Dynamic modelling of multiple domains involved in Alzheimer's disease: two approaches based on multivariate latent processes

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Résumé

Alzheimer's disease, the most frequent dementia in the elderly, is characterized by multiple progressive impairments in the brain structure and in clinical functions such as cognitive functioning and functional disability. Until recently, these domains were mostly studied independently while they are fundamentally inter-related in the degradation process towards dementia. We propose two statistical approaches to jointly model the dynamics of the multivariate domains involved in Alzheimer's disease. In both approaches, a domain is defined as a latent process for
which measures of one or several markers, possibly non Gaussian, are available at discrete visits in a cohort.
In the first approach, the main objective is to understand the link between the dimensions and the diagnosis of dementia. We thus propose a joint model in which the trajectories of the latent processes are described through a multivariate linear mixed model. Rather than considering the associated time to dementia as in standard joint models, we assume dementia diagnosis corresponds to the passing above a covariate-specific threshold of a pathological process modelled as a combination of the domain-specific latent processes. This definition captures the clinical complexity of dementia diagnosis but also benefits from an inference via Maximum Likelihood which does not suffer from the usual complications of joint models estimation. The model and the estimation procedure can also handle competing clinical endpoints, such as the competing death in Alzheimer's disease. The method is illustrated on a large French population-based cohort of cerebral aging in which we study the clinical manifestations (cognitive functioning, physical dependency and depressive symptoms) in link with repeated clinical diagnoses of dementia and death.

One limit of this approach is that the link between processes is only captured by correlations. In a second approach, we aim to model the dynamic influences between processes to

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understand the mecanisms underlying the dementia process. We define for this a dynamic causal model in discrete time based on both the linear mixed model theory to capture the correlation within a dimension and equations of difference to capture the temporal influences between dimensions. Parameters are estimated in the maximum likelihood framework enjoying a closed form for the likelihood. As causal relationships fundamentally lie in the continuous time framework, we evaluate the impact of the time discretization in simulations. The model is then applied to the data of the Alzheimer's Disease Neuroimaging Initiative. Three longitudinal general domains (cerebral anatomy, cognitive ability and functional autonomy) are analyzed and their causal structure is contrasted between different clinical stages of Alzheimer's disease.