The Time Complexity of Self-Assembly

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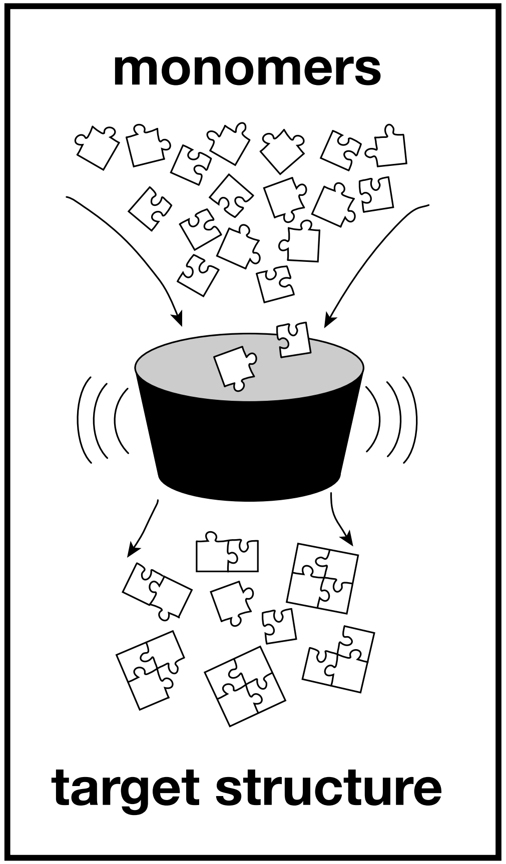
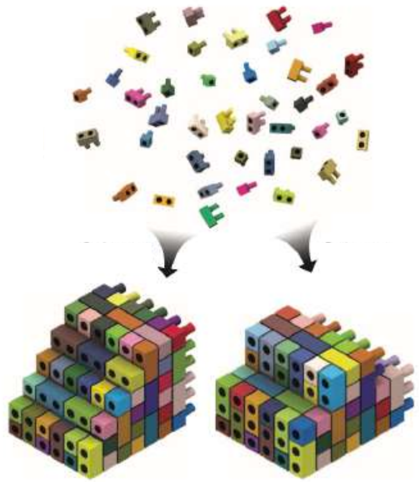
Heterogeneous & homogeneous self-assembly

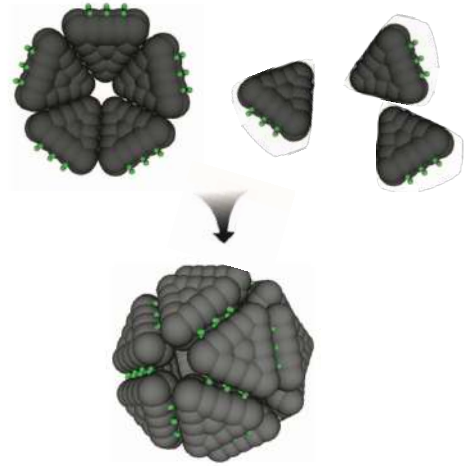


DNA Origami
(information-rich)



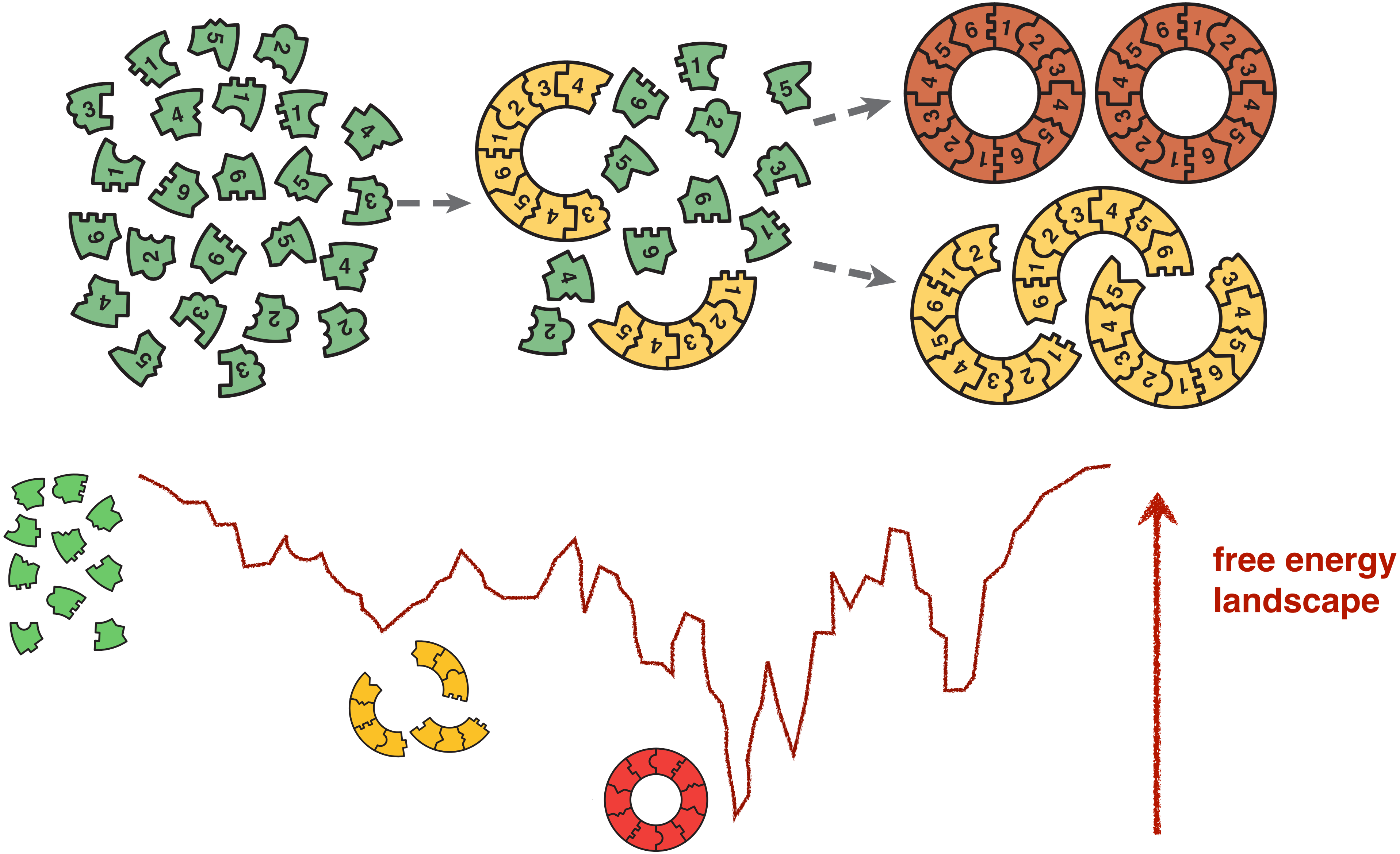
Hedges et al. Soft Matter 10, 6404 (2014)
Murugan et al. Nat Commun 6, 6203 (2015)

Viral Capsid Assembly
(information-poor)



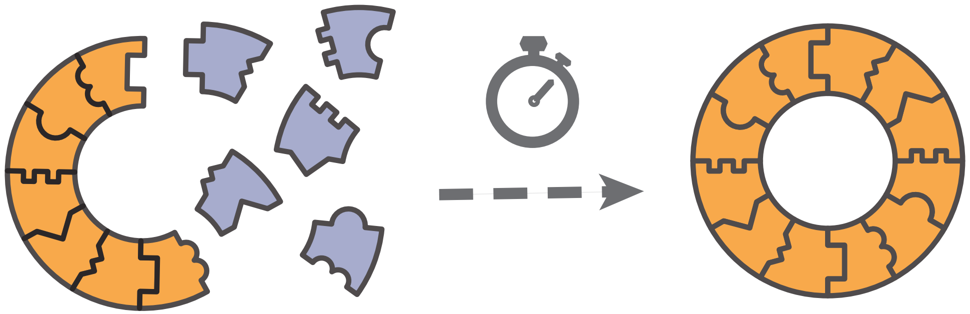
Chen et al. J Phys Chem A 112, 9405 (2008)
Hagan et al. J Chem Phys 135, 104115 (2011)
Michaels et al. Sci Rep 7, 12295 (2017)

Nucleation must be significantly slower than growth


free energy
landscape

Time complexity of self-assembly

How fast can one reach the self-assembled state?



