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DYNAMICS OF A POLYMERIZATION MODEL ON A GRAPH

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This work is concerned with the dynamics of a polymerization process coupled with mass transfer and monomers injection, modeled by means of an infinite-dimensional system of Smoluchowski's equations in a finite graph. Under suitable assumptions on the system's aggregation coefficients, we show that, as a consequence of the injection mechanism, a sizable depletion of the pool of available reacting substances occurs at some finite time, that can be estimated in terms of the parameters of the problem. By analogy with well-known results in chemical engineering, we interpret that result as the onset of a sol-gel phase transition. According to the chemical engineering terminology, a sol-gel transition is characterized by the appearance of a "gel" defined as a fraction of the total chemical species which is not able to add to the polymerization process anymore. A gel just removes reacting species from the available pool but does not contributes back to the ongoing reaction. We suggest that this property might have some interest in the mathematical modeling of neurodegenerative processes, where the polymerization of some soluble proteins and their eventual aggregation into insoluble plaques play a remarkable role, which is not well understood as yet.

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1. Introduction

This work deals with the behavior of solutions to an aggregation process defined on a finite graph G. Such graph is represented by a finite set of points $V = \{x_1, \ldots, x_h\}$, called nodes or vertices, linked among themselves by a set of edges E. We will think of nodes in V as places where monomers of a given substance undergo a polymerization process which results in the formation of aggregates with increasing chain length. At the same time as polymerization occurs, a mass transfer process takes also place, by means of which polymers are transferred along edges between adjacent nodes. Finally, we will assume that an external source is steadily increasing the amount of monomers available at each node.

To formulate an appropriate mathematical model, we introduce some notation as follows. We say that two vertices x_m, x_j are adjacent and write $x_j \sim x_m$, if they are connected by the same edge. A weighted graph is a graph G endowed with a non-negative function w such that $w(x_m, x_j) \geq 0$ for any m, j with $1 \leq m, j \leq h$. The weighted graph is said to be undirected if $w(x_m, x_j) = w(x_j, x_m)$ for any m, j. An undirected graph without loops or multiple edges connecting two nodes is said to be simple. A connected graph is a graph containing no isolated points.

We introduce a mass-transfer mechanism over a weighted, undirected graph G by means of the so-called graph Laplacian operator, $\mathbf{\Delta_G}$, defined as follows. Let $g(x)$ be any function defined over the vertices of the graph. Then, for any m, j with $1 \leq m, j \leq h$:

$$\mathbf{\Delta_G} g(x_m) = \sum_{x_j : x_j \sim x_m} (g(x_m) - g(x_j)) w(x_m, x_j) \,. \tag{1}$$

From now on, we shall deal with the following mathematical model defined on a weighted graph:

$$\frac{\partial u_1}{\partial t} = -d_1 \mathbf{\Delta_G} u_1 - u_1 \sum_{j=1}^{\infty} a_{1,j} u_j + f(x) \tag{2}$$

$$\frac{\partial u_i}{\partial t} = -d_i \mathbf{\Delta_G} u_i + \frac{1}{2} \sum_{j=1}^{i-1} a_{j,i-j} u_j u_{i-j} - u_i \sum_{j=1}^{\infty} a_{i,j} u_j \tag{3}$$

to be satisfied when $x \in V$, $t > 0$ and $i \in \mathbb{N}$. In system (2)-(3), the variable u_i represents the concentration of i-clusters, i.e. aggregates made of i identical monomers; $f = f(x)$ is a source term, consisting in a non-negative stationary function defined on the nodes of the graph. When written on the node $x_m \in V$, equations (2), (3) read:

$$\frac{\partial u_1(x_m,t)}{\partial t} = -d_1 \mathbf{\Delta_G} u_1(x_m,t) - u_1(x_m,t)\sum_{j=1}^{\infty} a_{1,j} u_j(x_m,t) + f(x_m) \quad (4)$$

$$\begin{aligned}\frac{\partial u_i(x_m,t)}{\partial t} &= -d_i \mathbf{\Delta_G} u_i(x_m,t) \\ &\quad + \frac{1}{2}\sum_{j=1}^{i-1} a_{j,i-j} u_j(x_m,t) u_{i-j}(x_m,t) - u_i(x_m,t)\sum_{j=1}^{\infty} a_{i,j} u_j(x_m,t)\,.\end{aligned} \quad (5)$$

To make up for a well-posed mathematical problem, the former equations should be supplemented with initial values for the concentrations:

$$u_i(x_m,0) := U_i(x_m) \geq 0 \quad \text{for any } i \in \mathbb{N} \text{ and for any } x_m \in V\,. \quad (6)$$

We further assume that:

$$\sum_{i=1}^{\infty} iU_i(x_m) < \infty \quad \text{for any } x_m \in V\,. \quad (7)$$

As a motivation for this work we remark that equations (2)-(3) provide a toy model to explore some hypotheses on the evolution of neurodegenerative disorders such as Alzheimer' s disease (AD). It has been long since that two anatomical findings are characteristic of AD: neurofibrillary tangles (NFT) and amyloid plaques (AP) ([3], [4] [10], [31]). NFT and AP consist of aggregates of (abnormal) τ protein (NFT) and of β-amyloid protein (AP) but the precise role played by each type of protein in disease progression has to be elucidated as yet [9],[30]. However, it is crucial to stress a deep difference between the two proteins: Aβ is an extracellular protein that diffuses *by proximity*, whereas the misfolded τ is mainly an intracellular protein which diffuses by *connectivity* along the neural network [2], [21]. Therefore, a natural model for the diffusion of τ is provided by a suitable graph obtained by means of magnetic resonance imaging (MRI) and tractography [38], [40], [16].

In addition, the so-called β-amyloid hypothesis holds that soluble β-amyloid polymers are highly toxic and are instrumental in neuronal death resulting eventually in dementia [44], whereas ordinary brains may contain a considerable load of AP without showing significant cognitive decay [13]. On the other hand, there is experimental evidence that polymers of misfolded tau protein have a definite impact in mental deficits associated with AD [24]. However, as in the case of AP, NFT are routinely

found in brains of healthy people [36]. Interestingly, the modification of tau-protein resulting in the toxic species previously mentioned might be enhanced by external sources, for instance by the action of toxic soluble oligomers of β-amyloid protein [26]. By the way, the presentation of the interaction between the proteins β-amyloid and tau is here a simplified one. It would be plausible to introduce an efficiency factor that is, a coefficient representing the fraction of toxic protein out of the total, but we believe that our arguments would remain substantially unchanged.
Furthermore, it has been observed that tau pathologies often begin in specific brain regions (i.e. entorhinal cortex) but ultimately involve much larger areas (i.e hippocampus) a fact that has been related with an intercellular transfer of non-homeostatic tau species through neural pathways from one cerebral area to another ([11, 12, 19, 29].)
This provides a background for a mathematical model in which a toxic species is simultaneously polymerizing and being transferred along suitable paths (edges) joining nodes, which are simplified representations of anatomical structures in a network. This last can be thought of as a blueprint for a larger area of the brain where the dynamics of the polymers under consideration are to be studied. We point out that the idea of representing brain regions by means of graphs similar to those mentioned before has already been proposed in a number of works ([8], [42], [37], [38], [7], [39] and the references therein).

Concerning our choice of equations in (2)-(3) we remark that ever since their introduction by Marian Smoluchowski in [41] the system of equations in (2)-(3) has played a key role in the study of aggregation problems in different physical contexts including polymerization ([43], [27], [47], [20]). The mathematical properties of their solutions have been extensively studied in standard open domains ([32], [33], [5], [6], [28], [14]). Particularly relevant to this work has been the attention paid to the occurrence of sol-gel phase transitions, whereby actively polymerizing oligomers are removed from the actual pool of aggregating substances [28], and to the impact of source terms in polymerization dynamics [14]. On the other hand Smoluchowski-type equations have been used in the specific context of neurodegenerative diseases first in [35] and then in [1],[17],[18]. Models based on truncated Smoluchowski-type equations in graphs can be found in [22],[38].

