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Modelling the effect of birth and feeding modes on the development of human gut microbiota

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The human gut microbiota is transmitted from mother to infant through vaginal birth and breastfeeding. *Bifidobacterium*, a genus that dominates the infants' gut, is adapted to breast milk in its ability to metabolize human milk oligosaccharides; it is regarded as a mutualist owing to its involvement in the development of the immune system. The composition of microbiota, including the abundance of Bifidobacteria, is highly variable between individuals and some microbial profiles are associated with diseases. However, whether and how birth and feeding practices contribute to such variation remains unclear. To understand how early events affect the establishment of microbiota, we develop a mathematical model of two types of Bifidobacteria and a generic compartment of commensal competitors. We show how early events affect competition between mutualists and commensals and microbe-host-immune interactions to cause long-term alterations in gut microbial profiles. Bifidobacteria associated with breast milk can trigger immune responses with lasting effects on the microbial community structure. Our model shows that, in response to a change in birth environment, competition alone can produce two distinct microbial profiles post-weaning. Adding immune regulation to our competition model allows for variations in microbial profiles in response to different feeding practices. This analysis highlights the importance of microbe–microbe and microbe–host interactions in shaping the gut populations following different birth and feeding modes.

1. Introduction

The human gut is a complex ecosystem whose bacterial residents play a crucial role in host health. Interactions between bacteria, including cooperation and competition, are essential in shaping the dynamics of the gut community. While cooperation can promote the colonization and growth of bacterial species, competition stabilizes the gut community by dampening the positive feedback from cooperation [1]. Discrete stable compositions of the adult gut microbiota have been recognized [2], and some are associated with diseases [3]. It is important, therefore, to understand how gut microbiotas are established and the mechanisms that result in different stable microbiota compositions. Early infancy is a key period in gut microbiota development, as microbes are vertically transmitted from mother to infant [4,5]. While considerable debate continues as to whether vertical transmission starts at or before birth [6,7], it is understood that vaginal birth [8] and breast feeding are two important transmission routes as infants collect maternal microbes from the birth canal and breast milk [9,10]. After weaning, the infant gut microbiota stabilizes to the adult form by around the age of 3 years [11,12].

Bifidobacterium, which is highly abundant in the infant's gut, is believed to exert positive health benefits to the host. The transmission of Bifidobacteria is facilitated by the consumption of breast milk [9,10,13]. Species of Bifidobacteria, namely *Bifidobacterium longum* subspecies *infantis* (*B. infantis*) [14], *Bifidobacterium longum* subspecies *longum* (*B. longum*) [15] and *Bifidobacterium bifidum* [16], are adapted

to the neonatal gut; they can metabolize the human milk oligosaccharides (HMO) that are present in breast milk. Other Bifidobacteria species benefit from the presence of these HMO metabolizing Bifidobacteria through cross-feeding as they use products of HMO degradation [17–19]. The presence of HMO in breast milk provides Bifidobacteria a competitive advantage over other species in the neonatal gut. Vaginal birth is also an important source of Bifidobacteria colonization: vaginally delivered infants share strains of Bifidobacteria with their mothers [8], and gut-derived and vaginal-derived Bifidobacteria strains are indistinguishable [20].

Bifidobacterium is considered an essential genus in the gut as it is involved in the development of the immune system. The abundance of Bifidobacteria varies across individuals [21], and is correlated with faecal immunoglobulin A (IgA) levels in infants [22,23] and children [24]. Bifidobacteria have been shown to stimulate the production of IgA [25,26]. This mediates immune exclusion by preventing pathogen adsorption to the mucosal epithelium [27,28]. Given that the abundance of Bifidobacteria affects the level of IgA and therefore the host's immune response to other bacteria, Bifidobacteria may have important regulatory effects on neonatal microbial populations.

Early interventions such as caesarean section (C-section) and formula feeding are believed to interrupt the vertical transmission of microbiota [29] and can have significant effects on neonatal gut composition. The microbiota of breastfed infants is characterized by the dominance of Bifidobacteria [11,30,31], while that of infants born through C-section or who receive formula milk are associated with a lower abundance of Bifidobacteria [11,30,32–34] and a high abundance of opportunistic pathogens [35].

While an increasing number of studies reveal correlations between birth mode or feeding practice on one hand and infant gut composition on the other, the empirical evidence for long-term effect of these interventions is mixed. The impact of C-sections appears to last for at least 2 years [36] or 7 years after birth [37]. By contrast, other studies found that the effect of birth mode on the variations in microbiota is no longer evident within a few months after birth [38,39], and that the effect of birth mode was not reflected in adult microbiota [40]. Breastfeeding is reported to have a significant effect on the composition of microbiota until 14 months of age [11], after which the profile of breastfed and formula-fed infants converged [11,41]. However, it has also been found that the microbiome community type in adults is associated with breastfeeding history [42]. Understanding the mechanisms by which different community structures are established, and therefore the effect of early events on their establishment can help to resolve these apparently contradictory results.

