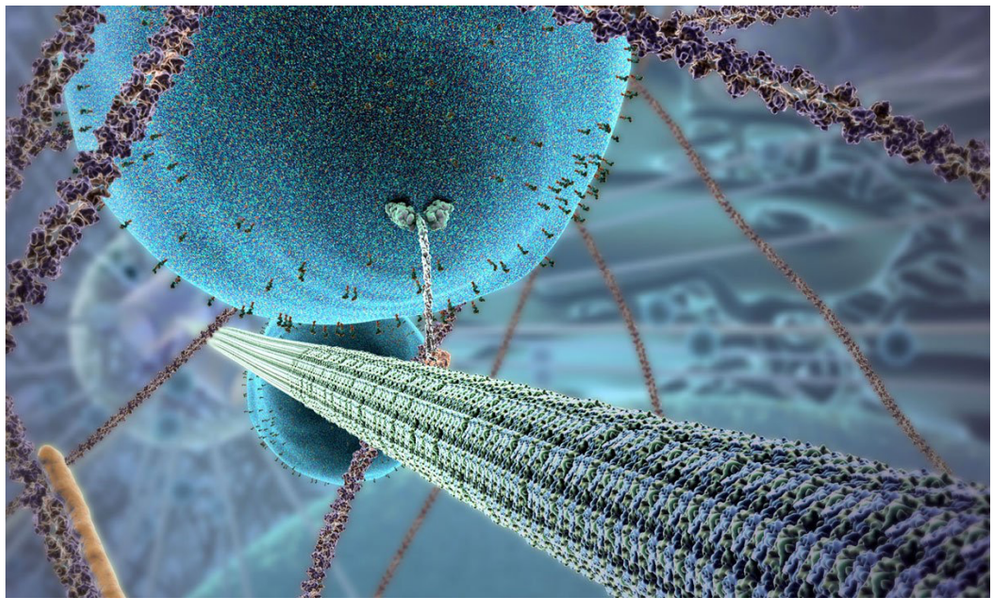
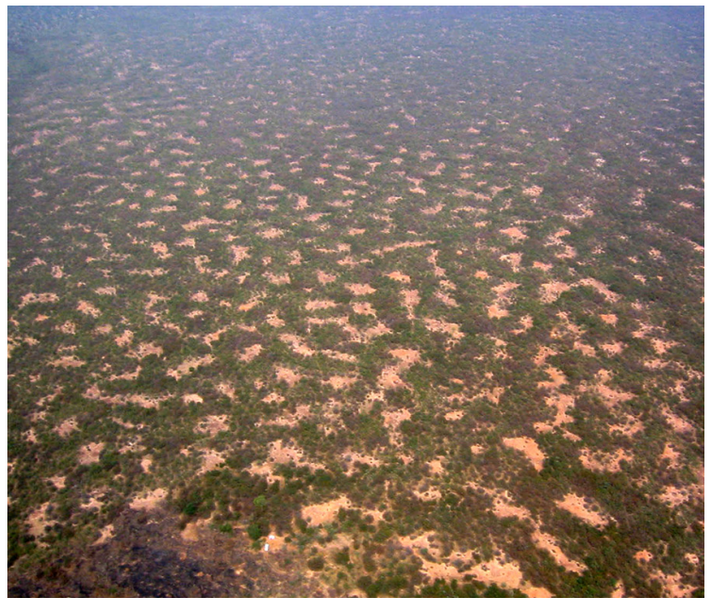
MAE 545: Lecture 21 (5/4)

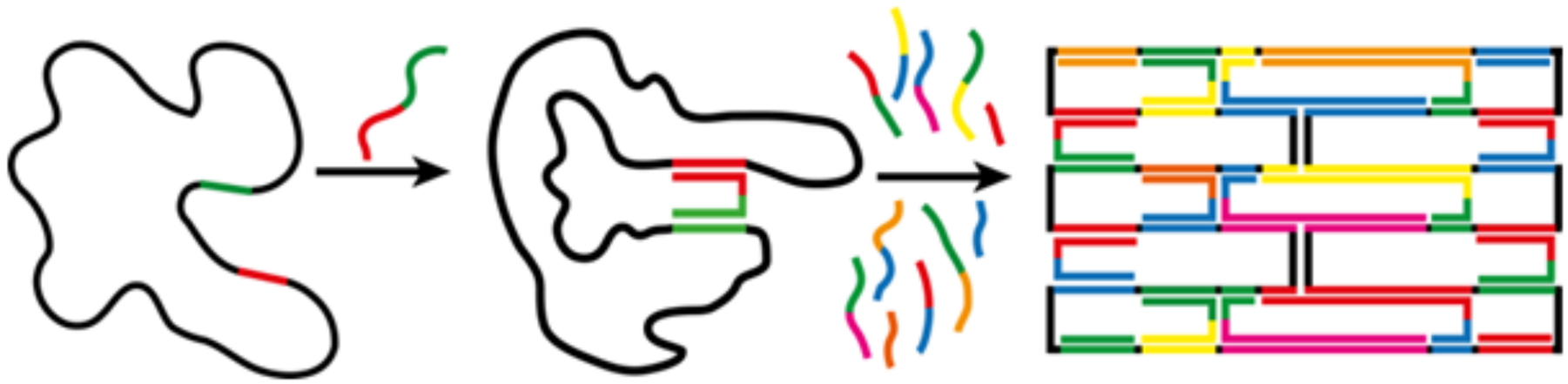
Dynamics of molecular motors (continued)



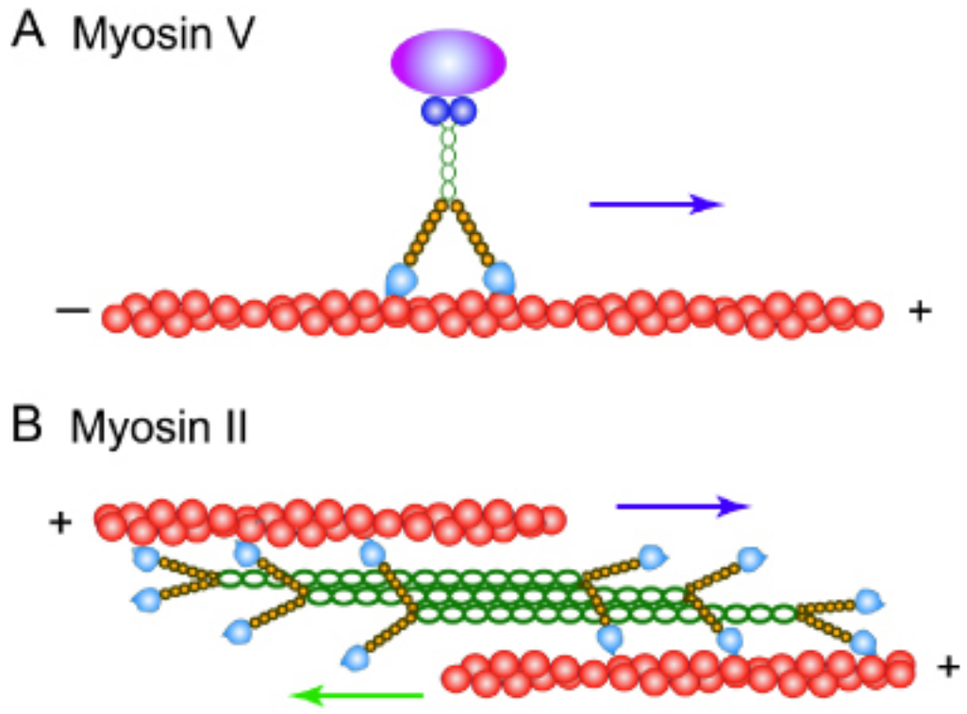
Touring patterns



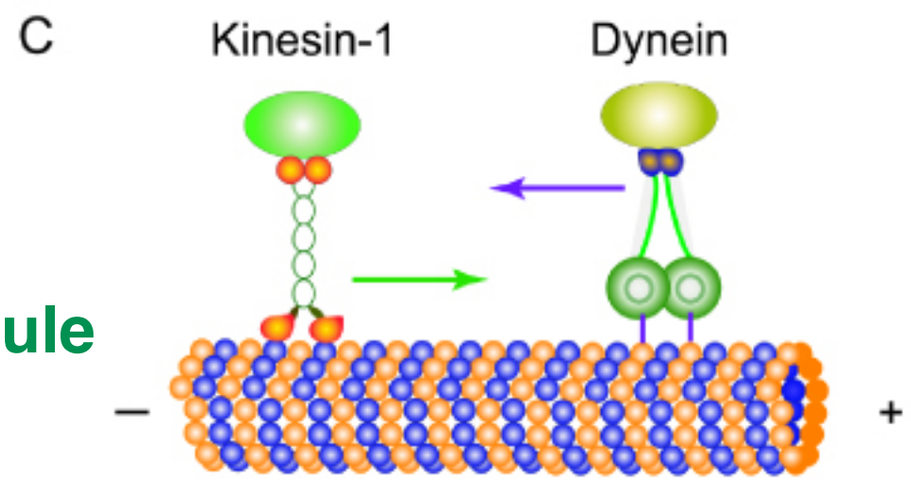
DNA origami



Molecular motors



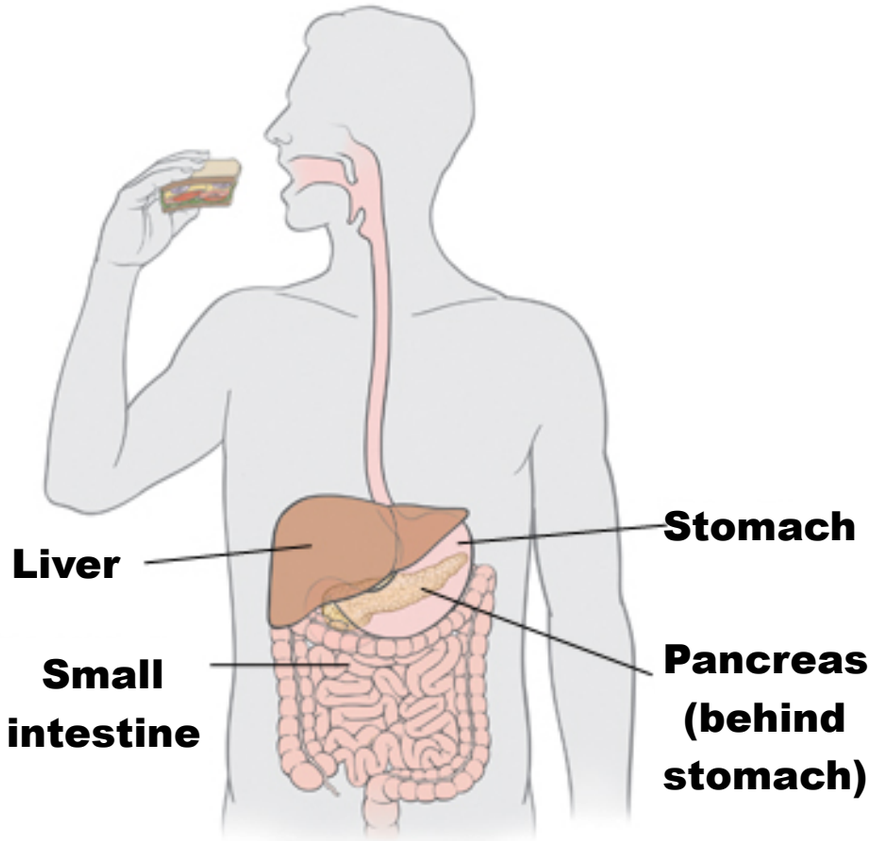
Molecular motors are fueled by ATP

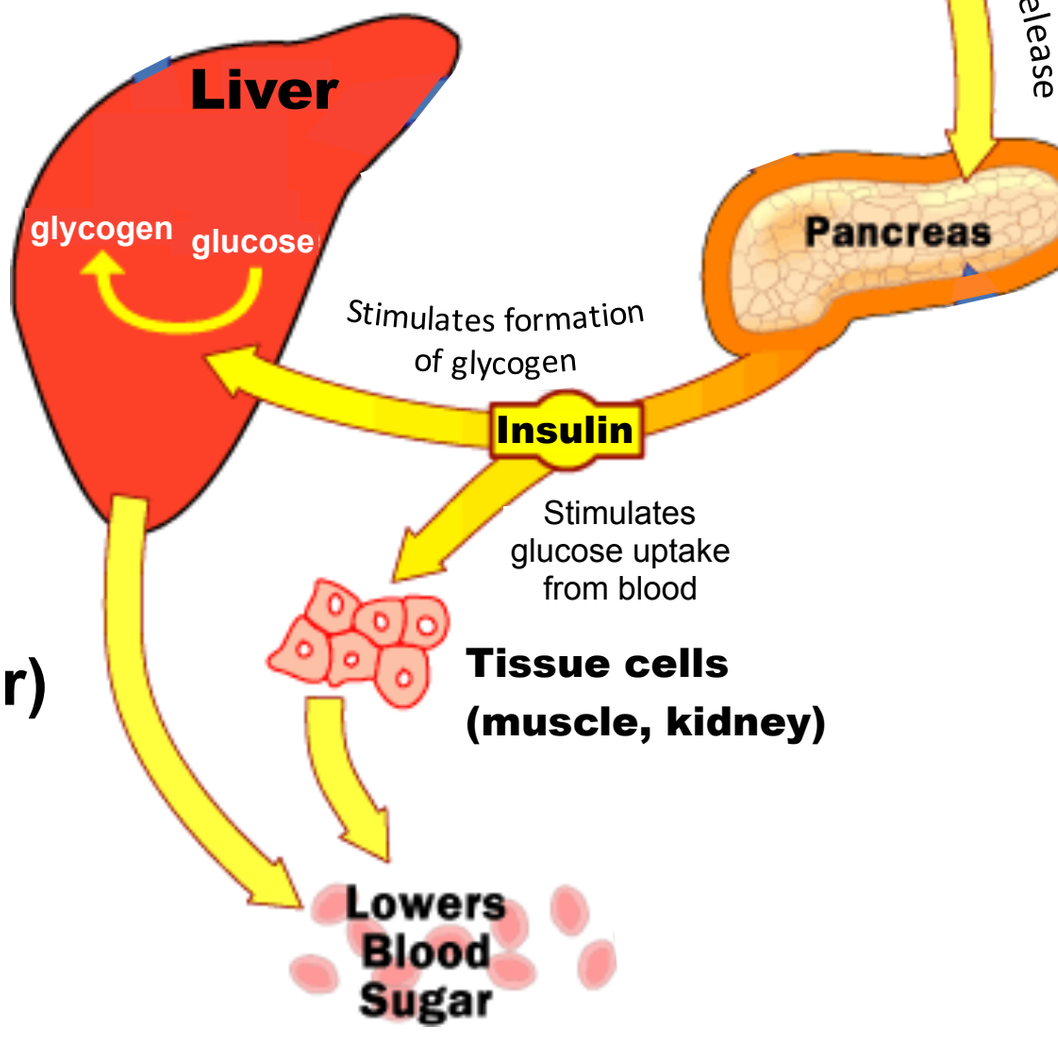


How is ATP produced?

