Deciphering the principles of cell decision-making in multicellular systems: The Least microEnvironmental Uncertainty Principle (LEUP)

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Cell decision-making is the process of cells changing their phenotype according to their intrinsic programming and in response to the micro-environmental cues. Currently, little is known about the principles dictating cell decision-making in multicellular systems. Regarding cells as Bayesian decision-makers under energetic constraints, this work proposes that organisms of all domains of life operate using a "Least microEnvironmental Uncertainty Principle (LEUP)" for their decision-making processes. This is translated into a free-energy principle, implying a statistical mechanics theory for cell decision-making. Here, three fundamental challenges will be addressed: a) the uncertainty/ stochasticity of subcellular regulatory cell decision-making mechanisms; b) lack of knowledge in the relative contribution of intrinsic and extrinsic cell decision-making factors to multicellular spatiotemporal dynamics; c) a unified theory for different types of cell decision-making. Such a statistical mechanics reduction allows for simplifying many parameters into a low-dimensional mathematical description and circumvent the uncertainty about the underlying mechanisms. Moreover, it allows integrating heterogeneous types of data as constraints of LEUP energy optimization. Using LEUP in close relation to experiments enables to determine model details for different general cell decision-making problems: (i) cell fate determination of hematopoietic stem cells, (ii) local interactions during T-cell differentiation, (iii) macrophage phenotypic plasticity and (iv) flagella assembly during bacterial cell division.

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