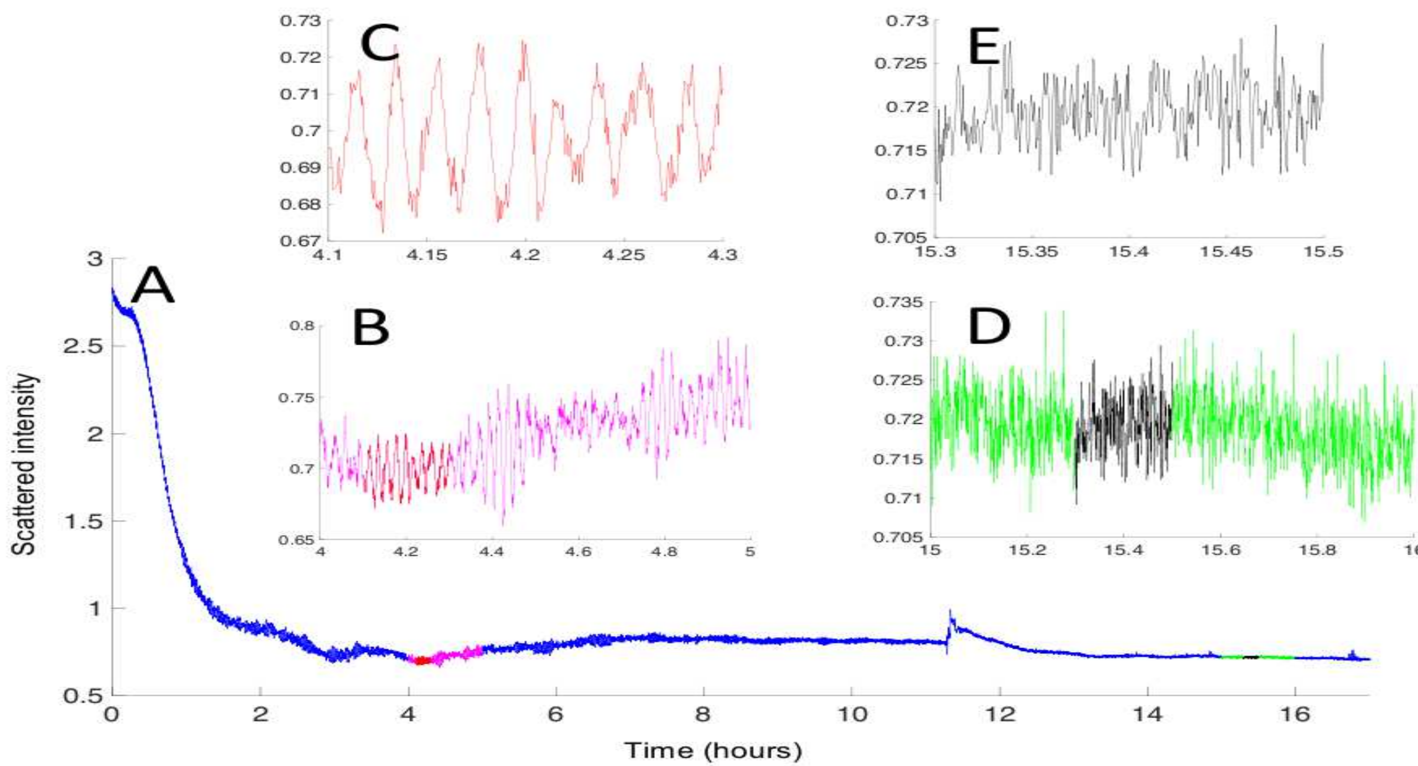
Different phenotype are associated to structural differences in PrPSc assemblies.

Introduction

The experiment

Experiments of the depolymerisation kinetics of recombinant PrP amyloid fibrils in the lab of Human Rezaei:

Static Light Scattering shows surprising, transient oscillations!



Coagulation-Fragmentation Models

Macroscopic viewpoint

The Formation and Break-up of Clusters/Polymers

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

Discrete Coagulation-Fragmentation Models

The Smoluchowski coagulation equation [1916/17]

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

$$\begin{aligned} d_t c_i(t) &= Q_{i,coag}(c,c) + Q_{i,frag}(c) \\ &= Q_{i,1}(c,c) - Q_{i,2}(c,c) + Q_{i,3}(c) - Q_{i,4}(c) \end{aligned}$$

Binary coagulation:

$Q_{i,1}(c,c)$: gain of particles of size i

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

$Q_{i,2}(c,c)$: 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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$$d_t c_i(t) = Q_{i,coag}(c,c) + Q_{i,frag}(c)$$
$$= Q_{i,1}(c,c) - Q_{i,2}(c,c) + Q_{i,3}(c) - Q_{i,4}(c)$$

Fragmentation:

$Q_{i,3}(c)$: gain of particles of size i

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

$Q_{i,4}(c)$: 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 Models

Strong formulation

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

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

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

(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 and 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:

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

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

The Becker-Döring model is detailed balanced!

The associated entropy functional prevents sustained oscillatory behaviour.