Even if the steady state is an equilibrium state
this is a question of dynamics!

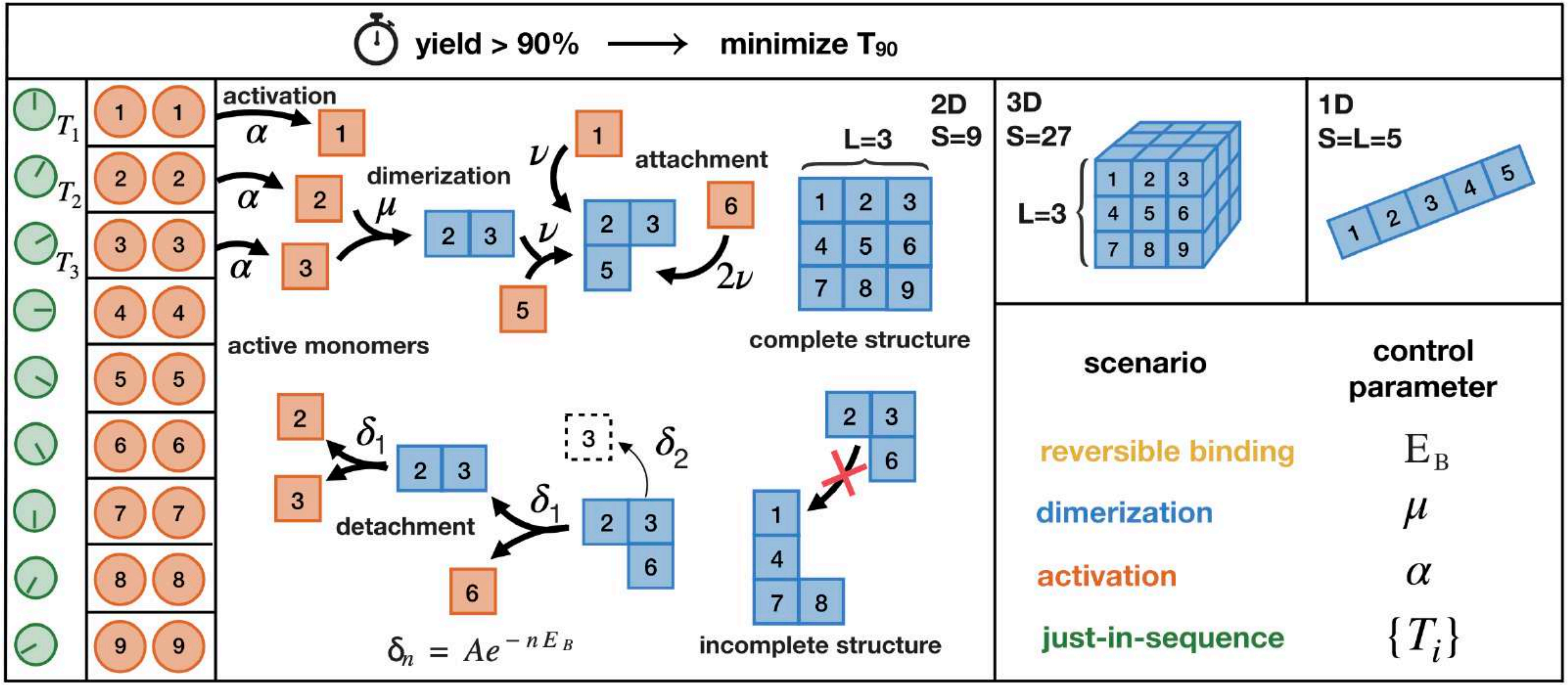
Gartner, Graf & Frey, eLife 9, e51020 (2020), PNAS 119, e2116373119 (2022)

Self-assembly “algorithms”

Assembly is a “computational problem”

Gartner, Graf & Frey, eLife 9, e51020 (2020), PNAS 119, e2116373119 (2022)

A conceptual self-assembly model



Gartner, Graf & Frey, eLife 9, e51020 (2020), PNAS 119, e2116373119 (2022)

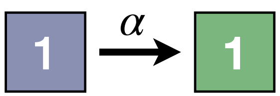
Self-assembly scenarios (control)

supply control

just-in-sequence scenario

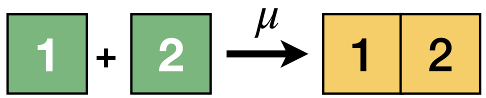
$T_1 < T_2 < T_3 < \dots$

activation scenario

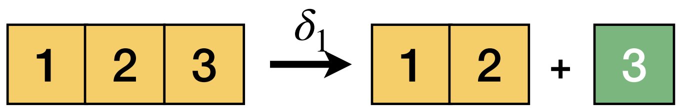


molecular control

dimerization scenario

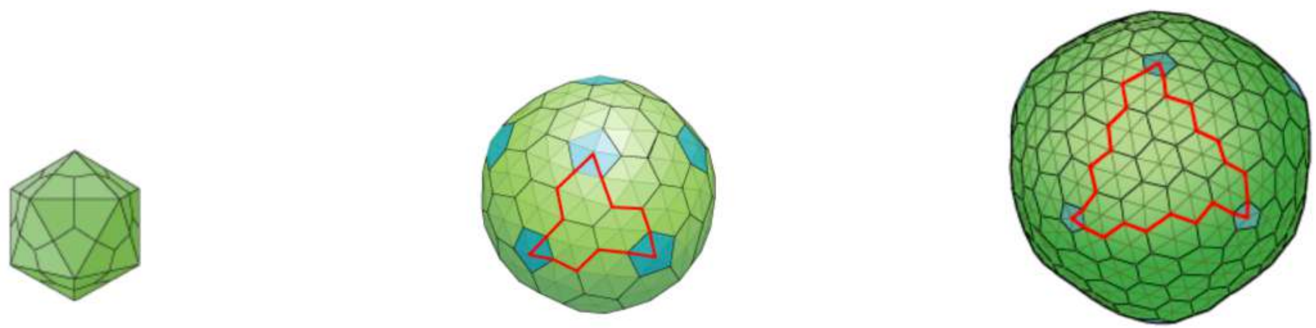


reversible binding scenario



Computer Science	Self-Assembly
computational problem	biological self-assembly
algorithm	assembly scenario
termination criterion	90% yield
CPU time	**real time**
input size	**size of target structure**

