# Toward a Quantitative Systems Pharmacology framework of cell-level alpha-synuclein dynamics


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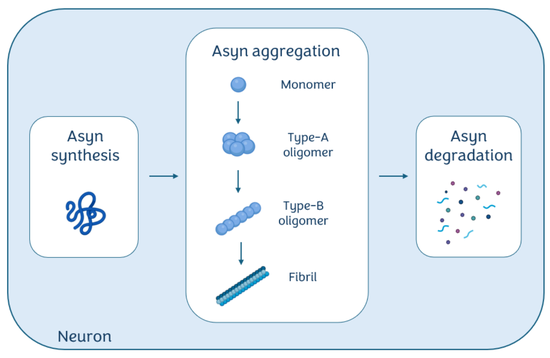
## Introduction

**Parkinson's disease** (PD) – the second most prevalent neurodegenerative disorder worldwide [1] – is characterized by the **progressive accumulation** of misfolded and aggregated alpha-synuclein (**aSyn**), whose toxic oligomeric and fibrillar species are closely associated with disease onset and progression [1]. While in vitro studies have clarified aSyn aggregation kinetics under controlled conditions**, the cellular environment remains more complex and less understood**. In cells, aSyn synthesis, proteasomal and lysosomal degradation, lipid interactions, and other cellular components can strongly modify aggregation dynamics compared to test-tube conditions [2]. Therefore, translating aSyn aggregation into a physiologically relevant cellular context requires the explicit representation of intracellular protein turnover.

## Objectives

This study builds an **in-silico model** of α-syn homeostasis by extending the aggregation model from [5] **to include protein synthesis and degradation**. This approach helps to better understand how **changes in aSyn** aggregation and degradation can contribute to Parkinson's disease.




## Methods

- The model captures the kinetics of aSyn production, aggregation, and degradation, enabling quantitative predictions at the cellular level.
- Implemented using ordinary differential equations (ODEs).

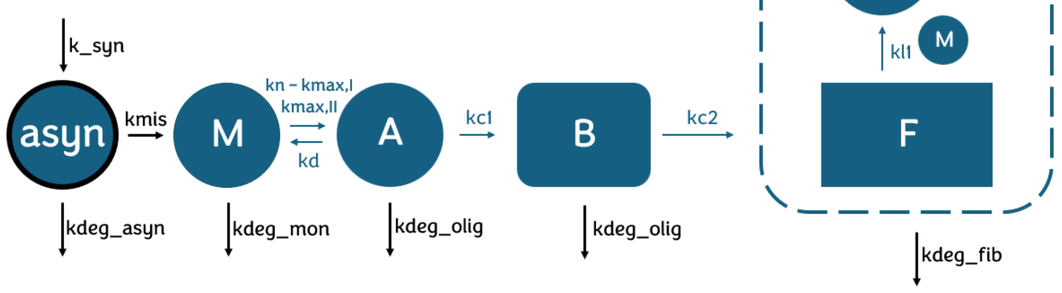



**Figure 1: Schematic representation of the deterministic model.** Dark blue arrows indicate reactions previously established in [2]. Black arrows represent newly added reactions modeling aSyn degradation. A new variable (*asyn* - highlighted with black outline) represents the concentration of non-misfolded aSyn. Other variables in the model include *M* (concentration of free monomers in solution), *Mf* (concentration of monomers in fibril), *A* (type-A oligomer concentration), *B* (type-B oligomer concentration), and *F* (fibril concentration).

## Results

After ensuring the model captures experimental variability, sensitivity analysis was performed to identify the key rate constants driving the system's dynamics.

### Model calibration

Deterministic simulations of systems of ODEs.