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)

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

Key modifications compared to Becker-Döring:

- two monomeric species
- $\mathcal{V}$ 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: equilibria

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

Boundary equilibria:

$(\bar{v}, \bar{w}) = (M, 0) \rightarrow$ no conformers

$(\bar{v}, \bar{w}) = (0, M - P_0)$ (in case $M \geq P_0$) $\rightarrow$ only conformers

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

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

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

Rescaling two polymer model

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

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

Hamiltonian for $\varepsilon = 0$: $H(v,w) = v - v_\infty \ln v + w - w_\infty \ln w$

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

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

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:

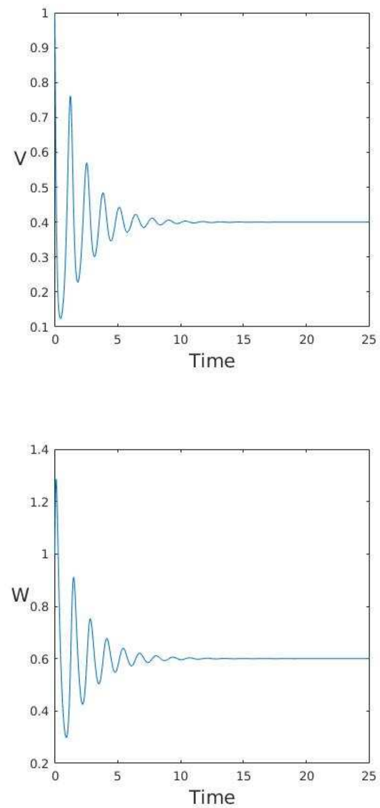
$$p = 0 \quad \iff \quad w - w_\infty = -(v - v_\infty).$$

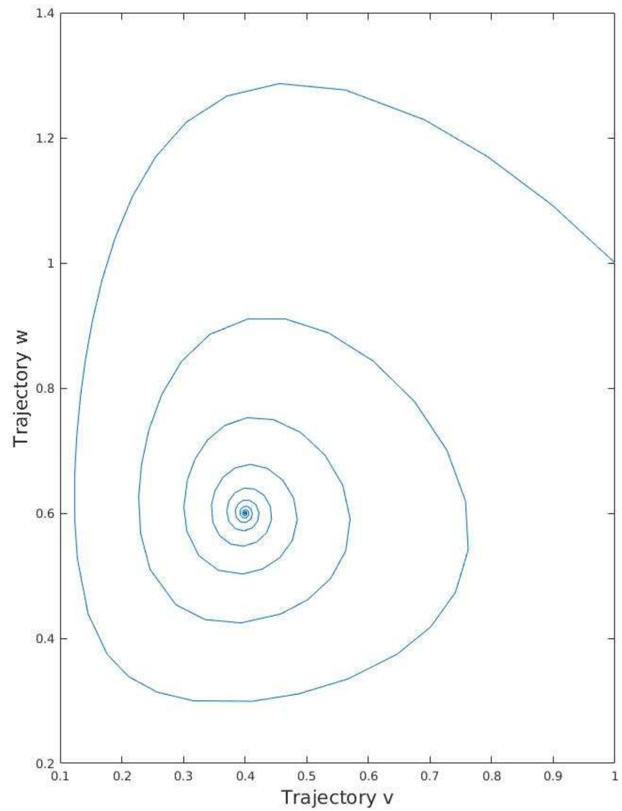
Workaround: Show that trajectories cross an area containing $p = 0$ in finite time with finite, positive speed.

Numerics

Oscillatory mechanism of two polymer model

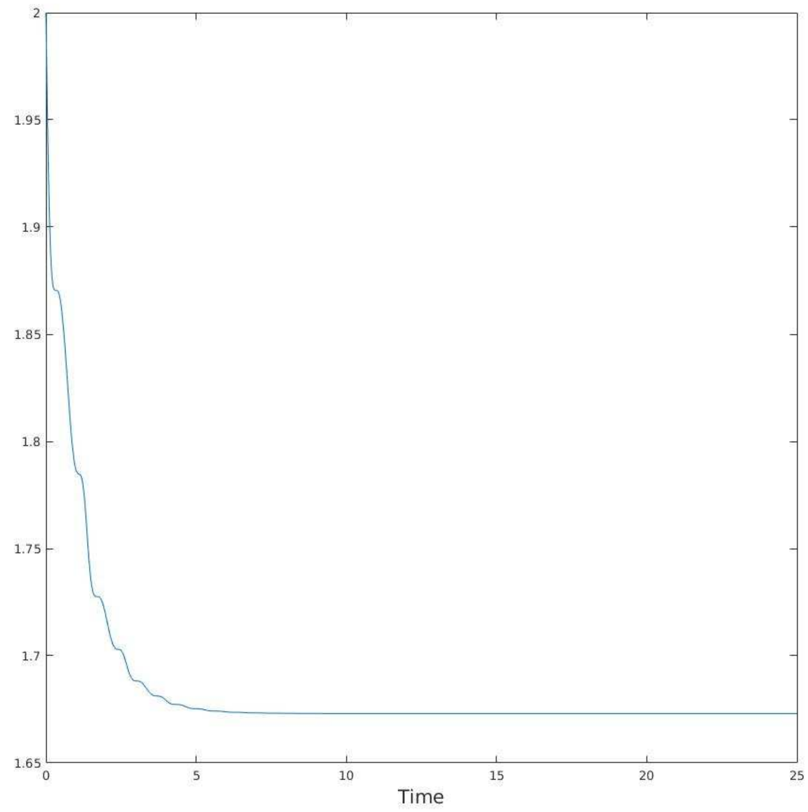
Trajectories of the monomeric concentrations v and w for the two-polymer model for $k = 10$, $a = b = 1$ and $\frac{kM}{1+k} < P_0 < kM$.





