

Deciphering Population Heterogeneity in Vaccine-induced Immunity: A Mechanistic Model for Immune Fingerprinting

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INTRODUCTION

Vaccines are pivotal in combating infectious diseases, saving millions of lives worldwide and vastly improving public health. Despite their success, the effectiveness of vaccines varies across individuals, posing a significant challenge in achieving optimal community-wide immunity. Several host factors such as virus pre-exposure, age, sex, genetics, and co-morbidities can influence the strength of the vaccine-induced immune response[1,2]. This variability thus affects the population-scale efficacy of vaccines and underlines the necessity for an approach to optimize the use of vaccines to improve outcomes

RESEARCH QUESTION

To overcome the vaccination challenges we investigated how do demographic factors influence population variability, and how can these influences be quantified to provide insights into the distribution of immunological parameters. This study employs a robust mathematical model to analyze variations within a population, attributing specific changes to demographic influences. Our objective is to decipher complex demographic data and convert these variables into actionable information that can enhance our understanding of immunological trends and their impacts.

DISCUSSION

Based on our previous work [3], we developed a model based on a system of ordinary differential equations to define the temporal evolution of the key immunological variables, including CD4+ T-cells, antibody-secreting plasmablasts, neutralizing antibodies, and cytokines (IL-2 and IFN-gamma) (**Fig.1A**). A closed form solution of the kinetics of the injected antigen governs the activation of CD4+ T-cells, which initiate the downstream immunological processes leading to antibody-induced immunity. The whole set of equations is given by :

$$\left\{ \begin{aligned} \frac{dCD4(t)}{dt} &= \frac{A(t)}{A_0 + A(t)} \cdot CD4(t) \cdot P_{CD4} * \left(1 + \frac{IFN\gamma(t)}{IFN\gamma(t) + IFN\gamma} \right) - \delta_{CD4} \cdot CD4(t) \\ \frac{dPB(t)}{dt} &= \left(1 + \frac{IL2(t)}{IL2(t) + IL2} \right) \cdot P_{PB}(t) \cdot P_{PB} \cdot \frac{A(t)}{A_0 + A(t)} - \delta_B \cdot P_{PB}(t) \\ \frac{dAb(t)}{dt} &= P_{Ab} \cdot Pb(t) - \delta_{Ab} \cdot Ab(t) \\ \frac{dIFN\gamma(t)}{dt} &= P_{IFN\gamma} \cdot CD4(t) - \delta_{IFN\gamma} \cdot IFN\gamma(t) \\ \frac{dIL2(t)}{dt} &= P_{IL2} \cdot CD4(t) - \delta_{IL2} \cdot IL2(t) \end{aligned} \right.$$

We explored extensive individual clinical data (N~3700 patients) from literature and used immune response to COVID-19 vaccines in healthy adults for the population fit. Despite being healthy, these individuals exhibited significant variability in antibody response. We fitted our model to population-scale immune response kinetics data (over 230 days) to estimate unknown model parameters (**Fig.1B-F**). This was followed by global sensitivity analysis (GSA) to identify the key parameters influencing antibody response (**Fig.1G**).

The model was fit to the individual patients data obtaining a set of parameters and metrics able to describe each patient response. Using those we evaluated the distribution of the area under the curve of the antibody response for different demographic categories revealing a strong role played by the demography. To further explore the impact of demographic features, we analyzed several metrics related to individual antibody responses, including **area under the curve (AUC)**, **peak response**, **time to peak**, **duration of protection**, and **the initial rate of change**. We applied t-SNE to reduce dimensionality and subsequently used k-means clustering to categorize the data into two distinct groups: 'high responders' and 'low responders' (**Fig. 3A**). We then assessed the relative frequency of each group and illustrated how specific demographic features influenced these outcomes (**Figs. 3B-D**).

DISCUSSION

Our study presents a quantitative model that elucidates the underlying variability in vaccine-induced immune responses. By identifying distinct immunogenic profiles within the population, we offer a novel lens through which vaccine efficacy can be optimized on a demographic basis. This approach not only enhances our understanding of immune response dynamics but also holds the promise of refining vaccine distribution strategies to achieve more uniform community-wide immunity. Furthermore, the insights garnered from this research could be instrumental in streamlining the design of clinical trials, particularly in the rapid development of vaccines during pandemics when resource allocation and participant recruitment are constrained.

