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# The structure of the food matrix at different length scales drives the mechanism of digestion and the nutrient bioaccessibility and bioavailability

Didier Dupont

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Didier Dupont. The structure of the food matrix at different length scales drives the mechanism of digestion and the nutrient bioaccessibility and bioavailability. <https://www.foodomics.org/>, Feb 2024, Cesena (IT), Italy. hal-04465062

**HAL Id: hal-04465062**

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Submitted on 19 Feb 2024

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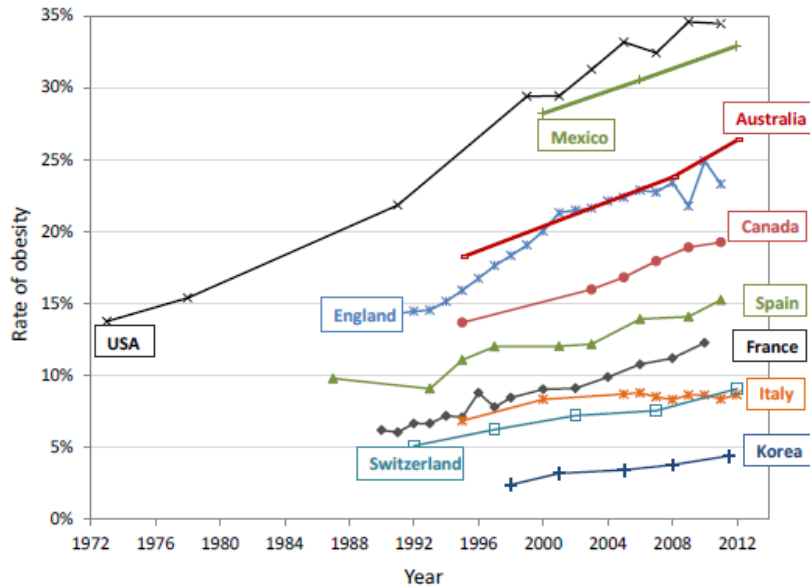
# The structure of the food matrix at different length scales drives the mechanism of digestion and the nutrient bioaccessibility and bioavailability



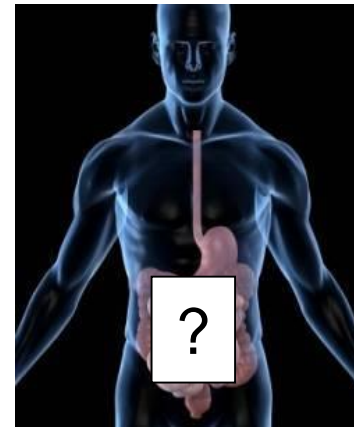
Dr Didier DUPONT, INRAE, STLO, Rennes, France



# Food and human health: the key role of digestion



Diet-related diseases ↑  
Prevent these pathologies rather than  
cure them



**Gut = interface between food and human body**

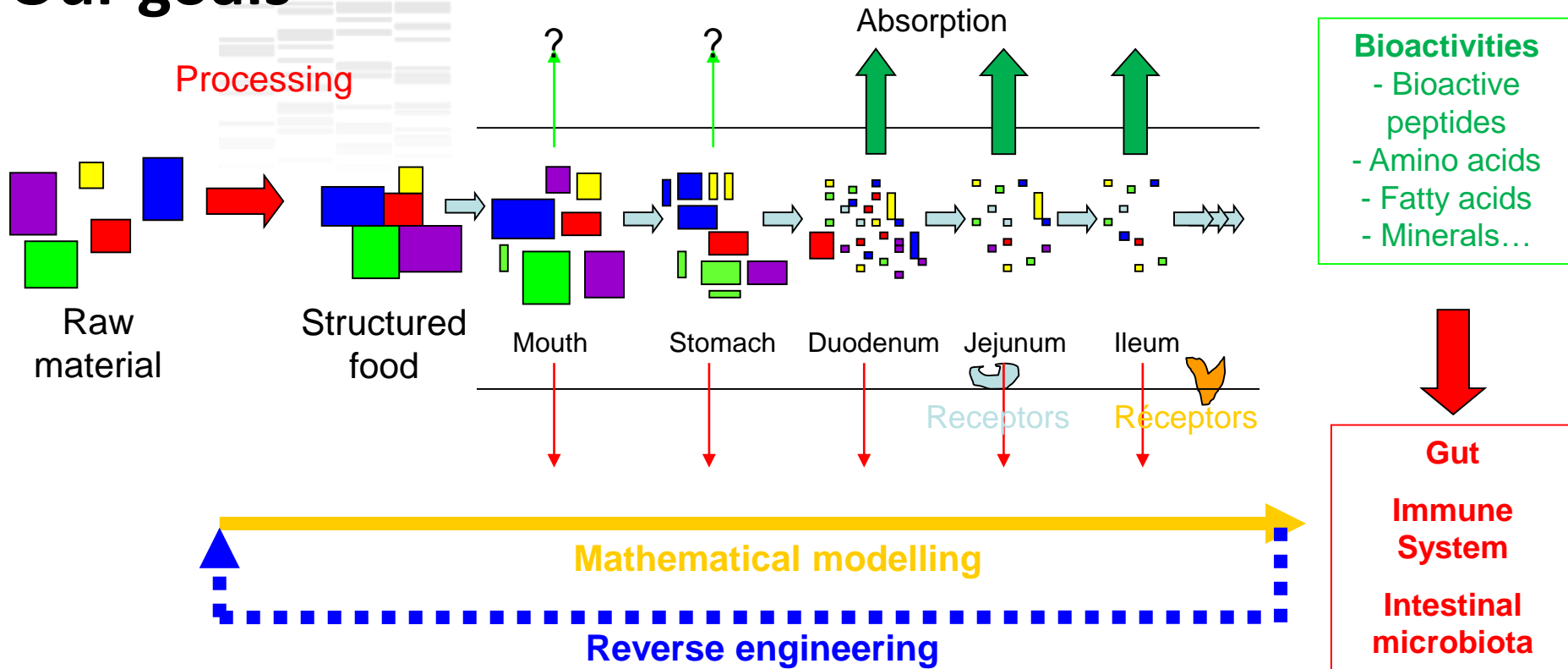
**Digestion releases food components that can have a beneficial or a deleterious effect on human health**

... but the mechanisms of food disintegration in the gastrointestinal tract remain unclear and the digestive process has been considered as a black box so far

**By increasing our knowledge on food digestion, we will increase our knowledge on the effect of food on human health**

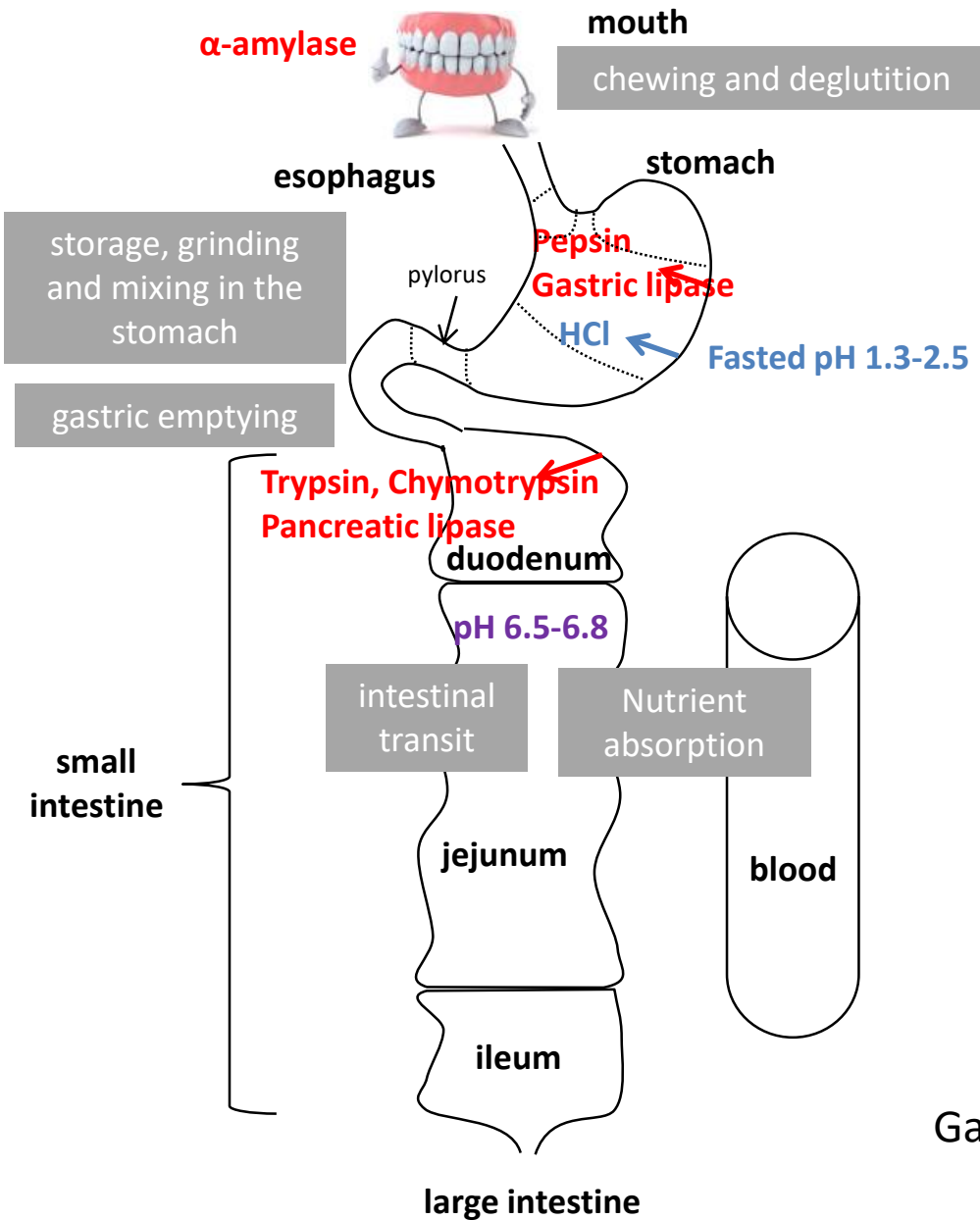
# Our goals

Healthy Adult/ Infant / Elderly

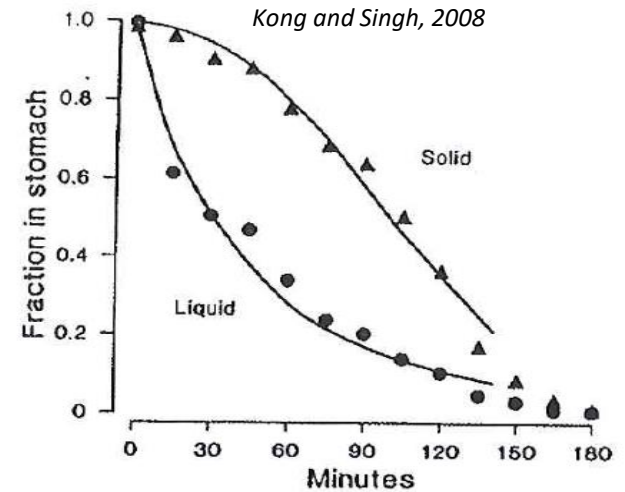


- ☞ To understand the mechanisms of breakdown of food matrices and their constituents in the gut and identify the beneficial/deleterious food components released during digestion
- ☞ To determine the impact of the structure of food matrices on nutrient bioavailability
- ☞ To model these phenomena in order to develop a reverse engineering approach

# The digestive process



From Roger Lentle, Massey Univ. NZ



Gastric phase = a very complex but crucial step for the whole digestion process

# Models available at INRAE for simulating digestion

Menard et al. 2018, 2023  
Wang et al. 2022



*In vitro static models  
(infant, adult, elderly)*

*In silico  
models*



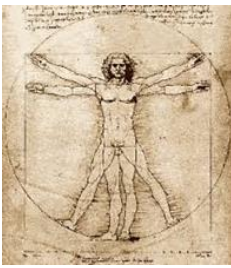
*In vitro dynamic models  
(infant, adult, elderly)*



Peng et al. 2021  
Halabi et al. 2021  
Giribaldi et al. 2021  
Chauvet et al. 2023  
Nebbia et al. 2022, 2023

Le Feunteun et al.  
2014, 2020

$$\Phi_{12} = k_{12whey} \times (V_1 - m_{caswpd1} \times \alpha) + k_{12aggr} \times m_{caswpd1} \times \alpha$$



*Human models*



*Animal models*



De Oliveira et al. 2016  
De Oliveira et al. 2017  
Buffière et al. 2020  
Boulier et al. 2023



