Modelling Immune Dynamics in Coeliac Disease

A multiscale kinetic approach

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Joint work with
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D. Burini, D.A. Knopoff & L. Serrano, *Multiscale kinetic model for the immune reaction in Coeliac Disease*, Mathematics, 2026.

What is coeliac disease?

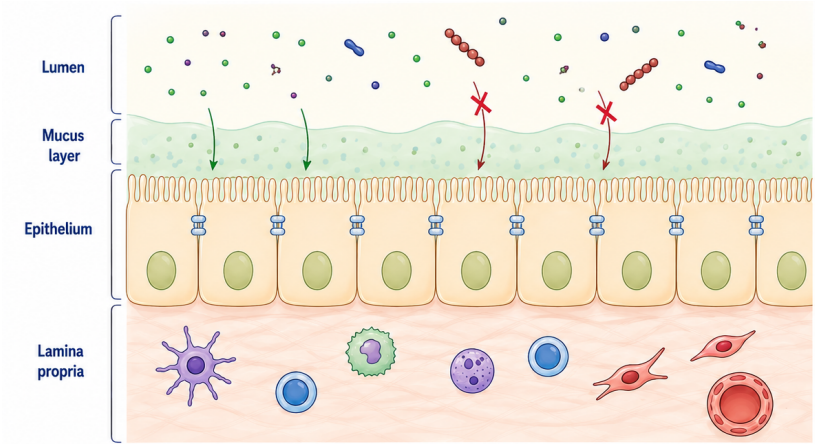
Coeliac disease is a chronic immune-mediated disorder triggered by gluten in genetically susceptible individuals.

The pathological response develops mainly in the small intestine, where immune activation progressively alters the epithelial barrier and damages the intestinal tissue.

Modelling point of view:

coeliac disease is a cascade of interacting mechanisms linking gluten transport, barrier permeability, immune activation, and inflammatory feedback.

Healthy intestinal barrier



Selective barrier

Nutrients and small molecules can cross through physiological transport, whereas large immunogenic peptides and other antigens are prevented from reaching the lamina propria.

Barrier protection

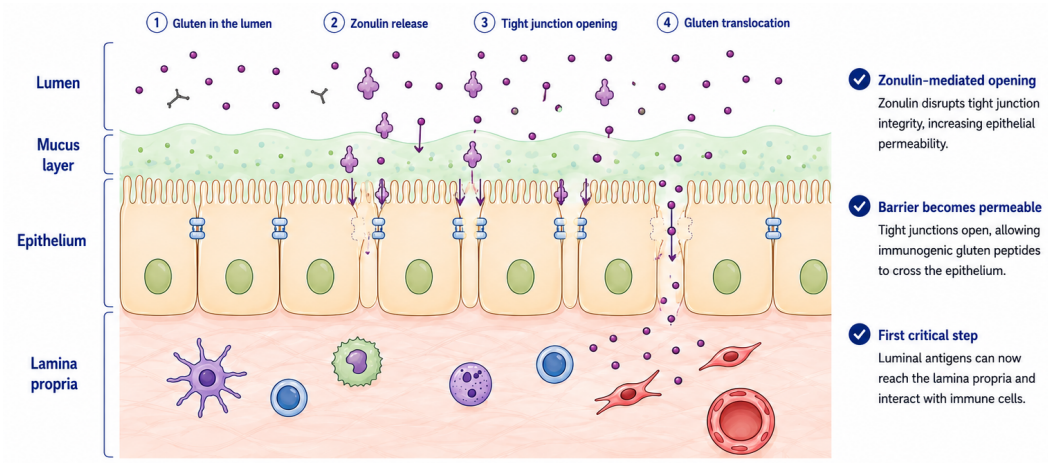
Tight junctions and mucus layer provide a physical and functional barrier.

Immune surveillance

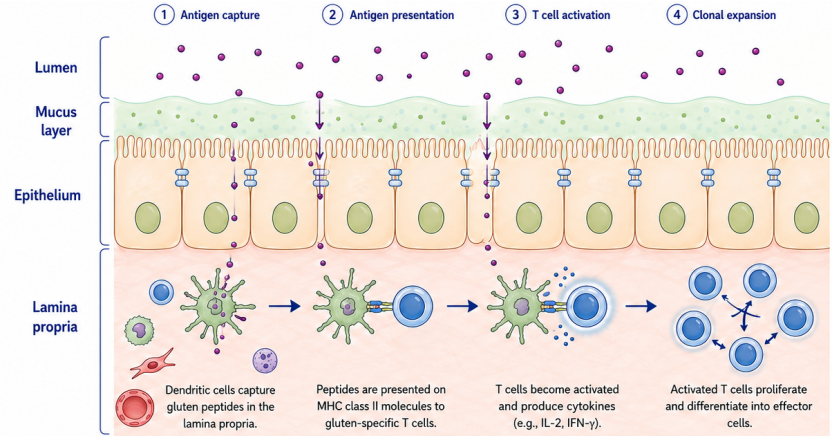
Immune cells remain in a state of surveillance without triggering inflammation.

