Computational Modeling of the Dynamic Biomarker Cascade in Alzheimer's Disease

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Abstract:

Background: The heterogeneity and complexity of Alzheimer's disease (AD) lends itself to dynamic causal modeling, a computational systems biology approach to simulate complex systems.

Methods: We implemented a computational dynamic causal model (DCM) to test the common descriptive assumptions of biomarker evolution in AD. We modeled beta-amyloid, tau, neuro-degeneration and cognitive impairment as first order non-linear differential equations to include beta-amyloid dependent and non-dependent neurodegenerative cascades. We tested the DCM, by adjusting its parameters to simulate three specific simulation scenarios in early-onset autosomal dominant AD and late-onset AD, to determine whether computed biomarker trajectories agreed with current assumptions of AD progression. We also simulated the effects of anti-amyloid therapy in late-onset AD.

Results: The computational model of early-onset "pure AD" demonstrated the initial appearance of amyloid, followed by other biomarkers of tau and neurodegeneration, followed by the onset of cognitive decline as predicted by prior literature. The model also showed the ability to vary onset of cognitive decline based on cognitive reserve. Similarly, the late-onset AD computational models demonstrated the first appearance of amyloid-related or non-amyloid-related tauopathy, depending on the magnitude of age-related comorbid pathology, and also closely matched the cascade predicted by prior literature. Forward simulation of anti-amyloid therapy in symptomatic late-onset AD failed to demonstrate any benefit on cognitive decline, consistent with prior failed clinical trials in symptomatic patients.

Conclusions: To our knowledge, this is the first computational model of the dynamic biomarker cascade in autosomal dominant and late-onset AD. Such models, with refinement using actual molecular, clinical and genomic data, are an important tool towards developing a systems biology precision medicine approach for understanding and preventing AD.

Introduction:

Alzheimer's disease (AD), one of the leading public health priorities in the U.S., is projected to affect over 15 million people by 2050. The high failure rate of clinical drug trials over the past decade is in large part rooted in an incomplete understanding of AD at a systems or network level (1). Two components are necessary to realize this systems approach, an abundance of data covering many aspects of the person from health to disease, combined with computational methods capable of integrating and analyzing it. The tools of computational systems biology enable not only creation of quantitative averaged disease models, but also personalization of these models, based on individualized data to yield personal risk profiles and simulate a variety of potential prevention/treatment strategies. Such an approach has been highlighted as a high priority in AD (2).

AD progression can be measured through neuronal loss biomarkers (e.g. FDG-PET and volumetric MR imaging) as well as pathological biomarkers (CSF and PET scan markers of beta-amyloid and tau). ADNI data as well as data from other naturalistic studies, have led to a dynamic biomarker cascade model of AD progression, (3) which suggests that AD biomarkers evolve in a sequential, but temporally overlapping manner. Jack et al. have operationalized this model into a descriptive classification scheme for patients, based on 3 binary categories of biomarkers, amyloid-opathy, tau-opathy, and neurodegeneration (4).

However, current hypothetical and purely data-driven models on AD biomarker evolution have a number of shortcomings, such as lack the ability to simulate potential causal associations and their interactions (5-8). They also cannot be used simulate the multifactorial effects of either single-target or combinatorial intervention strategies (9). These shortcomings argue for the development of a data-driven systems biology "causal" (with assumptions) model of AD biomarker progression to complement existing models. The term causal modeling is widely used in disease modeling and refers to a model

explicitly formulated, based on existing knowledge, in terms of cause and effect relationships occurring at the individual level. Dynamic causal models are based on systems modeling with differential equations, capable of yielding a time-series analysis of the sequences and patterns of changes in various clinical and biomarker trajectories. To our knowledge, while there have been computational models of AD at a pharmacology or molecular level (10, 11), there has not been a DCM of the biomarker cascade.