Lemaire et al. 2021  
Nau et al. 2022  
Jimenez-Barrios et al. 2023  
Charton et al. 2022, 2023

# NERDT™ : the NEAR Real Digestive Tract




Xiao Dong Pro-Health  
Smart Digestion  
Suzhou University



INRAE

L'INSTITUT  
agro Rennes  
Angers





# From the protein molecular structure to the the food microstructure: The case of egg white gels



Nau F, & Dupont D.  
INRAE, Rennes, France

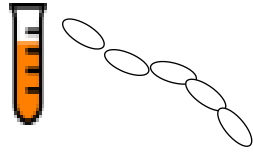




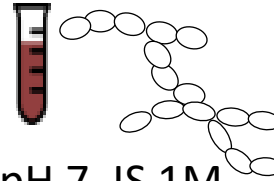
# The microstructure of egg-white gels made from different types of aggregates affects the kinetics of proteolysis

Microscopic scale

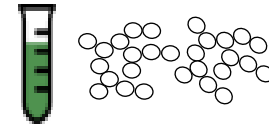
80°C/6h



pH 9, IS 1M



pH 7, IS 1M



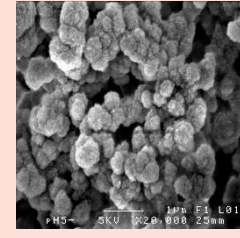
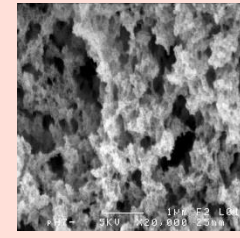
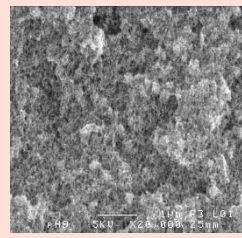
pH 5, IS 1M



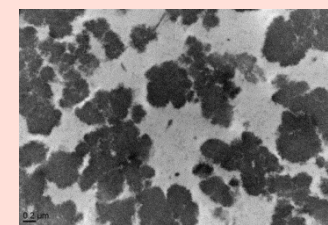
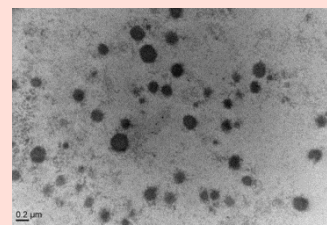
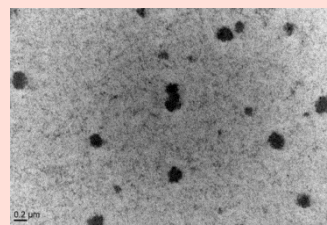
Aggregates	linear	branched	spherical
Rate of <i>in vitro</i> digestion	+++	++	+

Gels 90°C/2.5 h			
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Nyemb *et al.*  
Food Hydro. 2016  
Nyemb *et al.*  
Food Res Int 2016

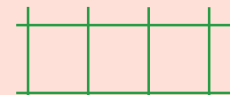
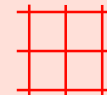


SEM



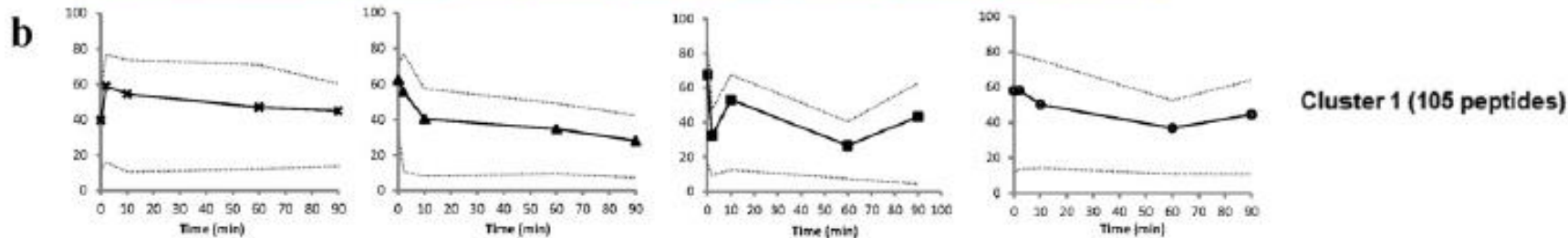
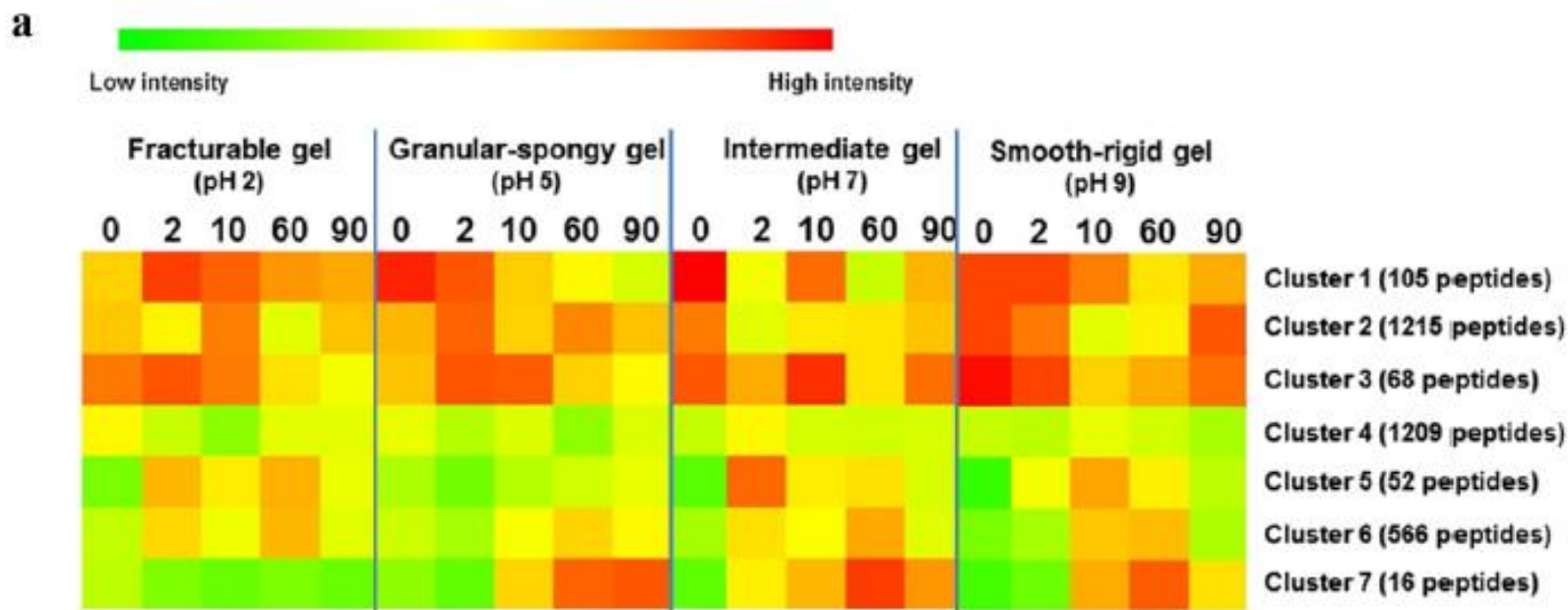
CRYO-TEM

Rate of <i>in vitro</i> digestion	+	++	+++
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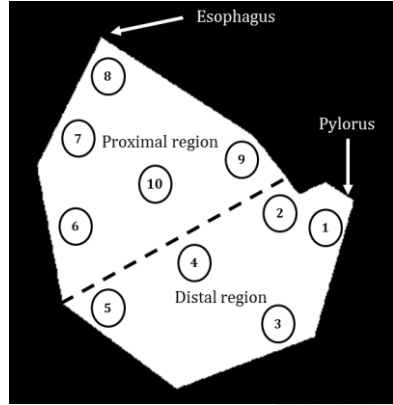
# Peptidomics reveals significant differences in the peptide pattern released during digestion

More than 3200 individual peptides identified



# Spatial-temporal evolution of pH during an *in vivo* digestion

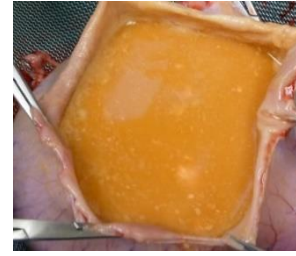
Microscopic scale



20 min



60 min



120 min



240 min

pH 7.0

n=33



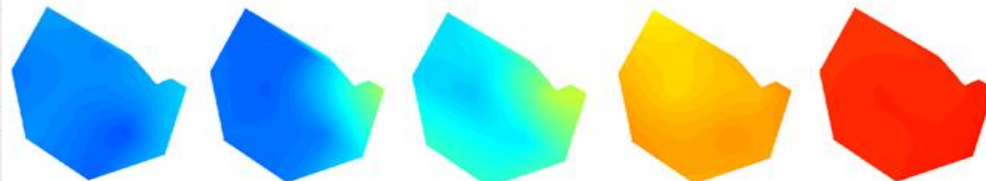
Gel pH 5



n=33



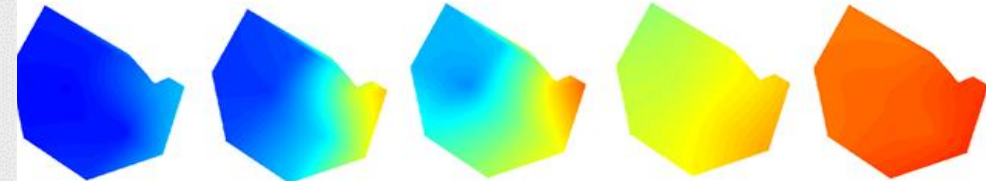
Gel pH 7



n=33



Gel pH 9



20 min

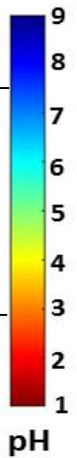
60 min

120 min

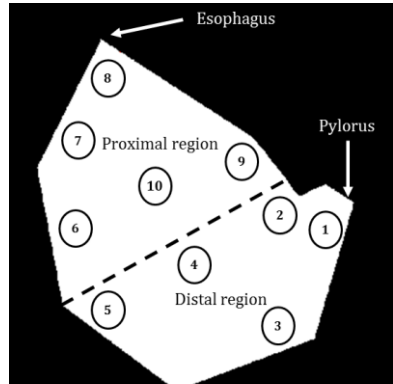
240 min

360 min

Digestion time



# Spatial-temporal evolution of pH during an *in vivo* digestion



20 min



60 min

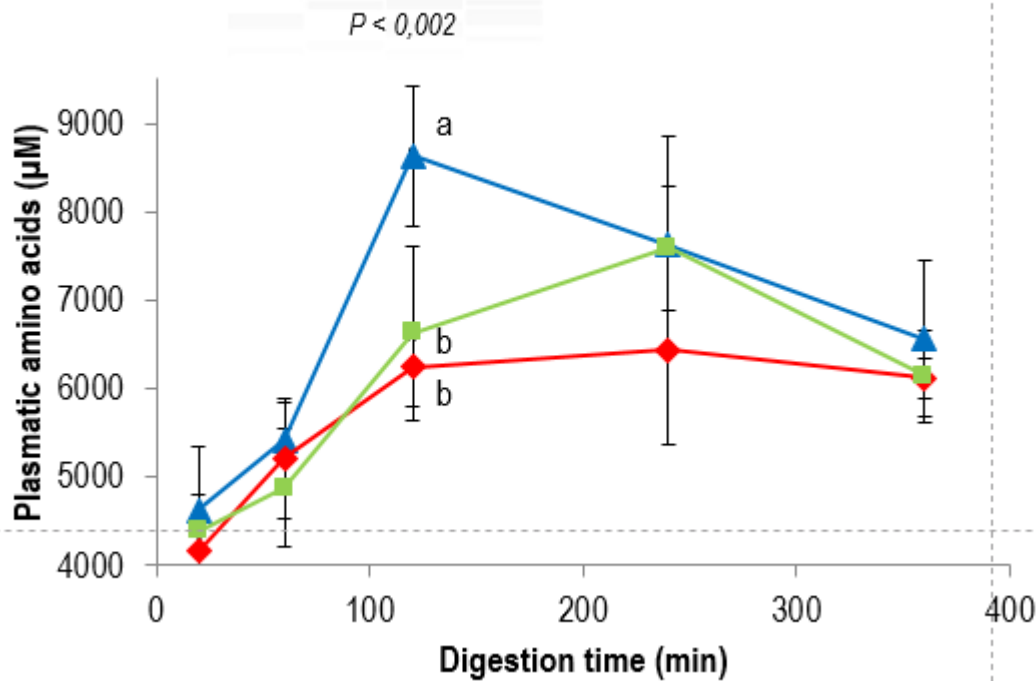


120 min



240 min

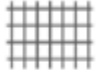
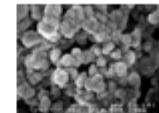
pH 7.0



