Dynamic properties of the intestinal ecosystem

Diagnostics and role in the remission from Ulcerative Colitis

RÉPUBLIQUE FRANÇAISE
Liberté Égalité Fraternité

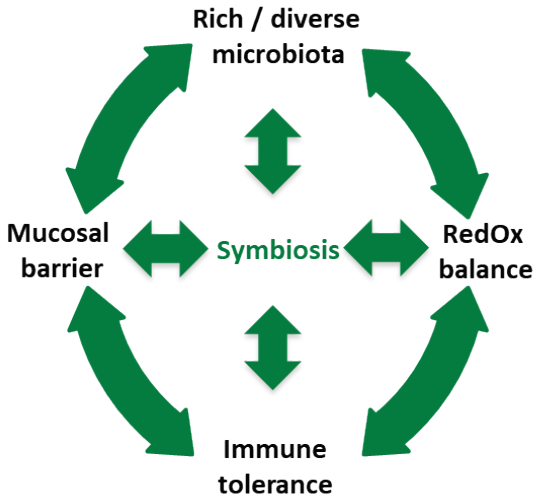
INRAE

Maarten van de Guchte

Alternative stable states of the intestinal ecosystem

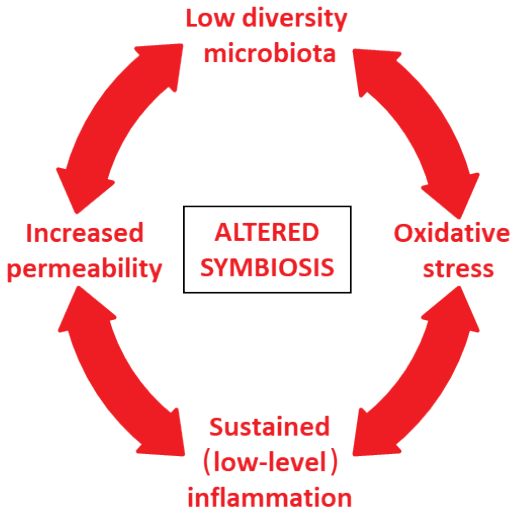
Microbiota

Health

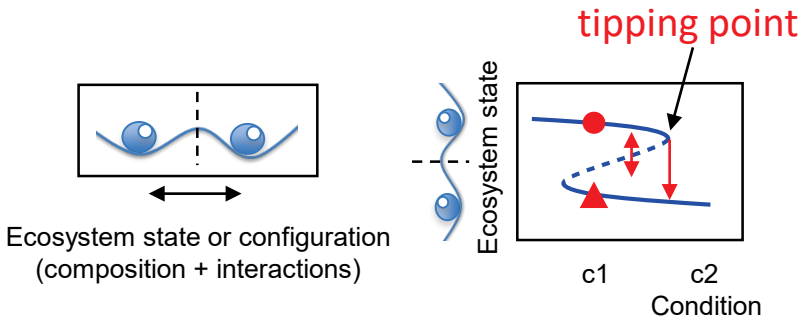


Host + Microbiota

Chronic Inflammatory Disease



Alternative stable states
Impact?



Alternative stable states
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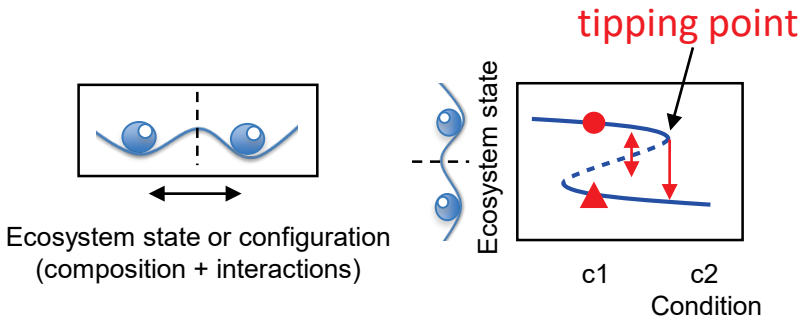
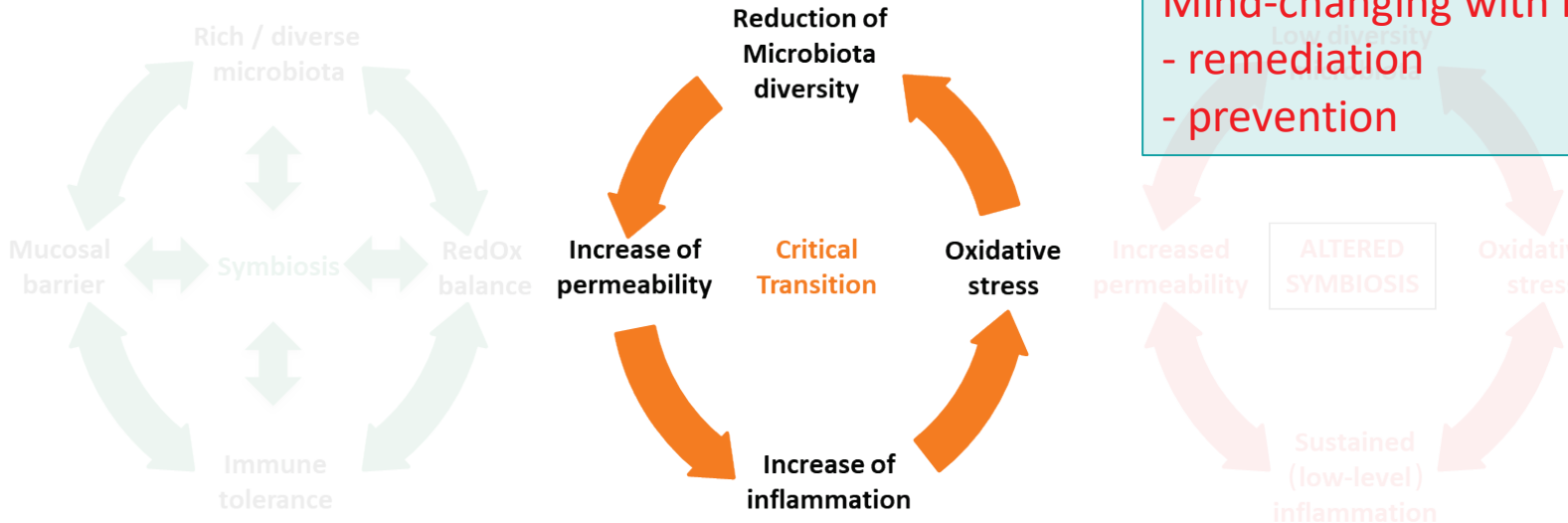


