Agent-based modelling of enzymatic digestion using experimental data

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Human digestion is a complex process that involves diffusion and reaction effects where enzymes govern the denaturation and breakdown of proteins. In this work we build an agent-based model of gastric digestion of gel pieces of plant proteins (rapeseed). This model has been designed with the aim to obtain a faster computation than dynamic molecular models [1], as fast simulations are actually a prerequisite for learning the values of model parameters from experimental data. We have so far exploited additional coarse-grained equation-based models to learn part of the parameters values using evolutionary optimization. Future developments will be devoted to extend the learning process to all parameters in the model.

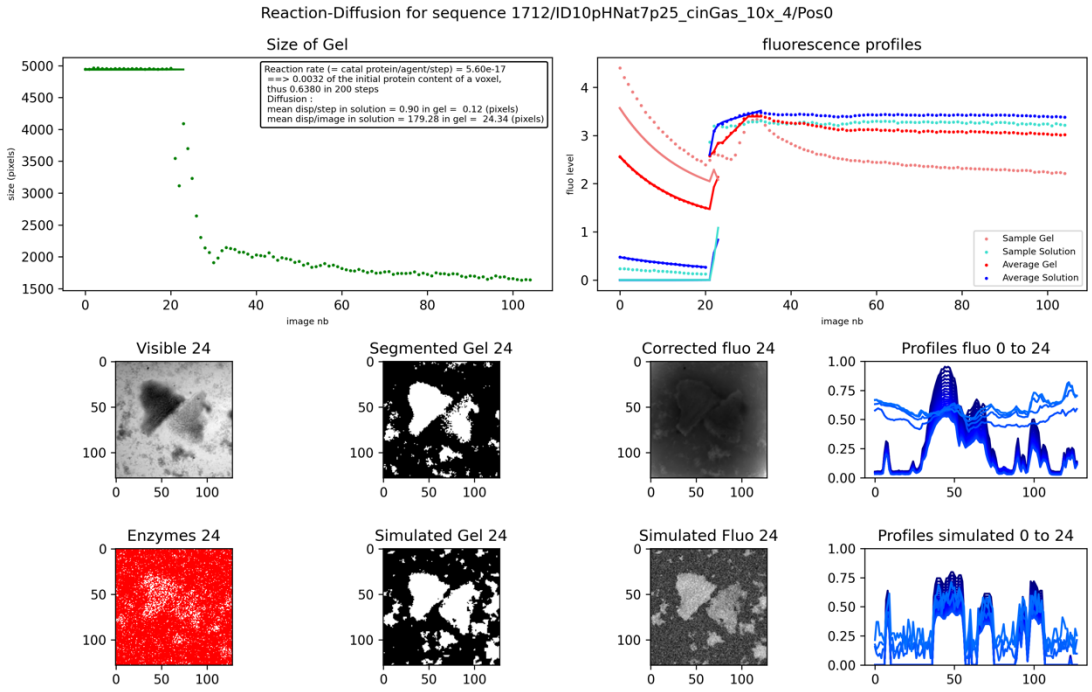

Figure 1*: A snapshot of the monitoring of the agent-based model at step 24 (injection step). The top row displays the average experimental values along time (dots) and simulation until current step (lines): size of gel areas (left) and average fluorescence values (right). The middle and bottom rows display the experimental images (visible, segmented and corrected fluo at step 24) and the simulated images (position of enzymes, simulated gel areas and simulated fluorescence). The evolution of profiles for experimental and simulated fluorescence images till the current step are displayed in the last column (blue curves).*

The experimental data have been collected in 2020 at the DISCO beamline of Synchrotron Soleil with an UV fluorescence microscope (TELEMOS device): in-vitro gastric digestion is based on a standardized method [3] and gels were made from canola proteins solutions [4]. Less than (100×100×100) micron gels pieces were positioned in the UV light beam thanks to a special injection cell designed on purpose, and the temperature was regulated at 37 °C.

The experimental process is divided into three steps, to deal with a complex effect known as photobleaching [5], which is due to a damage on proteins fluorophores induced by Xray-light: (1) *a bleaching period* where the gel gets UV exposure (during 20 min, when fluorescence makes its strong decay); (2) *an injection period* where the gastric solution is injected at constant speed using automated syringes; (3) *a reaction-diffusion period* where the enzyme effect is observed during a period ranging from a few minutes to several hours.

Two sequences of images, visible and fluorescence microscopy, were captured (one couple of images per minute). Visible images are segmented to identify gel and solution areas and average values were computed for both areas on the fluorescence images (see fig 1).

Our model of the fluorescence dynamic is designed as follows. For the fluorescence bleaching step, a double exponential equation is fitted to the mean grey levels of the sequence of fluorescence images, for the gel and solution areas. For the injection step, we have built a model based on equations that combines bleaching, absorption, average diffusion in solution and other factors. The parameters have also been calibrated on the mean grey levels sequence using an evolutionary algorithm (CMA-ES [2]). The previous parameters are then used to govern the agent-based model.

The agent-based model maintains a set of agents representing a number of enzymes (a fraction of a mole of enzymes), inside a 3D volume (N*M*H voxels), where some voxels are occupied by proteins gel and others by enzymatic solution. This volume is initialized with a "backprojection" of the first image of the sequence (a gel pixel is considered as the projection of the voxels above him, with height proportional to the intensity of the visible image and content given by the level of the fluorescence image). Agents are moving with different diffusion rates for gel and solution. Once an agent is on a gel voxel, it reacts and catalyzes a given amount of gel (governed by a reaction rate). Movements occur at discrete time, δ_t, with a few hundreds of iterations (typically 200 to 600) between two images.

This study proves the feasibility of an agent-based modelling for protein digestion. Several aspects remain to be improved to get more precise results, for instance introducing a more complex reaction model. In the future, calibration will be performed for part of the parameters (reaction and diffusion rates, currently fixed with theoretical values). We will also consider different proteins systems, different enzymes (intestinal) and deal with other experimental setup such as Xray diffraction measurements using capillary tubes (SAXS or SANS measurements).

References

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