RESULTS

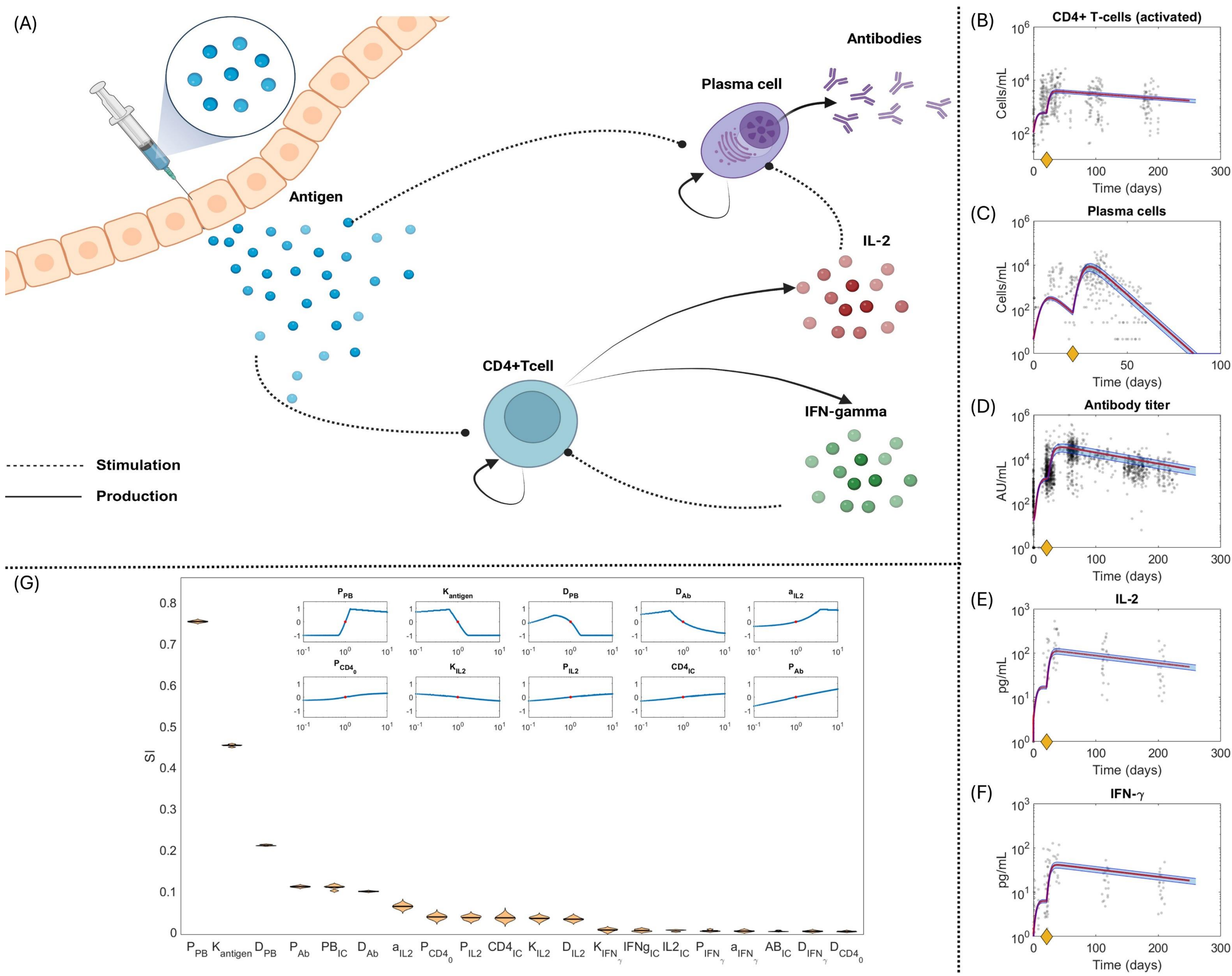


Fig. 1 (A) Model description with key mechanism indicated by dotted lines for stimulation and continuous lines for production (B-F) Results from the fit process, red line is the model prediction while the blue band is the confidence interval calculated. (G) GSA of the model using immunogenicity as a variable, the insert is the local sensitivity analysis (LSA) of the top 10 parameters.

