Supplementary Material

MECHANISTIC MODEL CONSTRUCTION
The model of Crohn’s disease (CD) incorporates current understanding of the pathophysiology of the disease. The description is mechanistic, but biological processes are represented at adequate levels of abstraction based on the purpose and availability of supporting data. The model is organized in three main modules. The first, the tissue module, represents mechanisms responsible for homeostasis and damage in epithelial tissue and the mucosal layer. The second, the inflammation module, represents recruitment, maturation, activation, and death of immune cells that control inflammation. Both the tissue and the inflammation module are represented in the form of a system of ordinary differential equations that describe changes over time of cell populations and tissue state. The third, the steady-state cytokine module, is a set of equations to estimate the quasi-steady-state concentrations of cytokines in various compartments. The model components are listed in Tables S1.1 and S1.2. The state variables and equations are presented in Tables S2.1 and S2.2.

Compartments
Immune processes occur in separate compartments representing segments of the gastrointestinal (GI) tract (ileum, ascending colon, transverse colon, descending-sigmoid colon, and rectum) and circulation (Fig. S1a). The gut compartments differ in their dimensions and certain physiological aspects, such as the ability of the mucus to protect the epithelial layer and the presence of antimicrobial agents [1]. Each compartment is divided into subcompartments representing the lamina propria and other subepithelial tissues (here referred to as “lamina”), lymph nodes (“lymph”), and the epithelium (“tissue”). The major compartments are connected through the circulation (“blood”) compartment. Intracompartment connectivity was simplified to represent flow of cells and cytokines. Local inflammation mediators originating in the lamina or tissue compartments migrate to the lymph compartment where they promote lymphocyte differentiation and proliferation. Lymphocytes enter the blood compartment (bloodstream) and from there can migrate into any of the lamina compartments at rates controlled by the concentration of specific cytokines. Drugs are added to the blood compartment from which they may reach other compartments.

Tissue Damage, Repair, and Remodeling
The epithelial layer or tissue is represented by an epithelium species that can transition between four states: healthy (EPh), active (EPa), damaged (EPd), and remodeled (EPr) (Fig. S1b). Activation is caused by luminal antigen (Ag) reaching the epithelial layer. Antigen is eliminated through continuous clearance (either by mucus or antimicrobial peptides) and the action of innate immune cells [2] (represented by neutrophil activity in the model). Damaged tissue allows Ag to reach the gut tissue more readily. Active tissue eventually becomes damaged (characterized by a propensity for the damage parameter). Damage in both healthy and active tissue is promoted by inflammation. This process has been included in the model in the form of IFN-γ- and TNF-α-dependent damage reactions [3]. Both active and damaged tissue can revert to a healthy state, a process that is promoted by IL-22. Remodeling, however, is irreversible [4] (Table S2.2, equation serial numbers 6–8). Each of the four states of the epithelial layer is represented in the model as a percentage of epithelium that exists in that state at a given time.

Mucus Dynamics
The state of the mucus layer is determined by the balance between mucus generation by specialized cells and clearance through natural processes. Disease-induced damage to the epithelium is used as a proxy to estimate the level of impairment in mucus production. The
layer is restored as new mucus-producing cells differentiate from stem cells upon healing [5] (Table S2.2, equation 2).

**Immune Processes**
The immune system module represents pro- and anti-inflammatory activity (Fig. S2a). The module includes a set of cell types interacting via cytokine/chemokine production (Tables S1.1 and S1.2). Cells migrate between compartments depending on the cytokine milieu. The model starts in homeostasis. The disease state in the model results from breakdown of immune tolerance as Agl, reaching the epithelial layer, activates an immune response that initiates a vicious feedback cycle of inflammatory activity and tissue damage. This initial infection event shifts the model from homeostasis to inflammation. The model does not make any assumptions on the underlying cause of the triggering event.

Homeostasis is maintained through a tolerogenic response. When inactive dendritic cells (DCi) sample Agl, they convert to tolerant dendritic cells (DCt) and drive tolerogenic response (Fig. S2b). DCt secrete the anti-inflammatory cytokines TGF-β and IL-10. DCt migrate to the mesenteric lymph nodes and promote differentiation of naive T cells to regulatory T cells (Fig. S2c). The latter produce more TGF-β and IL-10 [6, 7], driving a positive feedback loop of anti-inflammatory response [8]. TGF-β levels have a dual function, as TGF-β also participates in tissue remodeling [9]. Breakdown of tolerance occurs due to a reduction in mucus layer thickness or an increase in epithelial layer permeability (see section “Tissue Damage, Repair, and Remodeling”). This results in the movement of Ag across the epithelial barrier. Increased antigen load on the epithelium activates epithelial cells. Activated epithelium (EPa) promotes maturation of DCi to stimulatory DC (DCs) and drives the inflammatory response [10]. DCs secrete the proinflammatory cytokines TNF, IL-6, IL-12, and IL-23 [11, 12]. DCs migrate to mesenteric lymph nodes and promote differentiation of naive T cells to T helper 1 (Th1) and Th17 (Fig. S2b and S2c). Increased inflammatory activity causes further tissue and mucosal damage. In active disease, chemokine-driven leukocyte and lymphocyte migration sustains inflammation regardless of antigenic activity. EPa secretes chemokines that facilitate migration of α4β7+ T cells, monocytes, and neutrophils from the circulation into the lamina propria [13]. Newly migrated leukocytes further increase inflammation by secreting proinflammatory cytokines. TNF increases mucosal vascular addressin cell adhesion molecule 1 (MAdCAM1) expression on endothelial cells, which increases T-cell migration into the lamina propria [14, 15], further strengthening the positive feedback loop of inflammation.