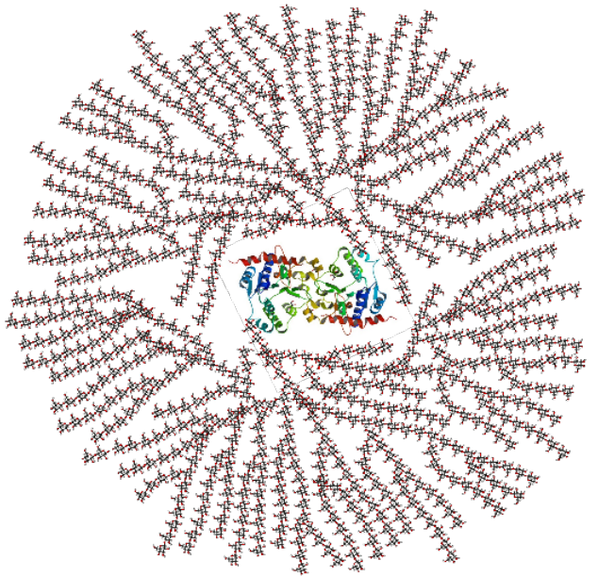
A.B. Kolomeisky, J. Phys.: Condens. Matter **25**, 463101 (2013)

Regulation of blood sugar levels

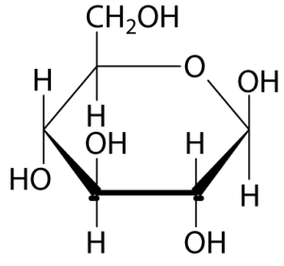




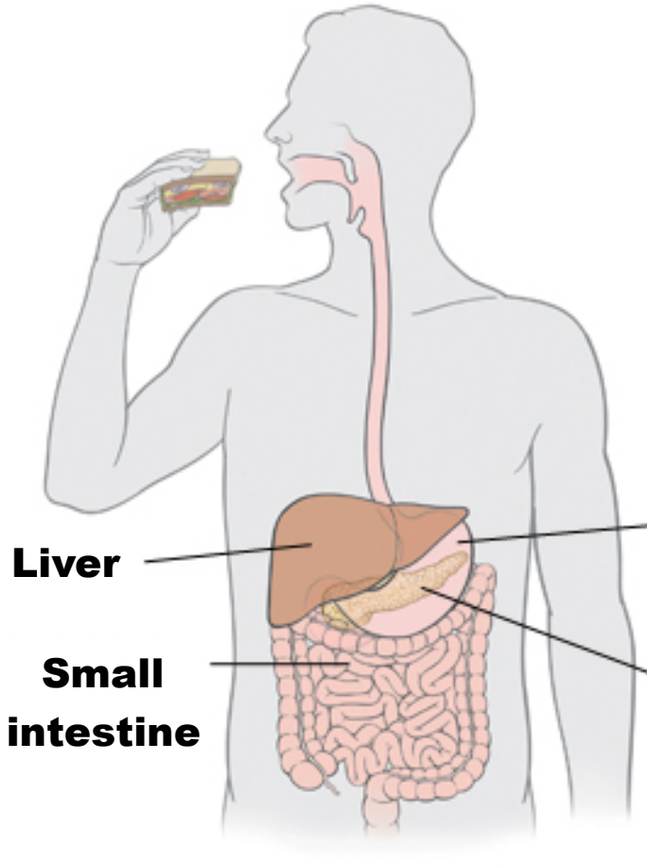
glycogen
(polysaccharide of glucose)

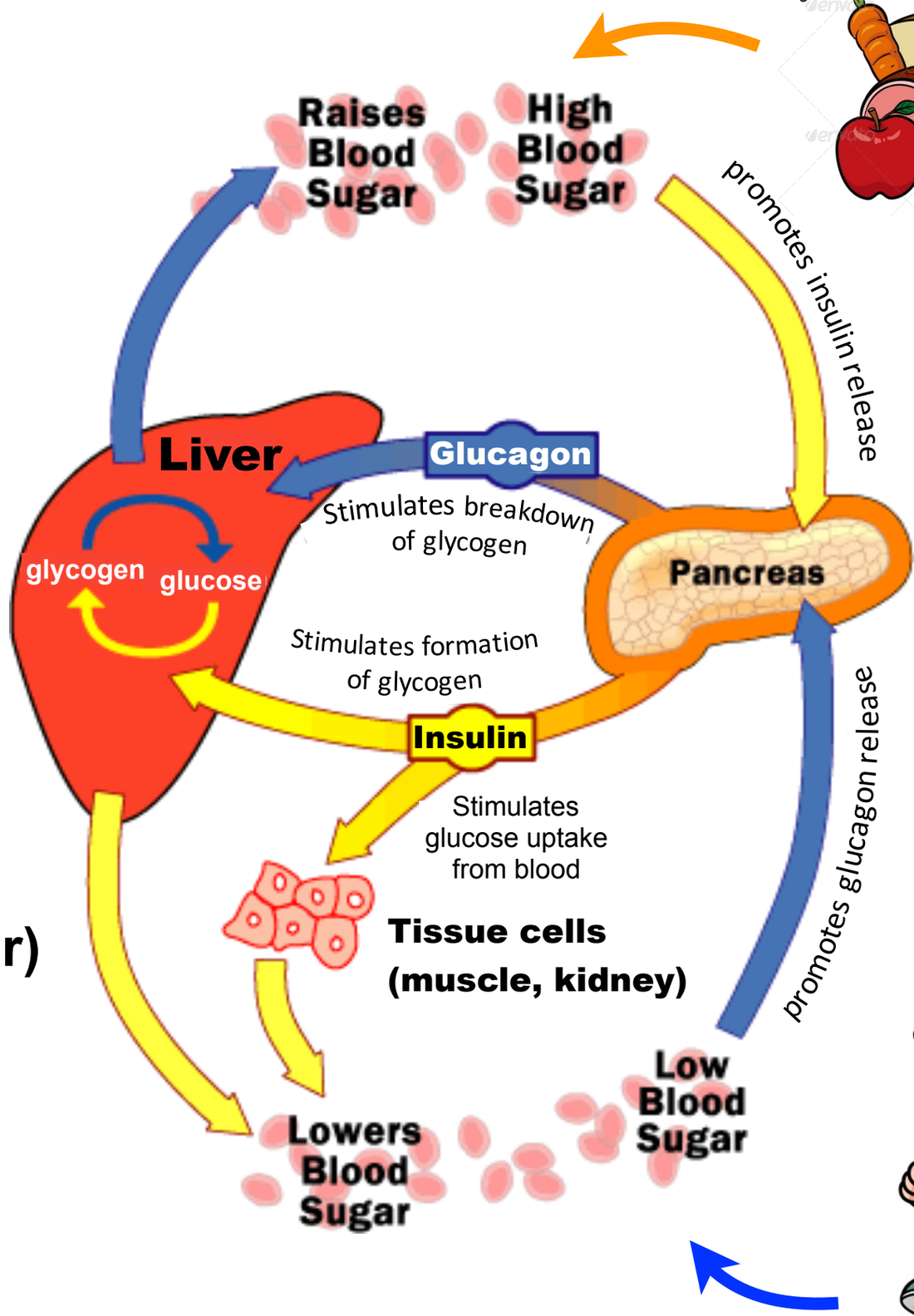


glucose
(blood sugar)

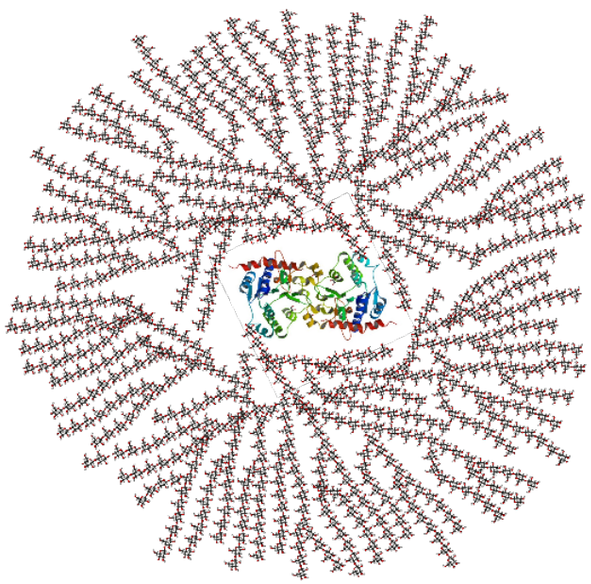


Regulation of blood sugar levels

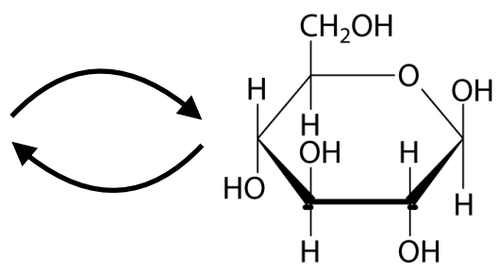




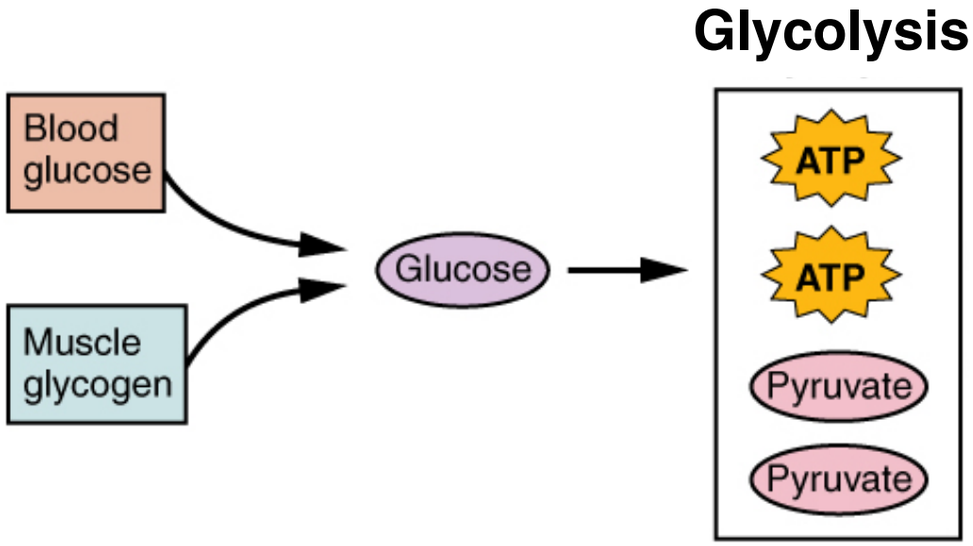
glycogen (polysaccharide of glucose)



glucose (blood sugar)



Conversion of blood sugars to ATP



O_2

$$C_6H_{12}O_6 + 6O_2 \Longrightarrow 6CO_2 + 6H_2O + 36ATP$$

Aerobic respiration

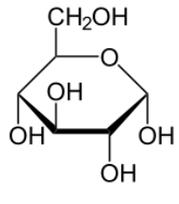
no O_2

$$C_6H_{12}O_6 \Longrightarrow 2\ \text{Lactic Acids} + 2ATP$$

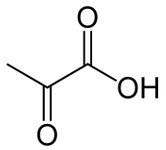
Anaerobic respiration

(muscle fatigue)