Bearing these previous remarks in mind, we now proceed to describe the results obtained in this work and the assumptions on which they are obtained; additional details can be found in subsequent Sections in this article. To begin with, we will be concerned with just one polymerizing chemical species (say, misfolded tau oligomers) for which the longer the polymer chain, the easier the polymerization process becomes. Arguably the simplest choice of aggregation coefficients in (2)-(3) satisfying this assumption is :

$$a_{i,j} = ij \quad \text{for } i,j \in \mathbb{N}\,; \tag{8}$$

(cf. [43], [33], [28]). The choice in (8) above is a particular case of the so-called Flory–Stockmayer condition, which has been extensively used in chemical engineering since the forties of last century. However, there is no precise biomedical indication concerning the form these coefficients should take. Indeed, it would be interesting to explore if (and how) systems with slowly-growing aggregation coefficients allow for mechanisms that could check the growth of free diffusing toxic tau proteins once a critical density threshold has been achieved, but an analysis of this type is far beyond the purposes of this work.

We will consider equations (2)-(3) above and discuss the occurrence of a sol-gel phase transition ([43], [33], [28]) whereupon a part of the soluble short-chain polymers which may link together to make up longer polymeric chains are withdrawn from the pool of reacting species, and become blocked in an inert phase which is commonly referred to as a gel. Besides, we assume that production of polymerizing units is stimulated by an external source (say, β-amyloid protein). Recalling our former example, the main result in this article can be reformulated as describing the formation of plaques originating from a sol-gel phase transition to be defined below. More precisely, let us define the total mass of reacting polymers $M_1(t)$ as follows:

$$M_1(t) = \sum_{x_m \in V} \sum_{i=1}^{\infty} i u_i(x_m,t) \quad \text{for } t \geq 0\,. \tag{9}$$

In agreement with known results for Smoluchowski-coagulation equation (see for instance [45], [46]), we expect that the total mass of the system will increase in time due to the presence of a source term $f(x)$:

$$M_1(t) = M_1(0) + t \sum_{x_m \in V} f(x_m) \quad \text{for } t \geq 0\,. \tag{10}$$

In this work we are only able to prove that, under mild assumption on the initial data, the total mass of system (2)-(3) exhibits a sub-linear growth. Namely:

$$M_1(t) \leq M_1(0) + t \sum_{x_m \in V} f(x_m) \quad \text{for } t \geq 0\,. \tag{11}$$

(see Theorem 1) in Appendix B). We then show that there exist solutions of our problem for which the total mass grows linearly in time for a while. More precisely:

$$M_1(t) = M_1(0) + t \sum_{x_m \in V} f(x_m) \quad \text{for } t \in [0, t_*) \,. \tag{12}$$

We will say that a sol-gel transition occurs at a time $t = t_*$ if (10) holds for times $t < t_*$ but

$$M_1(t) < M_1(0) + t \sum_{x_m \in V} f(x_m)$$

is satisfied instead for some times $t > t_*$.

Our main result in this work (Theorem 3 in the next Section) states that when system (2)-(3) is considered in a simple, connected, weighted and undirected graph G under the assumption (8) there exists a solution for which (10) is satisfied for times $t < t_*$ with $t_* > 0$, but

$$M_1(t_0) < M_1(0) + t_0 \sum_{x_m \in V} f(x_m) \tag{13}$$

for some $t_0 \in (t_*, t^*)$, $t^* < \infty$, where t^* can be estimated in terms of the data of the problem and the structure of the graph. In particular, it follows from Theorem 3 below (see Remark 1 there) that $t^* \to 0$ as the strength of the external source goes to infinity.

As long as the mass $M_1(t)$ is linear in time as in (10), if $0 \le t < \tau$ then $M_1(\tau) = M_1(t) + (\tau - t) \sum_{x_m \in V} f(x_m)$. In other words, the growth of the mass of the oligomers depends only on the source term, linearly in time. On the other hand, suppose $\bar{t} = \sup\{t > 0; (10) \text{ holds in } [0,t]\} < \infty$. If t_0 is as in (13), then it is easy to see that $M_1(t_0) < M_1(\bar{t}) + (t_0 - \bar{t}) \sum_{x_m \in V} f(x_m)$. In other words, the amount of mass of oligomers produced by the sources is (at least partially) balanced by a loss of soluble mass due to the sol-gel transition. A possible interpretation of this result is that a strong enhancement of polymerization leads to efficient (and fast) removal of polymerizing species to be deposited in inert plaques.

We conclude this Introduction by describing the plan of this paper. In the next Section 2 some preliminaries concerning existence of solutions to our model are gathered. To avoid technicalities at this stage, only the essential properties of the solutions under consideration will be recalled here, and relevant details are postponed to Appendixes A and B at the end of this paper. Our main result concerning the existence of a phase transition makes the content of Section 3. Finally, a discussion on the results obtained is presented in Section 4.

2. Preliminaries

In this Section we state some notation and provide some background for the formulation of our main results in Section 3. We begin by making precise what we mean by a solution of (2)-(3).
In the sequel, we write $u_i(x,t) = (u_i(x_1,t),\dots,u_i(x_h,t))$ for any $i \in \mathbb{N}$.

Definition 1. A weak solution to (2)-(3) on $[0,T_*)$, $T_* \in (0,+\infty]$, is a mapping $u = (u_i(x,t))_{i\geq 1}$ such that for any $T \in (0,T_*)$,

$$\sum_{i=1}^{\infty} i u_i(x_m,t) < \infty \quad \text{for any } t \in [0,T] \text{ and for any } x_m \in V\,.$$

In addition, for each $i \geq 1$ and for each $x_m \in V$ there holds:

- $u_i(x_m,\cdot) \in C([0,T],\mathbb{R})$ and $u_i(x_m,\cdot) \geq 0$, for $t \in [0,T]$
- $\int_0^T \sum_{j=1}^{\infty} a_{i,j} u_j(x_m,s)\,\mathrm{d}s < \infty$
- $\int_0^T \sum_{j=1}^{\infty} a_{i,j} u_i(x_m,s) u_j(x_m,s)\,\mathrm{d}s < \infty$
- u_i satisfies for each $t \in [0,T]$

$$\begin{aligned} u_i(t) = &\exp(-td_i\mathbf{\Delta_G})\mathbf{U}_i \\ &+ \int_0^t \exp((s-t)d_i\mathbf{\Delta_G})\Big(\frac{1}{2}\sum_{j=1}^{i-1} a_{i-j,j}u_{i-j}(s)u_j(s)\Big)\mathrm{d}s \\ &- \int_0^t \exp((s-t)d_i\mathbf{\Delta_G})u_i(s)\Big(\sum_{j=1}^{\infty} a_{i,j}u_j(s) + f(x)\Big)\mathrm{d}s\,. \end{aligned} \tag{14}$$

We will focus now on the meaning of some terms in equation (14). Let $\{\phi_j\}_{j=1}^h$ be an orthonormal basis of eigenfunctions of the graph laplacian $\mathbf{\Delta_G}$ with eigenvalues $\lambda_1,\dots,\lambda_h$ (see Appendix A below, where further details can be found). Then for each $i \geq 1$:

$$\exp(-td_i\mathbf{\Delta_G})\mathbf{U}_i = \sum_{j=1}^{h} \exp(-td_i\lambda_j)\langle \phi_j, \mathbf{U}_i\rangle \phi_j,$$

where $\mathbf{U}_i = [U_i(x_1,0),\dots,U_i(x_h,0)]$ is the vector of the initial data and for each $i \geq 1$

$$\langle \phi_j, \mathbf{U}_i\rangle = \sum_{m=1}^{h} \phi_j(x_m)U_i(x_m,0) \text{ for } j = 1,\dots,h\,.$$