Epithelial cell
Nutrients
Small molecules
Commensal bacteria
Immunogenic peptides / antigens
Tight junction
Dendritic cell
T lymphocyte
Macrophage
Mast cell
Fibroblast
Blood vessel

Gluten exposure and barrier opening



Immune activation in the lamina propria

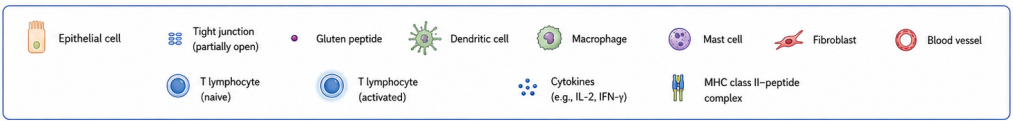


Antigen capture
Dendritic cells capture and process gluten peptides that have crossed the epithelium.

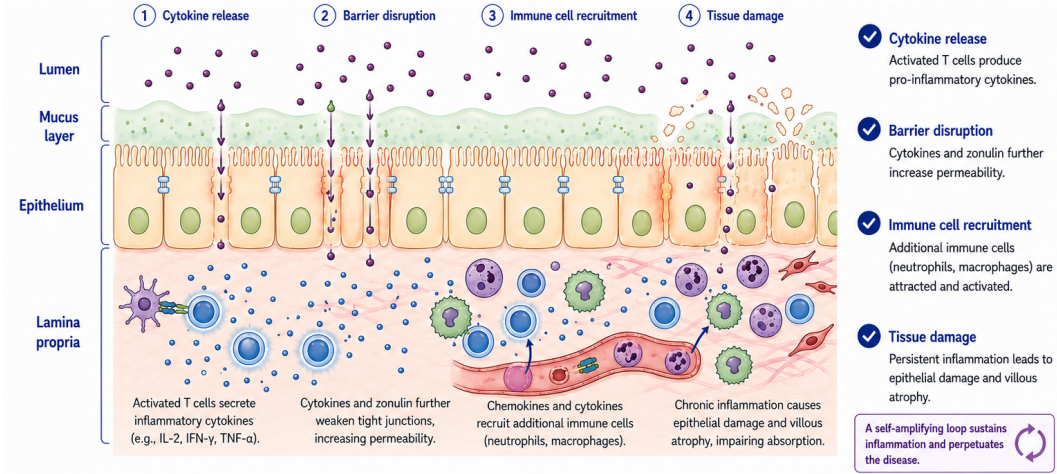
Antigen presentation
Peptides are presented to gluten-specific T cells

T cell activation
Gluten-specific T cells are activated and secrete cytokines.

Clonal expansion
Activated T cells proliferate and amplify the adaptive immune response.



