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# Imaging β-amyloid fibrils in Alzheimer's disease: a critical analysis through simulation of amyloid fibril polymerization

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**Abstract**

The polymerization of β-amyloid (Aβ) peptides into fibrillary plaques is implicated, in part, in the pathogenesis of Alzheimer's disease. Aβ molecular imaging probes (Aβ-MIPs) have been introduced in an effort to quantify amyloid burden or load, in subjects afflicted with AD by invoking the classic PET receptor model for the quantitation of neuronal receptor density. In this communication, we explore conceptual differences between imaging the density of amyloid fibril polymers and neuronal receptors. We formulate a mathematical model for the polymerization of Aβ with parameters that are mapped to biological modulators of fibrillogenesis and introduce a universal measure for amyloid load to accommodate various interactions of Aβ-MIPs with fibrils. Subsequently, we hypothesize four Aβ-MIPs and utilize the fibrillogenesis model to simulate PET tissue time activity curves (TACs). Given the unique nature of polymer growth and resulting PET TAC, the four probes report differing amyloid burdens for a given brain pathology, thus complicating the interpretation of PET images. In addition, we introduce the notion of an MIP's resolution, apparent maximal binding site concentration, optimal kinetic topology and its resolving power in characterizing the pathological progression of AD and the effectiveness of drug therapy. The concepts introduced in this work call for a new paradigm that goes beyond the classic parameters $B_{max}$ and $K_D$ to include binding characteristics to polymeric peptide aggregates such as amyloid fibrils, neurofibrillary tangles and prions.


*Keywords:* Alzheimer's disease; Amyloid fibril; Polymerization; Imaging; Amyloid burden; Mathematical model

## 1. Introduction

Alzheimer's disease (AD) is defined histologically by the presence of intraneuronal neurofibrillary tangles (NFTs) and extracellular β-amyloid (Aβ) plaques in cerebral cortex [1]. Neurofibrillary tangles are highly insoluble neurofibrils formed by hyperphosphorylation of the cytoskeletal protein tau [2]. Intraneuronal neurofibrillary tangles build-up renders cells ineffective resulting in complete degeneration of affected neurons and appearance of "tombstone" NFTs in the extracellular space [3]. On the other hand, Aβ plaques, are extracellular aggregates of polymeric fibrils which are in turn composed of Aβ peptide monomers. We and others have introduced molecular imaging probes (MIPs) in an effort to quantify Aβ burden in the living brains of individuals afflicted with AD [4–11]. In this endeavor, it is assumed that the quantitation of Aβ load would parallel the quantitation of neuronal receptor density. In this work, we offer insights on the intricacies of imaging Aβ polymeric aggregates in vivo. We will start with a brief cell biology of Aβ processing as well as theories of Aβ polymerization, which will serve as a basis for the formulation of a mathematical model for the polymerization of Aβ. We use the model to generate tissue time activity curves (TACs) for hypothetical MIPs and draw insights from these simulations to address the efficacy of a particular probe in imaging the pathological progression and therapeutic interventions in AD. We note that the concepts presented in this work may

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be applicable to the prospect of imaging other polymeric aggregates such as NFTs and prions [12,13].

### 1.1. Cell biology of Aβ processing

One of the characteristics of brains afflicted with AD is the presence of extracellular structural elements referred to as amyloid plaques. Plaques are, in part, composed of masses of filaments which are in turn composed of the insoluble form of the Aβ peptide. The Aβ peptide is formed as a cleavage byproduct of a larger amyloid precursor protein (APP) (Fig. 1) [14,15]. Amyloid precursor protein is a ubiquitous membrane glycoprotein encoded by a single gene on chromosome 21 [16,17]. It is cleaved either via the α-secretase or the β-secretase pathway, often referred to as the amyloidogenic pathway (Fig. 1). When APP is cleaved by α-secretase, it produces a large amino-terminal fragment APPα destined for secretion and a smaller carboxyl-terminal fragment. Further processing of the carboxyl-terminal fragment by γ-secretase produces a 22- to 24-residue fragment termed P3, which may or may not be amyloidogenic. Alternatively, when APP is cleaved by β-secretase it produces a soluble amino-terminal fragment, APPβ, and a carboxyl-terminal fragment containing the Aβ peptide. Cleavage of the carboxyl-terminal fragment by γ-secretase results in the formation of multiple Aβ variants of 40–43 amino acids, which are prone to aggregate. Aggregation in the extracellular environment contributes to Aβ fibril (fAβ) assembly through a nuclear-dependent polymerization (NDP) reaction [18] or variations thereof [19–21]. The plaques seen in the brains of AD patients are structural assemblies made up of fAβ and other extracellular material such as astrocytes and microglial cell residues (see Refs. [22–24]).

