Comment

# Nonlocal Models of Biological Phenomena
## Comment on "On the Interplay between Mathematical and Biology Hallmarks Towards a New System Biology" by Bellomo, Elaiw, Althiabi & Alghamdi

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The Bellomo *et al.* [3] review provides a general strategy for modelling living systems with particular attention to the description of biological processes at microscopic scale. Descriptions in different scales seem to be deeply justified because biological processes are inherently multi-scale. For instance, if we consider processes such as diseases we find that they are present over many biological scales. First symptoms are almost always observed at the clinical (macroscopic) level, but if we look more closely at the origins of those diseases, it is easy to see that the pathological process often begins with intracellular alterations (microscopic level). Therefore, there is a need for new mathematical tools that are suitable to capture such complexities. The methodology proposed by Bellomo *et al.* [3] is based on kinetic theory for active particles and multi–scale links between different levels of description. The mathematical structures may be the proper kinetic equations for both closed or open systems. The important step is understanding the essence of multi scale approaches and applying the asymptotic methods to derive of macro–scale models (cf. [3, 4] and also [2, 8] and references therein) for which the experimental identification of parameters is usually easier.

These macro–scale models may be connected with a microscopic level description, i.e. the level of interacting individual agents ("*active particles*") of a living system (cf. [3, 4]. Typically, biological processes are so complex that when constructing a mathematical model we need to make many simplifying assumptions. The trick is to propose a simplification which will make the processes easier to understand but that will not counterfeit it. An example of a mathematical technique that can be extremely useful in describing many phenomena in biological systems, and that is complementary to those indicated by

Bellomo *et al.* [3] are integral terms describing nonlocal interactions. For instance, nonlocal terms might be used to describe the phenomena of intercellular communication. Examples of such intercellular communication are paracrine signalling, when a cell produces chemical substance signals that are secreted to the extracellular space and induce changes in nearby cells and autocrine signalling when a cell produces chemical messengers that bind to the receptors on the same cell. In both types of signalling produced chemicals diffuse over a relatively small distance. Another example of process in which nonlocal interactions are particularly important, are processeses in which the cell size is relevant. This refers to models of such phenomena as chemotaxis, cell adhesion or aggregation processes. The nonlocal terms can describe cell size. In some cases it also ensures that the problem is mathematically well-posed [6]. A further important aspect is the *nonlinear interactions* (see [3]).

Referring to the former issue (*local — nonlocal interactions*) in many applications to Physical problems the idealisation of mass–point of the system, leading to the local interactions, is usually accepted. For example this holds in the case of kinetic theory and the Boltzmann equation for rarefied gases. But even here for the proper description of dense gases or complicated geometries of particles — a kind of non–local assumption, leading to Enskog–type equations ([5]) or averaged Boltzmann equations ([1]), is widely applied. We may note the the Enskog equation (in some its of its versions) involves a kind of *nonlinear interactions*. The necessity of including nonlocal interactions as we said before is even more evident for living systems.

The mathematical structures discussed in [3] are suitable to capture the nonlocal interactions. In fact one may consider that the abstract activity parameter $u$ may be a vector containing the position (e.g. of a center of mass) of the individual agent of the system. This leads to integral terms involving the position variable. One may relate such a description to corresponding Markov jump processes ([2, 7, 8]) similarly to the transition from the Liouville equation to the Boltzmann equation.

Finally, we may point out that the nonlocal models may also be considered at the macroscopic level — see [6, 9] and references therein.

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