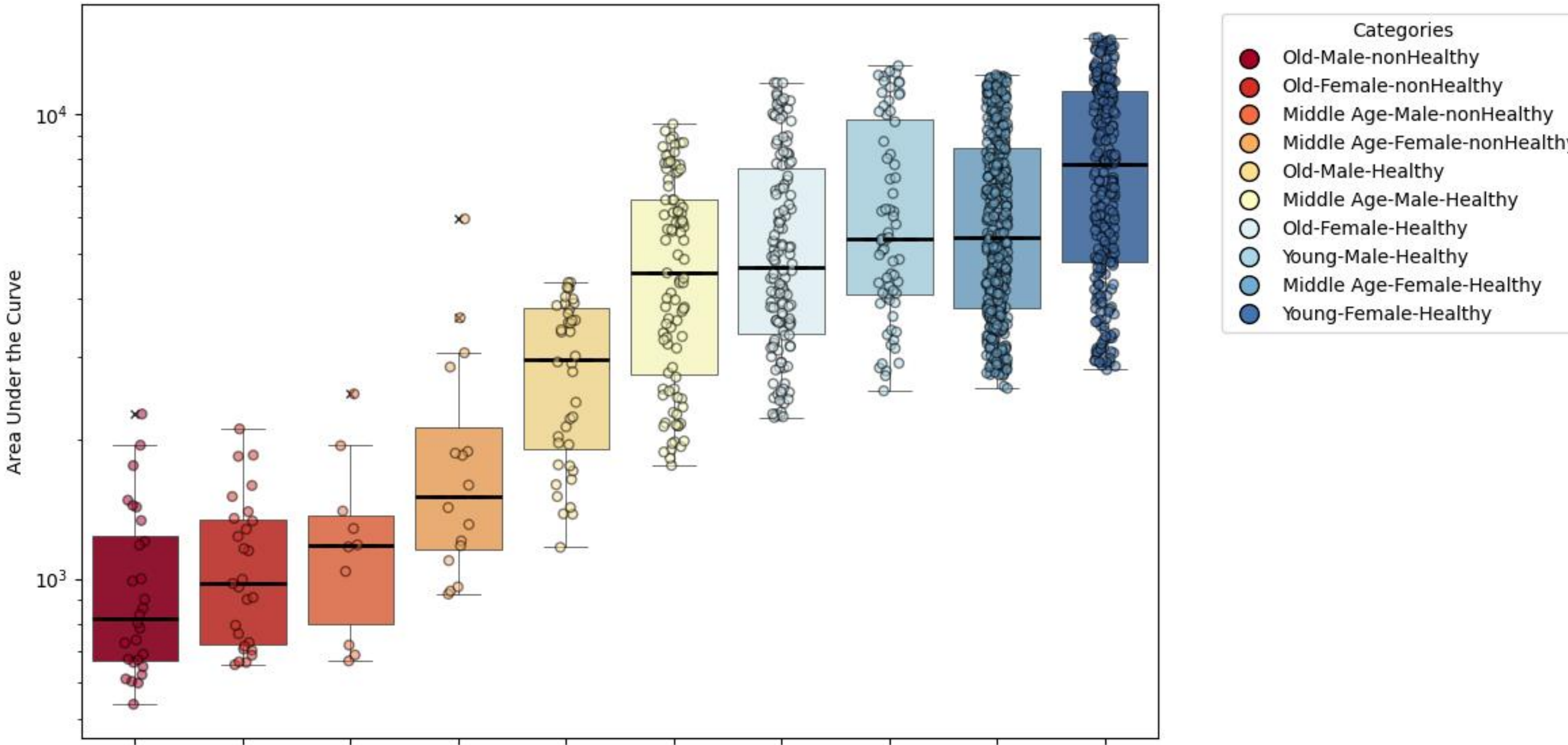


Fig. 2 Boxplots display the area under the curve (AUC) for the first 21 days across different demographic categories, sorted by median value. A black diamond on each plot marks the median of its respective category. The data show a natural clustering by demographic features, indicating differential responses: 'non-healthy' subjects exhibit the lowest scores, older individuals perform worse than younger ones, and women outperform men.

