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COMPUTATIONAL MODELS REVEAL THAT CELL-CELL INTERACTIONS ARE DIFFERENT IN 2D THAN IN 3D

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ABSTRACT

Although two-dimensional *in vitro* systems and computer models are routinely used to represent 3D systems, such as organs and tumours, computer simulations reported here show that the mechanics of 2D cell systems is fundamentally different from that of 3D systems.

How tissues organize themselves into aggregates, tissues, organs and other structures is central to biology, oncology and tissue engineering. During early embryogenesis, for example, cells arrange into distinct tissues and these tissues then undergo self-driven reshaping motions in order to form progressively more complex and mature organs. During cancer metastasis, groups of cells leave a primary tumour site and embed themselves elsewhere, one of the primary issues in modern oncology. Finally, regenerative medicine and tissue engineering strive to devise cells that will form prescribed structures. All of these processes involve the spontaneous rearrangement of cells and, evidently, all are governed by similar physical principles.

Over the years, computational models have provided many important insights into the mechanics of cell-cell rearrangements, especially in the context of cell sorting [1]. Sorting is an ideal context in which to study cell-cell interactions because large numbers of local rearrangements are involved, the process is easily observed, and a static equilibrium configuration is eventually reached.

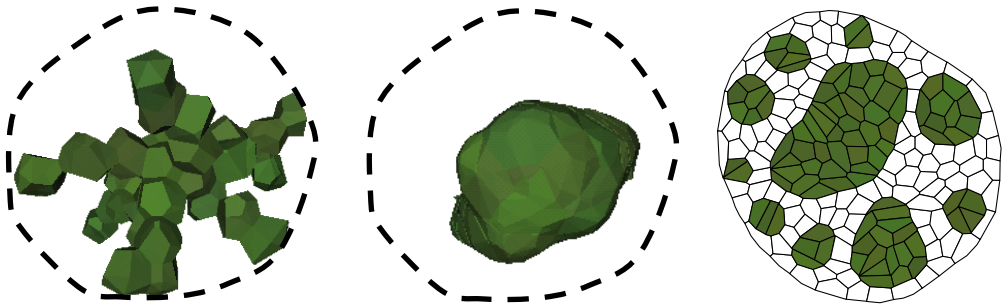
Like virtually all previous computational models, the present one assumes that each cell-cell and cell-medium interface carries a tension γ that is specific to the histological cell type(s) involved in the interface, an idea that is now enjoying wide acceptance [2]. The tension is assumed to arise from contraction of the cell membrane and its associated proteins, microfilament contraction and to be reduced by equivalent expansive forces associated with cell-cell adhesion systems. The cell cytoplasm and its embedded protein networks and organelles are assumed to generate an effective viscosity μ.

That significant discrepancies exist between typical 3D cell sorting experiments and the predictions of previously available 2D computational models, is well known. Whether these discrepancies result from dimensionality differences or are a consequence of model assumptions, however, has been less clear.

Here, 2D and 3D computational models [1,2] are used to explore the process of cell sorting. The new 3D models reported here predict final states very similar to those observed in 3D experiments, demonstrating that the discrepancies noted earlier are due to dimensionality differences and not model assumptions. Comparisons between 2D and 3D models reveal that differences between them arise from three factors:

1) Cells in 3D systems have 14.4 initial neighbours compared to cells in 2D systems which have only 5.6. As a consequence, cells in 3D are, in general, much more likely to be connected to other cells of their own type than are cells in 2D systems.
2) In 3D systems, groups of cells of like type are often multiply connected to others of their own type, a situation that is comparatively rare in 2D systems.
3) Chains of cells in 3D are subject to a Rayleigh-like instability that makes them unstable, while chains in 2D are durable and keep islands of like cells separated from each other.

Collectively, these factors cause 3D cell systems to exhibit mechanical characteristics that are fundamentally different from those of 2D systems. These findings have important implications for embryology, cancer metastases and tissue engineering, where 2D *in vitro* and computational models are often used to represent 3D tissues and organs. They also provide fundamental insights into the mechanics of cell adhesion and aggregation.



A. Initial Configuration (3D Model) | B. Final Configuration (3D Model) | C. Final Configuration (2D Model)

Fig 1. Typical Cell Sorting Simulations. A and B are 3D models, and only the minority cells are shown; the dashed line indicates the outside profile of the cell mass. C is a 2D model, and all cells are shown.

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