The model tracks cell population size (representing aggregates of multiple cellular subtypes) and, for some, activity level. These numbers should be considered rough estimates, reflecting the ratio between cell types and between the active disease and baseline that a histology study may show. Quantitatively, cell counts are meaningful only in the context of the strength of the interactions between cell types.

Cytokines and chemokines exist in the lamina, lymph, and blood compartments (Fig. S3). Cytokines produced in the lamina can be transported to the lymph compartment in the same GI segment and subsequently to the blood compartment. From the blood compartment, cytokines and cells can enter any of the gut compartments based on the cardiac output in the specific gut compartment [16, 17]. Cytokine production is controlled by the number of appropriate active cells (Table S1.2). Transport represents various processes, including diffusion of free molecules as well as migration of the producing cell types into different compartments. Because cytokine production, transport, and degradation occur at a fast time scale compared with immune cell maturation and proliferation, cytokine concentrations can be approximated by their quasi-equilibrium levels. Under this approximation, the concentration of a generic cytokine (cyt) in a compartment C with a given population of
producing cells and incoming flow from compartment S can be calculated analytically (Table S2.4).

Pharmacology
Action of pharmacological agents is simulated by dose-dependent modulation of model parameters according to the drug’s mode of action. Anti-TNF agents have the ultimate effect of promoting clearance of TNF from the circulation and tissue. Integrin-targeting drugs inhibit integrin-dependent adhesion and transmigration of lymphocytes and innate immune cells from the blood compartment into tissue [18-20]. Antibodies against IL-12/IL-23 promote clearance of these interleukins. The kinetics of drug-induced clearance are a function of the local drug concentration. Wherever applicable, published pharmacokinetic (PK) data were used to develop a dose-dependent concentration profile of different therapeutic agents in the model [21].

Parameter Estimation
Values for the model’s parameters are listed in Tables S3.1–3.3. Parameter names correspond to those in the model equations (Tables S2.2–2.4). In-vitro cell stimulation/cytokine production data are used to constrain the production rates of cytokines from each cell type. Half-lives for most cytokines in the model were obtained from the literature. Serum and tissue (colon) levels of cytokines in healthy and CD patients were used to constrain the remaining parameters, such as transport rates in the cytokine module. Missing biochemical parameters were estimated based on data for cytokines belonging to the same family. For example, parameters for IL-22 were estimated based on IL-10 data.

Parameters were estimated in one of two ways:
1. Literature-based: Because of the mechanistic nature of the model, most of the parameters are closely related to specific biological or biophysical processes for which published values or value ranges are often available (sources listed in Tables S3.1–3.3). Parameters in this category include dose–response curves for responses to cytokines, cytokine release rates, cell turnover, inhibition constants, PK data for drugs, and gut physiology (diameter and volume of gut segments).
2. Optimization: Parameters that could not be derived directly from the literature were estimated using optimization approaches against published in-vitro, ex-vivo, or in-vivo observations. In many instances, this was done on a module-by-module basis or with smaller portions of the model (at a specific cell type level). Furthermore, serum and tissue (colon) levels of cytokines and cell numbers in healthy and CD patients were used to constrain the parameters that control intercompartment processes, such as the cell migration rates or cytokine flow rates in the cytokine module.

The model contains parameters that can be linked to phenotypes in CD patients, and we denote these as patient parameters (Table S3.4). These patient parameters can take multiple values and are allowed to vary from patient to patient. For instance, the parameter that determines the antigen clearance rate could be considered patient-specific, as the antigen clearance rate depends on Paneth cell function and associated genetic variants that result in different phenotypes [22]. Boundaries for patient parameters were determined so as to ensure model dynamics and outputs were in the physiological range.

As with any model, there is a risk the model’s structure or parameters do not adequately reflect relevant physiology. To mitigate this risk, the model represents biology at a relatively high level of abstraction. Rate laws and empirical expressions correspond to coarse-grained versions of the processes in scope (e.g. integrin-dependent lymphocyte transmigration into the lamina is modeled as a first-order “reaction” catalyzed by the presence of integrin receptors). This approach limits the number of assumptions, making the model structure more robust at the expense of missing details.
SIMULATIONS STRATEGY
Simulations are performed in three steps: equilibration, disease progression, and treatment. For the equilibration phase, state variables (cell populations, cytokines, etc.) are set to arbitrary but reasonable values, and the model is run until equilibrium is achieved with all model components remaining at a constant value. Disease onset occurs once the system is in equilibrium and consists of a rapid change in parameters that simulate breakdown of immune tolerance leading to activation of an immune response by luminal antigens reaching the epithelial layer. This “trigger” event can occur at an arbitrary time set by the user but can also be configured to happen stochastically. The “duration of disease” in the model is measured from the moment this trigger occurs. Following the triggering event, the model is left to evolve during the disease-progression phase. The treatment phase starts when a pharmacological intervention is introduced. A simulation may include one, multiple, or no treatment stages as patients change therapies. During a treatment phase, parameters and processes representing the PKs and mode of action of the drug(s) are “turned” on.

VIRTUAL PATIENT LIBRARY
The core virtual patient library was created by simulating all possible combinations of values for the parameters in Table S3.5. This process resulted in a multidimensional grid with 34,992 unique value combinations (virtual patients).

