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Multiscale modeling of living systems and their regulation

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A possible definition of a complex system

Acknowledged features of a complex system are the following:
-- the system is composed of a large number of elements;
-- the elements are often of different types and have an essential internal structure;
-- the elements are related by nonlinear interactions, often of several different types;
-- the system experiences inputs at several scales.
But I argue that the main hallmark of complex systems is circular causality, namely, the presence of feedbacks of (macroscopic) collective properties and emergent features on the behavior of (microscopic) elements. Elements collectively modify the surroundings, which in turn exerts constraints on them and endow them with different possible states or behaviors. In complex systems, knowing the features and behavior of the single components in isolation is not sufficient to predict the behavior of the system as a whole.

Methods

To capture the mechanistic processes responsible for the system's behavior, it is necessary to dissect and explicitly describe the elementary components and their interactions. But such a reductionnist study has to be done within the context provided by emergent properties, i.e. one has to investigate the properties of single components, but not in isolation. Methods for unravelling multiscale feedbacks loops have thus necessarily to consider jointly several levels of organization. For the determination of emergent properties, in the bottom-up direction, I suggest to introduce effective parameters (e.g. homogenized diffusion coefficient, or apparent kinetic rates and coupling constants) retaining from microscopic details only what is essential to the macroscopic behavior. Conversely, in the top-down direction, effective inputs, fields and constraints allow to account for macroscopic influences in the microscopic description. Bridging these two approaches yields an integrated and consistent multilevel description.

An example (Malo et al. 2010)

The issue is to understand the mechanisms of early metastatic escape, a rare event that cannot be directly observed nor experimentally studied. Our working hypothesis is the key role of a protein, PAI-1, produced at high rate by cancer cells, and experimentally shown (in vitro) to trigger a transition of the cells from a proliferative state towards a state prone to migration. A monoscale model, e.g. in terms of partial différentail equations (reaction-diffusion model) cannot account of the escape and hiving of a few cells away from the tumor. By contrast, our proposed scenario is a collective process modifying the state of a few elements through a modification of the local environment, randomly selected by the history-dependent geometry of the tumor.In the framework of dynamical systems theory, we modeled the transition in a tunable environment, the control parameter being the external concentration of PAI-1 collectively produced by the tumor cells. We investigated using either a cellular-automaton or an individual-based simulation the localized accumulation of PAI-1, thus reaching locally values above the transition threshold. Then we bridged these top-down and bottom-up approaches into a spatio-temporal integrated process.

Results

This study offers a mechanistic explanation of the role of the intrinsically produced protein PAI-1 in metastatic escape, through the control of the cell motility. It led us to devise the protocol of new experiments, which evidenced the reverse transition (from motile cells back to proliferating cells) and definitely assessed that the transition to metastatic behavior does not require additional mutations of the involved cancer cells but is rather a dynamic and reversible change of state. On the long term, our study hints at therapeutic targets that would allow to lower the risk of metastasis.

Further reading

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