— Health

— Chronic Inflammatory Disease



Mind-changing with respect to
- remediation
- prevention

Microbiome 6:81 (2018)

A study on pediatric ulcerative colitis

Microbiome 6:81 (2018)

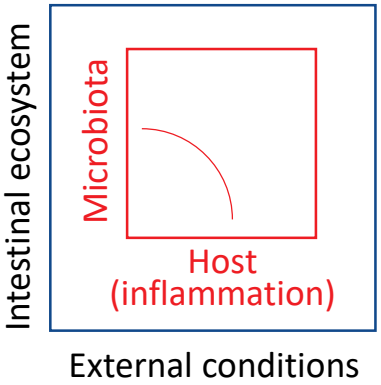
COMMENTARY Open Access

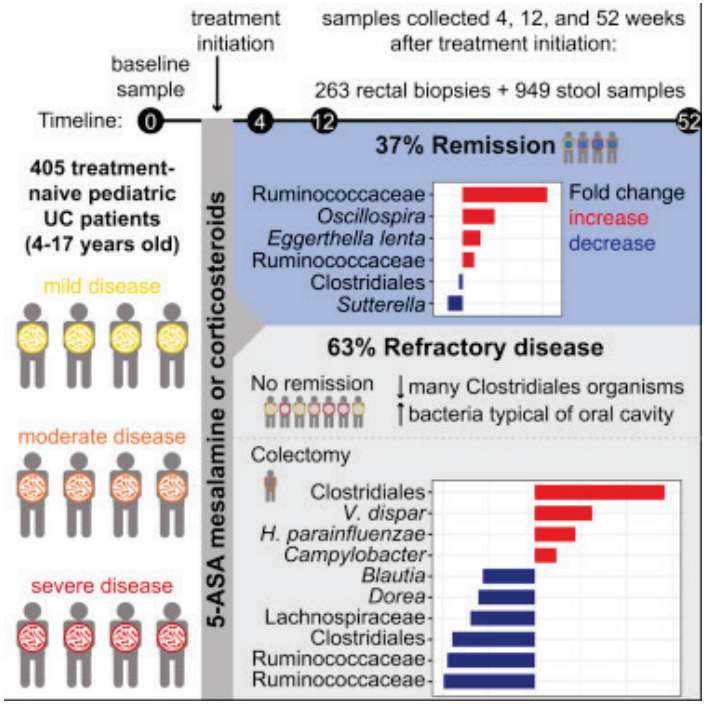
Humans as holobionts: implications for prevention and therapy

Microbiome 8:153 (2020)

RESEARCH Open Access

Alternative stable states in the intestinal ecosystem: proof of concept in a rat model and a perspective of therapeutic implications





Reflects current standard of care

Varying degrees of disease severity

Treatment naïve patients + follow-up (52 weeks)

