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# Neonatal Immune Cell Maturation Patterns in Relation to Maternal Metabolic Status

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**Abstract**

Maternal metabolic dysregulation during pregnancy has been increasingly associated with altered immune outcomes in early life. However, the mechanisms of maternal metabolism and neonatal immune maturation have not been clearly defined. This study aimed to build a systems-level, simulation-driven framework for modeling neonatal immune maturation as a process of emergence from coupled signals of maternal metabolism, modulation of inflammation, and the regulatory dynamics of the immune system. The model was designed to simulate the time-dependent trajectories of neonatal immune maturation, incorporating metabolic indices for maternal fuel and form, cytokine gain parameters as a proxy for maternal inflammation, and coupled innate and adaptive immune parameters for maternal dysregulation across the four categories of pregnancy metabolism: normometabolic, overweight/insulin resistance, and gestational diabetes. The simulations suggest that under maternal dysmetabolic conditions, the immune maturation phenotype will be characterized by delayed and attenuated development of adaptive immunity but tempered or enhanced maturation of the innate immune system. Overall, the findings detail the predictive model that simulation-derived immune features of delayed maturation provide, coupled to a sensitivity analysis and outlining the dominant drivers of variability within the immune system: the balance of inflammation and the thresholds of adaptive activation. Most importantly, the study offers simulation-informed biomarkers of maternal metabolic conditions to assess the early immune risk of neonates, highlighting the translational capability of the findings.

**Keywords**: neonatal immune maturation; maternal metabolic dysregulation; systems immunology

## 1. Introduction

The metabolic state of mothers when pregnant is a major factor in how a fetus will develop and how that development impacts the time after birth, infancy and the later stages of life. Maternal obesity, insulin resistance and gestational diabetes augmented by a chronic low-grade inflammation cross diverse population. Global nutrition and lifestyle changes trace back to the cause of the increasing cases of these conditions. These conditions change the intrauterine environment by modifying the glucose levels, lipid metabolism and endocrine signaling, and modifying the inflammatory tone that collectively change the signals that a fetus uses to develop [1-3]. There are studies done on maternal metabolic dysregulation on the growth of the fetus and the impacted cardiometabolic outcomes, in contrast, the studies on how it affects the development of the immune system, particularly on the neonatal immune maturation, remain sparse.

The developing immune system of a newborn baby is rapidly evolving rather than being a scaled down version of the adult's system. The developing immune system matures especially fast in the late gestational and early postnatal periods. Elements of the innate immune system, such as monocytes, neutrophils, and natural killer cells, are developed and present at birth. On the other hand, the adaptive immune system, which includes T and B lymphocytes, is present at birth but is functionally immature and is characterized by a lesser ability to respond to antigens [4,5]. The evolutionary reasons for this developmental asymmetry are speculated to be an attempt to protect the newborn from pathogens while also avoiding an immune response to the mother’s antigens and to the bacteria that are symbiotically present in the newborn's gut [6]. The process of immune system development can be disrupted by problems that happen during fetal development, which can have serious and long-term effects on the newborn's ability to cope with and the likelihood of developing immune related diseases [7].

Recent studies show that maternal metabolic disorders negatively affect the immune system development of the fetus. Maternal metabolic disorders may lead to hyperglycemia, a high level of free fatty acids, and changes to the profile of adipokines. All three problems have the potential to cross the placenta and affect the fetal development and the placental immune system in a negative way [8–10]. These problems have led to the development of negative maternal-fetal immune system interactions that results in a poorly composed immune system in the fetus, in particular the cord blood immune system [11,12]. Insufficient studies have been done on the changes that occur in the immunological response at the time of birth, and even less in regard to changes that occur over time, that are faced by infants whose mothers have metabolic disorders.

The placenta is key to the interaction between maternal metabolic processes and the developing fetus's immune system. In addition to its basic role in facilitating the exchange of nutrients and respiration, the placenta also manages immune signaling via the production of cytokines, the secretion of hormones, and the selective transport of certain metabolites [13]. Maternal metabolic dysregulation modifies the structure and function of the placenta, resulting in altered placental inflammation, oxidative stress, and the infiltration of immune cells [14]. Such

placental changes have the potential to alter the fetus's environment in terms of inflammatory substances and metabolic compounds, thus impacting immune lineage commitment and maturation pathways in utero [15]. Consequently, the integration of maternal metabolism, placental function, and the developing fetus's immune system is essential to understand the immune system of newborns.

Associational studies have linked obesity or diabetes in mothers to infections in newborns, altered responses to vaccines, and increased allergic and inflammatory disease risk in later childhood [16,17]. These studies are strong in support, but fail to answer the mechanisms involved in how, and what maternal metabolic factors are related to specific patterns of immune system development. The immune system's response is multifaceted and complex, as they possess feedback loops and synergy between different elements of the system. These elements are context dependent, and can create a variety of responses that end at the same point. The result of this synthesis is that few involved factors can be described in purely correlative terms.

There are few areas where mechanistic modeling would be fruitful, and this is one of them. By modeling different biological mechanisms, they can be used to describe them as a process in a system, and quantitatively measure the impact of changes to the system. More and more of these types of system models are being used to study different elements of the immune system, like in the study of the behavior of lymphocytes, cytokine production, and response to pathogens [18]. These same mechanistic models can describe different pathways of maternal metabolism and how they influence the immune system while passing through the placenta and fetal signaling, and can be used to understand what areas of maternal metabolism may need to be altered in order to improve the immune system of newborns.

Considering the ethics involved in studies pertaining to human pregnancies and the neonate population, a simulation-based approach is especially useful. Longitudinal studies involving immune system profiling of neonates is restricted due to a lack of available samples, and while studies pertaining to the controlled intervention of the maternal metabolism during a given pregnancy poses great challenges, the studies may also be deemed unethical. Computational studies/models may help to address these problems by checking biologically plausible hypotheses in silico, isolating the more sensitive parameters, and creating predictions to help guide an empirical study. Most importantly, these models do not substitute the need for experimental research; rather, they provide a constructive model for the analysis of research that has been previously conducted and the analysis of situations that may be considered outside the parameters of the original research [19].

The recent growth of fields such as systems biology and computational immunology has made it possible to develop models that treat the processes of differentiation and maturation of immune cells as dynamic processes that can be influenced by the surrounding ecosystem. These can be systems that range from population dynamics models using ordinary differential equations to systems that use an agent-based approach for modeling systems

of individual cells and systems of individual cell interactions. These models can be designed to cope with experimental data so as to maintain the desired characteristics of immune cell development, while also predicting the response to changes in the system with respect to things like cytokine variances and stressors that are related to metabolism. The next logical step in the development of the scientific understanding related to the immune cell development of the foetus in a maternal environment is the application of these systems to the study of maternal-fetal immune programming.

