

# Dynamic *in vitro* models of the gastrointestinal tract – tools to study what happens in the GI tract with food or drugs

## Accurately mimicking gastrointestinal digestion and fermentation

The models for gastrointestinal research, developed by TNO in The Netherlands, and implemented at Maastricht University – campus Venlo, represent the most advanced platforms for studying the fate of food (constituents), drugs and/or their interaction, both in the stomach and small intestine (TIM-1 system) and the large intestine (TIM-2 system).

The models (nick-named TIM, for TNO in vitro model of the GI tract), closely mimic human (or animal) digestion and fermentation, with dynamic changes of the physiological parameters, such as pH in the gastric compartment, and concentrations of bile and pancreatic enzymes in the small intestine. The colon (or large intestinal) model, is inoculated with a dense active microbiota of fecal origin, which contains all of the hundreds of microbial species that are normally present in the gut microbiota.

## Technology

The models simulate amongst others body temperature, intestinal secretions, transit of a 'meal' through the GI tract, and absorption. Especially the latter is an essential feature of the models. This is done with dialysis systems that simulate uptake by the body, and prevent product inhibition of digestive enzymes by digestion products, and inhibition of members of the gut microbiota by their own produced microbial metabolites. Normally in the body these digestion products and microbial metabolites are also absorbed. They represent the bioaccessible fraction.

## Different hosts, ages and meals

Different protocols are available for different age-categories (babies, adults and elderly), different hosts (human, pigs, dogs, pre-ruminant calves), different meals (e.g., glass of water, milk, yoghurt, FDA-approved high-fat meal, European breakfast, ...), and a few diseases (those for which literature data is available with respect to dynamic GI parameters).



TIM-1



TIM-2



## Validation, examples and mechanistic studies

### Validation

Both models have been validated extensively. For TIM-1 this has been done on the basis of comparisons between *in vivo* and *in vitro* data. Due to the limited accessibility of the colon, for TIM-2 this was done on the basis of sudden-death individuals.

### Examples of the use of TIM

Samples can be taken from the models at different locations and through time, mimicking a plasma curve, with the added benefit of being able to make a mass-balance and study underlying mechanisms.

The models can be used to study the stability and/or efficacy of functional (food) components or APIs. For instance, inhibition of fat and cholesterol absorption, aiding digestion using exogenously added enzymes, dissolution profiles of APIs from different formulations, release of antioxidants and/or vitamins, survival and effect of probiotics, effect of prebiotics.

### Regulatory aspects

Results of experiments in TIM are increasingly being used in regulatory dossiers, both in food and pharma. Clearly, the *in vitro* experiments cannot replace *in vivo* trials, but due to the very high predictability of TIM for clinical trials, the results are used as supportive evidence and to study the mode of action of functional food components and pharmaceuticals.

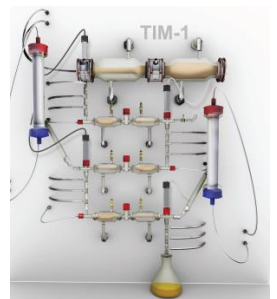
### Combinations with other research tools

Samples taken from TIM can be combined with other biological models, such as cultured epithelial cells (even biopsies), organoids, or immunological cells, to get an even better prediction for clinical trials, *e.g.*, with respect to absorption, epithelial damage, immunomodulation, *etc.*

### Validation examples

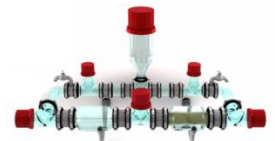
#### TIM-1

- carbohydrate digestion
- protein digestion
- fat digestion
- probiotic survival
- vitamin bioaccessibility
- drug formulations



#### Validation TIM-2

- microbial composition
- microbial activity



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