Methods:

The goal was to construct an initial cascade model that included biomarkers of cortical amyloid beta, tau, and neuronal dysfunction/loss along with cognitive decline. For the construction of the model actual biomarker values were not needed and we drew assumptions about their relationships and temporal course from prior literature such as the widely cited theoretical model of biomarker evolution in AD by Jack and colleagues (3, 12, 13).

Our primary aim was to test whether a computational DCM implementation of this model would lead to the predicted biomarker cascade described in the literature.

Computational Model Construction:

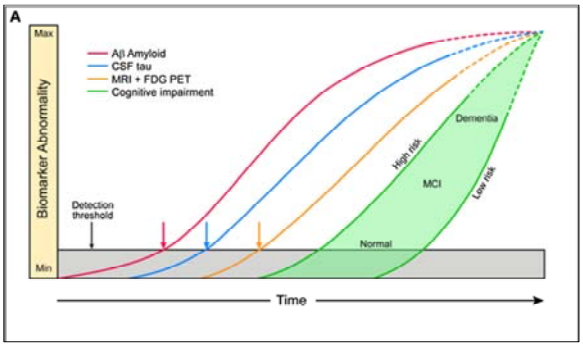
Implementation was performed using the ordinary differential equation toolbox in MATLAB (Mathworks®, Natwick, MA). We implemented the above DCM as system of first order non-linear differential equations to include amyloid dependent and non-dependent neurodegenerative cascades. The amyloid dependent cascade is initiated by amyloid beta, A_β, and mediated via phosphorylated tau, τ_ρ. The non-amyloid-dependent cascades are initiated by comorbidities, e.g., aging and/or suspected non-Alzheimer pathology (SNAP), either directly, or indirectly via non-amyloid dependent tauopathy, $\tau_{o,}$. Initiation of cognitive decline, C, is directly determined by neurodegeneration, comorbidities, genetic factors and cognitive reserve. Additional assumptions of the model exist.

We tested the DCM models using three simulation scenarios: 1) an autosomal dominant "pure" early-onset AD model, 2) a late-onset amyloid-first model mixed with SNAP comorbidities later, and 3) a late onset SNAP-first model mixed with amyloid later. Our goal was to determine whether manipulating parameters in the computational DCM in a physiological meaningful manner could reproduce computed biomarker trajectories that closely matched the visual depictions of the cascade in the literature. Lastly, we simulated the effects of anti-amyloid therapy administered in symptomatic late-onset AD to determine whether the model would predict the outcome of recently failed clinical trials.

Results:

1) Biomarker model of autosomal dominant "pure" AD

The simulated biomarker trajectories of early-onset "pure AD" visually matched those of the prior hypothetical model (12). Specifically, the early-onset AD model demonstrated the initial appearance of amyloid, followed by other biomarkers of tau and neurodegeneration, followed by the onset of cognitive decline depending on parameters related to cognitive reserve. Although tau in these figures represents total-tau, in this model, it is dominated by p-tau.



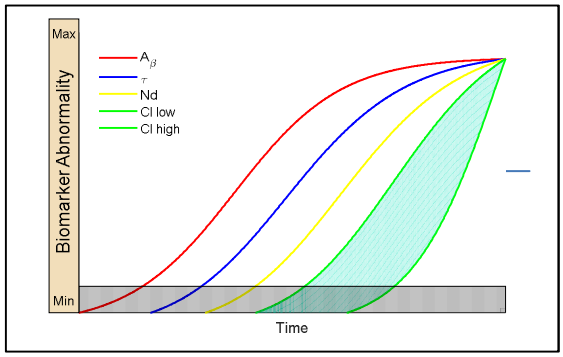


Figure 1: Model of early-onset “pure”AD; Literature model (left); Computational model (right).

2) Amyloid-first model of late-onset AD.

In this late-onset AD model amyloid appears first, followed by total tau and neurodegeneration. In this model, the arrival of amyloid is delayed compared to that in early-onset AD. Amyloid, however, reaches detection threshold prior to total tau.