In research on developmental immunology, there is growing interest in the intersections of the maternal metabolic status and the mechanistic models of neonatal immune maturation, However, very few of the studies conducted have focused on this intersection. It is common in the existing literature to characterize immunological outcomes as separate end phenomena of a given sequence rather than phenomena which actively unfold in a sequence over a given period of time, which limits our ability to identify whether a given phenomenon is a delay in immune maturation, or whether it is a persistent phenomenon, created by reprogramming mechanisms, which predisposes individuals to immune dysfunction for extended [long term] periods. There is a need for a dynamic modeling approach which focuses on the early neonatal period to track and disentangle the immune development pathways relative to maternal metabolic exposures.

The present study aims to fill this gap by considering neonatal immune maturation as a complex phenomenon resulting from coupled interactions of maternal metabolism and neonatal immune systems in postnatal period. It is of value to integrate maternal metabolic states, inflammatory signaling, and immune differentiation as separate components of a systems' simulation to determine the various pathways of neonatal immune maturation as a function of different states of maternal metabolism. This approach is innovative, as it focuses on the systemic behavior of the system over time, rather than the individual components, such as single biomarkers or one immune subset.

The present study attempts to interpret the associations between metabolic dysregulation in mothers and immune outcome modifications in neonates. The modeling framework outlines possible intervention strategies and guides the creation of risk stratification solutions by pinpointing sensitive pathways and parameters within the metabolic–immune network. Comprehending how the metabolic condition of mothers instructs immune responses in neonates may assist in developing focused interventions during pregnancy and in the early postnatal period that promote immune health and minimize the risk of disease throughout life, and this would be the aim of this study.

## 2. Model Framework for Neonatal Immune Maturation

The computational framework created in this study defines neonatal immune maturation as a process of dynamic system-level differentiation. This describes immune maturation as being coupled with maternal changes in metabolism, inflammation, and immune differentiation. Instead of viewing immune maturation as an isolated or

linear process, the framework explains the influence of the metabolic factors derived from conditions of pregnancy and their effects on biological systems and immune pathways in the postnatal period. This is especially important in the context of immune maturation in the face of metabolic changes, given the specific nonlinear and time-dependent immunological factors that pertain to the situation.

The highest order of the framework presents three interdependent layers: maternal metabolic signaling, inflammation and cytokine signaling, and neonatal immune differentiation. These are systems of hierarchical interdependence whereby the principal cause is taken to be from maternal system outcomes to neonatal immune system outcomes, while the immune system still retains the capacity to influence the system from within. This is further illustrated in Figure 1, which demonstrates the feedback system whereby the maternal metabolic state is linked to the differentiation of immune cell lineages by cytokines.

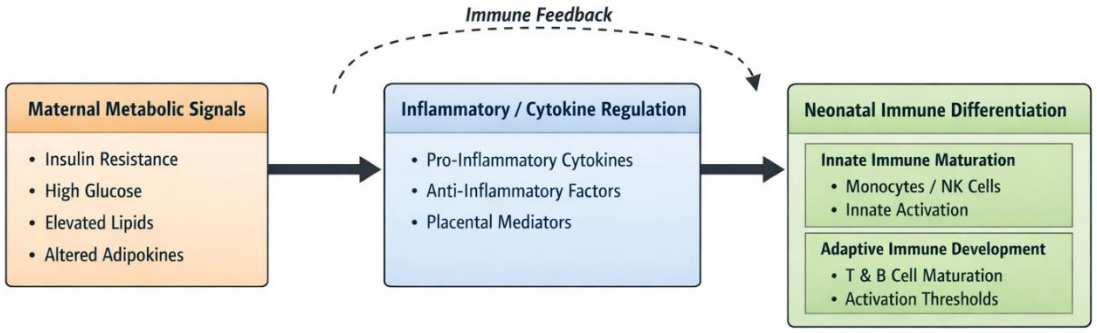


**Figure 1.** Conceptual systems-biology model linking maternal metabolic signals to neonatal immune cell differentiation

The mother's metabolic signal layer reflects the overall metabolic phenotype of the mother rather than more granular biochemical pathways. This abstraction helps the model emphasize the immune-relevant ramifications of metabolic dysregulation and avoid unwarranted complexity. Insulin resistance metrics, effective glucose availability, the inflammatory burden attributed to lipids, and the unbalanced levels of adipokines are constituent core state variables, all of which are known to affect inflammatory signaling during pregnancy.

These metabolic factors are defined within ranges that are physiologically plausible considering different maternal phenotype classes, such as, normometabolic, overweight, insulin resistant, and gestational diabetic. During the neonatal simulation period, these factors are treated as quasi-static to reflect the relative stability of metabolic maternal phenotype throughout the late gestation and early postpartum periods. This assumption is made to eliminate the impact of short-term metabolic variations, focusing solely on the effects of metabolic programming.

The maternal metabolic layer's outputs interface directly with the inflammatory-cytokine mediation layer, the primary biological interface between metabolism and immune system development. This layer captures the net

inflammatory milieu the fetus and neonate experience due to signaling from the placenta, inflammation in the mother’s system, and stress metabolism. It also refers to integrated models of individual cytokines and offers composite parameters for models of inflammation confirming a net gain in both the anti-inflammatory and the pro-inflammatory models of system design.

The modelling protocol assigns the use of composite cytokine parameters as the modelling rationale for why sustained inflammatory equilibrium, instead of ephemeral spikes in cytokines, is the primary factor guiding immune development. These gain parameters consider the pro-inflammatory cytokines interleukin-6 and TNF-α while also incorporating the effects of anti-inflammatory pathways. This way, the model captures chronic inflammatory bias while also eliminating excessive dimensionality.

Cytokine gain parameters act as immune differentiation influence rather than immune state drivers. In particular, they adjust the pace of maturation, survival rates, and functional thresholds of the immune differentiation layer. Higher pro-inflammatory gain heightens the stimulation of the innate immune system while also suppressing or delaying the maturation of the adaptive immune system, which is consistent with the inflammatory bias seen in early life.

The core dynamic element of the model is the layer of neonatal immune differentiation. Immune maturation is captured through indices of maturation for cell types' functionality, phonotypic differentiation, cell responsiveness, and, more importantly, does not utilize absolute cell counts. These indices assist in the comparison of the various compartmentalized immune cell components despite having varying baseline, proportionate, and reference values for cell abundances. Furthermore, the approach avoids overfitting to specific measurement technologies, platforms, or cell count values pertaining to specific cohorts.

Distinct indices measure the maturation of adaptive and innate immune systems. The indices for the innate immune system reflect the maturation of monocytes, NK cells, and other early responders. In contrast, the indices for adaptive immunity capture the maturation of T and B lymphocytes, including their proliferative, and effector-differentiating capacity as well. The differentiation of these indices assists the model to capture the distinct temporal disparity of the rapid maturation of the innate system and the delayed maturation of the adaptive immune system in neonates.

The temporal maturation of the immune system is framed by differential equations for the intrinsic and extrinsic systems, coupled with immune system hormonal modulation. The perturbation is incalculable, but it establishes baseline trajectories in accordance with the known immune system ontogeny. Maternal metabolic dysregulation alters the magnitude of the immune system’s maturation, the timing, and the immune system hormonal modulation.