$$T(S) = ?$$

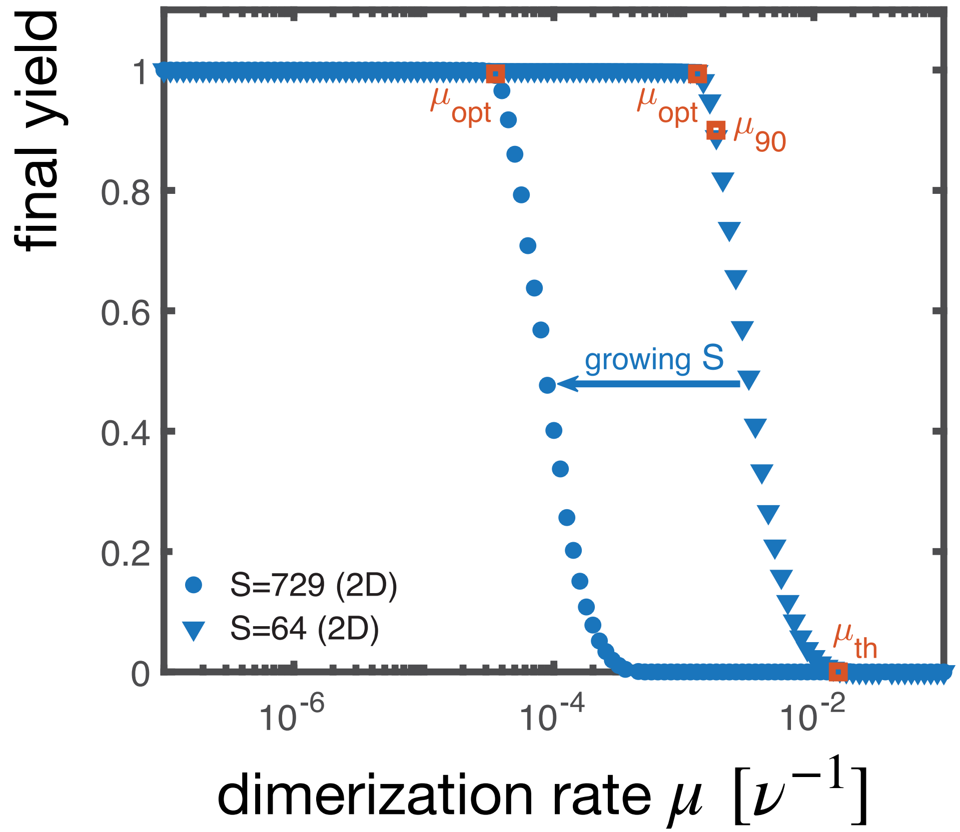


Yield curves (steady states)

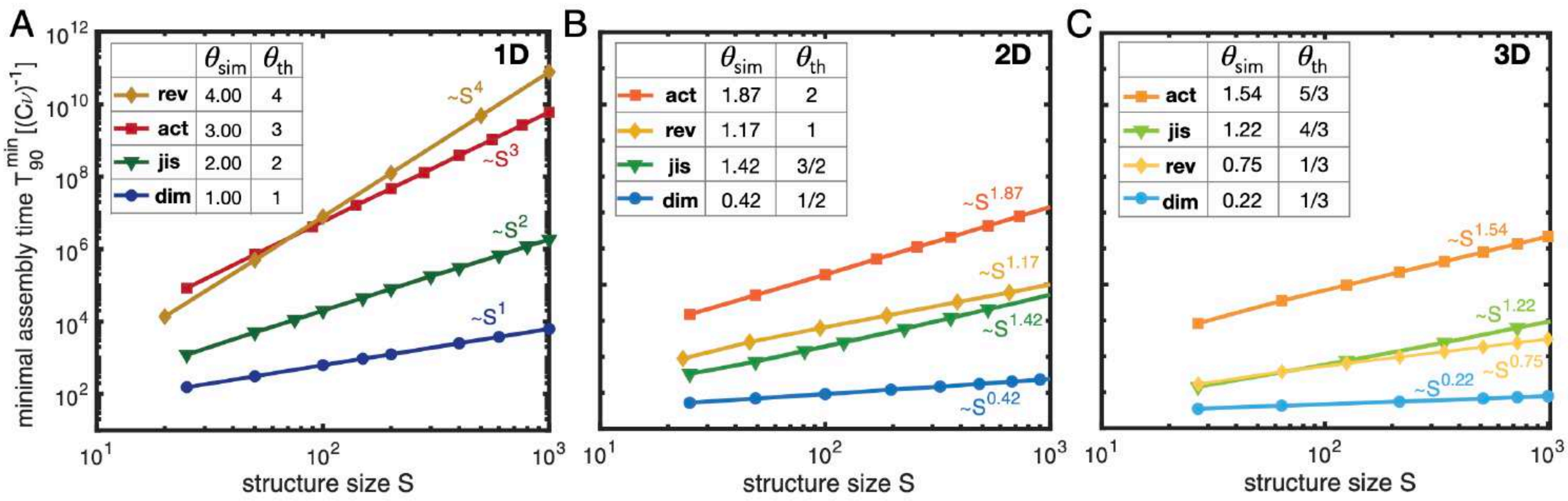
dimerization limits nucleation

What is the dimerisation rate that minimises the time to achieve a yield of 90%?

μ_{opt} : 90% yield in minimal time



Time complexity scaling (universality)



Control parameter P

Structure size S

$$P \sim S^{\phi} \quad \Rightarrow \quad T_{90} \sim S^{\theta}$$

ϕ : control parameter exponent

θ : time complexity exponent

Scaling analysis exemplified for dimerization

Slow nucleation principle:

$$\frac{\text{\# nucleation events}}{\text{\# attaching monomers}} \sim 1/S$$

Dimerization scenario: decreasing the dimerization rate μ disfavours initiation of new structures relative to the growth of existing structures.

$$\mu_{\text{opt}}\, S/\nu \sim 1/S$$

$$\mu_{\text{opt}} \sim \nu/S^2$$

Dimerization is the rate-limiting step.

$$T_{\min} \sim \left(C\,\mu_{\text{opt}}\,S\right)^{-1} \sim (C\nu)^{-1}\,S$$

Time complexity exponent: $\theta = 1$

How to transfer the result from 1d to 2d to 3d?

Volume $\sim R^d \sim S$

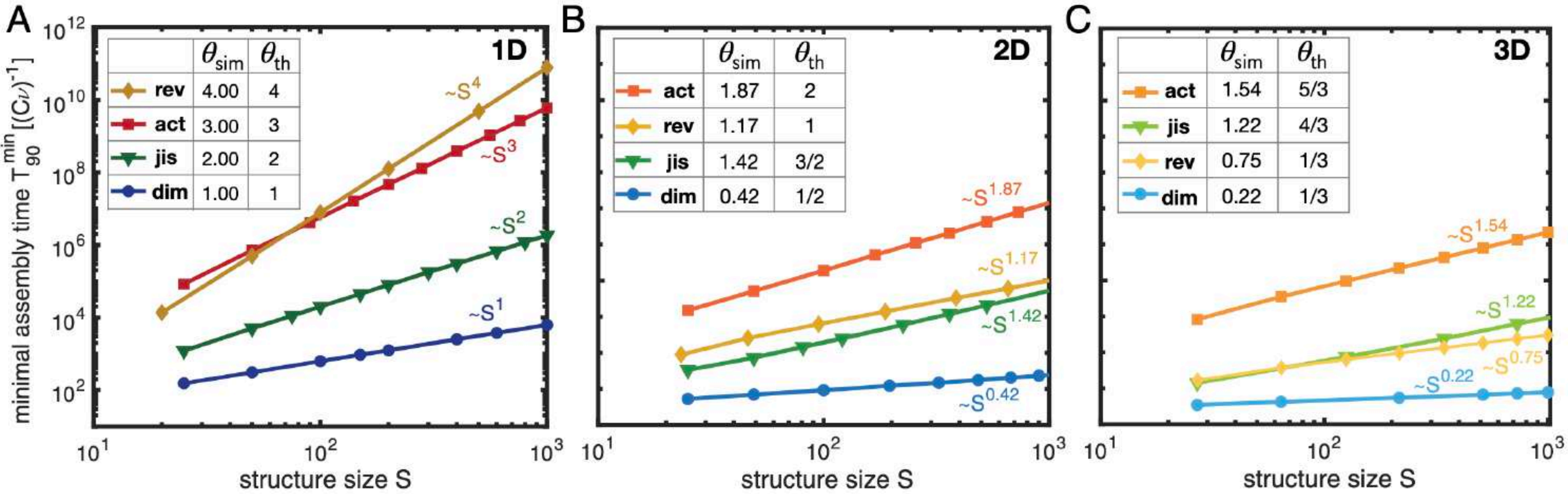
Area $\sim R^{d-1} \sim S^{(d-1)/d}$

$$\Rightarrow \nu \to \nu\, S^{(d-1)/d}$$

$$\Rightarrow T_{\min} \sim S^{\theta} \quad \text{with} \quad \theta = 1 - \frac{d-1}{d}$$