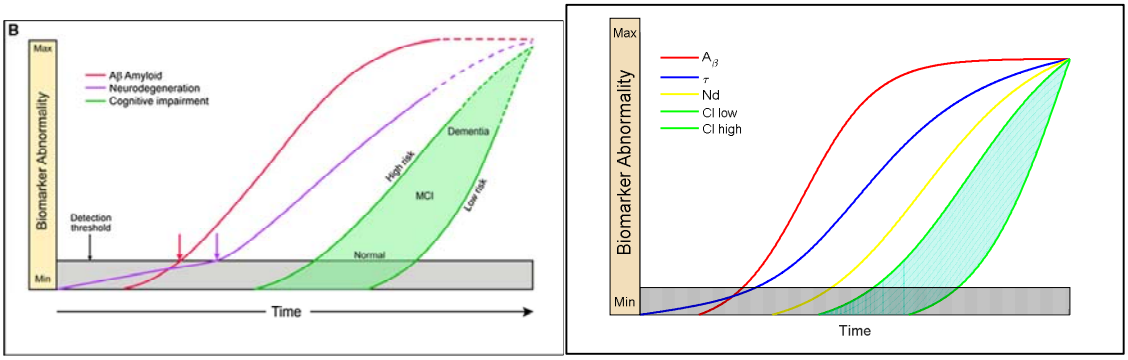


Figure 2: Amyloid-first biomarker model of late-onset AD; Literature model (left); Computational model (right).

3) Non-amyloid first model of late-onset AD with co-morbidities.

In this model, the arrival of total-tau precedes that of amyloid and initiates neurodegeneration, whereas subsequent appearance of amyloid accelerates this process.

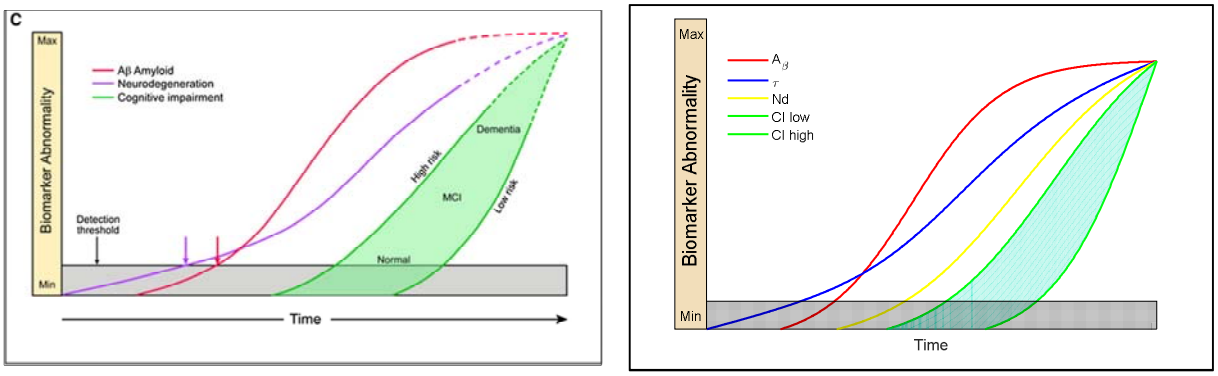


Figure 3: Tau-first model of late-onset AD; Literature model (left); Computational model (right).

4) Forward simulation of anti-amyloid therapy administered in late-onset AD, after symptoms begin.

Anti-amyloid therapy is added to the third model described immediately above. In the current model, amyloid accumulation begins to slow, then decline, after initiation of anti-amyloid therapy at 65 years of age; however, because the neurodegenerative and cognitive decline cascades have already begun by this time, there is no delay in onset of cognitive symptoms, and no effect on the slope of cognitive decline, despite amyloid level dropping over 75% from its peak.