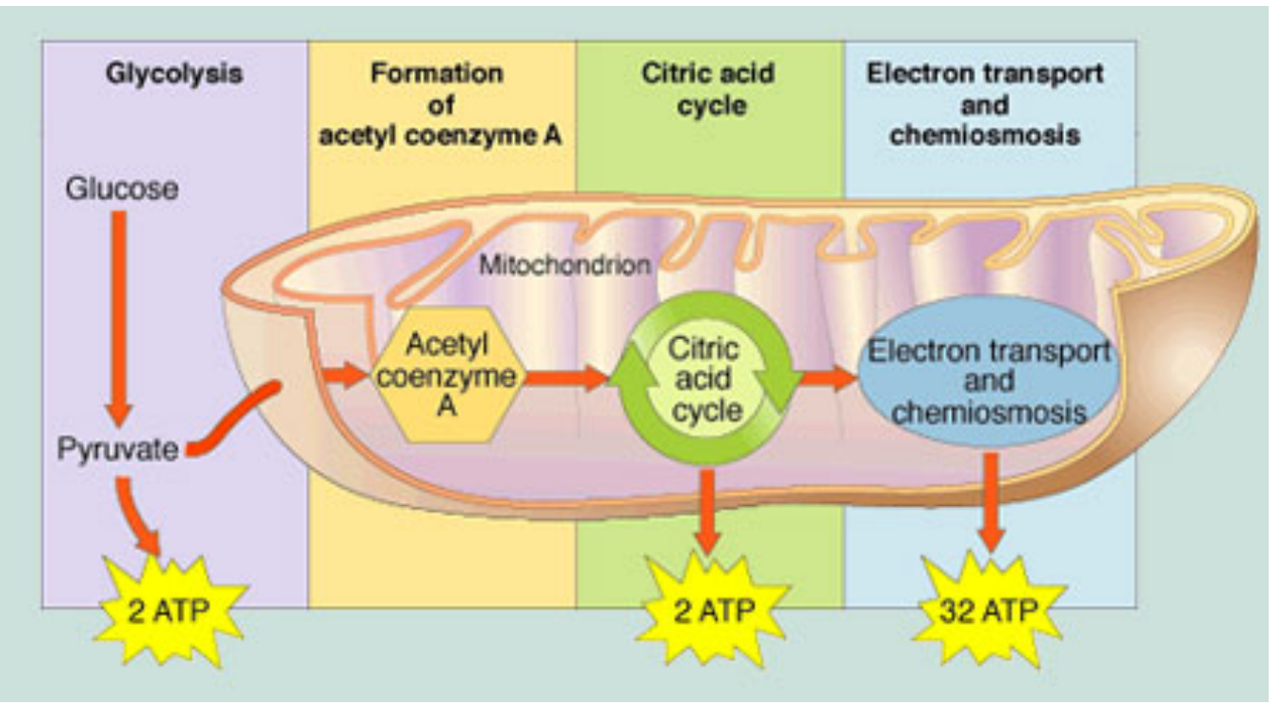
glucose



pyruvate



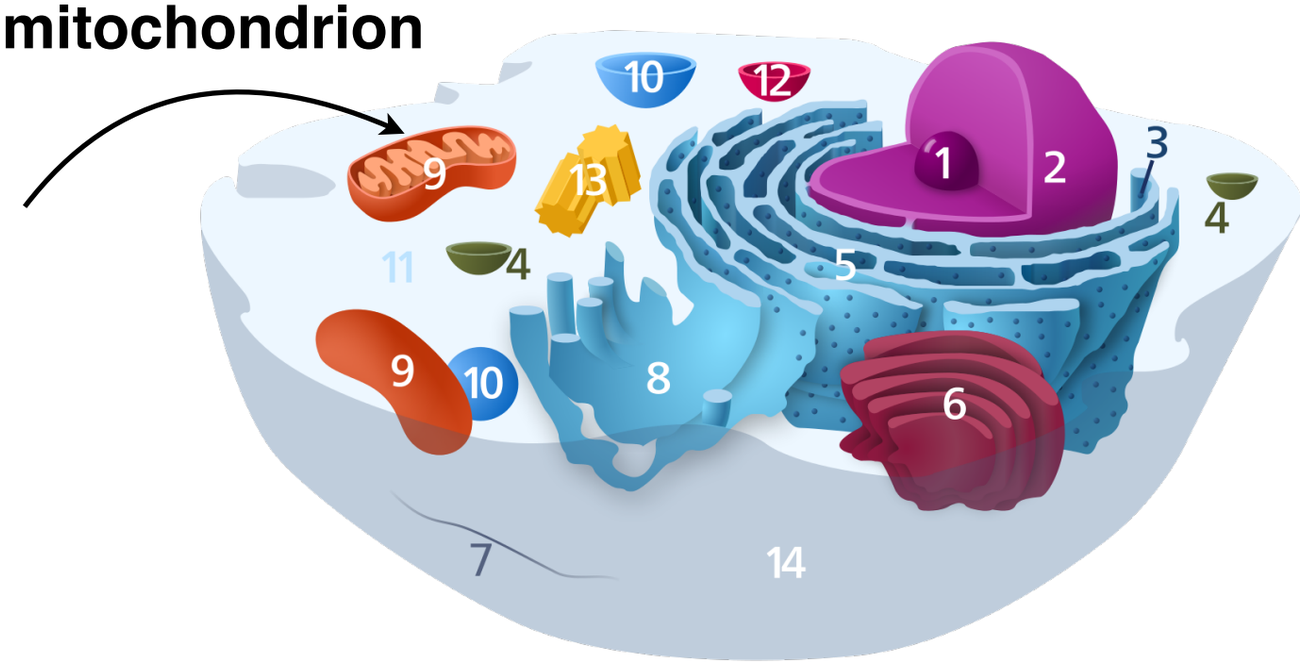
Aerobic respiration



Note: Citric acid cycle = Krebs cycle

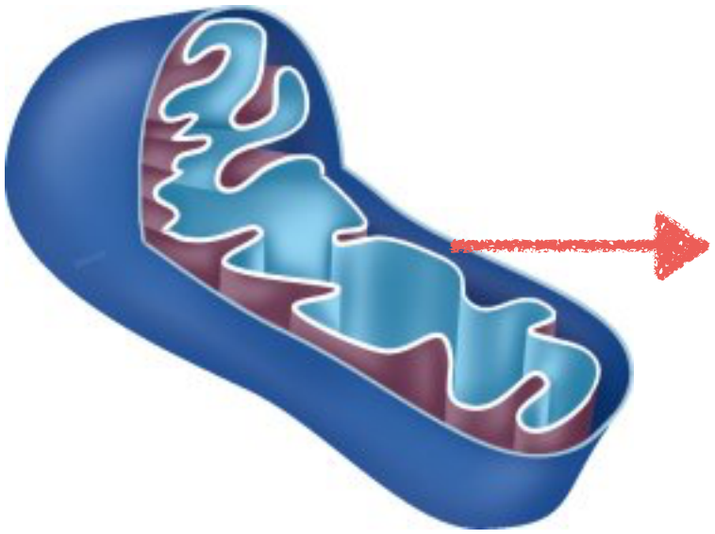
Cell

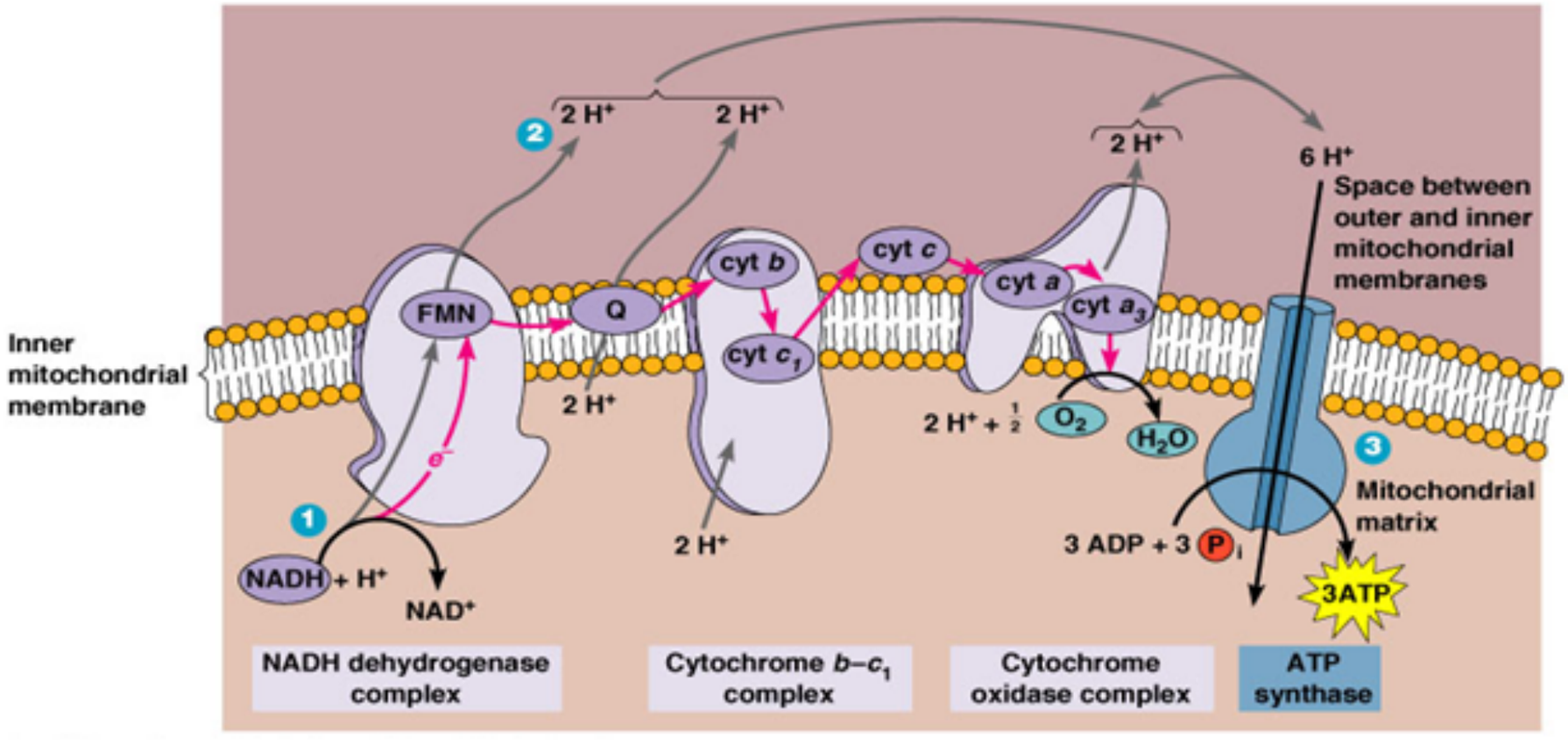
mitochondrion



ATP synthase

Mitochondrion



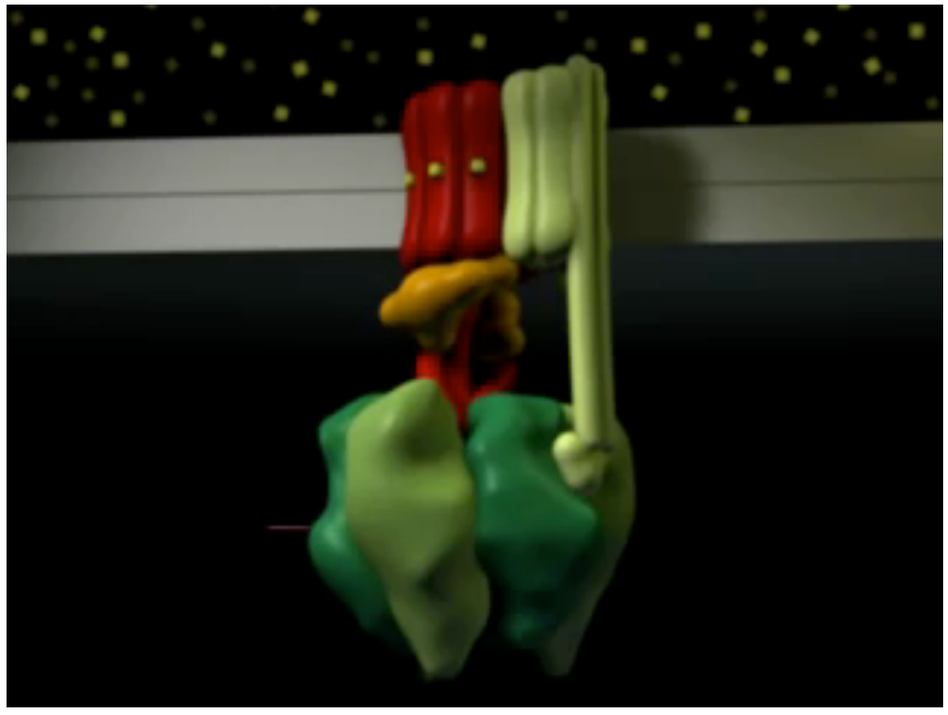


NADH products of the Cytric acid cycle are used to pump H^+ to the space between outer and inner mitochondrial membrane.

Gradient of H^+ concentration drives the ATP synthase motor that converts ADP to ATP.

