Cells 'speed date' to find their neighbors when forming tissues

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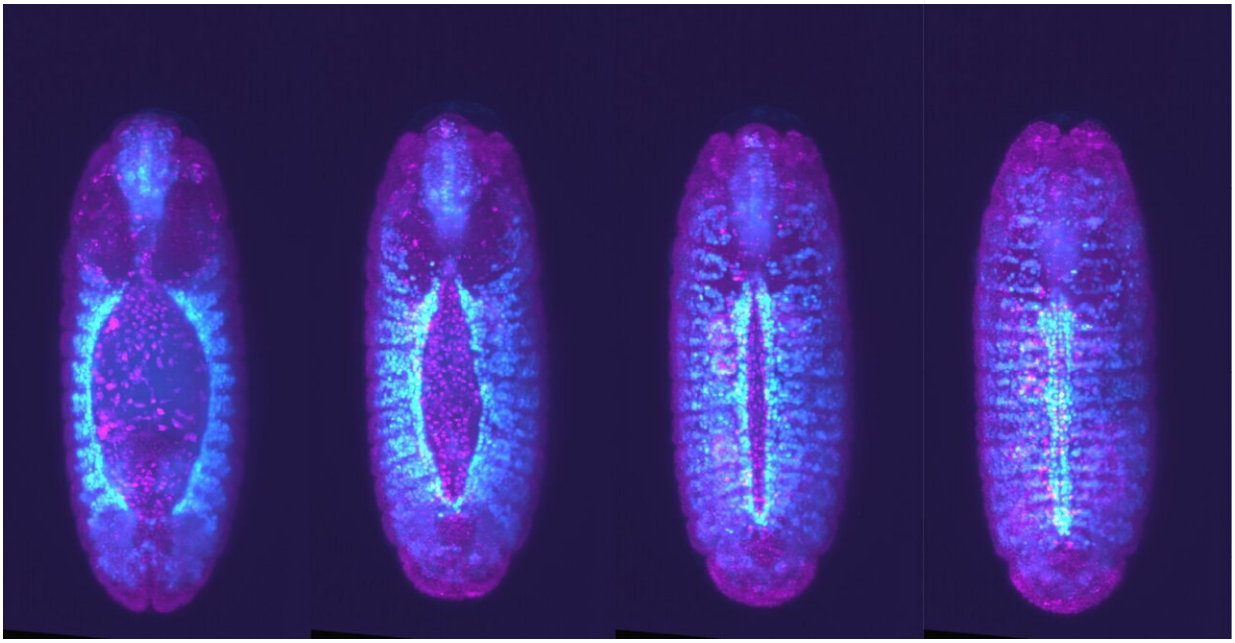

The heart (cyan) forms from two distant regions of the embryo (far left). These regions migrate to the embryo midline, where they fuse into a tube to make the first heart structure (far right). Precise alignment and pairing of these cells are crucial for proper heart development. Credit: Thamarailingam Athilingam and Kate McDole

In developing hearts, cells shuffle around, bumping into each other to find their place, and the stakes are high: pairing with the wrong cell could mean the difference between a beating heart and one that falters.

A study published in the *Biophysical Journal* demonstrates how heart cells go about this "matchmaking" process. The researchers model the intricate movements of these cells and predict how genetic variations could disrupt the heart development process in fruit flies.

In both humans and fruit flies, the heart's tissues arise from two distinct regions of the embryo, which are initially far apart. As development progresses, these cells journey toward each other, ultimately merging into a tube-like shape that will become the heart. For the heart to develop correctly, these cells must align and pair up precisely.

"As the cells come together, they jiggle and adjust, and somehow always end up pairing with a heart cell of the same type," says the lead author, Timothy Saunders of the University of Warwick. This observation inspired the team to explore how cells match up in the first place and how they know when they've found the right fit.

Developing heart cells have tentacle-like protrusions called filopodia, which probe and grab onto potential partners. Saunders' previous work found that proteins create waves that pull mismatched cells apart, giving them another chance to find the right match.

"It's basically like cells are speed dating," says Saunders. "They have just a few moments to determine if they're a good match, with molecular 'friends' ready to pull them apart if they're not compatible."

The researchers found that heart cells seek stability where they remain closest to stillness—like a rolling ball that eventually comes to a stop, known as energy equilibrium in physics.

In developing heart cells, this principle applies when cells find a balance between connection forces and their ability to adjust to strain—also known as adhesive energy and elasticity. Based on this observation, the

team developed a model that shows how cells can self-organize.

Next, the team tested their model on fruit fly hearts with mutations and misalignments. By calculating the adhesive energy between different cell types and assessing tissue elasticity, the model predicted how cells would match and rearrange.

"Although rare, sometimes the heart tube ends up with one cell on one side when it should have two, or two cells when there should be four," says Saunders. "We could input these imperfections into the model and run it." The model produced outcomes that closely mirrored what was observed in real embryos.

The team notes that their model not only enhances our understanding of how cells match and align during heart development but also has broader applications. Similar cell-matching processes are crucial in neuronal connections, wound repair, and facial development, where hiccups can lead to conditions like cleft lip.

"Essentially, we're putting numbers to biological processes to explain what we observe," Saunders adds.

More information: Interfacial energy constraints are sufficient to align cells over large distances, *Biophysical Journal* (2025). DOI: 10.1016/j.bpj.2025.02.011

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