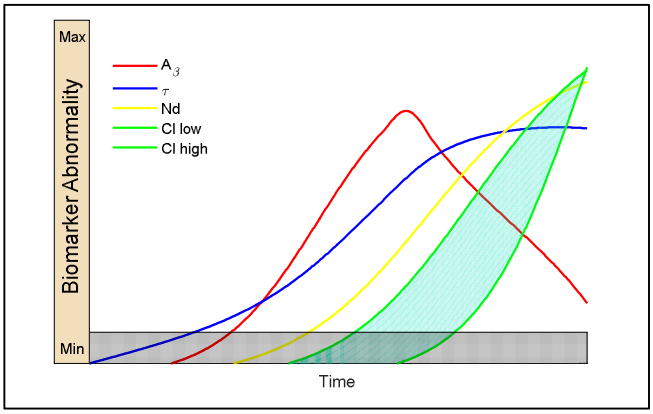


Figure 4: Forward simulation of the effect of anti-amyloid therapy in symptomatic late-onset AD. Model showing no benefits on cognitive decline slope, despite substantial reduction in amyloid load. Therapy initiated at age 65.

Discussion:

In this study we computationally implemented a mathematical formulation of the dynamic biomarker cascade model using a system of first order non-linear differential equations, and tested the model using several simulation scenarios to determine whether the model agreed with expected results. To our knowledge, this is the first computational implementation of a causal modeling approach to the hypothetical dynamic biomarker cascade model in AD (12), one of the most commonly referenced in the literature. The hypothetical model, originally published in 2010 and updated in 2013, postulates a temporal evolution of five validated AD biomarkers, markers of amyloid, tau, and neurodegeneration (3, 13). The temporal evolution is represented as sequential plots in plots of biomarker abnormality over time leading to cognitive impairment. The model takes into account varying age of onset and the existence of age-related and comorbid pathologies commonly seen in the elderly. While this theoretical model seeks to provide a unified understanding of biomarker evolution for several scenarios, to our knowledge, it has not yet been operationalized into a computational format. Several findings emerged from our modeling exercise. Our computational causal model of early-onset AD closely matched the theoretical model of "pure AD" envisioned by Jack et al. (13) and supported by other literature evidence from imaging studies such as ADNI. Secondly, our late onset models consider both an amyloid-first and a tau-first mixed model of AD neurodegeneration in certain patients, as envisioned in the updated model by Jack et al.(3) , where amyloid acts as an accelerator, rather than initiator, of the tau cascade. Lastly, our in-silico model of anti-amyloid therapy given after symptoms have begun in late-onset AD mimicked the findings from several failed clinical trials of anti-amyloid therapies in mild-moderate AD (14).

There are several strengths and limitations to our modeling approach. The key strengths are that our quantitative models not only match the widely cited descriptions of the dynamic biomarker cascade (3, 12, 13), but also will allow for future quantitative parametrization and validation of the model with real patient data, and for the addition of complex interactions among AD biomarkers and comorbid conditions that cannot be deduced by intuition alone. A computational model could initially be parameterized based on current ADNI biomarker data, and be incrementally modified with increasing complexity, yielding predictions for effects on cognition that could be tested and validated as new population data becomes available. In addition, the population-based parameterized model could be modified to yield personalized predictions of cognitive trajectory and response to a variety of in-silico interventions (15). Unlike existing computational or mathematical models of AD, which incorporate non-measurable quantities, in gene expression, metabolic and signaling pathway systems (11, 16-18), a model involving biomarker assays would lend itself more easily to implementation and validation in clinical research and patient care settings. Furthermore, the addition of cellular biological, genomic, and pharmacologic information could make the model attractive to understand complex disease mechanisms, predict natural history and accelerate drug discovery.

The main limitation of our work is the limited number of variables incorporated and its theoretical nature, without the use of patient data to parametrize the model. Our goal was to create as parsimonious a model as possible, while still incorporating all of the descriptive and graphic characteristics of the model as outlined in publications, so as to reproduce the predictions of the descriptive model in the literature, and illustrate how this might be extended to the therapeutic domain. Future work to parameterize and refine this model is warranted to extend its use to clinical research and patient care domains.

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