Inflammatory amplification and tissue damage



The intestinal microenvironment in coeliac disease

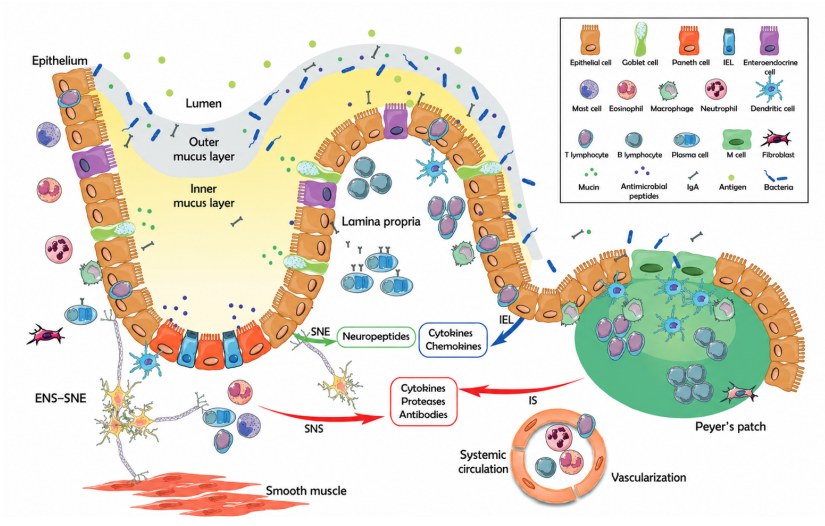
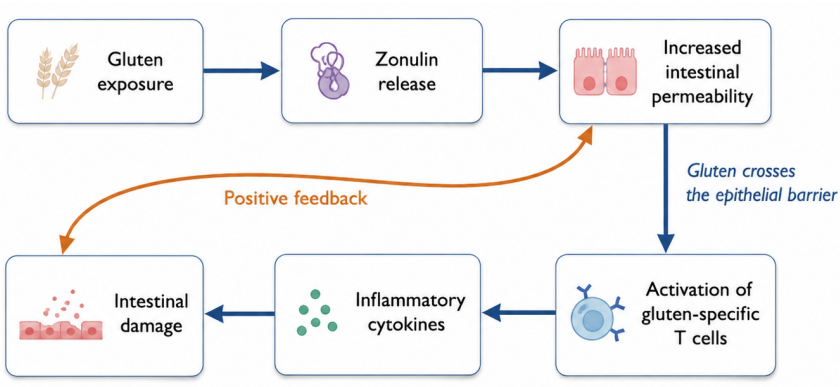


Illustration adapted from S. Martínez Velasco, *Permeabilidad intestinal en pacientes celíacos*, PhD Thesis, 2025.

The biological cascade

A positive feedback loop that sustain and amplify the inflammatory response



Intestinal permeability is not only a consequence of inflammation, but also one of the mechanisms driving disease progression

From biological mechanisms to a mathematical model:

the Kinetic Theory for Active Particles (KTAP)

N. Bellomo, D. Burini, G. Dosi, L. Gibelli, D.A. Knopoff, N. Outada, P. Terna, M.E. Virgillito, *What Is Life? A Perspective of the Mathematical Kinetic Theory of Active Particles*, M3AS 31 (2021), 1821–1866.

N. Bellomo, D. Burini, J. Liao, *New Trends in Kinetic Theory toward the Complexity of Living Systems*, M3AS 36 (2026), 341–397.

Coeliac disease involves interacting biological populations whose behaviour depends on **internal states**, **external stimuli**, and **adaptive responses**.

KTAP provides a natural framework to describe these populations through **microscopic activity variables** and **nonlinear interaction operators**.

This allows us to connect **gluten translocation**, **T-cell activation**, and **cytokine production** within the same kinetic description.

The key advantage is the coupling of microscopic immune dynamics with a macroscopic tissue property: intestinal permeability.

Functional subsystems

Subsystem	Biological population
f_1	Gluten in the intestinal lumen
f_2	Gluten in the lamina propria
f_3	Zonulin
f_4	Activated T cells
f_5	Inflammatory cytokines

Intestinal permeability is introduced as a macroscopic state variable.

Kinetic representation

The microscopic state of the system is described by a family of **distribution functions**

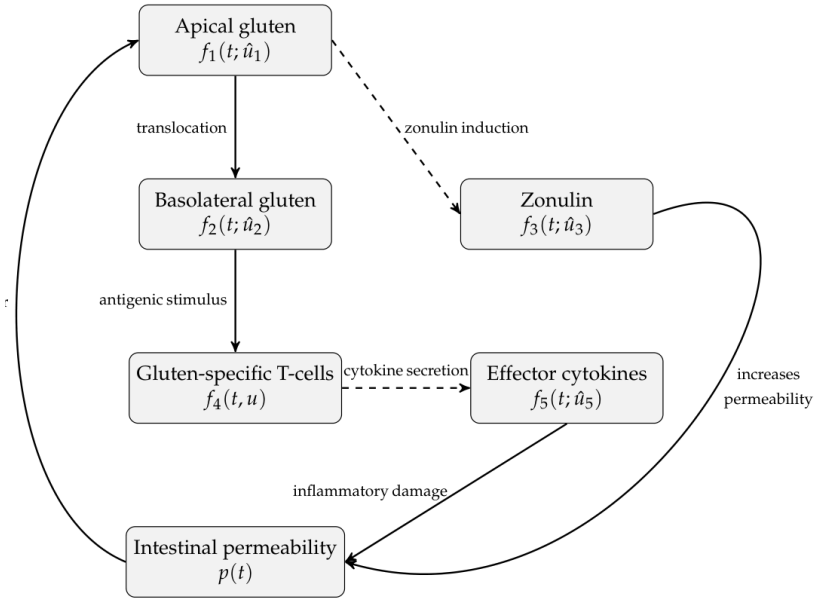
$$f_i = f_i(t, u) : [0, T] \times D_u \longrightarrow \mathbb{R}_+, \qquad i = 1, \ldots, 5$$

i identifies the functional subsystem;

$u \in D_u$ is the **microscopic activity variable**, which encodes the internal state of the active particles and provides a mathematical representation of biological heterogeneity.

