Within-host modeling to measure dynamics of antibody responses after natural infection or vaccination: A systematic review

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Background

Understanding the mechanisms of **within-host kinetics** of the humoral (and cellular) immune response to a viral, parasite, or bacterial infection is crucial to foresee better surveillance and intervention strategies in the context of infectious diseases.

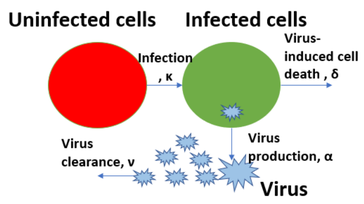


Figure 1: Flow describing the dynamics of uninfected cells, infected cells, and infectious virus [3]

Objectives

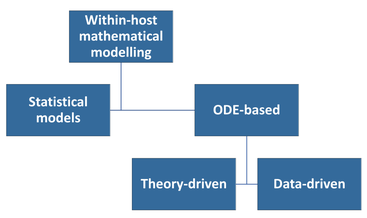
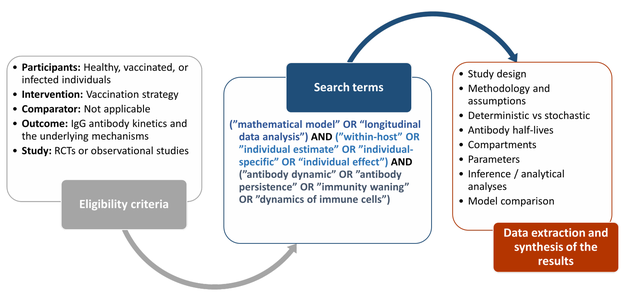


Fig. 2: Classification of the within-host mathematical models

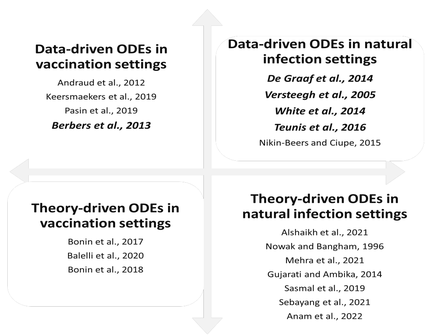
- To find within-host **mechanistic modeling to study humoral immunity processes** after vaccination or natural infection. This is crucial to unravel the specific components of the immune system and their dynamics.
- Describe the underlying dynamics of immune cells when encountering a pathogen, and how these processes can lead to an **individual-specific response**.

Methodology



Results

To date, only 20 publications out of 77 have relied on mechanistic models to study the dynamics of humoral immunity.

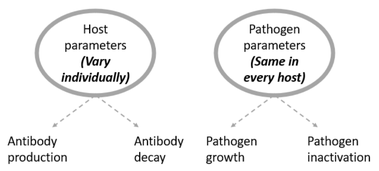


How can Bayesian methods be applied in the parameter estimation of such models?

Vaccine-induced setting: Berbers et al., [4]

Estimation of the model parameters and prediction of the **peak antibody concentrations together with half-time antibody values** were performed using Hierarchical Bayesian methods and Monte Carlo Markov Chain (MCMC).

- **Simple exponential decay**
- **Parametric distributions** for the antibody growth and decay (e.g., Gamma, Inverse gamma).



Natural infection setting: White et al., [1]

White et al., [1] studied the impact of maternal immunity on Malaria infections in children.
MCMC iteration using a random walk Metropolis-Hastings algorithm (Model 1):

1. Local parameter (n)
   - $\vec{\theta^{n\prime}} = [d_m^{n\prime}, d_a^{n\prime}, A_m^n, \theta_1^n ... \theta_N^n]$
   - $L_{mix}^n(\theta_n^{'}|D_n)$
   - Accept probability $min = \left\{1, \frac{L_{mix}^n(\theta_n^{'}|D_n)}{L_{mix}^n(\theta_n|D_n)}\right\}$
2. Nuisance parameter (n)
   - $\vec{\theta^{n\prime}} = [d_m^{n}, d_a^{n}, A_m^{n\prime}, \theta_1^{n\prime} ... \theta_N^{n\prime}]$
   - $L_{mix}^n(\theta_n^{'}|D_n)$
   - Accept probability $min = \left\{1, \frac{L_{mix}^n(\theta_n^{'}|D_n)}{L_{mix}^n(\theta_n|D_n)}\right\}$
3. Global parameter
   - $\vec{\theta} = [d_m^{'}, d_a^{'}, \sigma_m^{'}, \sigma_a^{'}, \sigma_{obs}^{'}, \theta^1 ... \theta^N]$
   - Calculate the total likelihood $L_{TOTAL}(\theta^{'}|D_n)$ and update the prior $P(\theta^{'})$
   - Accept probability $min = \left\{1, \frac{L_{TOTAL}(\theta^{'}|D_)*P(\theta^{'})}{L_{TOTAL}(\theta|D)*P(\theta)}\right\}$

Truncated normally distributed measurement error
200 million MCMC iterations computed with acceptance rates using Robins-Munro algorithm.

Natural infection setting: Teunis et al., [5]

Teunis et al, [5] extended the work by de Graaf et al., [6] defining multiple antibody production sites defined as c_k below.

Infection and waning immunity process respectively

$$b'(t) = \mu_0 * b(t) - \Sigma\, c_k * y_k(t) \qquad b(t) = 0$$
$$y_k'(t) = \mu_k * y_k(t) \qquad y_k'(t) = -w_k^* * y_k(t)$$

What functions are studied?

- Non-exponential decay
- Bi-exponential decay
- Power functions

All models used 3 chains and 10^6 iterations. A multivariate normal prior was chosen for the different model parameters, and a Wishart distribution for the random effects.

Findings

1. COMPARTMENTS
   - **Data-driven approaches:** Typically study the interaction between pathogen growth with antibody production, or the dynamics between short- and long-living cells with antibodies.
   - **Theory-driven approaches:** Typically study more complicated processes, starting from susceptible cells population to neutralizing antibody production.
2. PARAMETERS
   - **Data-driven approaches:** Linear, non-linear mixed approaches. **Exponential decay**, bi-exponential, power functions. Smoothing functions and binary functions represent normally the time of vaccination.
   - **Theory-driven approaches:** Simulation approaches to generate the parameters (e.g., Poisson or Binomial distributions).
3. INFERENCE/ANALYTICAL ANALYSES
   - **Data-driven approaches:** Use of Maximum likelihood estimation (MLE) and Bayesian hierarchical approaches with Monte Carlo Markov Chain (MCMC).
   - **Theory-driven approaches:** Model's equilibria and stability.
4. COVARIATES
   Study groups are widely studied. However, there is a **lack of information on geographical background**, surveillance systems, and age.
5. MODEL COMPARISON
   - **Data-driven approaches:** Difficulties in Bayesian approaches due to the number of parameters and complexity issues. WAIC (Watanabe-Akaike information criteria) for future modelling work AIC (Akaike information criteria) within MLE [2].
   - **Theory-driven approaches:** Comparison to simulated data.

Conclusion

- More research is needed on the **methods of inference** in data-driven mechanistic models, such as semi-parametric to full parametric tools.
- Biological mechanisms must be distinguished in vaccination or natural infection settings.

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