Gut populations are shaped by ecological interactions between microbes and by interactions between microbes and the immune system. It is unclear whether and how birth and feeding practices exert long-term effects on the microbiota. Here, we develop mathematical models to investigate how microbe-microbe and microbe–host interactions contribute to the varying abundance of Bifidobacteria post-weaning. We use these models to study the conditions under which birth environment and feeding practices alter the structure of bacterial communities in infants. The models include two Bifidobacteria populations (milk-consuming and fibre-consuming Bifidobacteria) and a commensal population. We also investigate the role of immune regulation on the effects of birth and feeding modes.

2. Methods

(a) Competition model

To study the effect of infant diet and delivery mode on infant microbiota development, we start with a model in which the dynamics are driven by competition between Bifidobacteria and commensals. Species of Bifidobacteria are coarsely divided into two types ($B1$ and $B2$) distinguished by their metabolic characteristics. One population of Bifidobacteria ($B1$) is able to metabolize HMO while the other ($B2$) is able to metabolize plant polysaccharides and the products of HMO degradation. Figure 1a illustrates our initial model, showing the cross-feeding behaviour between two Bifidobacteria populations and their competition with a generic group of commensal bacteria ($B3$). This compartment is non-specific in that it groups all species of commensals. We use $B1$, $B2$, $B3$ to refer to the (non-dimensionalized) density of these bacteria.

We introduce a system of ordinary differential equations (ODEs) to track the abundances of the three bacterial populations, as follows:

$$
\begin{aligned}
\dot{B_1} &= rB_1\left(Z(t) \quad \overbrace{-\tfrac{B_1+B_2}{K}}^{} \quad \overbrace{-\tfrac{\alpha B_3}{K}}^{\text{competition}} \right) \quad \overbrace{+f_z Z(t)}^{\substack{\text{supply}\\\text{from milk}}} , \\[2mm]
\dot{B_2} &= rB_2\left(1-\tfrac{B_1+B_2}{K} \quad \overbrace{+\tfrac{\alpha_c B_1}{K}}^{\text{cross-feeding}} \quad \overbrace{-\tfrac{\alpha B_3}{K}}^{\substack{\text{competition}\\B_3 \text{ on } B_2}} \right) \quad \overbrace{+f_2}^{\substack{\text{supply}\\\text{from}\\\text{environment}}} , \\[2mm]
\dot{B_3} &= rB_3\left(1-\tfrac{B_3}{K}-\overbrace{\tfrac{\alpha(B_1+B_2)}{K}}^{\text{competition}} \right) \quad \overbrace{+f_3}^{\substack{\text{supply}\\\text{from}\\\text{environment}}} .
\end{aligned}
$$

(2.1)

and

The strength of competition between Bifidobacteria and commensals is characterized by a competition coefficient α. If $\alpha > 1$ the competition between Bifidobacteria and commensals is stronger than the competition within each population; if $\alpha < 1$ the within-population competition is stronger; if $\alpha = 1$ between-population competition is exactly as strong as within-population
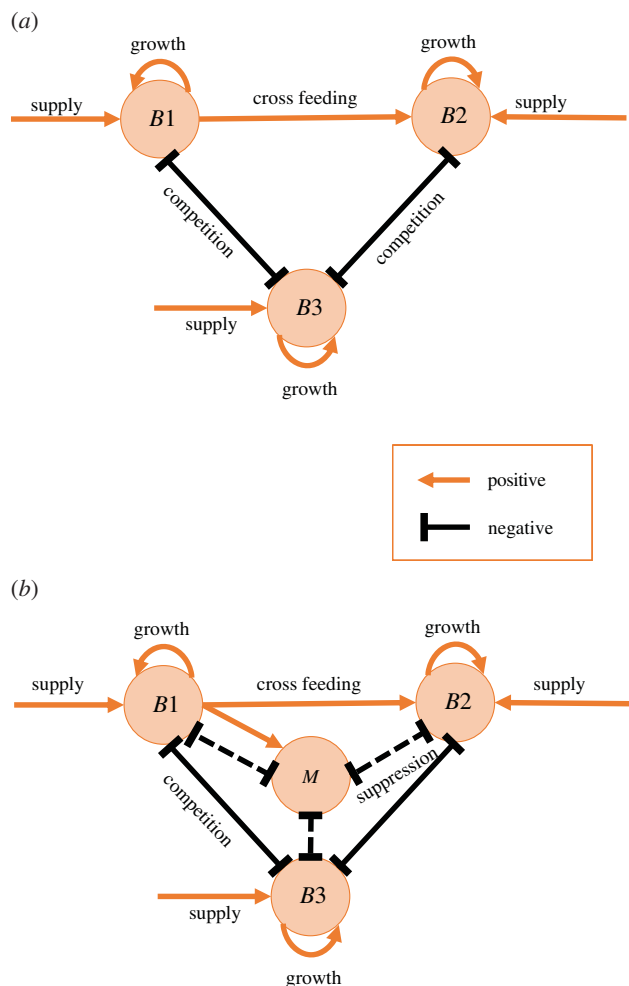
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(a)

