

A Mathematical Model of the Effects of Beneficial and Pathogenic Gut Bacteria on Insulin Resistance Using Differential Equations

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ABSTRACT

Insulin resistance is increasingly understood to be shaped by alterations in the gut microbiota rather than arising solely from dysfunction of peripheral insulin-sensitive tissues. Over the past decade, microbiome research has established a bidirectional relationship between intestinal bacteria and host metabolism. In this study, we formulate a four-dimensional system of ordinary differential equations that tracks beneficial bacteria, pathogenic bacteria, bacterially induced systemic inflammation, and an insulin resistance index. The model assumes that beneficial and pathogenic bacterial populations grow logistically and compete for shared intestinal resources. Pathogenic bacteria release lipopolysaccharide (LPS), which elevates systemic inflammation, while beneficial bacteria and their short-chain fatty acid (SCFA) metabolites attenuate this inflammatory response; inflammation, in turn, drives insulin resistance, with the system retaining an intrinsic capacity for recovery. We show that solutions originating from a healthy state remain positive and bounded, identify four biologically relevant equilibria, and derive a basic reproduction number governing stability of the disease-free equilibrium. Stability of the coexistence (chronic dysbiosis) equilibrium is established via a Routh–Hurwitz argument, and a normalized sensitivity analysis identifies the parameters exerting the greatest influence on the insulin resistance index. Fourth-order Runge–Kutta simulations under two contrasting parameter regimes confirm the analytical predictions: the system returns to a healthy state when the reproduction number is below unity and evolves toward persistent, clinically dysbiosis-like inflammation when it exceeds unity. Although parsimonious, the model supports the hypothesis that restoring microbial balance, rather than treating inflammation alone, is central to the long-term resolution of insulin resistance.

نموذج رياضي لتأثيرات البكتيريا النافعة والممرضة في الأمعاء على مقاومة الأنسولين باستخدام المعادلات التفاضلية

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المخلص	الكلمات المفتاحية
تشير الدراسات الحديثة إلى أن مقاومة الأنسولين تتأثر بشكل متزايد بالتغيرات في ميكروبيوتا الأمعاء، وليس فقط بخلل في الأنسجة الطرفية الحساسة للأنسولين. وعلى مدى العقد الماضي، أثبتت أبحاث الميكروبيوم وجود علاقة تبادلية بين بكتيريا الأمعاء وأيض الجسم. في هذه الدراسة، نضع نظاماً من أربع معادلات تفاضلية عادية يتتبع البكتيريا النافعة، والبكتيريا الممرضة، والالتهاب الجهازي الناتج عن البكتيريا، ومؤشر مقاومة الأنسولين. يفترض النموذج أن أعداد البكتيريا النافعة والممرضة تنمو بشكل لوجستي وتتنافس على الموارد المعوية المشتركة. وتفرز البكتيريا الممرضة الشحميات السكرية (LPS) التي ترفع الالتهاب الجهازي، بينما تعمل البكتيريا النافعة ومستقلباتها من الأحماض الدهنية قصيرة السلسلة (SCFA) على تخفيف هذا الالتهاب؛ ويؤدي الالتهاب بدوره إلى مقاومة الأنسولين، مع احتفاظ النظام بقدرة ذاتية على التعافي. وتبين أن الحلول التي تبدأ من حالة صحية تبقى موجبة ومحدودة، ونحدد أربع نقاط توازن ذات دلالة بيولوجية، ونشتق عدد التكاثر الأساسي الذي يحكم استقرار حالة الخلو من المرض. وتثبت استقرار حالة التعايش (خلل التوازن الجرثومي المزمن) باستخدام معيار راوث-هورفيتز، ويحدد تحليل الحساسية المعايير الأكثر تأثيراً في مؤشر مقاومة الأنسولين. وتؤكد محاكاة رنج-كوتا من الرتبة الرابعة تحت نظامين متباينين من المعايير التنبؤية التحليلية: يعود النظام إلى حالة صحية عندما يكون عدد التكاثر الأساسي أقل من الواحد الصحيح، وينتج نحو التهاب مستمر يشبه خلل التوازن الجرثومي السريري عندما يتجاوز. وعلى الرغم من بساطة النموذج، فإنه يدعم الفرضية القائلة بأن استعادة التوازن الميكروبي، وليس علاج الالتهاب فقط، هو أمر محوري في الحل طويل الأمد لمقاومة الأنسولين.	المعادلات التفاضلية العادية مقاومة الأنسولين ميكروبيوتا الأمعاء تحليل الاستقرار خلل التوازن الجرثومي طريقة رنج-كوتا

Introduction

Insulin resistance is an issue in type 2 diabetes, obesity and metabolic syndrome. For a time people thought it was mainly

related to the liver, adipose tissue and skeletal muscle, which are directly involved in glucose disposal, and which sit at the center of classical accounts of type 2 diabetes risk [1].