One of the adaptive immune system's distinct dimensions is the incorporation of non-linear threshold features. For adaptive maturation to occur, there is a requirement for particular cytokine and cellular metabolic resources to overcome the activation thresholds related to clonal proliferation and functional specialization. The model has these thresholds embedded and thus can simulate scenarios where adaptive maturation is either delayed or incomplete due to injurious inflammation or dysmetabolic states.

Biological feedback loops between adaptive and innate are mirrored in the model to embody their biological interconnectedness. In the model, the biological influence of moderate innate activation, which enables adaptive differentiation through antigen presentation and cytokine release, is counterbalanced by the influence of innate activation, which is prolonged or excessive, driving a suppressive influence through the induction of regulatory and exhaustion mechanisms. The model, therefore, captures these as feedback influences through bidirectional coupling terms to adaptive and innate state variables.

The simulations are temporally constrained to late gestation and the first month of life, capturing the period of immune system plasticity. The immune state variables at birth encode the impact of the in-utero environment characterized by maternal inflammation and metabolic state. Consequently, the trajectory of the immune system in the postnatal period is far from the neutral state and is influenced by this programmed baseline.

Instead of fitting model parameters to a single dataset, we apply parameters within ranges informed by biology and experimental and clinical literature. This approach emphasizes flexibility and generalizability over specificity and exactness. We ensure robustness to parameter uncertainty by using sensitivity analyses to pinpoint parameters that most strongly influence the outcomes of immune maturation.

The framework's modular design means that any layer can be incrementally improved as new information is incorporated. Without changing the core framework, new metabolic factors, specific types of cytokines, or greater granularity in immune cell lineages can be added. This capability guarantees that the model will retain its relevance as fields of research develop.

Finally, the framework allows for direct integration of immune maturation indexes and supporting simulations and analyses. In the upcoming sections, the immune maturation model outputs will serve as a foundation for phenotype comparison, sensitivity analysis, and risk stratification. This integration preserves the concordance of mechanistic modeling and predictive analysis while avoiding overlapping biological expectations and computational outcomes.

## 3. Simulation of Innate and Adaptive Immune Maturation Dynamics

The simulation framework discussed previously was employed to create time-dependent trajectories of neonatal immune maturation under varying maternal metabolic states. The main aim of these simulations was to capture

if changes in maternal metabolic and inflammatory parameters, within a reasonable biological range, could lead to distinct patterns of development in the innate and adaptive immune systems and inflammatory response during the first few days of life. Thus, immune maturation was reframed as an emergent property of coupled dynamic processes, rather than a static endpoint to be measured at birth.

Simulations were set to begin at delivery, with immune state variables representing the maternal inflammatory and metabolic in utero assimilation. These starting conditions were systematically varied across the maternal metabolic phenotypes to embed the immune programming that occurred prior to birth, and to design an immune response framework for postnatal adjustment. The postnatal immune development simulation spanned the first month of life, a time of intensive immune system plasticity and maturation. Because the immune system undergoes complex and sudden changes, time was divided into very small intervals in order to model such changes as accurately as possible.

To begin with, as the innate compartments are the earliest functioning immune system compartments in neonates, the dynamics of innate immune system maturation were simulated first. With normometabolic maternal conditions, innate immune maturation progresses along a smooth, monotonic trajectory, exhibiting rapid gains in function at early timepoints. This pattern corresponds to the postnatal activation of the monocytes, NK cells, and other similar innate effectors, which is supported by appropriate cytokine levels and a depressed inflammation. In our simulations, the innate maturation index rose quickly during the first week of life and levelled off by the third week, which correlates with early innate immune competence observation in healthy neonates.

Figure 2 demonstrates the simulation-derived paths of innate immune maturation in dysmetabolic versus normometabolic dysmetabolic conditions. Under these conditions, which represent a combination of gestational insulin resistance and diabetes, innate immune system maturation continued to progress more quickly than the adaptive contemporane subsystems, albeit it had some differences in the characteristics of the trajectory. More specifically, in our simulations, we have modeled an early period of innate activation that is followed by a period of insufficient late immune system maturation. This phenomenon was explained by an initial excess of the activation gain of pro-inflammatory cytokines, which stimulate the activation of the innate immune system, however, in a later stage of maturation, exert regulatory, and functionally suppressive, negative feedback.

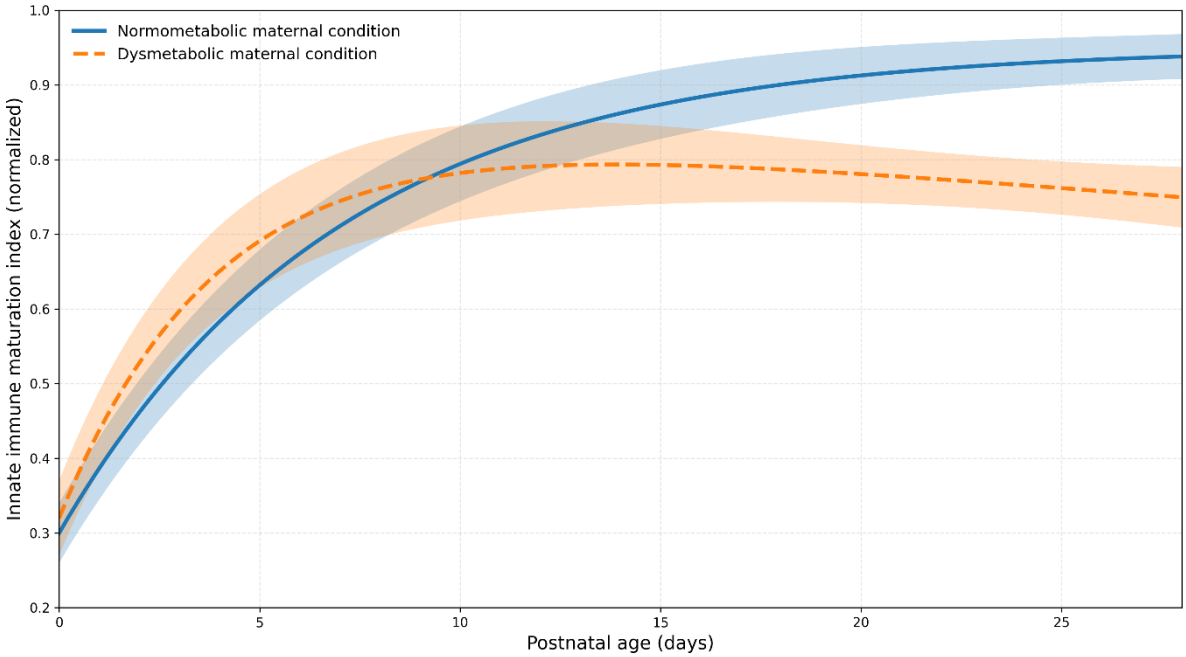


**Figure 2.** Simulation-derived maturation trajectories of innate immune compartments under normometabolic vs dysmetabolic maternal conditions

The most significant difference in trajectories under normometabolic vs dysmetabolic conditions was in dysmetabolic conditions in weeks 2 and 3. While normometabolic trajectories remained stable at higher levels of functional maturity, dysmetabolic trajectories platued at lower levels and at earlier indices of maturity. These results show that maternal dysregulation of metabolism does not only postpone developmental immune processes, but changes the processes involved, giving rise to an immune system that is hyperactive, yet does not mature. This is in line with the clinical manifestations that show that infants that have been exposed to maternal metabolic stress have an increased inflammatory tone, but have poor responses to pathogens.