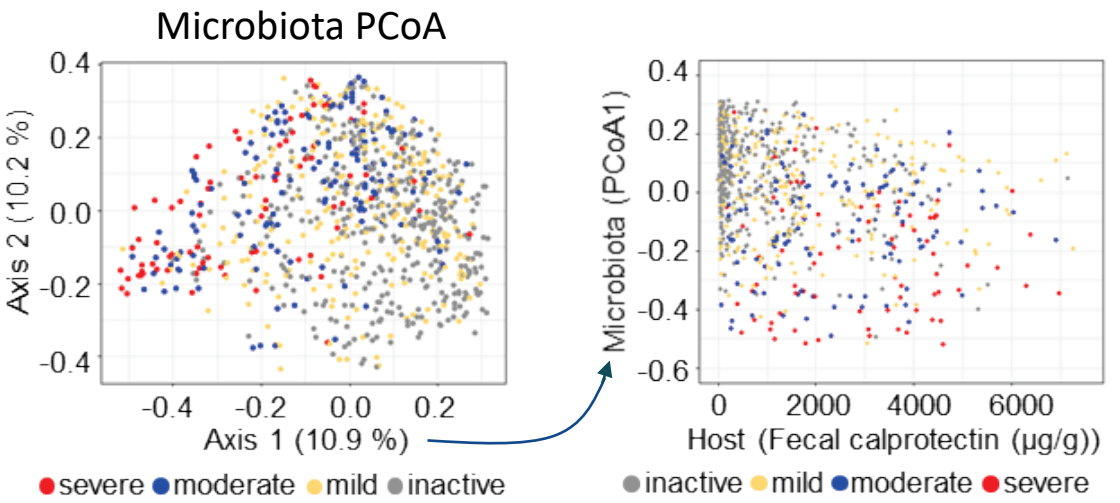
Microbiota 16S + fecal calprotectin

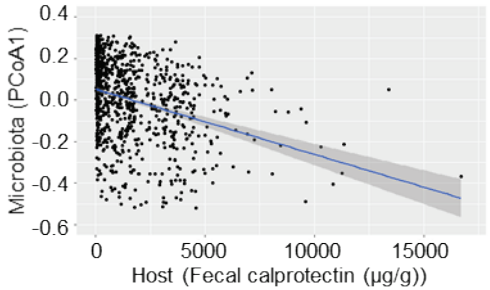
Compositional and Temporal Changes in the Gut Microbiome of Pediatric Ulcerative Colitis Patients Are Linked to Disease Course

M. Schirmer et al. 2018. Cell Host & Microbe 24:600-610.

Intestinal microbiota and host inflammatory status

Intestinal ecosystem

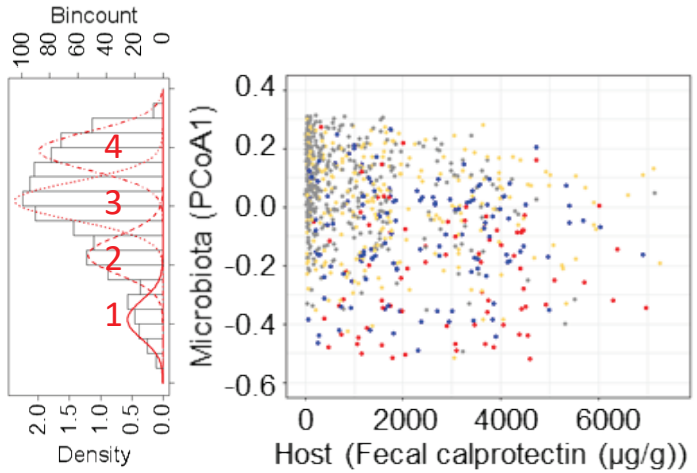




T0 + T4 + T12 +T52
n=881 / 367 patients

Alternative microbiota states in UC

M4: healthy
(nearly) absent at T0,
T52: 56 % remission
T52: 38 % remission



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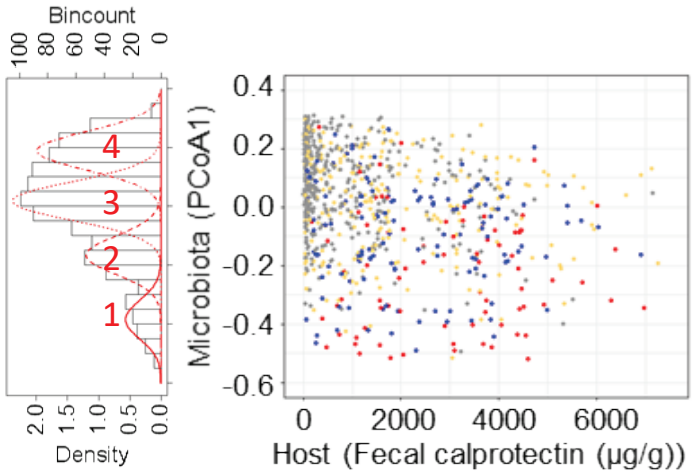

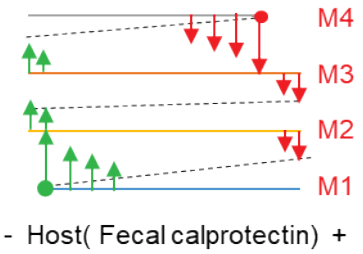

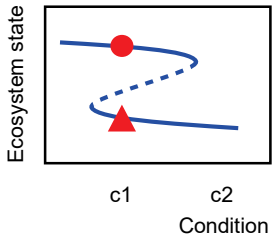

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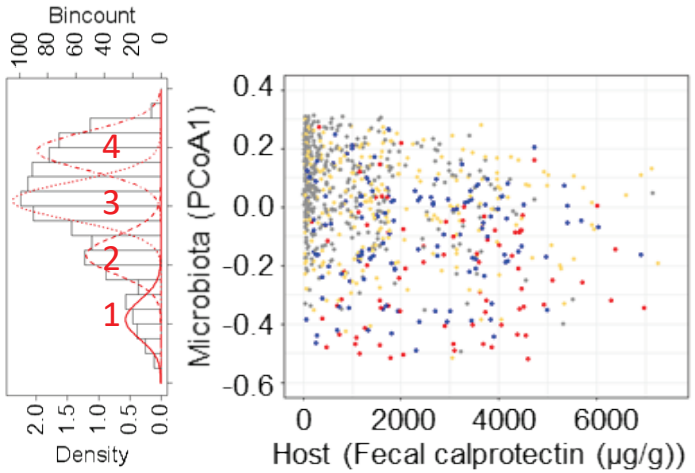
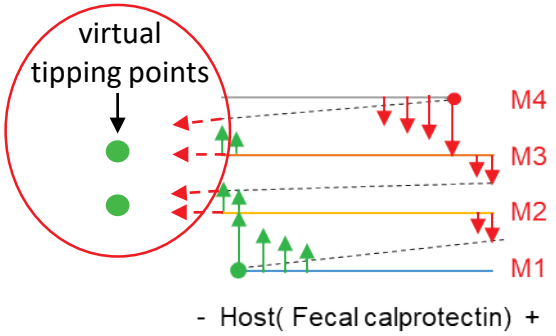
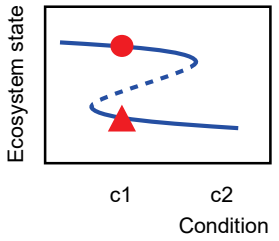
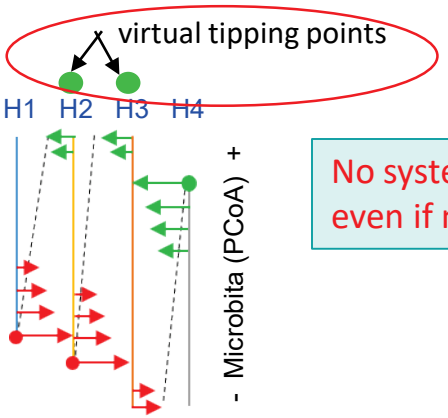