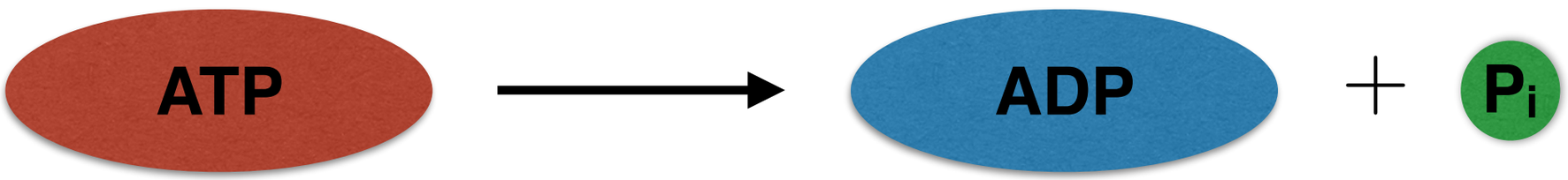
Note: ATP synthase can run in reverse and use ATP to pump H^+ at low concentrations.

ATP synthase



Energetics of ATP hydrolysis

How much energy is released during ATP hydrolysis?



$$\Delta G = \mu_{\mathrm{ADP}} + \mu_{\mathrm{P}} - \mu_{\mathrm{ATP}}$$

$$\Delta G = \mu^0_{\mathrm{ADP}} + \mu^0_{\mathrm{P}} - \mu^0_{\mathrm{ATP}} + k_B T \ln\left(\frac{[\mathrm{ADP}][\mathrm{P_i}]}{[\mathrm{ATP}]c_0}\right)$$

$-12.5 k_B T$

Under physiological conditions: $\Delta G \sim -20 k_B T$

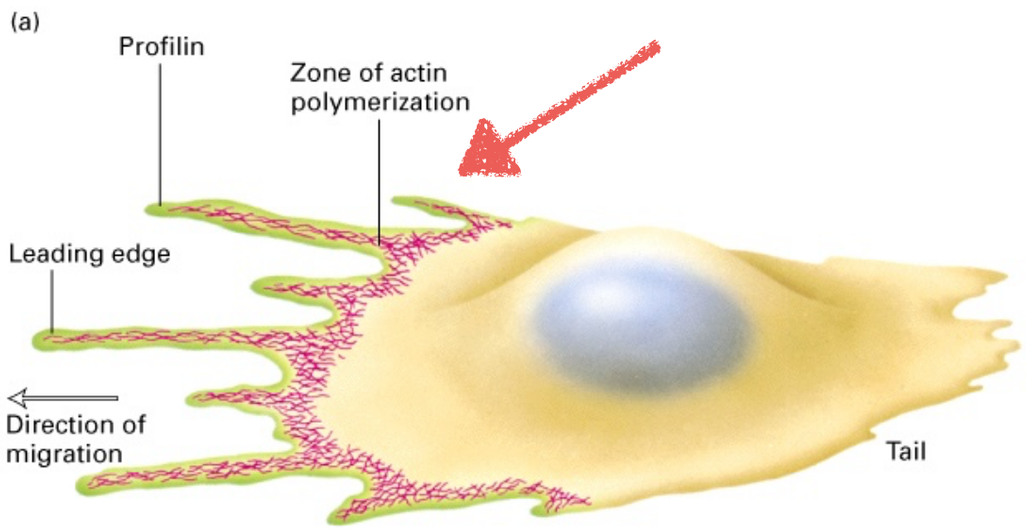
$([\mathrm{ATP}], [\mathrm{ADP}], [\mathrm{P}_i] \sim 1\mathrm{mM})$

Chemical potentials are typically defined relative to concentration $c_0 \sim 1$ M.

