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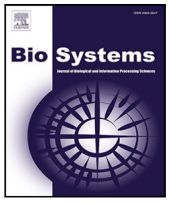

Short Communication

Extracellular interplay of amyloid fibrils and neural cells

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ABSTRACT

Some neurological disorders such e.g. as Alzheimer disease are accompanied by the appearance of amyloid fibrils inside and outside cells. Herein, I present a generic coarse-grained kinetic mean-field model describing at the extracellular level the interplay of fibrils and cells. It includes the formation and degradation of fibrils, activation of healthy cells with respect to the fabrication of fibrils, and death of activated cells. The corresponding analysis indicates that the disease development can occur in two qualitatively different regimes. The first one is controlled primarily by the intrinsic factors resulting in slow increase of fibril production inside cells. The second one implies faster self-promoted growth of the fibril population by analogy with explosion. This prediction reported as a hypothesis is of interest for conceptual understanding of the neurological disorders.

1. Introduction

Each disease is a complex phenomenon which can be experimentally explored and theoretically described at various levels. For example, the theoretical models used to interpret various aspects of the mechanisms of initiation and spread of viral infections can be divided into four categories aimed, respectively, at (i) mechanistic details of single steps, (ii) interplay of intracellular kinetic steps, (iii) populations of viruses and cells, or (iv) human or animal populations (see e.g. Zhdanov and Jackman, 2020, and references therein). The kinetic models of non-infectious diseases belong to categories (i)–(iii) provided "viruses" in (iii) is dropped or replaced by "intermediates".

Various age-related neurodegenerative disorders in general and Alzheimer and Parkinson diseases (AD and PD) in particular are non-infectious. Mechanistically, these disorders are accompanied by a complex process of peptide and protein aggregation, and this aggregation is now believed to be essential or even central in the pathology (reviewed from various perspectives by Iadanza et al., 2018; Ilie and Caflisch, 2019; Ke et al., 2020; Karran and De Strooper, 2022; Calabresi et al., 2023). In particular, extracellular deposition of amyloid-β plaque and intracellular accumulation of tau-protein neurofibrillary tangles are widely considered to be two of the characteristic hallmarks of AD (in addition to the reviews mentioned above, see, e.g., recent articles by Bellaver et al., 2023; Chen et al., 2023; Merz et al., 2023). In the amyloid-β case, self-assembly of a myloid-β peptides leads to sequential formation of relatively short oligomers, protofibrils, and fibrils which can be viewed as relatively long sheets. As fibrils grow, they can fragment, yielding more fibril ends that are capable of elongation, or associate further with each other or other protein species to form the amyloid plaques. Oligomers and fibrils are able to penetrate lipid membrane and cause membrane disruption by a variety of mechanisms, and accordingly both these species are likely to correlate with AD. The role of plaques in AD is less obvious because the severity of cognitive decline in patients with AD does not appear to correlate with plaque formation (Iadanza et al., 2018).

The proposed amyloid-β peptide and/or tau-protein scenarios of AD are now diverse. In addition to the conventional scenarios focused on aggregation of one of these species, there are complementary ones admitting the interplay of these species (Bellaver et al., 2023) or appreciable role of other species and processes including, e.g., β_2-microglobulin (Zhao et al., 2023), myelin (Depp et al., 2023), and brain-specific immune cells (Chen et al., 2023). Among alternative scenarios, one can mention e.g. that focused on neuroinflammation which disrupts brain networks independently of amyloid-β deposition (Leng et al., 2023). Regarding virology and the innate immune response, one can notice reports indicating that on one side, amyloids can interact with viruses and interfere with viral replication (Michiels et al., 2020) and on the other side, some viruses can encode amyloid-like fibril-forming proteins in the brain (Léger et al., 2020).

From the perspective of the classification given in the first paragraph above, the theoretical models related to AD and PD belong to categories (i) and (ii). In particular, the available kinetic models are aimed at protein aggregation occurring in solution *in vitro* or in single cells *in vivo* (reviewed by Ilie and Caflisch, 2019; Sharma et al.,

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2021; Righetti et al., 2022; see also early articles by Xue et al., 2008; Cohen et al., 2013; Zhdanov, 2016; recent articles by Dear et al., 2020; Joseph et al., 2020; Bridstrup et al., 2021; Zadeh and Peters, 2021; Krishnamurthy et al., 2022; Yang et al., 2022; Nguyen and Derreumaux, 2023; Pönisch et al., 2023; and references therein). The kinetic models of category (iii) aimed at the interplay of toxic species and cells are lacking. In this communication, I present a generic kinetic AD model of the latter category. The model is focused on the conventional amyloid-β AD scenario and, despite its simplicity, helps to understand conceptually the interplay under consideration.