(b)

Figure 1. Schematic of the competition model (a) and extended model (b). Orange arrows represent positive effects on the population. Black lines represent negative effects on the population. Fibre consuming Bifidobacteria B2 benefits from cross-feeding by metabolizing the HMO-degradation product of milk consuming Bifidobacteria B1. In the extended model (b), the presence of B1 stimulates the growth of the immune factor (M), which suppresses the growth of all bacterial populations. (Online version in colour.)

competition. The total population is constrained by a carrying capacity parameter K. The growth of the HMO-metabolizing Bifidobacteria B1 population depends on the proportion of milk in the diet, denoted by $Z(t)$; the supply of B1 is proportional to breast-feeding and maternal interaction and is given by $f_Z Z(t)$. The proportion of milk $Z(t)$ in the infant's diet is modelled by a logistic function, which reflects the gradual replacement of milk by solid food during the first 1000 days of life. The weaning process is characterized by the rate of weaning ω and the half-life of milk in infant's diet h, where half-life is the time required for milk to fall to 50% of an infant's diet. We define the function $Z(t)$ as

$$Z(t) = \frac{1}{1 + e^{\omega(t-h)}}. \tag{2.2}$$

Belonging to the same genus, fibre-consuming Bifidobacteria B2 are assumed to have similar competition properties as B1; therefore, the competition between B1 and B2 is considered as equivalent to intrapopulation competition. The presence of B1 is beneficial to the growth of B2 owing to cross-feeding activities described in the introduction and characterized by α_c. We assume a constant supply of Bifidobacteria B2 with rate f_2 and commensal competitor B3 with rate f_3 owing to environmental exposure.

Table 1. Summary of (non-dimensionalized) parameters in the model.

model parameters			
symbol	description	value	unit
r	growth rate of the bacterial populations	1	day^{-1}
μ_b	death rate of Bifidobacteria	50	day^{-1}
μ_c	death rate of commensal competitor	200	day^{-1}
α_c	effect of cross-feeding between B1 and B2	1.7	—
α	competitive effect between bacterial populations	2	—
f_z	supply of B1 associated with milk	0.01	day^{-1}
f_2	supply of B2 from the environment	0.03	day^{-1}
f_3	supply of B3 from the environment	0.05	day^{-1}
ω	rate of weaning	0.014	day^{-1}
h	day since birth when milk is half of diet	500	day
γ	immune effect	0.0001	—

To reduce the number of parameters, we non-dimensionalize the system by defining the following new variables and parameters

$$B_1^* = \frac{B_1}{K}, \quad B_2^* = \frac{B_2}{K}, \quad B_3^* = \frac{B_3}{K}, \quad f_z^* = \frac{f_z}{K}, \quad f_2^* = \frac{f_2}{K}, \quad f_3^* = \frac{f_3}{K}.$$

We omit the asterisk for notational simplicity and obtain the following non-dimensionalized system

$$\dot{B_1} = rB_1(Z(t) - (B_1 + B_2) - \alpha B_3) + f_z Z(t), \tag{2.3}$$

$$\dot{B_2} = rB_2(1 - (B_1 + B_2) + \alpha_c B_1 - \alpha B_3) + f_2, \tag{2.4}$$

$$\dot{B_3} = rB_3(1 - B_3 - \alpha(B_1 + B_2)) + f_3. \tag{2.5}$$

The parameters and their baseline values used in simulation are summarized in table 1.