The dynamics of the maturation of the adaptive immune responses revealed a distinctly different time profile under normometabolic conditions. Maturation of the adaptive immune system occurred progressively with a time lag compared to the innate systems. In the first week post birth, the simulated indices of adaptive maturation increased slowly, which is attributed to the limited activation of neonatal T and B cells. After this lag phase, maturation continued at an increased rate. This was due to the accumulation of supporting cytokines that crossed activation thresholds. Maturation is marked by an increase in number and functional differentiation.

Figure 3 shows the adaptive immune system maturation trajectories corresponding to each simulated maternal metabolic state. In the normometabolic state, adaptive maturation was characterized by a sigmoid trajectory with a distinct inflection during the second week postnatally. This inflection point reflects the threshold-dependent activation mechanisms built into the model, which include, among other things, adequate supportive cytokines and antigen presentation capacity from the innate immune system. By the 4th postnatal week, adaptive maturation indices were quite high, though they remained less than the breadth of functional adult immunity.

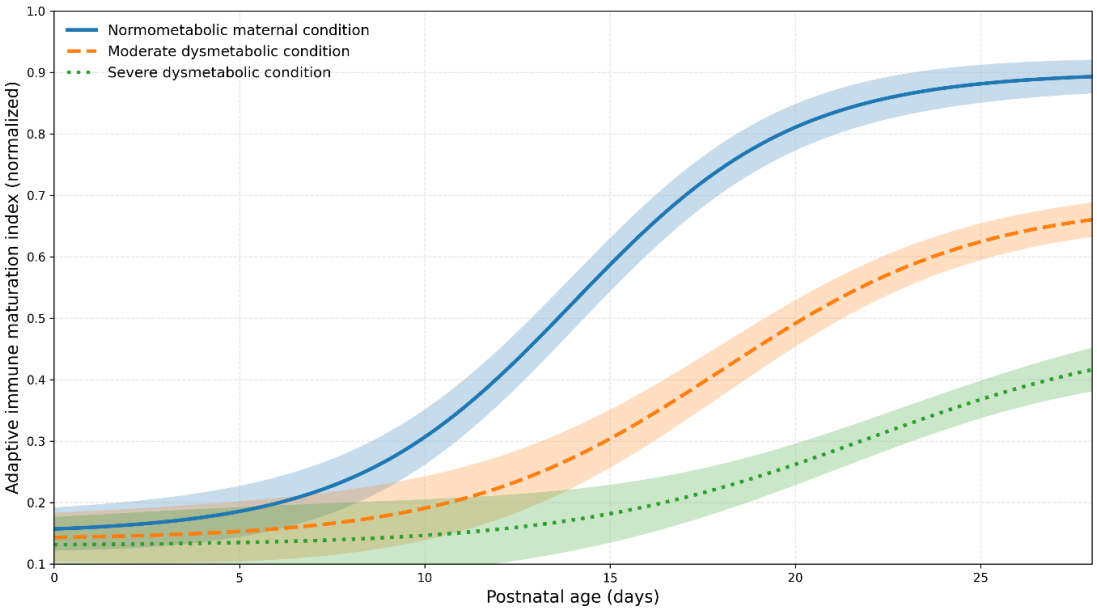


**Figure 3.** Simulation-derived maturation trajectories of adaptive immune compartments under varying maternal metabolic states

Differently from the other states, maternal dysmetabolic simulations exhibited substantial delays and reductions for adaptive immune system maturity. The high pro-inflammation gains and low anti-inflammatory buffer settings raised activation thresholds and inhibited adaptive immune maturation. For the more severe dysmetabolic cases (i.e., gestational diabetes phenotypes), the adaptive trajectories of the immune systems were mature enough, within the simulated neonatal period, to process the inflection point of the proposed sigmoid. This, in turn, led to functional maturity indices remaining low, up to and including 4 weeks of age.

The mechanisms behind the delayed adaptive trajectories present in Figure 3 are the result of multiple interacting factors within the simulation framework. Firstly, excessive inflammatory signaling caused adaptive differentiation suppression by changing the cytokine balance towards the favor of the activation of the innate immune system. Secondly, the lack of proper innate immune system development caused subpar antigen presenting and unsupportive cytokines, which resulted in indirect impairment of adaptive immune activation. Third, the non-linear threshold mechanisms cause the early inflammatory environment to create larger differences within the adaptive outcomes that were downstream. This shows that the inflammatory environment surrounding the adaptive immune system during prenatal and postnatal periods is highly sensitive.

The analysis of the innate and adaptive immune system trajectories illustrates the temporal disconnection between these systems which occurs as a result of dysmetabolic conditions. Over the early phases, adaptive immune suppression was sustained, while innate immune maturation was preserved to a point where it was exaggerated. This disassociation resulted in immune maturation profiles of innate immune system dominance and adaptive immune system deficiency. This profile is often associated with an increased susceptibility to infections, changes to the responses to vaccines, increased inflammatory responses, and reactivity during early life.

The simulation findings show that an adaptive immune delay is not purely a function of a lack of postnatal time, and is more indicative of factors failing to cross activation thresholds in the simulation environment. Analyses of the data showed that a lack of inflection points and a decrease in inflammation and an increase in the rate of inflammation control were adaptive, suggesting that the adaptive delay is a reversible phenomenon, and not an irreversible developmental defect. This discovery signals that developmental inflammation control may be an important target in early interventional strategies.

The biological milestones that align temporally with the trajectories of the simulation lend more support to the model. Immune adaptation and the model's result of maturation under consistent metabolic conditions almost perfectly match observations of immune system development in the first month of life. The persistently adaptive, underdeveloped immunity of the simulation model in the context of metabolic dysregulation mirrors the predictive pathway of immune delay in infants with compromised maternal metabolism.

An additional important observation related to simulation outputs is heightened inter-individual variability in the presence of dysmetabolic conditions. Despite the fact that normometabolic trajectories demonstrated considerable cross-sectional tightness, dysmetabolic simulations demonstrated confidence envelopes that are much broader, reflecting the simulation being responsive to changes in parameters. Greater simulation variability may indicate that maternal metabolic dysregulation magnifies stochasticity and the biological diversity in the immunological maturation process. This may explain the diverse class of immune phenotypes that are observed in clinical practice in neonates that are most recently exposed to maternal metabolic dysregulation.