SPECIES AND INTERACTIONS IN THE MODEL
Table S1.1 Cell types and their corresponding modulating cytokines

| Cell type            | Modulating factors                                         |
|----------------------|------------------------------------------------------------|
| Activated epithelial cells | Antigen at the epithelial layer                          |
| Damaged epithelial cells       | TNF-α, IFN-γ                                              |
| Tolerogenic DC          | Antigen in the lumen                                       |
| Stimulatory DC         | Antigen at the epithelial layer                           |
| Th1                   | IL-12, IFN-γ, IL-8 (migration)                            |
| Th17                  | IL-6, IL-23, TGF-β, IL-8 (migration)                      |
| Tregs                 | IL-10, TGF-β, IL-6 (inhibitory), IL-8 (migration)         |
| Neutrophils           | IL-17 (proliferation), IL-8 (migration)                   |
| Monocytes             | IL-8 (migration)                                          |

DC dendritic cells, Th T-helper, Treg regulatory T cell.
Table S1.2 Cytokines and their sources in the model

| Cytokine | Source in lamina/tissue | Source in lymph |
|---------|-------------------------|----------------|
| IFN-γ  | Stimulatory DC, Th1, macrophage | Stimulatory DC, Th1 |
| IL-6   | Stimulatory DC, macrophage | Stimulatory DC |
| IL-8   | Active epithelial cell | |
| IL-10  | Tolerogenic DC, Treg, macrophage | Tolerogenic DC, Treg, neutrophil |
| IL-12  | Stimulatory DC, macrophage | Stimulatory DC, neutrophil |
| IL-22  | Th17, macrophage, neutrophil | Th17, neutrophil |
| IL-23  | Stimulatory DC, macrophage | Stimulatory DC, neutrophil |
| TGF-β | Tolerogenic DC, Treg, macrophage | Tolerogenic DC, Treg, neutrophil |
| TNF-α | Stimulatory DC, Th1, macrophage | Stimulatory DC, Th1, neutrophil |

DC dendritic cells, Th T-helper, Treg regulatory T cell.

MODEL VARIABLES AND EQUATIONS

Table S2.1 Model state variables

| State variable | Description |
|----------------|-------------|
| ag_e           | Antigen proximal to the epithelial layer |
| muc            | Mucus |
| dci_t          | DC inactive in lamina propria |
| dct_t          | DC tolerogenic in lamina propria |
| dcs_t          | DC stimulatory in lamina propria |
| ep_h           | Percentage of healthy epithelial layer |
| ep_a           | Percentage of the epithelial layer activated by antigen |
| ep_d           | Percentage of damaged epithelial layer |
| th1_t          | Th1 cells in lamina propria |
| th17_t         | Th17 cells in lamina propria |
| treg_t         | Tregs in lamina propria |
| nu_t           | Neutrophils in lamina propria |
| mac_t          | Macrophages in lamina propria |
| dct_l          | Tolerogenic DC in lymph node |
| dcs_l          | Stimulatory DC in lymph node |
| th1_l          | Th1 cells in lymph node |
| th17_l         | Th17 cells in lymph node |
| S.No | Species | Ordinary differential equation | Description |
|------|---------|--------------------------------|-------------|
| 1    | Antigen proximal to the epithelial layer | \[ \frac{d[ag_{l}]}{dt} = \left( \frac{k_{ag_{l}\_age} + v_{max\_age\_epd} \cdot [ep_{a}] (1 + \frac{n_{muc}/k_{inh\_muc\_age}}{1 + \frac{m}{d_{agg}}})}{1 + \frac{n_{muc}/k_{inh\_muc\_age}}{1 + \frac{m}{d_{agg}}}} \right) \cdot a_{agg_{l}} \] | Conversion of Ag_{l} to Ag_{e} occurs at a constitutive rate and is enhanced by a damaged epithelial layer. The mucus layer inhibits this process. Neutrophils promote antigen clearance, whereas TNF inhibits this process. |
| 2    | Mucus | \[ \frac{d[muc]}{dt} = s_{muc\_eph} \cdot [ep_{a}] - d_{muc} \cdot [muc] \] | Mucus secretion is proportional to the fraction of healthy epithelial layer (assuming goblet cells that secrete mucus are proportional to healthy epithelial cells). |
| 3    | DC inactive in lamina propria | \[ \frac{d[dc_{i}]}{dt} = \left( s_{dc_{i}} - k_{dc_{i}\_dct} \cdot [dc_{i}] \cdot [ag_{e}] \right) \cdot \frac{k_{dc_{i}\_dcs} \cdot [dc_{i}] \cdot [ag_{e}]}{1 + [il10]/k_{inh\_il10\_dcs} - d_{dc} \cdot [dc_{i}]} \] | Ag_{e} promotes conversion of inactive DCs to tolerogenic DCs, whereas Ag_{l} promotes conversion of inactive DCs to stimulatory DCs. |
| 4    | DC tolerogenic in lamina propria | \[ \frac{d[dc_{t}]}{dt} = k_{dc_{i}\_dct} \cdot [dc_{i}] \cdot [ag_{e}] - (d_{dc} + k_{dc\_t\_l}) \cdot [dc_{t}] \] | Dendritic cells sample antigen in the lumen and become tolerogenic. Subsequently, tolerogenic DCs migrate into the lymph node. |
| 5    | DC stimulatory in lamina propria | \[ \frac{d[dc_{s}]}{dt} = k_{dc_{i}\_dcs} \cdot [dc_{i}] \cdot [ag_{e}] - (d_{dc} + k_{dc\_s\_l}) \cdot [dc_{s}] \] | Ag_{e} promotes conversion of inactive DCs to stimulatory DCs. Subsequently, stimulatory DCs migrate into lymph node. |
6 Percentage of healthy epithelial layer
\[
\frac{d[ep_h]}{dt} = \left( k_{epa, eph} + m_{epa, eph} \cdot [iI22] \cdot [ep_h] \right) + \left( k_{epd, eph} + m_{epd, eph} \cdot [iI22] \cdot [ep_d] \right) - k_{epa, eph} \cdot [ep_h] \cdot [ag_s] - k_{epd, eph} \cdot [ep_d] \cdot [nf] + \left( \frac{vmax_{epd, tfn} \cdot [nf]}{km_{epd, tfn}} + \frac{vmax_{epd, ifng} \cdot [ifng]}{km_{epd, ifng}} \right)
\]
Healthy EPs get activated by exposure to Ags. TNF and IFNγ mediate damage of healthy EPs. IL22 enhances the healing from active and damaged states.

