Transient oscillatory behaviours for polymerisation-depolymerisation systems

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in collaboration with

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Becker-Döring vs. Lifshitz-Slyozov: $n_i + V \underset{d_{i+1}}{\overset{a_i}{\rightleftharpoons}} n_{i+1}$

V : monomers, n_i : polymers containing i monomers

Discrete: Becker-Döring

$$\begin{cases} \frac{dn_i}{dt} = V(t)(a_{i-1}n_{i-1} - a_i n_i) + d_{i+1}n_{i+1} - d_i n_i, \\ \\ \frac{d}{dt}\left(V(t) + \sum_{i=1}^{\infty} i n_i(t)\right) = 0. \end{cases}$$

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Continuous: Lifshitz-Slyozov

$$\begin{cases} \frac{\partial n}{\partial t} + \frac{\partial n}{\partial x}\big((V(t)a(x) - d(x))n\big) = 0, \\ \\ \frac{d}{dt}\left(V(t) + \int_0^{\infty} xn(t,x)dx\right) = 0. \end{cases}$$

(Becker & Döring, 1935; Lifshitz & Slyozov, 1961; Wagner, 1961; Laurençot & Mischler, Collet et al., 2003 & 2004; ... Cañizo, Einav, Lods, 2017, Stolz & Terrier, 2019)

Outline

- Continuous framework: a new application of the Lifshitz-Slyozov system
  - Biological question: how to obtain stability?
  - Lifshitz-Slyozov revisited
  - steady state with the help of fragmentation

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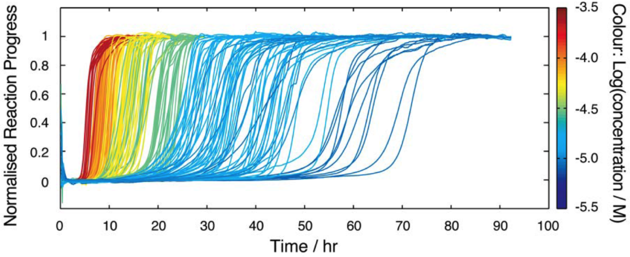
- Continuous framework: a new application of the Lifshitz-Slyozov system
  - Biological question: how to obtain stability?
  - Lifshitz-Slyozov revisited
  - steady state with the help of fragmentation
- Discrete case: an oscillatory variant of Becker-Döring
  - Experimental observations: how to obtain periodic oscillations?
  - steady states
  - damped oscillations

Growth-fragmentation equations to model protein polymerization

Long-time asymptotics

(J. Calvo, MD, B. Perthame, Comm. Math. Phys., 2018)

Aim: modelling nucleation, growth and long-time asymptotics for *in vitro* spontenous fibril formation



In vitro polymerization of $\beta 2m$ (from Radford & Xue, PNAS, 2008).

Starting point: original models for protein polymerisation

PDE system for the "Prion" Model
(Greer, Pujo-Menjouet, Webb, 2005)

Considered reactions: polymerization and fragmentation

$$\begin{cases} \frac{\partial n}{\partial t} + \frac{\partial n}{\partial x}\big(V(t)a(x)n\big) = -B(x)n(t,x) + 2\int_x^{\infty} B(y)\frac{1}{y}k_0(\frac{x}{y})n(t,y)dy, \\ \frac{d}{dt}\left(V(t) + \int_0^{\infty} xn(t,x)dx\right) = \pi - \gamma V. \end{cases}$$

Long-time asymptotics: still partially open

(Calvez, Lenuzza et al., 2009 & 2010; P. Gabriel, 2012 & 2015)

In vitro growth-fragmentation model

The most natural: adapt the prion model

Prion model but mass conservation + nucleation:

$$\begin{cases} \frac{\partial n}{\partial t} + \frac{\partial}{\partial x}\big(V(t)an\big) = -B(x)n(t,x) + 2\int_x^\infty B(y)\frac{1}{y}k_0(\frac{x}{y})\, n(t,y)dy, \\ \\ \frac{d}{dt}\left(V(t) + \int_0^\infty xn(t,x)dx\right) = 0, \\ \\ V(t)a(0)n(t,0) = \alpha V(t)^{i_0}, \qquad i_0 \geq 1, \\ \\ V(0) = C_0, \quad n(0,x) = 0. \end{cases}$$

In vitro growth-fragmentation model

Asymptotic paradox

Linearised growth-fragmentation equation around $V(t) = \bar{V}$:

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}\left(\bar{V} a n\right) + B(x) n(t,x) = 2 \int_x^\infty B(y) \frac{1}{y} k_0\left(\frac{x}{y}\right) n(t,y) dy,$$

under balance assumptions on (B, a, k), tends exponentially fast towards $N_{\bar{V}}(x) e^{\lambda(\bar{V}) t}$

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How to avoid this "fibril instability" ?

