Designing an Agent-based Model of Placental Development During Gestation
(Technical Paper)

Obstetrics and Gynecological Health Disparities in Cis Women of Different Racial Groups
(STS Paper)

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

Neonates, on account of developing in the semi-allogeneic, sterile environment of the womb, are at considerable risk of infection upon birth, when they are exposed to the microorganism-rich world (1). About 40% of the 3 million neonatal deaths worldwide are caused by infections, and while neonatal vaccines have proven useful for older babies and children, they are least effective in the first month of life (2-4). Antibodies transferred from the pregnant person to the fetus via the placenta during pregnancy provides the neonate with passive immunity to pathogens for about 6 months *ex utero* (5), and this process has been leveraged to administer vaccinations to the pregnant person (6-7). However, little is known regarding the mechanisms of transplacental antibody transfer, the dynamic regulation of it throughout placental development, and the effects of the pregnant person's health factors.

The placenta cannot be studied longitudinally in humans because it is invasive and could cause harm to the fetus and the pregnant person, so researchers are confined to one static time point (when the placenta is expelled from the body). It is also unideal to study via animal models because it is not conserved across species. This does not allow for a comprehensive look into the development. Thus, computational methods are being employed to uncover the dynamics of placental development. Recently, a quantitative mechanistic model has been designed to find out what the determinants of transplacental antibody transfer are, and how the process may be used to inform patient-specific pregnancy treatment and immunization approaches (8).

There is evidence that prenatal vaccines are less effective than they could be in transferring antibodies optimally to all populations. For example, the pertussis vaccine's effectiveness against hospitalization was only 73% in preterms as opposed to 95% in full-terms (9). For another, several studies found that the Hib and TDap vaccines in early pregnancy

resulted in insufficient antibodies in term neonates to protect against infection (10-11). Accordingly, a model that predicts a personalized approach to pregnancy vaccinations is greatly beneficial by promoting neonatal immunity.

A major limitation of the current quantitative mechanistic model, however, is that it does not consider spatial heterogeneity over time, which is crucial in this biological context: the placenta is changing in shape and constitution throughout gestation (12). To fill in this gap of knowledge, we are using a different modeling platform that can simulate structural changes. Agent-based models (ABMs) consist of a system of autonomous, decision-making individuals called agents which assess their situations, make decisions, and execute behaviors in response to interactions with each other and the environment based on a set of given rules (13). In this biological model, agents are individual cells, the environment consists of chemical concentration gradients, and the agent behaviors are governed by rules derived from literature (13-14).

This first version of the ABM is of fetal angiogenesis at the placental interface. Eventually, we will be able to more accurately develop patient-specific pregnancy treatment and vaccination plans that maximize neonatal immunity (Fig 1). Correspondingly, the STS topic will delve into the health disparities faced in obstetrics and gynecology by people of marginalized races and genders, and how we may work to resolve them.

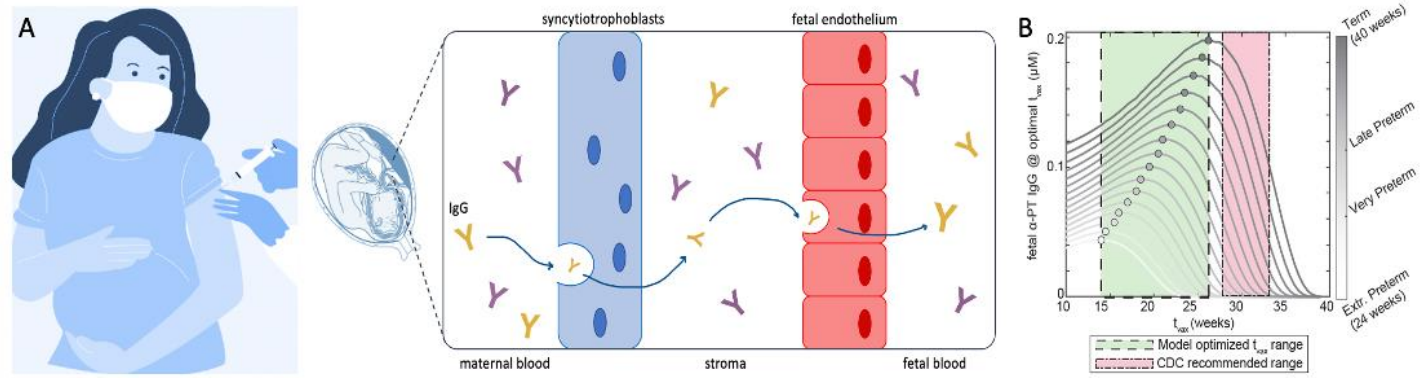

Figure 1. A) Antibody transfer from pregnant person to fetus via the placenta during gestation. B) ODE model output depicting the amount of antibody (IgG) present in the fetus depending on the time of vaccine administration to the pregnant person and the fetus's gestational age.