7 Percentage of the epithelial layer activated by antigen
\[
\frac{d[ep_a]}{dt} = \left( k_{epa, eph} \cdot [ep_a] \cdot [ag_s] \right) - \left( k_{epa, eph} + m_{epa, eph} \cdot [iI22] \cdot [ep_a] \right) - k_{epa, eph} \cdot [ep_a] \cdot [ep_d] + \left( \frac{vmax_{epa, tfn} \cdot [nf]}{km_{epa, tfn}} + \frac{vmax_{epa, ifng} \cdot [ifng]}{km_{epa, ifng}} \right)
\]
Active EPs are formed when healthy EPs are exposed to age. Subsequently, TNF and IFNγ mediate damage of active EPs. IL22 promotes healing.

8 Percentage of damaged epithelial layer
\[
\frac{d[ep_d]}{dt} = \left( k_{epa, eph} \cdot [ep_d] \cdot [ag_s] \right) - \left( k_{epa, eph} + m_{epa, eph} \cdot [iI22] \cdot [ep_a] \right) - k_{epa, eph} \cdot [ep_d] \cdot [ep_a] + \left( \frac{vmax_{epd, tfn} \cdot [nf]}{km_{epd, tfn}} + \frac{vmax_{epd, ifng} \cdot [ifng]}{km_{epd, ifng}} \right)
\]
TNF and IFNγ mediate damage of healthy and active EPs. IL22 promotes healing. A fraction of damaged EPs undergo irreversible remodeling.

9 Th1 cells in lamina propria
\[
\frac{d[th1]}{dt} = \left( k_{th1, b \cdot t} + [th1] + (1 + km_{il8, th1} \cdot [il8]) \cdot (1 + km_{tnf, madcam} \cdot [nf]) \cdot \left( \frac{d_{th1} \cdot [th1]}{1 + [nf] / km_{th1, tfn}} \right) \right)
\]
Th1 migration from circulation into the tissue is mediated by MAdCAM and IL8.

10 Th17 cells in lamina propria
\[
\frac{d[th17]}{dt} = \left( k_{th17, b \cdot t} + [th17] + (1 + km_{il8, th17} \cdot [il8]) \cdot (1 + km_{tnf, madcam} \cdot [nf]) \cdot \left( \frac{d_{th17} \cdot [th17]}{1 + [nf] / km_{th17, tfn}} \right) \right)
\]
Th17 migration from circulation into the tissue is mediated by MAdCAM and IL8.

11 Tregs in lamina propria
\[
\frac{d[reg]}{dt} = \left( k_{reg, b \cdot t} + [reg] + (1 + km_{il8, reg} \cdot [il8]) \cdot (1 + km_{tnf, madcam} \cdot [nf]) \cdot \left( \frac{d_{reg} \cdot [reg]}{1 + [nf] / km_{reg, tfn}} \right) \right)
\]
Treg migration from circulation into the tissue is mediated by MAdCAM and IL8.

12 Neutrophils in lamina propria
\[
\frac{d[nu]}{dt} = (k_{nu, b \cdot t} \cdot km_{il8, nu} \cdot cafrac \cdot [il8]) \cdot [nu] - d_{nu} \cdot [nu] + \left( km_{il8, nu} \cdot cafrac \cdot [il8] \cdot [nu] \right)
\]
IL8 mediated cell migration.

13 Macrophages in lamina propria
\[
\frac{d[mac]}{dt} = (k_{mac, b \cdot t} \cdot km_{il8, mo} \cdot cafrac \cdot [il8]) \cdot [mac] - d_{mac} \cdot [mac] + \left( km_{il8, mo} \cdot cafrac \cdot [il8] \cdot [mac] \right)
\]
IL8 mediated cell migration.

14 Tolerogenic DC in lymph node
\[
\frac{d[dc_t]}{dt} = k_{dc_t, l \cdot t} \cdot [dc_t] - \left( d_{dc} + d_{dcreg} + [reg] \right) \cdot [dc_t]
\]
Migration of tolerogenic DCS into the lymph node.

15 Stimulatory DC in lymph node
\[
\frac{d[dc_s]}{dt} = \left( k_{dc_s, l \cdot t} + [dc_s] \right) - \left( d_{dc} + d_{dcreg} + [reg] + d_{dc11} \cdot [th1] + d_{dc17} \cdot [th17] \right) \cdot [dc_s]
\]
Migration of stimulatory DCS into the lymph node.