Lifshitz-Slyozov revisited

Without nucleation

$$
\begin{cases}
\dfrac{\partial n}{\partial t} + \dfrac{\partial}{\partial x}\big((V(t)a - d(x))n\big) = 0, \\[2ex]
\frac{d}{dt}\left(V(t) + \int\limits_0^\infty xn(t,x)dx\right) = 0, \\[2ex]
V(0) = V_0, \quad n(0,x) = n^{in}(x), \\[2ex]
\int n^{in}(x)dx = \rho_0,\ M = V_0 + \int xn^{in}(x)dx.
\end{cases}
\tag{1}
$$

Physical usual assumptions (grain formation, supersaturated solid solutions): $d(x) = 1$, $a(x) = x^{\frac{1}{3}}$: for large sizes, growth dominates

$\Longrightarrow$ mass goes to infinity (Ostwald ripening)

refs: e.g. Niethammer, Pego, 2000 & 2001, Goudon, Tine & Lagoutière, 2013

Lifshitz-Slyozov revisited

Without nucleation

For fibrils: $a(x) = 1$ constant, $d(x)$ increasing: for large sizes, decay dominates $\implies$ Need for a boundary condition at $x = 0$:

$$(V(t) - d(0))n(t,0)\mathbf{1}_{Va(0)-d(0)>0} = \mathbf{1}_{Va(0)-d(0)>0} \qquad (2)$$

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Lemma (Characteristic curves - inspired by P. Michel, 2008)

Under the previous assumptions, let us define

$$\frac{d}{dt}X(t,z) = V(t) - d(X(t,z)), \quad X(0,z) = z.$$

We have

$$\int_0^\infty n(t,x)|X(t,z) - x|^2\,dx \le e^{-2\alpha t}\int_0^\infty |z - x|^2 n(0,x)dx.$$

Lifshitz-Slyozov revisited

With or without nucleation - entropy-like inequality

Lemma (Entropy inequality - "reverse" of Collet et al., 2002)

Let k a $\mathcal{C}^1$ convex positive function, $\int_0^\infty k(x) n_0(x) dx < +\infty$

$$H_k(t) := \int_0^\infty k(x) n(t,x)\, dx + K(V(t)), \quad K(v) = \int_{d(0)}^{v} k'(b^{-1}(s))\, ds.$$

$$\implies \frac{d}{dt} H_k(t) = \int_0^\infty n(t,x)(V(t) - d(x))(k'(x) - k'(d^{-1}(V(t)))\, dx \leq 0.$$

Lifshitz-Slyozov revisited

without nucleation

Theorem (J. Calvo, MD, B. Perthame, 2018)

For $d(x)$ increasing, $0 < \alpha \leq d' \leq \beta$, and $a(x) = 1$, (V, n) solution to (1) (2) with $V(0) > d(0)$ satisfies

$$\begin{cases} \lim_{t\to\infty} V(t) = \bar{V} = d(\bar{x}), & \forall\, z \geq 0, \quad \lim_{t\to\infty} X(t;z) = \bar{x}, \\ \lim_{t\to\infty} n(t,x) = \rho_0 \delta(x - \bar{x}), & \text{weakly in measures}, \end{cases}$$

where $\bar{x} > 0$ is the unique solution to $M = \rho_0 \bar{x} + d(\bar{x})$.
More precisely we have for the Wasserstein distance:

$$W_2(u(t,\cdot), \rho_0 \delta_{\bar{x}}) \leq Ce^{-\alpha t}, \qquad |V(t) - d(\bar{x})| \leq Ce^{-\alpha t}.$$

Lifshitz-Slyozov revisited

With nucleation

Add nucleation to model *in vitro* experiments:

$$(V(t) - d(0))n(t,0)\mathbf{1}_{Va(0)-d(0)>0} = \alpha V(t)^{i_0}\mathbf{1}_{Va(0)-d(0)>0} \quad (3)$$

Lifshitz-Slyozov revisited

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For $d(x)$ increasing and $a(x) = 1$, (V, n) solution to (1) (3) satisfies

$$\begin{cases} \lim_{t\to\infty} \rho(t) = +\infty, \quad \lim_{t\to\infty} V(t) = d(0), \\ \lim_{t\to\infty} xn(t,x) = \big(M - d(0)\big)\delta(x), \qquad \textit{weakly in measures.} \end{cases}$$

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With nucleation

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$\Longrightarrow$ nucleation destabilizes the system

Lifshitz-Slyozov revisited

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Add fragmentation? accelerated destabilization!