▲ Granular-spongy EWG

■ Smooth-rigid EWG

◆ Intermediate EWG



Microscopic scale



# Food structure as modified by processing affects the kinetics of food digestion



Le Feunteun S, Menard O, Dupont D.  
INRAE, Rennes, France



# Comparison of 6 dairy products of identical composition but different structure



Macroscopic scale

Ultra Low Heat powder



rehydration in water 14.5%

unheated milk ("raw" milk)



heat treatment 90°C-10 min

microstructure

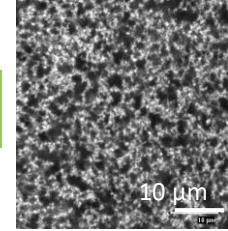
heated milk



macrostructure

rennet gel

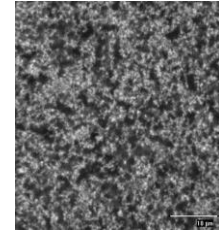
24h-20°C, rennet 0.003 % v/w



pH 6.6

rennet gel

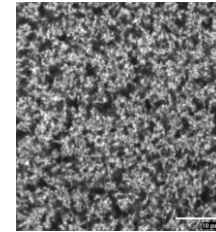
24h-20°C, rennet 0.3 % v/w



pH 6.6

acid gel

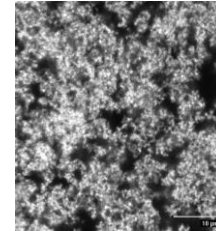
24h-20°C, GDL 3 % w/w



pH 4

stirred acid gel

24h-20°C, GDL 3 % w/w + mixer 2 min



pH 4

Fat-free matrices:

40 g/L caseins, 10 g/L whey proteins, 95 g/L lactose and minerals

+ marker of the meal transit ( $\text{Cr}^{2+}$ -EDTA) → Gastric emptying half-time

# The multi-cannulated mini-pigs

SOLID

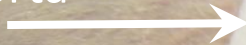
LIQUID



Macroscopic scale

6 minipigs (20 ± 1kg)

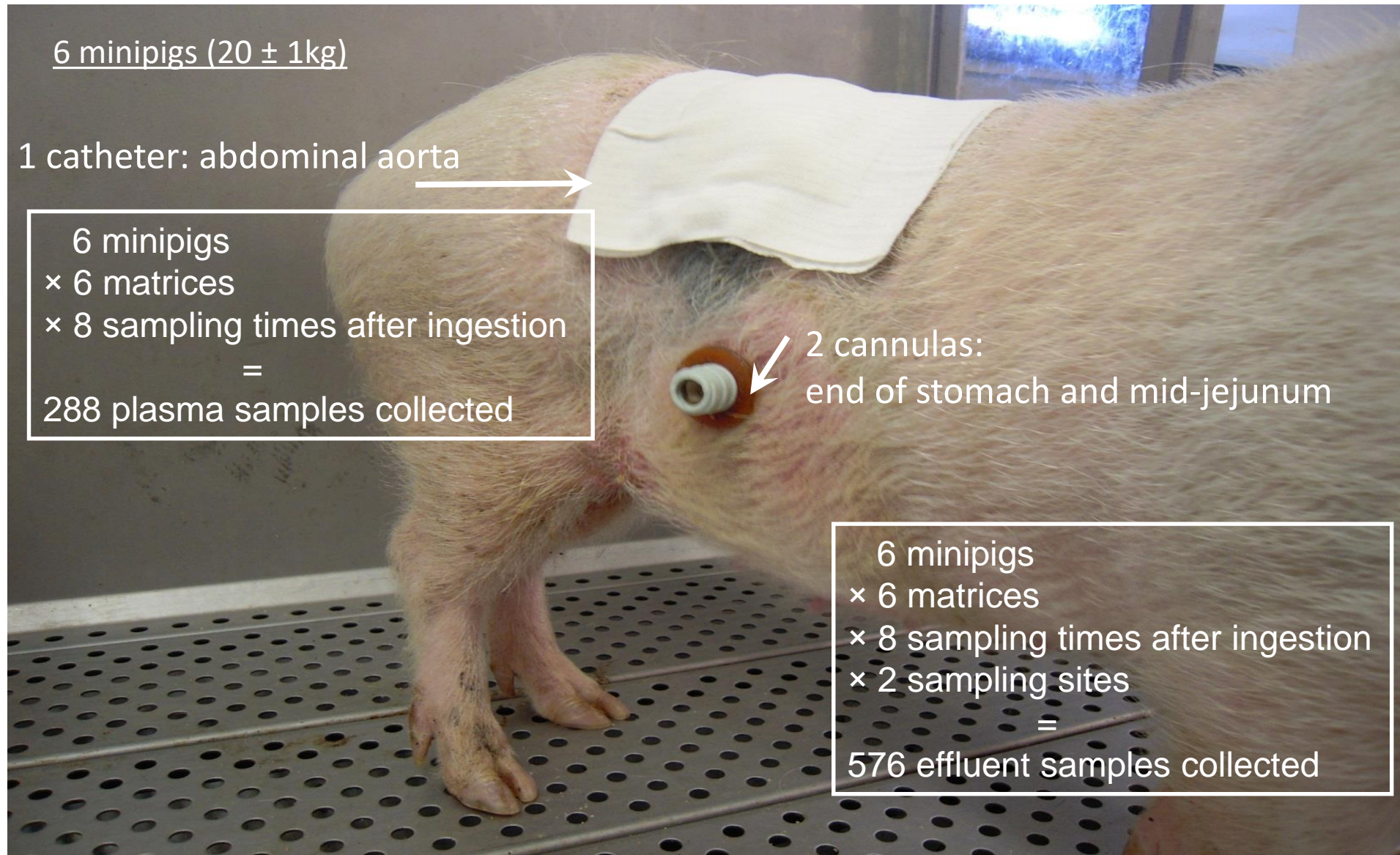
1 catheter: abdominal aorta



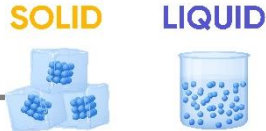
6 minipigs  
× 6 matrices  
× 8 sampling times after ingestion  
=  
288 plasma samples collected

2 cannulas:  
end of stomach and mid-jejunum

6 minipigs  
× 6 matrices  
× 8 sampling times after ingestion  
× 2 sampling sites  
=  
576 effluent samples collected

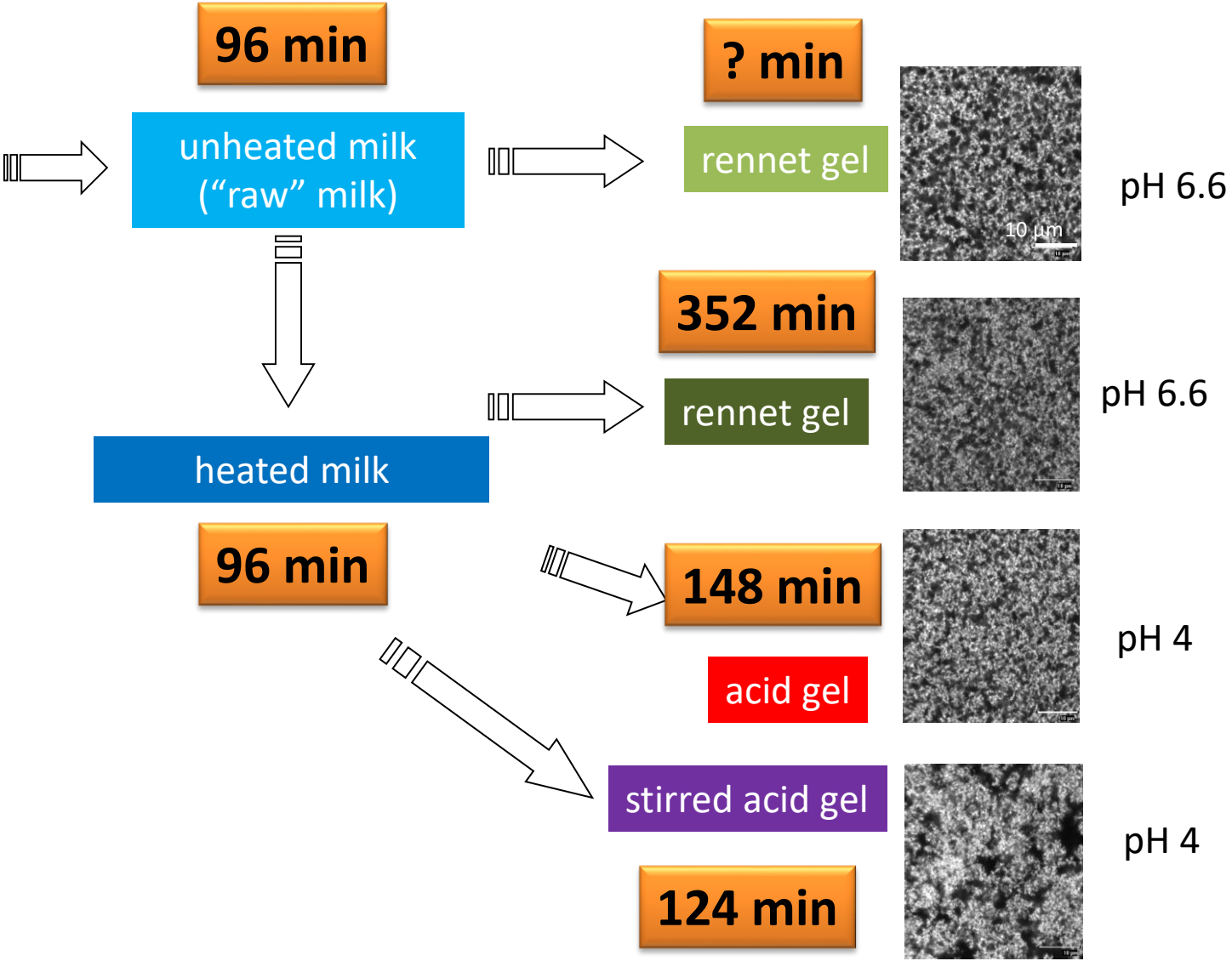


# Gastric emptying half time



Macroscopic scale

Ultra Low Heat powder



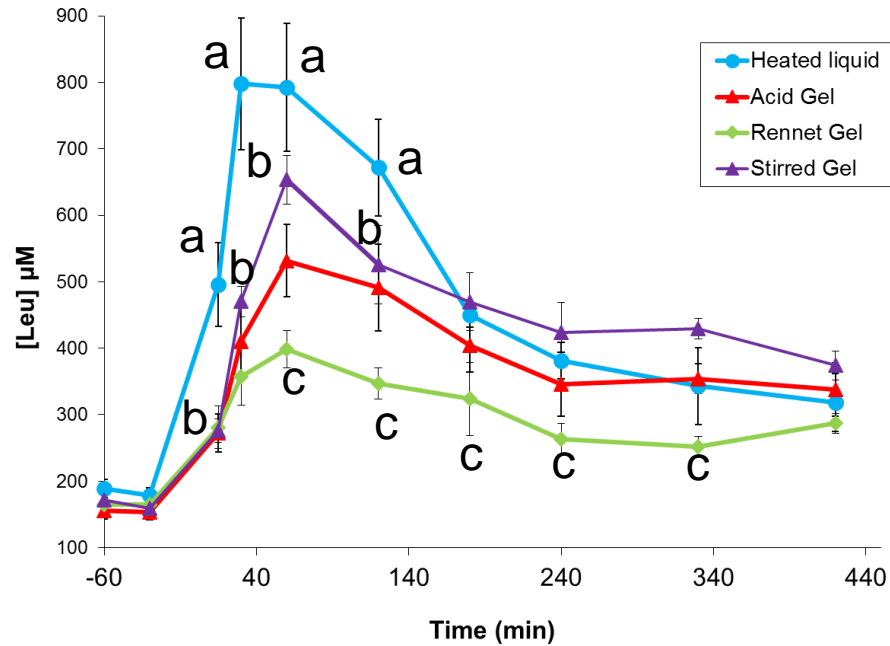


# The liquid-gel transition



Macroscopic scale

## Effect on absorption

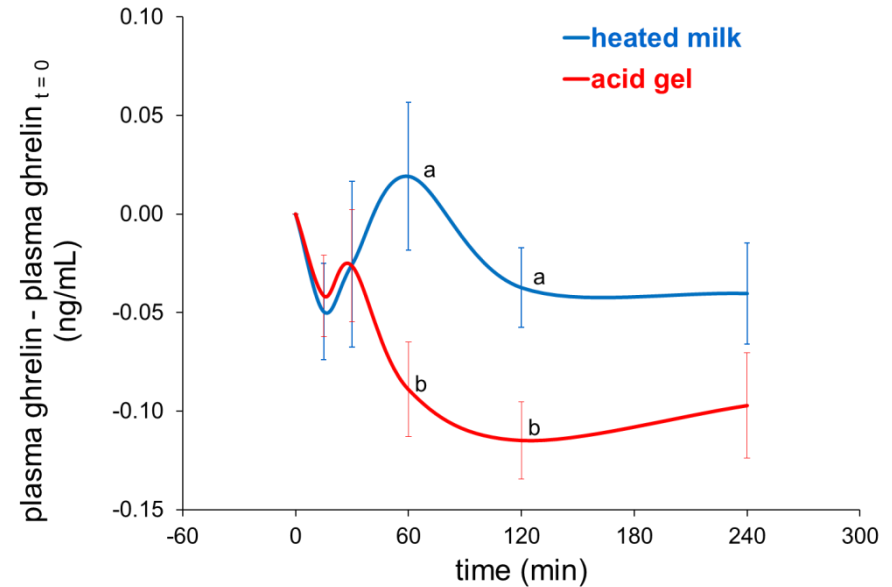


milk gelation:

→ delayed proteins transit → delayed AA absorption  
maximal AA concentration in the plasma

## Potential effect on satiety

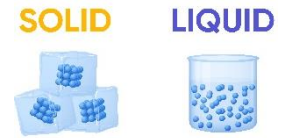
ghrelin (gastrointestinal hormone → appetite stimulation)



milk gelation:

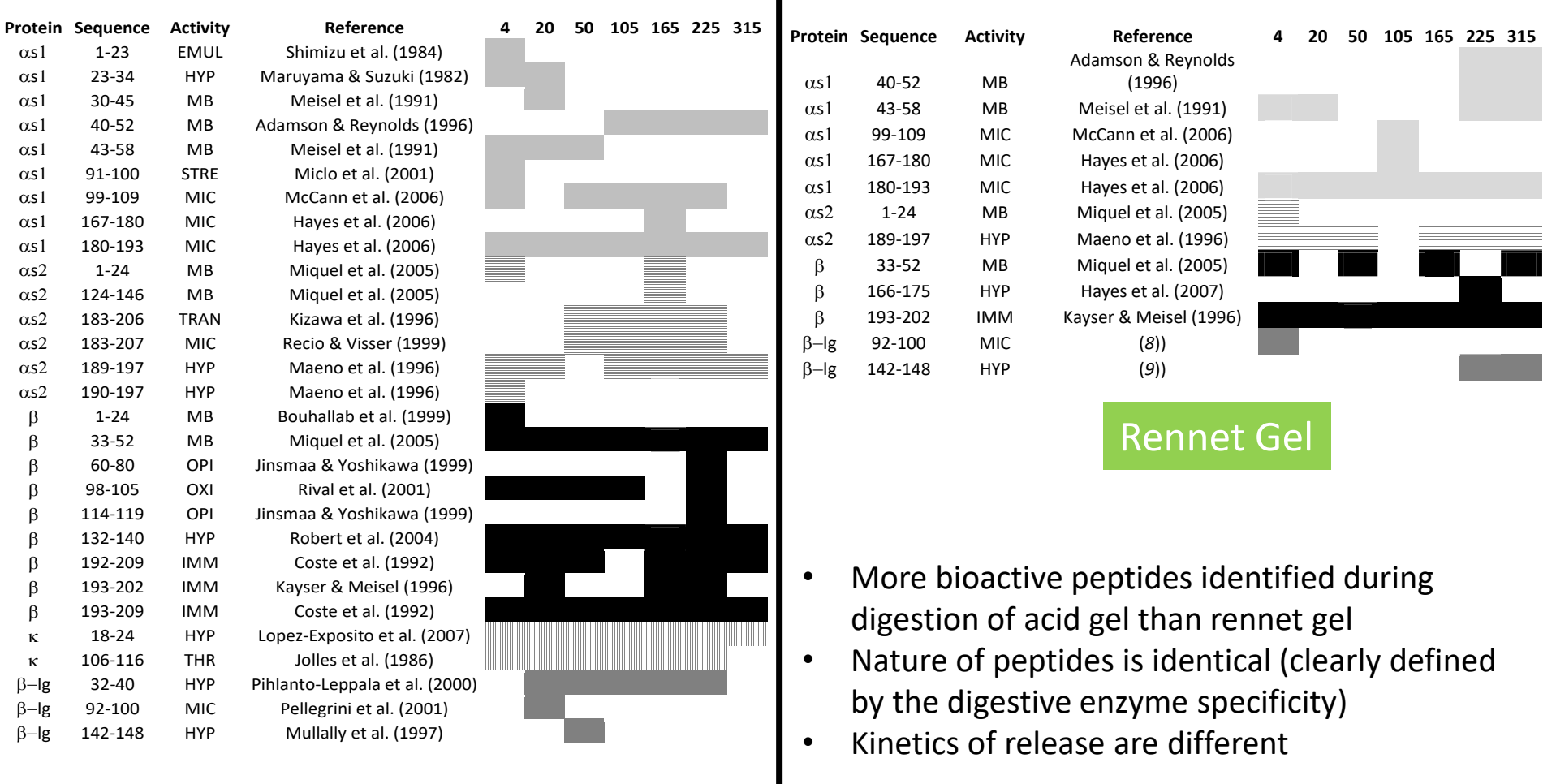
↘ postprandial ghrelin concentration =  
↑ satiety ?

# Bioactive peptides released during digestion differ from one matrix to another



Macroscopic scale

More than 16000 peptides identified by LC-MS-MS in the jejunum



Acid Gel

Rennet Gel

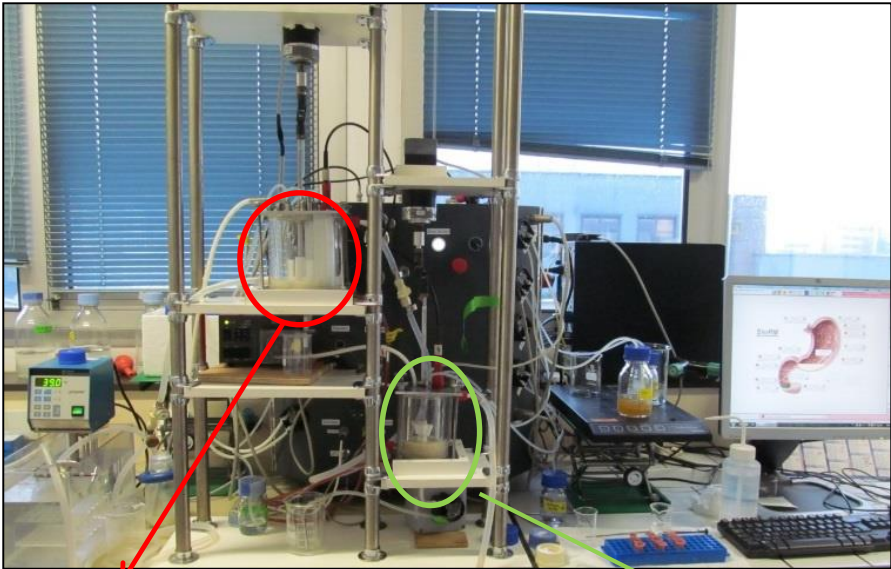
- More bioactive peptides identified during digestion of acid gel than rennet gel
- Nature of peptides is identical (clearly defined by the digestive enzyme specificity)
- Kinetics of release are different

Barbé et al. 2014  
Food Res Int

# Differential behaviour of acid/rennet gels in gastric conditions

- ☞ Acid/Rennet gel: identical composition, similar pore size
- ☞ ≠ Time of residence in the stomach (Acid 148 min /Rennet 352 min)
  - ☞ How can we explain this difference? Dynamic *in vitro* digestion of the 2 gels

**Ménard *et al.*  
Food Chem 2014**



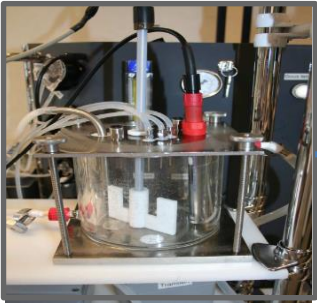
**DIDGI®**

**StoRM® software**

**Stomach**

**Small intestine**

- Pepsine
- Gastric lipase
- Simulated gastric fluid
- HCl



**Emptying :  
Elashoff's model**



- Pancreatin
- Bile
- Simulated intestinal fluid
- NaHCO<sub>3</sub>

**Emptying :  
Elashoff's model**

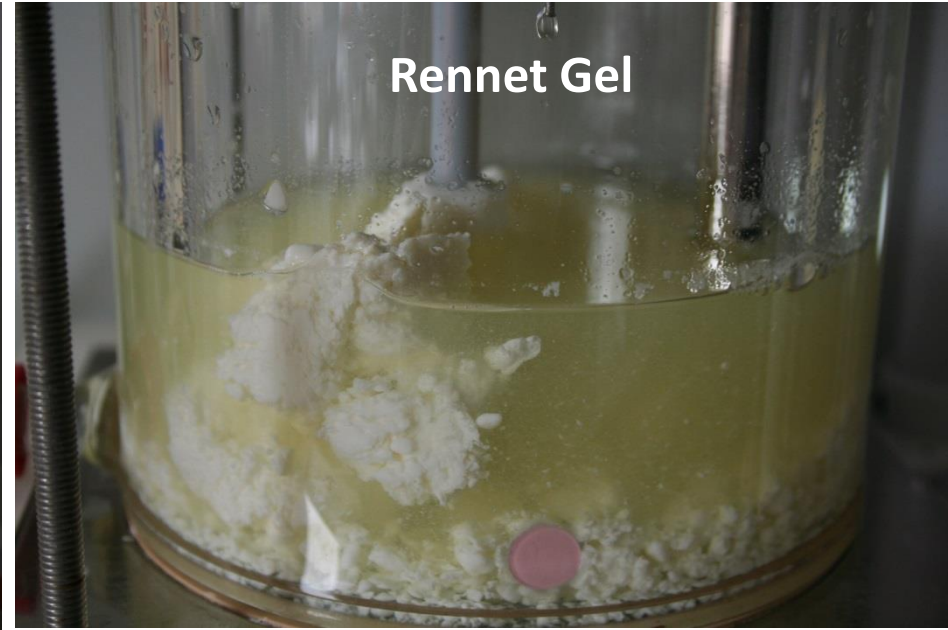
# Behaviour of acid and rennet gels in the stomach during *in vitro* dynamic digestion

Barbé et al.  
Food Chem. 2014

Acid Gel



Rennet Gel



Formation of a strong coagulum with rennet gel → slow down the gastric emptying of caseins

**The structure that a food adopts in the stomach is essential to understand its digestion**

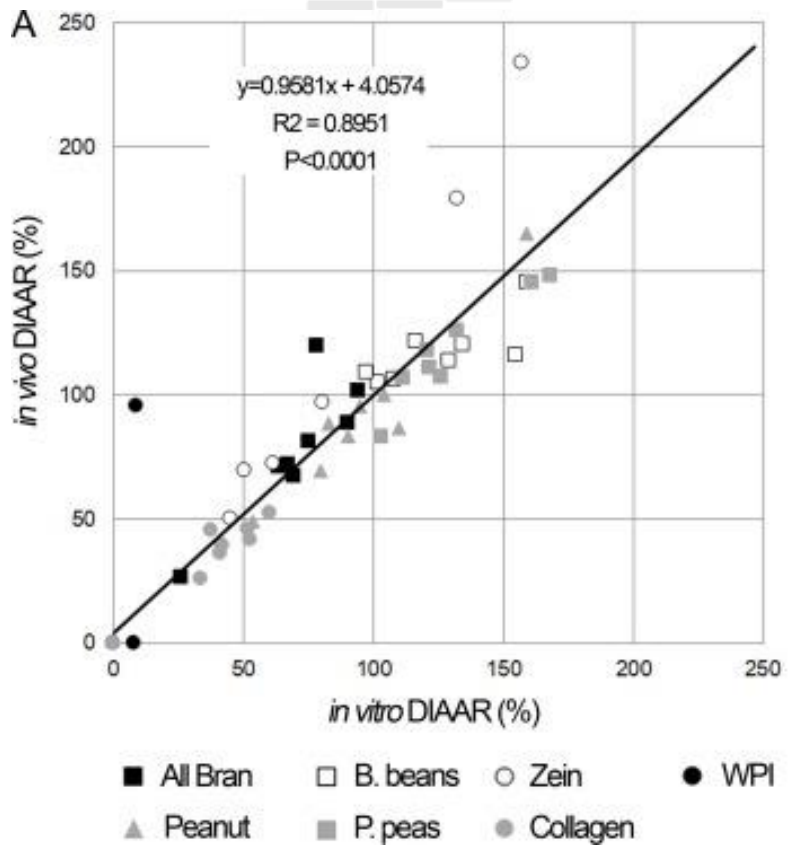
# Can we estimate plant protein digestibility with *in vitro* digestion models?