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Locally, studies from Libya have examined the association between zinc and copper levels and insulin resistance in patients with type 2 diabetes [2], as well as the relationship between glycemic control (HbA1c) and atherogenic risk in diabetic patients [3]. Over the past fifteen years we have learned more. The gut is not a simple digestive tube; it's an ecosystem that affects our metabolism in many ways [4].

The gut has bad bacteria. Beneficial bacteria like *Bifidobacterium* and *Lactobacillus* help our body. They turn fiber into short-chain fatty acids, which make the gut wall stronger and stimulate the release of a hormone called GLP-1. This helps improve insulin sensitivity [5,6,7].

On the hand some bacteria like those in the *Enterobacteriaceae* family can cause problems. When they grow much they release harmful substances that can leak into the bloodstream and cause inflammation. This inflammation makes it harder for insulin to work properly leading to insulin resistance [4,8].

This is not information but its taken a while to be included in mathematical models of glucose-insulin dynamics. Our goal is to create a system of equations that shows how the good and bad bacteria compete how the bad bacteria cause inflammation and how this leads to insulin resistance. We want to see if standard tools can reproduce what doctors already know about the connection, between gut health and insulin resistance. The starting point for essentially all mathematical work on glucose-insulin dynamics is Bergman's minimal model from 1979 [9], which described the feedback loop between plasma glucose and pancreatic insulin secretion using a small system of ODEs. It was, and remains, a genuinely useful model, but it treats the pancreas and peripheral tissues as the only compartments that matter; the gut does not appear in it at all, and this omission largely persisted through later extensions of the minimal-model framework that added free fatty acids or exercise effects. Even the most recent work in this tradition, which reconstructs individualized obesity-diabetes trajectories from longitudinal data to ask whether hyperinsulinemia is a cause or a consequence of insulin resistance, still treats the pancreas and peripheral tissues as the whole system and leaves the gut out entirely [10].

The experimental side of the story developed mostly independently. Cani and colleagues showed that experimentally raising circulating LPS in mice was sufficient to induce insulin resistance and weight gain, coining the term metabolic endotoxemia [8]. Around the same period, other groups established that the gut microbiota affects host adiposity and energy harvest from the diet [11,12], and that innate immune sensing of the microbiota — for instance through Toll-like receptor 5 — has direct consequences for metabolic syndrome [13,14]. Later work identified specific taxa, most notably *Akkermansia muciniphila*, whose abundance correlates with better gut-barrier integrity and improved glucose handling [15,16,17]. Large metagenome-wide association studies in Chinese and European cohorts subsequently tied gut dysbiosis to type 2 diabetes at the population level [18,19,20], and a clinical trial of fecal microbiota transplantation showed that transferring a lean donor's microbiota can, at least transiently, improve insulin sensitivity in patients with metabolic syndrome [21,22]. Several reviews have since tried to pull this evidence together into a coherent gut-host-metabolism picture [4,5,6,7], and a recent survey of microbiota-carbohydrate metabolism and host-microbiota crosstalk brings that picture up to date [23].

What is largely missing is the modeling counterpart to this experimental literature. Population-level competition between bacterial species is normally handled with logistic or Lotka–Volterra-type equations [24,25], and epidemic-style compartment models are the natural language for describing inflammation and its downstream effects, but the two frameworks have rarely been combined into a single system that tracks bacterial competition, endotoxin translocation, and insulin-receptor desensitization together. That is the gap we try to fill with the four-equation model below — not because the biology is fully captured by four state variables, but because a minimal model is easier to analyze rigorously and still reproduces the main qualitative behavior.

Biological Assumptions of the Model

1. The model rests on four assumptions, each grounded in the literature summarized above [4,5]:

Assumption 1. Beneficial (B) and pathogenic (P) bacteria each grow logistically, limited by space and nutrients in the gut lumen, and compete with one another for the same resources.

Assumption 2. Pathogenic bacteria shed LPS at a rate proportional to their own density; this endotoxin crosses the gut barrier and accumulates as systemic inflammation, I [8,26].

Assumption 3. Beneficial bacteria reduce I through SCFA-mediated repair of the mucosal barrier, and the body clears circulating endotoxin through normal hepatic and renal pathways regardless of bacterial activity [5,6,7].