16 Th1 cells in lymph node
\[
\frac{d[th1]}{dt} = \left( s_{th1, il12, ifng} \cdot [il12] \cdot [ifng] + s_{th1} \cdot [th1] \right) \cdot \left( km_{th1, il12} + [th1] \right) \cdot \left( 1 + [reg] / km_{reg, dc} \right) - k_{th1, l \cdot b} \cdot [th1] - d_{th1} \cdot [th1] \right)
\]
Th1 differentiation in lymph is dependent on IL12 and IFNγ.
Algebraic equation for the inflammation module

\[
\begin{align*}
\frac{d[th17]}{dt} &= \left( s_{th17\_tgfb\_il6\_il123} \cdot [tgfb] \cdot [il6] \cdot [il23] + s_{th17} \cdot [th17] \
&- k_{th17\_b} \cdot [th17] \right) \\
&\quad \cdot \frac{1 + [reg]/k_{inh\_treg\_dcx}}{1 + [tnf]/k_{ths\_th1}} \\
\frac{d[reg]}{dt} &= \left( s_{reg\_tgfb\_il10} \cdot [tgfb] \cdot [il10] + s_{reg} \cdot [reg] \
&- k_{reg\_b} \cdot [reg] \right) \\
&\quad \cdot \frac{1 + [il6]/k_{inh\_il6\_treg}}{1 + [fnf]/k_{inh\_fnf\_th1}} \\
\frac{d[th1]}{dt} &= \left( k_{th1\_b} \cdot [th1] - k_{th1\_b\_t} \right) \\
&\quad \cdot \frac{1 + [km\_il8\_th1\_b]}{1 + [fnf]/k_{inh\_fnf\_th1}} \\
\frac{d[th17]}{dt} &= \left( k_{th17\_b} \cdot [th17] - k_{th17\_b\_t} \right) \\
&\quad \cdot \frac{1 + [km\_il8\_th17\_b]}{1 + [fnf]/k_{inh\_fnf\_th1}} \\
\frac{d[reg\_b]}{dt} &= \left( k_{reg\_b\_t} \cdot [reg\_b] \right) \\
&\quad \cdot \frac{1 + [km\_il8\_reg\_b]}{1 + [fnf]/k_{inh\_fnf\_th1}} \\
\frac{d[nu]}{dt} &= \left( s_{nu} \cdot \left( 1 + k_{nu\_nu} \cdot [th17] \right) \
&- (k_{nu\_b\_t} \cdot \left( km_{il8\_nu} \cdot [il8] \right) + d_{nu}) \
&+ [nu_b] \right) \\
\frac{d[mo]}{dt} &= s_{mo} - (k_{mo\_b\_t} \cdot \left( km_{il8\_mo} \cdot [il8] \right) + d_{mo}) \cdot [mo_b]
\end{align*}
\]

\[Th17 \text{ differentiation in lymph is dependent on TGFb, IL6, and IL23.}\]

\[Treg \text{ differentiation in lymph is dependent on TGFb and IL10.}\]

\[Th1 \text{ recruitment from circulation into the tissue is mediated by chemokine IL8 and MAdCAM.}\]

\[Th17 \text{ recruitment from circulation into the tissue is mediated by chemokine IL8 and MAdCAM.}\]

\[Treg \text{ recruitment from circulation into the tissue is mediated by chemokine IL8 and MAdCAM.}\]

\[Recruitment \text{ of neutrophils into the tissue is promoted by chemokine IL8. Neutrophil maturation is enhanced by IL17 (Th17 dependent process).}\]

\[Recruitment \text{ of monocytes into the tissue is promoted by chemokine IL8}\]

Ag, antigen proximal to the epithelial layer, Ag luminal antigen, DC dendritic cells, EP epithelium, IFN interferon, IL interleukin, MAdCAM, mucosal addressin cell adhesion molecule, TGF transforming growth factor, Th T-helper, TNF tumor necrosis factor, Treg regulatory T cell.

Table S2.3 Algebraic equation for the inflammation module

| S.No | Term                                | Algebraic equation                                                                 |
|------|-------------------------------------|------------------------------------------------------------------------------------|
| 1    | Percentage of remodeled epithelial layer | \([ep_r] = 1 - (\{ep_h\} + \{ep_a\} + \{ep_d\})\)                              |
Table S2.4 Algebraic equations for the cytokine module

| S.No | Term                                      | Algebraic equation                                                                 |
|------|-------------------------------------------|-------------------------------------------------------------------------------------|
| 1    | Cytokine production rate                  | \(\text{cyt\_prod\_rate} = (k_{\text{source\_arr}}) \times (\text{cell\_conc\_arr})\) |
| 2    | Cytokine source rate at steady state      | \(c_{\text{ss\_source}} = \frac{\text{cyt\_prod\_rate}}{1 + \frac{c_{\text{inh}}}{k_{\text{inh}}} + k_{\text{in}} \times c_{\text{ss\_in}}}\) |
| 3    | Steady-state cytokine concentration       | \(c_{ss} = \frac{c_{\text{ss\_source}}}{k_{\text{deg}} + k_{\text{out}}}\) |

MODEL PARAMETERS

Table S3.1 Gut and blood compartment parameters

| Parameter                | Value       | Units | Source |
|--------------------------|-------------|-------|--------|
| vol\_blood               | 5.0         | L     |        |
| dia\_small\_intestine    | 2.5         | cm    |        |
| dia\_colon               | 7.5         | cm    |        |
| len\_ileum               | 180         | cm    |        |
| vol\_ileum               | 1.413       | L     |        |
| len\_acolon              | 20          | cm    |        |
| vol\_acolon              | 0.471       | L     |        |
| len\_tcolon              | 50          | cm    |        |
| vol\_tcolon              | 1.1775      | L     |        |
| len\_dcolon              | 65          | cm    |        |
| vol\_dcolon              | 1.5307      | L     |        |
| len\_rectum              | 15          | cm    |        |
| vol\_rectum              | 0.3532      | L     |        |
| cardiac\_output\_gut     | 0.25        | Dimensionless | [16] |

