

Unveiling the Kinetics of Immunity: Mechanistic Insights into COVID-19 Vaccine Responses and Population Stratification

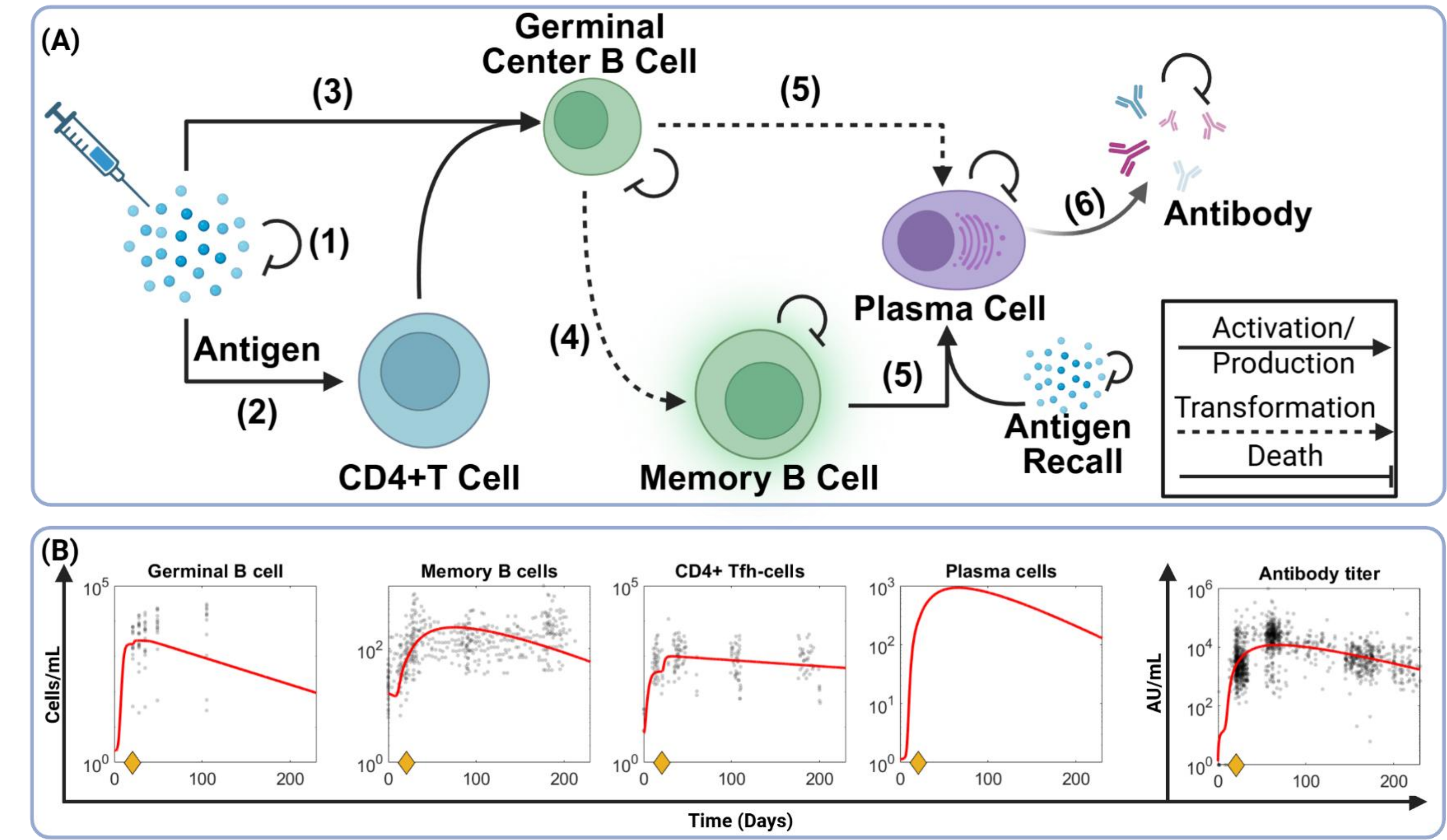
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ABSTRACT