We assume that the supply of bacteria is small relative to the carrying capacity, and that the environmental supply of fibre-consuming Bifidobacteria B2 is higher than the milk-facilitated supply of HMO-consuming Bifidobacteria B1. Because the commensal population B3 includes a broader range of species, we assume that the supply of commensals is higher than that of the Bifidobacteria. Therefore, f_z, f_2 and f_3, which represent the supply of B_1, B_2 and B_3, respectively, are set at 1%, 3% and 5% of the carrying capacity. We focus on the mutalistic interaction between different types of Bifidobacteria [17–19] as the HMO-consuming Bifidobacteria B1 help the other Bifidobacteria population B2 survive through infancy. Therefore, we assume the effect of cross-feeding α_c to be higher than the within-population competition ($\alpha_c > 1$) and set $\alpha_c = 1.7$ (we note that α_c does not affect the equilibria because it is linked to B1, which is eventually eliminated). Furthermore, to specify high between-population competition (between both Bifidobacteria populations and the generic commensal population), we set the competition coefficient α at 2. We choose $h = 500$ following the recommendation of the World Health Organisation to introduce solid food at around six months ($\simeq 180$ days) and continuous breastfeeding for 2 years ($\simeq 730$ days) or more [43].
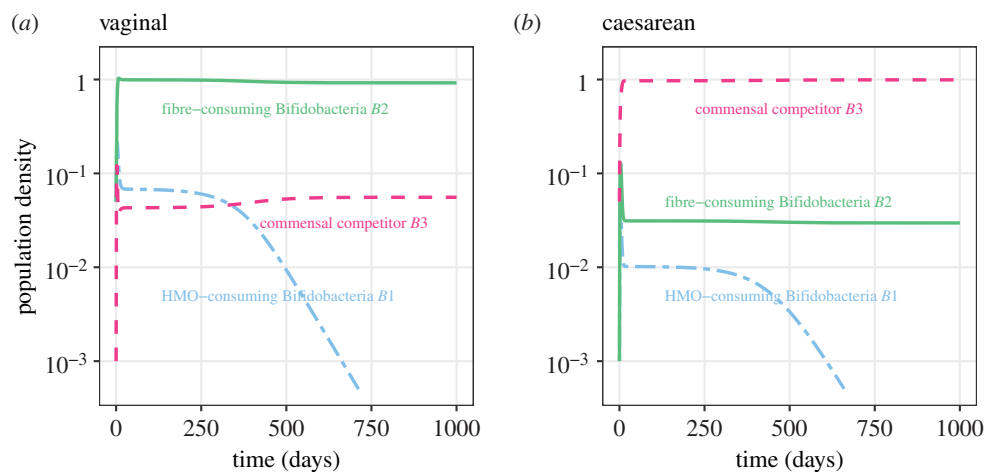
Figure 2. Longitudinal dynamics of the three bacterial population abundances (on a log scale) using baseline parameter values in table 1 and initial conditions representing vaginal birth (*a*) and C-section (*b*). The blue two-dash line represents the infant-type Bifidobacteria $B1$, the green solid line represents the adult-type Bifidobacteria $B2$ and the red dashed line represents the commensal competitor $B3$. The dynamics are simulated for 3 years allowing the system to reach a post-weaning steady state. (Online version in colour.)

To study the effects of birth mode on gut bacterial population, we choose two sets of initial conditions representing vaginal birth and C-section; those values are our non-dimensionalized variables and thus represent a fraction of the carrying capacity K. For vaginal birth, the initial colonisation of Bifidobacteria and commensal are set at 0.05 and 0.001, respectively; for C-section, the initial colonization of Bifidobacteria and commensal are set at 0.001 and 0.05. These two conditions qualitatively reflect the higher initial colonization of maternal Bifidobacteria during a vaginal birth and the higher initial colonization of commensals from health care facilities during a C-section [35]. While we choose the default parameters in table 1 based on general empirical observations, we also investigate the sensitivity of our model to variation in a few key parameters.

(b) An extension with immune effects
To investigate the effect of birth and feeding modes under immune regulation as well as competition, we extend the above model by introducing an immune factor M. As highlighted in the introduction, Bifidobacteria stimulates the production of IgA; thus the supply of Bifidobacteria associated with breast milk is likely to trigger immune reaction that suppresses the gut populations. In this modified model, HMO-consuming Bifidobacteria promotes the growth of the immune factor M, and M, in turn, suppresses all bacterial populations. The extended model schematic is given in figure 1b.

The expansion of the immune factor M depends linearly on Bifidobacteria $B1$ with rate parameter γ. The level of immune reaction is thus determined by the cumulative abundance of Bifidobacteria $B1$ in the system. The initial condition for M is set at 0.001 for both birth modes. IgA stimulated by Bifidobacteria restricts pathogen and potentially harmful attachment of commensals to the epithlelium [27,28]. Thus, we assume that the immune system favours the establishment of mutualists by making them more resistant to the immune response than commensals. Because we include a wider range of species in the commensal population, we assume that they are more susceptible to this immune clearance. Therefore, denoting death rates of Bifidobacteria and commensals by μ_b and μ_c, respectively, we take $\mu_c > \mu_b$. The extended system is described by the following differential equations:

$$
\begin{aligned}
\dot{M} &= \gamma B_1, \\
\dot{B}_1 &= rB_1(Z(t) - (B_1 + B_2) - \alpha B_3) + f_z Z(t) - \mu_b B_1 M, \\
\dot{B}_2 &= rB_2(1 - (B_1 + B_2) + \alpha_c B_1 - \alpha B_3) + f_2 - \mu_b B_2 M \\
\text{and} \quad \dot{B}_3 &= rB_3(1 - B_3 - \alpha(B_1 + B_2)) + f_3 - \mu_c B_3 M.
\end{aligned}
$$

$$(2.6)$$

In addition to this model, we considered a generalization in which fibre-consuming Bifidobacteria $B2$ also contribute to immune stimulation and in which the immune response decays (see electronic supplementary material, figures S10 and S11).

