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Nested Selves: Self-Organization and Shared Markov Blankets in Prenatal Development in Humans

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Abstract

The immune system is a central component of organismic function in humans. This paper addresses self-organization of biological systems in relation to—and nested within—other biological systems in pregnancy. Pregnancy constitutes a fundamental state for human embodiment and a key step in the evolution and conservation of our species. While not all humans can be pregnant, our initial state of emerging and growing within another person's body is universal. Hence, the pregnant state does not concern *some* individuals but *all* individuals. Indeed, the hierarchical relationship in pregnancy reflects an even earlier autopoietic process in the embryo by which the number of individuals in a single blastoderm is dynamically determined by cell– interactions. The relationship and the interactions between the two self-organizing systems during pregnancy may play a pivotal role in understanding the

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nature of biological self-organization per se in humans. Specifically, we consider the role of the immune system in biological *self*-organization in addition to neural/brain systems that furnish us with a sense of self. We examine the complex case of pregnancy, whereby two immune systems need to negotiate the exchange of resources and information in order to maintain viable self-regulation of nested systems. We conclude with a proposal for the mechanisms—that scaffold the complex relationship between two self-organising systems in pregnancy—through the lens of the Active Inference, with a focus on shared Markov blankets.

Keywords: Self-organization; Immune system; Pregnancy; Self; Co-embodiment; Active Inference; Markov blankets

1. Introduction: Self-organization of biological systems nested within other biological systems

The question of what the "self" is and how it is related to bodily and brain processes has attracted a considerable number of empirical and theoretical treatments (Gallagher, 2000; see Northoff et al., 2006; Qin et al., 2021, for reviews). Recent work proposed a biologically grounded framework for understanding selfhood (Levin, 2021; Lyon, 2020). It starts with the insight that human bodies—biological self-organizing systems, driven by the imperative to survive, thrive, and reproduce in volatile and uncertain environments— arise from the cooperative and competitive action of cells during embryogenesis. Adult bodies are formed from an agential material (i.e., cells), which retain many complex behavioral repertoires, preferences, and homeodynamic states from their evolutionary origin, as single-cell organisms surviving in complex and challenging environments. During the process of embryogenesis, cell-level competencies and setpoints are scaled up toward body-wide anatomical, physiological, and behavioral specifications. Thus, we are fundamentally created and maintained via a multiscale architecture of agency (Levin, 2022).

Seminally developed by Varela et al. (1991), and inspired by the pioneering work of Merleau-Ponty (1945), the embodied cognition approach builds upon the key idea that our perception and action do not emerge in a vacuum, but they are given to us dynamically through our body situated in a wider environment (de Jaegher et al., 2007; Thompson, 2007). While the question "what is a self" has been the subject of a plethora of theoretical and empirical research, the question "how one *becomes* a self" in early life has received less attention (Ciaunica, 2017). This gap is noteworthy, given that human adults, like all living biological systems, are born, develop, decay, and eventually die. Understanding selfhood cannot thus be addressed in isolation from its developmental bodily roots.

However, when focusing on human selfhood, previous approaches tended to overlook the fundamental fact that human bodies first develop *within* another human body (Ciaunica, Constant, Preissl, & Fotopoulou, 2021). That is, the closest and most primitive "environment" of a developing self-organizing human organism is another biological self-organizing system—that is, the mother's[1] body. Importantly, this primitive environment is not objectual (i.e., the uterus is not an object), rather it is another living self-organizing system, and the

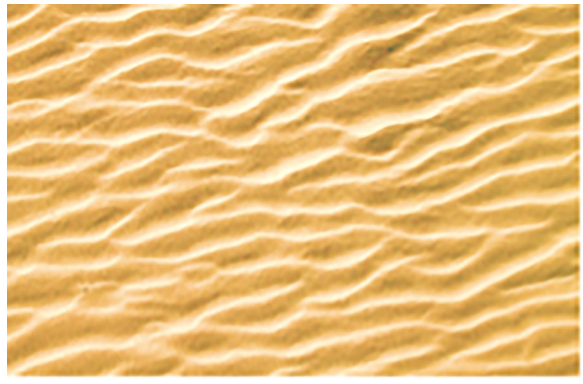

Fig. 1. Ripples in the sand caused by wind, where wind is shaped by the sand.

dynamics between the two may be foundational in understanding the emergence of the human embodiment in early life. The biological fact that the pregnant person's body is a living system with its own "interests," that is, represented by their own neural immune systems, may cast pregnancy as a fundamental state of human embodiment and a key step in the evolution and conservation of our species. Not all humans have the capacity for being pregnant. However, if one considers the perspective of the developing human body, then one notes that all humans grew in relation to—and within—another person's body. Hence, the pregnant state does not concern *some* individuals but *all* developing individuals universally.

Because the pregnant state is universal in this sense, it is reasonable to expect that the processes and interactions between the two self-organizing systems during pregnancy may play a pivotal role in establishing the nature of the biological self-organization per se in humans. Hence, we need to address the question of self-organization of a biological system in relation to and *nested within an other* biological system.

The notion of self-organization was originally formalized in the field of cybernetics (Ashby, 1947; Foerster, 1960) and expanded subsequently to various disciplines including physics (Haken, 1983), biology (Bell & Deater-Deckard, 2007; Camazine, 2003) and neuroscience (Friston, 2010; Kelso, 1997; Tognoli & Kelso, 2014). Self-organization is typically defined as the spontaneous emergence of spatiotemporal order or pattern-formation processes in physical and biological systems resulting from interactions of its components with the environment (Camazine et al., 2001; Rosas et al., 2018; Seeley, 2002). Properties of a global higher-scale system emerge from—and are dependent upon—interactions of its components at lower scales. For example, when the wind blows over a uniform surface of sand, regularly spaced ridges emerge (cf. Fig. 1) as a combination of gravity and wind speed acts on the sand particles (Forrest & Haff, 1992). In turn, the surface of the sand determines the flow of air, shaping the ripples. Self-organization therefore entails both bottom-up and top-down causation (Ellis, Noble, & O'Connor, 2011) that is reflected in the circular causality implicit in the enslaving principle (Haken & Portugali, 2015) in synergetics or the center manifold theorem in dynamical systems theory (Carr, 1981).