Dimerization

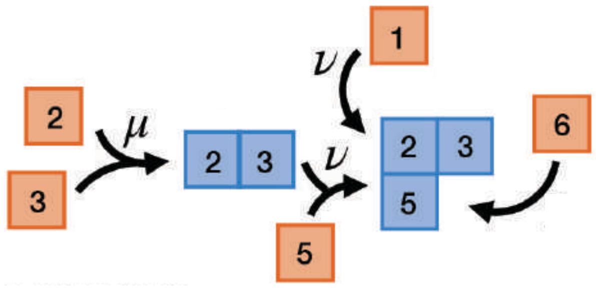
$$T_{\min} \sim S^{\theta} \quad \text{with} \quad \theta = 1 - \frac{d-1}{d} = \frac{1}{d}$$



Dimerization scenario

$$\mu \ll \nu$$

allosteric effects, enzymes

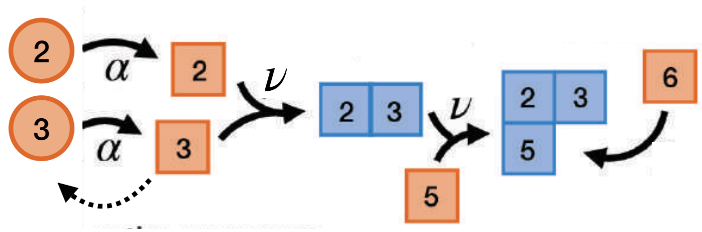


flagellum[1], viruses[2], ribosomes

Activation scenario

$$\alpha \ll C\nu$$

slow production/injection, NTPases



viruses[2], membrane attack complex[3]

(1) Caspar, D. L. Movement and self-control in protein assemblies. Quasi-equivalence revisited. Biophysical Journal, 32(1), 103–138 (1980)

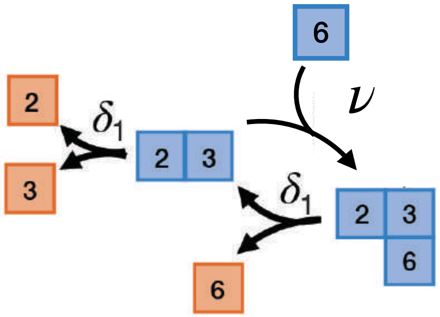
(2) Lazaro, G. R. & Hagan, M. F. Allosteric Control of Icosahedral Capsid Assembly. *J. Phys. Chem. B* **120**, 6306–6318 (2016).

(3) Leung, C. *et al.* Stepwise visualization of membrane pore formation by suilysin, a bacterial cholesterol-dependent cytolysin. *Elife* **3**, e04247 (2014).

Reversible binding scenario

$$\delta \gg C\nu$$

reduced binding energy, high temperature



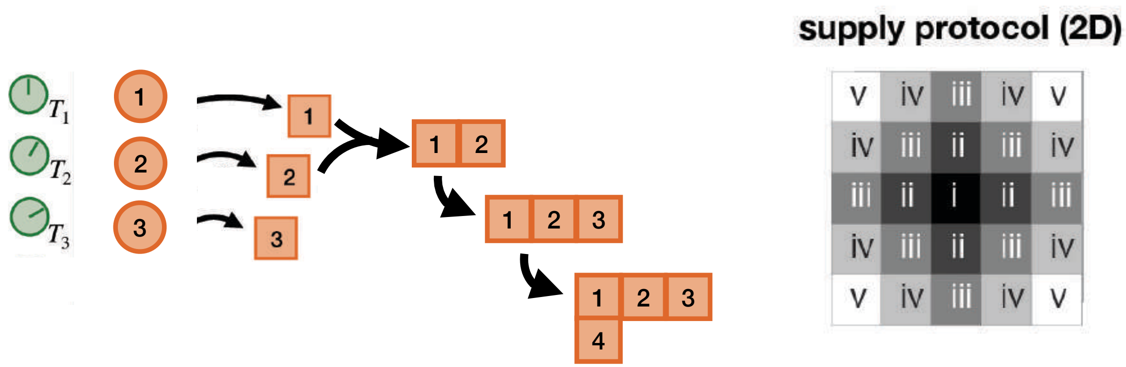
$$\delta_n = Ae^{-nE_B}$$

virus capsids(3), DNA nanotechnology(4)

Just-in-sequence scenario

$$T_1 < T_2 < T_3 < \ldots$$

coordinated supply, gene expression



DNA nanotechnology

(3) Rapaport, D. C. Role of reversibility in viral capsid growth: A paradigm for self-assembly. *Phys. Rev. Lett.* **101**, 1–4 (2008).
(4) Hong, F., Zhang, F., Liu, Y. & Yan, H. *DNA Origami: Scaffolds for Creating Higher Order Structures*. *Chemical Reviews* **117**, (2017).

Morphology of building blocks

Shape matters!

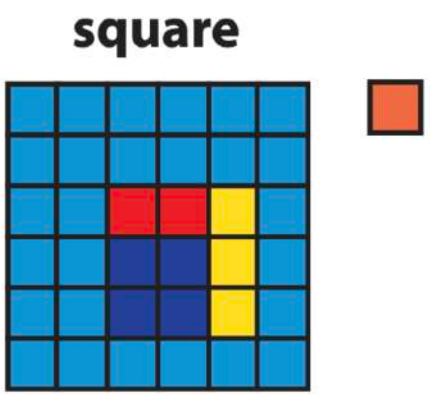
Gartner & Frey, under review

Strong binding & preferred kinetic pathways

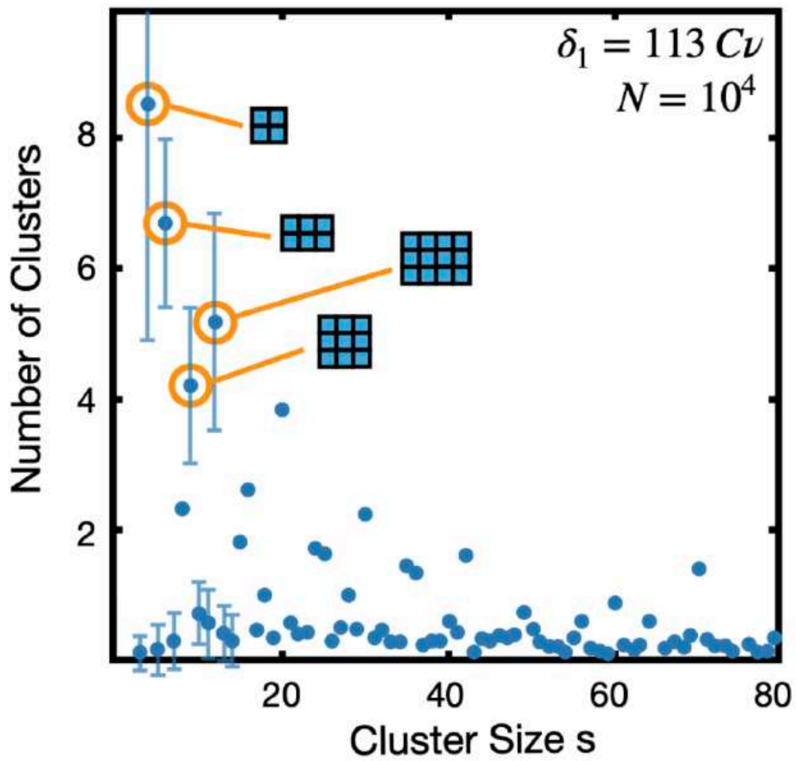
Detachment rate: $\delta_n \sim \exp[-n\, E_{\text{bind}}/k_B T]$