The **density** of each functional subsystem is obtained as

$$n_i(t) = \int_{D_u} f_i(t, u)\, du.$$


Apical gluten
$f_1(t;\hat{u}_1)$
translocation
zonulin induction
Basolateral gluten
$f_2(t;\hat{u}_2)$
Zonulin
$f_3(t;\hat{u}_3)$
antigenic stimulus
Gluten-specific T-cells
$f_4(t,u)$
cytokine secretion
Effector cytokines
$f_5(t;\hat{u}_5)$
increases
permeability
inflammatory damage
Intestinal permeability
$p(t)$

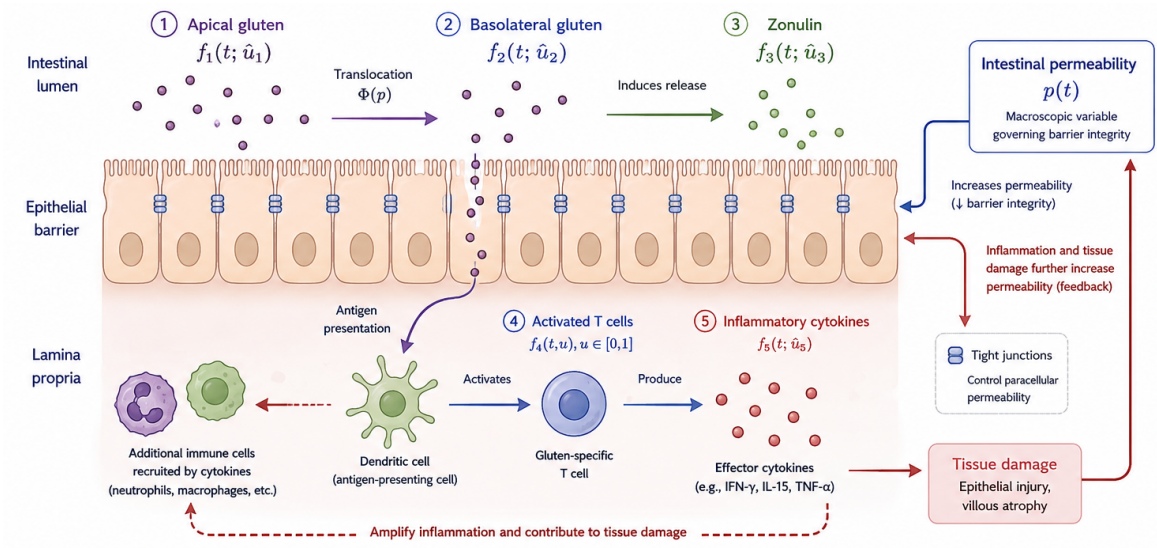
State representation of the functional subsystems

FS	Active particles	Microscopic activity	State variable
f_1	Gluten peptides	Fixed state $\hat{u}_1$	$f_1(t;\hat{u}_1)$
f_2	Gluten peptides	Fixed state $\hat{u}_2$	$f_2(t;\hat{u}_2)$
f_3	Zonulin molecules	Fixed state $\hat{u}_3$	$f_3(t;\hat{u}_3)$
f_4	Activated T cells	Activation level $u \in [0,1]$	$f_4(t,u)$
f_5	Cytokines	Fixed state $\hat{u}_5$	$f_5(t;\hat{u}_5)$

$$n_4(t) = \int_0^1 f_4(t,u)\,du$$

Only gluten-specific T cells retain a distributed microscopic activity.

Multiscale interactions encoded in the KTAP model



Evolution equations

$$\boxed{\begin{aligned} &\partial_t f_i = J_i[\mathbf{f}, p], \qquad i = 1, \dots, 5, \\ &\frac{dp}{dt} = H(\mathbf{f}, p). \end{aligned}}$$

- J_i describes the evolution of the i-th functional subsystem through biological interactions.
- H governs the evolution of the macroscopic permeability.
- The complete model consists of five kinetic equations coupled with one ordinary differential equation.