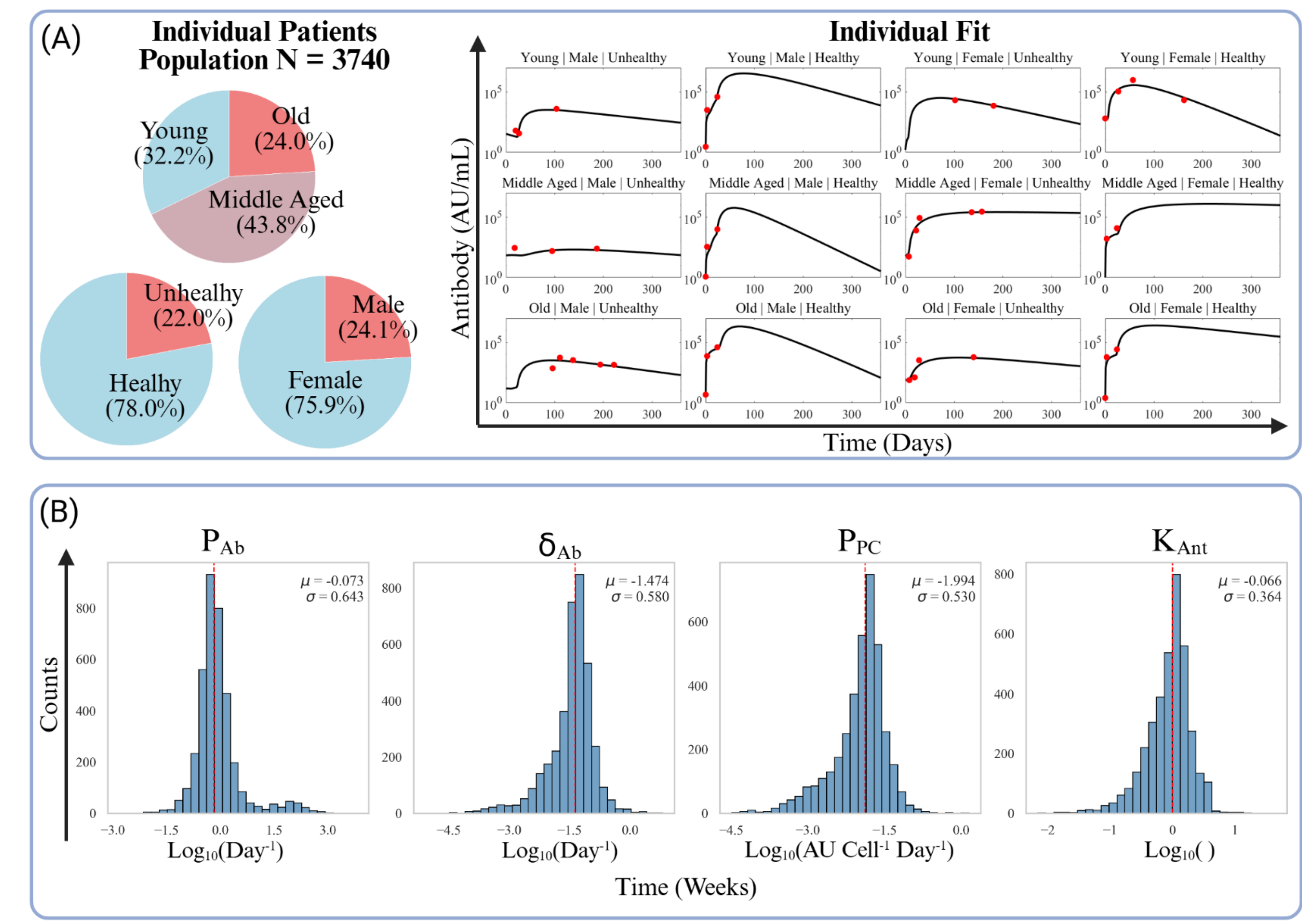
Vaccines are pivotal in combating infectious diseases, saving millions of lives worldwide and vastly improving public health. Despite their success, vaccine effectiveness varies among individuals due to factors such as previous viral exposure, age, sex, genetic predisposition, and co-morbidities (1,2). This variability presents a significant challenge in achieving optimal community-wide immunity. To address this challenge, we developed a mechanistic model that integrates the key phases of the immune response following vaccination. Our objective is to use this model to gain a deeper understanding of individual immune trajectories and to identify sub-categories of subjects with similar immune response patterns. This, in turn, will help rationalize vaccine distribution and improve immune protection in special populations.