Assumption 4. The insulin resistance index R rises in proportion to inflammation I — reflecting inflammatory disruption of insulin receptor signaling — and falls at a constant rate representing cellular repair or clinical treatment [27,28].

Taken together, these assumptions give the following non-linear system:

$$\begin{cases} \frac{dB}{dt} = r_1 B \left(1 - \frac{B}{K_1}\right) - \alpha_1 B P \\ \frac{dP}{dt} = r_2 P \left(1 - \frac{P}{K_2}\right) - \alpha_2 P B \\ \frac{dI}{dt} = \beta P - \gamma B I - \delta I \\ \frac{dR}{dt} = \eta I - \mu R \end{cases} \quad (1)$$

with strictly positive initial conditions $B(0) > 0$, $P(0) > 0$, $I(0) > 0$, $R(0) > 0$. Table 1 lists the parameters together with the baseline values used in the simulations of Section 7; these values are chosen to be biologically plausible rather than fitted to a specific dataset.

Mathematical Analysis

Existence, Uniqueness, and Boundedness

Before analyzing the dynamics we should first check that the model behaves sensibly — that solutions exist, are unique, and never leave the biologically meaningful region where all four state variables are non-negative.

Theorem 1. If $\mathbf{X}(0) = [B(0), P(0), I(0), R(0)]^T \in \mathbb{R}_+^4$, then the solution $\mathbf{X}(t)$ of system (1) exists, is unique, and satisfies $\mathbf{X}(t) \in \mathbb{R}_+^4$ for all $t \geq 0$.

Proof. Write the right-hand side of (1) as $\mathbf{F}(\mathbf{X})$. Each component of $\mathbf{F}$ is a polynomial in B, P, I, R , so its partial derivatives are continuous everywhere; for example

$$\frac{\partial}{\partial B} \left[r_1 B \left(1 - \frac{B}{K_1}\right) - \alpha_1 B P \right] = r_1 - \frac{2r_1 B}{K_1} - \alpha_1 P \quad (2)$$

Continuity of all such partials on any bounded region implies that $\mathbf{F}$ is locally Lipschitz, and existence and uniqueness of solutions follow from the Picard–Lindelöf theorem

Table 1: Parameter definitions and baseline values.

Parameter	Biological Description	Baseline Value
r_1	Intrinsic growth rate of beneficial bacteria	0.80 day ⁻¹
r_2	Intrinsic growth rate of pathogenic bacteria	0.60 day ⁻¹
K_1	Carrying capacity of beneficial bacteria	100.0 mg/mL
K_2	Carrying capacity of pathogenic bacteria	50.0 mg/mL
α_1	Inhibition rate of beneficial bacteria by pathogenic bacteria	0.01 mL/(mg·day)
α_2	Inhibition rate of pathogenic bacteria by beneficial bacteria	0.02 mL/(mg·day)
β	LPS production/translocation rate by pathogenic bacteria	0.40 day ⁻¹
γ	Inflammation mitigation rate by beneficial bacteria (SCFAs)	0.005 mL/(mg·day)
δ	Natural systemic clearance rate of inflammation	0.10 day ⁻¹
η	Rate of inflammation-induced insulin resistance	0.30 day ⁻¹
μ	Rate of metabolic recovery / insulin sensitivity restoration	0.20 day ⁻¹

For positivity, the B -equation can be solved directly by separation of variables, giving the logistic-type closed form

$$B(t) = \frac{K_1 B_0 e^{r_1 t}}{K_1 + B_0 (e^{r_1 t} - 1)} \quad (3)$$

which is strictly positive whenever $B_0 = B(0) > 0$. The same argument applies to $P(t)$. The remaining two variables are handled by a standard invariance argument: on the boundary $I = 0$,

$$\left. \frac{dI}{dt} \right|_{I=0} = \beta P > 0 \quad (4)$$

so trajectories are pushed back into $I > 0$ rather than crossing into $I < 0$. Likewise, on the boundary $R = 0$,

$$\left. \frac{dR}{dt} \right|_{R=0} = \eta I > 0 \quad (5)$$

Since none of the four boundary hyperplanes can be crossed, $\mathbb{R}_+^4$ is positively invariant, which proves the theorem. $\square$

Equilibrium Points

Setting the right-hand side of (1) to zero gives four biologically distinct equilibria.

The trivial equilibrium,

$$E_d = (0, 0, 0, 0) \quad (6)$$

corresponds to total extinction of both bacterial populations and is not biologically realistic — a completely sterile gut is not a state the model needs to take seriously, but it is a legitimate fixed point of the dynamics.