Oscillatory mechanism of two polymer model

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



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:

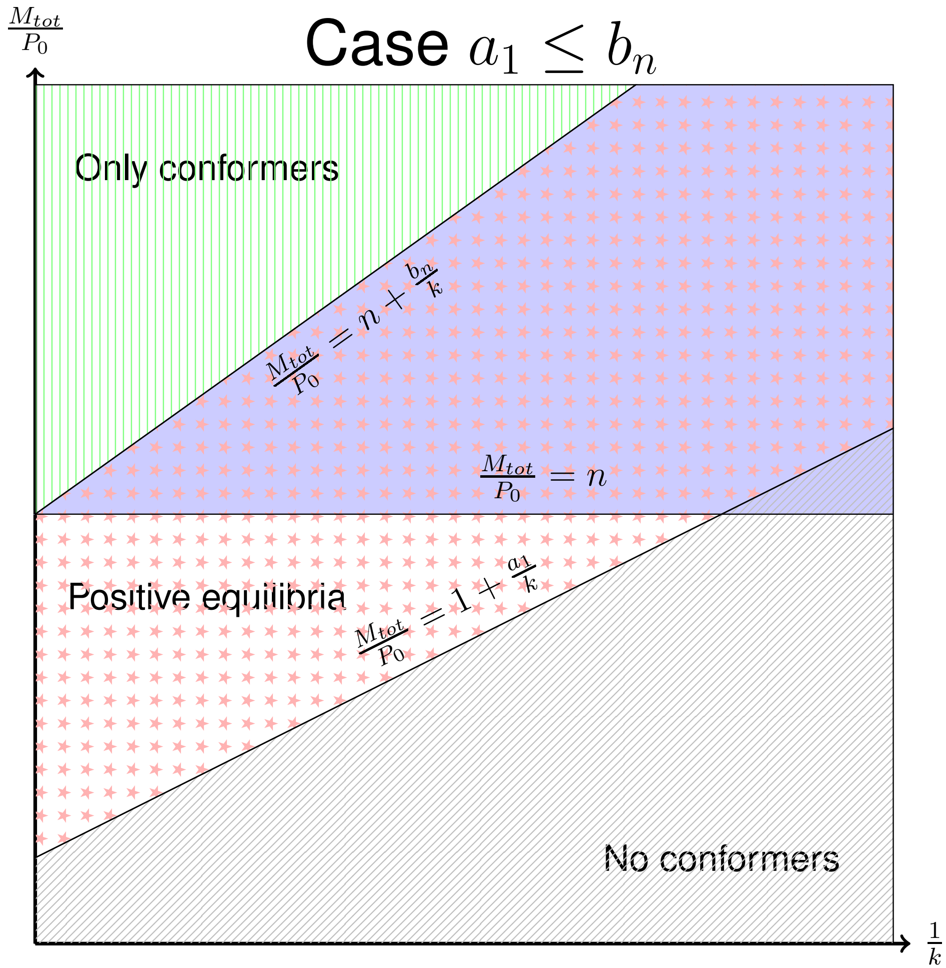
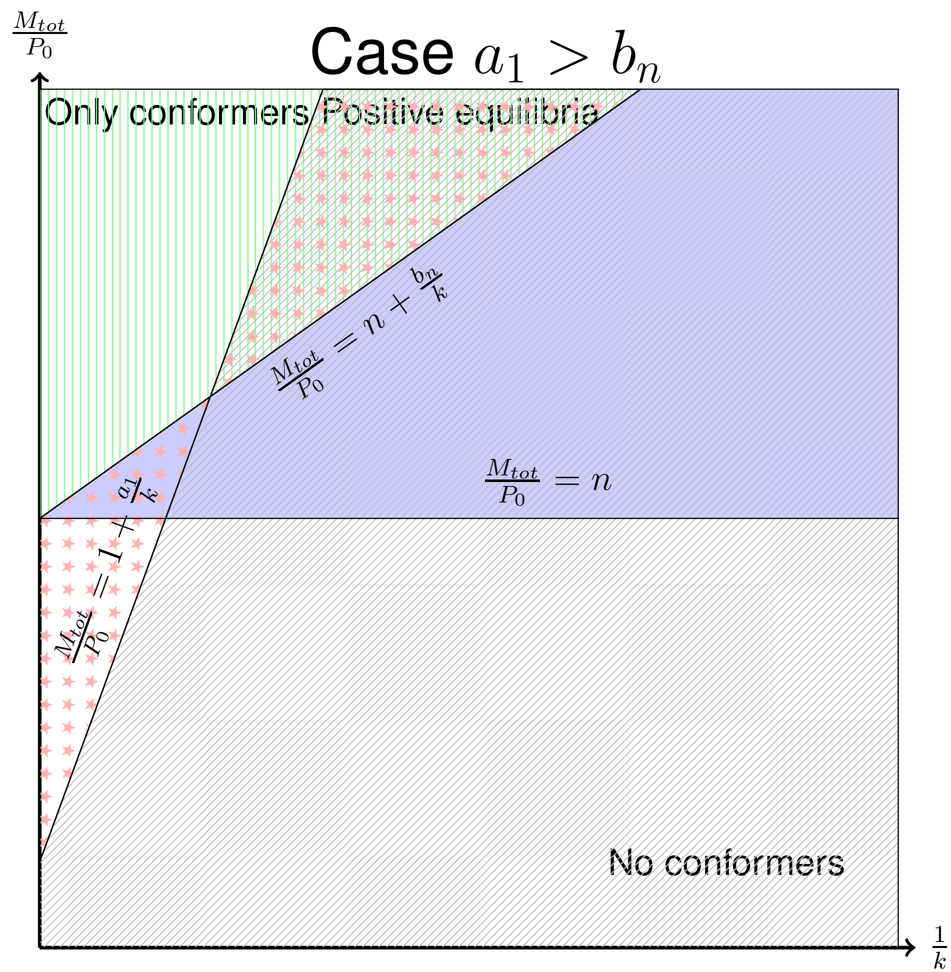


