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# AN EXTHENDED DYNAMICAL MODEL OF $\alpha$-SYNUCLIEN METABOLISM

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$\alpha$-synuclein ($\alpha$-syn) is a 140 amino acid protein that is abundantly expressed in the nervous system and contributes to the control of neurotransmitter release [1]. In addition, aggregates of misfolded $\alpha$-syn are the main component of Lewy bodies, fibril-like agglomerates. High abundances of Lewy bodies impair the production of dopamine leading to severe neurogenerative diseases such as Parkinson's disease (PD) or Lewy Body dementia [2].

Under normal conditions, $\alpha$-syn metabolism rarely promotes the formation of aggregates, such as dimers or oligomers, which, in the long run, lead to the formation of Lewy bodies. However, different external factors as oxidative stress or the mutation of genes such as SNCA, LRRK2, and Parkin result in promoting the aggregation of $\alpha$-syn [2]. As a consequence, these risk factors increase the likelihood of developing the diseases of several folds.

In recent years, different mathematical models have been proposed to provide a dynamical description of $\alpha$-syn metabolism and the formation of aggregates [3]. However, most of these models could not depict the entire $\alpha$-syn metabolism and its interactions with the cellular environment. To provide a complete picture of the $\alpha$-syn dynamics, to elucidate the processes that lead to its aggregation, and to better characterize its interaction with the other cellular processes, we introduce an enhanced dynamical model of $\alpha$-syn metabolism, which combines and extends existing mechanistic models. We parametrize the model by combining the existing knowledge and the available literature data. Moreover, we explore the $\alpha$-syn dynamics by using a combination of stochastic and deterministic simulations [4].

Through sensitivity analysis [5] and in-silico experiments, we quantify the effect of different causes in perturbing or affecting the course of the aggregation. In this way, we can provide a cause-effect map that includes several risk factors for the accumulation of $\alpha$-syn. Moreover, the model can support the development of new drugs and identify relevant metabolic processes for the occurrence of Lewy body related

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diseases. Potentially, the model may provide a tool to in-silico asses the effect of candidate therapeutics to ameliorate patient conditions or slow down the progress of neurodegeneration.

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