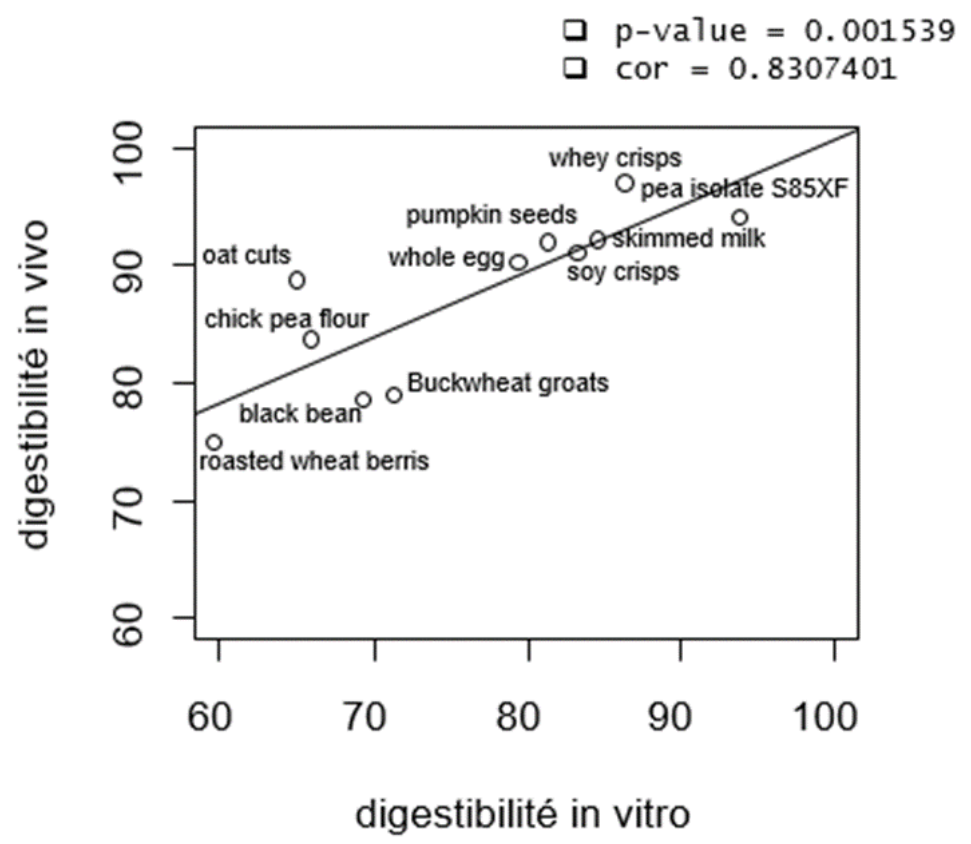
Le Feunteun S, Menard O, Dupont D.  
INRAE, Rennes, France



# In vitro/ in vivo correlation for protein digestibility measurement



Sousa et al. 2023



Nau et al. unpublished

Overall, good correlation are observed but some differences between studies persist

# Protein digestibility with a dynamic *in vitro* digestion model

Study of 4 plant-based foods: 2 solids / 2 liquids

Tofu



Seitan



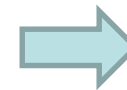
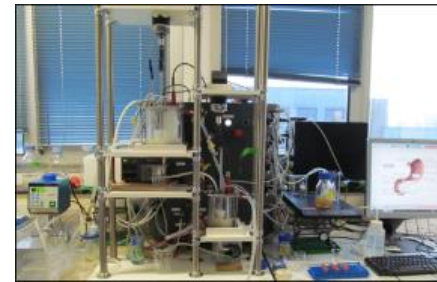
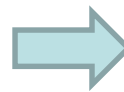
Soy milk



Pea Emulsion



Reynaud et al. 2021  
Food Chem. 341

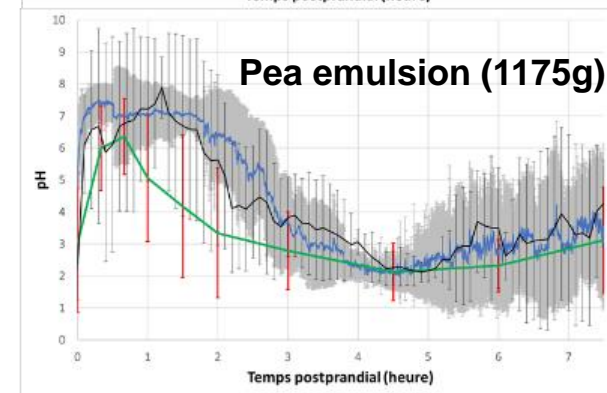
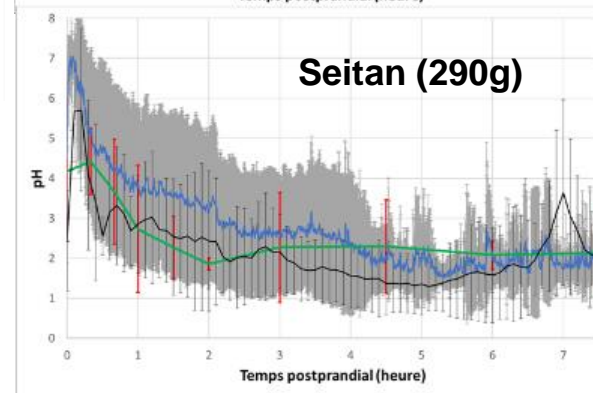
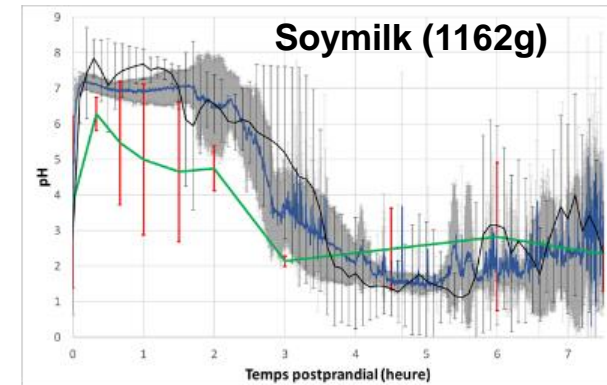
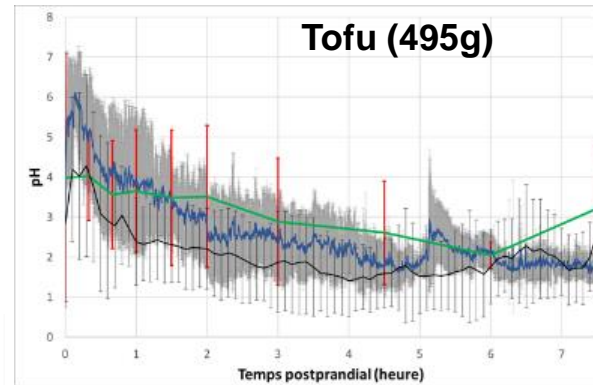
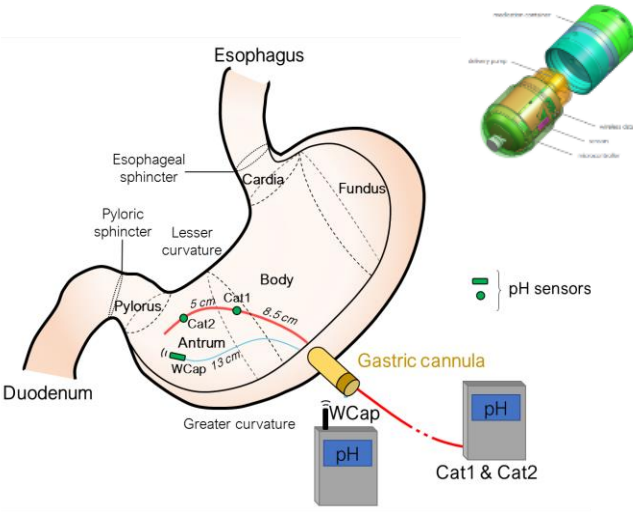


*In vitro*  
digestibility  
(%)

Dynamic *in vitro* digestion DiDGi®

# In vivo data are needed to program the digestion simulator

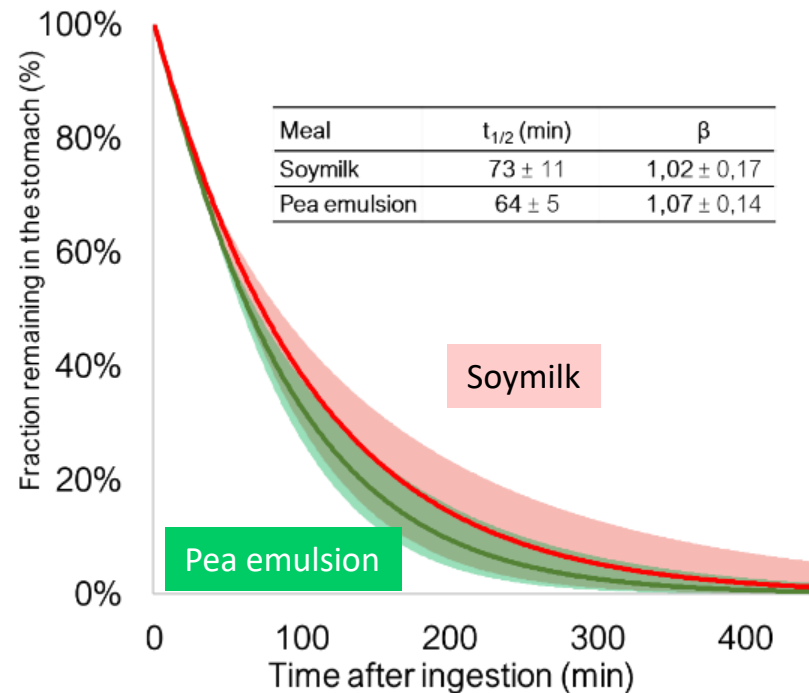
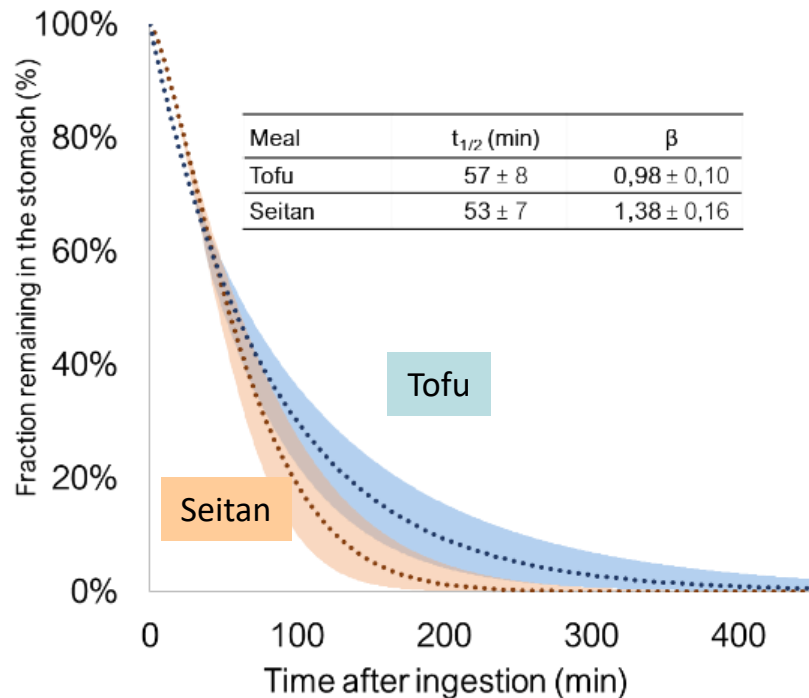
## Evolution of gastric pH