Strong binding limit: $\delta_1 \gg \delta_2$

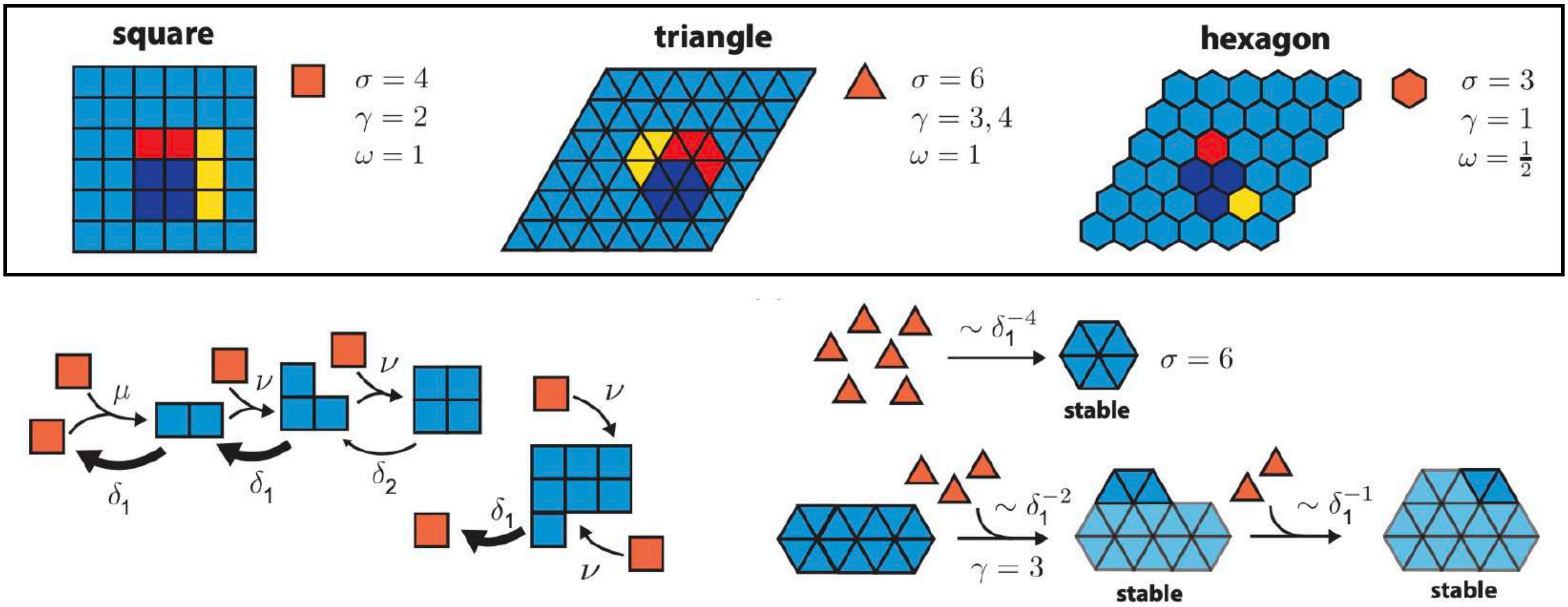
Bonds with two binding partners are unbreakable



$\sigma = 4$	nucleation size
$\gamma = 2$	attachment order
$\omega = 1$	growth exponent

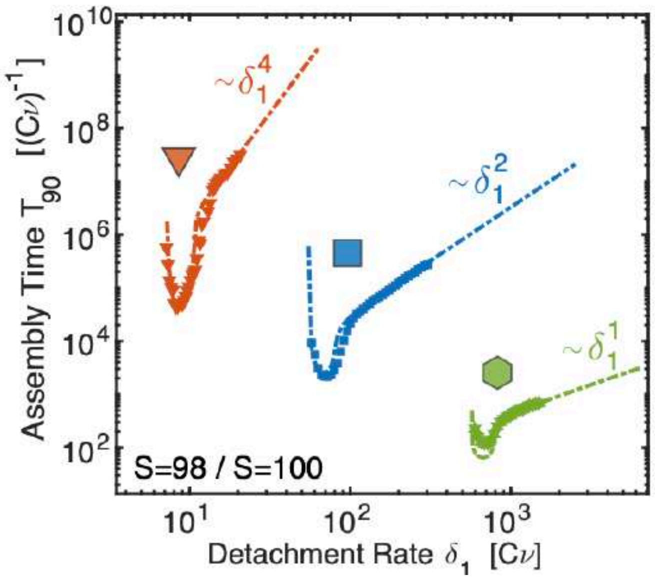


Initial nucleation — Secondary nucleation — Growth (‘domino effect’)

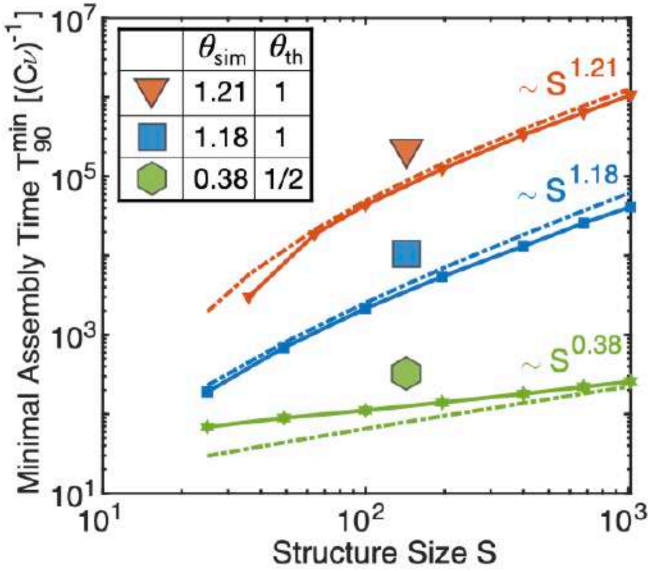


Initial nucleation — Secondary nucleation — Growth ('domino effect')

Scaling laws & assembly exponents

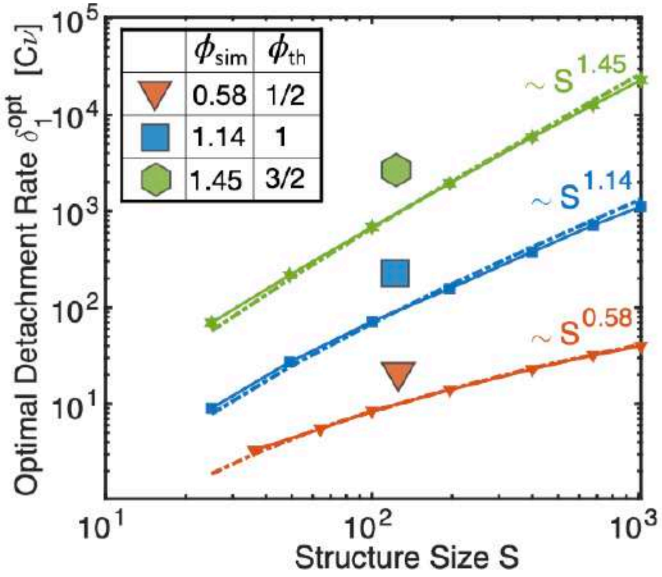


There is a optimal detachment rate (control parameter)