Figure 1

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

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

A bi-monomeric Becker-Döring Model

Normalised coefficients $a_i = b_i = 1$

Assume: total mass $M_{tot} = 1$, total number of polymers $P_0 = \varepsilon$

$$\frac{dv}{dt} = -vw + v\left(\varepsilon - c_1\right)$$

$$\frac{dw}{dt} = vw - \varepsilon w$$

$$\frac{dc_j}{dt} = J_{j-1} - J_j, \quad j \geq 1, \qquad J_0 = 0, \ J_j = wc_j - vc_{j+1}, \quad j \geq 1$$

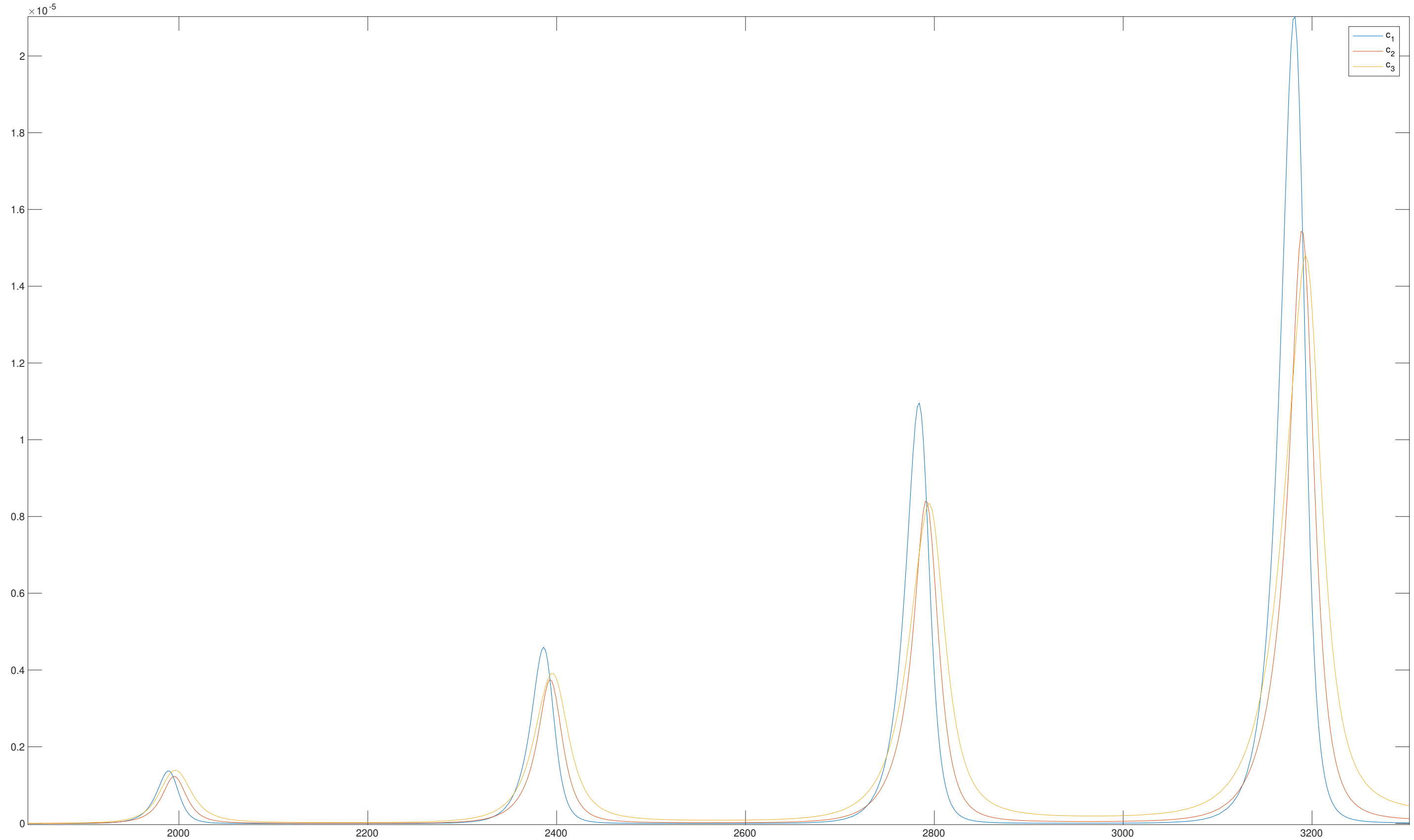
If $c_1 \ll 1$ the Lotka-Volterra for (v,w): Movie LVandPolymers

Polymers obey a discrete advection-diffusion system:

$$\frac{dc_j}{dt} = \frac{1}{2}\left(w - v\right)\left(c_{j-1} - c_{j+1}\right) + \frac{w+v}{2}\left[c_{j-1} - 2c_j + c_{j+1}\right]$$

A bi-monomeric Becker-Döring Model

What happens with c_1: The onset of oscillations



Observation: nonlinear oscillation, far from linearised LV.