No systematic return to healthy microbiota, even if inflammation completely suppressed



Alternative host states in UC



No systematic return to healthy host state, even if microbiota completely re-established

M4: healthy
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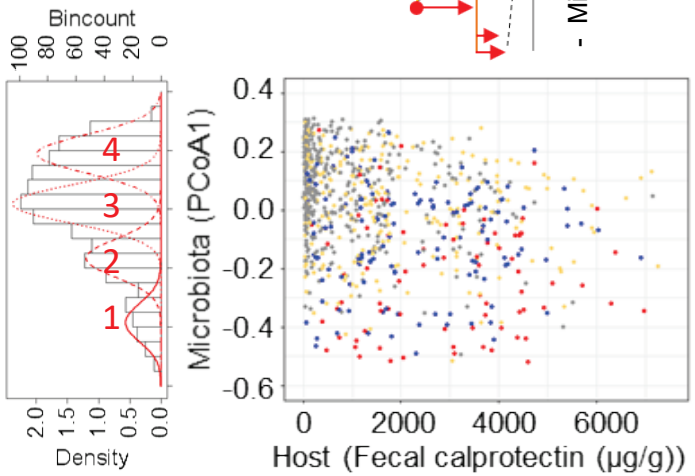

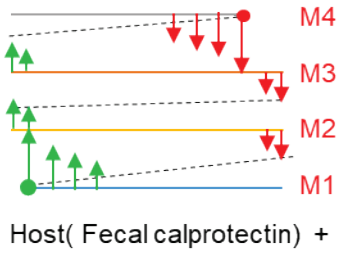

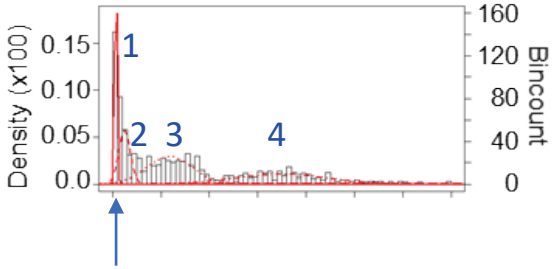

H1: non-pathological

Alternative intestinal ecosystem states in UC

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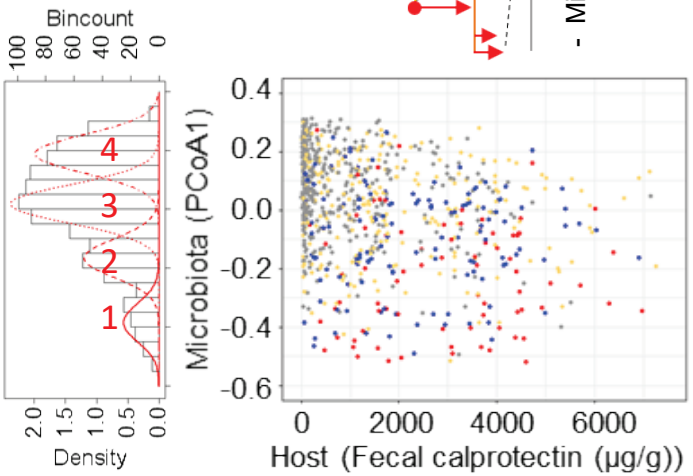
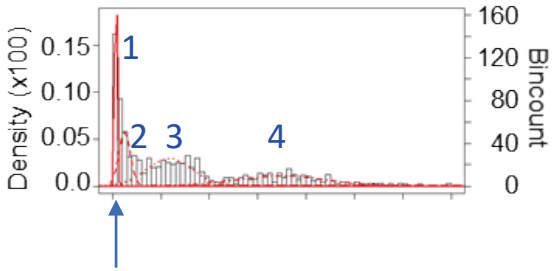
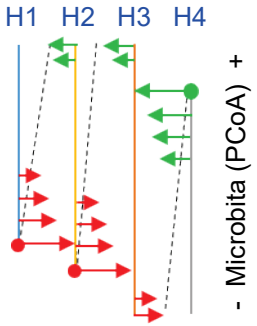
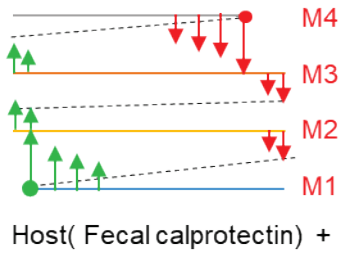
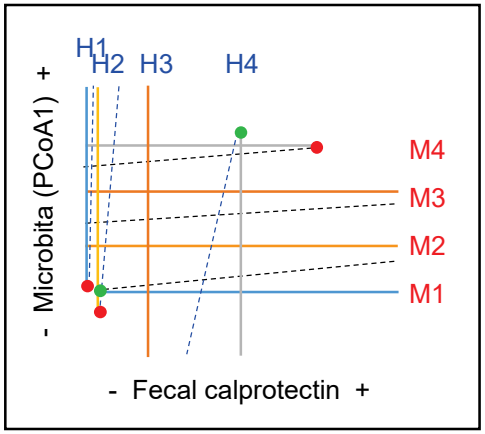