MODEL DEFINITION AND POPULATION FIT



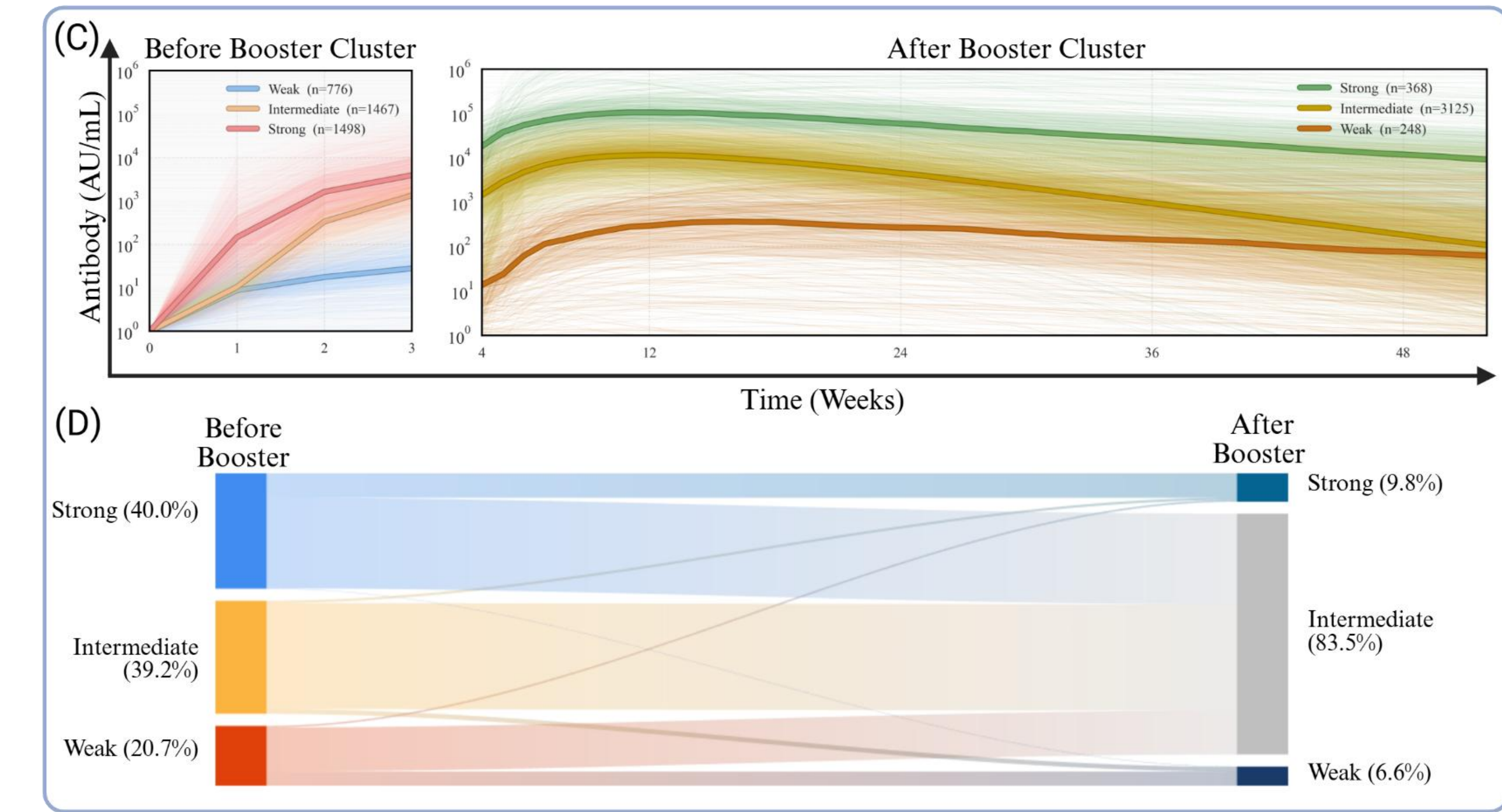
Building on our previous work (3), we constructed a system of ordinary differential equations that describes the temporal evolution of crucial immunological variables, including CD4+ T follicular helper cells, B germinal center cells, memory B cells, antibody-secreting plasma cells, and IgG antibodies. The model incorporates a closed-form solution for the kinetics of the injected antigen, which triggers the activation of CD4+ T cells and initiates downstream immunological processes leading to antibody production. Additionally, we represent the innate immune response by integrating the antigen concentration over a defined time window characterized by parameters τ_{CD4} and τ_B . Extensive clinical data from over 5,000 subjects vaccinated against COVID-19 were used to test the model, with particular attention to the significant variability in antibody responses even among healthy individuals. The model was fitted to individual-scale immune response kinetics data spanning 360 days to estimate unknown parameters, and a global sensitivity analysis (GSA) was performed to identify the key parameters influencing the antibody response.