Minimal assembly time shows power law in structure size

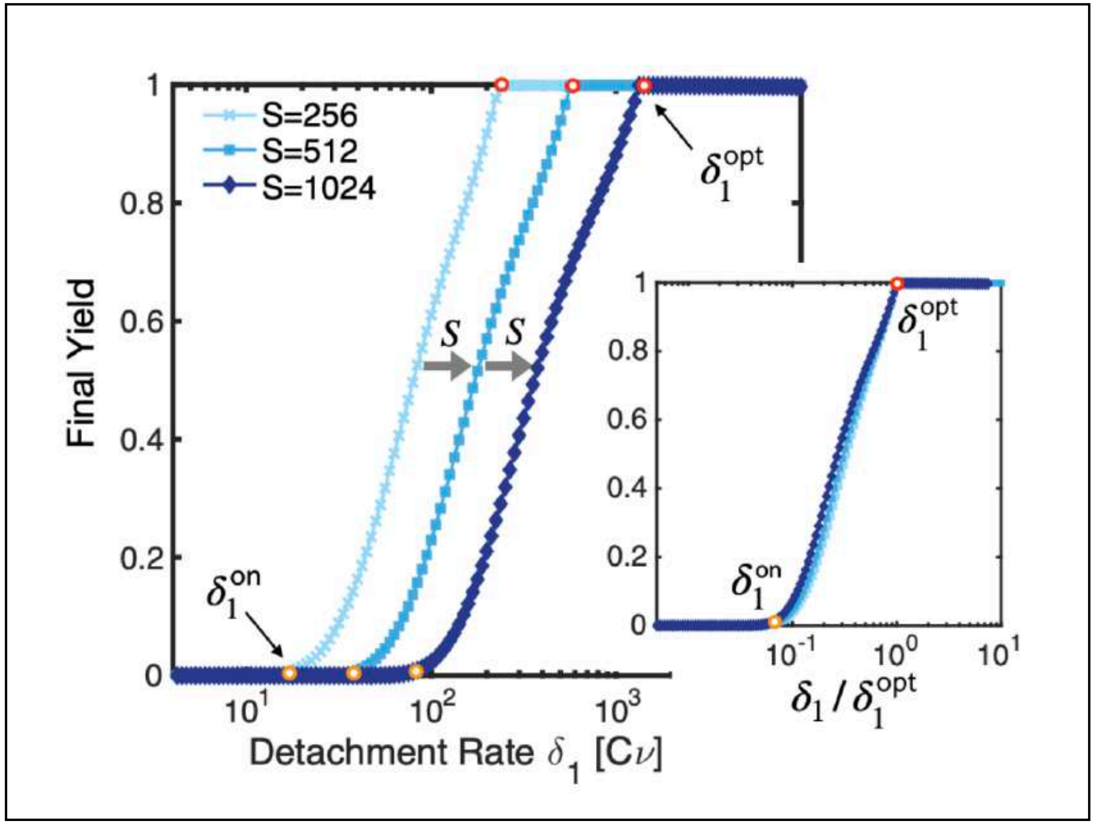
$$T_{\min} \sim S^{\theta}$$



Optimal detachment rate shows power law in structure size

$$\delta_1^{\mathrm{opt}} \sim S^{\phi}$$

Scale invariance!



There is a scaling curve for the final yield as a function of the detachment rate.

Effective kinetic model

Monomers

Nucleus

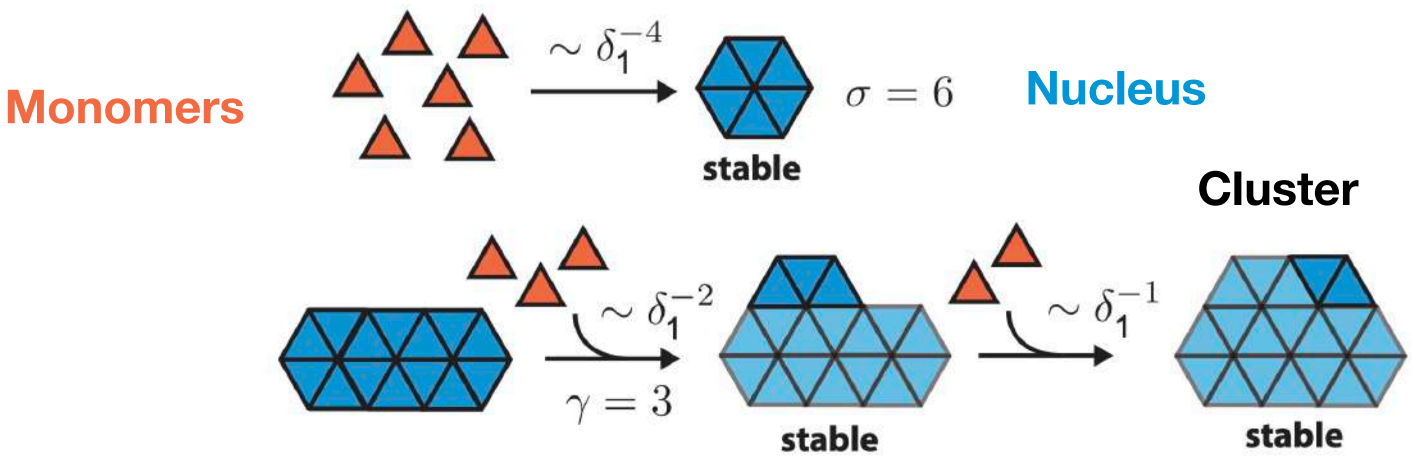
Cluster

$$\partial_t m(t) = -\sigma\,\bar{\mu}\,m^{\sigma}(t) - \bar{\nu}\,m^{\gamma}(t)\sum_{s=\sigma}^{S-1} f_s\,c_s(t)\,,$$

$$\partial_t c_{\sigma}(t) = \bar{\mu}\,m^{\sigma}(t) - \bar{\nu}\,m^{\gamma}(t)\,f_{\sigma}\,c_{\sigma}(t)\,,$$

$$\partial_t c_s(t) = \bar{\nu}\,m^{\gamma}(t)\left[f_{s-1}\,c_{s-1}(t) - f_s\,c_s(t)\right].$$

combinatorial factor: $f_s = a\,s^{\omega}$



Scale invariance of assembly kinetics

Monomers $$\partial_t m(t) = -a\,\bar{\nu}\,m^{\gamma}\int_{\sigma}^{S} s^{\omega} c(s)\;ds$$

Nucleus $$a\bar{\nu}\,m^{\gamma}(t)\,\sigma^{\omega} c(\sigma, t) = \bar{\mu}\,m^{\sigma}(t)$$