However, biological organization is more than emergent complexity. It is fundamentally composed of nested goal-seeking (homeostatic and allostatic) agents, ranging from molecular pathways to whole-organ systems and beyond. These not only exhibit complex behavior but also specifically act to minimize and maximize various quantities and solve problems by navigating (with diverse degrees of competency) a variety of spaces including transcriptional, physiological, and anatomical spaces in addition to the familiar space of behavior (Fields & Levin, 2022).

Human bodies are biological systems that share—with all other physical systems—the property of being instantiated in time and space (e.g., our body occupies a given position and volume in space at a given time). Unlike physical objects like sand particles, however, living organisms tend to avoid entropic dissipation (Schrödinger, 1956) by engaging in self-organization, with the (apparent or manifest) goal of maintaining their internal and sensory states within certain bounds, thereby evincing a homeostatic balance (Friston, 2005).

Homeostasis is typically defined as "the regulation by an organism of the chemical composition of its body fluids and other aspects of its internal environment so that physiological processes can proceed at optimum rates. It involves monitoring changes in the external and internal environments by means of receptors and adjusting the composition of the body fluids accordingly; excretion and (osmotic) regulation are important in this process" (Martin & Hine, 2000). Biological systems also expand on this basic scheme to implement allostasis (McEwen, 1998; Schulkin & Sterling, 2019) and homeorhesis (Colditz, 2020; Matsushita & Kaneko, 2020), which enable the organism to take a more active role in dealing with its environment and its own components.

The homeostatic balance—of a biological self-organizing system—crucially depends on its capacity to engage with the environment, and therefore cannot be achieved in isolation from the environment. From the perspective of physics, biological systems are therefore open systems that manage to attain a nonequilibrium (or far from equilibrium) steady state. Allostasis or anticipatory homeostatic control is typically defined as the process whereby agents select actions that (will most probably) bring about desired sensory outcomes, explicitly or implicitly modifying the causal structure of the environment, so as to guarantee the recurrence of desired outcomes in the future (Sterling, 2012). Seen through the lens of a physicist, these desired states just are those states that the system or agent characteristically occupies, speaking to a set of attracting states to which the system self-organizes (Crauel & Flandoli, 1994; Friston, 2013; Kwon & Ao, 2011).

Biological self-organization includes complex phenomena such as chaos, bifurcation, patterning, dissipation, and synchronization (Kapitaniak & Jafari, 2018; Levin, 2021; Prigogine & Nicolis, 1967). In their seminal work, biologists Maturana and Varela (1980) proposed the notion of "autopoiesis" to describe the minimal self-organization of living systems, focusing on the metabolic self-production of single-cell organisms and homeostatic regulation. Crucially, self-organizing autonomous systems are organizationally closed, such that the network of processes depends recursively on each other, in the generation and realization of the processes themselves (Rosen, 2005). Self-organization in living systems must however feature the emergence of boundaries that define an internal space: the boundaries of the self (Levin, 2021a; Pradeu, 2009), while keeping the states open to—and coupled with—their

surroundings (Palacios, Razi, Parr, Kirchhoff, & Friston, 2017). Dynamical systems endowed with "open" boundaries may therefore be described as a self-organizing system, striving to maintain its functional and structural integrity.

Recent work has emphasized the importance of a developmental perspective—in understanding human embodiment—by looking at self-organization as a process co-embodiment and "co-homeostasis" (Ciaunica et al., 2021). This work builds upon the idea that while homeostasis and allostasis are conceptually distinct, both processes are intrinsically coupled in a dynamic loop that involves minimizing error with respect to a target state and additional ("meta-cognitive") context-sensitive processes that adaptively change the target state as a function of time and other inputs. Indeed, human bodies are dynamic open systems, dependent on rich environmental resources and social interactions to achieve survival and reproduction. Co-homeostasis has been defined as the process of homeostatic self-regulation *through* others' homeostatic and al coupled states (Ciaunica et al., 2021). Indeed, normal morphogenesis includes a large host of cooperating and competing subunits (Gawne, McKenna, & Levin, 2020; Smiley & Levin, 2022), which interact within and across levels of organization.

It is commonly acknowledged that biological self-organization in humans—orchestrated by natural selection (Glass, 2005; Kirschner & Gerhart, 2005)—also includes context-responsiveness to developmental, metabolic, immune, and endocrine processes (Koban, Gianaros, Kober, & Wager, 2021). However, the link between two immune systems in human prenatal development, and how this link is related to embodied self-organization—and self and other differentiation—remains largely unexplored.

In this paper, we use the Active Inference framework (Friston, Parr, & de Vries, 2017) to propose an analysis of biological self-organization in utero through a developmental lens, with focus on the immune system as a fundamental aspect of human embodiment. We suggest that understanding the developing self-organizing system in relation to another self-organizing system (i.e., the mother), as opposed to a mere objectual environment, may cast new light on the fundamental question: How one becomes a self from an assembly of cells? The focus on the immune system foregrounds the fact that the pregnant body is a living organism with its own "self-interests," that is, represented by its own immune system. This paper aims thus to shift the focus from the individualistic and adult-centric perspective in understanding embodied selfhood to a more literally "embedded" or "nested" perspective on how the self emerges relationally from a dialogue with another self. We consider, from a theoretical perspective, how nested selves interact with—and individuate from—each other, in order to maintain a delicate self-regulatory balance.