In addition, for each $x_m \in V$ and for each $i \geq 1$ we define:

$$F_i(x_m, s) = \frac{1}{2} \sum_{j=1}^{i-1} a_{i-j,j} u_{i-j}(x_m, s) u_j(x_m, s) - u_i(x_m, s) \sum_{j=1}^{\infty} a_{i,j} u_j(x_m, s) + f(x_m) \, .$$

For simplicity, we set for each $i \geq 1$ $F_i(s) = (F_i(x_1, s), \ldots, F_i(x_h, s))$; then

$$\exp(s d_i \mathbf{\Delta_G}) F_i(s) = \sum_{j=1}^{h} \langle \phi_j, F_i(s) \rangle \exp(s d_i \lambda_j) \phi_j,$$

where for each $i \geq 1$

$$\langle \phi_j(\cdot), F_i(\cdot, s) \rangle = \sum_{m=1}^{h} \phi_j(x_m) F_i(x_m, s) \text{ for } j = 1, \ldots, h \, .$$

From now on we shall deal with finite, weighted and undirected graphs which are connected and simple. For any node $x_m \in V$, we define its degree as follows:

$$deg(x_m) = \sum_{x_j \in V \, : \, x_j \sim x_m} w(x_m, x_j) \, . \tag{15}$$

and denote by $vol(G)$ the (weighted) volume of the graph:

$$vol(G) = \sum_{m=1}^{h} deg(x_m) \, . \tag{16}$$

The order of a graph is denoted by $|V|$, where

$$|V| = h \, . \tag{17}$$

Notice that from (15)-(17) it follows that:

$$|V| \min_m deg(x_m) \leq vol(G) \leq |V| \max_m deg(x_m), \tag{18}$$

whence

$$|V| \leq vol(G) \frac{\max_m deg(x_m)}{\left(\min_m deg(x_m)\right)^2} \leq |V| \left(\frac{\max_m deg(x_m)}{\min_m deg(x_m)} \right)^2 . \tag{19}$$

Write now:

$$R(G) = vol(G) \frac{\max_m deg(x_m)}{\left(\min_m deg(x_m)\right)^2} \, . \tag{20}$$

We now have that:

Theorem 1. Let G be a a simple, finite weighted undirected and connected graph and assume that (8) holds. Then there exists a non negative weak solution of (2)-(3) which is global in time and satisfies

$$M_1(t) \leq M_1(0) + t \sum_{x_m \in V} f(x_m) \quad \text{for } t > 0\,. \tag{21}$$

Moreover, the following estimate holds:

$$\int_0^t (M_1(\tau))^2 \, \mathrm{d}\tau \leq 4R(G)(M_1(0) + t \sum_{x_m \in V} f(x_m)) \quad \text{for } t > 0 \tag{22}$$

where $M_1(\tau)$ and $R(G)$ are respectively given by (9) and (20).

To keep the flow of the main arguments here, the proof of this result is postponed to Appendix B.

Definition 2. A classical solution to (2)-(3) on $[0,T_*)$, $T_* \in (0,+\infty]$, is a weak solution which satisfies for any $T \in (0,T_*)$:

- $u_i(x_m,t) \in C^1([0,T],\mathbb{R})$, for each $x_m \in V$ and for each $i \geq 1$;
- $\sum_{j=1}^{\infty} a_{i,j} u_j(x_m,\cdot) \in C([0,T],\mathbb{R})$, for each $x_m \in V$ and for each $i \geq 1$.

We then have:

Theorem 2. Suppose that (8) holds and

$$0 < M_2(0) := \sum_{x_m \in V} \sum_{i=1}^{\infty} i^2 U_i(x_m) < \infty\,. \tag{23}$$

Then, the weak solution $\{u_i\}$; $1 \leq i \leq \infty$ of (2)-(3) obtained in Theorem 1 is classical and satisfies:

$$M_1(t) = M_1(0) + t \sum_{x_m \in V} f(x_m) \quad \text{for all } t \in [0,t_*) \tag{24}$$

where

$$t_* = \frac{\arctan\left(\frac{\sqrt{\sum_{x_m \in V} f(x_m)}}{M_2(0)}\right)}{\sqrt{\sum_{x_m \in V} f(x_m)}}\,. \tag{25}$$

Again, the proof of this result is postponed to Appendix B at the end of this article.

3. The main result

We are now ready to formulate the main result in this work, namely:

Theorem 3. Suppose that (23), (8) hold and $0 < M_1(0) < \infty$ where $M_1(0)$ is given as in (9). Set now

$$\chi = \frac{4R(G)}{M_1(0)}, \tag{26}$$

where $R(G)$ is given by (20). Then, there exists a solution of (2)-(3) which satisfies:

$$M_1(t) = M_1(0) + t \sum_{x_m \in V} f(x_m) \quad \text{for } 0 \le t \le \bar{t} \tag{27}$$

for a suitable $\bar{t} \ge t_*$ (where t_* is as in (25) of Theorem 2). In addition,

$$M_1(t_0) < M_1(0) + t_0 \sum_{x_m \in V} f(x_m) \tag{28}$$

for a suitable $t_0 \in (\bar{t}, t^*)$, where

$$t^* = \begin{cases} \chi & \text{if } \frac{4\,R(G)\sum_{x_m\in V} f(x_m)}{3} < M_1(0)^2 \\ \sqrt{\frac{12\,R(G)}{\sum_{x_m\in V} f(x_m)}} & \text{if } \frac{4\,R(G)\sum_{x_m\in V} f(x_m)}{3} > M_1(0)^2\,. \end{cases} \tag{29}$$

Remark 1. Note that the estimate obtained for t^* is sharp, since

$$\chi = \sqrt{\frac{12R(G)}{\sum_{x_m\in V} f(x_m)}} \quad \text{when} \quad 4R(G) \sum_{x_m \in V} f(x_m) = 3M_1(0)^2\,.$$

On the other hand, we see that for a fixed given graph $t^* \to \chi$ as $\sum_{x_m\in V} f(x_m) \to 0$ (which is compatible with the life-span estimate derived in Theorem 2), whereas $t^* \to 0$ as $\sum_{x_m\in V} f(x_m) \to \infty$, as one could expect.

Remark 2. The quotient between the lower bound t_* and the upper bound t^* of the time $\bar{t}$ of the sol-gel phase transition depends only on the geometry of the graph and on the initial data.
More precisely, a computation shows that:

$$\frac{M_1(0)\; M_2(0)}{4\,R(G)\; M_2(0)^2 + 3\; M_1(0)^2} \le \frac{t_*}{t^*} < 1\,. \tag{30}$$

Proof. Let us consider the solution of (2) -(3) for which Theorems 1 and 2 simultaneously hold. We know that such solution is classical for sufficiently small times, say for $t < \bar{t}_0$ and some $\bar{t}_0 > 0$. Since our solution exists globally in time as a weak solution, it should satisfy (22) for any $t > 0$. We now discuss the conditions under which (10) and (22) are simultaneously satisfied. For notational simplicity we shall write:

$$F = \sum_{x_m \in V} f(x_m)\,. \tag{31}$$

Then, on substituting (10) into (22) we obtain that, as long as these two conditions are simultaneously satisfied we should have:

$$\int_0^t (M_1(0) + \tau F)^2 \, \mathrm{d}\tau \leq 4R(G)(M_1(0) + t \sum_{x_m \in V} f(x_m)) \quad \text{for } t > 0 \tag{32}$$

from which it results:

$$p(t) \equiv \frac{1}{3}t^3 + \frac{M_1(0)}{F}\, t^2 + \left(\frac{M_1(0)^2}{F^2} - \chi\frac{M_1(0)}{F}\right) t - \chi\frac{M_1(0)^2}{F^2} \leq 0\,. \tag{33}$$

The function defined as in the left-hand side of (33) is such that $p(t) \to +\infty$ for $t \to +\infty$, so that (33) cannot hold for arbitrarily large times. If $M(t) = M(0) + t\,F$ in $[0, \tau]$, then $p(\tau) \leq 0$. Let us define now:

$$\bar{t} \equiv \sup\{\tau > 0 \, : \, M(t) = M(0) + t\,F \;\; \text{in } [0, \tau]\}\,. \tag{34}$$

Clearly, $p(\bar{t}) \leq 0$. Therefore, if $p(t^{**}) > 0$ for some $t^{**} > 0$, then $\bar{t} < t^{**}$ and, for any $\delta > 0$, $\bar{t} + \delta < t^{**}$ by (11), (34) there exists $t_\delta \in (\bar{t}, \bar{t} + \delta)$ such that $M(t_\delta) < M(0) + t_\delta\, F$.