2. Results and discussion

Aiming at the interplay of toxic species and cells during AD, one can complement the ingredients of the available models describing the amyloid oligomer, fibril, and plaque formation inside cells by those for the formation of these species outside cells (such models are mentioned in the Introduction). The former models are, however, now incomplete and cumbersome, and their extension with the inclusion of the extracellular steps is not straightforward. The situation here is similar to that with the models of viral infection (reviewed by Handel et al., 2020; Zhdanov and Jackman, 2020). Under such circumstances, it makes sense to use a course-grained approach and to operate at the level of healthy cells, cells plagued by fibrils, and fibrils outside cells. Oligomers outside cells can be viewed as a part of the fibril population and not treated explicitly. Taking into account that the severity of cognitive decline in patients with AD does not correlate with plaque formation (Iadanza et al., 2018), plaques outside cells can be not treated explicitly either. The healthy cells can be considered to dominate, i.e., their number is much larger than that of cells plagued by fibrils (this is the case provided the disease is not too severe). With these specification and simplifications, the mean-field model presented is focused on the number (or concentration) of cells plagued by fibrils, N, and the number (or concentration) of fibrils, n, outside cells.

The kinetic equations for the populations introduced are as follows

$$dn/dt = kN - \kappa n - \eta n, \tag{1}$$

$$dN/dt = w + \beta\kappa n - rN, \tag{2}$$

where k, κ, η, w, β, and r are the parameters. The first term, kN, on the right-hand side of Eq. (1) describes in a lumped way the release of fibrils by the plagued cells. The second term, κn, is associated with absorption of fibrils by healthy cells, and this process is assumed to be accompanied by plaguing of a cell. This is possible e.g. provided the cell state is kinetically bistable with respect to amyloids due to feedback (see e.g. a kinetic model by Zhdanov, 2016). The third term, ηn, corresponds to disappearance of fibrils via other channels including extracellular degradation and association with plaques. In Eq. (2), the first term, w, takes into account that healthy cells can become intrinsically plagued due to the intracellular evolution (w is the corresponding rate). The second term, $\beta\kappa n$, in Eq. (2) is similar to the second one in Eq. (1) (an additional dimensionless factor, β, is introduced in order to take into account that the plaguing of a healthy cell is expected to occur on average after absorption of a few fibrils). The third term, rN, represents the death of plagued cells.

The course-grained model defined by Eqs. (1) and (2) operates at the extracellular level. As usual in such biophysical models, the corresponding steps are lumped, and the rate constants (k, w, β, κ, and r) are effective, i.e., are implicitly dependent on the concentrations of the species which are not described explicitly. To specify some of these rate constants, one can use and/or design the models operating at the intracellular level.

Of note, as already noticed in the introduction, the framework outlined above is similar to that used to describe the interplay of virions and cells in the kinetic models of category (iii) in theoretical virology (the corresponding models are reviewed e.g. by Handel et al., 2020). In particular, the fibrils and plagued cells play in the model under consideration qualitatively the same roles as virions and infected cells in the models aimed at infections (see the equations reproduced in Fig. 2 of the review by Handel et al., 2020).

The timescales of neural diseases are typically long. In the context of the model under consideration, this means that all the effective rate constants in Eqs. (1) and (2) can depend on time at least slightly. To illustrate the predictions of the model, it is instructive to consider that all the parameters except w are independent of time and admit the dependence of w on time, because the latter dependence is expected to be crucial for the development of disease. With these simplification, Eqs. (1) and (2) are linear and can be solved analytically. To avoid simple but cumbersome expressions and to keep the presentation suitable for general readership, it makes sense to take into account that the processes including fibrils are relatively fast, and accordingly n can be expressed via N by solving Eq. (1) in the steady-state approximation as

$$n = kN/(\kappa + \eta). \tag{3}$$

Substituting this expression into Eq. (2) yields

$$dN/dt = w(t) + \gamma N, \tag{4}$$

where

$$\gamma \equiv \frac{\beta\kappa k}{\kappa + \eta} - r \tag{5}$$

is a lumped rate constant.

The general solution of Eq. (4) is

$$N(t) = N(0)\exp(\gamma t) + \int_0^t w(\tau)\exp[\gamma(t-\tau)]d\tau. \tag{6}$$

The simplest reasonable approximation for $w(t)$ is exponential,

$$w(t) = w(0)\exp(\mu t), \tag{7}$$

where μ is the corresponding constant. With (7), Eq. (6) yields

$$N(t) = N(0)\exp(\gamma t) + \frac{w(0)}{\gamma - \mu}[\exp(\gamma t) - \exp(\mu t)]. \tag{8}$$

Expression (8) for the number (or concentration) of cells plagued by fibrils [in combination with (3) for the number (or concentration) of fibrils] allows us to illustrate the main predictions of the model under consideration. In particular, the analysis shows that the kinetics predicted depends on three introduced parameters, $N(0)$, $w(0)$, and μ, and one lumped parameter, γ, defined by (5). Regarding the sign of these parameters, we have $N(0) > 0$, $w(0) \geq 0$, $\mu > 0$, whereas γ can be negative and positive. The type of the kinetics is determined by two main parameters, μ and γ. The former parameter corresponds to the intracellular evolution. The latter parameter characterizes the ability of fibrils to promote kinetically their own growth (this is possible provided $\gamma > 0$).

