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Multistability in a prion replication interconnected cell reaction network ⋆

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Abstract:
Aggregation of misfolded proteins has been implicated in a number of neurodegenerative disorders including prion disease. In spite of intensive research, the detailed mechanisms of protein misfolding leading to protein aggregation remain unsolved. Here, we explore the capacity for bistability of several classes of mechanisms proposed in the literature and compatible with protein aggregation kinetic data sets (it has been shown that bistability explains thresholds phenomena observed in protein aggregation *in vitro* and *in vivo*). Using a novel method for bistability detection we find a plausible scenario for which the so called subsequent monomer addition model leads to bistability.

Keywords: Bistability, Prion kinetics, Interconnected cells, Biochemical Reaction Network

1. INTRODUCTION

Prion diseases are infectious neurodegenerative diseases occurring in humans and animals with a lethal outcome (e.g. Creutzfeld-Jakob, Gerstmann-Strausssler-Scheinker and Ahlzheimer diseases in humans). The key issue of prion diseases is the misfolding of the prion cellular protein, PrP^C, into its pathogen form, PrP^{Sc} (Aguzzi et al., 2008; Cohen and Prusiner, 1998). The detailed molecular process that change the structure of PrP^C into a rich and lethal β-sheet structure, PrP^{Sc}, and later replication, is not yet fully understood (Watts et al., 2006). The characteristic event in prion diseases is the aggregation of PrP^{Sc} into large amyloid plaques and fibrous structures associated with neurodegeneration; at sufficiently high concentration of PrP^{Sc}, it self-aggregates irreversibly (Cohen and Prusiner, 1998). Replication by autocatalysis of the PrP^{Sc} conformation is a plausible mechanism (Mendez and Femat, 2011).

Besides autocatalysis there are well documented alternative protein aggregation mechanisms that fit the experimental data collected within a period of 50 years among 30 laboratories (Morris et al., 2008, 2009; Finney and Finke, 2017). In particular, the mechanism proposed by Wegner and Engel (WE) (Morris et al., 2008, Table 1, entry 4) consider the subsequent monomer addition for actin fibril formation, and the binding and dissociation of protomers, with a critical nucleus size of three or four. As stated, such mechanism does not exhibits bistability. However, bistability seems to be crucial in protein aggregation systems since, as it has been demonstrated by Rieger et al. (2006) it explains the threshold phenomena observed in protein aggregation both *in vitro* and *in vivo*.

Brain dynamics are influenced by specific neural networks structures; hence, a brain disease is also structure dependent (Sporns, 2011). Thus, in order to explore the possible dynamics (e.g. bistability) a protein aggregation mechanism might engender, we interconnect two WE reaction networks. Such reactive cell interconnection mimics a minimal neural network within the brain where protein aggregation starts to outbreak.

2. MATERIALS AND METHODS

Results from Chemical Reaction Theory (Feinberg, 1978) allow to assess the capacity of a chemical reaction network to admit multiple steady states. In a series of works developed within this framework (Otero-Muras et al., 2009, 2012, 2014, 2017) parametric conditions for multistationarity and effective methods to find bistable regimes in biochemical networks have been proposed.

Here we apply these methodologies to explore the capacity for bistability of protein aggregation mechanisms proposed in the literature (Morris et al., 2008, 2009; Finney and Finke, 2017). For each network we perform the analysis in three variants (closed network, open network considering diffusion and basal formation of proteins and cell interconnected network). The latter variant accounts for a minimal neural network within the brain. In Fig. 1, the Wegner Engel mechanism for a nucleus size of three is depicted in an interconnected cell scheme. Our objective is not only to detect bistability, but also to understand how the bistability is originated.

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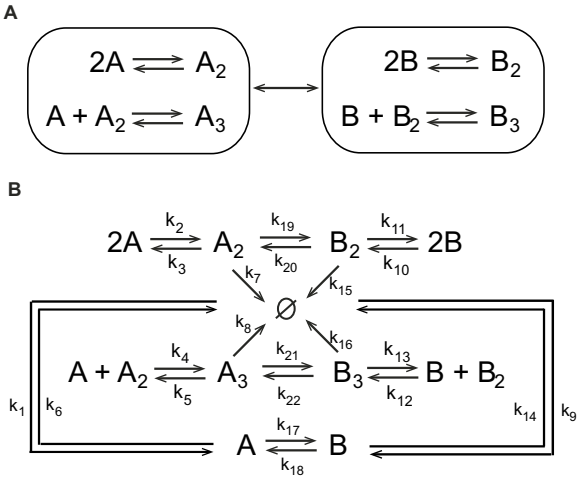

Fig. 1. Wegner Engel interconnected cell reaction mechanism and corresponding graph of complexes considering degradation of all species and monomer basal formation.

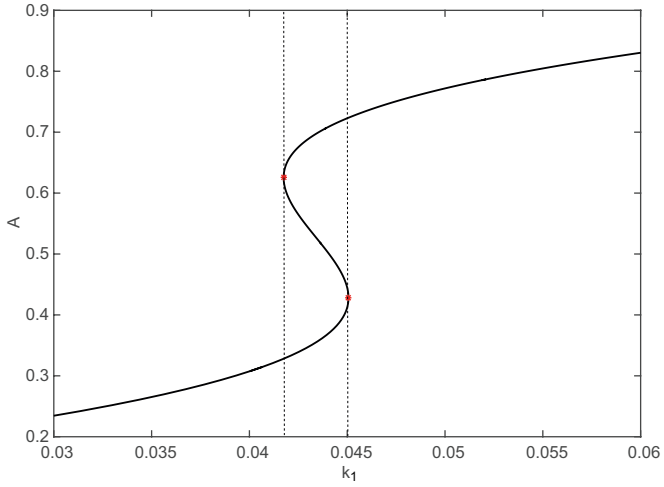

Fig. 2. Bifurcation diagram corresponding to the Wegner-Engel interconnected cell reaction network.The bistability region is enclosed within the dashed lines.

3. RESULTS AND DISCUSSION

As a result of our analysis, we have found that the Wegner Engel mechanism shows bistability in a cell interconnected scheme. As it can be seen in Fig 1 B, the network corresponds to a semi-diffusive system, so the method for effective bistability detection recently developed by Otero-Muras et al. (2017) can be directly applied. A set of parameters leading to bistability and the corresponding bifurcation diagram showing the bistable region are provided in Table 1 and Fig 2 respectively.

Importantly, the original mechanism does not admit multistationarity, so the neural network structure is in this case crucial for bistability.

Table 1. Parameters leading to bistability in Wegner-Engel interconnected cell reaction network

k_2	k_3	k_4	k_5	k_6	k_7	k_8
1.7885	2.0616	9.9120	0.2850	0.4986	0.0052	0.0014
k_9	k_{10}	k_{11}	k_{12}	k_{13}	k_{14}	k_{15}
4.3992	0.0229	0.4089	9.7683	0.0012	8.5685	0.6144
k_{16}	k_{17}	k_{18}	k_{19}	k_{20}	k_{21}	k_{22}
0.0012	0.0799	0.0799	6.9340	6.9340	9.2190	9.2190

Our present result suggest that connectivity among simple reaction networks experimentally validated for protein aggregation might display bistability. Future research will delve into the biologically relevant kinetic constants intervals for which bistability is supported.

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