This paper is set up as follows: Section 2 foregrounds the immune system in consideration of biological *self*-organization in addition to central and peripheral neuronal systems. In Section 3, we look at the complex case of pregnancy, whereby two immune systems need to negotiate and exchange resources and information. Section 4 puts forward a proposal for the mechanisms underlining the complex relationship between two self-organizing systems in pregnancy by appealing to Active Inference through shared Markov blankets.

2. Who keeps track of the "self" in self-models? The brain-immune networks tandem

How do selves emerge from cells? One potential way to address this question is in terms of Active Inference, that is, a process theory of sentient behavior (Friston et al., 2017), which is one of a class of approaches to formalize the processes by which independent subunits such as cells generate a higher-order system that has goals, memories, preferences, and other cognitive capacities that are functionally unified and not present in its components (Levin, 2019, 2020, 2021). Active Inference tries to formalize the capacity of biological organisms to persist in unpredictable environments. Active Inference is an application of the free energy principle (FEP; Friston, 2005), which is a formalization and extension of Schrodinger's (1956) notion that living organisms avoid entropy, maintaining themselves within an optimal (i.e., characteristic) set of states. This "self-organization" underwrites survival and reproduction. Survival-driven constraints act upon the brain during evolution and cannot be uncoupled from those acting upon the body. Hence, control of physiological homeostatic balance must constitute a "purpose" of—or constraint on—brain function (Cannon, 1929). This control has long been known to involve reflex-like actions (comprising motor, endocrine, immunological, and autonomic processes) that are driven by feedback and the resulting "prediction error"—the discrepancy between an expected bodily state (i.e., an equilibrium or homeostatic setpoint) and its actual level as signaled by interoceptive sensory inputs from the body (Feldman, 2009; Modell et al., 2015).

FEP entails von Helmholtz's (1878/1971) seminal idea that the brain constructs a mental representation of self- and world-related sensory inputs via perceptual inference. Prior constraints automatically shape the percept that is informed by the incoming sensory information. This idea has inspired the modern approach of perception as hypothesis testing or predictive processing (PP) (Friston, 2005; Gregory, 1968, 1980; Knill, & Pouget, 2004; Rao & Ballard, 1999). The idea that our perceptions in the here and now are influenced by prior events and experiences has recently received substantial support and attention from the proponents of the PP framework in philosophy and neuroscience (Clark, 2013; Hohwy, 2013, 2020). Of course, given the fundamental conservation between neural and non-neural processes, these same concepts have now been extended to morphogenetic and control of body systems outside the brain (Friston, Levin, Sengupta, & Pezzulo, 2015; Pezzulo, LaPalme, Durant, & Levin, 2021; Pezzulo & Levin, 2015; Pio-Lopez, Kuchling, Tung, Pezzulo, & Levin, 2022).

Within this framework, it has been proposed that embodied agents act as self-modeling systems in the game of maximizing evidence for their self-model (Apps & Tsakiris, 2014; Hohwy, 2014; Limanowski & Friston, 2018; Limanowski & Blankenburg, 2013; Seth, 2013). These self-modeling systems are organized in a dynamic and hierarchical fashion. Prior beliefs[2] about the embodied self (and extrapersonal world) generate predictions that are conveyed by the top-down (backward) connections to lower hierarchical levels. Bottom-up (forward connections) return prediction errors to update prior beliefs—into posterior beliefs—until prediction errors are explained away by ensuing belief updating. In a hierarchical setting, this enables sensory input at the lowest level of the hierarchy to be assimilated through PP under a world model generating predictions. On this view, posterior beliefs[3] are hypotheses concerning the causes of sensory input at any hierarchical level that therefore rest

on (1) *prior beliefs* about the self and world and (2) *current sensory evidence* gathered from a changing environment.

Here, we explore the idea that—from the very start—the most "newsworthy" and prescient information that our brain receives is *self*-related information. By maintaining and regulating the physiological needs and integrity of the organism (the human body), perceptual and sensory inputs at the most basic sensory level are inherently self-centered and "selfish" (Ciaunica & Crucianelli, 2019; Seth & Tsakiris, 2018). A comprehensive review of the rich literature on the different facets of selfhood lies beyond the scope of this paper (see Allen & Friston, 2016; Northoff et al., 2006; Qin et al., 2020, for a review). Here, we limit ourselves to a minimal (basal) selfhood implicit in the kind of *self*–organization sometimes described under the FEP as *self*-evidencing (Hohwy, 2014). In this setting, free energy provides a computable or biophysically realizable measure of *self*-information (or, more simply, surprise). Technically, the negative *self*-information is the log evidence maximized during *self*-evidencing (viz., the log evidence for generative models of the sensed world entailed by the system in question). Importantly, in this paper, we endorse a neutral stance regarding the ontological question whether the systems do actively compute self-information using Bayesian means. Rather, we take a pragmatic stance, and we use Active Inference as the most promising framework to advance the question while keeping ontological commitments to the minimum.

Crucially, however, adaptive responses to changes in the environment require flexible adjustments not only through neural but also through metabolic, cellular, and immunological processing at multiple organizational levels of the biological system (Lyon, 2020; Markose, 2022). Indeed, one fundamental mechanism underlying the processing of *self*-related information at the cellular organismic level is *the immune system*. The idea that the "brain's privilege" is not an outcome of its long-assumed isolation from the immune system (Schwartz, Abellanas, Tsitsou-Kampeli, & Suzzi, 2022) gains traction in current approaches in cognitive neuroscience and neurobiology both in health and disease (e.g., Bhat et al., 2021).