For healthy people, one expects to have $w(0) = 0$. In this case, (8) is reduced to

$$N(t) = N(0)\exp(\gamma t), \tag{9}$$

and accordingly disease is still possible provided $\gamma > 0$. Thus, the healthy state is associated with $w(0) = 0$ and $\gamma < 0$.

If $w(0) > 0$ and $\gamma < \mu$, the kinetics rapidly becomes exponential,

$$N(t) \simeq [w(0)/(\mu - \gamma)]\exp(\mu t). \tag{10}$$

This regime corresponds to the disease controlled by intracellular evolution.

If $w(0) > 0$ and $\gamma > \mu$, the kinetics rapidly becomes exponential as well but with another exponent,

$$N(t) \simeq [N(0) + w(0)/(\gamma - \mu)]\exp(\gamma t). \tag{11}$$

The latter regime corresponds to the disease controlled by self-promoted growth of fibrils.

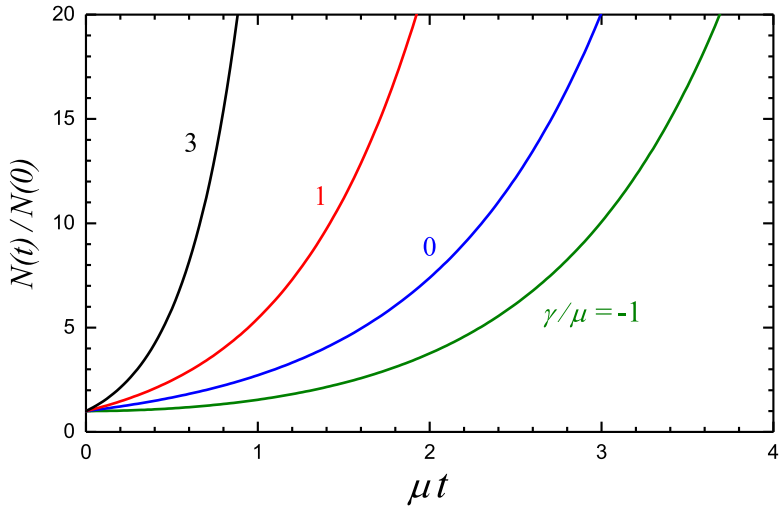

Fig. 1. Normalized population of plagued cells, $N/N(0)$, as a function of normalized time, μt, according to Eq. (8) with $w(0)/\mu = N(0)$ for $\gamma/\mu = -1$, 0, 1, and 3.

Although expression (8) is simple, it makes sense to show explicitly the shape of the corresponding kinetics. To be specific, I consider somewhat arbitrarily that $w(0)/\mu = N(0)$. In this case, the normalized population of plagued cells, $N/N(0)$, exhibited as a function μt depends only on the ratio γ/μ as shown in Fig. 1.

3. Conclusion

I have proposed a coarse-grained kinetic model describing at the extracellular level the interplay of amyloid fibrils and cells during AD. The key novel prediction of the analysis based on this model is that the disease development can occur in two qualitatively different regimes. The first one is controlled primarily by the intrinsic factors resulting in the increase of fibril production. The second one implies self-promoted growth of the fibril population by analogy with explosion. As declared in the Abstract, this prediction can now be viewed as a hypothesis which is of interest for conceptual understanding of the neurological disorders.

To test this hypothesis, one is expected to verify by using the samples obtained *in vivo* whether the system is bistable, i.e., whether the cells can be in two (healthy and plagued) states with respect to amyloid fibrils. One of the options here is to employ microscopy. This may, however, be challenging because the concentration of plagued cells can be low. Another less direct approach is to measure the fibril concentration, n, in the brain during a long period and to scrutinize the dependence of $\ln(n)$ on time. This dependence may exhibit the transition from one kinetic regime to another regime as predicted by the model presented. The interpretation of such measurements is, however, not expected to be unique.

Finally, I can repeat that the model I used is focused on the conventional amyloid-β AD scenario and operates at the extracellular level. It can be extended in various directions and/or combined with the models operating at the intracellular level. In this context, one can notice (cf. the Introduction) that the AD scenarios are diverse, and the corresponding specific kinetic models are lacking. For example, the already mentioned reports about the interference of amyloids and viruses (Michiels et al., 2020; Léger et al., 2020) appear to indicate that AD may depend on the function of the immune system which deteriorates with the age. The kinetic models describing the interplay of viral replication and the immune system (reviewed by Handel et al., 2020) or e.g. cancer and the immune system (reviewed by Zhdanov, 2021) are numerous. Some ingredients of these models can potentially be used in the AD case as well.

Declaration of competing interest

I declare that I have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

No data was used for the research described in the article

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