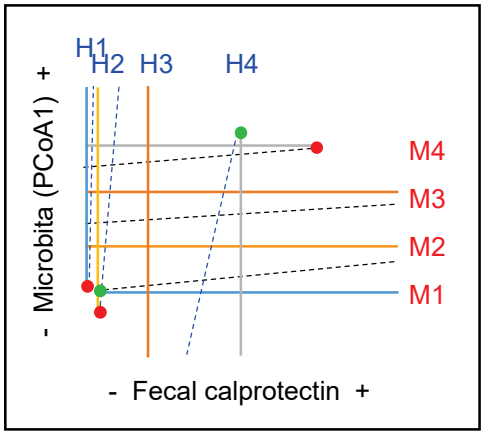
H1: non-pathological

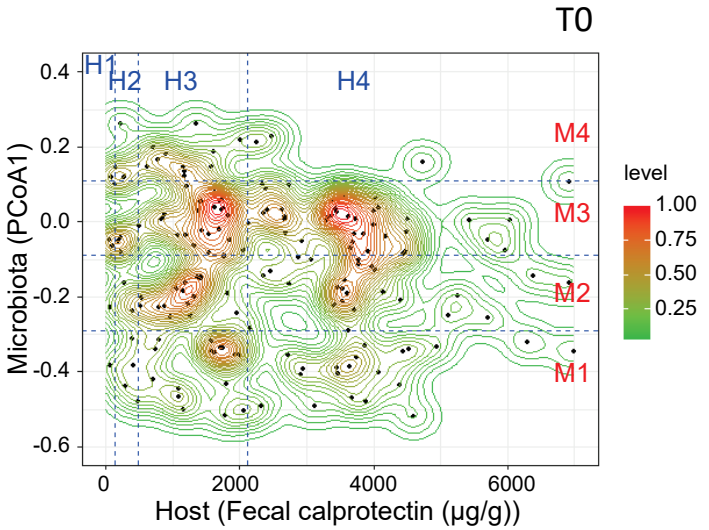






Alternative intestinal ecosystem states in UC



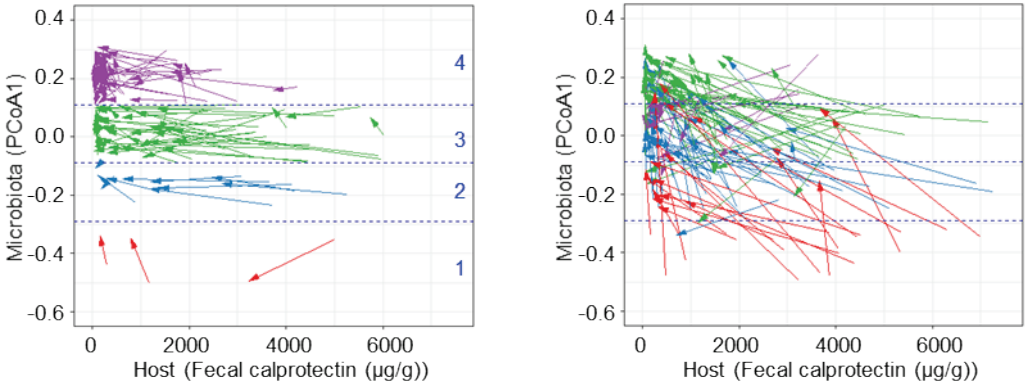


Alternative microbiota and host states define alternative intestinal ecosystem states

Alternative ecosystem states can be recognized in treatment naïve patients

System dynamics: evolution of the ecosystem under anti-inflammatory treatment

dCalprotectin < 0 (anti-inflammatory pressure)



Conservation of microbiota state

- in spite of reaching low calprotectin levels

Alternative microbiota state properties appear to hinder the reconstitution of a healthy microbiota