We now claim that:

$$t^* \leq \bar{t} < \min\{\chi, \sqrt{\frac{12R(G)}{F}}\}, \tag{35}$$

where t^* is provided by (25) in Theorem 2. The lower bound for $\bar{t}$ in (35) is obvious. Concerning the upper bound, it suffices to remark that the continuous function $p(t)$ in (33) is such that:

$$p(0) = -\chi\frac{M_1(0)^2}{F^2} < 0 \tag{36}$$

whence $\bar{t} > 0$, whereas

$$p(\chi) = \frac{1}{3}\chi^3 > 0\,. \tag{37}$$

Moreover, for any $\epsilon > 0$

$$\begin{aligned} p(\frac{\epsilon}{\sqrt{F}}) =& \frac{\epsilon^3}{3F^{\frac{3}{2}}} + \frac{M_1(0)\epsilon^2}{F^2} + \frac{M_1(0)^2\epsilon}{F^{\frac{5}{2}}} - \frac{4R(G)\epsilon}{F^{\frac{3}{2}}} - \frac{4R(G)M_1(0)}{F^2} \\ &> \frac{\epsilon}{F^{\frac{3}{2}}}\left(\frac{\epsilon^2}{3} - 4R(G)\right) + \frac{M_1(0)}{F^2}\left(\epsilon^2 - 4R(G)\right) \end{aligned}$$

so that

$$p(\frac{\epsilon}{\sqrt{F}}) \geq 0 \quad \text{for } \epsilon \geq \sqrt{12R(G)}\,. \tag{38}$$

Since (35) follows from (36)-(38), the proof is now concluded taking

$$\delta < \min\{\chi, \sqrt{\frac{12R(G)}{F}}\} - \bar{t}.$$

□

4. Discussion

In this work we have considered a mathematical model accounting for mass transport and polymerization in a network represented by a finite graph. In our model, mass transport is assumed to proceed along the edges joining nodes of the graph according to the Laplacian rule in (1), whereas polymerization is proposed to occur exclusively in the nodes of the graph, according to well-known Smoluchowski's equations (see (4)-(5)) with aggregation coefficients given by (8) that is:

$$a_{i,j} = ij \quad i,j \geq 1\,.$$

In addition, a non-negative source term (independent of time) is assumed to produce a steady injection of reacting polymers at each node. Our main result in Theorem 3 points out a remarkable effect of such injection term when assumption (8) holds. Namely, at some time (that can be estimated; see Theorem 3) such polymerizing species undergoes a depletion in the pool of available reacting substances, thus disrupting the trend towards a linear growth of polymerizing substance triggered by the source term. It is natural to interpret such slowdown in the growth of the reacting polymer fraction as the onset of a phase transition, a well-known scenario in chemical engineering. In the context of neurodegenerative diseases, such phase transition might correspond, for instance, to the generation of some neurofibrillary tangles (NFT) if the polymerizing substance is taken to consist of toxic, misfolded tau protein molecules.

It is natural to wonder what the system evolution might be after a first phase transition has stopped, at least momentarily, the linear build-up of the reacting species under consideration. It is conceivable that, after a part of the reacting pool has been removed from the polymerizing fraction, linear mass growth would resume, until in due time a new phase transition (in our background example, a new NFT formation event) leads to a new halt in the mass fraction growth, a situation that might be repeated as times goes on. Models leading to the sequence of events just sketched have been described in other physical situations (see for instance [15]) but a detailed study in our current context is well beyond the reach of this work. We have shown that under suitable assumptions on the size of the graph and other data of the problem, the stronger the source is, the faster a phase transition occurs. In the context of the neurodegenerative disorders briefly mentioned at the Introduction, this might be thought of as an auxiliary tool to better evaluate some of the current hypotheses on the role of two outstanding anatomical findings in Alzheimer's disease (neurofibrillary tangles (NFT) and amyloid plaques (AP)). More precisely, the results in this paper are compatible with the hypothesis that the formation of NFT might have a homeostatic consequence, namely to clear out toxic, rapidly polymerizing units of altered tau protein. Interestingly, such response would be more efficient when the turnout rate of such toxic species is stimulated by an external source (for instance, the amyloid protein) irrespective of the cause of such stimulus, that might even be consequence of a pathologic inflammatory response.

While we retain this argument to have some interest, it is clear that only an experimental study could prove (or disprove) causality assumptions on the interaction between different agents as toxic tau protein and beta amyloid proteins. However, we believe that arguments as those presented in this work may contribute to identify particular assumptions (and interactions) that should be experimentally tested to better understand the underlying mechanisms.

Keeping to the mathematical model in itself, we point out that we consider it a first, preliminary step towards more comprehensive models accounting for more complex dynamics. In particular, only one single ingredient in a signaling pathway, whereby one external source acts on one polymerizing species, has been examined here. Moreover, at a modeling level, significant simplifications have been assumed to deal with a relatively simple mathematical problem. For instance, the structural parameters of the graph considered have been reduced to a minimum, and the same occurs with the mass transport mechanism, which is assumed to be given by the Laplace operator in the graph. As for the aggregation process itself, assumption (8) (which can be relaxed somewhat without compromising the basic result in this work) prescribes increasing polymerizing activity as the chain length of the reacting species increases. While this assumption has been proved valuable in chemical engineering, and has been proposed in some biomedical settings like blood coagulation (cf. for instance [25]) its actual relevance in our current context remains to be ascertained. We point out, however, that a study in the spirit of that performed here might be done under different assumptions on the polymerization rates. In such cases the relevant criterion for lowering the pace at which toxic species accumulate need not be the onset of a phase transition, since these do not occur in problems posed in standard open domains under coagulation rates significantly smaller than those in (8) (cf. [33], [45]). We intend to address some of these issues in future work.

A. Basic concepts of graph theory

For convenience of the reader we gather below a few standard results on graphs, and we refer to [23] and [34] for further details.

A finite graph G is a finite set of points $V = \{x_1, \dots, x_h\}$, called nodes or vertices, linked by a set of edges E. We shall write $G = (V, E)$. We shall always assume that G is a *s*imple graph, i.e. there are no loops or multiple edges connecting two nodes. We say that two vertices x_m, x_j are adjacent and write $x_j \sim x_m$, if they are connected by one edge. A weighted graph is a graph $G = (V, E)$ endowed with a non-negative function $w : V \times V \to \mathbb{R}$ such that $w(x_m, x_j) \geq 0$ for any m, j with $1 \leq m, j \leq h$ and $w(x_j, x_m) > 0$ if and only if $x_j \sim x_m$. The weighted graph is said to be undirected if $w(x_m, x_j) = w(x_j, x_m)$ for any m, j. A connected graph is a graph containing no isolated points.