Movie Bumpingintoboundary

A bi-monomeric Becker-Döring Model

Self-similar behaviour of continuous approximation

Four different phases:[a]

1. Energy remains nearly const. Period $O(\varepsilon^{-2})$,
   polymer distribution spreads like $\varepsilon^{-1/2}$
2. Energy decays from $O(1)$ to $O(\varepsilon)$, Period $O(\varepsilon^{-2})$,
   polymers spread like $\varepsilon^{-1/2}$
   about $n \sim \varepsilon^{-1}$ many oscillations
3. Energy decays from $O(\varepsilon)$ to $O(\varepsilon^{2})$, Period $O(\varepsilon^{-2})$,
   mainly small polymers oscillate,
   about $n \sim \varepsilon^{-1}$ many oscillations
4. convergence to equilibrium

[a] [Asymptotic Analysis of a bi-monomeric nonlinear Becker-Döring, system Doumic, F., Mezache, Velázquez]

A bi-monomeric Becker-Döring Model

Self-similar behaviour of continuous approximation

Movie advectionofpolymers

continuous approximation: $c_k(0) = \frac{\varepsilon}{L_0}\Phi\left(\frac{k}{L_0}\right)$.

PDE advection-diffusion equation for polymers:

$$\frac{\partial}{\partial t}\Phi(x,t) + \frac{(w-v)}{L_0}\partial_x\Phi(x,t) = \frac{v+w}{2}\frac{1}{L_0^2}\partial_x^2\Phi(x,t)$$

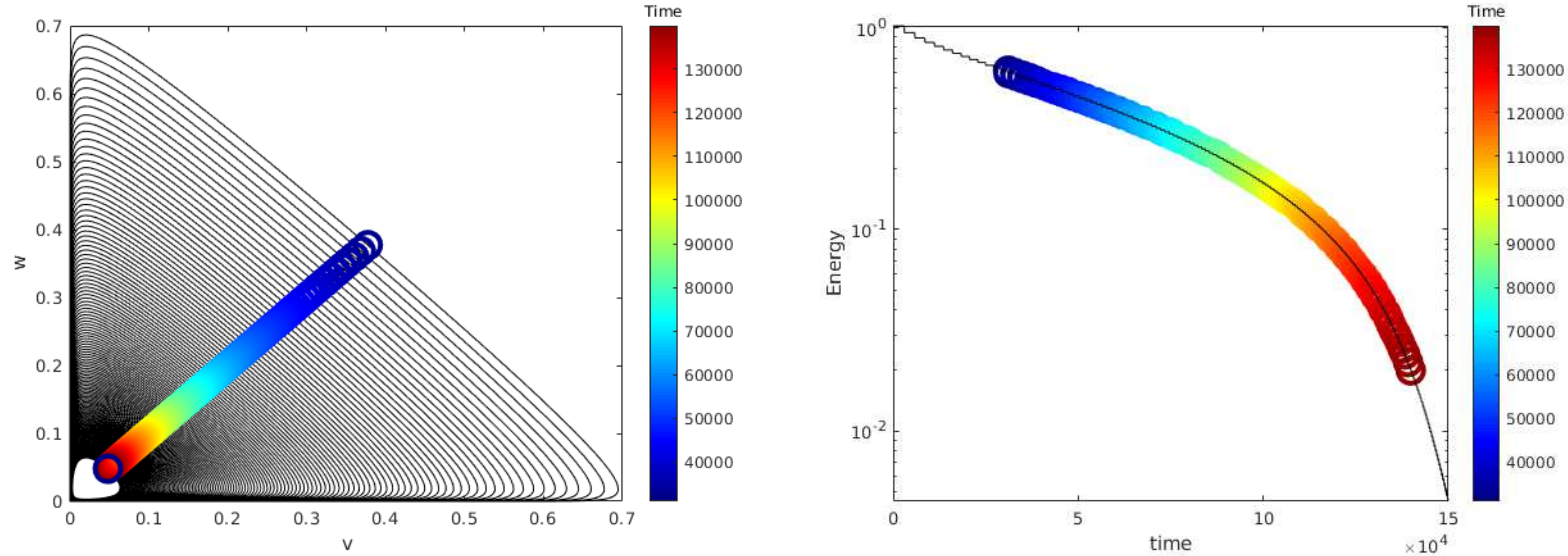
Period τ for given LV solution (v,w):

$$\tau = \frac{1}{L_0^2}\int_0^{T(E_0)} \frac{v+w}{2}(s)ds = \frac{1}{L_0^2}\frac{d(E_0)}{\varepsilon} = \tau(E_0, L_0).$$

Assume LV (v,w) given and characterised by energy level E_0.