3. Results

(a) Competition model: the effect of birth environment
The temporal dynamics of the competition model given by equations (2.3)–(2.5) are shown in figure 2. The populations stabilize at the age of 3 years by the end of weaning as the proportion of milk drops from one to zero (electronic supplementary material, figure S1). During this transitional period Bifidobacteria $B1$ decreases and is eliminated, leaving the system with two populations. With our baseline parameter values (table 1), the system stabilizes such that under vaginal birth there is a high abundance of Bifidobacteria $B2$ (figure 2a), while under C-section there is a high abundance of commensal competitor $B3$ (figure 2b). When the between-population competition is weaker than within-population competition ($\alpha = 0.7$), the system stabilizes at the same equilibrium regardless of the birth mode (electronic supplementary material, figure S2). We next explore the conditions within which either of these equilibrium patterns arise.

We observed a drop of HMO-consuming Bifidobacteria $B1$ closely following the drop of milk in infant diet $Z(t)$ (dynamics shown in figure 2, and the function $Z(t)$ shown in the electronic supplementary material, figure S1). Studies show that the gut microbiota stabilizes after the cessation of milk [11]. Thus, we make the assumption that $B1$ reaches its steady state before the other bacterial populations equilibrate, and as $Z(t) \to 0$. We first solve for the steady state of $B1$ by applying $Z(t) = 0$ and $\dot{B}_1 = 0$; the HMO-consuming Bifidobacteria $B1$ goes to zero at equilibrium. We approximate the model using a quasi-steady state with $\hat{B}_1 = 0$ and reduce our system to two dimensions (see the electronic supplementary material, equations (S1)–(S2)).

To check the accuracy of our quasi-steady-state approximation against the behaviour of the full model, we compared the numerical solution of the original system with the quasi-steady-state approximation (electronic supplementary material, figure S3) and find a close match under baseline
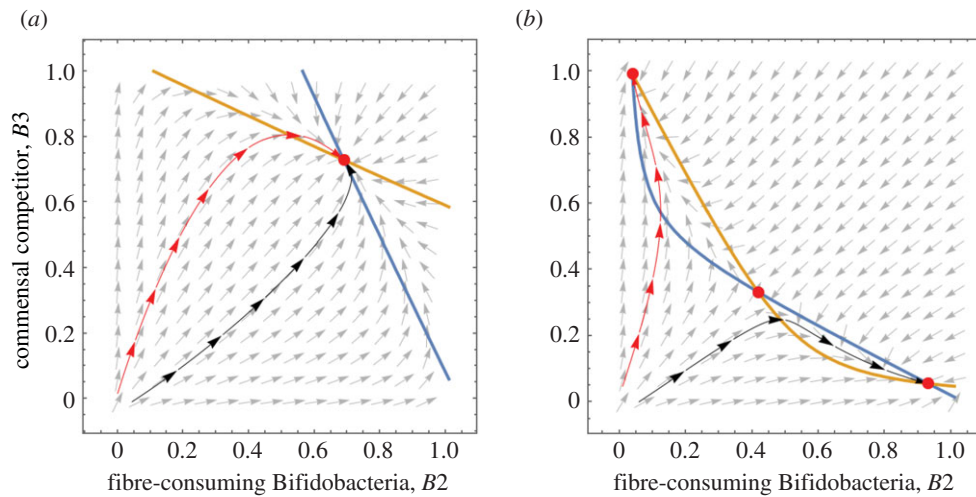
Figure 3. Vector plot and nullclines of $B2$ (blue) and $B3$ (yellow). Two nullclines meet at a stable equilibria. Black and red lines are the trajectories of the population dynamics following an initial condition representing vaginal birth and C-section, respectively. (a) $\alpha = 0.7$, other parameters are as specified in table 1. (b) Parameters specified in table 1. (Online version in colour.)

parameters. Under different competition strengths α and weaning schedule h (electronic supplementary material, figures S4 and S5) the approximation shows slight mismatch in the time at which the dominating population switches from commensal $B3$ to Bifidobacteria $B2$ (electronic supplementary material, figure S4). However, in general, the approximate equilibria match the full model within the range of parameter values we consider (electronic supplementary material, figures S4 and S5).