For example, Ciaunica, Shmeleva, and Levin (2023) recently proposed a focus on immune processing as a key actor in complementing neuronal processing for self-organization and adaptation in an ever-changing environment. An understanding of the emergence of self-organizing systems needs to address how neurons work in tandem with other types of cells (e.g., immune cells) to subserve biological self-organization and adaptive behavior of the human organism as a whole (Schwartz, Abellanas, Tsitsou-Kampeli, & Suzzi, 2022; Ciaunica et al., 2023). The key idea is that the development of the immune system precedes and complements brain neural networks in achieving successful self-organization and adaptation of the human organism. Hence, understanding self-models may require stepping out from the neuro-centric view to consider different systems in the body that subserve optimal self-organization of biological systems (Ciaunica et al., 2023).

This approach is in line with recent work by Schwartz et al. (2022) who propose the idea of a brain-immune network "ecosystem." The brain-immune network refers to the idea that "the cellular elements of this immunological network, together with the non-immune cells of the brain—neurons, astrocytes, and oligodendrocytes—constitute a functional structure with properties of an "ecosystem," characterized by interdependent compartments of immune cells that interact with each other within a physically connected microenvironment, thereby

contributing to increased stability and resilience of the central nervous system (CNS) in the face of continuous disruption in its day-to-day activities" (Schwartz et al., 2022, p. 1)

Previously the brain was regarded as a self-contained organ, responsible for its own immune protection and equipped with microglia, acting as internal immune sentinels. However, as Schwartz and colleagues note, CNS repair (Shechter, London, & Schwartz, 2013) and higher brain function (Ziv et al., 2006) have been found to depend on adaptive and innate immune cells, derived from the circulatory system. These findings opened the search for regions within the brain containing adaptive immune cells, which are considered able to affect the brain *from distance*. Intriguingly, the discovery of border structures—through which reparative immune cells can enter the brain without breaching the blood–brain barrier (Shechter et al., 2013)—opens a new window into the complex relationship between the CNS and immune networks.

A detailed discussion of this approach lies beyond the scope of this paper. However, we celebrate the key insight that the brain's activity—subserving self-organization—should not be regarded in isolation from the immune system. Indeed, at the cellular level, the immune system plays a privileged role in determining what counts as the "self" in biological self-organization. See Markose (2022) for a Gödelian formulation of self-referential processing and an appeal to the notion of the "thymic self" in immunological terms (Geenen, 2021). Importantly, the developing immune system needs to be successfully in place well before the neuronal system develops, in order to keep track of the most primitive self-models (Geenen, 2021).

As outlined above, one key (yet overlooked) aspect is that developing human bodies are nested within another self-organizing living system (i.e., the mother's body). This means that during pregnancy, two (or more) immune systems coordinate in tandem to subserve the development of human bodies. Such complex organization leaves us with open questions about how these nested neural-immune ecosystems operate successfully during the delicate process of co-homeostasis and co-embodiment in early life. We now turn to this discussion.

3. Pregnancy and the immune system: A delicate liaison

The immune system is a fundamental component of organismic self-organization in humans. It comprises a cellular network able of distinguishing between self, non-self, missing self, and aberrant self, including misplaced cells and aberrant intracellular and extracellular molecules (Coers, 2013; Di Virgilio, Sarti, & Coutinho-Silva, 2020; Zindel & Kubes, 2020; Iwasaki et al., 2015). It presents an innate capacity to underpin cell organization, mitigation, and migration for checking and responding to invading foreign organisms. Functions of the immune system include detection, recognition, and elimination of pathogens, foreign substances, cancer cells, or damaged cells. It also plays a key role in inflammation, tissue repair, tissue remodeling, and regulation of immune response magnitude. An optimal immune system maintains a balance between responding to harmful and tolerating harmless agents or, in some cases, even tolerating harmful agents (Medzhitov, 2008; Medzhitov, Schneider, & Soares, 2012). In addition, the immune system also regulates the nervous system, behavior,

metabolism, and thermogenesis and takes part in the fight-or-flight response (Dantzer, 2018; Medzhitov, 2021; Rankin & Artis, 2018).

While the functioning of the immune system in an individual is already complex, its functioning during pregnancy represents an even more complex and unique process (Mor & Cardenas, 2010; Racicot, Kwon, Aldo, Silasi, & Mor, 2014). While it is well established that pregnancy is supported by significant hormonal, immunological, and microbial changes, the exact nature of the processes furnishing these changes remains elusive (Fuhler, 2020).

The mother's body undergoes significant changes in pregnancy to ensure an optimal outcome. Complementing anatomical and physiological changes, complex hormonal and immunological responses play a pivotal role in supporting successful fetal development and delivery. The implantation of a fertilized egg triggers the production of human chorionic gonadotrophin (hCG) by placental cells. hCG initiates the production of hormones (progesterone and estrogen) and stimulates fetal organ growth and differentiation (Cole, 2009). The trophoblast is the cellular unit of the placenta and has a key role in recognizing microorganisms, to initiate a prompt immune response (Abrahams, Kim, Straszewski, Romero, & Mor, 2004; Mor, Romero, Aldo, & Abrahams, 2005, 2011). During this key period, the maternal and the fetus immune systems develop—in tandem—a web of recognition, communication, migration, and repair of the cellular processing.

During pregnancy, the constant changes in the maternal body require substantial energy supply; hence, insulin sensitivity fluctuates over time. For example, in the first stages of gestation, insulin sensitivity is enhanced to ensure fat stores for later energy demands. In some cases (i.e., up to 10% of women), this drop can be drastic and lead to gestational diabetes mellitus (Behboudi-Gandevani, Bidhendi-Yarandi, Panahi, & Vaismoradi, 2021). By contrast, toward the end of the pregnancy, insulin sensitivity decreases to allow endogenous glucose production to rise (Catalano, 2014). There is however little consensus regarding the immunological changes taking place in the peripheral blood or other tissues during a healthy pregnancy (Fuhler, 2020, p. 6).