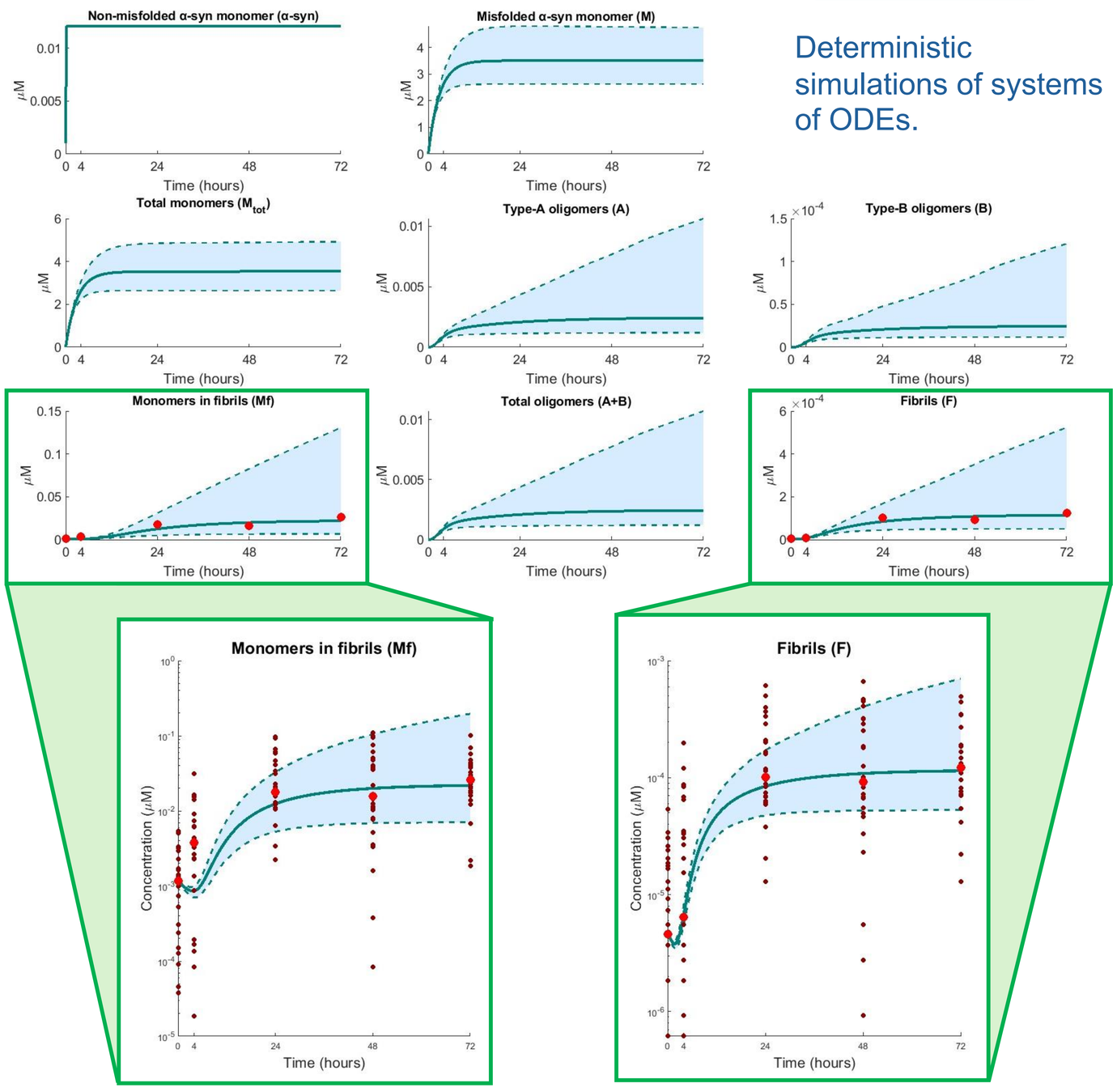



**Figure 2**: **Model calibration and uncertainty quantification.** Red points represent the median experimental data used for parameter estimation [6]. Shaded bands indicate the 5th–95th percentile intervals derived from 400 Monte Carlo simulations (*CV = 20%*). The green inset highlights model performance for *Mf* and *F* species on a log scale, demonstrating the model's ability to capture high dataset variability.