System dynamics: evolution of the ecosystem under anti-inflammatory treatment

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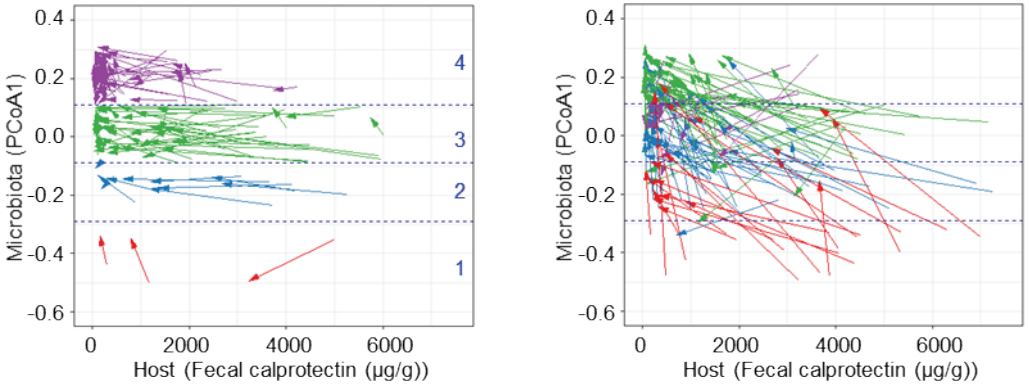
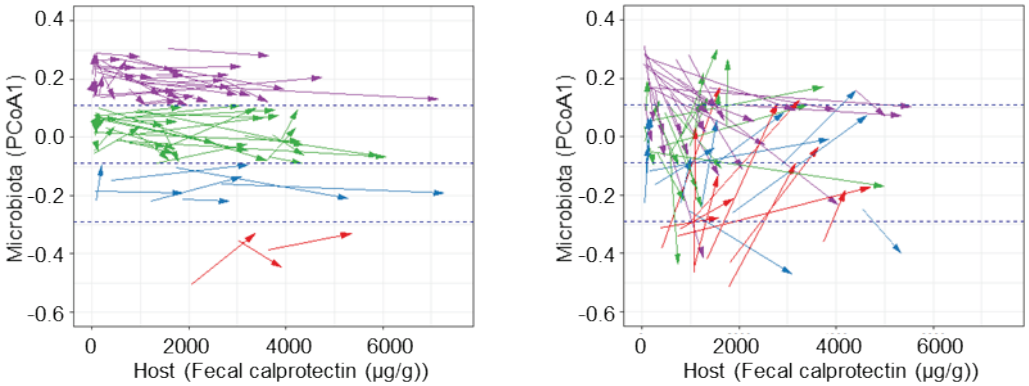


dCalprotectin > 0 (inflammatory pressure)



Conservation of microbiota state

- in spite of reaching low calprotectin levels

- in spite of reaching high calprotectin levels

Alternative microbiota state properties appear to hinder the reconstitution of a healthy microbiota

System dynamics: evolution of the ecosystem under anti-inflammatory treatment

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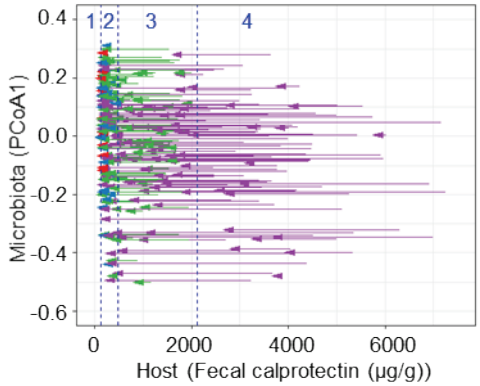
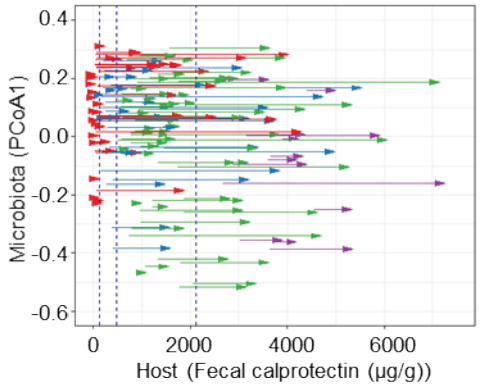


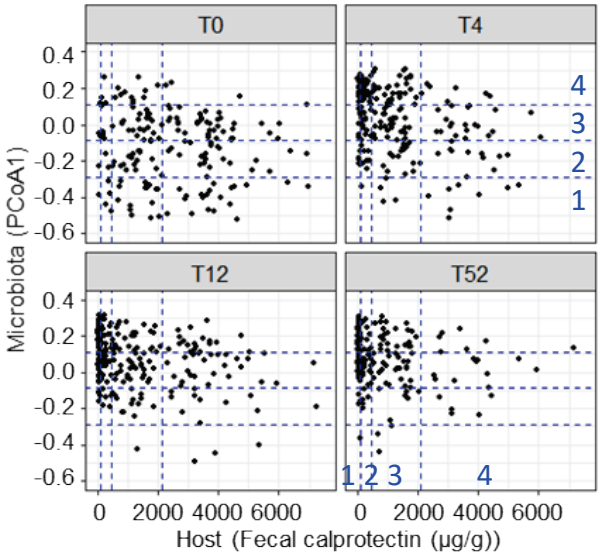
dCalprotectin > 0



Pausing of host state changes

Alternative host state barriers appear to cause pausing or blocking of host restoration or deterioration

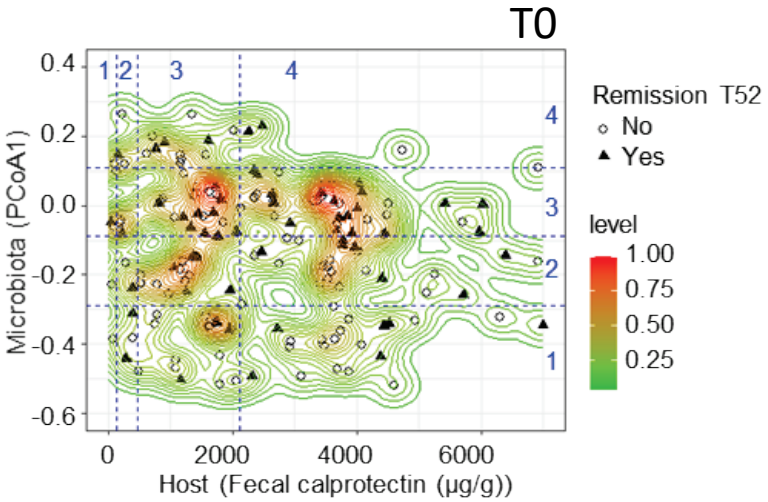
System dynamics: evolution of the ecosystem under anti-inflammatory treatment