We use this approximate system to explore the long-term equilibria of the fibre-consuming Bifidobacteria $B2$ and commensal competitor $B3$ by considering a phase portrait (figure 3). Figure 3a shows the nullclines and trajectories of this approximate system where between-population competition is weaker than within-population competition ($\alpha < 1$). Two trajectories, with initial conditions representing C-section (red) and vaginal birth (black) meet at a stable node (the red dot) in the positive quadrant. There is only one positive equilibrium, which is consistent with the temporal dynamics of the full model at $\alpha = 0.7$ (electronic supplementary material, figure S2). This implies a long-term population dynamic independent of birth mode; both birth modes stabilize at the same state.

We also find three positive equilibria when between-population competition is higher than within-population competition ($\alpha > 1$) (electronic supplementary material, table S1). A phase portrait with $\alpha = 2$ (our baseline value) shows bistability, with two stable nodes and a saddle point (figure 3b). A higher initial Bifidobacteria $B2$ colonization (vaginal birth) leads to an equilibrium dominated by $B2$ while higher initial commensal $B3$ colonization (C-section) leads to an equilibrium dominated by $B3$.

Whether a trajectory goes to one equilibrium or the other depends on the initial ratio of Bifidobacteria to the commensal competitor. To investigate this dependence on the initial conditions, we further explore the population dynamics by numerically solving the ODEs of the original system to obtain the long-term equilibria at a range of initial conditions (electronic supplementary material, figure S6). As the ratio of initial Bifidobacteria to commensals increases from 0 to 2, the equilibrium switches from one dominated by the commensal to one dominated by Bifidobacteria.

Both our analytic and numerical results imply that birth mode may impose a long term effect on the gut microbiota. We then investigate the long-term effect of feeding practices. Breastfeeding involves a higher level of mother-infant interaction compared with formula feeding, and breast milk carries maternal microbes that are absent in formula milk. Therefore, we assume that the supply (f_z) of HMO-metabolizing Bifidobacteria is positively associated with the amount of breast milk given to infants. Different f_z values correspond to various feeding practices such as exclusive formula feeding (low f_z) and exclusive breastfeeding (high f_z). It also reflects the individual differences in the amount of HMO present in breast milk. Under this assumption, we numerically solve the system against a range of milk-associated Bifidobacteria supply f_z (electronic supplementary material, figure S7). The model shows a compensatory effect of breastfeeding on C-section delivered infants. Their microbiota composition may eventually resemble that of vagina-delivered infants provided enough Bifidobacteria is supplied (electronic supplementary material, figure S7b). However, the system is generally insensitive to changes in feeding practices as the amount of breast milk has no effect on the population dynamics following vaginal birth (electronic supplementary material, figure S7a).

In this model, variation in response to different birth environment and feeding practices is limited. At low between-species competition ($\alpha < 1$), the long-term population dynamics is independent of birth environment (figure 3a). At high between-species competition ($\alpha > 1$), the system is highly constrained to approaching one of two equilibria, where either Bifidobacteria $B2$ or commensal competitor $B3$ dominates.