$$\mu_s(c_s) = \mu_s(c_0) + k_B T \ln(c_s/c_0)$$

Crawling of cells

Actin

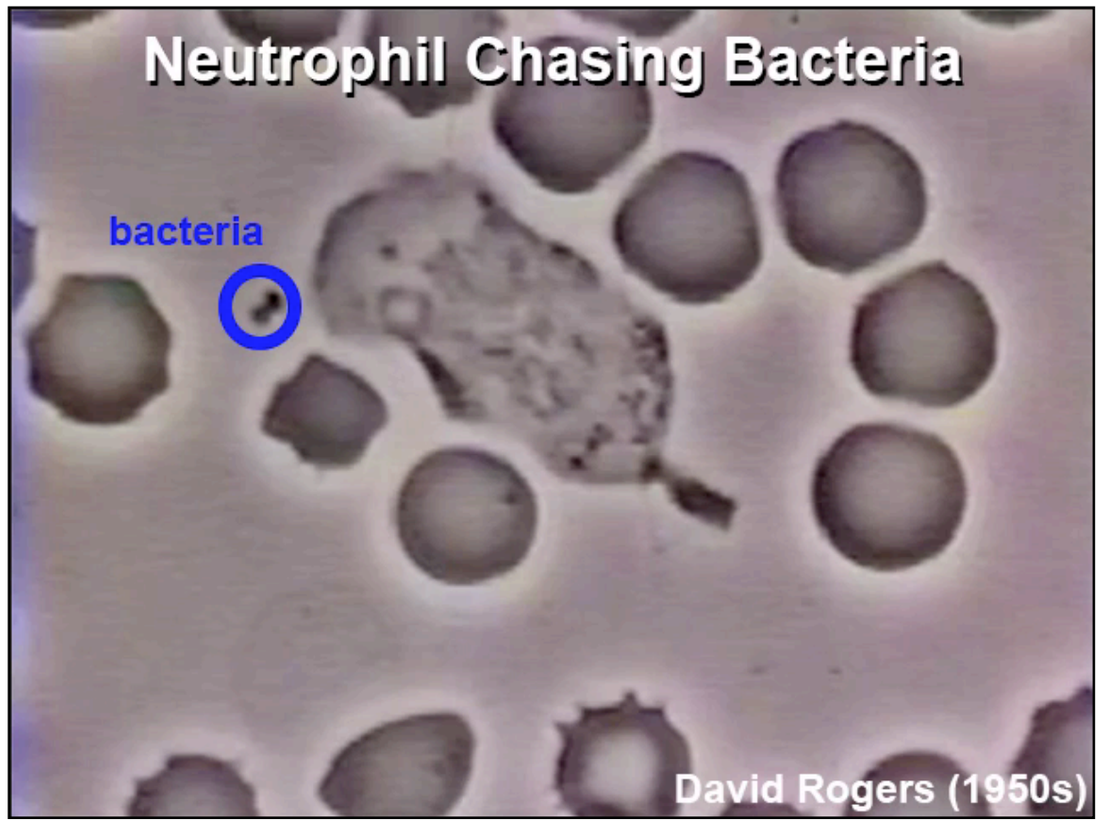


migration of skin cells during wound healing

spread of cancer cells during metastasis of tumors

amoeba searching for food

Immune system: neutrophils chasing bacteria

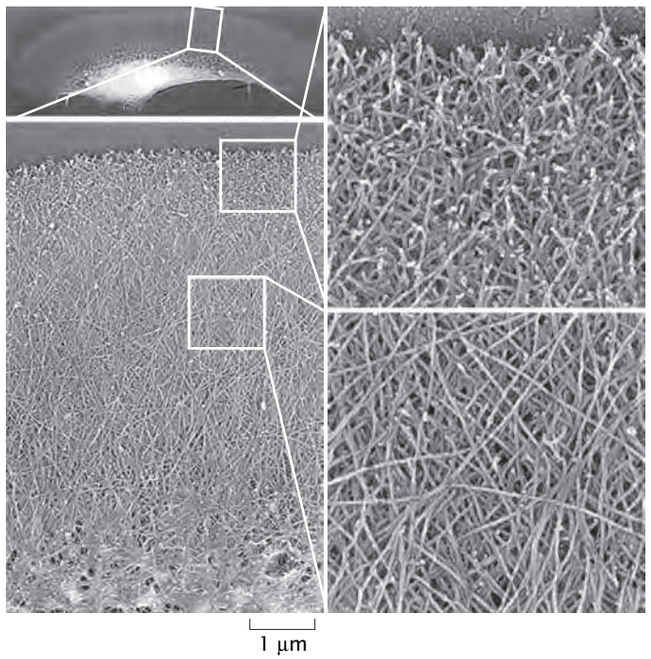


David Rogers, 1950s

$$v \sim 0.1 \mu \mathrm{m/s}$$

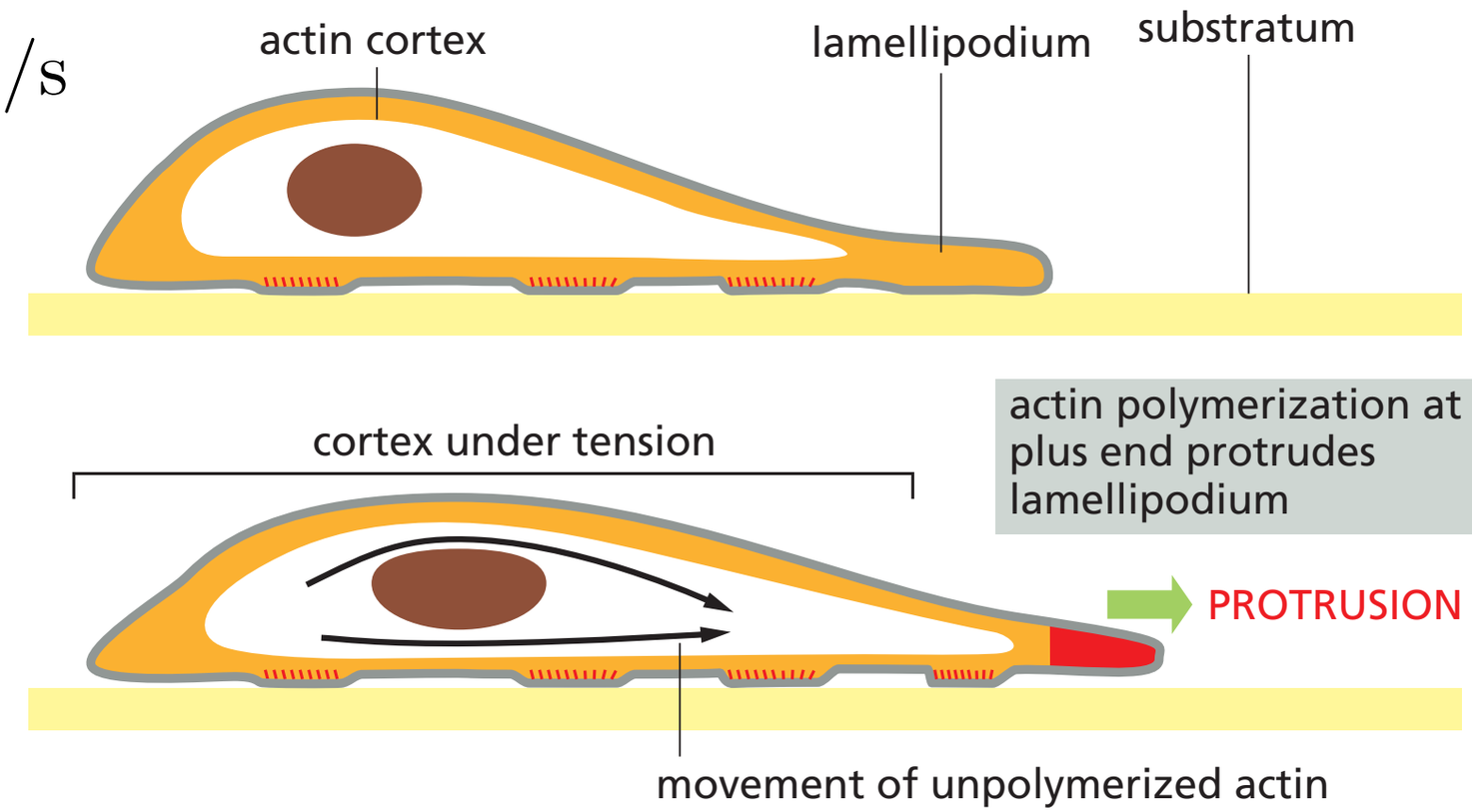
Crawling of cells

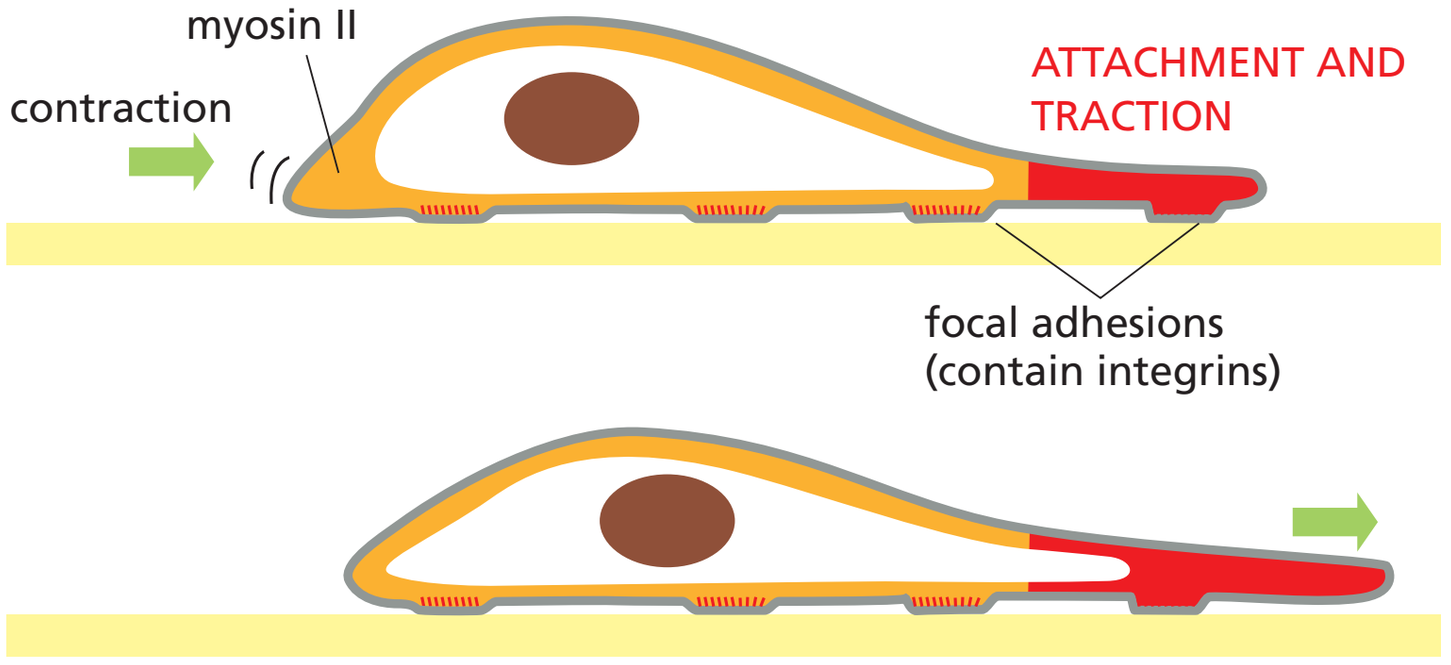
fish skin cell $v = 0.2\mu\mathrm{m/s}$



actin

R. Phillips et al., Physical Biology of the Cell

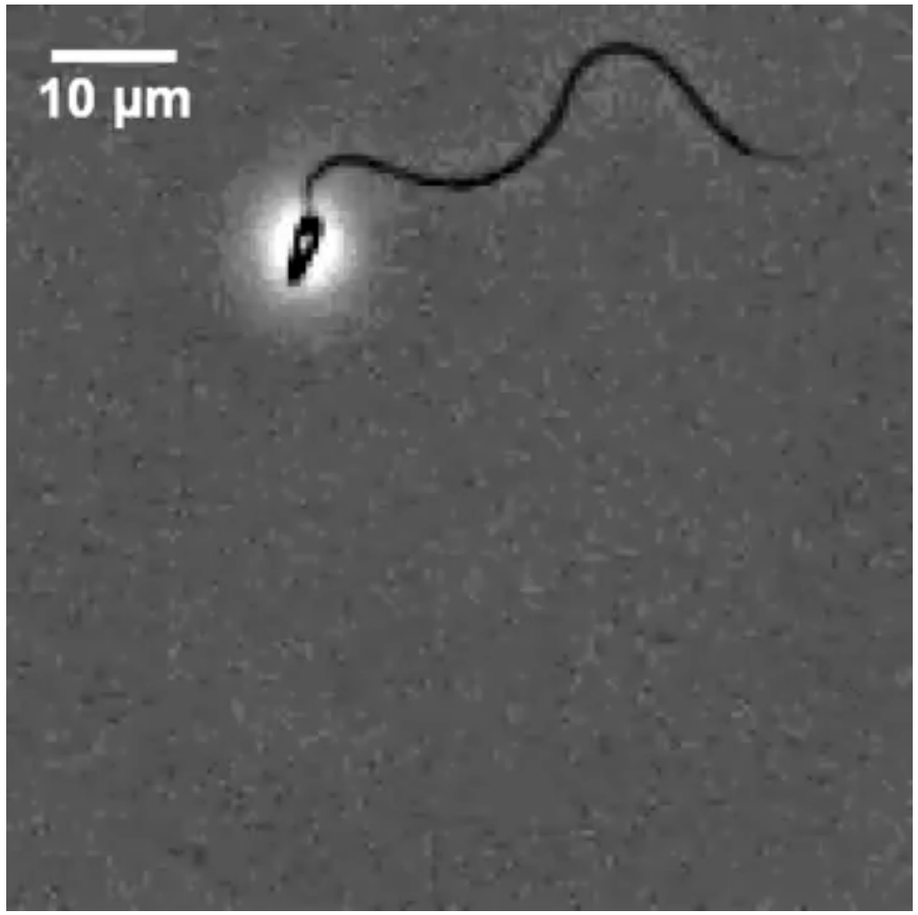




Alberts et al., Molecular Biology of the Cell

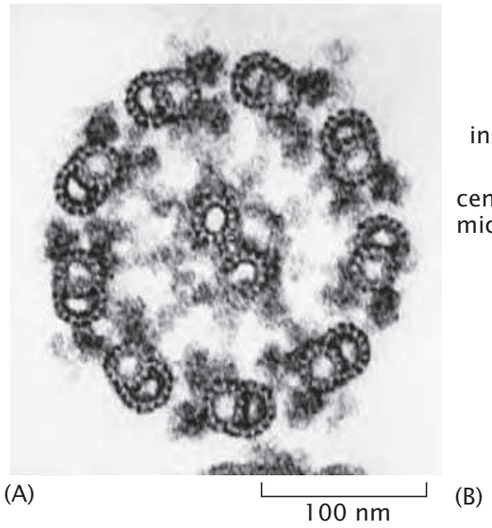
Swimming of sperm cells

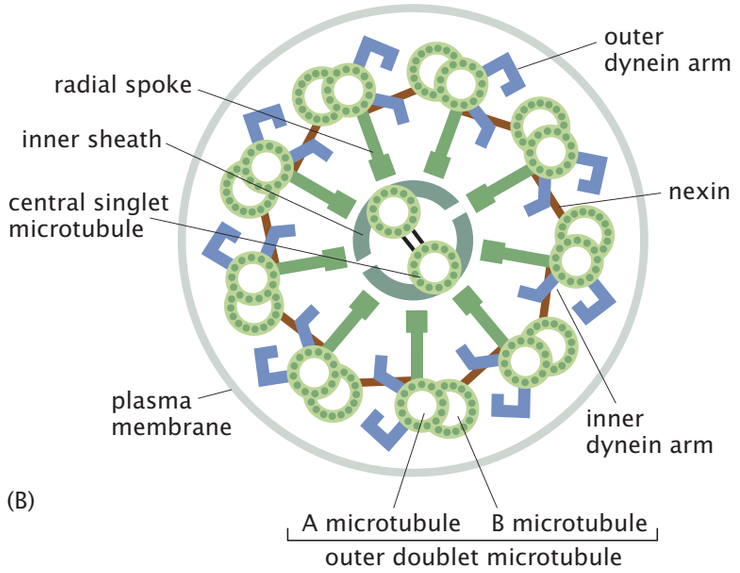
Sperm flagellum is constructed from microtubules

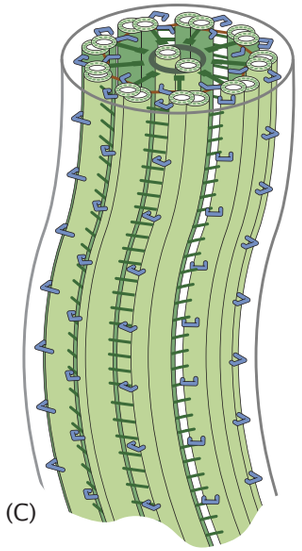


Jeff Guasto

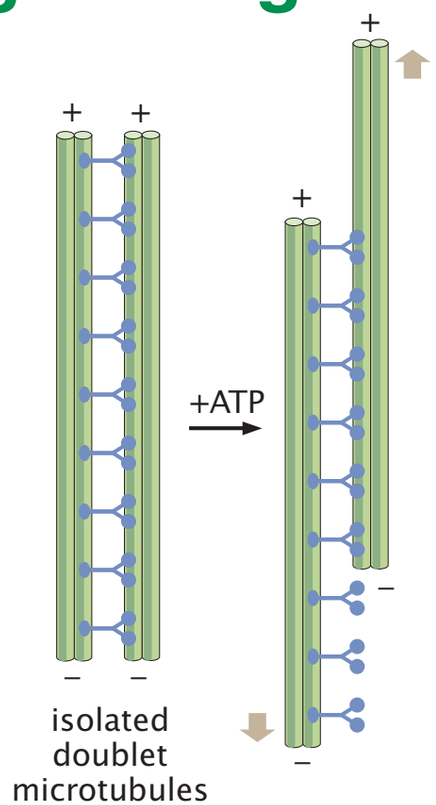
$v \sim 50 \mu \mathrm{m/s}$

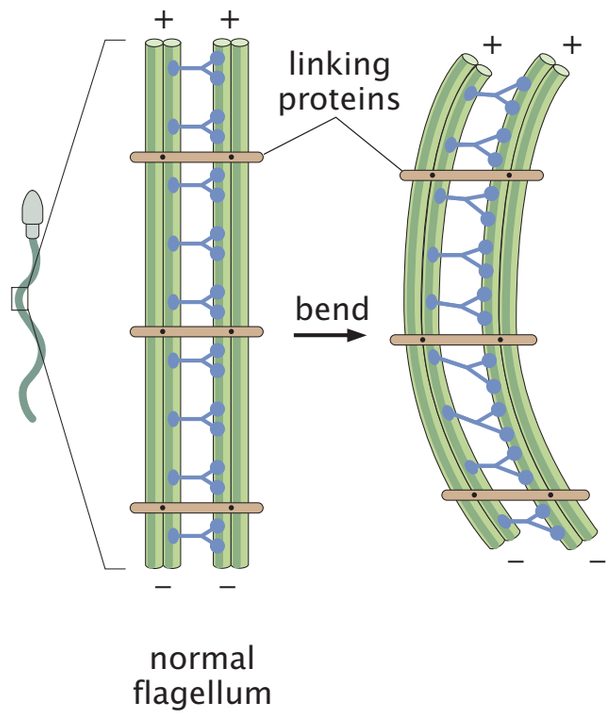






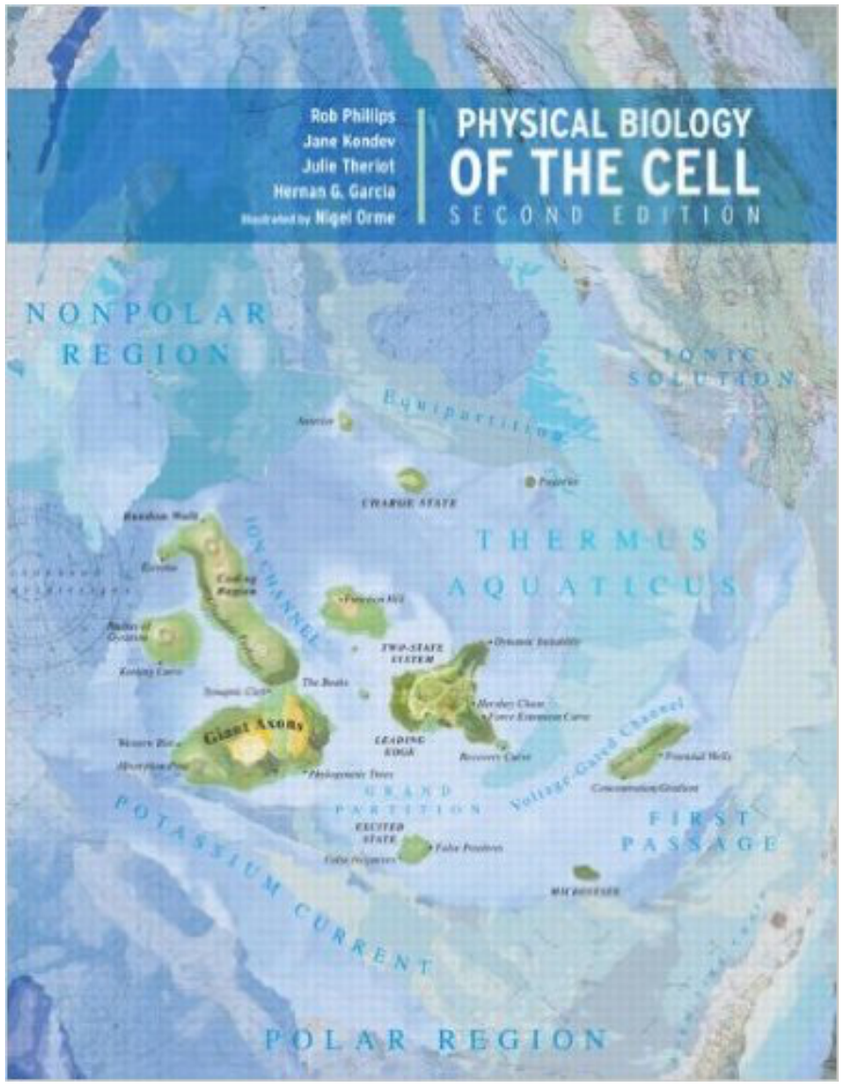
Bending is produced by motors walking on neighboring cross-linked microtubules