# In vivo data are needed to program the digestion simulator

## Gastric emptying



**Reynaud et al. 2020**  
**Food Res Int, 128**

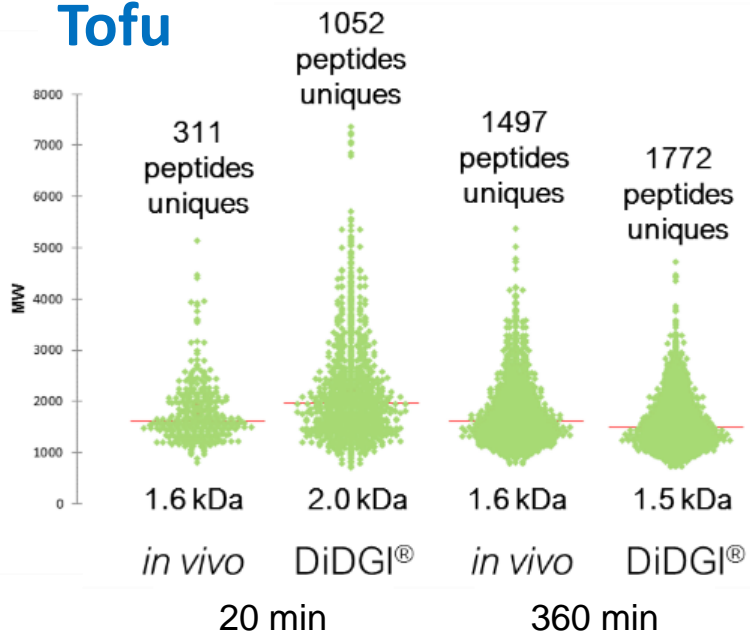
# Comparison between pig and *in vitro* data



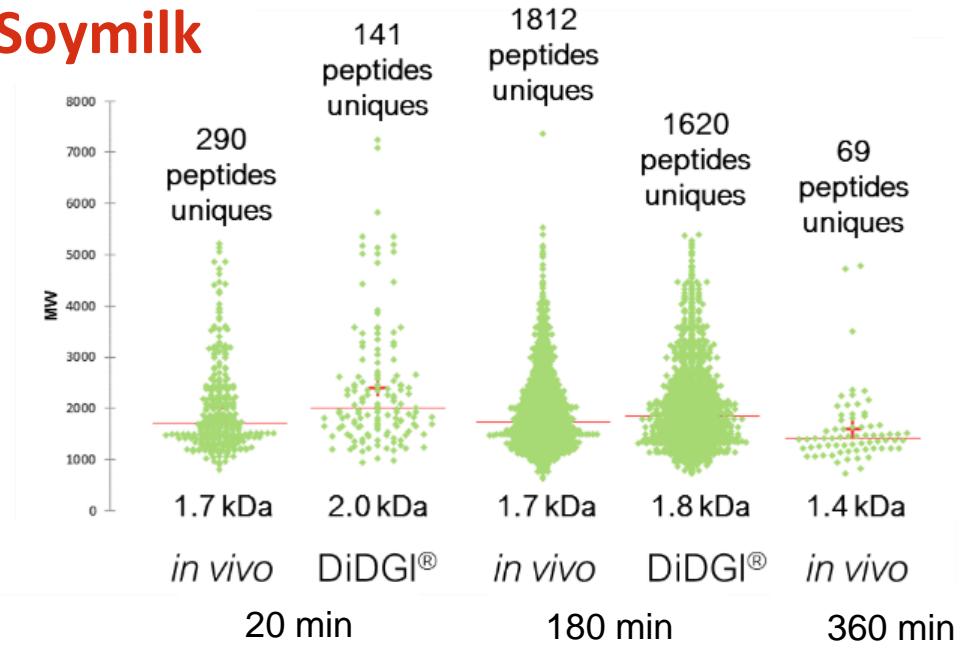
Model	Digestibility	Tofu	Soy milk
<i>in vivo</i>	True	97.1 ± 4.8%	99.4 ± 2.2%
	Apparent	56.5 ± 7.8% <sup>b</sup>	71.3 ± 2.5% <sup>a</sup>
<i>in vitro</i>	Apparent simulated	63.7 ± 3.5% <sup>b</sup>	72.7 ± 1.4% <sup>a</sup>

## Comparison of the gastric peptidome

### Tofu



### Soy milk



# Improving DHA delivery by encapsulation and design of functional foods

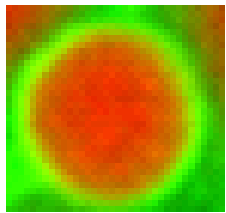
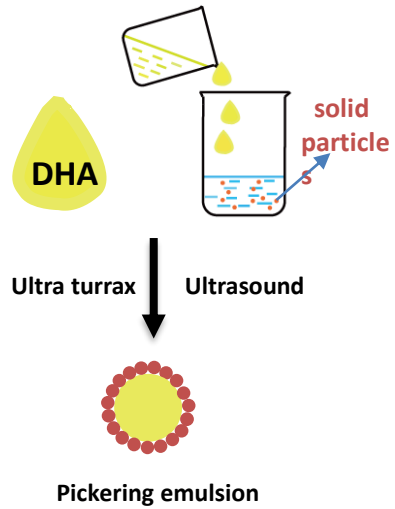


Wang J, Pedrono F, & Dupont D.  
INRAE, Rennes, France



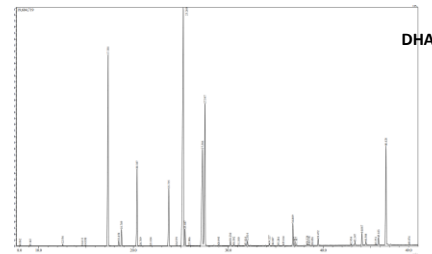
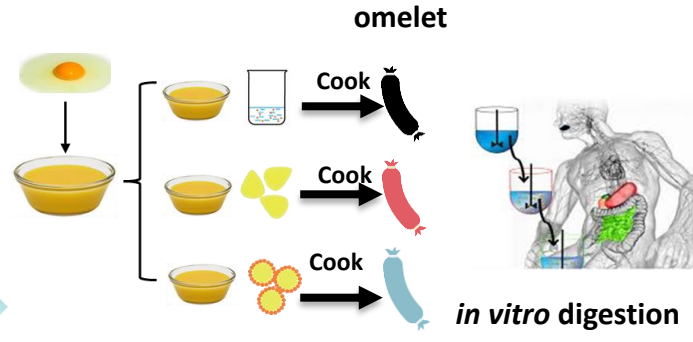
# General strategy

## DHA oil encapsulation



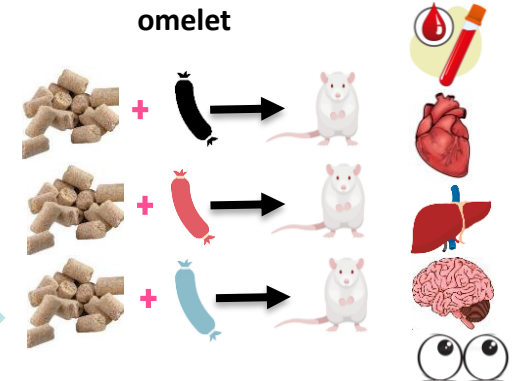
Characterization by CLSM

## DHA bioaccessibility



GC-MS

## DHA bioavailability, accretion and metabolism

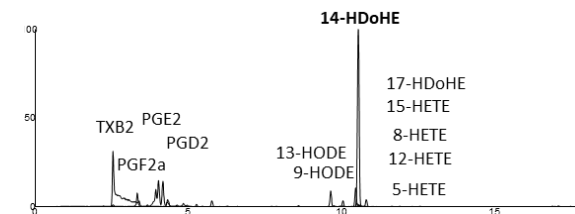


in a rat model

GC-MS



LC-QQQ



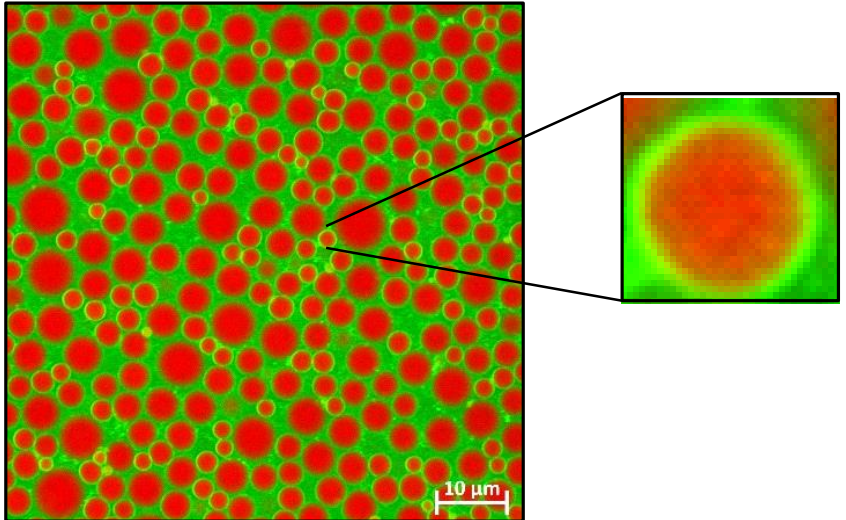
Wang et al.  
Food Res Int 2022

Wang et al.  
Frontiers in Nutr  
2022

Wang et al.  
Nutrients 2023

# DHA oil in emulsion and omelet

## In emulsion

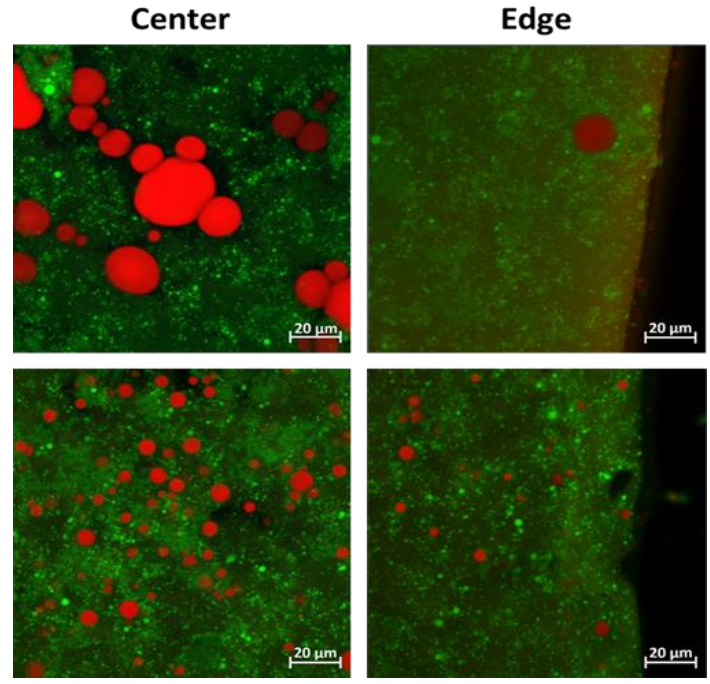


### Encapsulated DHA oil with heat-denatured WPI

DHA oil stained with Nile Red and proteins stained with Fast Green.

The particle size of heat-denatured WPI on average is 42 nm.

## In omelet



Non-encapsulated DHA oil

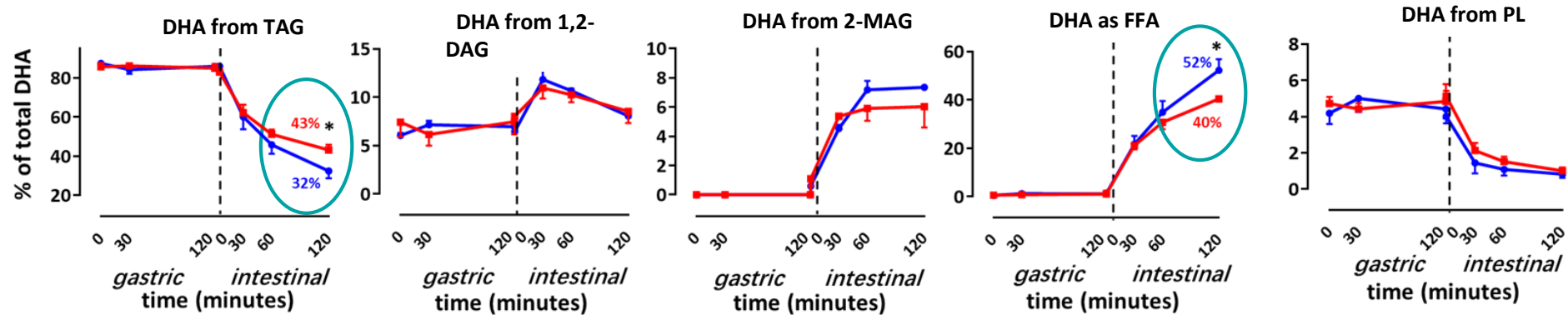
Encapsulated DHA oil

### Distribution of non-encapsulated and encapsulated DHA oil in omelets.

# Lipidomics allows to assess the bioaccessibility of DHA from different lipid species during digestion

Non-encapsulated DHA oil —■—

Encapsulated DHA oil —●—



The evolution DHA from different lipid species during digestion.

In gastric phase (pepsin and RGE):

- DHA oil was not hydrolyzed in gastric phase.