(b) Extended model: effect of breast milk and weaning schedule

The extended model (equation (2.6)) helps us to gain further insight into the long-term effect of feeding practices on the population dynamics. In figure 4, we show the effect of feeding practices (breast milk f_z and half life of milk h) on the equilibria at different initial conditions (which themselves represent birth mode). The dynamics of the bacterial populations in response to feeding practices are influenced by
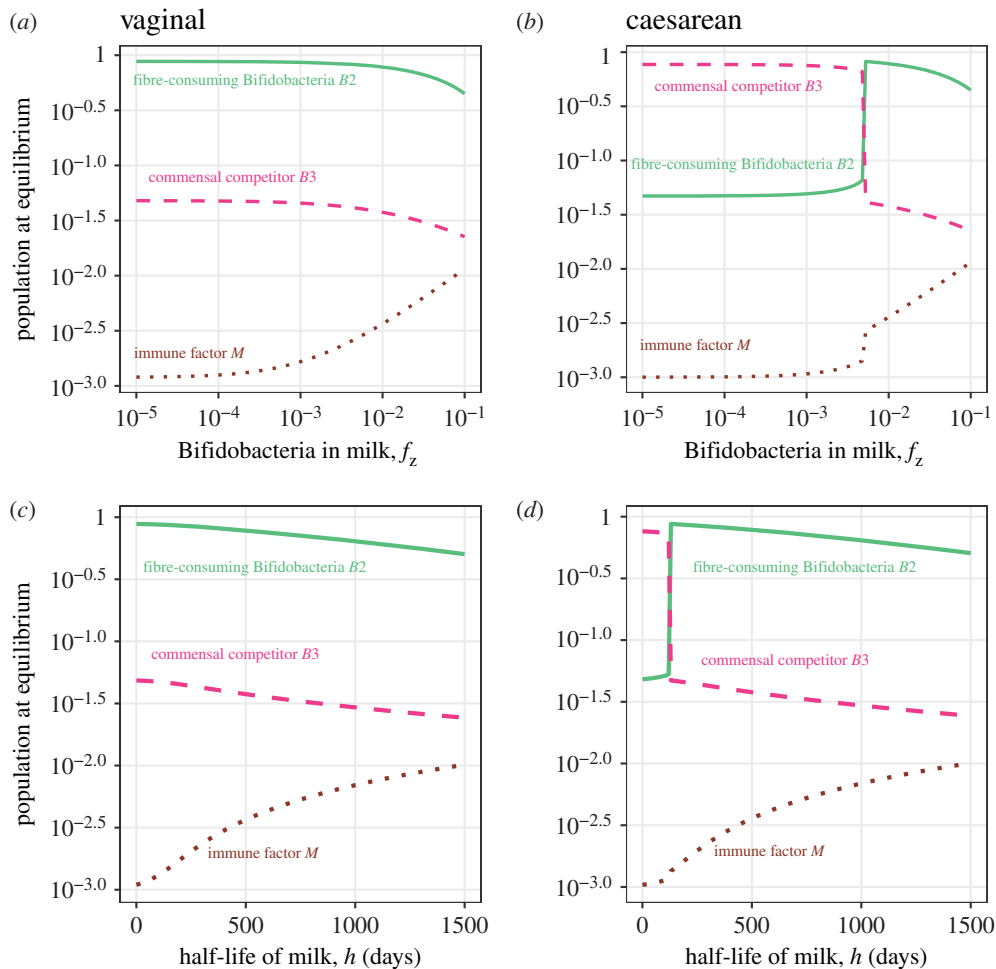
Figure 4. Steady states of the three bacterial populations and the immune factor M in response to feeding practices. The simulations used the baseline parameter values in table 1 and the initial conditions representing vaginal birth (a and c) and C-section (b and d). The green solid line represents the adult-type Bifidobacteria $B2$, the red dashed line represents the commensal competitor $B3$ and the brown dotted line represents immune factor M. The y-axes are log-scaled population densities at equilibria. The x-axes are log-scaled Bifidobacteria levels carried by milk f_z representing the amount of breast milk in diet (a and b), and the time h when milk takes up 50% of the diet representing the duration of breastfeeding (c and d). (Online version in colour.)

birth mode. Unlike the simple competition model, the population dynamics change continuously with breast milk (rather than abruptly) in this extended model, exhibiting a range of possible outcomes in an individual (figure 4).

The half-life of milk h has a similar effect on the population dynamics to the input of Bifidobacteria in breast milk f_z (figure 4). Vaginal birth promotes the dominance of fibre-consuming Bifidobacteria $B2$. The increase of breast milk and age of weaning reduces the abundance of both Bifidobacteria $B2$ and commensals $B3$, with Bifidobacteria decreasing at a lower rate. C-sections tend to promote the dominance of commensals $B3$. The abundance of fibre-consuming Bifidobacteria increases with breast milk until a turning point is reached, after which the trajectory resembles that following a vaginal birth. This again indicates the compensatory effect of breast milk on infants delivered by C-section.

The dynamics of $B2$ and $B3$ in response to the amount of breast milk and weaning schedule reflect the combined effect of cross-feeding, immune reaction and competition between the populations. Similar to increasing the amount of breast milk f_z, a higher half-life of milk h, which models weaning at an older age, increases the total supply of HMO-consuming Bifidobacteria $B1$ to the system. This can increase the level of cross-feeding between $B1$ and $B2$ as well as the immune

factor M. While cross-feeding tends to increase the abundance of Bifidobacteria $B2$ at equilibrium, increasing the immune factor has the opposite effect. As Bifidobacteria is more resistant to the immune clearance, $B2$ decreases at a slower rate than commensal $B3$ in response to higher level of breast milk and older weaning age. If Bifidobacteria are subject to the same strength of immune clearance as the commensals, the immune effect together with competition tends to suppress its abundance at stable state (electronic supplementary material, figure S8).

The ratio of Bifidobacteria $B2$ to commensal $B3$ at equilibria is sensitive to the changes of their supply from the environment (f_2 and f_3, respectively). The supply of Bifidobacteria increases the relative abundance of Bifidobacteria while the supply of commensals causes a decrease (electronic supplementary material, figure S9). With a low supply of Bifidobacteria and a high supply of commensals, an increase in breast milk, which facilitates the transmission of maternal Bifidobacteria, can promote the relative abundance of Bifidobacteria. As the supply of Bifidobacteria and commensals increases, the relative abundance of Bifidobacteria at equilibria becomes less sensitive to changes in breast milk. With a high Bifidobacteria supply and low commensal supply, the Bifidobacteria population dominates over the commensals

regardless of feeding practices (electronic supplementary material, figure S9).