Lifshitz-Slyozov revisited

Fragmentation + decreasing depolymerisation

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Lifshitz-Slyozov + fragmentation with decreasing depolymerisation:
the nucleation stops after some time

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Theorem (J. Calvo, MD, B. Perthame)

For $d(x)$ decreasing, $a(x)=1$, under balance assumptions on (B,k,d), there exists a steady state solution:

$$\frac{\partial}{\partial x}\big((\bar V - d(x))N\big) - B(x)N(x) = 2\int_x^\infty B(y)k(x,y)\,N(y)dy$$

$$\bar V \int_0^\infty N(x)dx = \int_0^\infty d(x)n(t,x)dx,$$

Lifshitz-Slyozov revisited

Fragmentation + decreasing depolymerisation

Lifshitz-Slyozov + fragmentation with decreasing depolymerisation: the nucleation stops after some time

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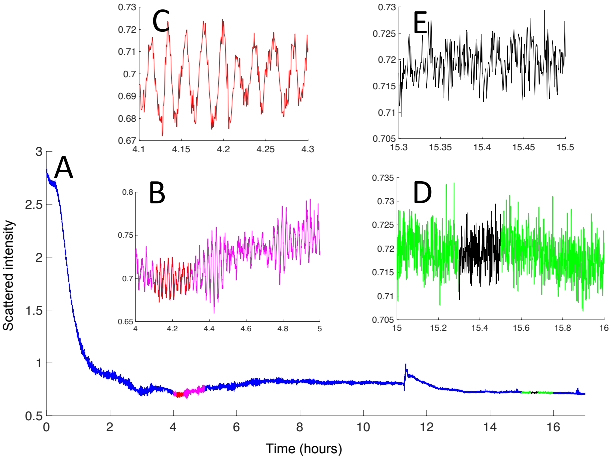
$$\bar{V}\int_0^{\infty} N(x)dx = \int_0^{\infty} d(x)n(t,x)dx,$$

$\Longrightarrow$ Depolymerisation may stabilize the system. Convergence?

Another experiment: Oscillatory behaviour

With K. Fellner, M. Mezache and H. Rezaei, J. Theor. Biol., 2019



Human PrP amyloid fibrils (Hu fibrils) by SLS, $0.35\mu M$

How to build a statistical test to evidence the presence of oscillations:
with M. Hoffmann and M. Mezache, arXiv

Search for an oscillatory polymerisation/depolymerisation model

Seminal "natural" model for polymerisation/depolymerisation:

$$\begin{cases} \mathcal{C}_1 + \mathcal{C}_i & \xrightarrow{a_i} & \mathcal{C}_{i+1}, & i \geq 1, \\ \mathcal{C}_i & \xrightarrow{d_i} & \mathcal{C}_{i-1} + \mathcal{C}_1, & i \geq 2. \end{cases}$$

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Which simplest reaction system oscillates?

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Which simplest reaction system oscillates?

Ivanova/simplified Belousov-Zhabotinsky model:

$$\mathcal{V}+\mathcal{W} \xrightarrow{k} 2\mathcal{W}, \quad \mathcal{W}+\mathcal{M} \xrightarrow{a} 2\mathcal{M}, \quad \mathcal{M}+\mathcal{V} \xrightarrow{d} 2\mathcal{V}.$$

OR: (Becker-Döring + atomization reaction: Pego & Velàzquez, 2019)

Search for an oscillatory polymerisation/depolymerisation model

Combination of both models:

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

$$\begin{cases} \frac{dv}{dt} = -kvw + v \sum_{i=2}^{n} d_i c_i, \\ \frac{dw}{dt} = -w \sum_{i=1}^{n-1} a_i c_i + kvw, \\ \frac{dc_i}{dt} = w(-a_i c_i + a_{i-1} c_{i-1}) + v(d_{i+1} c_{i+1} - d_i c_i), \quad 2 \leq i \leq n-1. \end{cases}$$

2 conserved quantities:

$$P_0 := \sum_{i=1}^{n} c_i^0, \qquad M_{tot} := v^0 + w^0 + \sum_{i=1}^{n} i c_i^0.$$

Case $n = 2$

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

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2 conserved quantities M_{tot} and $P_0 \implies$ reduced system

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

where $M = M_{tot} - P_0 \implies$ generalised Lotka-Volterra system.

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where $M = M_{tot} - P_0 \implies$ generalised Lotka-Volterra system.

- damped oscillations
- Existence of a Lyapunov functional
- exponential convergence to equilibrium despite oscillatory behaviour

Case n=2

Let $(v_\infty, w_\infty) > 0$ a positive steady state and
$H(v, w) = v - v_\infty \log(v) + w - w_\infty \log(w)$.

