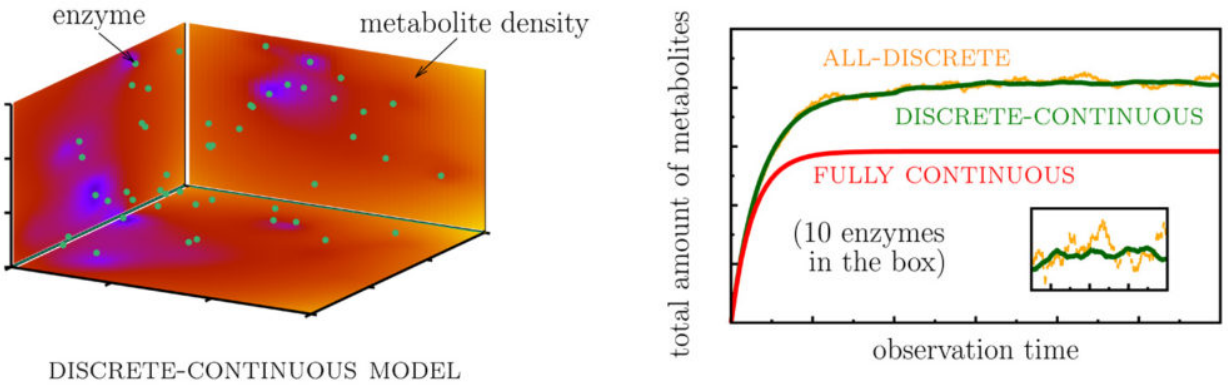
Combining discrete and continuous for a clever multiscale modelling

There is rarely a process in physical, biological or chemical sciences that spans a single time or length scale. Computational methods must be chosen accordingly when modeling such processes. For instance, *ab initio* quantum-mechanical calculations or molecular dynamics simulations, although highly reliable, are computationally inefficient for large-scale systems or long-lasting processes. One way to proceed in such cases is to develop multiscale approaches. Multiscale means that methods applicable at different scales are combined into a single computational framework. Typically this is done by using high resolution simulations on short length and time scales, to calculate quantities that are needed as input parameters for lower resolution models, applicable on longer time and length scales. This is known as the bottom-up approach. In the top-down approach, in contrast, the observed properties of a system on a high level are used to deduce the mechanisms or parameters for a lower lever model.



Discrete-continuous model and the comparison with the all-discrete and fully continuous approaches, in which all molecular species in a system are treated as discrete particles or described by continuous fields, respectively

An alternative is to combine two or more approaches on equal footing. A scientifically sound example is the enzyme kinetics. Enzymes are large proteins that catalyse many important reactions in living organism and are ubiquitously used in biotechnological applications. The metabolites, *ie* the reactants that these proteins catalyze, are typically much smaller and move faster than the enzymes. Additionally, in a typical living cell or a catalytic reactor, there is abundance of reactants but only relatively few enzymes present. Thus, it must be possible to describe the behaviour of reactants by continuous fields, representing their densities in space and time, and to use discrete particles to represent the enzymes. The enzymes will then change the

values of these fields locally where they reside, similarly as it happens in nature.

What are the advantages of such an approach? The figure on the right shows that at a low concentration of enzymes, the discrete-continuous method agrees with the all-discrete, stochastic simulations of the same system, but both approaches differ qualitatively from a fully continuous model, in which both enzymes and reactants are described by continuous fields. This effect is long known in the literature and means that continuous models are inappropriate when the number of molecules is low.

Now, while it is unphysical to describe enzymes by continuous fields at low enzyme concentrations, it might be possible to treat all molecules as discrete particles, as the figure demonstrates. However, at high concentrations of metabolites the methods developed so far become inefficient because computational cost increases at best linearly with the number of molecules in a system. The advantage of the discrete-continuous method is that we pay nearly the same price, independently of the density of metabolites.

Stochastic systems contain random elements, and their behaviour can therefore be predicted only with certain probability. This is unlike deterministic systems whose behaviours are absolutely destined. Examples of stochastic systems are numerous and include practically all processes in living organisms, business economies and market behaviour, social systems, etc. It is frequently the case that there is more than one source of stochasticity (randomness) in a system, and it becomes increasingly important, in particular for understanding living systems, to separate different sources of stochasticity. The discrete-continuous method can help do this job. When appropriate, a system can be divided into stochastic and deterministic subsystems, where the latter results merely from averaging of the originally stochastic subsystem. For instance, the enzyme-metabolite system is stochastic in nature, where the stochasticity is in particular due to diffusive (or random, Brownian) motion of both enzymes and metabolites. By averaging out the stochastic degrees of freedom of metabolites, we end up with a deterministic continuous model that is naturally coupled with the enzyme subsystem, as described above. The stochastic behaviour due to enzymes alone can now be studied more conveniently (see the figure and note much stronger stochastic fluctuations by the all-discrete, stochastic approach). Inverse is also possible when needed, provided of course the concentration of enzymes is appreciable. This approach can be applied to other systems as well.

Although methods similar to the discrete-continuous model have been previously used by other researchers, the approach undertaken by Kondrat *et al.* has the advantage of being more rigorously established, and has therefore the potential to be extended and adjusted to a large variety of systems. The method can also be naturally placed within the bottom-up or top-down frameworks. For instance, the diffusion and reaction properties of enzymes and metabolites can be obtained from Brownian or molecular dynamics simulations and transition path sampling simulations, respectively, or by using other techniques. In this way the method can become an efficient and reliable computational framework for studying physical, chemical, biological and other

problems.

Publication

Discrete-continuous reaction-diffusion model with mobile point-like sources and sinks.
Kondrat S, Zimmermann O, Wiechert W, von Lieres E
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