Disease System Analysis: Evaluate the structural properties and the physiological implications of an indirect physiologic response model describing the degenerative progression of Alzheimer’s disease using a closed-form solution

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Background
Several acetylcholinesterase inhibitors (AChEIs) are currently approved as treatments for patients with mild-to-moderate AD, and have been shown to transiently improve the cognitive, functional, and behavioural symptoms of AD without affecting the natural course of the disease. Understanding progression in a patient population treated with AChEIs is of paramount importance for the evaluation of potential benefits deriving from the use of novel medicines for the treatment of AD. Various descriptive models were proposed to quantitatively describe the progression of Alzheimer’s disease (AD) [1,2,3].

In these models, cognitive deterioration is a function of the natural disease progression, placebo and treatment effects, but without characterization of the underlying biological system. In a previous communication [4], we proposed alternative mechanistic model assumptions [5] to characterise the progression of cognitive deterioration in AD patients on stable AChEI therapy. We concluded that a time-varying impairment of cognitive status in the absence of proper homeostatic compensation was the most efficient mechanism for describing AD progression.

Objectives
The objectives of the present effort were to derive a closed-form solution of this indirect-response model with a time-varying impairment of the cognitive function, to evaluate the physiological implication of this mechanistic model and to compare it with the previous empirical models.

Disease system analysis
The best performing mechanistic model was:

\[
\frac{d\text{ADAS}(t)}{dt} = k_0(t) - k_{out}(t) \cdot \text{ADAS}(t)
\]

\[k_0(t) = k_0 + k_1 \cdot t\]

\[k_{out}(t) = k_{out}\]

\[\text{ADAS}(0) = \text{Baseline}\]

(1)

Where: ADAS(t) is the time-varying level of cognitive function, expressed by the cognitive portion of the AD Assessment Scale (ADAS-cog), ranging from 0 to 70, with higher scores indicating greater cognitive impairment. \(k_i(t)\) is the time-varying impairment rate of ADAS(t), \(k_0\) is the deterioration rate of cognitive function at baseline, \(k_1\) is a constant characterising the time-varying rate describing the loss of cognition in patients with AD and \(k_{out}\) is the first order constant controlling the compensatory regulatory response performed by homeostatic control systems.

Results

The Closed-Form Solution
The closed-form solution of the equation system (1) was derived using the Laplace transform method:

\[
\text{ADAS}(t) = \left(\frac{k_0}{k_{out}} + 1\right) \cdot e^{-k_{out}t} + k_0 \cdot \left(\frac{k_1}{k_{out}} \cdot e^{-k_{out}t} - 1\right) + ADAS_0
\]

(2)

With the slope of the ADAS-Cog trajectory varying with time:

\[
\text{ADAS}'(t) = k_0(t) - k_{out}(t) \cdot \text{ADAS}(t)
\]

(3)

The analysis of the first derivative, \(\text{ADAS}'(t)\) indicates that ADAS(t) is monotonically increasing (impairment in cognitive functions, ADAS(t) strictly positive) when:

\[
\text{ADAS}_0 < \frac{k_0}{k_{out}}\]

(4)

This relationship discriminates subjects with a transient (for \(k_1>0\)) improvement on cognitive degenerative process (Figure 1, upper panel), for which \(\text{ADAS}'(t)\) will be negative over a time interval and/or null in one time point, from subjects where the process is purely degenerative (Figure 1, bottom panel). The degenerative process occurs when the ratio between the loss of cognition (\(k_i(t)\)) and the homeostatic controlling process (\(k_{out}\)) becomes greater than the current disease status (\(\text{ADAS}_0\)) and the system is no longer able to compensate for the natural fluctuations in cognitive functioning. This is the case when \(k_i(t)\) is no longer constant and equal to \(k_0\) like in normal subjects, but continues to increase from \(k_0\) according to a linear, not proportional relationship with time.

Comparison with Empirical Models
The profiles of the majority of the empirical models so far presented [6] are a subset of the profiles described by the mechanistic model, imposing particular relationships among its parameters. In this way these empirical models can be reparametrized with parameters meaningful from a mechanistic point of view.

Relationship among the mechanistic model parameters

ADAS0 < \(\frac{k_0}{k_{out}}\)

\[\text{ADAS}_0 = \text{ADAS}_0 + K_j + A \left(\text{e}^{-k_{out}t} - 1\right)\]

(5)

ADAS0 < \(\frac{k_0}{k_{out}}\)

\[\text{ADAS}_0 = \text{ADAS}_0 + K_j + A \left(\text{e}^{-k_{out}t} - 1\right)\]

(6)

Conclusions
An explicit solution of the indirect-response model with a time-varying impairment of cognitive function was derived.

This equation was used to evaluate the physiological meaning of the model parameters and for discriminating subjects with a transient improvement on cognitive degenerative process from subjects where the process is purely degenerative.

References