The dynamics of interest were, in part, determined by the interactivity between the adaptive and innate immune systems. Simulations where innate-adaptive coupling was artificially reduced revealed a partial inflammatory persistence adaptive bias inflammatory net reduction was observed. This emphasizes the role of cross-chamber interactivity. Conversely, within dysmetabolic simulations, a greater coupling of adaptive and innate systems suppression was observed. This observation reinforces the importance of dominant inflammatory suppressive drives from the innate pathways.

In summary, figures 2 and 3 collectively depict the temporal and differential nature of the effects of maternal metabolic condition on neonatal immune maturation, further corroborating the role of metabolic dysregulation in maternal immunological programming of fetuses, by biasing the developmental trajectories of immunity rather than uniformly downward altering the immunological states of the fetuses.

The outcome of simulations in this section forms an understanding of possible mechanisms leading to the formation of early-life immune phenotypes in the absence of frank infections or genetic anomalies. The model shows possible developmental mechanisms of clinically observed associations by demonstrating realistic metabolic and inflammatory disturbances sufficient to cause the phenomena of delayed adaptive immunity and

changed dynamics of innate immunity. These mechanisms will form the basis of the analyses at the phenotypic level, including analyses of patterning, sensitivity to perturbation, and parameter predictive modeling of immune risk of the neonate.

## 4. Results: Emergent Immune Phenotypes Under Altered Maternal Metabolic Conditions

Simulation results provided evidence of unique and reproducible immune maturation phenotypes and suggested these arise directly from parameterization of the maternal metabolic state. For each of the simulated cases, immune maturation phenotypes were distinct and did not scale linearly with the metabolic perturbations imposed. Instead, there were threshold-dependent shifts, and clustering of distinct phenotypes emerged. These patterns were still present despite the phenotypes being distributed across maternal metabolic phenotypes, highlighting the system-level alterations due to changes in the metabolic–immune coupling.

Figure 4 shows simulated immune maturation landscapes comparing immune maturation index simulations across normometabolic, overweight, insulin resistant, and gestational diabetes-like maternal metabolic states. These landscapes illustrate the immune maturation index across the neonatal time axis, allowing the characterization of the outcome as a process rather than an end state. Under normometabolic conditions, the landscape demonstrated a clear sequence with rapid maturation of the innate compartment, and then a subsequent temporal increase in adaptive compartment maturation. By the end of the neonatal period, the phenotype demonstrated a high maturity state of the phase space, indicating synchronized maturation of both immune compartments.

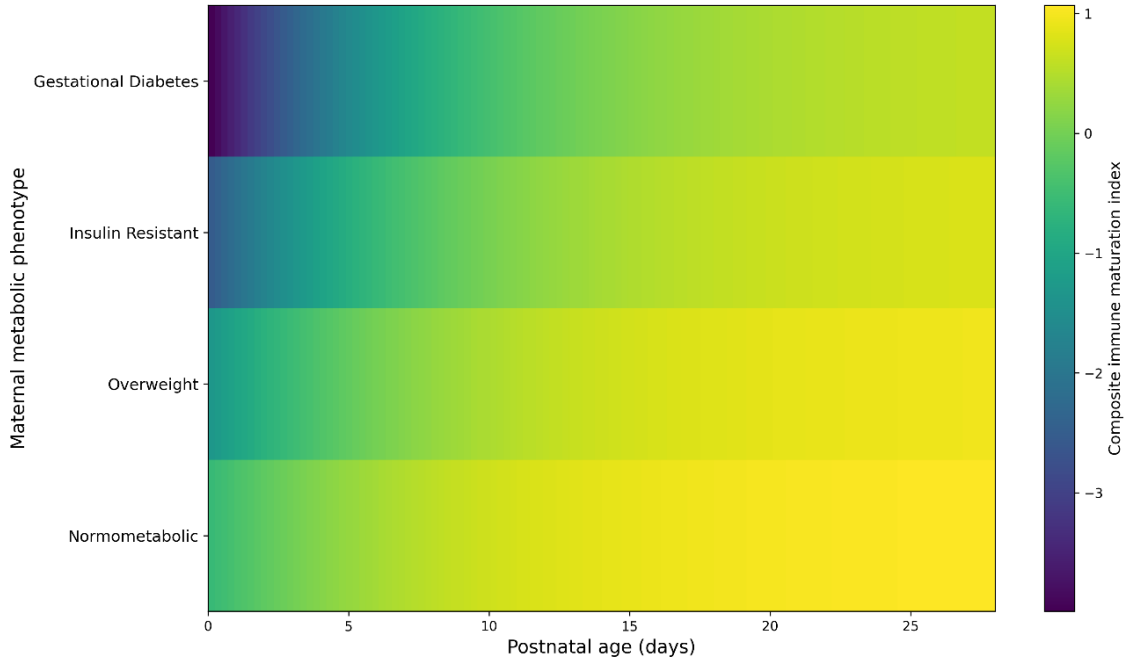


**Figure 4.** Comparative immune maturation landscapes generated by simulation across maternal metabolic phenotypes

Overweight maternal phenotypes simulations resulted in landscapes with slight temporal distortion. Innate maturation was mostly preserved, but adaptive maturation trajectories shifted to the right along the time axis, representing delayed activation. Although there was a delay, adaptive maturation moved to moderate functional levels producing a phenotype with immune immaturity, which was transient, not persistent. The maturation index, as shown in Figure 4, indicates that this phenotype is in a position that is intermediate between normometabolic and worse dysmetabolic states.

Immune maturation landscapes in the presence of insulin-resistant maternal conditions were distinct from the rest. With these simulations, innate immune maturation showed a delayed but early elevation in growth, and this was even without achieving terminal levels of adequate maturity as was the case in normometabolic conditions. There was a considerable lag in adaptive immune maturation, with most of the early maturity period exhibiting low levels of maturation indices. The resultant landscape showed a clear separation of innate and adaptive immune systems, with immune states in the regions of innate dominance and adaptive deficiency. The outcome of this behavior is indicative of a permanent immune phenotype in the landscape, instead of just a delay in its development.

In these simulations where parameters were set as resembling gestational diabetes, the most extreme immune maturation landscapes were generated. Here, innate immune maturation was characterized by exaggerated early activation, followed by early plateauing, and adaptive maturation was suppressed throughout the simulated window. As shown in Figure 4, these trajectories fail to cross the relevant phase-space regions pertaining to adaptive activation, leaving them in the immune states of low adaptive maturity. The consistent pattern across various simulation runs suggests that it is driven more from the parameter configuration and not random variation.

When inspecting the maturation landscapes in phase-space, there were distinct phenotype basins attributable to the tiers of maternal metabolism. Instead of demonstrating a progressive immune maturation continuum, the clustering of regions shows the outcomes of immune maturation and is a demonstration of the system behaving in a manner that is not linearly progressive. The proximity of the parameters to the threshold boundary and the effects of large changes in one side of the boundary and a smaller change in the other side of the boundary describe the behavior of a non-linear dynamical system reflected in immune maturation and demonstrates the sensitivity to upstream metabolic adjustments.