The operator J_1: apical gluten

$$\partial_t f_1(t;\hat{u}_1) = \underbrace{I(t)}_{\text{gluten intake}} - \underbrace{d_1\, f_1(t;\hat{u}_1)}_{\text{clearance}} - \underbrace{\Phi(p(t))\, f_1(t;\hat{u}_1)}_{\text{gluten translocation}}$$

Term	Biological interpretation
$I(t)$	Dietary gluten intake
d_1	Natural degradation and clearance
$\Phi(p)$	Permeability-dependent gluten translocation

The operator J_2: basolateral gluten

$$\partial_t f_2(t;\hat{u}_2) = \underbrace{\Phi(p(t))\, f_1(t;\hat{u}_1)}_{\text{gluten translocation}} - \underbrace{d_2\, f_2(t;\hat{u}_2)}_{\text{clearance}}$$

Term	Biological interpretation
$\Phi(p)$	Transfer from the intestinal lumen
d_2	Natural degradation and clearance

The operator J_3: zonulin

$$\partial_t f_3(t;\hat{u}_3) = \underbrace{c\, f_1(t;\hat{u}_1)}_{\text{zonulin production}} - \underbrace{d_3\, f_3(t;\hat{u}_3)}_{\text{decay}}$$

Term	Biological interpretation
c	Gluten-induced zonulin production rate
d_3	Natural degradation rate

The operator J_4: gluten-specific T cells

$$\partial_t f_4(t,u) = \underbrace{f_2(t;\hat{u}_2)\int_0^1 \mu_{42}(u^*)\,\mathcal{B}_{42}(u^* \to u \,|\, u^*)\, f_4(t,u^*)\,du^*}_{\text{gain}}$$
$$- \underbrace{\mu_{42}(u)\, f_4(t,u)\, f_2(t;\hat{u}_2)}_{\text{loss}} - \underbrace{d_4\, f_4(t,u)}_{\text{relaxation / death}} + \underbrace{\kappa(u)\, f_2(t;\hat{u}_2)\, f_4(t,u)}_{\text{clonal expansion}}.$$

Mechanism	Biological role
Gain–loss interaction	Gluten-induced redistribution across activation states
Proliferation and death	Regulation of the total T-cell population

$$\int_0^1 (G_4 - L_4)\,du = 0$$

Interactions redistribute T cells across activation states without changing their total number.

KTAP ingredients for T-cell activation

Interaction rate

$$\mu_{42}(u) = \hat{\mu}_{42}(1 + u)$$

$\hat{\mu}_{42}$ controls the baseline sensitivity of T cells to gluten.

Larger values correspond to stronger antigenic responsiveness.

Clonal expansion

$$\kappa(u) = \hat{\kappa}(1 + u)$$

$\kappa(u)$ is the proliferation rate of T cells with activation level u.

$\hat{\kappa}$ controls the baseline proliferation rate.

More highly activated T cells proliferate more strongly.

Transition probability density

$$\mathcal{B}_{42}(u^* \to u \,|\, u^*) \geq 0, \qquad \int_0^1 \mathcal{B}_{42}(u^* \to u \,|\, u^*)\, du = 1$$

The transition kernel determines the post-interaction activation state. It is biased toward larger values of u, so antigenic interaction tends to move T cells toward higher activation levels.

The operator J_5: effector cytokines

$$\partial_t f_5(t;\hat{u}_5) = \underbrace{\int_0^1 r_5(u)\, f_4(t,u)\, du}_{\text{cytokine production}} - \underbrace{d_5\, f_5(t;\hat{u}_5)}_{\text{natural decay}}$$

Term	Biological interpretation
$r_5(u)$	Cytokine production rate of T cells with activity u
$f_4(t,u)$	Distribution of gluten-specific T cells
d_5	Natural degradation and clearance rate

More highly activated T cells produce more inflammatory cytokines:
in our simulations we adopt the simple increasing law $r_5(u) = \hat{r}_5(1+u)$.