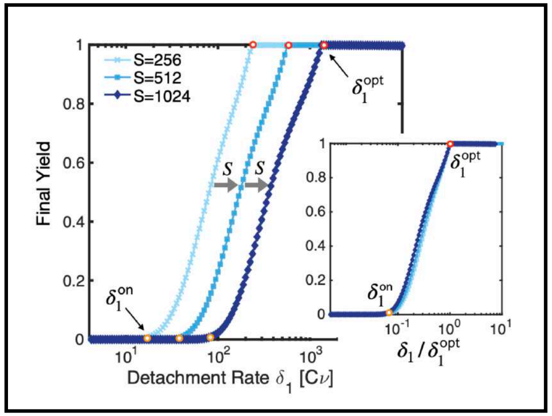
Cluster $$\partial_t c(s,t) = -a\,\bar{\nu}\,m^{\gamma}\partial_s[s^{\omega} c(s)]$$

These differential equations exhibit scale invariance!

$$m(t, \delta_1, S) = C\,\tilde{m}(S^{-\theta}\,\tilde{t},\; S^{-\phi}\,\tilde{\delta}_1)$$

$$c(s, t, \delta_1, S) = C S^{-2}\,\tilde{c}(S^{-1}s,\; S^{-\theta}\,\tilde{t},\; S^{-\phi}\,\tilde{\delta}_1)$$

Scaling law: $$T_Y(\delta_1, S) = S^{\theta}\,\tilde{T}_Y(S^{-\phi}\,\delta_1)$$



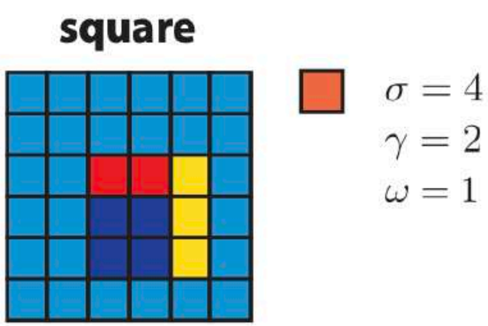
Exponents determined by assembly parameters

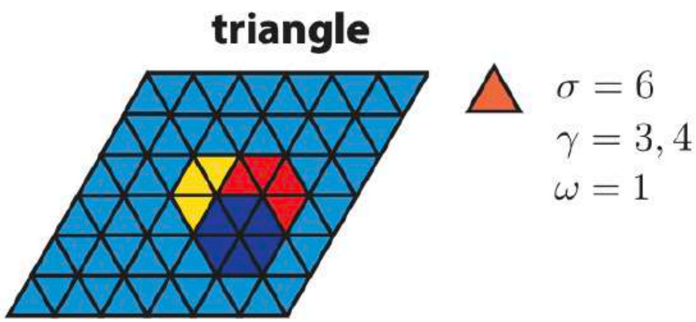
Control parameter exponent: $\delta_1^{\text{opt}} \sim S^{\phi}$

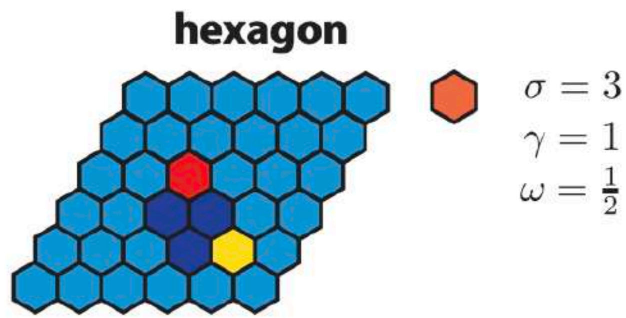
$$\phi = \frac{2-\omega}{\sigma-\gamma-1}$$

Time complexity exponent: $T_{90}^{\min} \sim S^{\theta}$

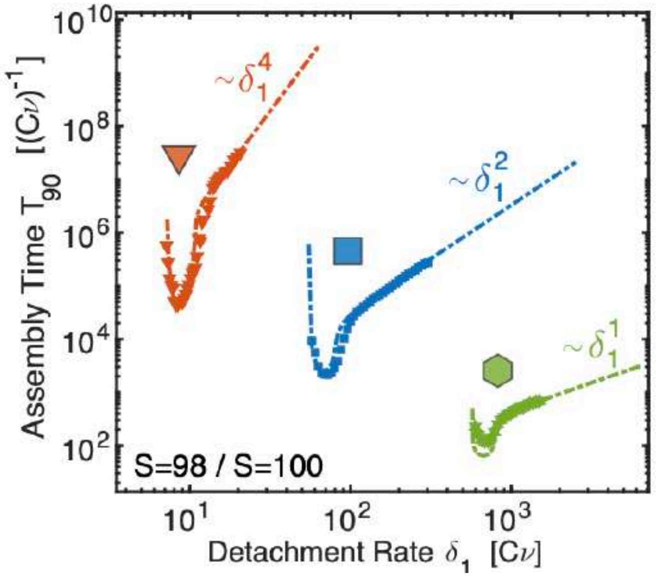
$$\theta = \frac{(1-\omega)\,\sigma+\gamma+2\omega-3}{\sigma-\gamma-1}$$







Scaling laws & assembly exponents



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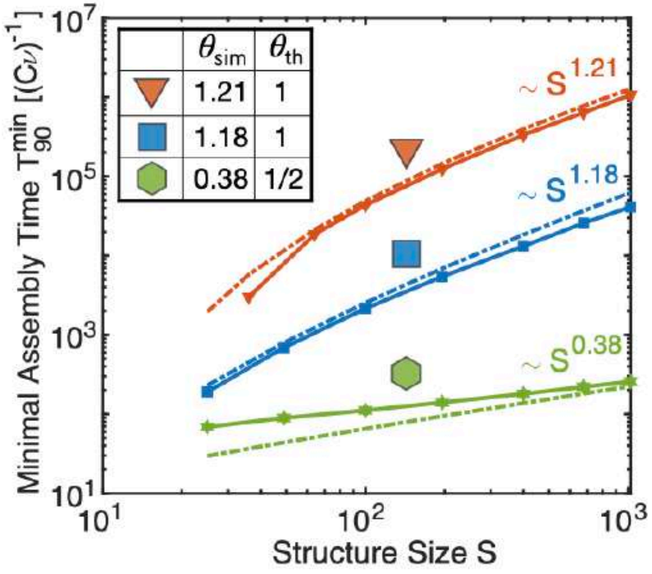