Let G be a simple, weighted, undirected and connected graph. If x_m is a vertex of G, we set

$$deg(x_m) := \sum_{x_j \sim x_m} w(x_m, x_j) > 0.$$

We define the so-called graph Laplacian operator, $\mathbf{\Delta_G}$ as follows. Let $g(x)$ be any function in the space of real functions defined on the nodes of G, denoted as $F(V)$. Then, for any m, j with $1 \leq m, j \leq h$:

$$\mathbf{\Delta_G} g(x_m) = \sum_{x_j : x_j \sim x_m} (g(x_m) - g(x_j)) w(x_m, x_j) \, . \tag{A.1}$$

A direct computation reveals that, for any function $g \in F(V)$

$$\sum_{x_m \in V} \mathbf{\Delta_G}\, g(x_m) = 0 \tag{A.2}$$

a fact that will be used in Appendix B below.
The consideration of $\mathbf{\Delta_G}$ as a linear operator in $F(V)$ permits to precisely describe the way in which $\mathbf{\Delta_G}$ prescribes mass transfer across G, a process where eigenvalues and eigenfunctions of $\mathbf{\Delta_G}$ play a key role. In fact, $\mathbf{\Delta_G}$ is shown to be self-adjoint with respect to the inner product in $F(V)$ given by

$$(g,h) = \sum_{x_m \in V} g(x_m)\, h(x_m)\,. \tag{A.3}$$

Hence, all the eigenvalues of $\mathbf{\Delta_G}$ are real and can be listed as an increasing sequence $\lambda_1, \lambda_2, \ldots, \lambda_h$, where $h = |V|$ is the dimension of $F(V)$, where some eigenvalues might be repeated according to their multiplicity. Moreover, there exists an orthonormal basis of eigenfunctions $\{\phi_k\}$ with $1 \leq k \leq h$ such that $\mathbf{\Delta_G}\, \phi_k = \lambda_k\, \phi_k$ and $(\phi_k, \phi_k) = 1$. Any function $g \in F(V)$ can be written in the form:

$$g = \sum_{k=1}^{h} (g, \phi_k)\phi_k \tag{A.4}$$

where (g, ϕ_k) is defined as in (A.3). Operational calculus required to solve differential equations is then defined in a straightforward manner. For instance:

$$\exp(-\mathbf{\Delta_G})g = \sum_{k=1}^{h} \exp(-\lambda_k)\, (\phi_k, g)\phi_k\,. \tag{A.5}$$

We conclude by pointing out that in the case of operator $\mathbf{\Delta_G}$ defined as in (A.1) the first (and lowest) eigenvalue is zero and has multiplicity one. It is then customary to rewrite the set of eigenvalues as $(\lambda_0, \lambda_1, \ldots, \lambda_{h-1})$ instead of $(\lambda_1, \lambda_2, \ldots, \lambda_h)$.

B. Existence results

We summarize here the arguments leading to the proofs of Theorems 1 and 2 in Section 2. Our basic starting point is an adaptation on graphs of the argument introduced in [6] (cf. also [45]) where reaction-diffusion Smoluchowski-type systems were studied in the euclidean space $\mathbb{R}^N$. More precisely, we will approximate the full, infinite system (2)-(3) by means of the finite systems ($\mathbf{S}^N$) with $N \geq 1$ consisting in $2N$ equations and defined as follows:

$$\frac{\partial u_1^N}{\partial t} = -d_1 \mathbf{\Delta_G} u_1^N - u_1^N \sum_{j=1}^{N} a_{1,j} u_j^N + f(x) \tag{B.1}$$

$$\frac{\partial u_i^N}{\partial t} = -d_i \mathbf{\Delta_G} u_i^N + \frac{1}{2} \sum_{j=1}^{i-1} a_{j,i-j} u_j^N u_{i-j}^N - u_i^N \sum_{j=1}^{N} a_{i,j} u_j^N \qquad \text{for } i = 2, \dots N, \tag{B.2}$$

and

$$\frac{\partial u_i^N}{\partial t} = -d_i \mathbf{\Delta_G} u_i^N + \frac{1}{2} \sum_{j=i-N}^{N} a_{j,i-j} u_j^N u_{i-j}^N \tag{B.3}$$

for $N+1 \leq i \leq 2N$. The functions u_i^N are subject to initial conditions as in (6). This system corresponds to the first $2N$ equations of the system (2), (3) where $a_{ij} = 0$ for $i > N$ or $j > N$.
We recall that a solution of ($\mathbf{S}^N$) is a function

$$u^N = u^N(x,t) : V \times \mathbb{R}^+ \longrightarrow \mathbb{R}^{2Nh} ,$$

where

$$u^N(t) := \Big(u_1^N(\cdot,t), \dots, u_{2N}^N(\cdot,t) \Big)$$

and

$$u_i^N(x,t) := \Big(u_i^N(x_1,t), \dots, u_i^N(x_h,t) \Big)$$

for $i = 1, \dots, 2N$ and $x = (x_1, \dots, x_h) \in V$. We notice that (B.1)-(B.3) is a system of $2Nh$ ODEs for the $2Nh$ unknown functions $u_i^N(x_m,\cdot)$, with $m = 1, \dots, h$ and $i = 1, \dots, 2N$. Classical results in ODE theory and a minor modification of the arguments in [45], [6] yield:

Lemma B.1. *Assume that $f(x_m) \geq 0$ and $u_i(x_m,0) \geq 0$ for all $x_m \in V$ and for all $1 \leq i \leq 2N$. Then the initial value problem consisting of* (B.1)-(B.3) *and* (6) *has a unique solution which exists for all times $t > 0$ and is non-negative, that is:*

$$u_i^N(x_m,t) \geq 0 \quad \textit{for any}\, t \geq 0, \textit{ for any}\, x_m \in V \textit{ and}\, 1 \leq i \leq 2N.$$

In addition, for any $T > 0$ the following estimates hold when $0 \leq t \leq T$:

$$\sup_{x_m \in V} |u_1^N(x_m,t)| \leq K_1 := \Big(\big(\|U_1\|^2 + T\|f(\cdot)\|^2 \big) \exp(T) \Big)^{\frac{1}{2}} \tag{B.4}$$

$$\sup_{x_m\in V}|u_i^N(x_m,t)|\le K_i:=\left((\|U_i\|^2+\frac{T}{2}(\sum_{j=1}^{i-1}a_{j,i-j}K_jK_{i-j})^2)\exp\left(\frac{T}{2}\right)\right)^{\frac{1}{2}} \tag{B.5}$$

for $1<i\le N$, *and*

$$\sup_{x_m\in V}|u_i^N(x_m,t)|\le K_i:=\left((\|U_i\|^2+\frac{T}{2}(\sum_{j=i-N}^{N}a_{j,i-j}K_jK_{i-j})^2)\exp\left(\frac{T}{2}\right)\right)^{\frac{1}{2}} \tag{B.6}$$

for $N+1\le i\le 2N$, *where* $\|\cdot\|$ *is the Euclidean norm in* $\mathbb{R}^h$.

To proceed further we take up an argument introduced in [6]. Namely, on multiplying the i-th equation in $(\mathbf{S}^N)$ by an arbitrary real number g_i and then adding up all the equations, we obtain the following useful identity written on the vertex x_m of G:

$$\begin{aligned}\sum_{i=1}^{2N}g_i\frac{\partial u_i^N(x_m,t)}{\partial t}&+\sum_{i=1}^{2N}g_id_i\mathbf{\Delta_G}u_i^N(x_m,t)\\&=\frac{1}{2}\sum_{i=1}^{N}\sum_{j=1}^{N}(g_{i+j}-g_i-g_j)a_{ij}u_i^N(x_m,t)u_j^N(x_m,t)+g_1f(x_m).\end{aligned} \tag{B.7}$$

After having chosen $g_i=i$ for $i=1,\dots,2N$ in (B.7), we sum up over all $x_m\in V$ and integrate between 0 and t to obtain:

$$\sum_{x_m\in V}\sum_{i=1}^{2N}iu_i^N(x_m,t)=\sum_{x_m\in V}\sum_{i=1}^{2N}iU_i(x_m)+t\,F\le M_1(0)+t\,F. \tag{B.8}$$

where we use (A.2) and we set $\sum_{x_m\in V}f(x_m)=F$. We will keep this notation from now on.
We will prove now Theorem 1 as stated in Section 2.

