**Mathematical Models**

1. **The Virtual Brain (TVB) Framework:**
   * The Virtual Brain (TVB) platform was employed to simulate whole-brain dynamics using structural connectivity (SC) from diffusion MRI data. This framework integrates molecular, cellular, and large-scale neuronal data.
2. **Jansen-Rit Neural Mass Model:**
   * This model simulates neuronal population dynamics, including pyramidal cells, excitatory interneurons, and inhibitory interneurons. It was adapted to model the impaired inhibitory function caused by Abeta accumulation.
   * Key modifications included:
     + Altering inhibitory postsynaptic potentials (IPSP) based on Abeta burden, quantified through PET imaging.
     + Introducing spatial heterogeneity by linking regional Abeta distribution to inhibitory time constants (τi).
3. **Abeta Effect Implementation:**
   * A sigmoid function was developed to model the relationship between Abeta burden (measured via standardized uptake value ratios, SUVR) and the inhibitory time constant (τi). Higher Abeta levels reduced inhibitory function, leading to hyperexcitability.
4. **Biophysical Parameters:**
   * Excitatory and inhibitory time constants (τe and τi), synaptic weights, and global coupling factors were adjusted to mimic realistic brain activity patterns, particularly the transition from alpha to theta rhythms observed in AD patients.

**Simulations**

1. **Setup:**
   * Virtual brains were constructed using averaged SC data from healthy controls and personalized Abeta distributions derived from PET scans of AD patients, individuals with mild cognitive impairment (MCI), and healthy controls.
2. **Simulated Outputs:**
   * Simulated electroencephalograms (EEG) replicated empirical findings:
     + AD patients exhibited slower brain oscillations (shift from alpha to theta frequencies) compared to healthy controls.
     + Abeta-induced hyperexcitability primarily impacted network hubs, even in spatially distributed regions.
3. **Drug Intervention Modeling:**
   * The NMDA receptor antagonist memantine was modeled to evaluate its potential to reverse Abeta-induced alterations. Simulations suggested partial functional restoration of the disrupted excitation-inhibition balance.
4. **Network and Parameter Analysis:**
   * By performing bifurcation analyses, the researchers explored how variations in excitatory and inhibitory parameters influenced local and global brain dynamics. The bistable regimes of the Jansen-Rit model captured transitions between physiological and pathological states.

**Key Findings**

* The integration of molecular-level Abeta data with meso- and macro-scale brain dynamics provides insights into AD mechanisms.
* The slowing of neural rhythms and hyperexcitability linked to Abeta were successfully reproduced in silico.
* This approach supports the identification of potential therapeutic targets and the evaluation of pharmacodynamic effects.

If you'd like, I can provide further insights or visual summaries from specific sections of the paper!