INDIVIDUAL PATIENT FIT



To evaluate inter-individual variability in immune responses, we applied the previously calibrated model to a large cohort of individual patients, each with longitudinal antibody measurements. As illustrated, the model was successfully adapted to fit individual-level data using a Markov Chain Monte Carlo (MCMC) algorithm. Examples of representative fits are shown in the central panel, where the model captures diverse antibody kinetics with low root mean squared error (RMSE), and the global goodness-of-fit (right panel) confirms high concordance between simulated and measured values across the cohort (Pearson $r \gg 0.9$, log-log scale). We extracted individual-level parameter estimates from the MCMC posterior distributions and analyzed the resulting population distributions for four key parameters: the antigen stimulation rate K_{Ant} , antibody degradation rate δ_{Ab} , antibody production rate P_{Ab} , and plasma cell generation rate P_{Pc} . Each parameter exhibited a unimodal but substantially wide distribution, with standard deviations ranging from 0.36 to 0.64 in log10-space. This dispersion suggests marked heterogeneity in individual immune kinetics, even under a shared modeling structure. Importantly, although the majority of individuals clustered around population-level means (red dashed lines), several outliers displayed parameter values significantly deviating from the central tendency, hinting at alternative immune response regimes.

IDENTIFICATION OF COMMON IMMUNOLOGICAL TRAJECTORIES



We used growth mixture modeling to identify strong, intermediate, and weak antibody response clusters before and after boosting. Pre-booster responses were heterogeneous, while post-booster trajectories converged, especially in strong and weak responders, showing a sharp rise followed by a plateau. Intermediate responses remained distinct, with a gradual decline after the peak, indicating lower durability. A Sankey diagram revealed both stable (e.g., strong-to-strong) and dynamic (e.g., weak-to-strong, strong-to-weak) transitions, reflecting varied recall dynamics. To interpret these shifts, we analyzed mechanistic parameters across all pre/post cluster pairs. Weak-to-weak transitions showed high K_{Ant} (poor antigen sensitivity); strong-to-weak, high δ_{Ab} (rapid antibody decay); and persistent strong/intermediate profiles showed higher P_{Ab} and P_{Pc} (antibody production and plasma cell longevity). These patterns support the biological relevance of the clusters and highlight the value of mechanistic modeling for interpreting immune variability and guiding personalized vaccine strategies.

References :
[1] Klein SL, Flanagan KL. Sex differences in immune responses. Nature Reviews Immunology. 2016/10/01 2016;16(10):626-638. doi:10.1038/nri.2016.90
[2] Lynn DJ, Benson SC, Lynn MA, Pulendran B. Modulation of immune responses to vaccination by the microbiota: implications and potential mechanisms. Nature Reviews Immunology. 2022/01/01 2022;22(1):33-46. doi:10.1038/s41577-021-00554-7
[3]Dogra P, Schiavone C, Wang Z, et al. A modeling-based approach to optimize COVID-19 vaccine dosing schedules for improved protection. JCI Insight. 05/25/2023;doi:10.1172/jci.insight.169860