Temporal analysis showed that phenotypes began to differ at the earliest stages of the neonatal period. Differences in maturation trajectories were observed in the first postnatal week, while adaptive divergence expanded during weeks two and three. The timing of these divergences was consistent across simulations and underscored the importance of early-life intervals of immune plasticity in shaping enduring maturation pathways.

Significantly, once trajectories settled into a particular phenotype basin, convergence was infrequently observed, and was rarely seen within the time span of the simulations. The immune maturation indices examined quantitatively the phenotype showed the most consistent changes in the number and the order of the changes. The simulations of the Normometabolic phenotype had the highest values of combined innate–adaptive maturity, while the rest, in decreasing order, were Overweight, Insulin Resistant, and Gestational Diabetes phenotypes. Most of the Variability among the phenotypes was accounted for by the indices of adaptive maturation, while the indices of innate maturation had a smaller range of Variability. This difference in the range of Variability showed more importance for the adaptive immunity as the main driver for the separation of the phenotypes in the conditions of metabolic disturbance.

The consistency of emergent phenotypes were tested by the introduction of controlled stochastic variation in the gain of cytokines and the coupling of immune parameters. While the normometabolic and overweight phenotypes showed slight dispersion, the insulin resistant and gestational diabetic phenotypes showed greater dispersion, and especially in the outcomes of adaptive maturation. Despite this variability, the average of each cluster of phenotypes was distinguishable, which means that the lack of or excess of certain metabolites was the cause of varying heterogeneity and did not eliminate the identity of each phenotype.

Table 1 presents the parameters of the simulations that correspond to each of the maternal metabolic states, which include metabolic indices, cytokine gain coefficients, and the coupling strengths of immune regulatory parameters. These parameter sets were constant during the simulation runs for each phenotype and were used to immune outcomes to the specific infla-metamorphic configuration of the parameters. The table illustrates the pheno-type variation, which is characterized by the absence of inflammation and the attenuation of inflammation, and the pro-inflammatory gain and anti-inflammatory buffering, providing the pattern of immune maturation a basis for the phenomenon.

**Table 1.** Simulation parameter sets representing maternal metabolic states and immune regulatory coefficients

| **Maternal state** | **IR** | **GL** | **Lep/Adipo** | $\mathbf{G_{pro}}$ | $\mathbf{G_{anti}}$ | $\mathbf{K_{inn}}$ | $\boldsymbol{\theta_a d_{ap}}$ | $\boldsymbol{\kappa^{IA}}$ | $\boldsymbol{\rho_{re}g}$ |
|---|---|---|---|---|---|---|---|---|---|
| Normometabolic | 0.90 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 0.45 | 1.00 | 1.00 |
| Overweight | 1.15 | 1.10 | 1.35 | 1.20 | 0.90 | 1.10 | 0.55 | 0.92 | 1.08 |
| Insulin-resistant | 1.45 | 1.25 | 1.70 | 1.55 | 0.75 | 1.25 | 0.70 | 0.85 | 1.20 |
| Gestational diabetes | 1.80 | 1.45 | 2.05 | 1.90 | 0.60 | 1.40 | 0.85 | 0.78 | 1.35 |

The analysis of individual parameters showed that there was more than one parameter involved in governing the emergence of a phenotype. For example, there was insufficient adaptive suppression to be severe to accompany increased pro inflammatory gain without the absence of anti-inflammatory buffering, and an shift in adaptive-innate coupling. The combinatorial dependence of the parameters reiterates the need to consider the entire system of immune system maturation and suggests the outcomes cannot be rationalized solely to a few metabolic indicators.

The analysis of different phases of development showed that there is an imbalance in the sensitivity of the immune system compartments. Adaptive maturation was particularly sensitive to the changes in parameters, in contrast to innate maturation which showed a certain degree of resistance. The difference in the adaptive capacity of the system is the reason why phases with the same innate maturation score, are different adaptive maturation capacity. The imbalance explains the paradox of some dysmetabolic phases that are highly inflammatory and lack immune protection, which is a common clinical reality.

Delayed dysmetabolic states highlighted the role of temporal compression while demarcating the maturation landscapes spatially. In the simulations of insulin-resistant and gestational diabetes, the adaptive activation time frame was considerably narrowed, thus restricting the system's potential for the upward maturity state transactions. In figure 4, this compression effect was visible as trajectories that were truncated, thus not establishing the full phase space. This behavior depicts the relationship between constrained developmental time and delayed threshold crossing.

Cross-phenotype analysis indicates that overweight maternal conditions lie at a transitional position within the immune maturation landscapes. These simulations approached adaptive activation thresholds frequently, albeit not early and consistently crossing them. Therefore, due to stochastic variation, the outcomes were contingent from near normometabolic to adaptive maturation, mildly suppressed the dysregulated state. This positions overweight phenotypes as potentially responsive to small parameter changes, in contrast to more rigid states of dysmetabolism.

The simulation outcomes illustrate that discrete emergent neonatal immune phenotypes with distinct patterns of innate and adaptive coordination, timing, and maturation efficiency. These phenotypes result directly from specific parameter configurations of the simulation and remain the same across simulations, creating a reproducible relationship between maternal metabolic state and the developmental trajectory of neonatal immunity.

**5. Sensitivity Analysis and Predictive Modeling**

We conducted a sensitivity analysis to ascertain the robustness of the simulation results and the dominant parameters that affect the trajectories of neonatal immune maturation. Each coefficient of the metabolism and immune regulation was varied independently and within a reasonable biological range, keeping the rest of the parameters fixed. The immune maturation indices were recorded within the neonatal time frame. The results allowed variability from outcomes to be ascribed to specific components of the metabolic–immune coupling framework.

In the sensitivity analysis, we summarize the impacts of the parameters and the changes in adaptive immunity at the end of neonatal period in a tornado style Figure 5. Of the dominant metabolic factors, the most significant

negative changes in adaptive maturation indices were caused by the cytokine gain and imbalance of the adipokine. In contrast, changes in glycemic load elicited smaller impacts unless paired with changes in inflammatory buffering. This suggests that the outcome of immune maturation is affected more by the balance of inflammatory signaling than by the presence of individual metabolic factors.