### Local sensitivity analysis

Sensitivity analysis evaluates how parameter changes influence model species, providing a framework to virtually simulate the efficacy of potential anti-aggregation pharmacological interventions. Among the parameters tested, synthesis and monomer degradation were identified as the most sensitive regulators across nearly all model species.

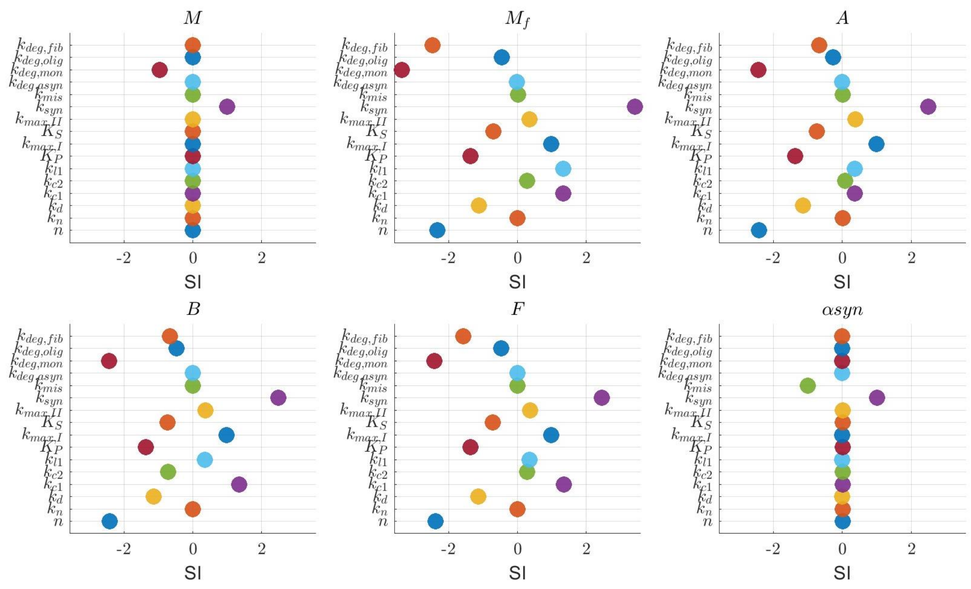



**Figure 3: Local Sensitivity Analysis of model species.** To assess parameter influence, we calculated the relative AUC-based sensitivity index (SI) by applying a 1% perturbation to each rate constant. On the SI scale, a positive value (right) indicates that increasing the parameter value raises the species concentration, while a negative value (left) indicates an inverse relationship where increasing the parameter leads to a decrease in the species. While *Mf*, *A*, *B*, and *F* show sensitivity across a wide range of parameters, particularly *kdeg_mon*, *kdeg_fib*, and *n*, the species *M* and *asyn* exhibit a much more selective response. For these two, the dynamics are almost entirely driven by the synthesis (*k_syn*) and monomer degradation or misfolding rates (*kdeg_mon, kmis*). Overall, *k_syn* and *kdeg_mon* appear to be the primary regulators of the system across nearly all modeled species. In addition to these core drivers, *Mf*, *A*, *B*, and *F* are sensitive to specific kinetic transitions: *Mf* is influenced by *K_P*, *kd*, *kI1*, and *kc2*, while the aggregated forms *A*, *B*, and *F* show strong dependence on *K_P*, *kd*, *kmax,I* and *kc1*. We refer to Fig. 1 for a graphical description of the model parameters.

## Future perspectives

- Incorporate explicit modeling of **proteasomal** and **lysosomal degradation pathways** into the framework.
- Extend the model by building a **microglia module** to represent aggregate clearance and neuroinflammatory responses.
- Extend the model to investigate the effects of **GBA gene mutations**.
- Develop an integrated **QSP framework** connecting molecular mechanisms to cellular and tissue-level dynamics.

## References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