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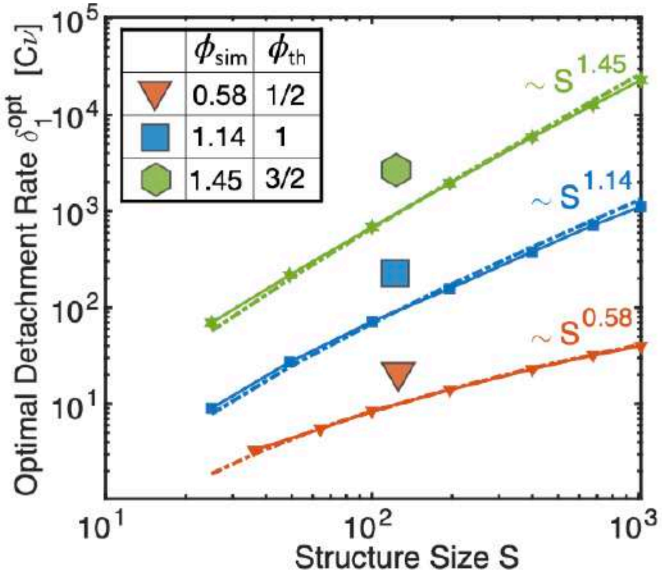
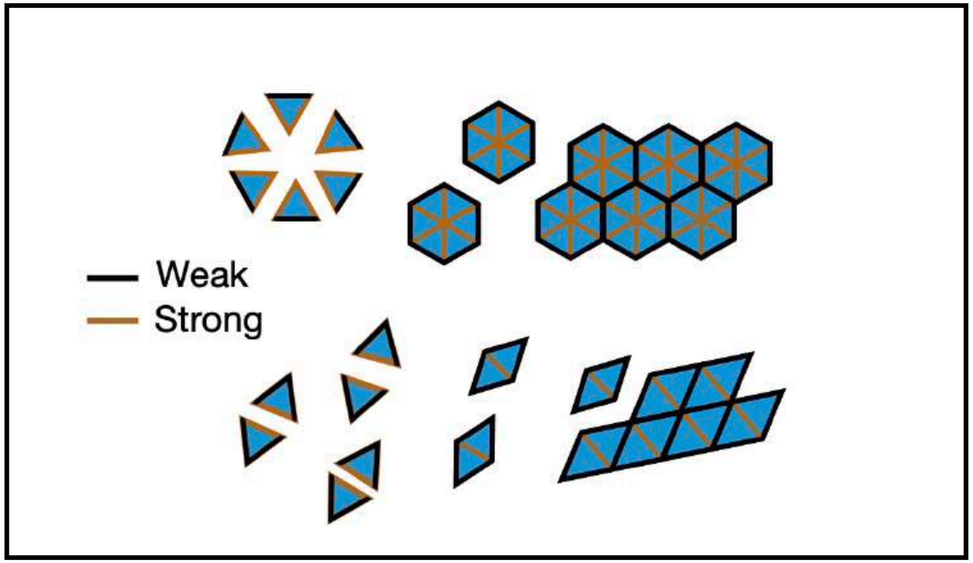
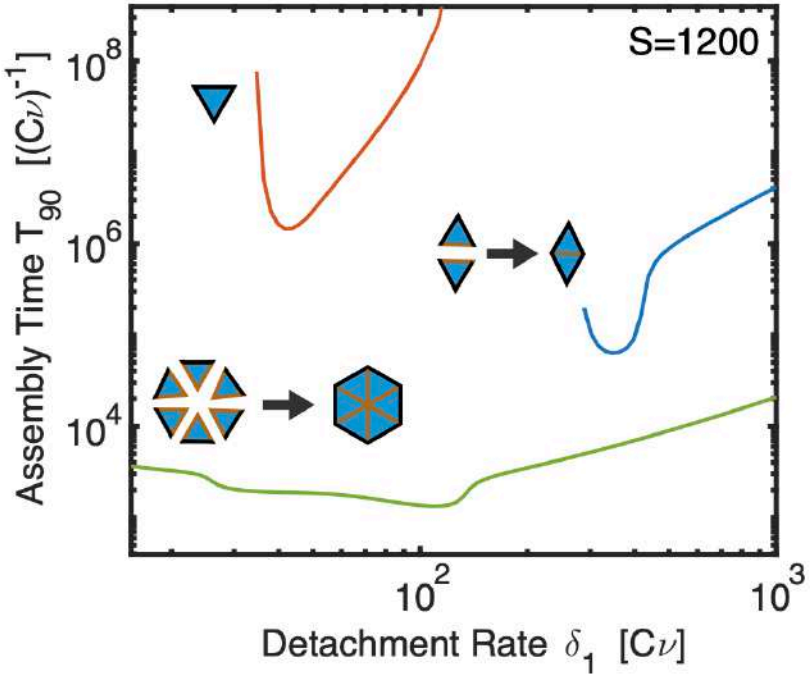


Optimal detachment rate shows power law in structure size

$$\delta_1^{\text{opt}} \sim S^{\phi}$$

How can we make assembly robust?



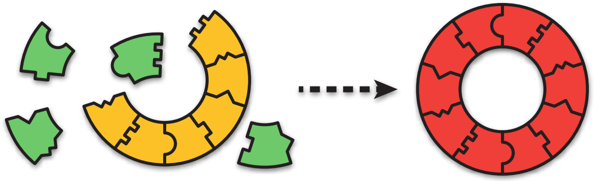


Hierarchical self-assembly schemes

Make triangle-shaped building blocks form higher-order constituents

Huge reduction in assembly time

Increased robustness to parameter variations



Self-assembly dynamics - What we know

Slow nucleation principle

Time complexity of self-assembly T(S) = ?

Power laws and scaling laws

Morphology of the building blocks matters

Self-assembly dynamics - What we do not know

Information-rich vs. information-poor

Spatial and temporal organization

Size and shape control

Acknowledgements

Florian Gartner
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erc

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Matter to Life

LMU
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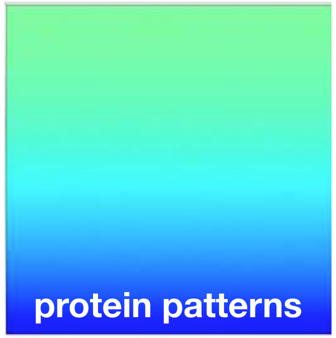
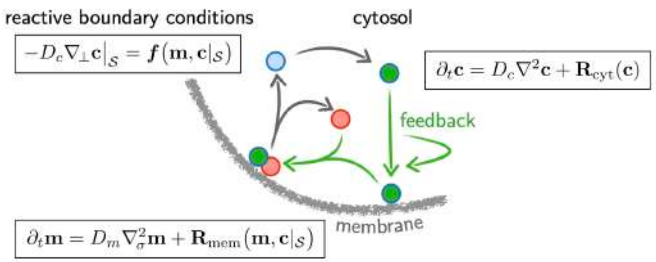
CENTER FOR THEORETICAL PHYSICS

PhysicsOfLifeLMU

Theory of Living and Soft Matter

Pattern formation in mass-conserving systems

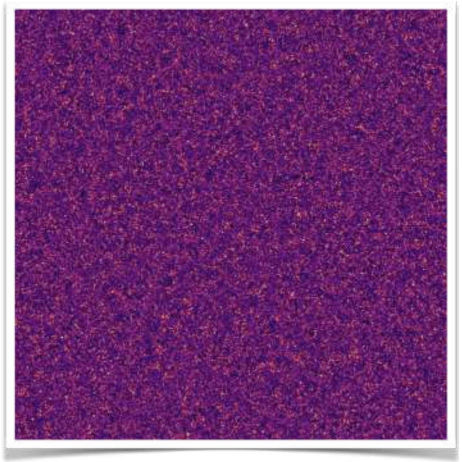




Nat Phys 21, PNAS 22, Nat Rev Phys 22,
Nat Comm 20-22, eLife 19, eLife 21

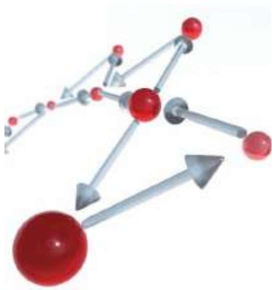
Nat Phys 18, PNAS 18
PRL 19, PRX 20, Nat Phys 21, PRL 21

Active matter



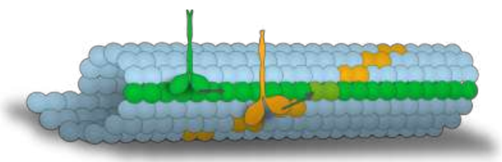
Science 18, PNAS 20,
Nat Mat 22, Nat Comm 22

Topological phases in population dynamics



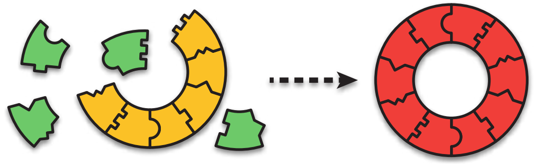
PRL 20, PRE 18

Intracellular transport



PRX 18, PRL 18, PNAS 20, PRL 21,
Science Adv 21, PRL 22

Self-assembly dynamics



eLife 20, PNAS 22, PRL 23