Asymptotics: phase 2

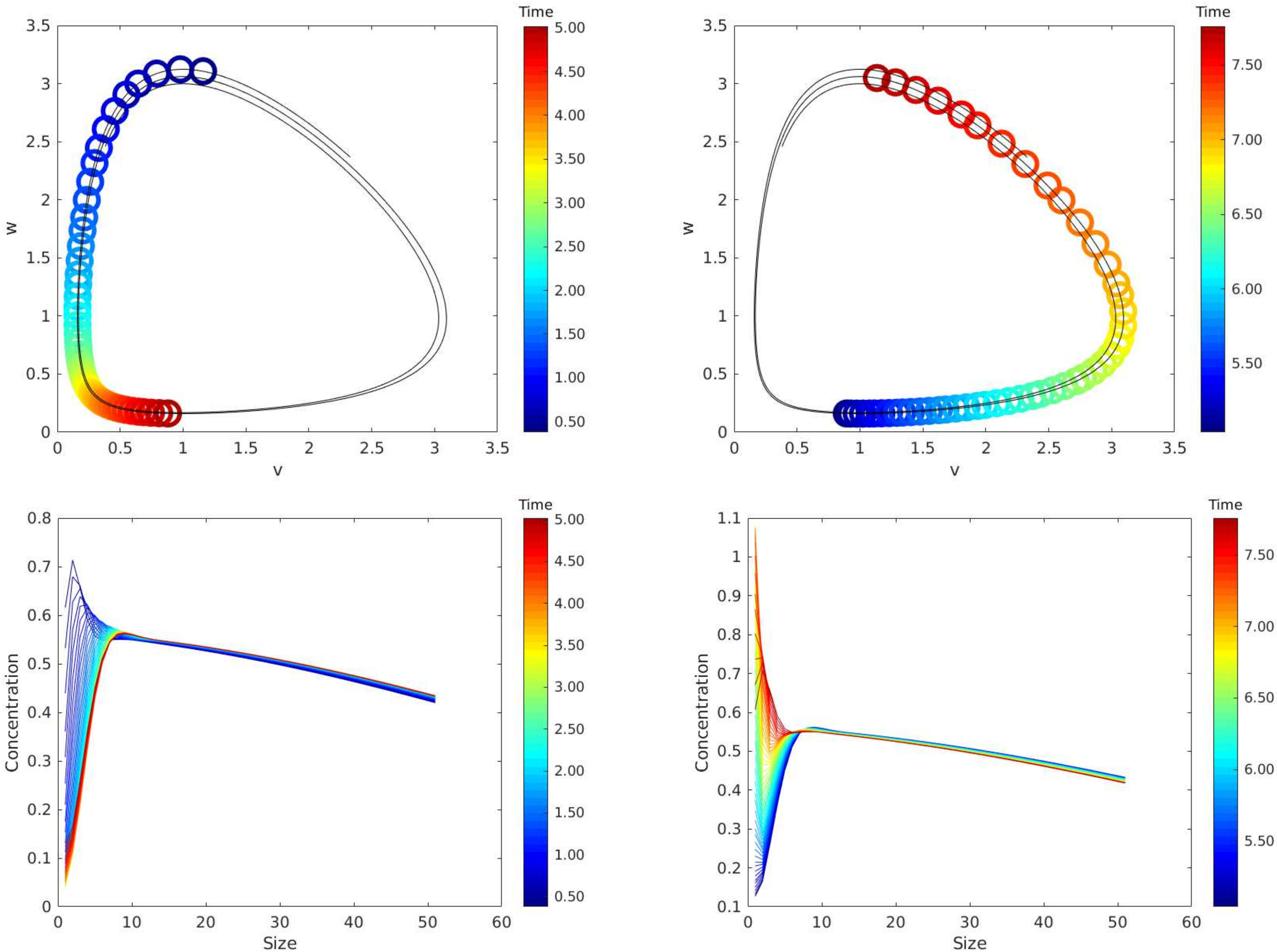
(v, w) Phase space and energy decay during phase 2