Microbota state 4
- most favorable microbiota

Host state 1 - non-pathological calprotectin levels
- only 36% of patients after one year of treatments
- only ~1/2 of these (19%) in most favorable microbiota state 4

Microbiota states, host states and remission



Microbiota state T0	Remission T52 (%)	n
3/4	43	86
2	34	44
1	26	46

Host state T0		
1/2	35	17
3	36	64
4	37	95

After one year of personalized anti-inflammatory treatment

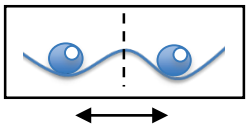
- remission depends on initial microbiota state

- remission does not depend on initial host state (inflammation)

Anti-inflammatory treatments push the ecosystem over part of the alternative host state hurdles, clearing much of the initial differences (but only 36% of patients reach non pathological state H1)

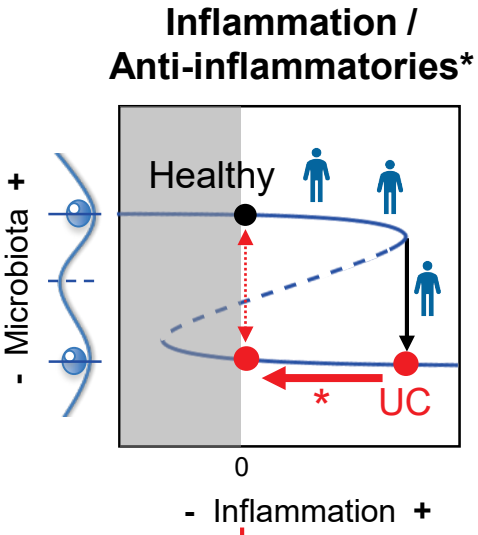
Alternative microbiota states remain a problem if not actively worked upon

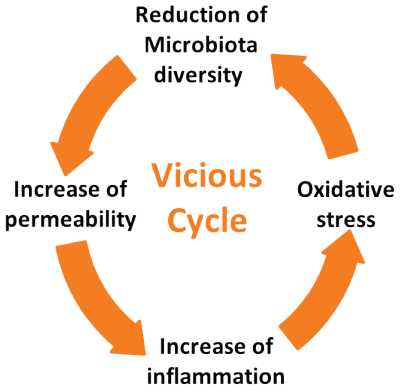
What does this mean for clinical practice?

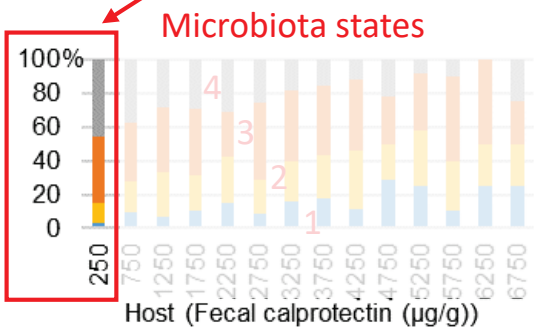


Alternative intestinal ecosystem states related to UC

Interfere with anti-inflammatory treatments



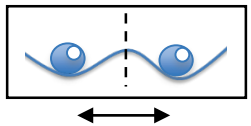




Alternative host states:
Complete suppression of inflammation is hard to attain
- low success rate of current treatments
- risk of relapse

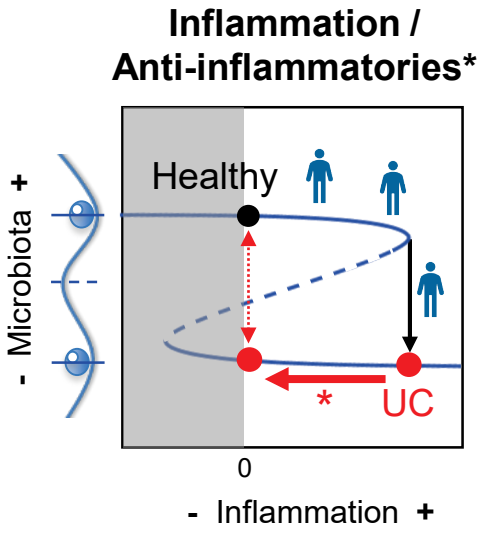
Even if complete suppression of inflammation
- no systematic restoration of a healthy microbiota
- risk of relapse

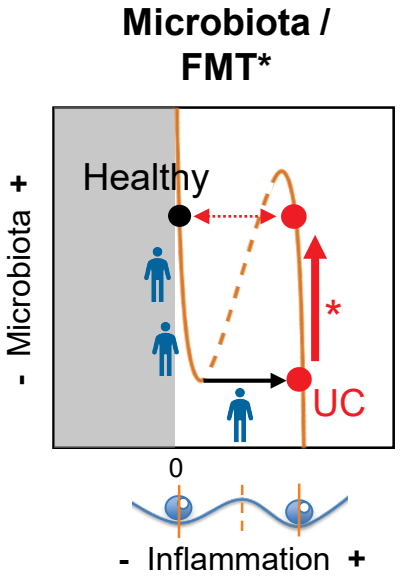
What does this mean for clinical practice?

