**Title:**

**Simulation of Cognitive Decline in Alzheimer's Disease and the Impact of Mild vs Strong Therapeutic Interventions**

**1. Objective**

To simulate Alzheimer's disease progression over 5 years and evaluate the impact of different drug strengths (mild and strong) on delaying cognitive worsening, using Simulx platform.

**2. Model Summary**

* **Disease progression model**:
  + Cognitive function (similar to MMSE score) declines slowly over time.
  + Rate of decline is modified by the drug effect.
* **Model equations**:
  + Delayed drug effect:  
    effect=DRUG\_EFF×tT50+t\text{effect} = \text{DRUG\\_EFF} \times \frac{t}{T50 + t}effect=DRUG\_EFF×T50+tt​
  + Corrected progression rate:  
    PROG\_RATE\_per\_day=PROG\_RATE365\text{PROG\\_RATE\\_per\\_day} = \frac{\text{PROG\\_RATE}}{365}PROG\_RATE\_per\_day=365PROG\_RATE​
  + Cognitive decline:  
    d(Cognitive)dt=−PROG\_RATE\_per\_day×(1−effect)\frac{d(\text{Cognitive})}{dt} = - \text{PROG\\_RATE\\_per\\_day} \times (1 - \text{effect})dtd(Cognitive)​=−PROG\_RATE\_per\_day×(1−effect)
* **Initial condition**:
  + Cognitive0=BASELINE\text{Cognitive}\_0 = \text{BASELINE}Cognitive0​=BASELINE

**3. Parameters Used**

| **Parameter** | **Description** | **Typical Value** | **Variability (SD)** |
| --- | --- | --- | --- |
| BASELINE | Initial cognitive score | 30 | ±1 |
| PROG\_RATE | Cognitive decline per year | 2 points/year | ±0.2 |
| DRUG\_EFF (Mild Drug) | Drug effect | 0.3 | ±0.05 |
| DRUG\_EFF (Strong Drug) | Drug effect | 0.5 | ±0.05 |
| T50 | Time for half drug effect | 180 days | ±20 |

**4. Simulation Settings**

* **Population**:
  + 50 Treated patients (Mild Drug)
  + 50 Treated patients (Strong Drug)
  + 50 Untreated patients (DRUG\_EFF = 0)
* **Timeframe**:  
  0 to 5 years (1825 days), evaluated every 30 days.
* **Variability**:  
  Inter-individual variability applied on BASELINE, PROG\_RATE, DRUG\_EFF, and T50.

**5. Results**

**Cognitive Trajectories:**

* **Untreated**: fastest cognitive decline.
* **Mild Drug**: slower decline compared to untreated.
* **Strong Drug**: slowest decline; best preservation of cognitive function.

**Summary Table of Cognitive Worsening (MMSE < 24):**

| **Group** | **Median Time to Worsening** | **% Patients Worsened** |
| --- | --- | --- |
| Mild Drug | ~1230 days (~3.4 years) | 92% |
| Strong Drug | ~1530 days (~4.2 years) | 66% |

*(Mild Drug and Untreated group were merged earlier. Strong Drug group showed clear benefits.)*

**6. Clinical Interpretation**

* Patients under **mild treatment** still experienced rapid cognitive decline, with most worsening within ~3.4 years.
* **Stronger treatment** extended the median time to worsening by almost **1 year** and **reduced the proportion of worsened patients by 26%**.
* Strong drugs provide **clinically meaningful slowing** of disease.

**7. Conclusion**

This Simulx project successfully modeled Alzheimer's disease progression and quantified the clinical benefit of different therapeutic strengths. Stronger drugs significantly delayed cognitive worsening, supporting the need for treatments that maximize drug efficacy early in the disease course.





 