Following egg fertilization, the implanted embryo carries half of the DNA of paternal origin. The fetal placenta also expresses paternal and fetal antigens, which can be detected by the maternal immune system, and typically tolerated in healthy pregnancies. To protect both the mother and the offspring, in typical pregnancies, the human decidua contains a large number of immune cells, such as macrophages, natural killer (NK) cells, and regulatory T cells (Bulmer, Pace, & Ritson, 1988). Seventy percent of decidual leukocytes are NK cells, 20%–25% are macrophages, and 1.7% are dendritic cells (King, Loke, & Chaouat, 1997; Mor, Straszewski-Chavez, & Abrahams, 2006). Macrophages are the predominant subset of human leukocytes antigen-presenting cells in the human decidua (Nagamatsu & Schust, 2010). The trophoblast expresses pattern recognition receptors that function as "sensors" of the surrounding environment (Racicot et al., 2014, p. 3). These "sensors" allow detection and recognition of bacteria, viruses, dying cells, and so forth. Once the pathogen is recognized, the trophoblast produces a specific set of cytokines that work in tandem with the other immune cells in the decidua (i.e., macrophages, T cells [TCs], uterine NK [uNK cells]), "educating" them to work together to support successful outcomes (Racicot et al., 2014, p. 3).

While pregnancy was commonly considered as a single event, it is now becoming more and more evident that it displays three distinct biological processes, reflected in the subjective phenomenology of the pregnant person. First, implantation and placentation—during the first and early second trimester—where the maternal body shows a strong inflammatory response to the new "organism." During this stage, the blastocyst needs to literally "break through" (Mor & Cardenas, 2010; Moser et al., 2018) the epithelial lining of the uterus to ensure successful implantation. An ensuing complex and delicate orchestration of new cells, dying cells, and repairing cells supports this key phase, often experienced at the phenomenological level by the pregnant person as "morning sickness," fatigue, and apathy. After this first stage, the second stage consists of rapid fetal growth, whereby the fetus, placenta, and the mother's body behave as symbiotic states, with predominant anti-inflammatory aspects. Cellular populations in the uterus witness an increase in T-cell numbers, while macrophages decrease, leading to a tolerogenic phenotype. Finally, during the last period of the gestation, a new pro-inflammatory state emerges to trigger the labor. Hence, pregnancy can be seen as moving through both pro-inflammatory and anti-inflammatory states, depending on the stage of the gestation.

Some studies have found that pregnancy is accompanied by a reduction in adaptive immunity, with decreased frequencies of TCs and B cells (Kraus et al., 2012, Lima et al., 2016; Liu et al., 2022). For decades, it was commonly assumed that pregnancy is linked to immune suppression to allow the egg implantation. The placenta was viewed as a transplant allograft (and the fetus as a semi-allograft), expressing paternal proteins and therefore, under normal immunological conditions, facing potential rejection from the maternal body. However, new evidence supports the idea that the fetal–maternal immune interaction is more complex than interactions with a transplant allograft. As Fuhler notes, "the presence of large numbers of NK cells in the decidua might be expected to result in cytolysis of the foetal 'missing self' cells, as has been suggested in the organ transplantation setting (Benichou et al., 2011). However, uNK cells express different cell-surface receptors from peripheral NK cells and are not cytotoxic (Vos et al., 2011)." It has been thus suggested that local decidual responses are designed to trigger the production of regulatory T-cells.

Based on this evidence, the presence of immune cells at the implantation site may not be associated with a response to the "foreign" fetus but with a need to facilitate and protect the pregnancy. Hence, "the immune system at the implantation site is not suppressed, on the contrary it is active, functional and is carefully controlled." (Mor & Cardenas, 2010, p. 426). It has therefore been proposed that it is more appropriate to refer to pregnancy as a unique immune condition that is modulated but not suppressed (Racicot et al., 2014). Contra the received view—that the placenta and decidua are non-active immunological organs, fully dependent only on the action of the maternal immune system—recent observations point to the conclusion that both the placenta and the decidua constitute essential immune modulators that affect the global response of the maternal body to infections (Racicot et al., 2014).

The immune system during pregnancy is thus functional and highly active, whereby the trophoblast and the maternal immune system have established a "cooperative status" (Mor & Cardenas, 2010; Racicot et al., 2014). In the dénouement of this review, we suggest that

Active Inference may provide a fecund framework to better understand the nature of this key "cooperation" between an emerging and an adult self-organizing system.

4. Not one, not two, but three? Sharing Markov blankets in early life

Understanding the link between self-organizing systems and their approximate environment is at the core of embodied cognition approaches. Within this literature, pioneering work by Varela (1991), Vaz (2011), Maturana (2002), Vaz and Varela (1978), and Coutinho (2003) outlined the key role of the immune system in understanding the nature of biological self-organizing systems such as human bodies. For example, Vaz and Varela noted that: "the transformations of the cognitive domain of the immune network in an organism's ontogeny are a combination of its recursivity (its closure) and the fact that it is exposed to random perturbations or fluctuations from the environment (its openness). In other words, it exhibits self-organisation, the transformation of the environmental noise into adaptive functional order, in a manner similar to many other biological systems such as cells, nervous systems, and animal populations" (1978, p. 33).