Proof of Theorem 1. We shall split it into several steps.
Step 1: We first show that from the class of functions $\{u_i^N(x_m,t)\}_{N\ge i}$ with $m=1,\dots,h$ and $i\le N$, we can obtain functions $u=(u_i(x,t))$ with $i\ge 1$ such that the u_i' s are continuous in the time interval $[0,T]$ with $T>0$ fixed (but otherwise arbitrary) and satisfy

$$u_i^{M_\ell}(x_m,t)\to u_i(x_m,t) \tag{B.9}$$

uniformly for any $i=1,2,\dots$, where $(u_i^{M_\ell})_{\ell\in\mathbb{N}}$, is a sub-sequence of $(u_i^N)_{N\ge i}$ for $i=1,2,\dots$, obtained through a diagonal procedure. To do this, we observe that, by (B.4) and (B.5), for any $i = 1, 2, \ldots$ the family $\{u_i^N(x_m, t)\}_{N \geq i}$ is equibounded with respect to the indexes N and m. Moreover, the same family satisfies a uniform Lipschitz condition in t with respect to the same set of indexes. To show this we take advantage of (B.8), (B.4) and the choice of coagulation coefficient in (8) to obtain:

$$\sup_{(x_m,t)\in V\times[0,T]} \frac{\partial u_1^N}{\partial t}(x_m, t) \leq D_1 \,,$$
$$\text{with } D_1 = K_1(2d_1 \max_{x_m\in V}\{deg(x_m)\} + M_1(0) + TF) + \sup_{x_m \in V} f(x_m) \,. \tag{B.10}$$

In addition, we have that for $N \geq i$, the i-equation of the N-th system gives by (B.8), (B.5):

$$\sup_{(x_m,t)\in V\times(0,T)} \frac{\partial u_i^N}{\partial t}(x_m, t) \leq D_i,$$
$$\text{with } D_i = K_i(2d_i \max_{x_m\in V}\{deg(x_m)\} + i(M_1(0) + TF)) + \frac{1}{2}\sum_{j=1}^{i-1} a_{j,i-j} K_j K_{i-j} \,. \tag{B.11}$$

Step 2: We observe that for fixed ℓ and $i \leq M_\ell$ the function $u_i^{M_\ell}$ is the solution given by the Duhamel formula:

$$\begin{aligned} u_i^{M_\ell}(t) = &\exp(-t d_i \mathbf{\Delta_G})\mathbf{U}_i \\ &+ \int_0^t \exp((s-t)d_i\mathbf{\Delta_G})(l_i^{M_\ell}(s) - u_i^{M_\ell}(s) g_i^{M_\ell}(s) + f(x))\, \mathrm{d}s \end{aligned} \tag{B.12}$$

with $t \leq T$ and

$$\begin{cases} l_i^{M_\ell} = \frac{1}{2}\sum_{j=1}^{i-1} a_{j,i-j} u_j^{M_\ell} u_{i-j}^{M_\ell} \\ g_i^{M_\ell} = \sum_{j=1}^{M_\ell} a_{ij} u_j^{M_\ell} \qquad \text{for } i \leq M_\ell \,. \end{cases} \tag{B.13}$$

In order to pass to the limit in (B.12) we first show that for each $i \geq 1$ and for each $x_m \in V$:

$$\int_0^T |\sum_{j=1}^{M_\ell} a_{i,j} u_j^{M_\ell}(x_m, s) - \sum_{j=1}^{\infty} a_{i,j} u_j(x_m, s)|\, \mathrm{d}s \to 0 \qquad \text{for } \ell \to \infty; \tag{B.14}$$

and

$$\int_0^T |\frac{1}{2}\sum_{j=1}^{i-1} a_{j,i-j}(u_j^{M_\ell}(x_m,s)u_{i-j}^{M_\ell}(x_m,s) - u_j(x_m,s)u_{i-j}(x_m,s))| \,\mathrm{d}s \to 0$$

for $\ell \to \infty$.

$$\tag{B.15}$$

First, we notice that (B.15) follows from (B.9) by dominated convergence theorem, since
$u_j^{M_\ell}(x_m,s)u_{i-j}^{M_\ell}(x_m,s) \le K_j K_{i-j}$, for $0 \le s \le T$. We now argue as in [6],[28]. We set $g_j = j^{\frac{1}{2}}$ in (B.7) for $j = 1,..,M_\ell$, $g_j = 0$ for $M_\ell + 1 \le j \le 2M_\ell$. Using the following inequality

$$i^{\frac{1}{2}} + j^{\frac{1}{2}} - (i+j)^{\frac{1}{2}} \ge \frac{1}{2}(\min\{i,j\})^{\frac{1}{2}},$$

and after integrating in time in (B.7) and summing up over all $x_m \in V$, by (A.2) and (8) we see that for any $s,t : s < t$:

$$\begin{aligned}\int_s^t \sum_{x_m\in V} \frac{1}{4}\sum_{i=1}^{M_\ell}\sum_{j=1}^{M_\ell}(\min\{i,j\})^{\frac{1}{2}} ij u_i^{M_\ell}(x_m,\tau)u_j^{M_\ell}(x_m,\tau)\mathrm{d}\tau \\ \le \sum_{x_m\in V}\sum_{i=1}^{M_\ell} i^{\frac{1}{2}} u_i^{M_\ell}(x_m,s) + (t-s)\,F.\end{aligned}$$

Therefore, for any k such that $1 < k < M_\ell$ and for any $s,t : s < t$ it follows:

$$\begin{aligned}k^{\frac{1}{2}}\int_s^t \sum_{x_m\in V}\sum_{i=k}^{M_\ell}\sum_{j=k}^{M_\ell} ij u_i^{M_\ell}(x_m,\tau)u_j^{M_\ell}(x_m,\tau)\,\mathrm{d}\tau \\ \le 4\sum_{x_m\in V}\sum_{i=1}^{M_\ell} i^{\frac{1}{2}} u_i^{M_\ell}(x_m,s) + 4(t-s)\,F.\end{aligned} \tag{B.16}$$

We then set $s = 0$ and $t = T$ in (B.16) in order to have for any k such that $1 \le k < M_\ell$:

$$k^{\frac{1}{2}}\int_0^T \sum_{x_m\in V}(\sum_{j=k}^{M_\ell} j u_j^{M_\ell}(x_m,s))^2 \mathrm{d}s \le 4(\sum_{x_m\in V}\sum_{j=1}^{\infty} j^{\frac{1}{2}} U_j(x_m) + TF)\,. \tag{B.17}$$

Hence, for fixed $i \ge 1$ and for $1 \le k < M_\ell$, by (B.17), (8) and Hölder inequality we have:

$$\int_0^T \sum_{j=k}^{M_\ell} a_{i,j} u_j^{M_\ell}(x_m,s)\mathrm{d}s \le i \left(\int_0^T \sum_{x_m\in V} (\sum_{j=k}^{M_\ell} j u_j^{M_\ell}(x_m,s))^2 \mathrm{d}s \right)^{\frac{1}{2}} T^{\frac{1}{2}}$$
$$\le \frac{C_i(T)}{k^{\frac{1}{4}}}$$
$$\text{with } C_i(T) = 2i(M_1(0)+TF)^{\frac{1}{2}} T^{\frac{1}{2}} . \tag{B.18}$$

It follows that, for fixed i and arbitrary $\epsilon > 0$ there exists ℓ_0 such that for any $\ell > \ell_0$

$$\int_0^T \sum_{j=M_{\ell_0}}^{M_\ell} a_{i,j} u_j^{M_\ell}(x_m,s))\mathrm{d}s \le \frac{C_i(T)}{M_{\ell_0}^{\frac{1}{4}}} < \frac{\epsilon}{3} . \tag{B.19}$$

For fixed i and for $P' \in \mathbb{N}$ such that $M_{\ell_0} \le P' < M_\ell$,,by (B.18) and (B.9) we obtain:

$$\int_0^T \sum_{j=M_{\ell_0}}^{P'} a_{i,j} u_j(x_m,s)\mathrm{d}s = \lim_{\ell\to\infty} \int_0^T \sum_{j=M_{\ell_0}}^{P'} a_{i,j} u_j^{M_\ell}(x_m,s)\mathrm{d}s \le \frac{C_i(T)}{M_{\ell_0}^{\frac{1}{4}}} . \tag{B.20}$$

