Researchers offer new explanation for why protein fibers form

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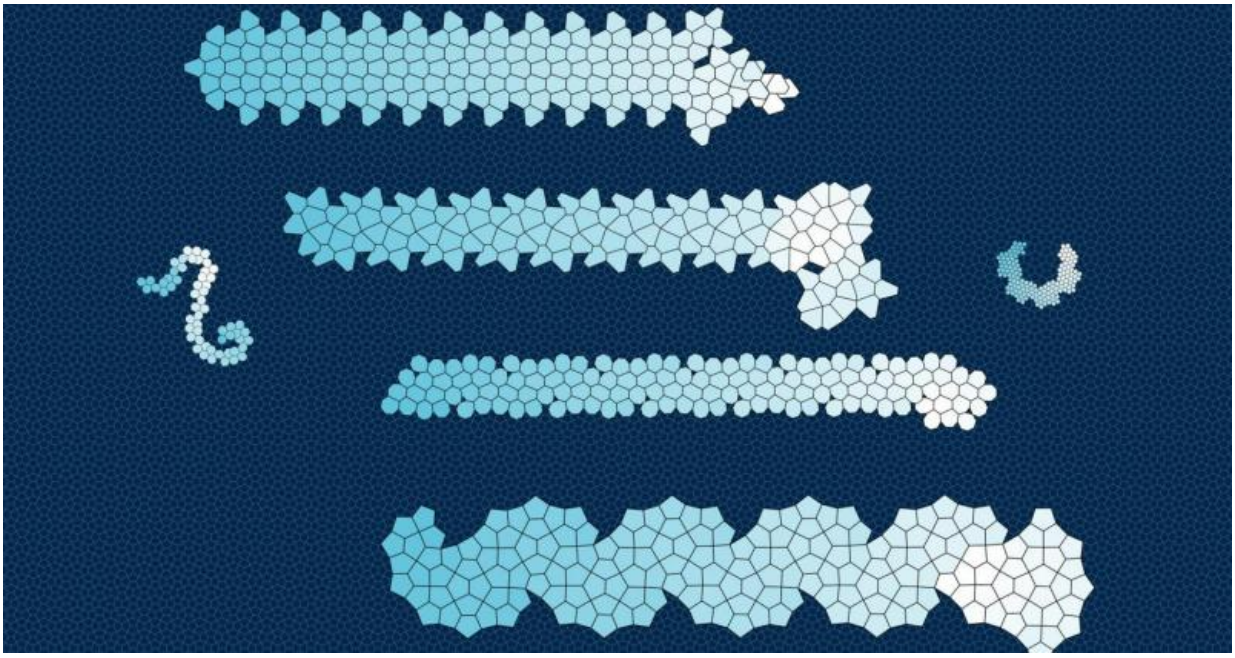

New study simulates the formation of protein fibers and suggests, contrary to other studies, that these structures all follow a general physical principle. Credit: Martin Lenz and Thomas Witten

Alzheimer's disease results from a dysfunctional stacking of protein molecules that form long fibers inside brain cells. Similar stacking occurs in sickle-cell anemia and mad cow disease.

Scientists know these orderly fibers develop from a wide variety of

molecules, but could there be a common reason they form?

In new research, physicists at the University of Chicago and Université Paris-Saclay suggest that such protein fibers are a manifestation of a general physical principle. And that principle offers the possibility of new medicines and tools for engineering desirable protein structures. The findings were published earlier this month in *Nature Physics*.

"We have strong evidence that there's a principle shaping how things aggregate that can be used both to understand disease and modify it and to make things self-assemble in a way that we dictate," said co-author Thomas Witten, the Homer J. Livingston Professor Emeritus of Physics at UChicago.

Proteins aggregate all the time. But mostly they make amorphous blobs similar to those in egg drop soup. "We're trying to find out what makes some molecules assemble to form a fiber instead of a glop," Witten said.

The proteins that form fibers are identical but irregular; they don't fit together cleanly. Witten and his collaborator Martin Lenz, a researcher at Université Paris-Saclay, wondered if that irregularity might hold a key to fiber formation. Using computers, Lenz, lead author of the study, devised a mathematical model to simulate how identical but ill-fitting objects would clump together. He used pentagons and other simple polygons to represent the irregular, fiber-forming proteins.

"We didn't have a lab and test tubes. We just had these little shapes," Witten said.

A simulation of how protein fibers form. Credit: Martin Levy and Thomas Witten

The researchers made the interaction of the polygons depend on just two attributes without incorporating any other features of real molecules. As in a real fiber, all of the sub-units are identical and irregular. They are also what Witten calls "sticky"—they attract each other but they don't feel the attraction until they touch. They "want" to touch, and they gain energy if they do. But because the shapes don't fit together cleanly, "their surfaces can't touch and feel the stickiness and get that energy unless they distort," Witten said.

Their propensity is to elongate themselves as much as possible to maximize the amount of their surface that is in contact. "But distortion

costs them energy," Witten said. "They have to exert forces to get the surfaces to meet. So there is a competition between the energy gained by sticking and the energy cost of distortion."

The simulations done by Lenz embodied that competition. The shapes could attach along any surface. The scientists varied the degree of stickiness relative to the energy cost of distortion for each shape and looked at the various structures that formed across the range of values. The results were striking: No matter what shape they used, when stickiness and the energy cost of distortion were more or less equal, they got fibers every time.

An additional feature was needed to form the fibers. The growth needed to be irreversible with every surface that sticks needing to stay stuck. Without this irreversible feature, often seen in real molecules, the long fibers would eventually melt into roundish blobs.

The research differs from the approach taken by scientists who study the diseases caused by protein fibers. "They have done a lot of work on the particulars of the molecules involved, and there are strongly held ideas about how those particulars cause the fibers to form," Lenz said.

"We're saying, 'You don't need a specific molecule: it's a general principle.' They're skeptical about that, but despite their skepticism, they acknowledge that our idea deserves a hearing," Witten said.

So far, Lenz and Witten have tried only a small array of shapes in two dimensions. They plan to try to see if the principle holds true for arbitrary shapes, in three dimensions, and abstract the essence of what's going on in the simulations.

"We want to have a theory that predicts things that we can then verify on the computer, a theory that doesn't use specific features of a particular

particle shape but just uses the stickiness and the distortion," said Witten. "We may be able to prevent the mad-cow and the sickle cell fibers, if we understand this principle. And we should be able to use the principle to make fibers when they are beneficial. Just put in the right stickiness, put in the right distortion, adjust everything and get the fibers we want."

More information: Martin Lenz et al. Geometrical frustration yields fibre formation in self-assembly, *Nature Physics* (2017). DOI: 10.1038/nphys4184

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