Theorem (Exponential convergence to positive equilibrium)

Let $P_0 \in \left(\frac{kM}{1+k}, kM\right)$ *Then, H is a convex Lyapunov functional.*

$$\frac{d}{dt} H(v(t), w(t)) = -\frac{1}{k} \left[(v(t) - v_\infty) + (w(t) - w_\infty)\right]^2 .$$

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$$\frac{d}{dt} H(v(t), w(t)) = -\frac{1}{k} \left[(v(t) - v_\infty) + (w(t) - w_\infty)\right]^2 .$$

Moreover, for $\frac{1}{k} \ll 1$*, every solution* $(v(t), w(t))$ *with initial data* $(v_0, w_0) > 0$ *converges exponentially to* (v_∞, w_∞)*, i.e.*

$$|v - v_\infty|^2 + |w - w_\infty|^2 \leq C \left(H^0 - H_\infty\right) e^{-\frac{1}{k} rt},$$

where the positive rate r and constant C depend only on $H^0 := H(v^0, w^0)$ *and* (v_∞, w_∞)*.*

Case $n = \infty$: well-posedness

Theorem

Assume

$$a_i = O(i), \qquad b_{i+1} = O(i+1) \quad \forall\, i \geq 1.$$

Then the system

$$\begin{cases} \frac{dv}{dt} = -kvw + v\sum_{i=2}^{n} d_i c_i, \\ \frac{dw}{dt} = -w\sum_{i=1}^{n-1} a_i c_i + kvw, \\ \frac{dc_i}{dt} = w(-a_i c_i + a_{i-1}c_{i-1}) + v(d_{i+1}c_{i+1} - d_i c_i), \quad 2 \leq i \leq n-1 \end{cases}$$

has a solution for $t \in [0, T)$, $v(t) \geq 0,\ w(t) \geq 0,\ c_i(t) \geq 0 \quad i \geq 1.$

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has a solution for $t \in [0, T),\ v(t) \geq 0,\ w(t) \geq 0,\ c_i(t) \geq 0 \quad i \geq 1.$

$$\sum_{i=1}^{\infty} i^2 c_i^0 < \infty \implies \sup_{t\in[0,T)} \sum_{i=1}^{\infty} i^2 c_i(t) < \infty + \textit{uniqueness.}$$

Case $n = \infty$: steady-states

Boundary steady-states: two types whether $v_\infty = 0$ or $w_\infty = 0$.

- $v_\infty = w_\infty = 0$ and any distribution of c_i such that $\sum ic_i = M_{tot}$.
- $w_\infty = 0$, $\bar{c}_i = 0$ for $i \geq 2$, $\bar{c}_1 = P_0$, and $v_\infty = M_{tot} - P_0$.

Proposition (Boundary steady-state (BSS) and their local stability.)

Let $M_{tot} > P_0 > 0$ and $b_i > 0$ for all i.
The BSS $v_\infty = w_\infty = 0$ are always unstable,
the BSS $v_\infty = M_{tot} - P_0,\ w_\infty = 0,\ c_1 = P_0,\ c_{i>1} = 0$ is locally linearly stable iff

$$\frac{M_{tot}}{P_0} < \frac{a_1}{k} + 1.$$

Proposition (Existence of non trivial steady state)

Let k, P_0 and M_{tot} be positive real constants. If

$$\frac{M_{tot}}{P_0} > \frac{a_1}{k} + 1, \tag{4}$$

there exists a strictly positive steady state (PSS) $(v_\infty, w_\infty, \bar{c}_i)$.

Remarks:

- (4) $\implies$ "there exists enough mass initially" to ignite the reactions.
- Conjecture : trend to the PSS if (4) is true and else a trend towards a BSS.

Damped oscillations and convergence towards PSS

Links with oscillatory models

Constant coefficients $\implies$ perturbed Lotka-Volterra system

$$\begin{cases} \frac{dv}{dt} = -kvw + bv(P_0 - c_1), \\ \frac{dw}{dt} = -awP_0 + kvw, \\ \frac{dc_i}{dt} = J_{i-1} - J_i, \qquad J_i = a_i w c_i - b_{i+1} v c_{i+1}. \end{cases}$$

Links with oscillatory models

Constant coefficients $\implies$ perturbed Lotka-Volterra system

$$\begin{cases} \frac{dv}{dt} = -kvw + bv(P_0 - c_1), \\ \frac{dw}{dt} = -awP_0 + kvw, \\ \frac{dc_i}{dt} = J_{i-1} - J_i, \qquad J_i = a_i w c_i - b_{i+1} v c_{i+1}. \end{cases}$$

Linear coefficients $\implies$ defining $M_1(t) = M_{tot} - v(t) - w(t)$, we get:

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

Construction of the continuous model (Collet et al., 2002)

