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Comment

Dynamics and equilibria of living systems Comment on "Answering Schrödinger's question: A free-energy formulation" by Maxwell James Dèsormeau Ramstead et al.

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Our comment is addressed to the review [1] inspired by the celebrated essay *What is life?* by Erwin Schrödinger. The focus of [1] is on the derivation and study of the dynamics of entropy functions appropriate to enlighten the natural ability of large systems of interacting living entities to drive their collective behaviors towards minimal entropy configurations. In addition the authors critically analyze possible dynamics, where these configurations act as attractor for the collective dynamics.

The reference to Erwin Schrödinger is properly chosen, as he is considered the pioneer of a modern systems biology thanks to his essay which has the merit of having proposed the conceptual foundations of multiscale problems. The complex dynamics which has been outlined above is related to the ability of living systems to extract energy from the surrounding environment.

The interest to understand the physics of living systems has a long story. We might start from Immanuel Kant (1724–1804) who proposed, in the celebrated "Critics of the Power of Judgement" [2], the following definition: *Living Systems: Special structures organized and with the ability to chase a purpose.*

The ability of living entities to develop specific strategies has been properly enlightened by a Nobel laureate, Leland, H. Hartwell [3] who, focusing on biological systems, indicates some important features which distinguish living systems from the inert matter:

> *Although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiates biology from other natural sciences. Organisms exist to reproduce, whereas, outside religious belief, rocks and stars have no purpose.*

I have found interesting that the authors of [1] present new ideas on the concept of stability of attractive configurations, where a living system can recursively reach depending also on the conditions of the external environment. It appears to me a new concept which can definitely attract the scientific curiosity of applied mathematicians. Indeed, the recent state of the art on the mathematical theory of living systems does not treated exhaustively this topic. However,

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a dynamics where trend to equilibrium is observed is followed by instability and again by trend to equilibrium, is observed by simulations related to specific systems, for instance when the competition between immune and cancer cells is modeled [4]. Therefore, applied mathematicians should be invited to go beyond the present state of the art by developing a deep analysis of stability properties.

We do agree that the review [1] motivates interesting research perspectives of interest in mathematical sciences. Accordingly, let us mention three key questions, which according to our bias, appear of great interest:

1. Should the derivation of entropy functions, and the subsequent stability analysis, distinguish between systems with constant number of entities and systems where competition occurs thus generating birth and death processes?
2. Should the study of the qualitative dynamics of systems be referred to the specific class of equations selected to model the large systems of interacting entities, for instance ordinary differential equations, kinetic type equations [5,6], or even hybrid systems mixing both aforementioned class of systems [7,8]?
3. How the approach under consideration can be developed whenever Darwinist mutations and selection appear [9]?

We do not naively claim that the answer to these questions can be immediate. We can only say that applied mathematicians would be happy to provide an answer even to only one of them. Indeed, searching for an answer is not an easy task and various difficulties have to be tackled. One of them, it might be the most challenging, consists in the modeling of the role of space dynamics, starting from the modeling of interactions which might not be localized, but distributed in space or even sensitive to networks [10,11].

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