### 1.2. Polymerization and structural features of amyloid fibrils

Nuclear-dependent polymerization is characterized by a slow, rate-limiting, nucleation step (Fig. 2A). The formation of a nucleus requires a series of monomeric Aβ (mAβ) association steps, which are thermodynamically unfavorable. Once the nucleus is formed, it extends to form larger polymers. The addition of mAβs at this stage is thermodynamically more favorable. The extension of amyloid fibrils (fAβ) is characterized by a steady-state phase in which the polymeric aggregates (fAβ) and monomeric Aβs (mAβs) are in dynamic equilibrium [18,25,26]. The steady-state concentration of mAβ is defined as the critical concentration ($X_C$) for polymer extension, and hence for fAβ formation. Below the critical concentration, there is a lag phase during which mAβ aggregate into β-sheet tapes [27]. With increased concentration of mAβ, the concentration of tapes reaches a level at which the tapes stack — forming ribbons — and extend by the deposition of mAβ [27]. At this stage, the Aβ structures are referred to as protofibrils (or protofilaments, Fig. 2B) [19,28]. Above the critical concentration $X_C$, protofibrils interweave to form fibrils (Fig. 2C) which further polymerize by the addition of mAβ [29,30].

## 2. Imaging statement

An ideal MIP should be sensitive to changes in the underlying biological processes in the progression of the

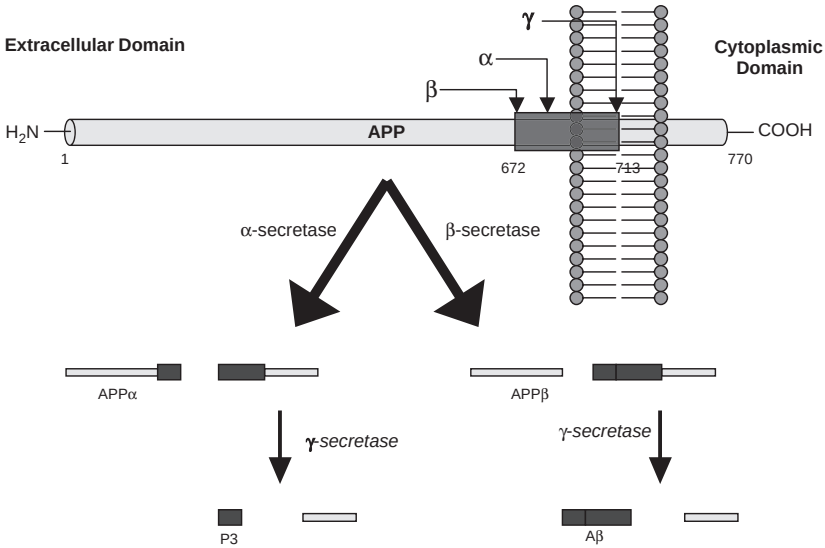


Fig. 1. Proteolytic cleavage of APP by α-secretase, β-secretase and γ-secretase. Amyloid precursor protein is a ubiquitous membrane glycoprotein encoded by a single gene on chromosome 21 [16,17]. Amyloid precursor protein is cleaved either via the α-secretase or the β-secretase pathway, often referred to as the amyloidogenic pathway. When APP is cleaved by α-secretase, it produces a large amino-terminal fragment APPα destined for secretion and a smaller carboxyl-terminal fragment. Further processing of the carboxyl-terminal fragment by γ-secretase produces a 22- to 24-residue fragment termed P3, which may or may not be amyloidogenic. Alternatively, when APP is cleaved by β-secretase it produces a soluble amino-terminal fragment, APPβ (sometimes referred to as sAPP), and a carboxyl-terminal fragment containing the Aβ peptide. Cleavage of the carboxyl-terminal fragment by γ-secretase results in the formation of multiple peptides of length 40–43. The two most common ones are $Aβ_{40}$, with 40-amino-acid residues, and $Aβ_{42}$, with 42-amino-acid residues [29,89].