Table S3.2 Cytokine module parameters

| Parameter                  | Value                     | Units   | Source |
|----------------------------|---------------------------|---------|--------|
| ifng\_k\_inh              | 1.0313853573862533        | ng/L    |        |
| ifng\_k\_source\_arr      | [1.75e-03, 3.5e-04, 1.0e-04] | ng/week |        |
| ifng\_t\_half             | 30                        | min     | [24]   |
| ifng\_n\_source           | 3                         | Dimensionless |        |
| ifng\_flow\_rates         | [0.0009931, 0.00097664, 0.00973698] | 1/week |        |
| il6\_k\_inh               | 0.6685874179561395        | ng/L    |        |
| il6\_k\_source\_arr       | [0.12906913, 0.00357998]  | ng/week |        |
| Parameter          | Value                                                                 |
|-------------------|----------------------------------------------------------------------|
| il6_t_half        | 3 min                                                                 |
| il6_n_source      | 2 Dimensionless                                                       |
| il6_flow_rates    | [0.00154909, 0.01698216, 0.00430632] 1/week                           |
| il8_k_inh         | 6.6 ng/L                                                              |
| il8_k_source_arr  | [0.6] ng/week                                                         |
| il8_t_half        | 10 hr                                                                 |
| il8_n_source      | 1 Dimensionless                                                       |
| il8_flow_rates    | [0, 0, 0] 1/week                                                      |
| il10_k_inh        | 1.0 ng/L                                                              |
| il10_k_source_arr | [1.39896362e–05, 1.56754042e–05, 1.99890509e–05, 2.99423387e–07] ng/week |
| il10_t_half       | 30 min (Same as IL-22)                                               |
| il10_n_source     | 4 Dimensionless                                                       |
| il10_flow_rates   | [0.00993427, 0.00010262, 0.04957607] 1/week                           |
| il12_k_inh        | 1.0678125133786 ng/L                                                  |
| il12_k_source_arr | [3.33208484e–06, 2.44324073e–07, 9.62727091e–09] ng/week             |
| il12_t_half       | 7.5 hr                                                                |
| il12_n_source     | 3 Dimensionless                                                       |
| il12_flow_rates   | [0.00101388, 0.00102004, 0.00095256] 1/week                           |
| il22_k_inh        | 1.8326437484516203 ng/L                                               |
| il22_k_source_arr | [3.10905015e–05, 1.90934442e–03, 1.68003911e–09] ng/week             |
| il22_t_half       | 30 min (Same as IL-12)                                               |
| il22_n_source     | 3 Dimensionless                                                       |
| il22_flow_rates   | [0.20435706, 0.02846599, 0.3279132] 1/week                            |
| il23_k_inh        | 1.06036863982098 ng/L                                                 |
| il23_k_source_arr | [6.97490498e–07, 1.16123737e–06, 3.82458148e–08] ng/week             |
| il23_t_half       | 7.5 hr                                                                |
| il23_n_source     | 3 Dimensionless                                                       |
| il23_flow_rates   | [0.00010143, 0.0010428, 0.00234504] 1/week                            |
| tgfb_k_inh        | 1.843224675198807 ng/L                                                |
| tgfb_k_source_arr | [2.12959416e–01, 3.83023049e–02, 1.68608337e–02, 3.23903119e–05] ng/week |
| Parameter            | Value                                      | Units  |
|----------------------|--------------------------------------------|--------|
| tgfβ_t_half          | 2 min                                      | [29]   |
| tgfβ_n_source        | 4 Dimensionless                            |        |
| tgfβ_flow_rates      | [0.00154909, 0.01698216, 0.00430632]        | 1/week |
| tnf_k_inh            | 1.9578842412364774 ng/L                   |        |
| tnf_k_source_arr     | [1.04683751e–03, 2.60804692e–03, 2.82188543e–03, 2.50339778e–07] ng/week |        |
| tnf_t_half           | 18.2 min                                   | [30]   |
| tnf_n_source         | 4 Dimensionless                            |        |
| tnf_flow_rates       | [0.00137425, 0.00241456, 0.20005329]       | 1/week |