The operator H: intestinal permeability

$$p'(t) = \underbrace{\alpha_3 \frac{f_3(t;\hat{u}_3)}{a_3 + f_3(t;\hat{u}_3)}}_{\text{zonulin-induced modulation}} + \underbrace{\alpha_5 \frac{\left(f_5(t;\hat{u}_5) - f_5^{\text{phys}}\right)_+}{a_5 + \left(f_5(t;\hat{u}_5) - f_5^{\text{phys}}\right)_+}}_{\text{cytokine-induced damage}} - \underbrace{d_p\, p(t)}_{\text{barrier recovery}}$$

Term	Biological interpretation
$\alpha_3,\ a_3$	Strength and saturation of the zonulin effect
$\alpha_5,\ a_5$	Strength and saturation of cytokine-induced damage
f_5^{phys}	Physiological cytokine level
d_p	Recovery rate of the epithelial barrier
$(\cdot)_+$	Positive part: $(x)_+ = \max\{x, 0\}$

Modelling gluten translocation

$$\Phi(p) = \alpha_p \frac{(p - P_{\mathrm{crit}})_+}{a_p + (p - P_{\mathrm{crit}})_+}$$

Biological observation	**Model assumption**
Healthy barrier	No significant gluten translocation
Barrier disruption	Transfer starts only above P_{crit}
Highly damaged barrier	Transfer saturates for large permeability

A thresholded Hill function reproduces the nonlinear behaviour of the epithelial barrier.

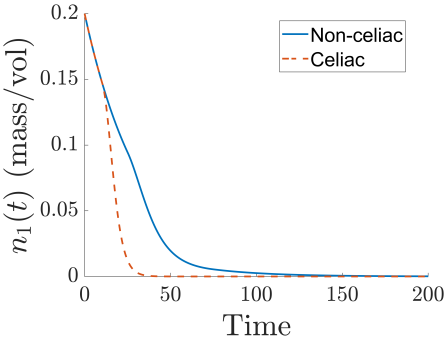
The complete multiscale model

$$
\begin{cases}
\partial_t f_1(t;\hat{u}_1) = I(t) - d_1 f_1(t;\hat{u}_1) - \Phi\big(p(t)\big)\, f_1(t;\hat{u}_1), \\
\partial_t f_2(t;\hat{u}_2) = \Phi\big(p(t)\big)\, f_1(t;\hat{u}_1) - d_2 f_2(t;\hat{u}_2), \\
\partial_t f_3(t;\hat{u}_3) = c\, f_1(t;\hat{u}_1) - d_3 f_3(t;\hat{u}_3), \\
\partial_t f_4(t,u) = f_2(t;\hat{u}_2) \displaystyle\int_0^1 \mu_{42}(u_*)\, \mathcal{B}_{42}(u_* \to u \mid u_*)\, f_4(t,u_*)\, du_* \\
\qquad\qquad -\mu_{42}(u)\, f_4(t,u)\, f_2(t;\hat{u}_2) - d_4\, f_4(t,u) + \kappa(u) f_2(t;\hat{u}_2) f_4(t,u), \\
\partial_t f_5(t;\hat{u}_5) = \displaystyle\int_0^1 r_5(u)\, f_4(t,u)\, du - d_5 f_5(t;\hat{u}_5), \\
p'(t) = \alpha_3 \dfrac{f_3(t;\hat{u}_3)}{a_3 + f_3(t;\hat{u}_3)} + \alpha_5 \dfrac{\big(f_5(t;\hat{u}_5) - f_5^{\mathrm{phys}}\big)_+}{a_5 + \big(f_5(t;\hat{u}_5) - f_5^{\mathrm{phys}}\big)_+} - d_p\, p(t).
\end{cases}
$$

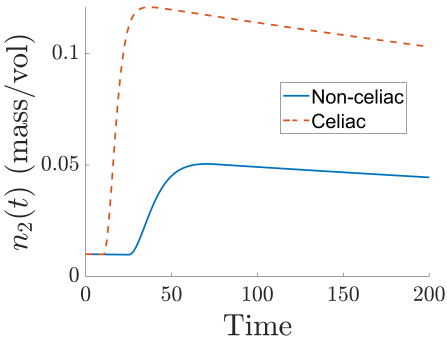
Numerical Simulations

- Single gluten exposure
- Repeated gluten exposure

Single gluten exposure: gluten dynamics



(a) Apical gluten $n_1(t)$



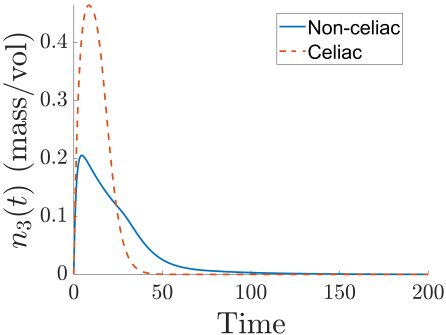
(b) Basolateral gluten $n_2(t)$

(a) Similar apical gluten profiles due to the same external input.