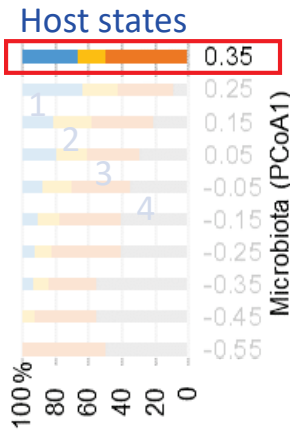


Alternative intestinal ecosystem states related to UC

Interfere with anti-inflammatory and FMT treatments



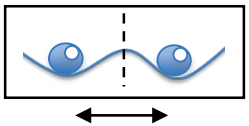




Alternative microbiota states:
Restoration of healthy microbiota is hard to attain
- risk of relapse

Even if restoration of a healthy microbiota
- no systematic suppression of inflammation
=> variable success of FMT
- risk of relapse if low-level inflammation remains

What does this mean for clinical practice?

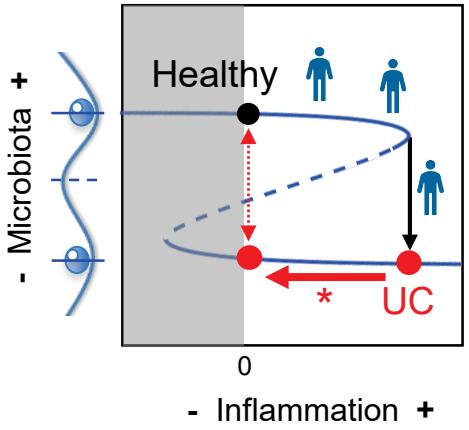


Alternative intestinal ecosystem states related to UC

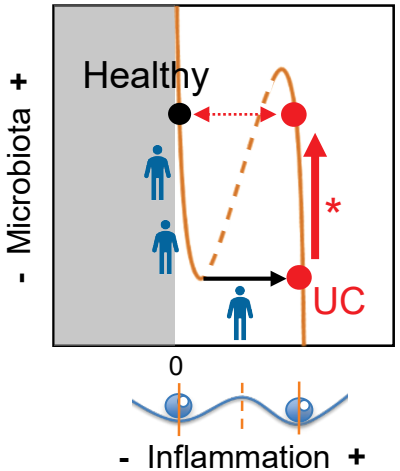
Interfere with anti-inflammatory and FMT treatments

Combination therapy could facilitate remission

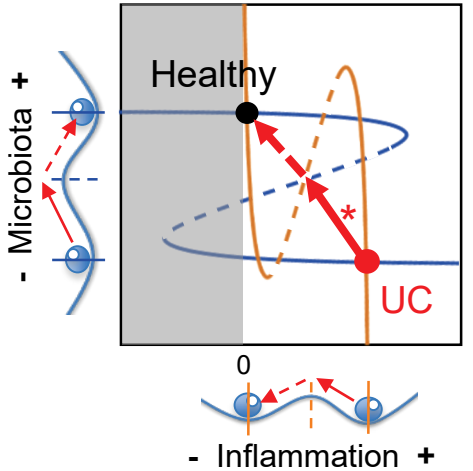
Inflammation / Anti-inflammatories*

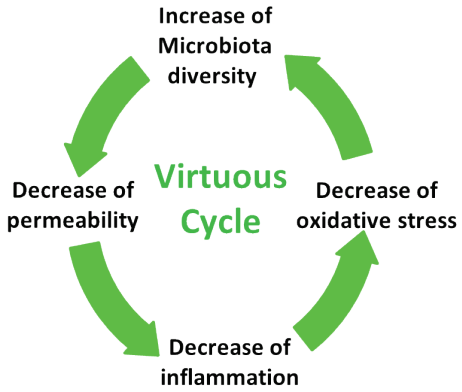


Microbiota / FMT*



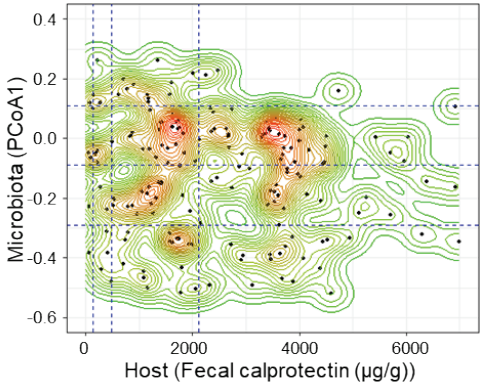
Combination therapy*





Combination therapy
- Demands less effort on each parameter
- Self-propelling evolution to healthy state

What does this mean for clinical practice?



The model may be used to personalize and monitor treatment strategies

- Reference map
- Diagnostic use of fecal samples to position patients with respect to microbiota and host state

Conclusions

- Existence of alternative stable states of the intestinal ecosystem

- Enhanced understanding of the evolution of patient's clinical pictures under treatment

- Alternative states can delay or prevent remission from disease,
  and perpetuate a risk of relapse

- Alternative states can also delay or prevent the progress of disease

- Model provides a strong rationale for combination therapies, targeting inflammation
  and microbiota, to promote remission from UC

- Framework to monitor and direct disease treatment

M. van de Guchte, S. Mondot, J. Doré. 2021.
Gastroenterology, in press.

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