(v, w) Phase space and energy decay during phase 2

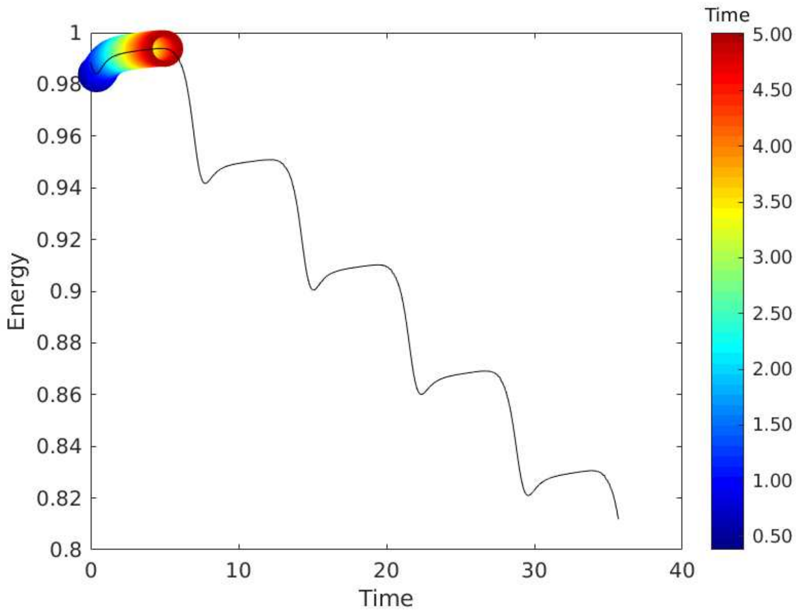
Asymptotics: phase 3

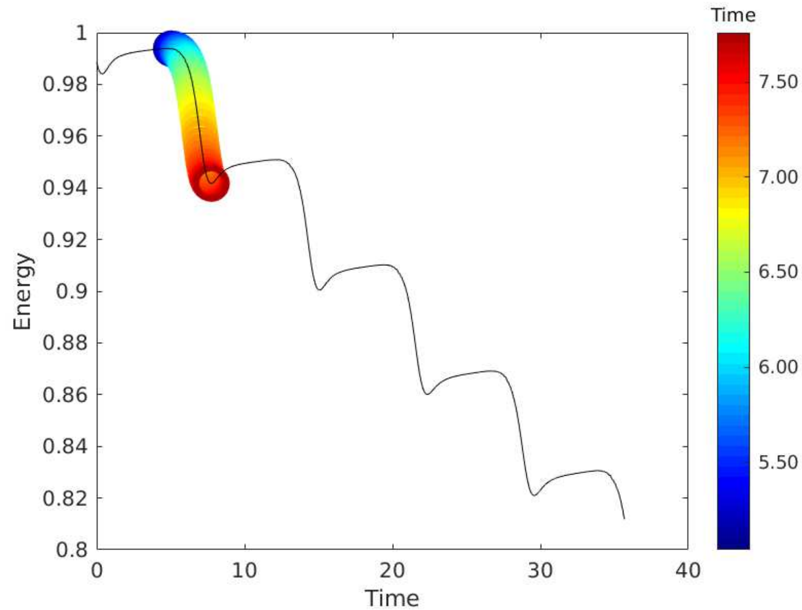
(v, w) Phase space and energy decay during phase 3



Asymptotics: phase 3

(v, w) Phase space and energy decay during phase 3





A bi-monomeric Becker-Döring Model

Self-similar behaviour of continuous approximation

Movie advectionofpolymers

Poincaré-type map: solutions after one LV period τ.

Solutions consists of a Dirac at zero with mass m
and a continuous profile $\psi(x)$ for $x \geq 0$, $\psi(0) > 0$.
Iterations of LV periods:

$$\begin{pmatrix} \psi_{n+1} \\ m_{n+1} \end{pmatrix} = T \begin{pmatrix} \psi_n \\ m_n \end{pmatrix} = \begin{pmatrix} \chi_{(0,\infty)}(\cdot)\,(S(\tau_n)\psi_n) + m_n G(\cdot, \tau_n) \\ J[\psi_n] + \frac{m_n}{2} \end{pmatrix}$$

Need to rescale solution with λ_n to find self-similar profile:

$$\varphi_n(x) = \lambda_n \psi_n(\lambda_n x)$$

calculate m and ψ via matching inner and outer solutions

A bi-monomeric Becker-Döring Model

Self-similar behaviour of continuous approximation

Inner solution: Non-local problem for approximation profile

$$\psi_n\left(\sqrt{\tau_*^{(n)}}\xi\right) \simeq U(\xi) \quad , \quad m_n \simeq \sqrt{\tau_*^{(n)}} M \quad , \quad \tau_*^{(n)} = \frac{D(E,\varepsilon)}{(L_n)^2}$$

where U and M solve the following equations

$$U(\xi) = \int_0^\infty G(\xi-\zeta;1)\,U(\zeta)\,d\zeta + MG(\xi;1) \quad , \quad \xi > 0$$