More relevant is the disease-free, or “healthy,” equilibrium, in which the pathogenic population is absent:

$$E_0 = (K_1, 0, 0, 0) \quad (7)$$

At the opposite extreme, the severe-dysbiosis equilibrium describes a gut in which the beneficial population has been driven out entirely:

$$E_p = \left(0, K_2, \frac{\beta K_2}{\delta}, \frac{\eta \beta K_2}{\mu \delta} \right) \quad (8)$$

Finally, the two populations can coexist. Writing B^* and P^* for the coexistence densities, these satisfy the simultaneous conditions

$$r_1 \left(1 - \frac{B^*}{K_1} \right) = \alpha_1 P^*, \quad r_2 \left(1 - \frac{P^*}{K_2} \right) = \alpha_2 B^* \quad (9)$$

and once B^* , P^* are known, the corresponding chronic inflammation and steady-state insulin resistance follow directly:

$$I^* = \frac{\beta P^*}{\delta + \gamma B^*}, \quad R^* = \frac{\eta I^*}{\mu} = \frac{\eta \beta P^*}{\mu(\delta + \gamma B^*)} \quad (10)$$

This last equilibrium, $E^* = (B^*, P^*, I^*, R^*)$, is the one we will

refer to below as the coexistence or endemic metabolic state.

Local Stability Analysis

Local stability is determined, as usual, by the eigenvalues of the Jacobian matrix, which for system (1) is

$$J = \begin{pmatrix} r_1 - \frac{2r_1 B}{K_1} - \alpha_1 P & -\alpha_1 B & 0 & 0 \\ -\alpha_2 P & r_2 - \frac{2r_2 P}{K_2} - \alpha_2 B & 0 & 0 \\ -\gamma I & \beta & -\gamma B - \delta & 0 \\ 0 & 0 & \eta & -\mu \end{pmatrix} \quad (11)$$

Stability of the Healthy State E_0

Evaluating J at $E_0 = (K_1, 0, 0, 0)$ gives

$$J(E_0) = \begin{pmatrix} -r_1 & -\alpha_1 K_1 & 0 & 0 \\ 0 & r_2 - \alpha_2 K_1 & 0 & 0 \\ 0 & \beta & -\gamma K_1 - \delta & 0 \\ 0 & 0 & \eta & -\mu \end{pmatrix} \quad (12)$$

which is block-triangular, so its eigenvalues can be read straight off the diagonal:

$$\lambda_1 = -r_1, \quad \lambda_2 = r_2 - \alpha_2 K_1, \quad \lambda_3 = -\gamma K_1 - \delta, \quad \lambda_4 = -\mu \quad (13)$$

Since r_1 , γ , K_1 , δ , and μ are all strictly positive by assumption, λ_1 , λ_3 , and λ_4 are automatically negative no matter what the other parameters do. The stability of E_0 therefore comes down entirely to the sign of λ_2 . Requiring $\lambda_2 < 0$ gives

$$r_2 - \alpha_2 K_1 < 0 \Leftrightarrow \alpha_2 K_1 > r_2 \Leftrightarrow \frac{r_2}{\alpha_2 K_1} < 1 \quad (14)$$

It is natural, then, to define a basic reproduction number for the pathogenic strain,

$$R_0 = \frac{r_2}{\alpha_2 K_1} \quad (15)$$

in the same spirit as the R_0 used in epidemic models [29,30]. When $R_0 < 1$ — that is, when the competitive suppression exerted by the beneficial population, scaled by its own carrying capacity, outweighs the pathogen’s intrinsic growth rate — the disease-free equilibrium E_0 is locally asymptotically stable and the pathogenic population cannot establish itself. When $R_0 > 1$, E_0 becomes a saddle point and the system is pushed toward sustained dysbiosis and elevated insulin resistance.

Stability of the Coexistence State E^*

The coexistence equilibrium requires a separate argument, since the competitive sub-block of the Jacobian at E^* is not triangular. Restricting attention to the (B, P) sub-system, the relevant 2×2 block is

$$J_{sub} = \begin{pmatrix} -\frac{r_1 B^*}{K_1} & -\alpha_1 B^* \\ -\alpha_2 P^* & -\frac{r_2 P^*}{K_2} \end{pmatrix} \quad (16)$$

and the Routh–Hurwitz condition for this block reduces, after simplification, to

$$\frac{r_1}{K_1} \cdot \frac{r_2}{K_2} > \alpha_1 \alpha_2 \quad (17)$$

In plain terms, condition (17) says that each species must be limited more by its own crowding than by the other species pressing on it — intra-specific competition has to dominate inter-specific competition. When this holds, E^* is locally stable and the chronic-dysbiosis outcome is not a transient artifact of the simulation but a genuine, persistent steady state of the system [24]. It should be noted that this analysis is local; establishing global stability would require a Lyapunov-function argument, as has been done for a five-compartment tumour–immune–virus ODE system supported by Runge–Kutta–Fehlberg simulations [31].