In progress by M. Mezache

$$v(t),\ w(t),\ c_i(t) \to v(t),\ w(t),\ c(t,x)$$

$$J_{i-1}(t) - J_i(t) \to -\frac{\partial}{\partial x} J(t,x) = -\frac{\partial}{\partial x}\left(\big(a(x)w(t) - b(x)v(t)\big)c(t,x)\right)$$

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$$\begin{cases} \frac{\partial}{\partial t}c(t,x) = -w(t)\frac{\partial}{\partial x}a(x)c(t,x) + v(t)\frac{\partial}{\partial x}b(x)c(t,x) \\ \frac{d}{dt}v(t) = -k_1 v(t)w(t) + v(t)\int_0^\infty b(y)c(t,y)dy \\ \frac{d}{dt}w(t) = -w(t)\int_0^\infty a(y)c(t,y)dy + k_1 v(t)w(t) \\ v(0) = v_0, \quad w(0) = w_0, \quad c(0,x) = c_0(x) \end{cases} \tag{5}$$

Conservation of mass: $M_{tot} = v(t) + w(t) + \int_0^\infty xc(t,x)dx$

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$$\begin{cases} \frac{\partial}{\partial t} c(t,x) = -w(t)\frac{\partial}{\partial x} a(x)c(t,x) + v(t)\frac{\partial}{\partial x} b(x)c(t,x) \\ \frac{d}{dt} v(t) = -k_1 v(t)w(t) + v(t)\int_0^\infty b(y)c(t,y)dy \\ \frac{d}{dt} w(t) = -w(t)\int_0^\infty a(y)c(t,y)dy + k_1 v(t)w(t) \\ v(0) = v_0, \quad w(0) = w_0, \quad c(0,x) = c_0(x) \end{cases} \tag{5}$$

Conservation of mass: $M_{tot} = v(t) + w(t) + \int_0^\infty xc(t,x)dx$
$(v(t), w(t)) \implies$ almost "Lotka-Volterra" system where v is the prey and w is the predator.

Back to the experiment

Adding noncatalytic depolymerization $\mathcal{C}_i \longrightarrow \mathcal{C}_{i-1} + \mathcal{W}$

To conclude... and open

- powerful models, enriched by new applications
- Lifshitz-Slyozov with fragmentation: convergence towards the steady state?
- Oscillatory model: prove the conjecture (in progress with K. Fellner and J. Velàzquez; general case, link with the continuous version, parameter estimation...
- Statistical test for the oscillations

Ref:

- J. Calvo, MD, B. Perthame, Comm. in Math. Phys., 2018
- MD, K. Fellner, M. Mezache, H. Rezaei, J. Theor. Biol., 2019
- MD, M. Hoffmann, M. Mezache, arXiv: : 1911.12719

Linear coefficients and sustained oscillations

Suppose $\exists a,\ b > 0, \quad a(x) = ax, \quad b(x) = bx.$

Proposition (Periodic solutions - M. Mezache)

Let $(v, w, c) \in \mathcal{C}_b^1(\mathbb{R}_+) \times \mathcal{C}_b^1(\mathbb{R}_+) \times \mathcal{C}\left(\mathbb{R}_+, L^1\right)$ *be any nonnegative solution such that* $v_0, w_0 > 0$ *and* $v_0 + w_0 < M_{tot}$*. Then:*

1. $v(t), w(t)$ *are periodic of the same period* $T > 0$*.*
2. c *is periodic of the same period* T*.*

Depolymerization dominating

See J. Calvo, MD & Perthame, 2018

Hypotheses

1. $\exists b > 0 \quad a(x) = 1,\ b(x) = bx,\ \forall x > 0.$
2. Let $v_0, w_0 > 0$ and $v_0 + w_0 < M_{tot}$ and $c_0 \in L^1(\mathbb{R}_+, (1 + x^2)dx)$ with $\rho_0 = \int_0^\infty c_0(x)dx > 0.$
3. Let $k > 1$ with k large and $0 < \rho_0 < kM_{tot}$.

Depolymerization dominating

Theorem (Concentration at a critical size)

The solution $(v, w, c) \in \mathcal{C}_b^1(\mathbb{R}_+) \times \mathcal{C}_b^1(\mathbb{R}_+) \times \mathcal{C}\left(\mathbb{R}_+, L^1\right)$ *satisfies*

1. *for all* $z \geq 0$,

$$\int_0^\infty |X(t,z) - x|^2 c(t,x) dx \leq e^{-2bC_0 t} \int_0^\infty |z - x|^2 c_0(x) dx,$$

Depolymerization dominating

Theorem (Concentration at a critical size)

The solution $(v, w, c) \in \mathcal{C}_b^1(\mathbb{R}_+) \times \mathcal{C}_b^1(\mathbb{R}_+) \times \mathcal{C}\left(\mathbb{R}_+, L^1\right)$ *satisfies*