However, these approaches, as pioneering as they are, have left unaddressed the basic fact that the human organism's closest and most primitive environment is, from the outset, another human body (Ciaunica et al., 2021). During pregnancy, two (or more) neural and immune systems coordinate in tandem to subserve the development of human bodies. Such complex organization leaves us with the open question of how these nested neural-immune ecosystems operate successfully during the delicate process of co-homeostasis and co-embodiment in early life. This suggests that the functioning and the development of the neural and the immune system may need to be addressed primarily *in relation* to another immune system rather than in relation to an objectual, physical environment. This dynamic is a microcosm of the same scenario, which plays out *inside* each embryonic blastoderm. Many thousands of cells must cooperate toward the production of one "embryo"—achieving specific goals in their navigation of anatomical morphospace. But, if the blastoderm is temporarily or permanently cut into pieces (Lutz, 1949), each fragment self-organizes its own embryo, resulting in monozygotic twins, triplets, and so forth (which may or may not be conjoined). Thus, each cell is some other cell's "external" neighbor, and the collective must dynamically decide where the embryo ends, and the outside world begins. The number of individuals within a single blastoderm is not fixed by genetics but emerges from the physiology of an excitable medium of potentiality that performs symmetry breaking and dynamic coordination of boundaries of self versus not-self at the earliest stages of development. Indeed, some cells on the boundary of two such individuals have a hard time deciding which of two adjacent embryos they belong, explaining why conjoined twins often have laterality defects (Levin, Roberts, Holmes, & Tabin, 1996).

In addition, a dynamic and complex self-organizing system such as the human body needs to be able to play a double game, so to speak, in order to survive and potentially reproduce. First, it must successfully maintain sensory states within certain physiologically viable bounds. Second, it must flexibly change these states in order to adapt to a constantly changing

environment. One may argue that the boundary plays a key role in making sure this game is played successfully and flexibly enough to ensure the organism remains alive.

First introduced by Judea Pearl as a statistical construct (Pearl, 1988), the concept of "Markov blanket" is fundamental in defining boundaries in biological self-organizing systems (Da Costa, Friston, Heins, & Pavliotis, 2021; Friston et al., 2017; Kirchhoff, Parr, Palacios, Friston, & Kiverstein, 2018; Palacios, Razi, Parr, Kirchhoff, & Friston, 2020; Palacios et al., 2017; Parr, Da Costa, & Friston, 2020; Rubin, Parr, Da Costa, & Friston, 2020; Sakthivadivel, 2022). A Markov blankets can be roughly described as a statistical boundary that separates two sets of states. Markov blankets establish the informational boundary mediating the pushes and pulls that link interacting systems. When a system is differentiated from its environment, its corresponding Markov blanket consists of two elements: sensory variables, which encode how the environment can affect the state of the system, and action variables, which encode how the system affects the state of the environment. An intuitive example is the cellular membrane separating intracellular and extracellular dynamics. The boundary not only individuates the system from its environment but also, importantly, inherently relates the system to its environment, rendering the internal states separable from external states but also open via exchange across the Markov blanket.

Here, we suggest that this intrinsically dual function of a boundary—to separate *and* to relate—may be pre-eminent during pregnancy, via the placenta. As we saw earlier, the primary environment of a developing self-organizing human system is another human. The relationship between the two, while asymmetrical, remains bidirectional. This means that at the basic cellular level, fetal and maternal cells move in two directions (Mold et al., 2008; Mor, Aldo, & Alvero, 2017; Mor & Cardenas, 2010, p. 429; Stevens et al., 2004). This means that in pregnancy, the self-regulatory architecture is multi-layered: fetal self-regulatory processes are coupled with the mother's homeostatic–allostatic processes. This is achieved mainly through the placenta, an ephemeral and relational organ that enables vital, biological exchanges between two bodies. The placenta is a relational organ par excellence and also a universal organ (see Burton & Jauniaux, 2015). For example, it allows the infant to breathe, despite lacking proper lung regulation and it ensures the infant is fed despite lacking proper eating effectors. The placenta, like the later developing human skin, acts both as a barrier and a connector allowing nutrients, gases, hormones, and wastes to pass between the co-regulating organisms but also ensuring that both self-organizing systems work in tandem.

Indeed, the state of co-embodiment in pregnancy leaves room for a certain degree of bidirectionality. For example, the mother and fetus, through repeated trial and error, learn to mutually coordinate meal times and other embodied needs. Mothers may use signals from their body to allostatically regulate their own behavior and hence the fetus' feeding schedule, thereby ensuring regulation of key nutritional variables before some of the infant's homeostatic mechanisms kick in. As such, they shape their fetus' homeostasis (i.e., close the loop in homeostatic models) and they co-build their allostatic regulatory models (which allow learning and anticipatory models to be learned). This draws our attention to what is happening *in between* the two organisms. Indeed, homeostatic and anticipatory self-regulation depends not only on bodily states but also on the external environment and crucially on *the relation between the two*.

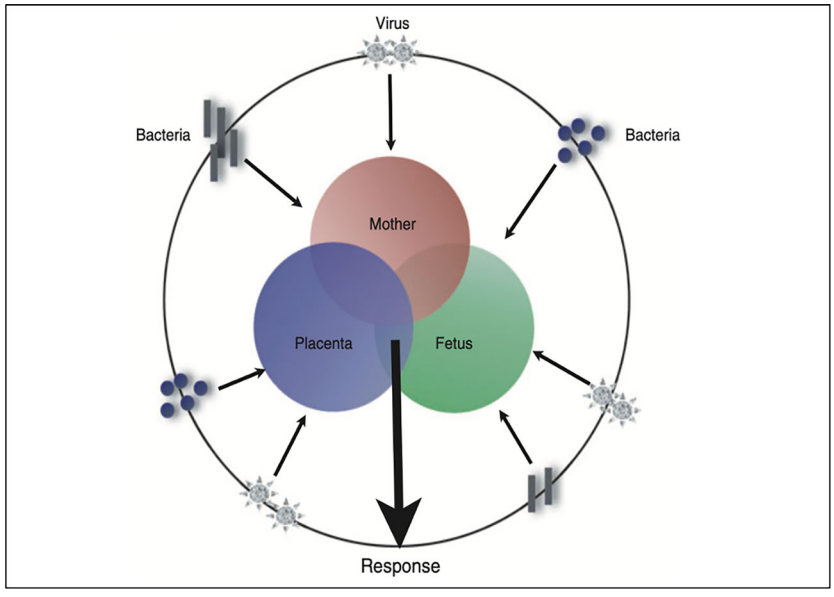

Fig. 2. Integrational view of the immune system during pregnancy. Adapted from Mor and Cardenas (2010, p. 428).