Table S3.3 Inflammation module parameters

| Parameter            | Value                                      | Units  |
|----------------------|--------------------------------------------|--------|
| d_ag                 | 0.01                                       | 1/week |
| km_age_epd           | 4 Dimensionless                            |        |
| vmax_age_epd         | 2.5                                        | 1/week |
| d_age_sm             | 2.5                                        | 1/week |
| d_age/lg             | 0.25                                       | 1/week |
| d_age_nu             | 0.2                                        | L/cells/week |
| kinh_tnf_age         | 1e–5                                       | L/ng   |
| kinh_muc_age         | 0.5                                        | L/ng   |
| kinh_il10_dcs        | 10                                         | L/ng   |
| s_dci                | 1.0                                        | cells/L/week |
| k_dci_dct            | 5e–3                                       | 1/week |
| k_dci_dcs            | 5e–2                                       | 1/week |
| k_dc_t_l             | 0.15                                       | 1/week |
| d_dc                 | 5e–2                                       | 1/week |
| d_dc_th1             | 1e–3                                       | 1/week |
| d_dc_th17            | 5e–2                                       | 1/week |
| d_dc_treg            | 0.1                                        | 1/week |
| s_muc_eph            | 0.2                                        | ng/L/week |
| d_muc                | 0.2                                        | 1/week |
| k_epa_eph            | 2e–3                                       | 1/week |
| m_epa_eph_il22       | 2.5e2                                      | L/ng/week |
| k_eph_epa            | 5e–3                                       | L/ng/week |
| k_eph_epd            | 5e–3                                       | 1/week |
| k_epa_epd            | 5e–3                                       | 1/week |
| Variable                      | Value          | Unit          |
|-------------------------------|----------------|---------------|
| k_epd_eph                     | 1e-3           | 1/week        |
| m_epd_eph_il22               | 5e-1           | L/ng/week     |
| k_epd_epr                     | 1e-4           | 1/week        |
| km_epd_tnf                    | 1.5e-4         | 1/week        |
| km_epd_ifng                   | 1e-4           | 1/week        |
| vmax_epd_tnf                  | 1.0            | L/ng/week     |
| vmax_epd_ifng                 | 1.0            | L/ng/week     |
| d_mac                         | 0.4386         | 1/week        |
| s_mo                          | 806.4          | cells/L/week  |
| k_mo_b_t                      | 1.7842e-2      | 1/week        |
| km_il8_mo                     | 1.8            | L/ng          |
| d_mo                          | 1.6128         | 1/week        |
| s_nu                          | 4019.4         | cells/L/week  |
| km_th17_nu                    | 4.45e-9        | L/cells       |
| k_nu_b_t                      | 1.1226e-2      | 1/week        |
| km_il8_nu                     | 0.095          | L/ng          |
| d_nu                          | 0.693          | 1/week        |
| k_th1_b_t                     | 0.2            | 1/week        |
| km_il8_th1                    | 0.1            | L/ng          |
| d_th1                         | 0.2695         | 1/week        |
| kinh_tnf_th1                  | 4.3e-3         | ng/L          |
| k_th17_b_t                    | 0.2            | 1/week        |
| km_il8_th17                   | 0.1            | L/ng          |
| d_th17                        | 0.2695         | 1/week        |
| kinh_tnf_th17                 | 4.3e-3         | ng/L          |
| k_treg_b_t                    | 0.2            | 1/week        |
| km_il8_treg                   | 0.1            | L/ng          |
| d_treg                        | 0.095          | 1/week        |
| kinh_tnf_treg                 | 4.3            | ng/L          |
| km_tnf_madcam                 | 2.17           | L/ng          |
| s_th1_il12_ifng               | 1.75e13        | cells*L/(ng*ng)/week |
| kinh_treg_dcs                 | 1.0            | cells/L       |
| k_th1_l_b                     | 0.9            | 1/week        |
| s_th17_lgfb_il6_il23          | 4.324e13       | cells*L/(ng*ng*ng)/week |
| k_th17_l_b                    | 0.9            | 1/week        |
| s_treg_lgfb_il10              | 2.85e8         | cells*L/(ng*ng)/week |
| kinh_il6_treg                 | 1.1297e3       | ng/L          |
Table S3.4 Patient parameters set for sensitivity analysis

A subset of the parameters from Table S3.3 have been identified as patient-specific parameters. The following were the ranges used for the patient parameters in the sensitivity analysis (Fig. 4a).

| Parameter       | Range                      |
|-----------------|----------------------------|
| km_age_epd      | 4                          |
| vmax_age_epd    | [0.1, 0.5, 1.0]             |
| d_age_sm        | 2.5                        |
| d_age lg        | 0.25                       |
| kinh_tnf_age    | 1.5e-5                     |
| kinh_muc_age    | [0.01, 0.1, 5.0]           |
| k_epa_eph      | [0.006, 0.04, 0.1]         |
| k_eph_epa      | [0.003, 0.01, 0.05]        |
| k_eph_epd      | 1e-2                       |
| k_epa_epd      | [0.004, 0.009, 0.04]       |
| k_epd_eph      | [0.001, 0.01, 0.1]         |
| km_epd_tnf     | 1.5e-4                     |
| km_epd_ifng    | 1.5e-4                     |
| vmax_epd_tnf   | [0.05, 0.1, 1.0, 2.0]      |
| vmax_epd_ifng  | [0.05, 0.1, 1.0, 2.0]      |

Additionally, k_agl_age (rate of infection) and ag0 (antigen load) are part of the disease trigger.

Table S3.5 Physiological mechanisms and their respective parameters for sensitivity analysis

| Name                          | Effect in the model | Description                                         |
|-------------------------------|---------------------|-----------------------------------------------------|
| Propensity to damage          | E\text{ACTIVE} \rightarrow E\text{DAMAGED} | Overall rate at which active ECs become damaged in the presence of inflammation |
| Immune signaling activation   | E\text{HEALTHY} \rightarrow E\text{ACTIVE} | Rate of AG-dependent EC activation                  |
| Immune signaling deactivation | $E_{CACTIVE} \rightarrow E_{CHEALTHY}$ | Together with EC activation control the sensitivity to AG |
|---|---|---|
| Epithelium healing | $E_{CDAMAGED} \rightarrow E_{CHEALTHY}$ | IL-22-independent rate at which damaged tissue regenerates |
| Sensitivity to inflammation-driven damage | $E_{CACTIVE, HEALTHY} \rightarrow E_{CDAMAGED}$ \ ($TNF-\alpha, IFN-\gamma$) | Effect of IFN-\(\gamma\)- and TNF-\(\alpha\)-dependent mechanisms on the rate of EC damage (both for active and healthy ECs) |
| Damaged tissue leakiness | $AG_{LUMEN} \rightarrow AG_{TISSUE}$ | Rate at which luminal AG becomes detectable by immune-sensing cells |
| Mucus regeneration | $\rightarrow$ mucus | Rate at which mucus is continuously generated by healthy epithelium |
| Barrier function | $AG_{LUMEN}$ (inh)$\rightarrow$ $AG_{TISSUE}$ | Inhibition of passage of luminal AG toward tissue |