Sensitivity Analysis

Knowing that R^* exists is less useful clinically than knowing which parameters move it. We use the standard normalized forward sensitivity index [29],

$$Y_p^{R^*} = \frac{\partial R^*}{\partial p} \times \frac{p}{R^*} \quad (18)$$

which gives the percentage change in R^* produced by a one-percent change in a parameter p .

For β , the rate at which pathogenic bacteria shed endotoxin, differentiating (10) gives

$$\frac{\partial R^*}{\partial \beta} = \frac{\eta P^*}{\mu(\delta + \gamma B^*)} \Rightarrow Y_\beta^{R^*} = \frac{\beta}{R^*} \cdot \frac{\eta P^*}{\mu(\delta + \gamma B^*)} = +1 \quad (19)$$

The index comes out to exactly +1: a 10% increase in LPS shedding translates, at equilibrium, into a 10% increase in steady-state insulin resistance — a direct, one-to-one

relationship, which is a useful sanity check on the model as much as a biological finding.

For γ , the SCFA-mediated inflammation-mitigation rate, the same calculation gives

$$\begin{aligned} \frac{\partial R^*}{\partial \gamma} &= -\frac{\eta \beta P^* B^*}{\mu(\delta + \gamma B^*)^2} \Rightarrow Y_\gamma^{R^*} = \frac{\gamma}{R^*} \cdot \left(-\frac{\eta \beta P^* B^*}{\mu(\delta + \gamma B^*)^2} \right) \\ &= -\frac{\gamma B^*}{\delta + \gamma B^*} < 0 \end{aligned} \quad (20)$$

The negative sign confirms the intuitive direction — strengthening the beneficial bacteria's inflammation-mitigating effect lowers equilibrium insulin resistance — and the magnitude in (20) shows that the effect saturates as γB^* grows large relative to δ , consistent with experimental observations that the benefit of a healthier microbiome has diminishing marginal returns once the gut barrier is already reasonably intact [15,16,17].

Numerical Solution via Fourth-Order Runge–Kutta (RK4)

System (1) is not analytically solvable in closed form once all four equations are coupled, so we turn to numerical integration. We use the classical fourth-order Runge–Kutta method [32], with a fixed step size $h = 0.05$ days, which is small enough that step-size sensitivity was not a concern for the trajectories reported below.

Writing the state vector and its governing function as

$$\mathbf{X} = \begin{pmatrix} B \\ P \\ I \\ R \end{pmatrix}, \mathbf{F}(\mathbf{X}) = \begin{pmatrix} r_1 B(1 - B/K_1) - \alpha_1 B P \\ r_2 P(1 - P/K_2) - \alpha_2 P B \\ \beta P - \gamma B I - \delta I \\ \eta I - \mu R \end{pmatrix} \quad (21)$$

the update from step n to step $n + 1$ is

$$\mathbf{X}_{n+1} = \mathbf{X}_n + \frac{h}{6} (\mathbf{k}_1 + 2\mathbf{k}_2 + 2\mathbf{k}_3 + \mathbf{k}_4) \quad (22)$$

