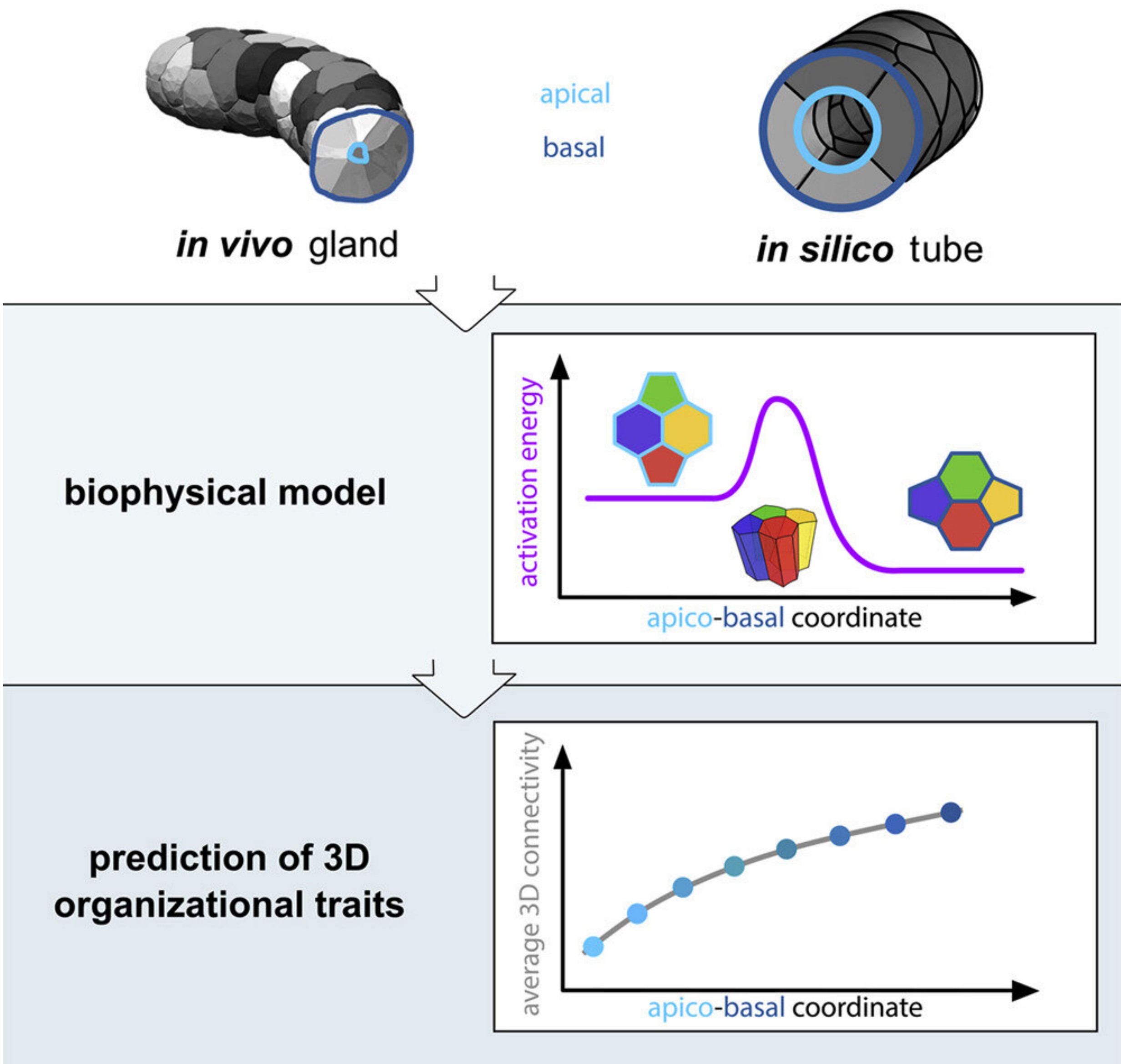
A mathematical principle explains how cells connect with each other to form tissues and organs

July 13 2022



Graphical abstract. Credit: *Cell Systems* (2022). DOI: 10.1016/j.cels.2022.06.003

An international team of scientists has discovered a new mathematical principle that explains how cells connect with each other to form tissues, an important step forward in understanding how organs are formed during embryonic development and the pathologies associated with this process. The finding is led by the Institute of Biomedicine of Seville (IBiS), a joint center of the Virgen del Rocío University Hospital, the Spanish National Research Council (CSIC) and the University of Seville; and the Institute for Integrative Systems Biology (I2SysBio), a joint center of the CSIC and the University of Valencia (UV).

The study, published in *Cell Systems*, has been carried out using the fruit fly (Drosophila melanogaster) as a model, and may have future implications for the creation of artificial tissues and organs in the laboratory, a great challenge for Biology and Biomedicine.

In 2018, this team published an article in the journal *Nature Communications* that had a great scientific and media impact, in which they demonstrated that epithelial cells can adopt a geometric shape during the formation of organs that had not been described until then: the scutoid.

"That the cells adopt this geometric shape is due to the energy savings that it entails when 'packaging' to form tissues when there is a certain level of curvature, for example when a fold is formed in a tissue," explains one of the authors who lead this work, Luisma Escudero, IBIS researcher. "Our research represented an important paradigm shift, because until then epithelia had always been studied using mathematical concepts to describe their organization in two dimensions, something that is related to the connection between cells and how they communicate with each other to form these organs correctly."

"However, we show that epithelial cells can have complex three-dimensional shapes like scutoids, and cells and organs are indeed three-dimensional. In this article we consider whether there are mathematical and/or biophysical principles in 3D and, by combining experiments with fly tissues and computational models of tubular tissues, we have been able to develop a biophysical model that relates, for the first time, the geometry of the tissue and the physical properties of the cells with how they are connected to each other," says Escudero.

The key, the 'social relationships' of cells

Javier Buceta, I2SysBio researcher and co-leader of the study, establishes a simile to explain this new scientific advance, resorting to Anthropology. "The anthropologist Robin Dunbar determined that human beings have an average of five close friends that are given by different social and personal factors. At the cellular level, our article has revealed that there is an 'equivalent' principle, concluding that the number of close 'neighbors' of a cell, that is, its 'close friends,' is determined in this case by the geometry of the tissue and its energy relationships.

"Thus, taking into account a series of energetic, biological and geometric considerations, we have discovered that, for example, the more connections an epithelial cell has with others, the more energy it needs to establish new connections with other cells, while if it is little connected to other 'neighbors,' the cell needs less energy to establish that link," says Buceta.

In this research, the scientists altered tissue, reducing adhesion between cells to put their model to the test. "This makes the organization change, as it is easier, less costly in energy terms, for cells to make new contacts," says Buceta. The results of the experiments confirmed the quantitative principle proposed by the researchers.

The researchers point out that, by analyzing the behavior of tissues from the point of view of materials, other previous works have observed that their "stiffness" depends on cellular connectivity. "In this way, tissues can behave in a more or less viscous way, that is, more solid-like or more fluid-like. Our results quantitatively show how the geometry of the scutoids determines cellular connectivity and, therefore, how they can be a biological instrument to regulate the material properties of tissues and organs," conclude Escudero and Buceta.

More information: Luis M. Escudero, A quantitative biophysical principle to explain the 3D cellular connectivity in curved epithelia, *Cell Systems* (2022). DOI: 10.1016/j.cels.2022.06.003. www.cell.com/cell-systems/full … 2405-4712(22)00273-3

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Provided by University of Seville

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