Finally, by monotone convergence theorem, (B.20), (B.19) it follows:

$$\int_0^T \sum_{j=M_{\ell_0}}^{\infty} a_{i,j} u_j(x_m,s)\,\mathrm{d}s = \lim_{P'\to\infty} \int_0^T \sum_{j=M_{\ell_0}}^{P'} a_{i,j} u_j(x_m,s)\,\mathrm{d}s \le \frac{C_i(T)}{M_{\ell_0}^{\frac{1}{4}}} < \frac{\epsilon}{3} . \tag{B.21}$$

By (B.9), there exists an $\ell_1 \ge \ell_0$ such that for any $\ell > \ell_1$

$$\int_0^T \sum_{j=1}^{M_{\ell_0}-1} a_{i,j} |u_j^{M_\ell}(x_m,s) - u_j(x_m,s)|\,\mathrm{d}s < \frac{\epsilon}{3} . \tag{B.22}$$

Hence, from (B.22), (B.21), (B.19) we obtain that for $\ell > \ell_1 > \ell_0$:

$$\int_0^T |\sum_{j=1}^{M_\ell} a_{i,j} u_j^{M_\ell}(x_m,s) - \sum_{j=1}^{\infty} a_{i,j} u_j(x_m,s)|\,\mathrm{d}s < \epsilon . \tag{B.23}$$

We will show, now, that for each i and for each $x_m \in V$

$$\int_0^T |u_i^{M_\ell}(x_m,s) \sum_{j=1}^{M_\ell} a_{i,j} u_j^{M_\ell}(x_m,s) - u_i(x_m,s) \sum_{j=1}^{\infty} a_{i,j} u_j(x_m,s)|\,\mathrm{d}s \to 0$$
$$\text{for } \ell \to \infty . \tag{B.24}$$

Indeed, for fixed $i \geq 1$, for each $x_m \in V$ and for each M_ℓ we have that:

$$\begin{aligned}\int_0^T &|u_i^{M_\ell}(x_m,s)\sum_{j=1}^{M_\ell} a_{i,j}u_j^{M_\ell}(x_m,s) - u_i(x_m,s)\sum_{j=1}^{\infty} a_{i,j}u_j(x_m,s)|\,\mathrm{d}s \\ &\leq K_i\int_0^T |\sum_{j=1}^{M_\ell} a_{i,j}u_j^{M_\ell}(x_m,s) - \sum_{j=1}^{\infty} a_{i,j}u_j(x_m,s)|\,\mathrm{d}s \\ &+ \int_0^T |u_i^{M_\ell}(x_m,s) - u_i(x_m,s)|\sum_{j=1}^{\infty} a_{i,j}u_j(x_m,s)\,\mathrm{d}s\end{aligned} \tag{B.25}$$

where we use Lemma B.1. Letting $\ell \to \infty$, convergence to zero of the first term of the right-hand in (B.25) is ensured by (B.23), while as regards the second term, convergence to zero is provided by (B.9) and dominated convergence theorem, since for each fixed i, by Lemma B.1, (8), we have:

$$|u_i^{M_\ell}(x_m,s) - u_i(x_m,s)|\sum_{j=1}^{\infty} a_{i,j}u_j(x_m,s) \leq 2iK_i\sum_{j=1}^{\infty} ju_j(x_m,s) < \infty\,.$$

From Lemma B.1, (B.8) and (8) we see that $\{u_i^{M_\ell}\sum_{j=1}^{M_\ell} a_{i,j}u_j^{M_\ell}(x_m,t)\}_{\ell\in\mathbf{N}}$ is a sequence of functions in $L^1(0,T)$. This implies, joint with (B.22) and (B.24), that also

$$\sum_{j=1}^{\infty} a_{i,j}u_i(x_m,\cdot)u_j(x_m,\cdot) \in L^1(0,T)\,.$$

.

Step 3: Let $\varphi_i^{M_\ell}(s) = l_i^{M_\ell}(s) - u_i^{M_\ell}(s)g_i^{M_\ell}(s) + f(x)$ with $i = 1,2,\ldots$. We want to show that

$$\exp(sd_i\mathbf{\Delta_G})\varphi_i^{M_\ell} \to \exp(sd_i\mathbf{\Delta_G})\varphi_i \qquad \text{for } \ell\to\infty \tag{B.26}$$

in $L^1(0,T)$ with $T > 0$ fixed (but otherwise arbitrary) where:

$$\varphi_i(s) = \frac{1}{2}\sum_{j=1}^{i-1} a_{j,i-j}u_ju_{i-j} - u_i\sum_{j=1}^{\infty} a_{ij}u_j + f(x)\,. \tag{B.27}$$

We have previously seen that:

$$\varphi_i^{M_\ell} \to \varphi_i \qquad \text{for } \ell\to\infty \tag{B.28}$$

in $L^1(0,T)$, due to (B.15),(B.23), (B.24). In view of (B.26)-(B.28), continuity of the operator $\mathbf{A} := \exp(sd_i\mathbf{\Delta_G}) : L^1(0,T) \to L^1(0,T)$ will follow if we show that $\mathbf{A}$ is bounded, i.e. there exists a real number $C \geq 0$ such that :

$$|\exp(sd_i\mathbf{\Delta_G})\bar{\varphi}|_{L^1(0,T)} \leq C|\bar{\varphi}|_{L^1(0,T)} \tag{B.29}$$

for every $\bar{\varphi} \in L^1(0,T)$. Let $\{\phi_j\}_{j=1}^h$ be an orthonormal basis of eigenfunctions of $\mathbf{\Delta_G}$. If $s \in [0,T]$, we can write

$$\bar{\varphi}(s) = \sum_{j=1}^{h} \langle \bar{\varphi}(s), \phi_j \rangle \phi_j \text{ and } |\bar{\varphi}(s)|^2 = \sum_{j=1}^{h} \langle \bar{\varphi}(s), \phi_j \rangle^2.$$

Since $\exp(sd_i\mathbf{\Delta_G})\bar{\varphi}(s) = \sum_{j=1}^{h} \langle \bar{\varphi}(s), \phi_j \rangle \exp(sd_i\lambda_j)\phi_j$, we have:

$$|\exp(sd_i\mathbf{\Delta_G})\bar{\varphi}(s)|^2 = \sum_{j=1}^{h} \langle \bar{\varphi}(s), \phi_j \rangle^2 \exp^{(2sd_i\lambda_j)} \leq C|\bar{\varphi}(s)|^2 ,$$

where $C = \max_{j=1,\dots,h} \exp\{2Td_i\lambda_j\}$. Integrating between 0 and t, (B.29) follows.

Step 4: We construct a solution of (2)- (3) defined on $V \times [0,\infty)$ arguing as in [45] (Theorem 3.1). Indeed, we consider an increasing sequence of positive numbers (T_n) with $n \in \mathbb{N}$ such that $T_n \to \infty$ as $n \to \infty$. Using the results of step one, for each n there exists a sequence $\{M_\ell^n\}_{l=1}^\infty$ such that for each $i = 1,2,\dots$ a solution $u_i^n(x_m,t)$ to (2)-(3), on the interval $[0,T_n]$ is defined as the limit of $\{u_i^{M_\ell^n}(x_m,t)|_{[0,T_n]}\}_{l=1}^\infty$. Taking into account the uniqueness of the solution of the finite dimensional Cauchy problem, the solution $u_i(x_m,t)$ of (2)-(3) on $[0,\infty)$ is obtained upon passing to the limit in $\{u_i^{M_\ell^\ell}(x_m,t)\}_{\ell=1}^\infty$ where $\{M_\ell^\ell\}_{\ell=1}^\infty$ is diagonal subsequence of $\{M_\ell^n\}_{l=1}^\infty$. We now set out to prove a basic estimate in this article, namely (22) in Theorem 1.