Technical Topic

During pregnancy, the placenta develops in the uterus alongside the fetus to provide it with oxygen, nutrients, and immunity. Proper development of the placenta is crucial to fetal health, specifically because antibodies transferred to the fetus confer early life immune protection. However, little is known about the mechanisms of antibody transfer through the placenta and how it is dynamically regulated throughout gestation, or how it is affected by the pregnant person's health (i.e., chronic stress, diabetes, etc) (15). Computational models can be used to uncover the dynamic regulation of transplacental antibody transfer to optimize therapeutic strategies administered to the pregnant person to boost neonatal immunity, specifically here the timing of prenatal vaccinations. We will use ABMs to fill in this gap. To reiterate, ABMs use a set of autonomous, decision-making individuals called agents that interact, act, and react to each other and the environment, governed by a set of rules. This model will uncover how the changes in placental shape and constitution over time affect transplacental antibody transfer to provide a more accurate model for predicting patient-specific approaches to pregnancy treatments and vaccines.

The Dolatshahi lab has developed an ordinary differential equation (ODE) model of antibody transfer between the syncytiotrophoblast layer and the endothelial layer of the placenta (Fig 1). However, this modeling framework does not consider the stromal compartment between these cellular compartments, regarding it as a constant in antibody transfer, and additionally ignores the placenta's dynamic spatial heterogeneity over time. Thus, I will be designing an ABM to model placental development through endothelial cell, cytotrophoblast, and syncytiotrophoblast interactions. Then, the model will be parameterized with immunohistochemical images of patient placenta samples.

To present the cellular interactions of endothelial cells, cytotrophoblasts, and syncytiotrophoblasts in the ABM, we have split the research into three main focuses. First, we will determine the process of endothelial cells undergoing angiogenesis. Second, we will investigate cytotrophoblasts, and their derivative syncytiotrophoblasts; how each interacts with signals from endothelial cells; and how the ratio of cytotrophoblast to syncytiotrophoblasts changes throughout gestation. We will accomplish both of these through literature review and scRNA sequencing data analysis. Finally, we will synthesize our findings to inform the ABM rules for angiogenesis, cytotrophoblast proliferation and differentiation, and antibody transfer through these layers.

Model parameterization and validation is crucial to ensure that it reflects real physiological observations. Thus, we will use a bulk RNA seq data set to determine if the model is able to predict the dynamic relationship between angiogenic activity and cytotrophoblast proliferation and differentiation. Secondly, we will conduct immunohistochemical analysis of endothelial cells in sample placenta to see if a greater degree of angiogenesis corresponds with increased transplacental antibody transfer.

This ABM fills a gap in the current knowledge of this understudied field by providing insight into a compartment of the placenta typically assumed as complacent and unchanging during antibody transfer, and by introducing a type of computational modeling as yet unimplemented for this particular system. In the future, medical professionals can use this complete dynamic model to predict the optimal time of vaccination for a patient based on their specific medical history to ensure maximum neonatal immunity.

STS Topic

Racial disparities in healthcare are vast and perpetuated by a history of systemic misrepresentation of, and a society that devalues, non-white people. Particularly in the fields of obstetrics and gynecology, there is a severe lack of research in general, and the existing research is almost exclusively for white women. Decades-long information about racial-ethnic disparities in reproductive healthcare suggests that the problem consists of systemic social and structural inequities rather than individual-level risk (16). They can be described in three main categories: socioeconomic, political, and environmental differences that have physiological effects; access to healthcare; and quality of healthcare received (17). There is an additional layer of difficulty for gender diverse individuals who were assigned female at birth, but this could be its own thesis. The scope of this paper will be limited to cis women and the disparities marginalized racial groups face in obstetric and gynecological healthcare in the United States.

Black and Hispanic people in the United States historically have had unequal opportunities for educational and economic advancement, which in turn affects their socioeconomic status. This defines where and how they live, especially considering redlining, a structurally racist US housing practice that forces people of color into specific neighborhoods that circles back around to people having unequal access to education, healthcare centers, and wealth. The incidence of unintended pregnancies is more than 20% higher in Black women than it is in white women (59.9%-71.8% versus 31.1%-41.7%) (18, 19). The rate of teen pregnancy, while declining overall in the last few decades, is higher for Black girls (20). The issues are highly correlated to a lack of comprehensive sex education in schools, access to healthcare providers and information about contraceptive methods, and family planning services in predominantly Black and/or Hispanic communities (17). The infant mortality rate per 1,000 live

births amongst non-Hispanic Black people was 10.6 in 2019 while that of non-Hispanic white people was less than half that at 4.5 (21). The rate of preterm births was also higher in Black women than white women at 14.39% and 9.26% respectively (22). This is often tied to a disparity in access to and quality of care which will be discussed later, but recent studies have shown that systemic racism causes perturbations in physiological systems, which informs epigenetic changes in people (23). There is research to suggest that chronic stress from living conditions and the like, experienced in higher incidence by Black and Hispanic women than white women, can have negative consequences on their neonate's immunity (24), especially because the chance of preterm labor is increased.

Conclusion

Obstetrics and gynecological research are making leaps from a biomedical perspective. Computational modeling is an excellent tool being used to study various biological contexts that are difficult to study *in vitro* or *in vivo* and implementing it for natal processes is uncovering mechanisms that were previously unreachable. The agent-based model, in its more advanced stages and in communication with the ODE model, will be able to predict the optimal treatment and vaccination plan for each specific patient. It will account for maternal health-factors and their effects on maternal-fetal antibody transfer to help bridge some of the physiological disparities faced by racial-ethnic minority women and their babies.

Count: 1598

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