Logistics of self-assembly processes

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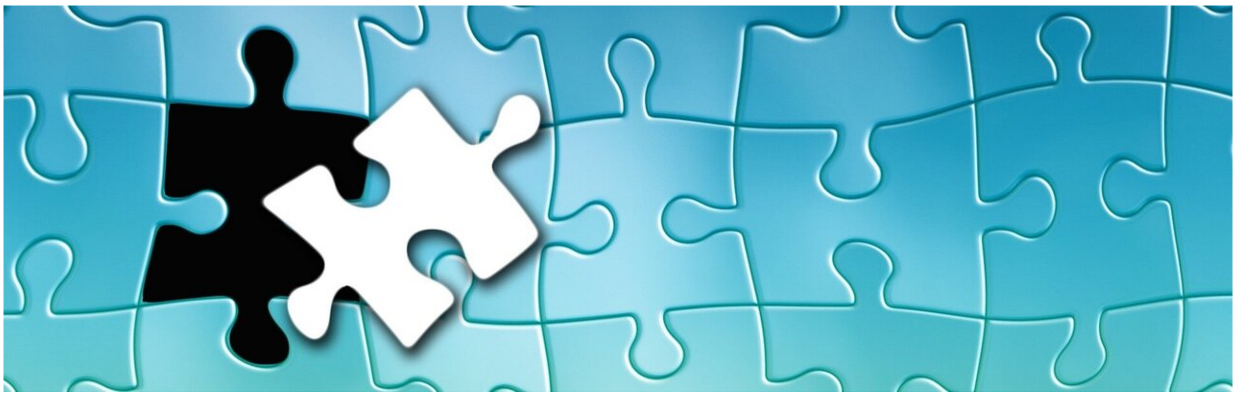

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The efficient self-assembly of functional protein complexes is a major goal of industrial biotechnology. A new LMU study shows that the productivity of such processes crucially depends on tight regulation of the supply of components.

Accurate and efficient assembly of multicomponent structures—such as ribosomes and flagella—is essential for cell function in all domains of life. The construction of such macromolecular machines is based on self-assembly processes in which a defined hierarchy of intermolecular interactions determines the sequence of addition of new components to the developing complex. Applications of this mode of macromolecular organization in fields such as nanotechnology and medicine will require a thorough understanding of the principles and mechanisms that underlie such self-organizing operations. Now researchers led by LMU biophysicist Professor Erwin Frey have elucidated the effects of random fluctuations on self-assembly processes. The new findings appear in the online journal *eLife*.

Frey and his colleagues set out to explore the behavior of a system in which a limited and biologically realistic number of homogeneous or heterogeneous subunits autonomously interact to yield particles with a defined polymeric structure. They first developed a mathematical model that describes the range and order of possible interactions, and used this as the basis for computer simulations of the assembly process. The results showed that, in a heterogeneous system consisting of a diverse set of structurally distinct components, random variations can lead to situations in which no correctly assembled multisubunit particles are constructed at all, even when equations that optimize interaction rates are employed in the simulations. The team refers to this phenomenon as a "stochastic yield catastrophe."

"The process can be compared to trying to put a magnetic jigsaw puzzle together correctly simply by shaking the box," says Florian Gartner, a member of Frey's group and lead author of the new paper. Even when each element of the puzzle is attracted to the correct companion piece, it would be extremely difficult to complete the assembly within a reasonable time. Moreover, in the model, this problem is exacerbated by the fact that the box contains many copies of the same puzzle. Under these circumstances, unfinished copies can compete for pieces, and this phenomenon can ultimately result in a failure to assemble any complete structures at all. .

"Since we have no control over the individual pieces, the yield catastrophe is a consequence of random forces, and therefore a stochastic event," Gartner explains. Only in cases in which the final structure is made up of a single, homogeneous type of subunit, or when all resources are present in excess, does the system escape such a catastrophe. The simulations therefore underline the need to optimize processes for the self-assembly of designer molecules in industrial settings so as to minimize wastage of potentially expensive chemical precursors.

"In principle, one would assume that the yield should be higher when structures are assembled in a defined sequence one after another, rather than putting many together simultaneously. That would in turn require that the initiation of a new structure should be a much slower process than its subsequent growth," says Gartner. However, the new study shows that, especially in simple systems with few distinct parts, the initiation of new structures is favored owing to fluctuations in the availability of the necessary components. This has the undesirable result that the self-assembly process generates an excess of incomplete structures.

"Our study strongly suggests that, the relative concentrations of the required subunits must be tightly controlled in order to optimize the yield of functional structures," says Frey. "One important goal of future research will be to develop strategies that dampen fluctuations in the supply of subunits and lead to efficient self-assembly protocols."

More information: Florian M Gartner et al. Stochastic yield catastrophes and robustness in self-assembly, *eLife* (2020). DOI: 10.7554/eLife.51020

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