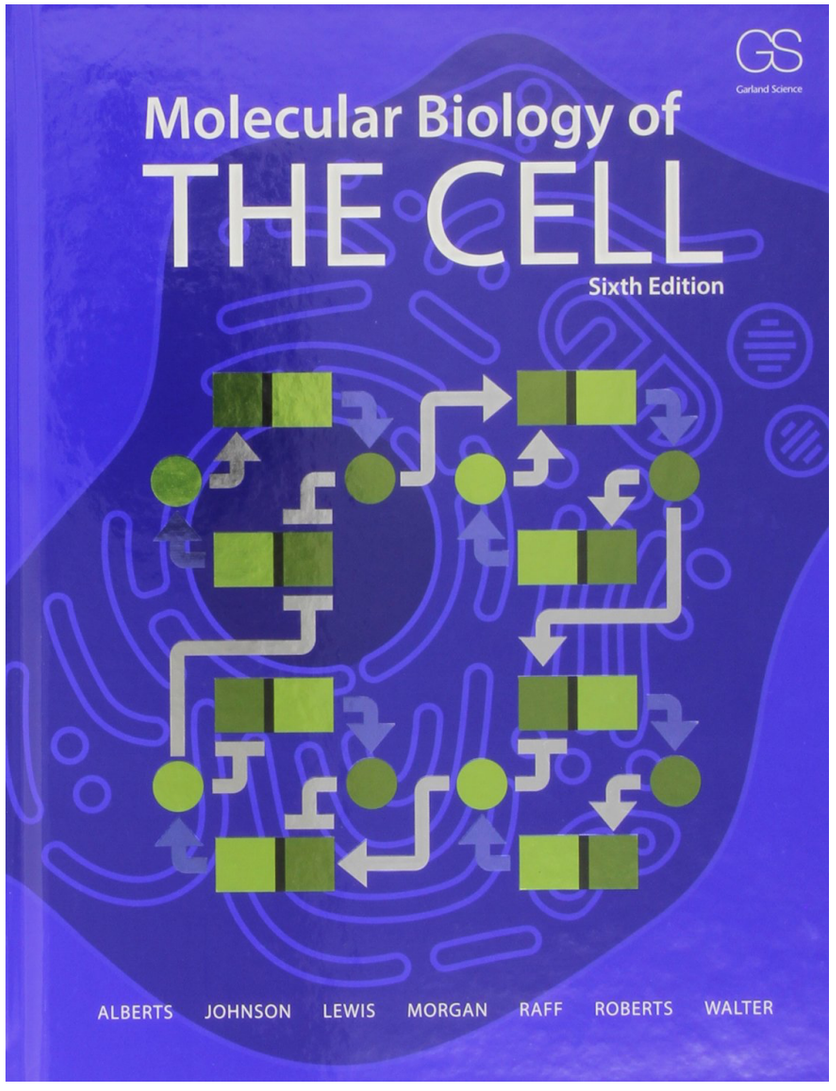


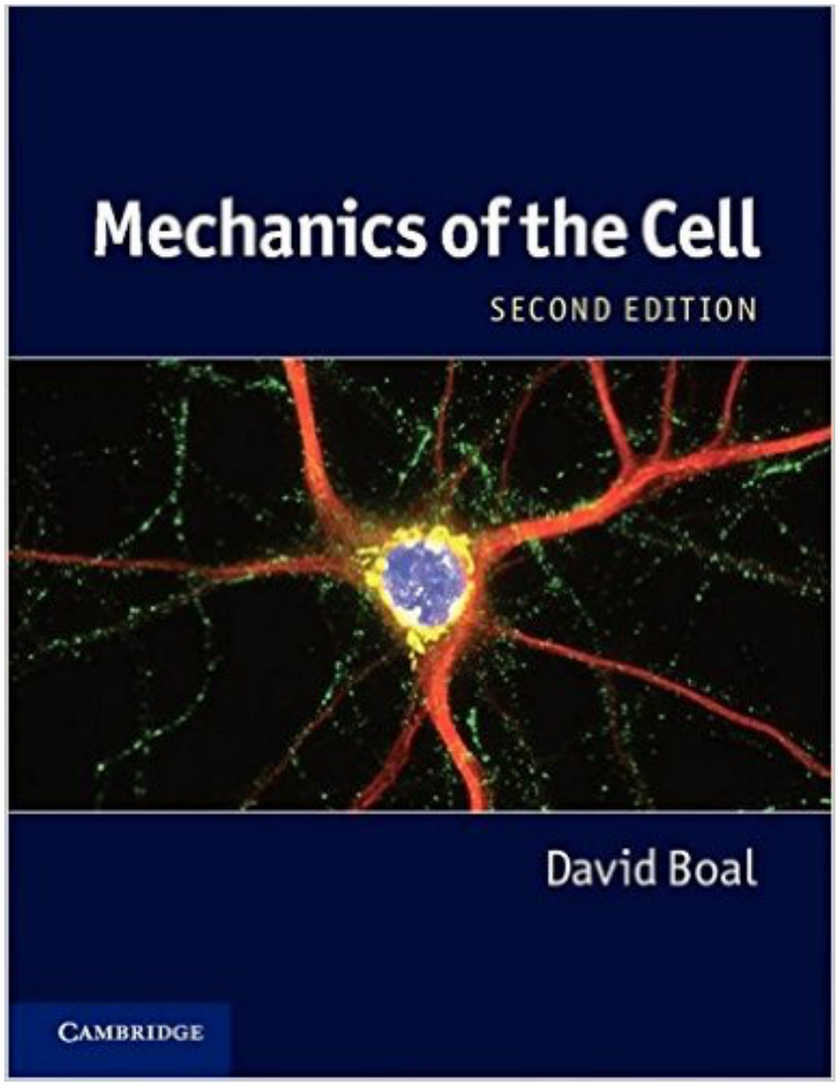


R. Phillips et al., Physical Biology of the Cell

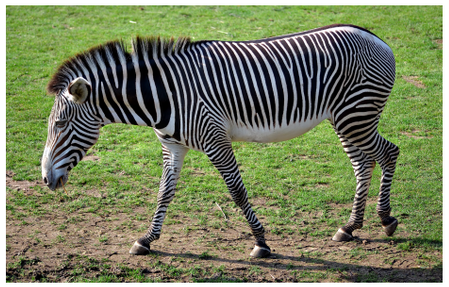
Further reading



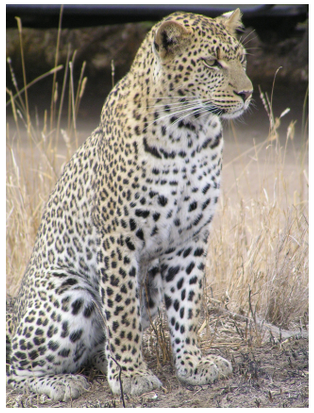




Patterns in nature



zebra

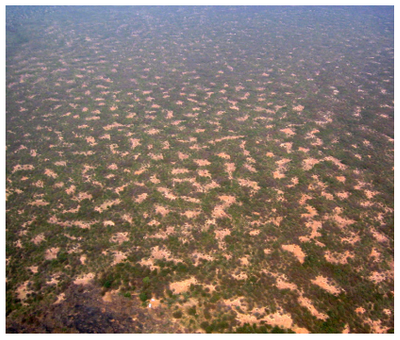


leopard

royal angelfish

peacock

giant pufferfish

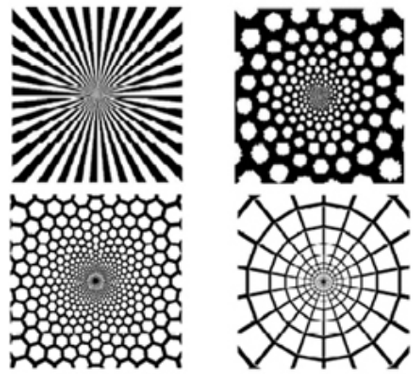


tiger bush

fir waves

mussels

clouds



hallucination patterns

1952: Alan Turing wrote “The Chemical Basis of Morphogenesis”

Many of these patterns can be constructed with reaction-diffusion models.

What are the minimal requirements that produce such patterns?

Reaction-diffusion equations

$$\frac{\partial C_i(\vec{r},t)}{\partial t} = F_i\left(\{C_j(\vec{r},t)\}\right) + D_i \nabla^2 C_i(\vec{r},t)$$

$i = 1, 2, \cdots, N$ **N interacting components**

First let's consider the case without diffusion (D_i=0) and find fixed points

$$F_i\left(\{C_j^*\}\right) = 0$$

Linear stability analysis

Linearize the PDE around the fixed point

$$\frac{\partial c_i(\vec{r},t)}{\partial t} = \sum_{j=1}^{N} M_{ij}^0 c_j(\vec{r},t)$$

$$c_i(\vec{r},t) = C_i(\vec{r},t) - C_i^* \qquad M_{ij}^0 = \left.\frac{\partial F_i}{\partial C_j}\right|_{C^*}$$

How can we determine whether fixed points are stable or not?

Reaction-diffusion equations

Linear stability analysis

$$\frac{\partial c_i(\vec{r},t)}{\partial t} = \sum_{j=1}^{N} M_{ij}^0 c_j(\vec{r},t)$$

General solution

$$c_i\left(\vec{r},t\right) = \sum_{\alpha=1}^{N} A_\alpha v_i^{(\alpha)} e^{\lambda_\alpha t}$$

λ and v_i correspond to eigenvalues and eigenvectors of matrix M_{ij}^0

$$\sum_{j=1}^{N} M_{ij}^0 v_j = \lambda v_i$$

Fixed point is linearly stable when real parts of all eigenvalues are negative:

$$\boxed{\mathrm{Re}(\lambda_\alpha) < 0}$$

Reaction-diffusion equations

Assume linearly stable fixed point in the absence of diffusion

$$\frac{\partial c_i(\vec{r},t)}{\partial t} = \sum_{j=1}^{N} M_{ij}^0 c_j(\vec{r},t)$$

$$\boxed{\mathrm{Re}(\lambda_\alpha) < 0}$$

Can diffusion destabilize fixed points?

$$\frac{\partial c_i(\vec{r},t)}{\partial t} = \sum_{j=1}^{N} M_{ij}^0 c_j(\vec{r},t) + D_i \nabla^2 c_i(\vec{r},t)$$

Fourier transform $c_i(\vec{r},t) = \int d\vec{k}\ \tilde{c}_i\left(\vec{k},t\right) e^{i\vec{k}\cdot\vec{r}}$

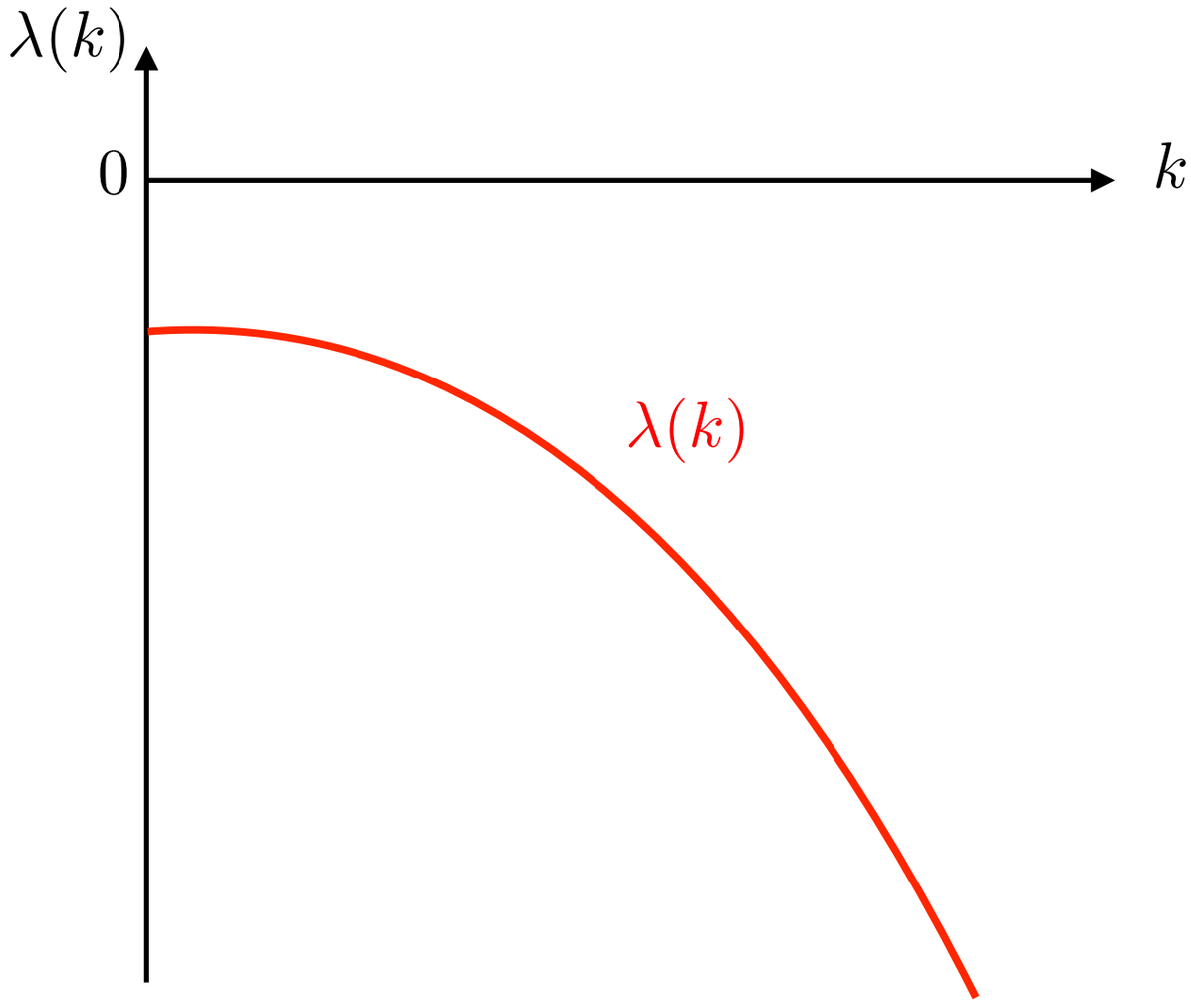
$$\frac{\partial \tilde{c}_i\left(\vec{k},t\right)}{\partial t} = \sum_{j=1}^{N} \left(M_{ij}^0 - \delta_{ij} k^2 D_i\right) \tilde{c}_j\left(\vec{k},t\right)$$

How are eigenvalues of the system affected due to diffusion?