Step 5: We set $k = 1$ and $s = 0$ in (B.16). Using Jensen's inequality, we obtain:

$$\begin{aligned}
&\int_0^t \left(\frac{\sum_{x_m \in V} deg(x_m) E^{M_\ell}(x_m,\tau)}{\sum_{x_m \in V} deg(x_m)} \right)^2 \mathrm{d}\tau \\
&\quad \leq \frac{\max_m deg(x_m)}{vol(G)} \int_0^t \sum_{x_m \in V} (E^{M_\ell}(x_m,\tau))^2 \,\mathrm{d}\tau \\
&\quad \leq 4\frac{\max_m deg(x_m)}{vol(G)} (M_1(0) + t\,F)
\end{aligned} \tag{B.30}$$

and eventually

$$\frac{\big(\min_m deg(x_m)\big)^2}{(vol(G))^2}\int_0^t \big(\sum_{x_m\in V} E^{M_\ell}(x_m,\tau)\big)^2\,\mathrm{d}\tau \le 4\frac{\max_m deg(x_m)}{vol(G)}(M_1(0)+tF), \tag{B.31}$$

where in both (B.30) and (B.31) $E^{M_\ell}(x_m,\tau)=\sum_{i=1}^{M_\ell} iu_i^{M_\ell}(x_m,\tau)$, $deg(x_m)$ and $vol(G)$ are respectively as in (15) and (16). Putting together (B.30) and (B.31) we see that:

$$\int_0^t \big(\sum_{x_m\in V} E^{M_\ell}(x_m,\tau)\big)^2\,\mathrm{d}\tau \le 4R(G)(M_1(0)+tF), \tag{B.32}$$

where $R(G)$ is as in (20). In addition, let $P\in\mathbb{N}$. For $1\le P<M_\ell$ and for each $t\ge 0$ we have:

$$\left(\sum_{x_m\in V}\sum_{i=1}^{P} iu_i^{M_\ell}(x_m,t)\right)^2 \le \left(\sum_{x_m\in V}\sum_{i=1}^{M_\ell} iu_i^{M_\ell}(x_m,t)\right)^2.$$

By (B.9), (B.30) and monotone convergence theorem, we have that for $t\ge 0$:

$$\int_0^t M_1(\tau)^2\,\mathrm{d}\tau = \lim_{P\to\infty}\int_0^t \big(\sum_{x_m\in V}\sum_{i=1}^{P} iu_i(x_m,\tau)\big)^2\,\mathrm{d}\tau \le 4R(G)(M_1(0)+tF), \tag{B.33}$$

which coincides with (22). The proof is now concluded. □

We will prove now Theorem 2 as enunciated in Section 2.

Proof of theorem 2. Consider the sequence $\{u_i^{M_\ell}\}_{\ell\in\mathbb{N}}$ for $i=1,2,\dots$ built in Theorem 1. By construction, for each fixed M_ℓ, $\{u_i^{M_\ell}\}_{i=1}^{2M_\ell}$ is the solution of the approximating system $(\mathbf{S}^{M_\ell})$ (B.1)-(B.3). We now argue as in Lemma 2.3 of [45] and Preposition 2.3 of [28]. After setting in (B.7) $g_i=i^2$ for $i=1,\cdots,2M_\ell$, we sum up over all $x_m\in V$ and use (A.2) in order to obtain:

$$\frac{\partial}{\partial t}\left(\sum_{x_m\in V}\sum_{i=1}^{2M_\ell} i^2u_i^{M_\ell}(x_m,t)\right) \le \left(\sum_{x_m\in V}\sum_{i=1}^{2M_\ell} i^2u_i^{M_\ell}(x_m,t)\right)^2 + \sum_{x_m\in V} f(x_m)\,. \tag{B.34}$$

For simplicity we set $\rho^{M_\ell}(t) = \sum_{x_m \in V} \sum_{i=1}^{2M_\ell} i^2 u_i^{M_\ell}(x_m,t)$. Standard comparison results for ODEs show that $\rho^{M_\ell}(t) \leq z(t)$ on $[0,t^*)$ where $z : [0,t_*) \to \mathbb{R}$ is the maximal solution of the ODE:

$$\frac{\partial z}{\partial t} = z^2 + \sum_{x_m \in V} f(x_m) \tag{B.35}$$

with initial data $z(0) = \sum_{x_m \in V} \sum_{i=1}^{\infty} i^2 U_i(x_m) \equiv M_2(0)$. Hence, it follows that:

$$\sum_{x_m \in V} \sum_{i=1}^{2M_\ell} i^2 u_i^{M_\ell}(x_m,t) \leq \sqrt{F} \tan\left(t\sqrt{F} + \arctan\left(\frac{M_2(0)}{\sqrt{F}} \right) \right) \tag{B.36}$$

for $0 \leq t < t_*$, where $t_* = \frac{\arctan\left(\frac{\sqrt{F}}{M_2(0)}\right)}{\sqrt{F}}$ and $F = \sum_{x_m \in V} f(x_m)$; in addition, for each $\bar{t} < t_*$ it holds:

$$\sup_{(x_m,t) \in V \times [0,\bar{t}]} \sum_{i=1}^{2M_\ell} i^2 u_i^{M_\ell}(x_m,t) \leq C(\bar{t}). \tag{B.37}$$

with $C(\bar{t}) = \sqrt{F} \tan\left(\bar{t}\sqrt{F} + \arctan\left(\frac{M_2(0)}{\sqrt{F}} \right) \right)$. Hence, for $1 \leq M_k < 2M_\ell$ and for $(x_m,t) \in V \times [0,\bar{t}]$ we have that:

$$\sum_{i=M_k}^{2M_\ell} i u_i^{M_\ell}(x_m,t) \leq \frac{\sup_{(x_m,t) \in V \times [0,\bar{t}]} \sum_{i=1}^{2M_\ell} i^2 u_i^{M_\ell}(x_m,t)}{M_k} \leq \frac{C(\bar{t})}{M_k} . \tag{B.38}$$

In particular, for any $\epsilon > 0$, there exists M_{ℓ_0} such that for any $M_\ell > M_{\ell_0}$

$$\sum_{i=M_{\ell_0}}^{2M_\ell} i u_i^{M_\ell}(x_m,t) \leq \frac{C(\bar{t})}{M_{\ell_0}} < \frac{\epsilon}{3} . \quad \text{for } t \in [0,\bar{t}],\ \bar{t} < t_* . \tag{B.39}$$

Taking into account (B.39) , (B.9), we have that for $M_{\ell_0} < P < 2M_\ell$ it holds:

$$\begin{aligned}
\sum_{i=M_{\ell_0}}^{\infty} i u_i(x_m,t) &= \lim_{P \to \infty} \sum_{i=M_{\ell_0}}^{P} i u_i(x_m,t) \\
&\leq \limsup_{l \to \infty} \sum_{i=M_{\ell_0}}^{2M_\ell} i u_i^{M_\ell}(x_m,t) \\
&\leq \frac{C(\bar{t})}{M_{\ell_0}} \\
&< \frac{\epsilon}{3} \qquad \text{for } t \in [0,\bar{t}] .
\end{aligned}$$

Thus, by (B.9),(B.40), (B.40), for any $(x_m,t) \in V \times [0,\bar{t}]$ and for any $\epsilon > 0$, there exists $M_{\ell_\epsilon} > M_{\ell_0}$ such that for any $M_\ell > M_{\ell_\epsilon}$:

$$|\sum_{i=1}^{\infty} iu_i(x_m,t) - \sum_{i=1}^{2M_\ell} iu_i^{M_\ell}(x_m,t)| < \epsilon. \tag{B.40}$$

Finally, (24) follows by (B.40) and (B.8) since the number of the vertex of the graph is finite. □

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Declarations

Conflict of interest: the authors declare that they have no conflict of interest.
Availability of data and material: the paper has no supplementary data or material.
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