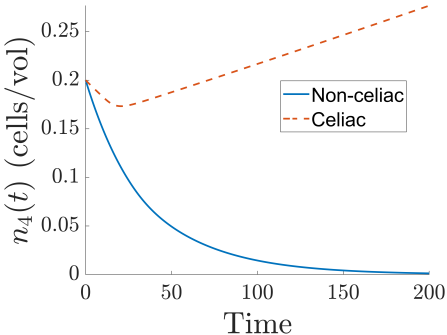
(b) Larger and more persistent basolateral gluten in the coeliac case.

A stronger antigenic stimulus reaches the lamina propria in the coeliac individual.

Single gluten exposure: immune activation



(c) Zonulin $n_3(t)$



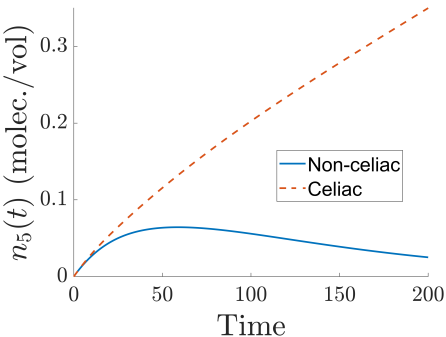
(d) Total T-cell density $n_4(t)$

(c) Stronger zonulin response in the coeliac case.

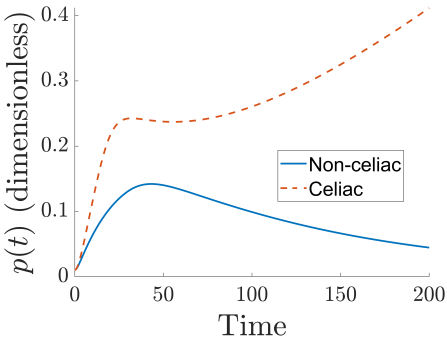
(d) More pronounced expansion of gluten-specific T cells.

Enhanced gluten translocation drives a stronger adaptive immune response.

Single gluten exposure: inflammatory amplification



(e) Effector cytokines $n_5(t)$



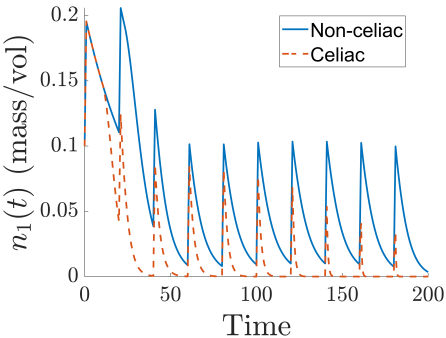
(f) Permeability $p(t)$

(e) Larger and more persistent cytokine response in the coeliac case.

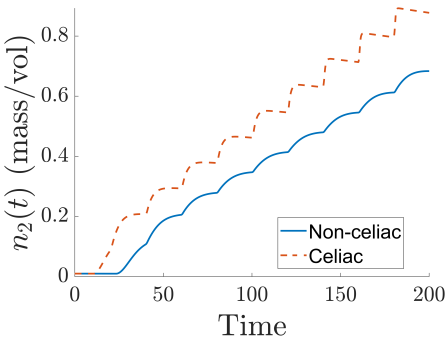
(f) Higher and sustained intestinal permeability.

Cytokines and permeability reinforce each other, closing the inflammatory feedback loop.

Repeated gluten exposure: gluten dynamics



(a) Apical gluten $n_1(t)$



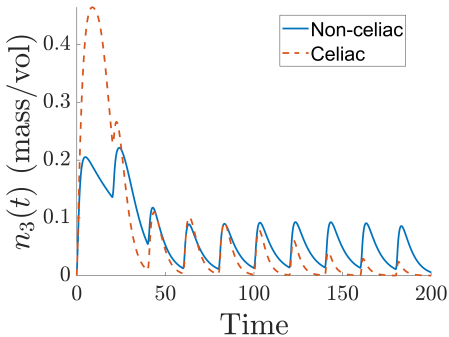
(b) Basolateral gluten $n_2(t)$

(a) Similar apical gluten oscillations due to the same repeated dietary input.