1. *for all* $z \geq 0$,

$$\int_0^\infty |X(t,z) - x|^2 c(t,x) dx \leq e^{-2bC_0 t} \int_0^\infty |z - x|^2 c_0(x) dx,$$

2. $c(t,x)$ *converges to* $\rho_0 \delta_{\frac{w_\infty}{bv_\infty}}$ *exponentially fast: for some constant* $C > 0$ *we have*

$$W_2\left(c(t,\cdot), \rho_0 \delta_{\frac{w_\infty}{bv_\infty}}\right) \leq Ce^{-\beta t},$$

where $W_2(g_1, g_2) := \left(\int \int |x - y|^2 g_1(x) g_2(y) dx dy\right)^{\frac{1}{2}}$.

Sketch of the proof

First step: Exponential convergence of $(v(t), w(t))$

$$\begin{cases} \frac{dv}{dt} & = v(bM_{tot} - bv - (k+b)w) \\ \frac{dw}{dt} & = w(kv - \rho_0) \end{cases}$$

- Generalized Lotka-Volterra system $\implies$ Lyapunov functional $F(v,w) = k(v - v_\infty \ln(v)) + (k+b)(w - w_\infty \ln(w))$, $\frac{d}{dt}F(v,w) = -kb(v - v_\infty)^2$
- local estimates near the degeneracy line $\implies$ $|v - v_\infty|^2 + |w - w_\infty|^2 \leq Ce^{-\alpha t}$

Sketch of the proof

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- local estimates near the degeneracy line $\implies$ $|v - v_\infty|^2 + |w - w_\infty|^2 \leq Ce^{-\alpha t}$

Second step: Entropy inequality and exponential convergence of the characteristic curves

$$\frac{d}{dt}X(t, z) = w(t) - bv(t)X(t, z) = h(t, X(t, z)), \quad X(0, z) = z \geq 0. \tag{6}$$

- $\int_0^\infty |X(t, z) - x|^2 c(t, x)dx \leq e^{-2bC_0 t} \int_0^\infty |z - x|^2 c_0(x)dx$
- (6) asymptotically autonomous differential equation $\implies$ $|X(t, z) - \frac{w_\infty}{bv_\infty}|^2 \leq Ce^{-\gamma t}$

Sketch of the proof

Final step: Entropy inequality + exponential convergence of the characteristics
$\implies$ exponential convergence to a Dirac for the Wasserstein distance

$$W_2\left(c(t,\cdot), \rho_0 \delta_{\frac{w_\infty}{bv_\infty}}\right) \leq \left(2|X(t,z) - \tfrac{w_\infty}{bv_\infty}|^2 \rho_0^2 + 2\rho_0 \int |X(t,z) - x|^2 c(t,x) dx\right)^{1/2}$$

Statistical test of presence of oscillations

Definition of the high-frequency features.

For some (large) $n \geq 1$, we observe

$$y_i^n = f\left(i/n\right) + \sigma \xi_i^n, \qquad i = 0, \ldots, n-1 \tag{7}$$

where:

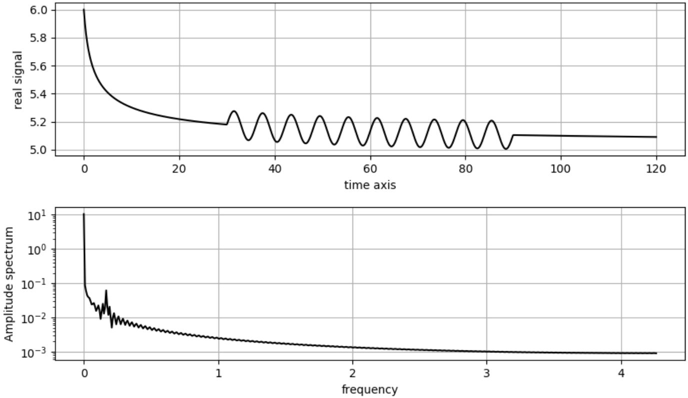
- $f : [0,1] \to \mathbb{R}$ is an, at least continuous, (unknown) signal of interest,
- the ξ_i are iid noise measurement assumed here to be standard Gaussian,
- $\sigma > 0$ is a (fixed) noise level.