One component system (N=1)

$$\frac{\partial \tilde{c}_1\left(\vec{k},t\right)}{\partial t} = \left(M_{11}^0 - k^2 D_1\right)\tilde{c}_1\left(\vec{k},t\right) \equiv \lambda(k)\tilde{c}_1\left(\vec{k},t\right)$$

Because fixed point is stable in the absence of diffusion, we must have $M_{11} < 0$.



There are no diffusion induced instabilities for one component system!

Two component system (*N*=2)

$$\frac{\partial}{\partial t}\begin{pmatrix}\tilde{c}_1(\vec{k},t)\\ \tilde{c}_2(\vec{k},t)\end{pmatrix}=\begin{pmatrix}M^0_{11}-k^2D_1, & M^0_{12}\\ M^0_{21}, & M^0_{22}-k^2D_2\end{pmatrix}\begin{pmatrix}\tilde{c}_1(\vec{k},t)\\ \tilde{c}_2(\vec{k},t)\end{pmatrix}$$

Stability in the absence of diffusion

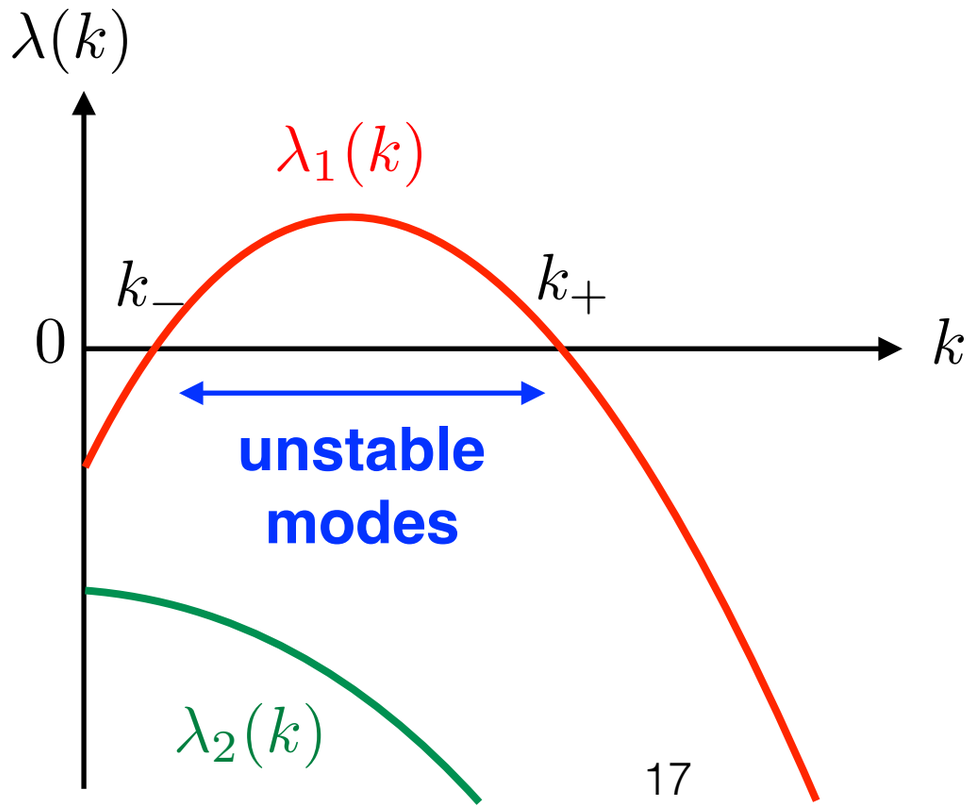
$$\mathrm{Re}(\lambda_1),\mathrm{Re}(\lambda_2)<0$$

Relation between eigenvalues and trace of the matrix

$$\lambda_1(0)+\lambda_2(0)=M^0_{11}+M^0_{22}<0$$
$$\lambda_1(k)+\lambda_2(k)=M^0_{11}+M^0_{22}-k^2(D_1+D_2)<0$$

Therefore we must have one positive and one negative eigenvalue for Turing instability!

No temporal oscillations are possible! $\mathrm{Im}(\lambda_1)=\mathrm{Im}(\lambda_2)=0$



What are the conditions for matrix M^0_{ij} that lead to Turing instability?

Two component system (*N*=2)

$$\frac{\partial}{\partial t}\begin{pmatrix} \tilde{c}_1(\vec{k},t) \\ \tilde{c}_2(\vec{k},t) \end{pmatrix} = \begin{pmatrix} M_{11}^0 - k^2 D_1, & M_{12}^0 \\ M_{21}^0, & M_{22}^0 - k^2 D_2 \end{pmatrix} \begin{pmatrix} \tilde{c}_1(\vec{k},t) \\ \tilde{c}_2(\vec{k},t) \end{pmatrix}$$

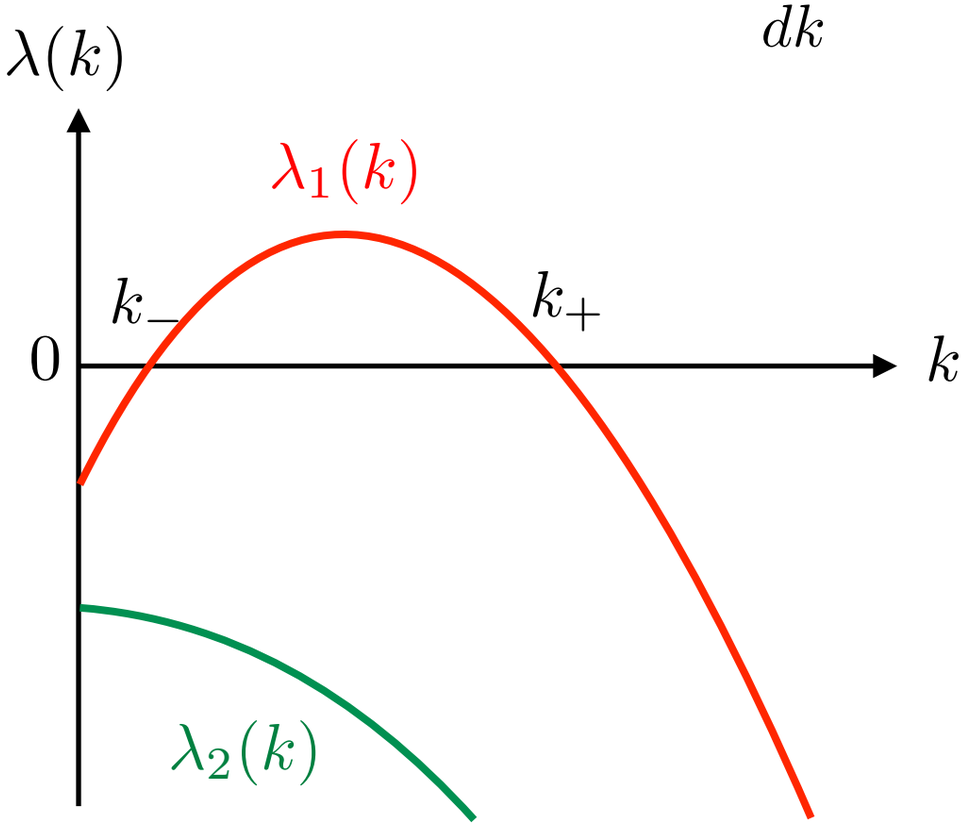
Relation between eigenvalues and determinant of the matrix

$$\lambda_1(k)\lambda_2(k) = (M_{11}^0 - k^2 D_1)(M_{22}^0 - k^2 D_2) - M_{12}^0 M_{21}^0$$

$$\lambda_1(k)\lambda_2(k) = M_{11}^0 M_{22}^0 - M_{12}^0 M_{21}^0 - k^2(M_{11}^0 D_2 + M_{22}^0 D_1) + k^4 D_1 D_2$$

Determinant becomes negative and reaches minimal value at $k^* \in (k_-, k_+)$**.**

$$\frac{d(\lambda_1(k)\lambda_2(k))}{dk} = 0 \longrightarrow k^{*2} = \frac{M_{11}^0 D_2 + M_{22}^0 D_1}{2 D_1 D_2} > 0$$



$$\lambda_1(0) + \lambda_2(0) < 0$$

$$M_{11}^0 M_{22}^0 < 0$$

$$\lambda_1(0)\lambda_2(0) > 0$$

$$M_{12}^0 M_{21}^0 < 0$$

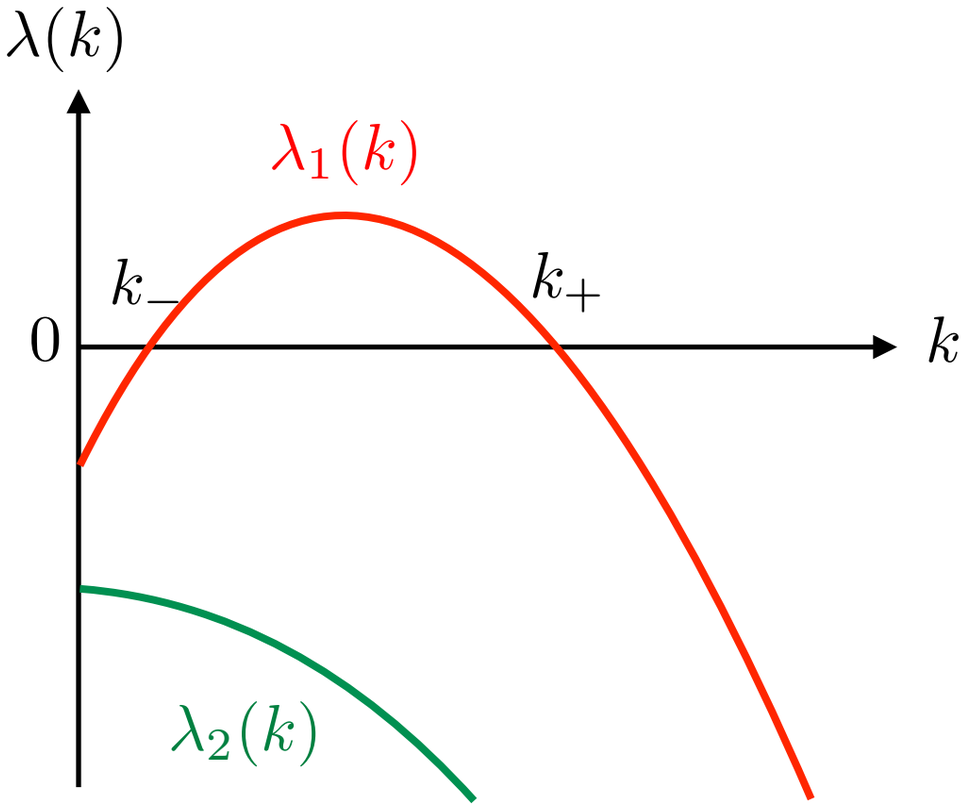
Two component system (*N*=2)

$$\frac{\partial}{\partial t}\begin{pmatrix} \tilde{c}_1(\vec{k},t) \\ \tilde{c}_2(\vec{k},t) \end{pmatrix} = \begin{pmatrix} M_{11}^0 - k^2 D_1, & M_{12}^0 \\ M_{21}^0, & M_{22}^0 - k^2 D_2 \end{pmatrix} \begin{pmatrix} \tilde{c}_1(\vec{k},t) \\ \tilde{c}_2(\vec{k},t) \end{pmatrix}$$

Without loss of generality we can assume $M_{11}^0 < 0$ **,** $M_{22}^0 > 0$

$$M_{11}^0 + M_{22}^0 < 0 \longrightarrow \boxed{|M_{11}^0| > |M_{22}^0|}$$

$$\frac{M_{11}^0 D_2 + M_{22}^0 D_1}{2D_1 D_2} > 0 \longrightarrow \boxed{D_1 > \frac{|M_{11}^0|}{|M_{22}^0|} D_2 > D_2}$$