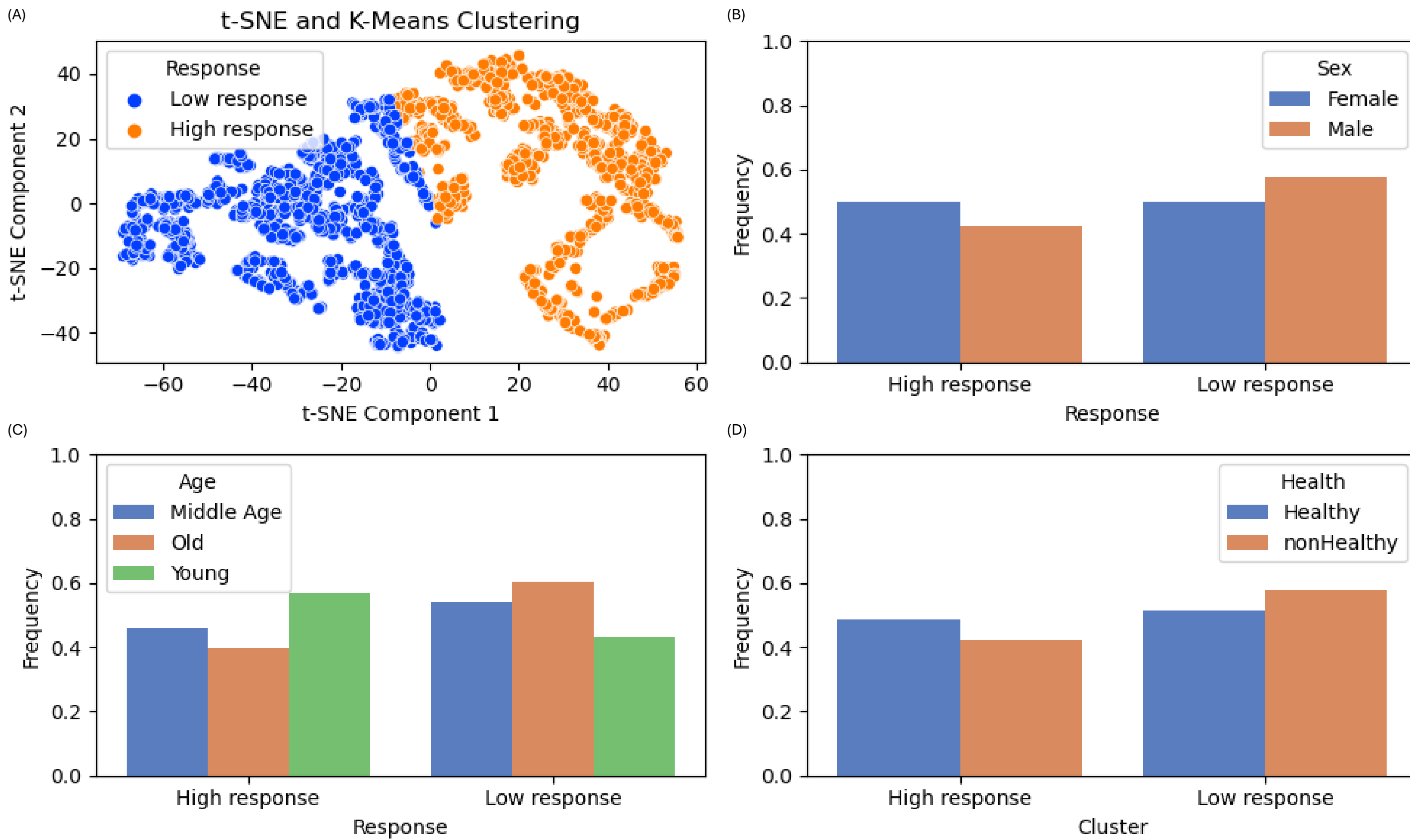


Fig. 3 (A) presents a dimensionality reduction of various immunological metrics using the t-SNE algorithm. The metrics analyzed include: Antibody levels at day 4 and day 7, Plasma Blast counts at day 4 and day 7, Antibody AUC before the second dose, Antibody peak before the second dose, Antibody AUC over 720 days, Time spent above the protection threshold, Time required to reach the protection threshold, Antibody AUC above the protection threshold, Antibody peak value over 720 days, and Time to reach the antibody peak. The data were clustered into two categories, 'low response' and 'high response'. Panels (B-D) analyze the frequency of various demographic characteristics relative to these clusters. The analysis reveals that males, older individuals, and nonhealthy subjects tend to fall predominantly into the 'low response' category.

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