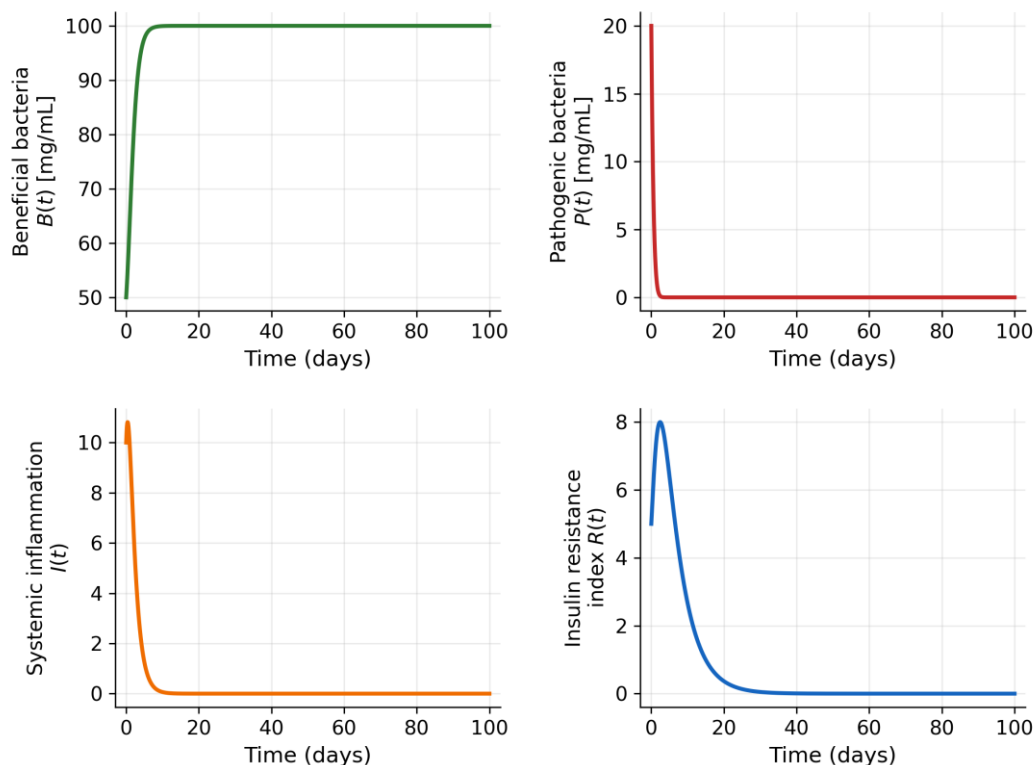


Figure 1: Scenario A — RK4 trajectories of $B(t)$, $P(t)$, $I(t)$, and $R(t)$ under conditions favoring the disease-free equilibrium ($R_0 = 0.15 < 1$).

with the four slope estimates given by

$$\mathbf{k}_1 = \mathbf{F}(\mathbf{X}_n) \quad (23)$$

$$\mathbf{k}_2 = \mathbf{F}\left(\mathbf{X}_n + \frac{h}{2}\mathbf{k}_1\right) \quad (24)$$

$$\mathbf{k}_3 = \mathbf{F}\left(\mathbf{X}_n + \frac{h}{2}\mathbf{k}_2\right) \quad (25)$$

$$\mathbf{k}_4 = \mathbf{F}(\mathbf{X}_n + h\mathbf{k}_3) \quad (26)$$

Simulation Results

We integrated (1) over a 100-day horizon under two parameter regimes chosen specifically to sit on either side of the $R_0 = 1$ threshold identified in Section 5.3.1.

Scenario A — recovery ($R_0 < 1$). Setting $\alpha_2 = 0.04$ (all other parameters at the baseline values in Table 1) and starting from $B = 50$, $P = 20$, $I = 10$, $R = 5$ gives $R_0 = 0.15$. As Figure 1 shows, the pathogenic population collapses almost immediately, inflammation follows it down within about two weeks, and the insulin resistance index — after a brief initial overshoot, since I has not yet caught up with the

falling pathogen load — relaxes back to a low baseline by around day 40.

Scenario B — chronic dysbiosis ($R_0 > 1$). Reducing the beneficial carrying capacity to $K_1 = 25$ and raising the pathogenic carrying capacity to $K_2 = 80$, meant to represent a sustained poor diet, gives $R_0 = 1.20$. The same starting point now produces the opposite trajectory (Figure 2): beneficial bacteria decline steadily, pathogenic bacteria expand to fill the space they vacate, and inflammation and insulin resistance both climb throughout the simulated period without showing signs of leveling off by day 100 — consistent with the kind of persistent, low-grade inflammatory state reported in human dysbiosis and type 2 diabetes cohorts [18,19].

Figure 3 puts the two $R(t)$ curves side by side, which makes the divergence between the two regimes easier to see than the individual panels above:

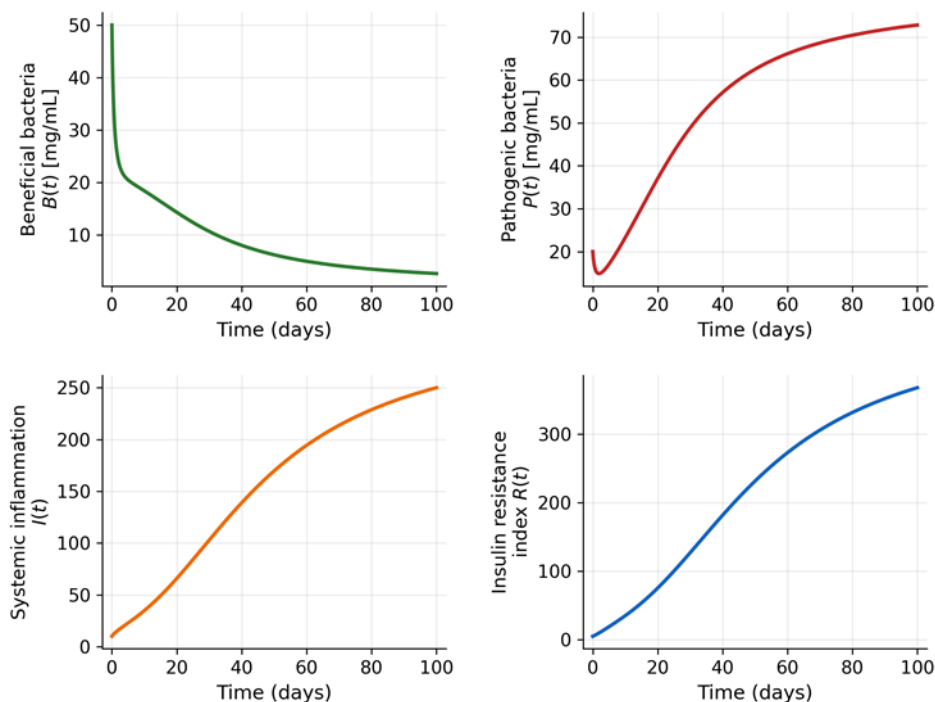


Figure 2: Scenario B — RK4 trajectories under a sustained poor-diet parameter regime favoring pathogen dominance ($R_0 = 1.20 > 1$).

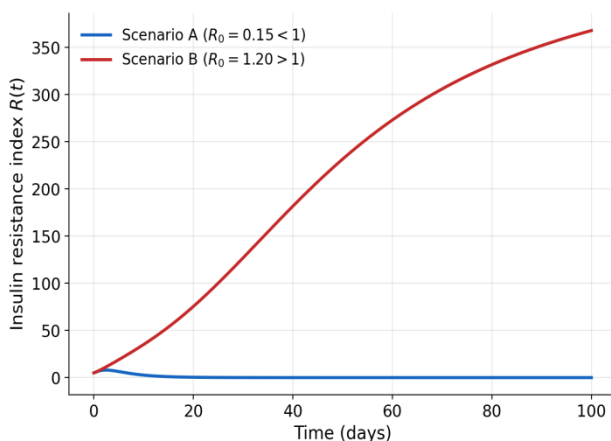


Figure 3: Insulin resistance index $R(t)$ compared across Scenario A ($R_0 < 1$) and Scenario B ($R_0 > 1$)

Figure 4 shows the same contrast from a different angle, plotting the trajectory in the (B, P) phase plane rather than against time. The two trajectories start at the same point but are pulled toward opposite corners of the plane — one toward the beneficial-dominant equilibrium, the other toward the pathogen-dominant one — which is a direct visualization of the bistability implied by the stability analysis in Section 5.3.

Biological and Medical Discussion

2. R_0 , K_1 , μ , and E^* The thing we learn from looking at how stable the system is that R_0 depends directly on K_1 , the carrying capacity of the beneficial bacterial population. It does not depend on any parameter that describes the host's inflammatory or insulin-signaling machinery. This has a clear meaning for medicine.

A drug like metformin mainly raises the somatic clearance rate μ . It treats the consequences of dysbiosis. It does not necessarily change the underlying microbial ecosystem. If the system stays near the coexistence equilibrium E^* treating the symptoms alone would probably not work well over time.

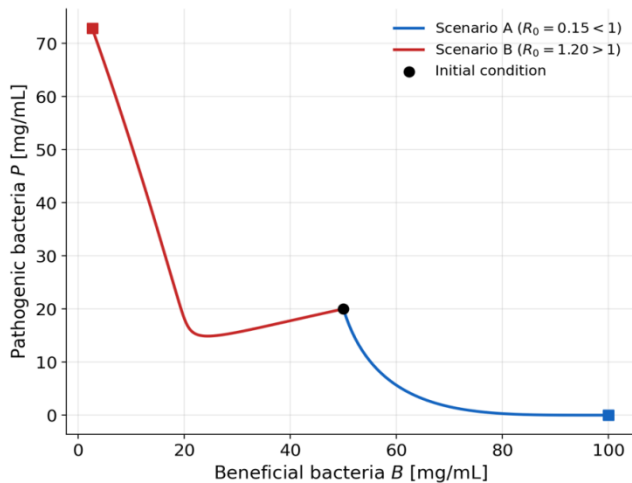


Figure 4: Phase portrait of B versus P, showing convergence toward the beneficial-dominant state in Scenario A and the pathogen-dominant state in Scenario B.