Projection on the Fourier Domain

We denote by $\big(\vartheta_{n,k}(y)\big)_{0\leq k\leq n-1}$ the discrete Fourier transform (DFT) of length n of $\big(y_i^n\big)_{0\leq i\leq n-1}$ (and by $\big(\vartheta_{n,k}(f)\big)_{0\leq k\leq n-1}$ the DFT of f):

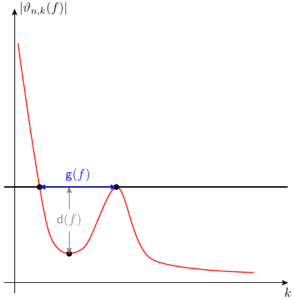
$$\vartheta_{n,k}(y) = n^{-1}\sum_{i=0}^{n-1} y_i^n \mathrm{e}^{-j2\pi ki/n}, \quad \vartheta_{n,k}(f) = n^{-1}\sum_{i=0}^{n-1} f(i/n)\mathrm{e}^{-j2\pi ki/n}.$$

Projection on the Fourier Domain



- Since f is real-valued, then $|\vartheta_{n,k}(f)| = |\vartheta_{n,-k}(f)|$.
- Replacing f by $f + C$ for some constant C, we assume that $|\vartheta_{n,0}(f)| > \max_{1\leq|k|\leq n} |\vartheta_{n,k}(f)|$.

Definitions of the high-frequency parameters



Idealized scheme of the parametrization of the HF features in the Fourier Domain.

The parameters $g(f) = G_{n,m}(f)$ and $d(f) = D_{n,m}(f)$ are two distances ($G_{n,m}(f)$ is a distance on the frequency axis and $D_{n,m}(f)$ on the intensity axis).

Definitions of the high-frequency parameters

Definition Let $f \in L^2([0,1])$, we associate a high-frequency feature (HF feature) $\big(G_{n,m}(f), D_{n,m}(f)\big)$ at discretisation level $n \geq 1$ and smoothing level $m \leq \frac{n-1}{2}$.

- $D_{n,m}(f)$ describes the peak with the highest distance between its amplitude and the minimum amplitude of the Fourier coefficients of lower frequencies.
- $\mathrm{G}_{n,m}(f)$ gives the distance in frequency indices between the peak and the components in the low frequencies with the same intensity.

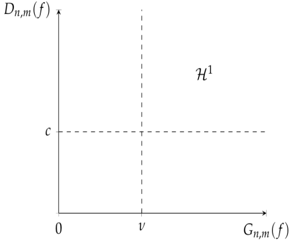
Test for high-frequency features

The null

$\mathcal{H}^0_{\nu,c}: \quad G_{n,m}(f) < \nu, \quad D_{n,m}(f) < c$

against the local alternative

$\mathcal{H}^1_{\nu,c}: \; G_{n,m}(f) \geq \nu \;$ and $\; D_{n,m}(f) \geq$



where $\nu > 0, \; c > 0$ are thresholds to determine significant HF features.

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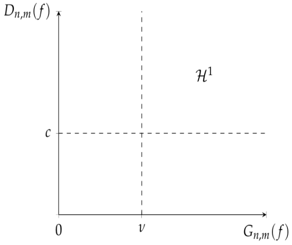

where $\nu > 0, \; c > 0$ are thresholds to determine significant HF features.

- $\mathcal{H}^0 \implies$ no significant HF feature in the tested signal,
- $\mathcal{H}^1 \implies$ the signal has significant HF feature.

Test for high-frequency features

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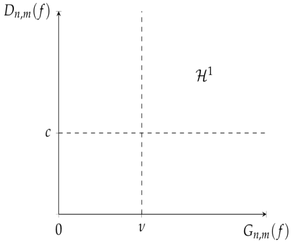


where $\nu > 0$, $c > 0$ are thresholds to determine significant HF features.

- $\mathcal{H}^0 \implies$ no significant HF feature in the tested signal,
- $\mathcal{H}^1 \implies$ the signal has significant HF feature.

For too small values of ν and c any signal shall reject $\mathcal{H}^0$ whereas for large values, any signal shall accept $\mathcal{H}^0$.

Monte Carlo Procedure and proxy of the p-value

First step: simulate N times $f_n^{(0)}$, the signal f with HF features removed but with additive Gaussian noise.

$$f_{n,k}^{(0)} \; k = 1, \ldots, N.$$

Monte Carlo Procedure and proxy of the p-value

First step: simulate N times $f_n^{(0)}$, the signal f with HF features removed but with additive Gaussian noise.

$$f_{n,k}^{(0)} \; k = 1, \ldots, N.$$

Second step: we denote E_N^0 the cloud of points representing the HF features parameters of signals with HF features removed but with Gaussian noise:

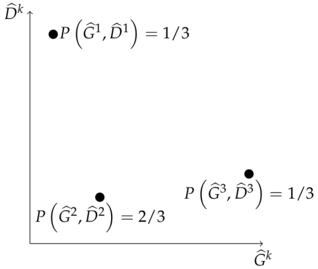
$$E_N^0 = \left\{ \left(G_{n,m}\left(f_{n,k}^{(0)}\right), D_{n,m}\left(f_{n,k}^{(0)}\right) \right) \mid k = 1, \ldots, N \right\}. \qquad (8)$$