While it was traditionally assumed that the placenta and the fetus are non-active immunological organs—largely depending on the maternal immune system—recent work suggests a more complex picture. The placenta and the fetus represent an "additional immunological organ which affects the global response of the mother to microbial infections" (Mor & Cardenas, 2010, p. 429; cf. Fig. 2). The type of response initiated in the placenta may determine the immunological response of the mother, impacting the pregnancy outcome. The placenta represents an active immunological organ, highly responsive to foreign pathogens. For example, it has been shown that the placenta functions as a regulator of, rather than a barrier to, the trafficking between the fetus and the mother. Both the fetus and the placenta present an active immune system that has a direct effect on the way the mother responds to the environment. Importantly, for our discussion here, the placental-immune system creates a pregnancy-friendly protective environment while still being fully operational and able to defend the mother and fetus against infections.

The placenta however is "more than a transplanted organ": "while there may be an active mechanism preventing a maternal immune response against paternal antigens, the trophoblast and the maternal immune system have evolved and established a cooperative status, helping each other for the success of the pregnancy (Mor et al., 2005; Mor, 2007). This cooperative work involves many tasks, some of which we are just starting to unveil" (Mor & Cardenas, 2010, p. 426). Traditionally, it has been assumed that the fetus has no metabolism of its own. Nowadays, it is well established that the placenta and fetal liver work in tandem as a coordinated multi-organ system to provide the necessary nutrients subserving the fetal metabolism and growth (Anderson, Fennessey, Meschia, Wilkening, & Battaglia, 1997; Vaughan & Fow-

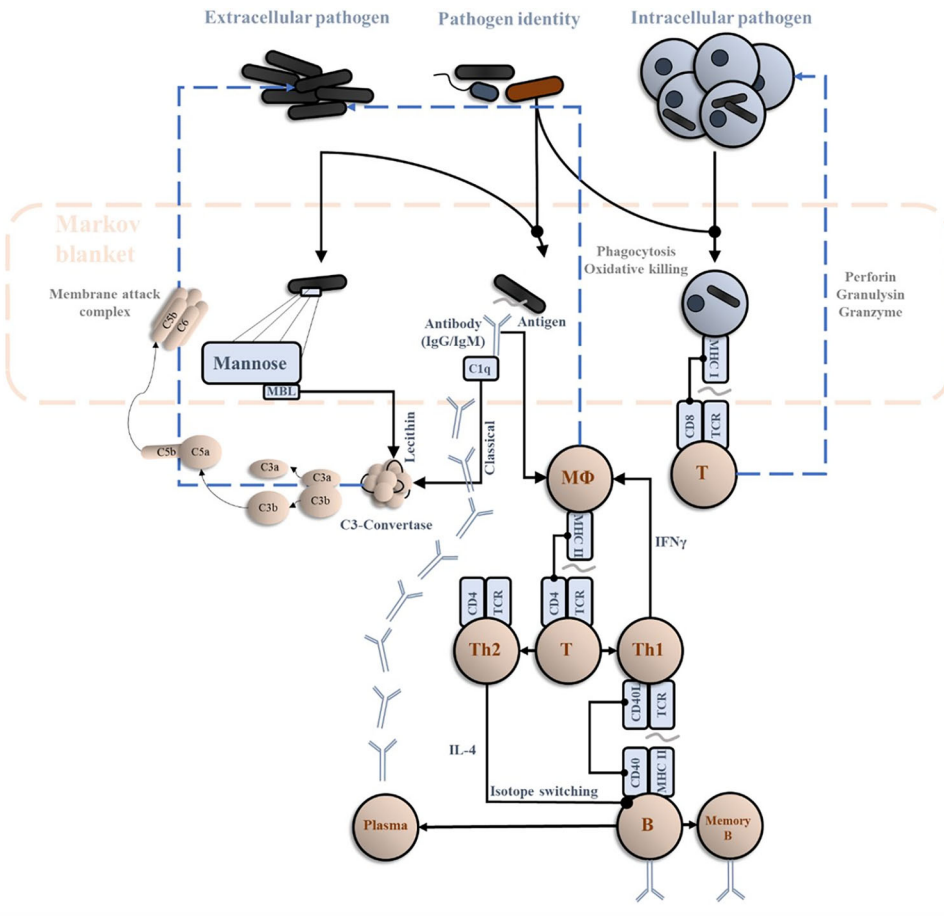

Fig. 3. Immunoceptive inference simplified account of an immune response to foreign pathogen. Adapted from Bhat et al. (2021, p. 27).

den, 2016). Significant attempts have been made to understand the fetal metabolism in a very low oxygen environment (pO2 16--27 mm Hg): the so-called "Mount Everest in utero" concept. Indeed, maintaining an optimal balance of continuous supply of nutrients from the mother to the fetus is crucial for development. There is accumulating evidence for a direct link between a mother's adverse bodily and mental health (e.g., depression and anxiety) during pregnancy and the child's mental and physical development (see Schetter & Tanner, 2012). This holds also for neutral states such as food preferences and flavors (Birch, 1999; Mennella, Jagnow, & Beauchamp, 2001; Venter et al., 2009), which are passed from the mother to the infant.