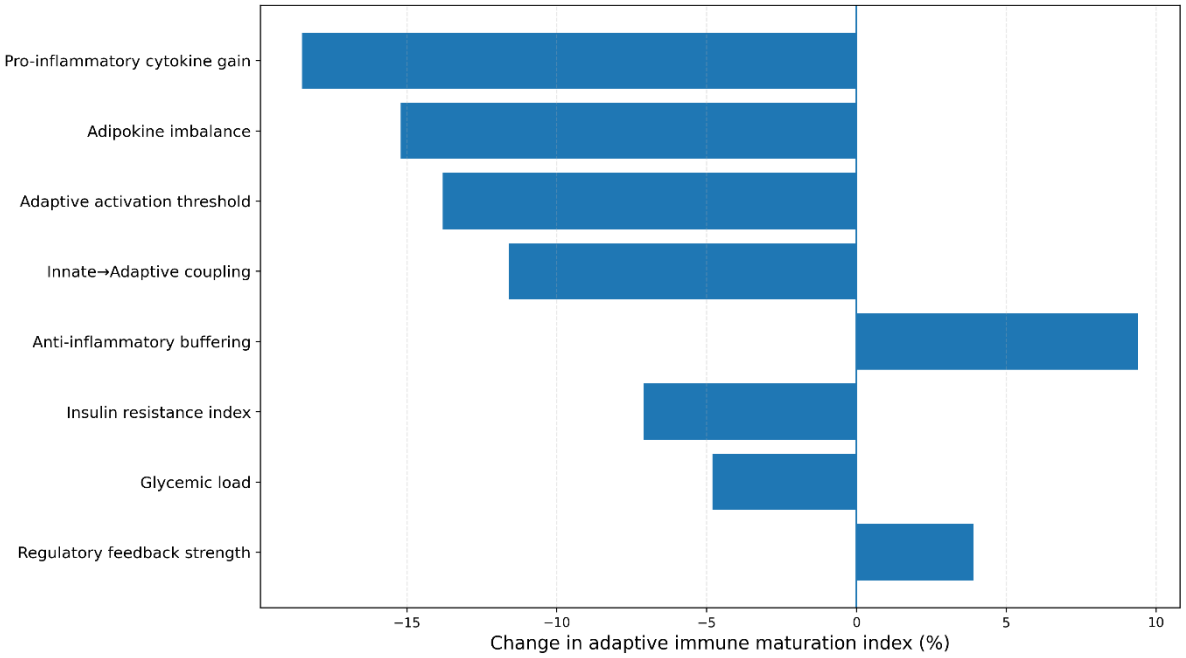


**Figure 5.** Sensitivity analysis of immune maturation outcomes to metabolic and inflammatory parameter perturbations

Adjustments of immune-specific parameters uncovered additional attributes of sensitivity. Maturation results were significantly impacted by the adaptive activation threshold parameter, with small shifts to the top causing greatly increased delays to adaptive expansion. Additionally, the adaptive coupling coefficient, coupled inner to outer, decreased the system's ability to propagate signals that were early innate to adaptive activation, resulting in low adaptive maturity that was persistent. The findings of these studies show that the immune control system, in terms of negative feedback, primarily functions to control the impact of upstream metabolic signals.

Effects of sensitivity were documentarily and contextually distributed. Under conditions of a negative metabolic baseline, parameters that displayed a surplus of positive effects resulted in a negative baseline condition. Under dysmetabolic configuration, the parameters displayed a positive surplus of effects. Under these negative baseline conditions, the system's level of stability decreased, resulting in a level of response that was close to the maximum. Therefore, the level of extreme variability of the immune response was documented.

For the purpose of determining the usefulness of a prediction, the outputs of the simulation were used to build the first of a kind risk modeling framework for the delay in neonatal immune system maturation. The simulation composite immune maturation indices (CMIs) were used as input for the probabilistic classifiers, which were previously trained for the task of distinguishing between the immediate and the delayed adaptive maturation

phenotypes. The metabolites, cytokine gain coefficients, and the slopes of the early postnatal immune system maturation were used as the predictor variables, representing the clinically actionable windows phenomena.

A predictive risk surface derived from the simulation dataset is shown in Figure 6 which describes the risk of delay in immune maturation in the multidimensional space of parameters defined and derived from the simulations. The areas defined by the parameters of insulin resistance and gestational diabetes were found to have a higher predicted risk. The parameters of normometabolic and mildly overweight, however, were found to have a clustered low risk. The surface of the risk is smooth, and this is because the immune system maturation is a continuous phenomena. However, the areas of the risk surface which contain a high gradient/are threshold continue to extreme predicted values.

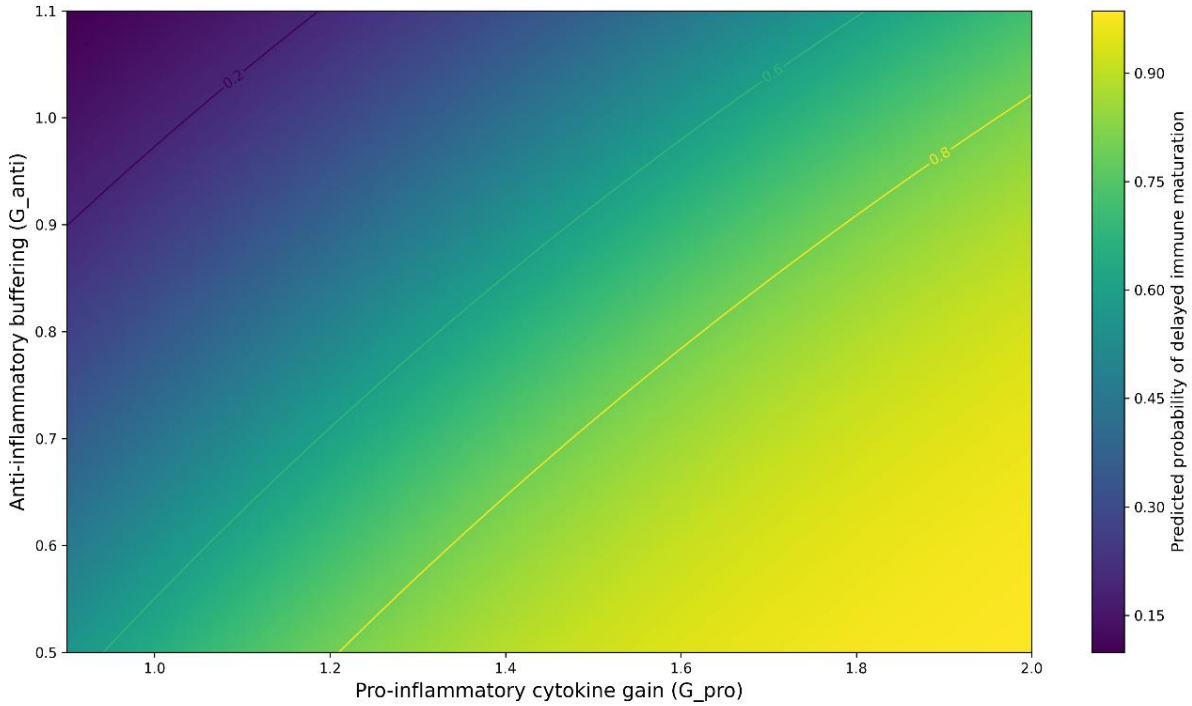


**Figure 6.** Predictive risk surface for delayed neonatal immune maturation derived from simulation outputs

Table 2 summarizes the standard classification metrics used to evaluate the models. The predictive framework demonstrated strong discrimination between delayed and non-delayed maturation across numerous cross-validation folds, as indicated by area-under-the-curve values across the folds. While high sensitivity was noted for all phenotypes, at Transitional Metabolic States (TMSs), a slight decrease in specificity was noted, which is attributed to the biological overlap rather than the model's overlapping states.