In intestinal phase (bile salt and pancreatin):

- Hydrolyzed TAG and released FFA encapsulation > unencapsulation

- Larger interaction area between DHA oil and pancreatic lipase made by emulsification (Maljaars, 2012).

- Around 10-25% and 40-70% of ingested TAG can be hydrolyzed in gastric and intestinal phase, respectively (Bauer et al; Carriere et al., 1993).

# Understanding human milk digestion to design new infant formulas that will have the same behaviour in the GI tract



Deglaire A., Menard O., De Oliveira S., Bourlieu C.  
& Dupont D.

INRAE, Rennes, France



# Human/ bovine milk / Infant Formula

## Lipid globule structure

Human milk

Bovine milk

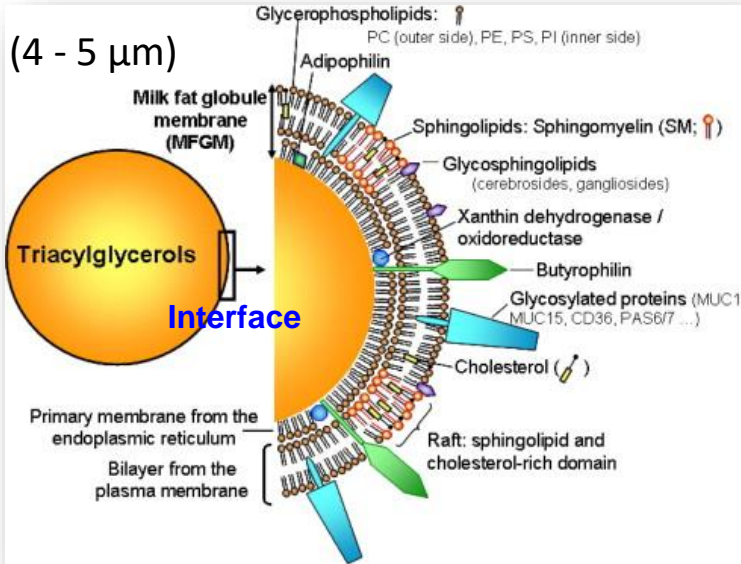
Infant Formula



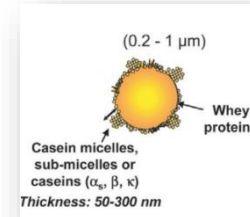
Native milk fat globule

Lipid droplets

Triacylglycerols



(Lopez, 2010)



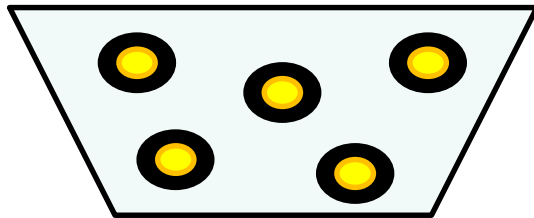
(0,2 - 1  $\mu\text{m}$ )

(Lopez and Briard-Bion, 2007)



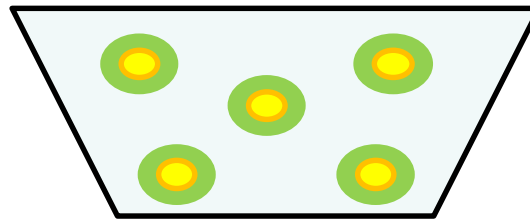
# Infant formulas: can we create lipid structures biomimetic on the native fat globule?

Formula  
T1



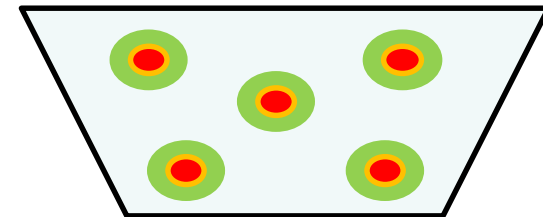
Interface 100 % Proteins  
100% vegetable oil

Formula  
T2

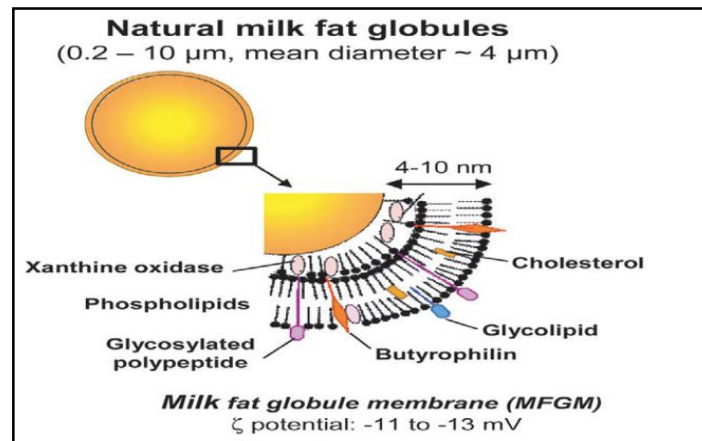


Interface 100 % phospholipids  
100% vegetable oil

Formula  
T3

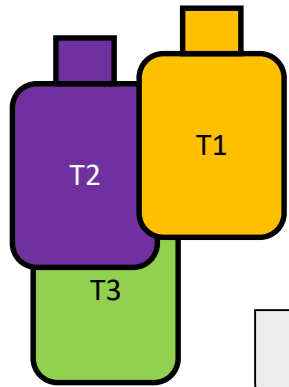


Interface 100 % phospholipids  
40% vegetable oil + 60% milk fat



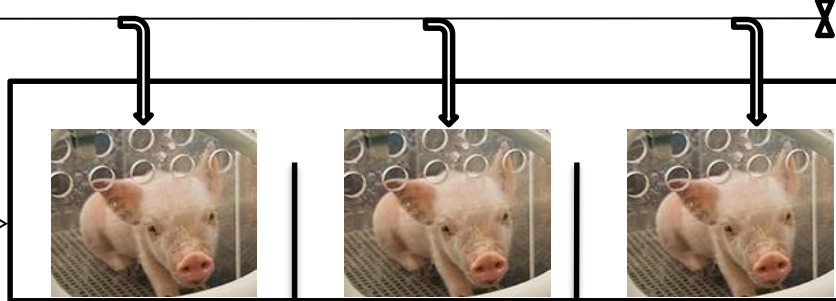
Lopez, (2007)

# Can the composition of infant formula modulate the physiological response of the neonate?



- Veg
- Veg + PL
- Dairy Fat + PL

Automatic meal delivery (10 meals/ day)



+  
Mother-fed piglets  
(MF = + control)



Slaughtering after

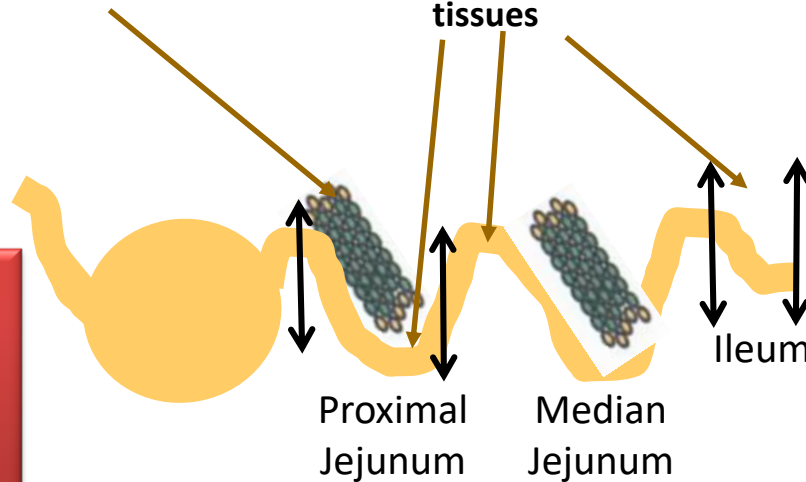
7 days

28 days

(90 min postprandial)

Mesenteric Lymph Nodes (MLN)

Collect of effluents and tissues

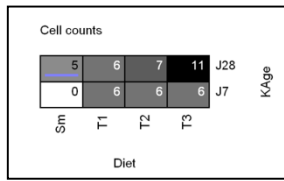


Effluents:  
-SDS-PAGE  
-Elisa

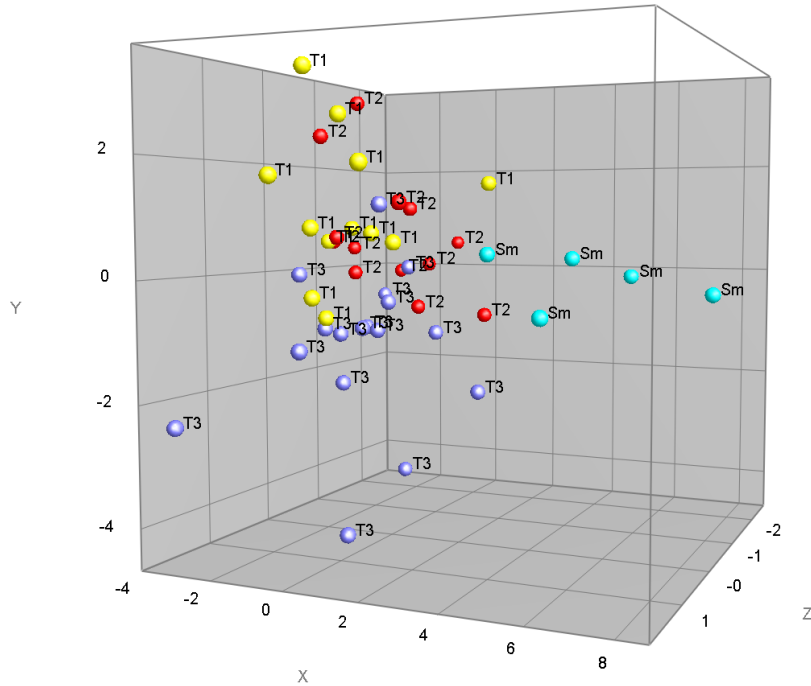
Tissues:

- Morphometry
- Enzyme Activities
- Intestinal Permeability
- Local immune response
- Microbiota