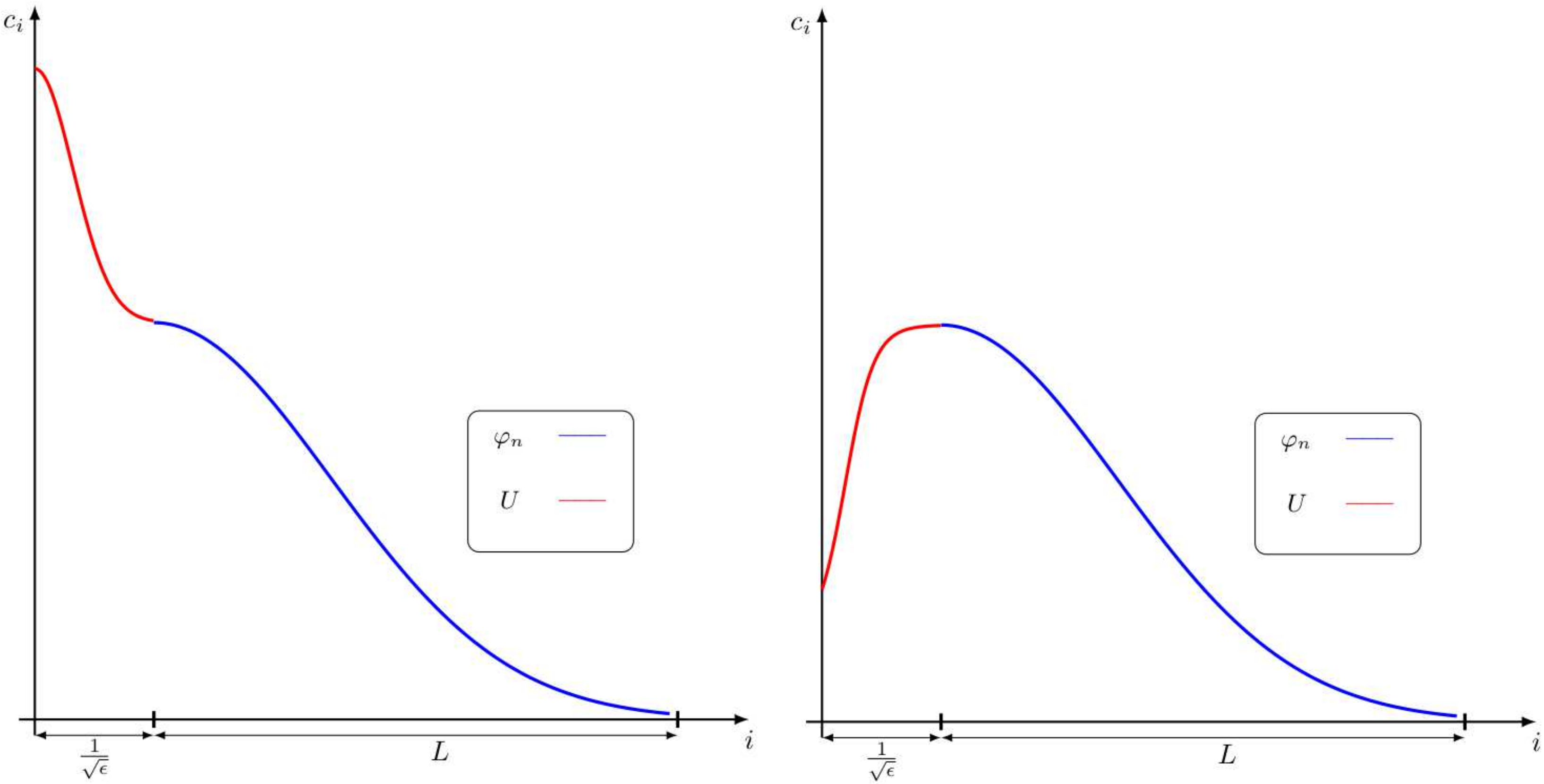
$$\frac{M}{2} = \int_{-\infty}^0 d\zeta \int_0^\infty G(\zeta-\xi;1)\,U(\xi)\,d\xi,$$

with the scaled boundary condition

$$U(\infty) = \frac{2}{\pi}.$$

A bi-monomeric Becker-Döring Model

Asymptotics: Inner solution numerics

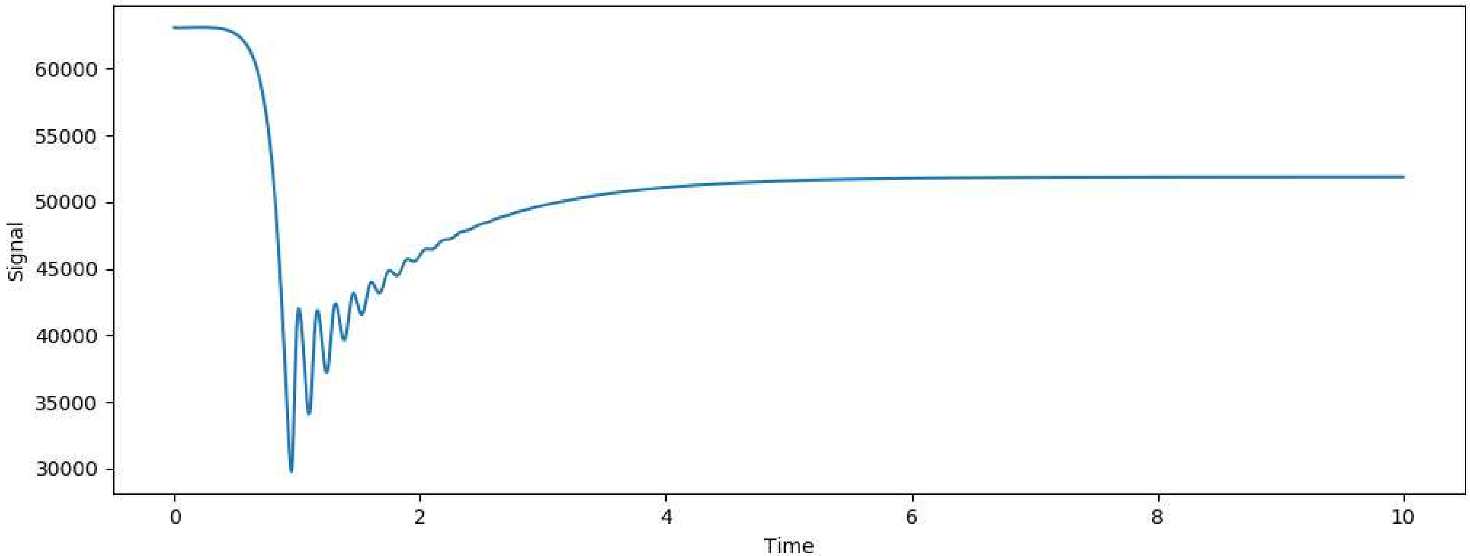


Another bi-monomeric Becker-Döring Model

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

- The models with $n \geq 3$ feature nonlinear oscillations as interaction of monomer species to polymer hierarchy.
- Biologist found experimental evidence of the suggested nonlinear depolymerisation
- Observed oscillatory behaviour should serves as hint towards unraveling the biological machinery.
- Preprint on asymptotic description in 2 weeks

THANK YOU VERY MUCH!