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An hybrid analysis of multiscale models for angiogenesis

Angiogenesis, the growth of new blood vessels, is an important natural process occurring in the body, both in health and in disease. It is an example of complex system: the endothelial cells are the building blocks for the vessels and they interact by regulation signals, forming a network of capillaries in order to reach every part of the body.

As examples of real experimental systems we consider tumour driven angiogenesis and the embryonic mouse retinal angiogenesis.

An angiogenic system is extremely complex, due to its intrinsic multiscale structure; a major source of complexity in the mathematical modelling derives from the strong coupling of the kinetic parameters of the relevant stochastic branching-and-growth of the capillary network at the microscale, with a family of interacting underlying fields at a macroscale. This is the reason why in literature we may find a large variety of mathematical models addressing some of the features of the angiogenic process, and still integration of all relevant features of the process is an open problem.

Thus our main goal is not in providing additional models for the angiogenic phenomenon but in addressing the mathematical problem of reduction of the complexity of such systems by taking advantage of their intrinsic multiscale structure. A satisfactory mathematical modelling of angiogenesis and of many other fiber processes requires a geometric theory of stochastic fibre processes. We present here a simplified stochastic geometric model, largely inspired by current literature, both mathematical and biological ones, for a spatially structured angiogenic process, strongly coupled with a family of relevant underlying fields.

The branching mechanism of blood vessels is modelled as a stochastic marked counting process describing the birth of endothelial cells, while the whole network of vessels is modelled as the union of their trajectories; finally, capillary extensions are expressed by a system of a random number of stochastic differential equations, coupled with the PDEs describing the evolution of the underlying fields involved in the process. On one side the kinetic parameters of the construction of the capillary network depend upon the family of underlying fields, on the other side the evolution of the underlying fields relies on the evolving capillary network. Since this one is a stochastic process, the evolution equations of these fields will be a set of random partial differential equations, leading to random kinetic parameters. We are thus facing a problem of double stochasticity. This is a major source of complexity which may tremendously increase as the number of cells becomes extremely large, as it may happen in many cases of real interest. Under these last circumstances,

by taking into account the natural multiple scale nature of the system a mesoscale may be introduced, which is sufficiently small with respect to the macroscale of the underlying fields, and sufficiently large with respect to typical cell size. At the level of this mesoscale, we may then approximate (law of large numbers) the contribution due to the vascularization process by local mean values, in the equations for the underlying fields thus providing a family of underlying deterministic fields. We may then use these approximate mean fields to drive the evolution of the relevant stochastic processes cells at the microscale. In this way only the simple stochasticity of the geometric processes of birth (branching) and growth is kept, and it is possible to generate a nontrivial and realistic geometric pattern of the capillary network. This kind of models are known as hybrid models since we have substituted all stochastic underlying fields by their averaged counterparts; most of the current literature could now be reinterpreted along these lines. It is necessary to stress that anyhow substituting mean geometric densities of tips, or of full vessels to the corresponding stochastic quantities leads to an acceptable coefficient of variation (percentage error) only when a law of large numbers can be applied, i.e. whenever the relevant numbers per unit volume are sufficiently large; otherwise stochasticity cannot be avoided, and in addition to mean values, the mathematical analysis and/or simulations should provide confidence bands for all quantities of interest. This fact is well evidenced by the numerical simulations. If we homogenize the underlying fields ab initio we obtain a trivial capillary network, which confirms that during the early phases of the network formation, the number of endothelial cells is not sufficiently large to let us apply laws of large numbers yet.