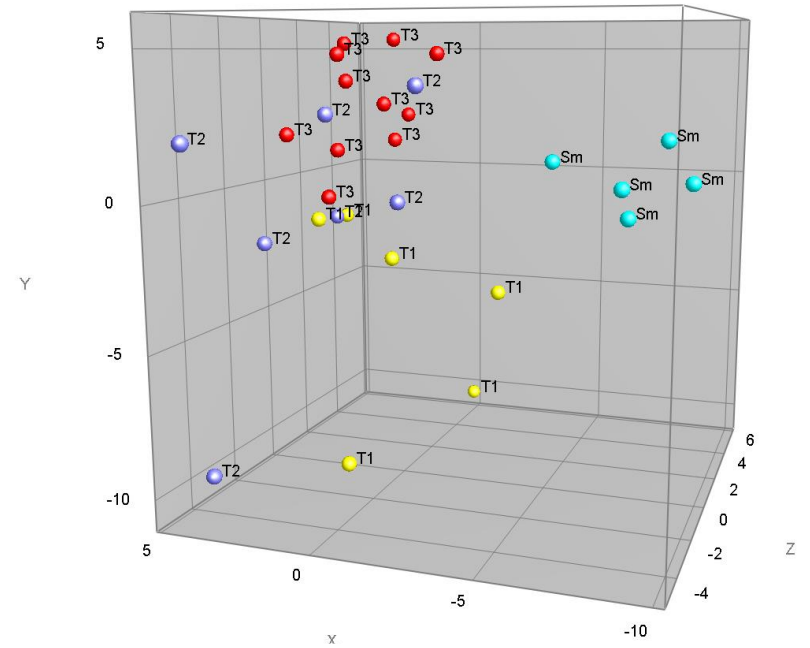
# Microbiota by DHPLC



D7 & D28

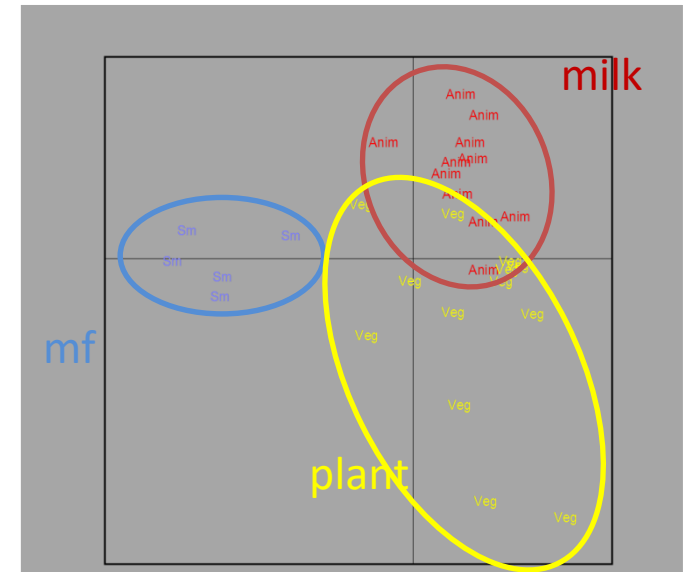


D28

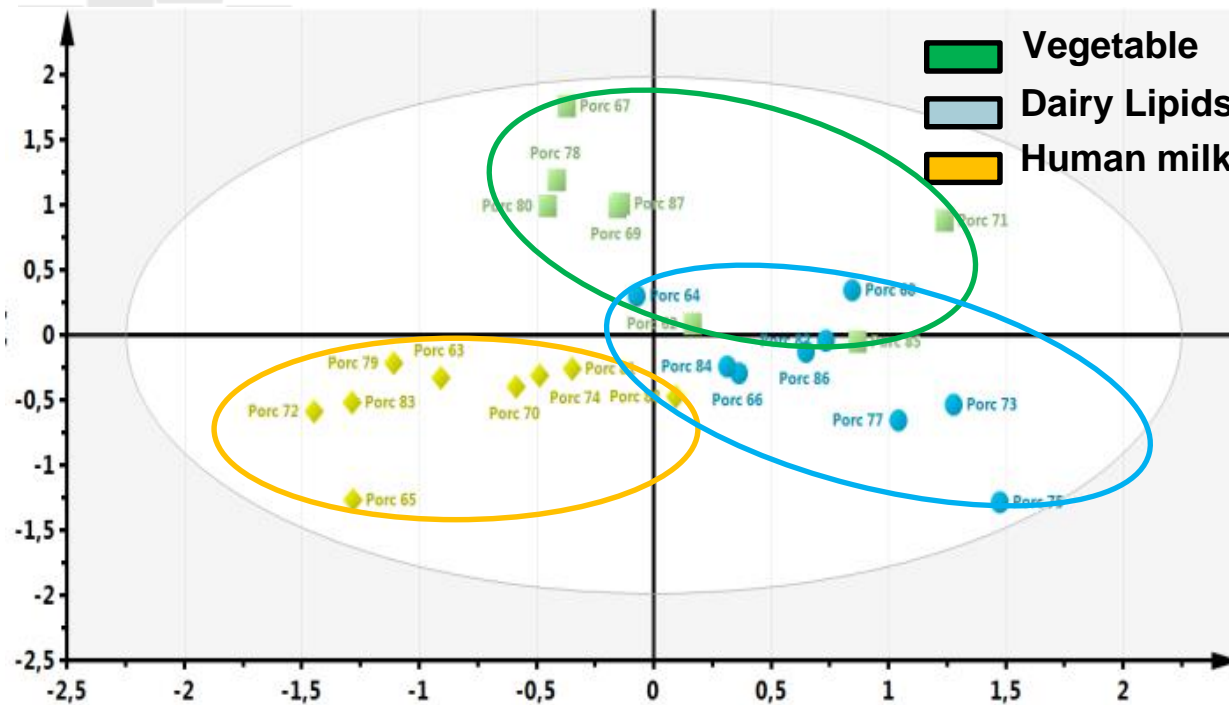


The composition/structure of the infant formula « orientates » the microbiota

More Proteobacteria with milk fat /  
More Firmicutes with plant oil



# What happens when they become older (140 d)?



If animals are submitted to a nutritional stress (high fat/sugar diet), some differences remain in:

- \* the microbiota composition
- \* the fecal metabolome with different metabolites (including propionate)
- \* the immune system with a reduced susceptibility to inflammation with milk lipids

# Conclusion

The structure/composition of food regulate the kinetics of protein digestion in the gastrointestinal tract and the release of amino acids in the bloodstream

Omic technologies (proteomics, peptidomics, lipidomics...) are great tools to identify the molecules that are released in the gut during digestion and assess the bioaccessibility of nutrients

Being able to design food structures for controlling the kinetics of hydrolysis of macronutrients will allow to obtain food particularly adapted to specific population



# The Bioactivity & Nutrition team at INRAE Rennes



## Scientists

Amélie DEGLAIRE – *Lecturer*  
Didier DUPONT – *Senior Scientist*  
Catherine GUERIN – *Lecturer*  
Steven LE FEUNTEUN – *Senior Scientist*  
Vincent Mathieu – *Senior Scientist*  
Martine MORZEL – *Senior Scientist*  
Françoise NAU – *Professor*  
Frédérique PEDRONO – *Lecturer*

Isuri JAYAWARDA – *Post-doc*  
Mathilde CANCELON – *Post-doc*  
Rozenn LE FOLL – *Post-doc*  
Anaïs LAVOISIER – *Post-doc*

## PhD students

Jiajun FENG  
Eleonora LOFFREDI  
Vibhu MISHRA  
Simon POGU  
Tanguy SAVIARD

## Technicians

Severine CHEVALIER  
Gwenaële HENRY  
Yann LE GOUAR

## Engineers

Marie-Françoise COCHET  
Julien JARDIN  
Olivia MENARD  
Jordane OSSEMOND

## Masters students

# Improving health properties of food by sharing our knowledge on the digestive process

## International Network

Dr. Didier DUPONT, Senior Scientist, INRAE, France

●  
**INFOGEST**  
●



# Main objective: understanding the mechanisms of food digestion

- Develop new *in vitro*, *in vivo* and *in silico* digestion models including some for specific populations (infant, elderly)
- Harmonize the methodologies and propose guidelines for performing experiments
- Validate *in vitro* models towards *in vivo* data (animal and/or human)
- Identify the beneficial/deleterious components that are released in the gut during food digestion
- Determine the effect of the matrix structure on the bioavailability of food nutrients and bioactive molecules





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 Norwegian Univ Life Sci Chalmers Univ Tech VTT Nofima Riga Stradin Univ Univ Ljubljana  
 Univ Zagreb  
 NIZO TNO Lund Univ

Wageningen UR  
 Teagasc Univ Reading  
 James Hutton Inst  
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 Agroscope Posieux  
 Inst Food Res  
 Agrocampus Ovest

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KTU Food Inst  
 Lithuanian Univ HS  
 Gdansk Univ Tech  
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NGO

**India**

Univ Belgrade  
 Polish Academy of Sci  
 Univ Novi Sau

Aristote Univ Thessaloniki  
 Centr Food Res Inst  
 Ben Gurion Univ  
 Technion

**New Zealand**

Pom Med Univ  
 Ege Univ  
 Univ California Davis

**USA**  
 Riddett Inst  
 Plant Food Res

**Japan**

767 scientists - 280 institutes - 60 countries

# Industry involvement

~ 60 private companies are following INFOGEST



# 7 Working Groups running in parallel



Chair  
Didier Dupont - France  
didier.dupont@inrae.fr



[www.cost-infogest.eu](http://www.cost-infogest.eu)



Vice-chair  
Alan Mackie - UK



In vitro  
models of  
digestion  
**WG1**



Isidra Recio



Food  
interaction –  
meal  
digestion  
**WG2**



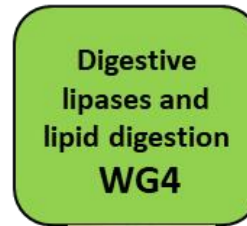
Pasquale Ferranti



Absorption  
models  
**WG3**



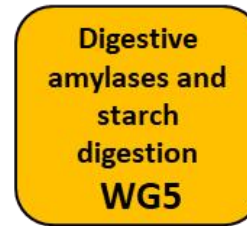
Linda Giblin



Digestive  
lipases and  
lipid digestion  
**WG4**



Frederic Carriere



Digestive  
amylases and  
starch  
digestion  
**WG5**



Daniela Freitas



In silico  
models of  
digestion  
**WG6**



Steven Le Feunteun



Imaging  
Technologies  
applied to  
digestion  
**WG7**



Paul Smeets



Andre  
Brodkorb



Lotti Egger



Uri Lesmes



Brigitte Graf



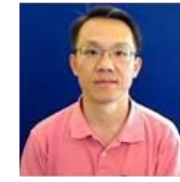
Marion Letisse



Leslie Couedelo



Marilisa Alongi



Choi-Hong Lan



Luca Marciani

# Some outputs

## *In vitro* gastrointestinal digestion Consensus INFOGEST protocol

Minekus et al. 2014  
Food & Function, 5, 1113-1124  
**3125 citations**

### Oral phase

Mix 1:1 with Simulated Salivary Fluid (SSF)  
salivary amylase (75 U/mL)  
2 min, pH 7

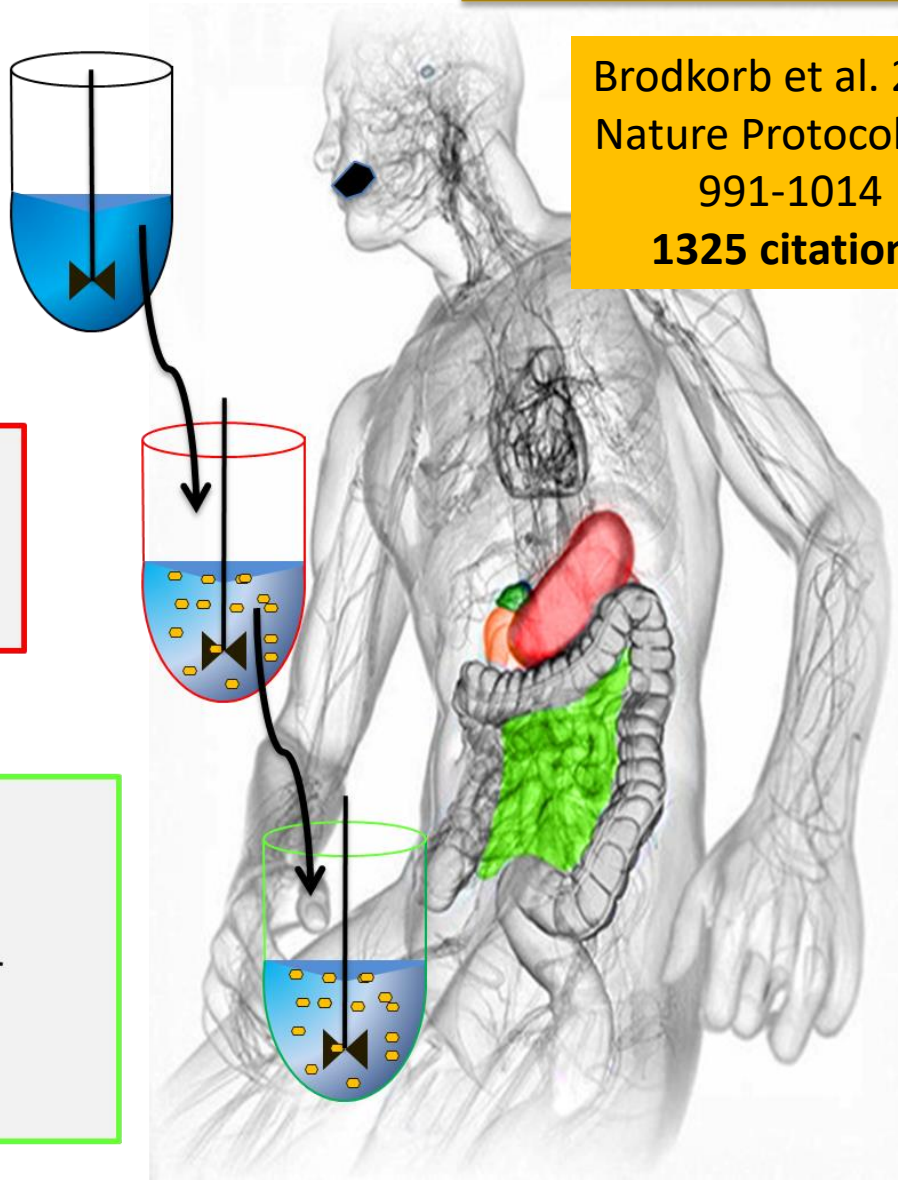
### Gastric Phase

Mix 1:1 with Simulated Gastric Fluid (SGF)  
Pepsin (2000 U/mL)  
2h, pH 3

### Intestinal Phase

Mix 1:1 with Simulated Intestinal Fluid (SIF)  
Enzymes  
Pancreatin (based on trypsin 100 U/mL) or  
Pure enzymes  
Bile (10mM)  
2h, pH 7

Brodkorb et al. 2019  
Nature Protocol, 14,  
991-1014  
**1325 citations**





We are pleased to announce the next  
**8<sup>th</sup> International Conference on Food Digestion**



**in Porto, Portugal, 9-11 April 2024**