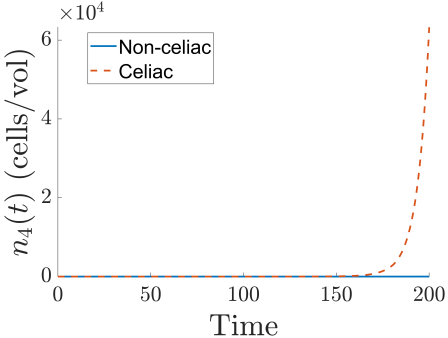
(b) Progressive accumulation of basolateral gluten in the coeliac case.

Repeated exposure sustains antigenic stimulation in coeliac disease.

Repeated gluten exposure: immune activation



(c) Zonulin $n_3(t)$



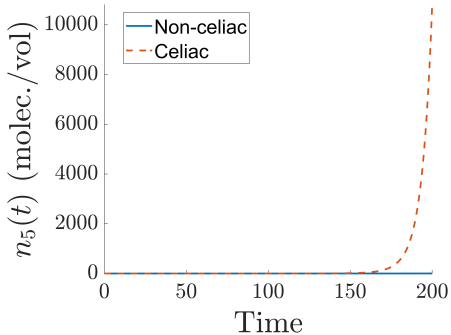
(d) Total T-cell density $n_4(t)$

(c) More persistent zonulin response in the coeliac case.

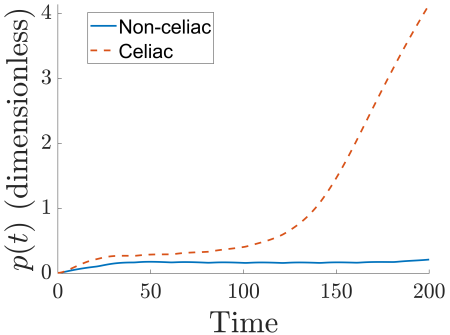
(d) Repeated T-cell activation and progressive expansion.

The adaptive immune response remains persistently stimulated.

Repeated gluten exposure: inflammatory amplification



(e) Effector cytokines $n_5(t)$



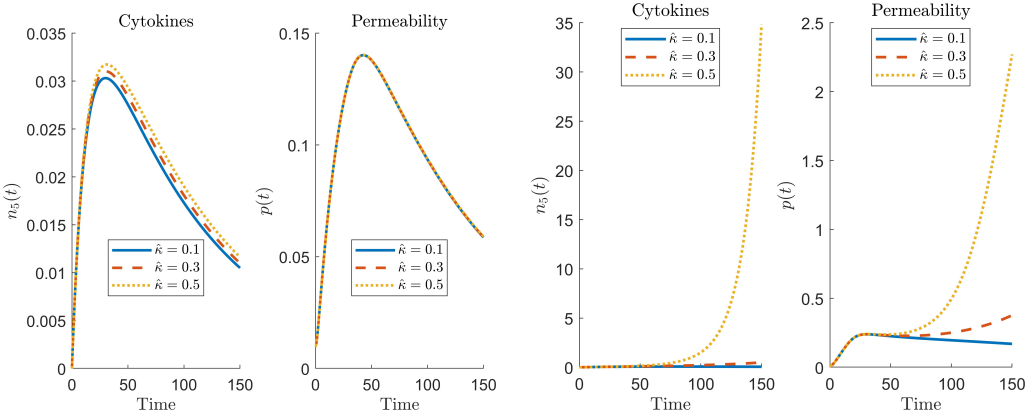
(f) Permeability $p(t)$

(e) Progressive increase of inflammatory cytokines in the coeliac case.

(f) Sustained increase in intestinal permeability.

Each exposure reinforces the next one, driving the system toward chronic inflammation.

Effect of the T-cell proliferation rate



(a) Non-coeliac individual **(b)** Coeliac individual

(a) Increasing $\hat{\kappa}$ produces only moderate changes in cytokines and permeability.

(b) The same increase in $\hat{\kappa}$ strongly amplifies both inflammatory cytokines and permeability.

Biological insights

Model outcome	Biological meaning
Repeated gluten exposure	Persistent antigenic stimulation
Sustained zonulin and cytokines	Progressive barrier disruption
Increased permeability	Enhanced gluten translocation
Feedback amplification	Self-sustained chronic inflammation
Higher T-cell proliferation	Stronger adaptive immune response

Future perspectives

Current model	Possible extensions
Representative parameter sets	Patient-specific calibration
Lumped cytokine population	Multiple inflammatory pathways
Macroscopic barrier description	Spatially resolved intestinal tissue
Deterministic parameter setting	Data assimilation and uncertainty quantification

Towards predictive, data-informed multiscale models of immune-mediated diseases.

Thank you!