**AG**, antigen, **EC**, epithelial cell.
**Fig. S1** Compartment structure and tissue module in the Crohn’s disease model. **a** Overview of the compartments in the model. Five gut compartments, namely ileum, three colon segments and rectum, all having the same overall structure, are connected by a single blood compartment. **b** Tissue-damage module describing the four possible states of the epithelium: EPh, EPa, EPd, and EPr, and the transitions between the four states. Exposure to AgE results in activation of the epithelium and transition of EPh to EPa. Both EPh and EPa become damaged in the presence of TNF-α and IFN-γ. Remodeling of epithelium (transition from EPd to EPr) is a slow, irreversible process. Regeneration of the epithelium (transition from both EPa and EPd to EPh) helps restore the mucus layer as EPh produces mucus. IL-22 enhances the epithelial regeneration rate and promotes healing. AgE antigen proximal to the epithelial layer, EPa active epithelium, EPd damaged epithelium, EPh healthy epithelium, EPr remodeled epithelium.
**Fig. S2** Crohn’s disease model diagram. **a** Model of disease progression and inflammation-driven tissue damage in Crohn's disease. Some cell types are represented using square boxes, proinflammatory cytokines in green, anti-inflammatory cytokines in red, and other cell types, like antigens, mucus, etc., represented using circles. Solid black arrows represent the conversion of one cell type to another. Synthesis of a cell type is represented by a solid blue arrow. Dashed black arrows represent induction of a process by a cell type, whereas inhibition is represented by dashed red arrows. Double stick arrows represent flow or migration of a cell type between different compartments. **b** DC module: Inactive DC sample AgL to induce a tolerogenic response via DCt. Exposure to AgE shifts DC from a tolerogenic to a proinflammatory polarization (DCs). DCt secrete anti-inflammatory cytokines, whereas DCs secrete proinflammatory cytokines. **C** T-cell differentiation module: T0 differentiate into Th1, Th17, or Tregs depending on the local cytokine milieu. Differentiated T cells produce cytokines, few of which induce T cells to differentiate in an autocrine manner. TNF prevents apoptosis of T cells. AgE antigen proximal to the epithelial layer, AgL luminal antigen, DC dendritic cells, DCi inactive dendritic cells, DCs stimulatory dendritic cells, DCt tolerogenic dendritic cells, EPa active epithelium, EPd damaged epithelium, EPh healthy epithelium, EPr remodeled epithelium, Mac macrophages, MAdCAM mucosal vascular addressin cell adhesion molecule, Mo monocytes, Muc mucus layer, Nu Neutrophils, T0 naïve T cells, Th T-helper cell, Treg regulatory T cell.
Fig. S3 Cytokine module. Cytokines are produced by specific sources in the lamina and the lymph node in each gut compartment. Cytokine from the lymph can move into the bloodstream to reach the lamina. Each cytokine type in a specific subcompartment (lamina, lymph, or blood) has two sources: production by specific cell types and inflow from an upstream subcompartment. Degradation and outflow to a downstream subcompartment represent the two sinks of cytokine concentration in a subcompartment. $\text{cyt}^B$ cytokine concentration in blood circulation, $\text{cyt}^L$ cytokine concentration in lymph, $\text{cyt}^T$ cytokine concentration in tissue, GI gastrointestinal, $\text{src}^L$ source of a cytokine in lymph, $\text{src}^T$ source of a cytokine in tissue.
Fig. S4 Example simulation output, a typical output of the Crohn’s disease model prediction for a patient in the validation set. Patient data are shown in blue. Model simulation output is shown in red. a Objective outcomes panel. Comparison of the tissue damage status between data and model prediction as measured by different components of SES-CD score such as affected surface area, ulcerated area, and ulcer type. The y-axis shows the SES-CD score severity category for each component, and the x-axis represents time in weeks since treatment initiation. SES-CD score categories by components: affected surface (category 0, none; category 1, <50% involved); ulcerated surface (category 0, none; category 1, <10% ulcerated); size of ulcers (category 0, none; category 1, aphthous ulcers). b Biomarker output panel. Comparison of fecal calprotectin and serum CRP levels between data and model prediction. The y-axis shows the concentration of the biomarker and the x-axis represents time in weeks since treatment initiation. Error bars represent intraindividual measurement variability for the biomarker.
**Fig. S5** Virtual patient library generation and expansion. **a** Virtual patient library, generated by sampling patient parameters within a specific range and simulating the mechanistic model using those parameters. The library was preclassified based on the PRS, to facilitate patient matching for digital-twin creation. **b** Virtual patient library was expanded to capture the diversity in patient phenotypes observed in VERSIFY dataset. All patients in the training dataset, created from the VERSIFY study population, who did not have a good match in the virtual patient library were calibrated manually, and the digital twins thus created were added to the virtual patient library.

**a**

**MECHANISTIC DISEASE MODEL**

- Inflammation
- Tissue damage
- Intestinal function

**VIRTUAL PATIENT LIBRARY**

- X-PRS
- Y-PRS

**b**

Patients from VERSIFY training dataset who do not have a digital twin match from virtual patient matching (step 3 of the platform)

Calibrate the patient parameters manually to create a digital twin

Add the digital twin to the virtual patient library
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