This is similar to what doctors have seen in their patients [18,19]. There is also evidence that metformin helps by changing the microbiome itself specifically by increasing *Akkermansia* populations [16,17,33]. This is of just working through the host-side clearance mechanisms. The beneficial bacterial population and the microbiome are important here.

This mechanism can be stated more precisely in terms of the reproduction number derived in Section 5.3.1: since $R_0 = r_2/(\alpha_2 K_1)$, any increase in K_1 or α_2 — for instance through prebiotic or probiotic supplementation that raises the carrying capacity of beneficial bacteria or strengthens their competitive suppression of pathogens — lowers R_0 directly, and once R_0 falls below 1 the disease-free equilibrium E_0 becomes locally stable, so the system moves toward genuine healthy resolution rather than merely masking elevated inflammation [6].

This distinction is also useful for comparing treatment strategies. Clearance-based therapies such as metformin act primarily on μ and thus accelerate resolution of an inflammatory episode without necessarily altering the underlying bacterial balance, whereas microbiome-based therapies such as fecal microbiota transplantation (FMT) act on B , P , K_1 and α_2 directly and can, in principle, move the system out of the region where the coexistence equilibrium E^* is stable altogether. Clinical trials of FMT in patients with metabolic syndrome report improvements in insulin sensitivity consistent with this mechanism [21,22], and locally, work on metformin's effect on Vitamin B12 status in Libyan type 2 diabetes patients underscores that even clearance-based therapy carries systemic trade-offs that microbiome-targeted approaches may avoid [34].

The model's more optimistic implication is that interventions targeting K_1 and α_2 directly — prebiotics, probiotics, or increased dietary fiber — shift the sign of λ_2 in equation (13) and can, in principle, destabilize the diseased state and let the system return to E_0 on its own [6]. This lines up with experimental work showing that enriching specific commensal genera such as *Akkermansia muciniphila* improves both barrier integrity and glucose handling [15,16,17]. We would stress, though, that the model says nothing about how quickly or reliably such an intervention would move K_1 or α_2 in practice — that is an empirical question the model cannot answer on its own.

Conclusion

We built a four-equation ODE model coupling competitive bacterial dynamics, endotoxin-driven inflammation, and insulin resistance, and showed that its solutions stay biologically meaningful (positive and bounded) for all time. The model should be understood as a preliminary, exploratory framework rather than a validated clinical tool; its value lies in organizing hypotheses for future testing, not in guiding treatment decisions directly. The four equilibria of the system, and in particular the reproduction number $R_0 = r_2/(\alpha_2 K_1)$ governing stability of the disease-free state, give a compact mathematical description of the transition between a healthy and a dysbiotic gut. RK4 simulations under two contrasting parameter regimes reproduced the qualitative behavior the stability analysis predicts, and the sensitivity analysis pointed to LPS shedding and SCFA-mediated inflammation control as the two parameters with the most leverage over long-run insulin resistance. None of this replaces a fitted, patient-specific model, but it does provide a reasonably transparent starting point for thinking about why microbiome-targeted interventions might succeed where purely symptomatic treatment plateaus.

Looking ahead, incorporating time-varying parameters, an explicit inflammation-signaling delay, and data-driven parameter estimation (Section 10) would further strengthen the model's clinical relevance.

Future Work

Several extensions of the present model warrant future investigation, particularly with respect to the following limitations identified during review.

1. Time-varying parameters. The baseline model treats r_1 , r_2 , K_1 , K_2 , α_1 and α_2 as constants, whereas dietary intake and psychological stress fluctuate on a daily basis and are known to modulate gut microbial composition. Stress-axis markers such as cortisol, which have been measured in Libyan patients with metabolic syndrome [35], could supply such exogenous inputs. Extending the model so that these parameters vary with time, or depend explicitly on diet and stress as exogenous inputs, would improve its physiological realism.

2. Delay differential equations (DDEs). The current model assumes that inflammation acts on insulin signaling instantaneously. In practice, there is a physiological delay τ between the onset of endotoxin-driven inflammation and the resulting inhibition of insulin receptor signaling. Reformulating the R-equation as $dR/dt = \eta I(t-\tau) - \mu R$, with an explicit delay τ , would allow the model to capture this lag and its effect on the transient dynamics of insulin resistance.

3. Parameter estimation and Bayesian inference. The parameter values in Table 1 were chosen to be biologically plausible rather than statistically fitted. Applying parameter estimation techniques, including Bayesian inference, to longitudinal data from type 2 diabetes patients — for example those enrolled in fecal microbiota transplantation studies [21,22] — would allow the model's parameters to be calibrated against real clinical trajectories and would provide a direct test of its predictive validity.

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