**Table 2.** Predictive performance metrics of simulation-derived neonatal immune maturation risk models

| Model variant | Feature set used | AUC (ROC) | Sensitivity (%) | Specificity (%) | Accuracy (%) | F1-score | Calibration error (Brier score) |
|---|---|---|---|---|---|---|---|
| Logistic risk surface | Metabolic + cytokine gains | 0.86 | 82.4 | 78.1 | 80.2 | 0.81 | 0.092 |
| Random forest classifier | Metabolic + immune coupling parameters | 0.90 | 85.7 | 80.6 | 83.1 | 0.84 | 0.078 |
| Gradient boosting model | Full simulation feature set | 0.93 | 88.9 | 84.3 | 86.5 | 0.87 | 0.061 |
| Reduced-feature model | Early immune trajectory slopes only | 0.88 | 83.5 | 79.4 | 81.3 | 0.82 | 0.085 |

It is also noteworthy that predictive uncertainty and moderate parameter noise is a sign of stability in the model. In other words, the Discriminative Ability is not defined by the values of the coefficients being precisely determined. The models' classification metrics demonstrated only minor changes. The predictive features derived from simulation are not artifacts of particular sets of parameters. The features are relevant to the phenomena.

The comparative analysis of predictor importance showed the early adaptive maturation slope and cytokine balance metrics were more contribute to risk classification than absolute metabolic indices. This denotes the greater importance of the dynamic features of the immune trajectory over the static descriptors of the mother. It also indicates the simulation framework features intermediate variables that capture the nexus of maternal metabolism and neonatal immune outcomes.

Combined, the sensitivity and predictive analyses confirm the simulation framework's ability to provide clinically relevant risk stratification signals while withstanding parameter uncertainty. The integration of parameter sensitivity mapping and probabilistic prediction shows that the outcomes of immune maturation are the consequence of model design, not random or inconsistent behavioral model outcomes.

## 6. Conclusion

The research defines the neonatal immune maturation as an emergent, non-linear phenomenon, influenced by the maternal metabolic state through intertwined metabolic–inflammatory–immune interactions. The findings, using a mechanistic simulation framework, suggest the realistic perturbations of maternal metabolic and cytokine parameters are sufficient to produce different phenotypes of neonatal immune maturation. These phenotypes do not necessitate genetic abnormalities or infection exposures postnatally, signifying a powerful intrauterine metabolic milieu that shapes immune developmental trajectories.

A particular asymmetry was present, across simulated maternal metabolic conditions, between the innate and adaptive immune compartments. Immature adaptive immunity was particularly sensitive to the balance,

thresholds, and regulatory coupling of inflammation, while the persistent or even exaggerated maturation of the adaptive immune system occurred under dysmetabolic conditions. This phenomenon resulted in immune states with innate dominance and with at best, delayed, adaptive competence. This was particularly true in states or configurations of maternal insulin resistance and gestational diabetes. The presence of discrete basins of phenotype further exemplifies the fact that the immune system development of the newborn operates within thresholds rather than on a discrete linear continuum.

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From a translational point of view, the findings indicate that the early-life immune risk stratification could be enhanced with the addition of simulation-informed biomarker(s) that reflect the dynamics of immune system development. The framework provides a quantitative method for assessing potential interventions focused on the regulation of inflammation rather than metabolic normalization. By connecting maternal metabolic states to specific immune mechanistic pathways, this study further develops a system's approach to understanding the neonatal immune risk and supports the advancement of hypothesized targeted interventions for early immune risk assessment and prevention.

**References**

1. Langley-Evans, Simon C., and Sarah McMullen. "Developmental origins of adult disease." *Medical principles and practice* 19.2 (2010): 87-98.
2. Catalano, Patrick M., and Kartik Shankar. "Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child." *Bmj* 356 (2017).
3. Poston, Lucilla, et al. "Preconceptional and maternal obesity: epidemiology and health consequences." *The lancet Diabetes & endocrinology* 4.12 (2016): 1025-1036.
4. Kollmann, Tobias R., et al. "Protecting the newborn and young infant from infectious diseases: lessons from immune ontogeny." *Immunity* 46.3 (2017): 350-363.
5. Simon, A. Katharina, Georg A. Hollander, and Andrew McMichael. "Evolution of the immune system in humans from infancy to old age." *Proceedings of the Royal Society B: Biological Sciences* 282.1821 (2015): 20143085.
6. Levy, Ofer. "Innate immunity of the newborn: basic mechanisms and clinical correlates." *Nature Reviews Immunology* 7.5 (2007): 379-390.
7. PrabhuDas, Mercy, et al. "Challenges in infant immunity: implications for responses to infection and vaccines." *Nature immunology* 12.3 (2011): 189-194.
8. Heerwagen, Margaret JR, et al. "Maternal obesity and fetal metabolic programming: a fertile epigenetic soil." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 299.3 (2010): R711-R722.

9. Pantham, Priyadarshini, Irving LMH Aye, and Theresa L. Powell. "Inflammation in maternal obesity and gestational diabetes mellitus." *Placenta* 36.7 (2015): 709-715.
10. Challier, J. C., et al. "Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta." *Placenta* 29.3 (2008): 274-281.
11. Zhang, Jian-Wei, Jie-Qiong Guan, and Yong-Xing Zhong. "Association of prenatal obesity and cord blood cytokine levels with allergic diseases in children: A 10-year follow-up cohort study." *Heliyon* 9.6 (2023).
12. Godfrey, Keith M., et al. "Epigenetic gene promoter methylation at birth is associated with child's later adiposity." *Diabetes* 60.5 (2011): 1528-1534.
13. Ander, Stephanie E., Michael S. Diamond, and Carolyn B. Coyne. "Immune responses at the maternal-fetal interface." *Science immunology* 4.31 (2019): eaat6114.
14. Roberts, K. A., et al. "Placental structure and inflammation in pregnancies associated with obesity." *Placenta* 32.3 (2011): 247-254.
15. Mor, Gil, and Ingrid Cardenas. "The immune system in pregnancy: a unique complexity." *American journal of reproductive immunology* 63.6 (2010): 425-433.
16. Shrestha, Nirajan, et al. "Developmental programming of peripheral diseases in offspring exposed to maternal obesity during pregnancy." *Am*
17. Gutvirtz, Gil, et al. "Maternal obesity and offspring long-term infectious morbidity." *Journal of Clinical Medicine* 8.9 (2019): 1466.
18. Bocharov, Gennady, et al. "Modelling the dynamics of virus infection and immune response in space and time." *International Journal of Parallel, Emergent and Distributed Systems* 34.4 (2019): 341-355.
19. An, Gary. "Agent-based modeling in translational systems biology." *Complex Systems and Computational Biology Approaches to Acute Inflammation: A Framework for Model-based Precision Medicine*. Cham: Springer International Publishing, 2020. 31-52.