The focus on pregnancy, a case where two individuating organisms literally grasp/grip one into each other, allows us to reconsider the common view of the fetus being passively "contained"[4] and solipsistically "trapped" in the solitude of the womb. Rather, there is evi-

dence speaking in favor of an active, precarious, and bidirectional negotiation between the two bodies (Ciaunica et al., 2021; Quintero & de Jaegher, 2020).

Crucially, this implies that the self-regulatory architecture during pregnancy is multi-layered: fetal self-regulatory processes are coupled with the mother's homeostatic–allostatic processes (Ciaunica et al., 2021). This discussion brings us to a critical realization—that the fetus–mother system, in their grasping of each other, give rise to *a multi-layered system* whose organization, coordination, and self-regulation ought to be understood as an interplay between three levels of self-organization: (i) the parts on their own (fetus and mother), (ii) the parts in their interactions, and (iii) the parts being one unified system oriented toward a larger external environment. The current picture suggests that neither of these levels of organization supersedes the other, but they coexist while playing different roles through the pregnancy process.

This view of pregnancy can be operationalized by leveraging the extended formalism of nested, multilevel Markov blankets. Building inspiration in condensed matter theory and statistical physics, and more specifically in renormalization group theory, this approach proposes that Markov blankets exist at all scales of the system—that is, that what is seen as a single individuated system delineated by a single blanket is, at a lower scale (i.e., higher resolution), a collection of individual systems each demarcated by their corresponding blankets. Importantly, this formal theory provides a way to understand the coexistence of blankets at multiple scales, which supports the fact that a system acts as a unity as one scale does not "compete" ontologically with the same system being seen as several differentiated parts interacting at another scale. This formalism provides a lens to contemplate the coexistence of multiple organizational levels of the mother–fetus dyad, which—we posit—is needed to account for the richness of the systems nature. This multilevel view of fetus and mothers may help us to better frame our current knowledge about the dynamics of the immune systems and the role of the placenta.

5. Conclusion and outlook

This paper addressed biological self-organization in pregnancy, a fundamental yet overlooked state of the human embodiment. We built upon the insight that the developing human organism's closest and most primitive environment is, from the outset, another human body (Ciaunica et al., 2021). Specifically, we suggested that the interactions between the two self-organizing systems during pregnancy may play a pivotal role in understanding the nature of biological self-organization per se in humans. We focused on the key role of the immune system in biological *self*-organization in addition to classical neural/brain systems that underpin discussions on human selfhood (Ciaunica et al., 2023). Given that during pregnancy, two (or more) neural and immune systems coordinate in tandem to subserve the development of human bodies, such complex orchestration leaves us with the open question of how these nested neural-immune ecosystems operate successfully in early life.

Future work on the mechanisms and the formalisms underlining the complex relationship between two self-organizing systems during pregnancy is currently in its infancy. Here, we

speculatively posit that a fruitful way forward of defining self-organization in utero is through immunoceptive inference (Bhat et al., 2021; Parr et al., 2020). Immunoceptive inference is the process by which the immune system perceives substances it encounters, recognizes them as "self" or "other," and initiates a response (cf., Fig 3), that is, inference from the perspective of the immune system (Bhat et al., 2021). This process is an action–perception cycle as can be understood in the context of Active Inference.

To briefly illustrate the sorts of insights available from this approach, we take our lead from Bhat et al. (2021) and note that the view of pregnancy as a succession of pro-and anti-inflammatory stages has exactly the same Bayesian mechanics seen in dyadic communication. In brief, in order to act (e.g., speak), one has to attenuate the evidence that one is not acting. In terms of psychophysics, this is known as sensory attenuation, namely, attenuating the sensory consequences of action. Conversely, when attending to the environment (e.g., listening), one has to increase the precision afforded sensory evidence, to select newsworthy information from a partner that underwrites generalized synchrony (Friston & Frith, 2015). Exactly the same cycle of attenuation and augmentation of precision may be evinced during pregnancy, in which the mother's immune system implements a form of sensory attenuation, enabling it to interact with the developing fetus. In both cases—dyadic communication and pregnancy—the endpoint is a generalized synchrony between two systems separated by a shared Markov blanket, namely, the sensorium or placenta.

Another important open question to be addressed in future work relates to the mechanisms underlying the processes of cooperation versus conflict between the mother and the embryo at the multicellular exchanges level (Durgam, Alegre, & Chong, 2022; Fowden & Moore, 2012; Moore, 2012).

In sum, philosophical, computational, and empirical future work may benefit from investigating the nature of the multi-layered interdependencies of the fetus–mother dyad. The aim is to clarify under what conditions these relationships are redundant—ensuring robustness—or synergistic—becoming more than the sum of the parts—or deleterious to both organisms—leading to conflict and disease. Overall, our understanding of the mechanisms underlining the complex relationship between two self-organizing systems during pregnancy is currently in its infancy. Yet, we believe this type of developmental approach may lead our theories and experiments along fruitful directions to better understand human embodiment. Finally, we suggest that the focus on the developing body in relation to another body may help us answer perennial questions about the very nature of the human selfhood as being not one, not two (Varela, 1976), but maybe three and even more.

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Notes

1 Throughout this paper, we will use the terms "pregnant person" and "mother" interchangeably, irrespective of their self-identified gender.
2 The terms "prior beliefs," "expectations," and "predictions" are used here interchangeably.
3 Beliefs here are read as Bayesian beliefs, namely, non-propositional probabilistic beliefs encoded by synaptic activity and efficacy.
4 For example, Kingma (2019) identified two options for conceiving of the relation between fetus and maternal body: (i) the fetus is merely contained within the maternal body, (ii) or it is a part of the maternal body.

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