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.

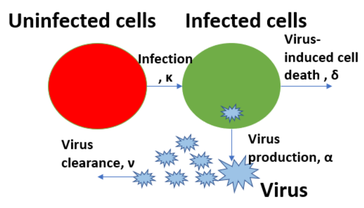


Figure 1: Flow describing the dynamics of uninfected cells, infected cells, and infectious virus [7]

Objectives

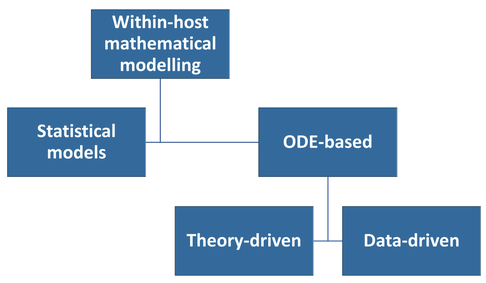
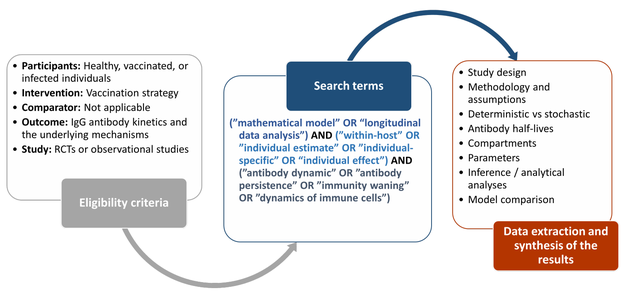


Fig. 2: Classification of the within-host mathematical models

- 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. In particular, we focus on data-driven and theory-driven **mechanistic approaches**.
- Describe the within-host models and the underlying dynamics of immune cells when encountering a pathogen, and how these processes can lead to an **individual-specific response**.

Methodology



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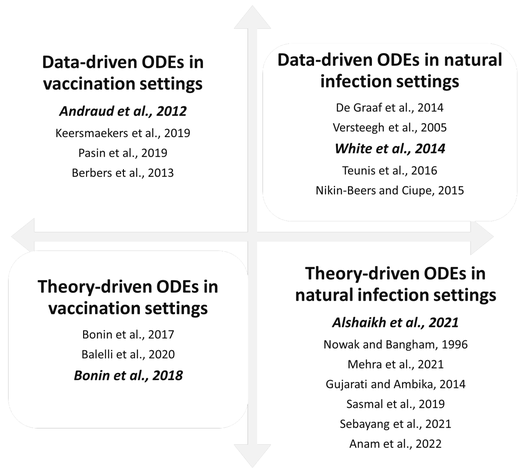
Results

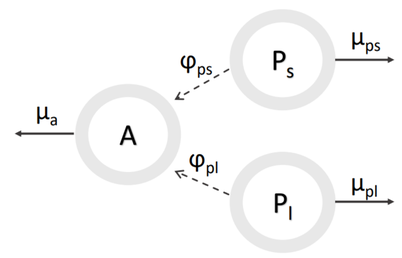
To date, only 20 publications out of 77 have relied on mechanistic models to study the dynamics of humoral immunity.



A. Data-driven in vaccination

Andraud et al., [1] assumed no renewal of plasma cells. P_s decline first, and P_l decline last since the latter reside in the bone marrow. Moreover, different models were studied:

- **Full model**
- **Asymptotic model:** $\mu_l = 0$
- **Plasma cell driven kinetic:** $\frac{\mu_s,\mu_l}{\mu_a} << 1$



B. Theory-driven in vaccination

Bonin et al. [4] accounted for a **pre-existing innate immune response**, defined as the homeostasis term. On top of that, there were **different subpopulations** of individuals, e.g., those having autoimmune diseases, or receiving immunomodulatory therapy.

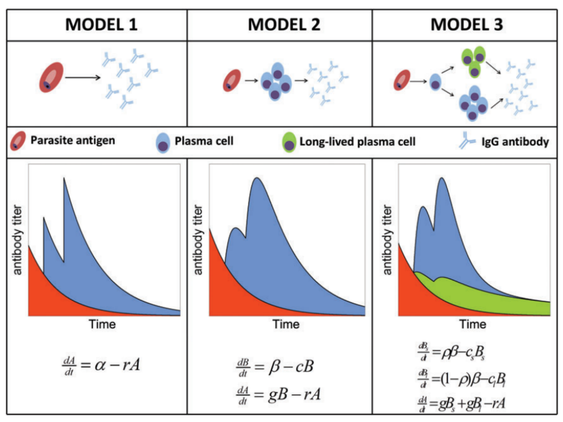
Populations
- Virus inoculation
- Antigen presenting cells
- Naive and effector CD8+ T cells
- Short- and long-living cells
- Memory B cells
- Antibodies

Simulation scenarios:

a) First Yellow Fever vaccine
b) Booster dose ten years after the first dose
c) Different levels of CD8+ T cells
d) Distinct doses of Yellow Fever vaccine

C. Data-driven in natural infection

White et al., [2] studied the impact of maternal immunity on Malaria infections in children.



D. Theory-driven in natural infection

Alshaikh et al., [5] modeled the co-infection between HIV/HTLV accounting for pre-existing HIV antibodies.

Populations
- Susceptible CD4+ T cells
- HIV-infected cells
- HTLV-infected cells
- Free-HIV particles from infected cells
- HIV-specific antibodies

Both HIV and HTLV have the same target of susceptible CD4+ T cells

Findings

1. COMPARTMENTS
   - **Data-driven approaches:** Tend to be more simplistic and have more similarities between them.
   - **Theory-driven approaches:** Typically study more complicated dynamics into various interconnections between these.
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. On the other hand, natural infection studies assumed a boost of antibody titer after exposure.
   - **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) 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 [3].
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 [6].
   - **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, as well as incorporating more data and measurements to feed the model.
- We emphasize that some of the biological mechanisms must be distinguished in vaccination or natural infection settings.

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