4. Discussion

We have introduced a simple ecological model to investigate the mechanisms of gut microbiota establishment. The dynamics of the gut populations in our model are driven by competition and can be affected by birth environment (initial colonization). The effects of initial colonization on the competitive outcome between an invasive and a commensal gut population have been studied with chemostat models [44,45] and a recent Lotka–Volterra-type ecological model [46]. The prevalence of competition has been shown in ecological network models [1,47] and human gut community interaction topologies [48,49]. While network models use data-driven inferences to learn microbial interactions, metabolic models reconstruct biochemical reactions to understand those interactions [50–52]. Here, we focused on the population dynamics affected by ecological interaction (competition) and host immune regulation in the context of early interventions. We studied the establishment of two mutualist populations (Bifidobacteria) and a generalized commensal population, and focused on the competition between those populations (Bifidobacteria and commensals) and the immune response triggered by the mutualist (Bifidobacteria). By considering just these two mechanisms, we have shown that immune regulation, along with competition, can produce long-term variation in gut microbial profile following different birth and feeding practices.

Inconsistent observations regarding the long-term effect of birth and feeding practices on microbiota profiles have been made [36,40,42,53]. We offer an explanation for this apparent contradiction. Under our model, it is possible to produce both kinds of outcomes; the impact of early interventions can be either inconsequential or significant depending on the magnitude of the intervention. A change in birth environment can alternatively lead to a long-term alteration in microbial populations, as shown in empirical studies [36,37]. This can occur if the between-population competition is sufficiently strong (higher than within-population competition), and the intervention causes a large enough difference in initial colonization for the populations to switch between two stable states. Following birth, infant feeding continues to shape the microbiota, and we find that its effect depends on birth environment. The gut microbial profile of formula-fed and breast-fed infants born through C-section may diverge [42]; we find a similar divergence by showing that the maternal microbes carried by breast milk can compensate for the loss of beneficial bacteria from C-section. However, if infants receive a large enough number of bacterial cells from vaginal birth, our model suggests that feeding practices early in life may not have a significant impact on the microbial composition, in agreement with findings of empirical studies [40,53].

We illustrate the importance of microbe–microbe and microbe–host interactions in shaping gut populations. Increased strength of competition leads to the divergence of microbial profile following different birth environments. The divergent outcomes are owing to bistability in the dynamics, which was also observed in studies that model commensal-pathogen competition [46] and microbe-immune system interaction [54]. Variation in post-weaning Bifidobacteria abundance in response to different birth and feeding modes

cannot be produced by competition alone. Interaction with the immune system facilitates the possibility of this variation in microbiome composition. Early differences in Bifidobacteria levels, driven by birth environment and consumption of breast milk, induce different levels of immune regulation, which in turn have a lasting effect on the microbial structure. While the gut microbiota is influenced by numerous lifestyle factors [55], our work implies that early events can contribute to regional differences observed in individuals from non-industrialized [12,56–59] and industrialized societies [12,60]. The effects of those early events are regulated by microbial competition and immune regulation.

Antibiotic exposure at birth, a common practice in industrialized societies, may also be part of the modern birth environment. This can be a form of early intervention that affects the microbial competition and immune regulation, and therefore the development of microbiota. While not modelled explicitly, antibiotic administration at birth is analogous in our model to restarting the microbial succession with different initial colonization conditions. Early antibiotic exposure has been reported to disrupt early microbial succession and alter the taxonomic composition of the infant gut [61,62]. Our model shows the divergence of microbial populations in response to altered initial colonization, implying the possibility of a long-term shift in microbial configuration owing to antimicrobial exposure. This aligns with other mathematical models that demonstrated the extinction of antimicrobial-sensitive bacteria in the gut after antibiotic treatments [47,63]. However, our results also show that the potential loss of Bifidobacteria resulting from an altered birth environment (initial colonization or, perhaps, antibiotic exposure) can be reversed with a sufficient supply of breast milk. This is consistent with studies showing that continued breastfeeding can compensate for disturbances caused by antibiotics [61].

While we have investigated the effect of early-life interventions on the establishment of infant microbiota, it is clear that the post-weaning diet also plays a key role in shaping gut microbial communities. Microbe acquisition from the environment, for example, has been shown to increase within-host microbiome diversity [64]. The composition of microbiota is shown to be dependent on long-term dietary practice [57,65]. This is reflected in our model where the microbial configuration is sensitive to the change in environmental supply of the bacteria. The microbiota is reported to be responsive to changes in diet [66–68]. However, our model does not capture the full range of possible changes in exposure to environmental microbes that may steer the microbial community to different configurations. In future work, our model can be extended to study the effect of long-term dietary patterns and drastic diet shifts.

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