We define the function $P : E_N^0 \to F \subset [\frac{1}{N}; 1]$:

$$P(g, d) = N^{-1} \sum_{k=1}^{N} \mathbf{1}_{\left\{ G_{n,m}\left(f_{n,k}^{(0)}\right) \geq g,\; D_{n,m}\left(f_{n,k}^{(0)}\right) \geq d \right\}}. \qquad (9)$$

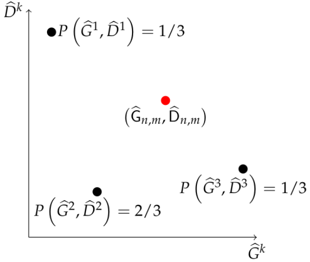
$P(g, d)$ is the proportion of points in E_N^0 located in the North-East quarter of the plane centered on (g, d).

Monte Carlo Procedure and proxy of the p-value



Cloud of points $\left(\widehat{G}^k, \widehat{D}^k\right) = \left(G_{n,m}\left(f_{n,k}^{(0)}\right), D_{n,m}\left(f_{n,k}^{(0)}\right)\right)$ for $k = 1, 2, 3$.

Monte Carlo Procedure and proxy of the p-value



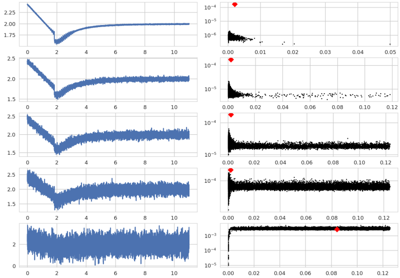
Cloud of points $\left(\widehat{G}^k, \widehat{D}^k\right) = \left(G_{n,m}\left(f_{n,k}^{(0)}\right), D_{n,m}\left(f_{n,k}^{(0)}\right)\right)$ for $k = 1, 2, 3$.

Third step: the p-value of the observations $(y_i^n)_{0 \leq i \leq n-1}$ is defined as

$$\text{p-value}\big((y_i^n)_{0 \leq i \leq n-1}\big) = \min\left\{\alpha \in \mathrm{Ran}(P) \mid G_{n,m}(y) \geq g^\alpha,\ D_{n,m}(y) \geq d^\alpha\right\} \quad (10)$$

where $(g^\alpha, d^\alpha) \in E_N^0$ such that $P(g^\alpha, d^\alpha) = \alpha$.

Numerical results on test signal



Numerical results of the procedure on the sanity-check signals

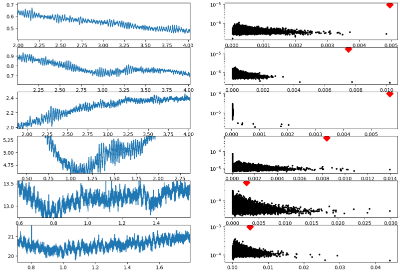
- (Left)Test signals when the noise level $\sigma \in \left\{ \frac{1}{10} c_a,\ \frac{1}{2} c_a,\ c_a,\ 2c_a,\ 10c_a \right\}$.
- (Right) Scatter points (black dots) and HF features parameters of the signal tested (red diamond).

Numerical results on test signal

σ	$\frac{1}{10}c_a$	$\frac{1}{2}c_a$	c_a	$2c_a$	$10c_a$
$G_{n,m}$ (Hz)	2.095e−3	2.095e−3	2.044e−3	2.12e−3	1.181e−1
$D_{n,m}$	1.768e−4	1.784e−4	1.918e−4	2.394e−4	3.593e−3
p-value	5e − 5	5e−5	5e−5	5e−5	5.32e−2

Table of estimators and p-values of the sanity-check signals.

Numerical results on SLS experiments



HF features of the SLS experiments observations

- (Left) Zoom on the SLS experimentation signals with initial concentration in μmol of $I_0 \in \{0.25,\ 0.35,\ 0.5,\ 1,\ 2,\ ,3\}$.
- (Right) (Right) Scatter points (black dots) and HF features parameters of the signal tested (red diamond).

Discussions

- Proof of oscillations in the SLS experiments AND parametric characterization of the HF features $\implies$ Sensitivity analysis.

Discussions

- Proof of oscillations in the SLS experiments AND parametric characterization of the HF features $\Longrightarrow$ Sensitivity analysis.

- Next step, definition and characterization of the HF features in a wavelet basis $\Longrightarrow$ 3 parameters (frequency resolution, amplitude, time localization) and extension of the test of hypothesis to this framework.