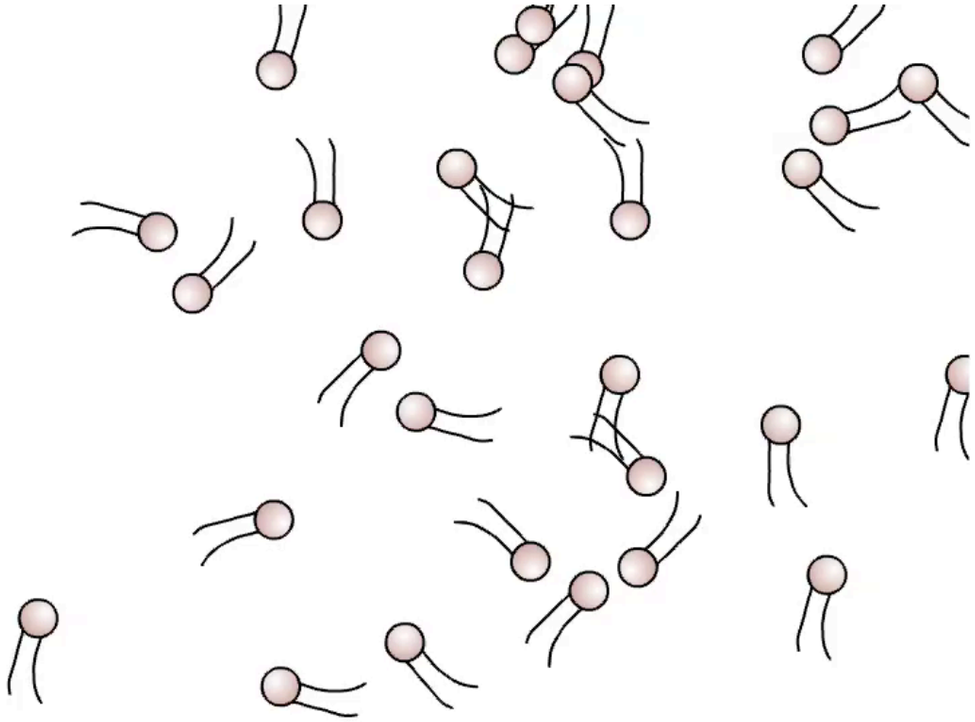


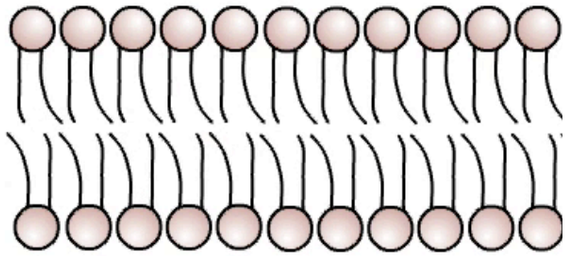
Finite wavelength Turing instabilities arise by long-ranged inhibition and short-range excitation. The resulting patterns are fixed in time.

In the system with 3 or more components oscillating patterns in time are also possible.

Self-assembly

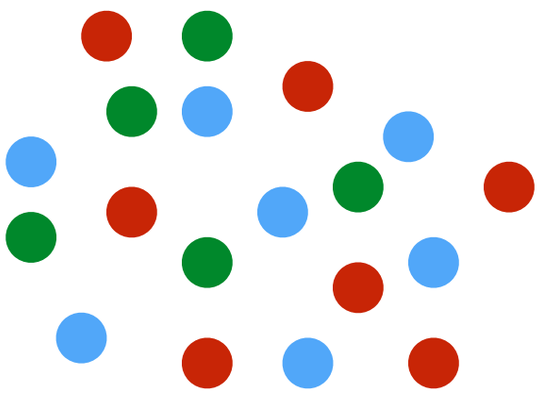
Lipid molecules in solution self-assemble into lipid bilayers



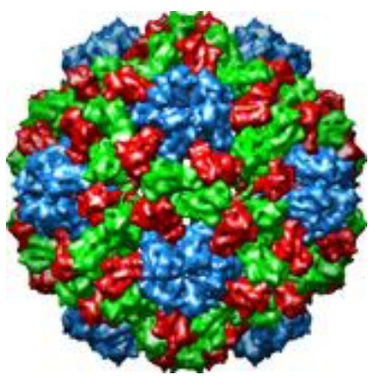


Self-assembly of viral capsids

capsid proteins in solution

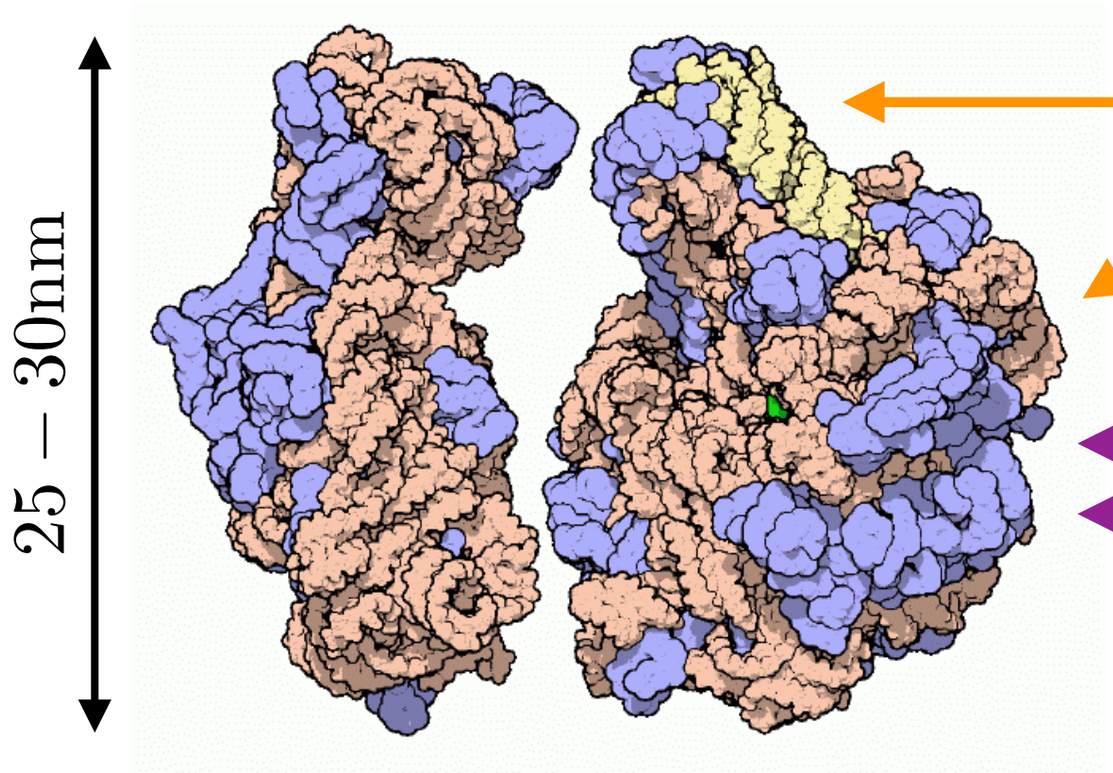


Cowpea Chlorotic Mottle virus



Complex self-assembly

Ribosomes are huge multi-protein complexes that are important for the synthesis of new proteins.



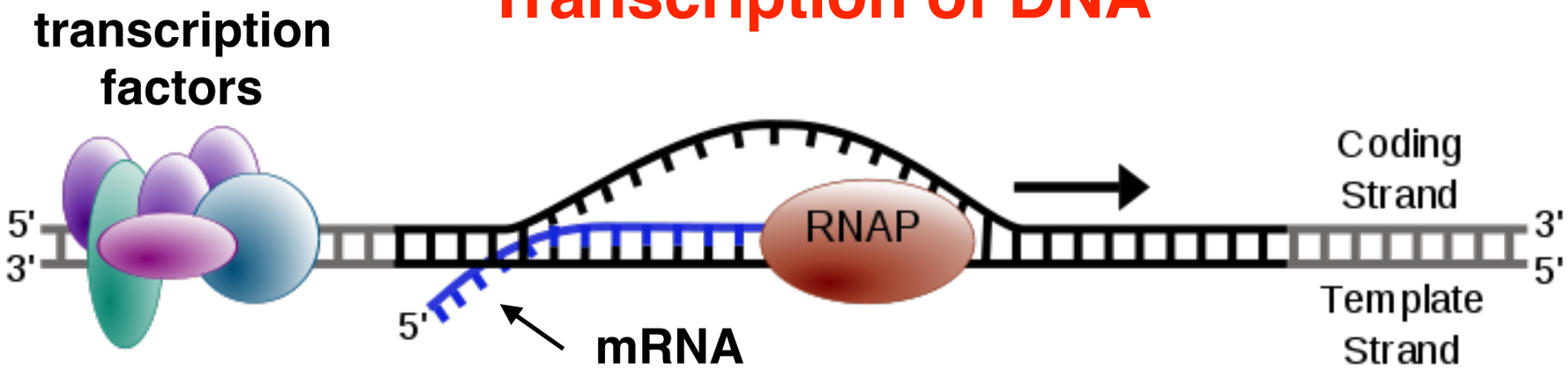
Multiple proteins fit together like a puzzle to make the desired structure.

Matching pieces are characterized with strong (specific) binding due to the shape complementarity.

Non-matching pieces bind weakly (non-specifically).

Production of new proteins

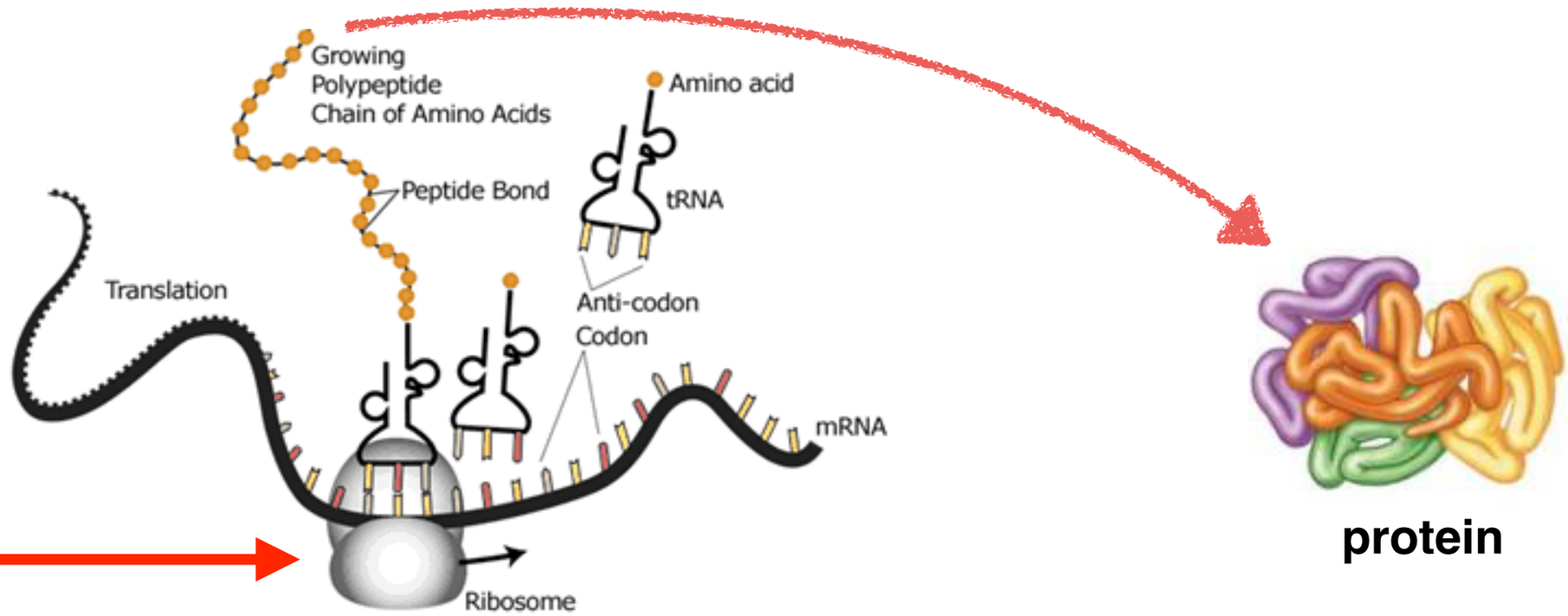
Transcription of DNA



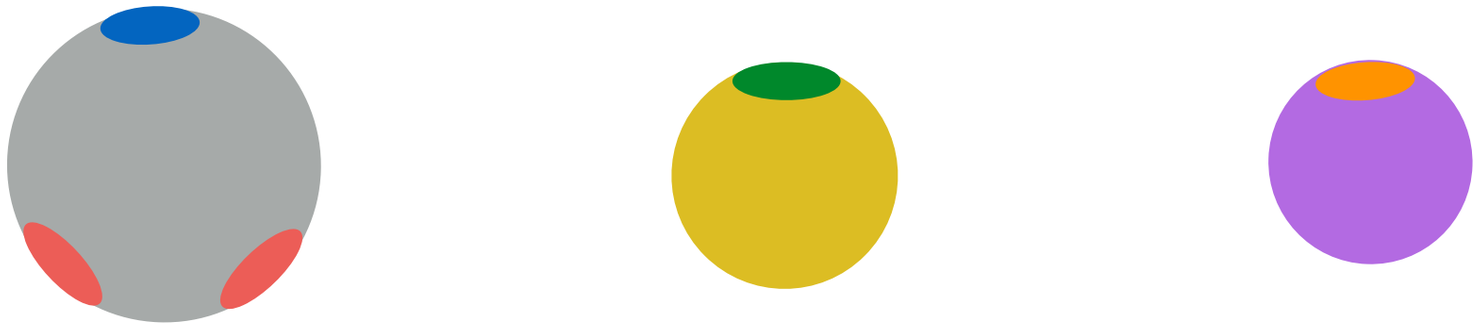
Transcription factors are proteins, which bind to specific locations on DNA, and they help recruiting RNA polymerase (RNAP) that makes a messenger RNA (mRNA) copy of certain DNA segment.

Note: some transcription factors (repressors) also prevent transcription.

Translation of mRNA

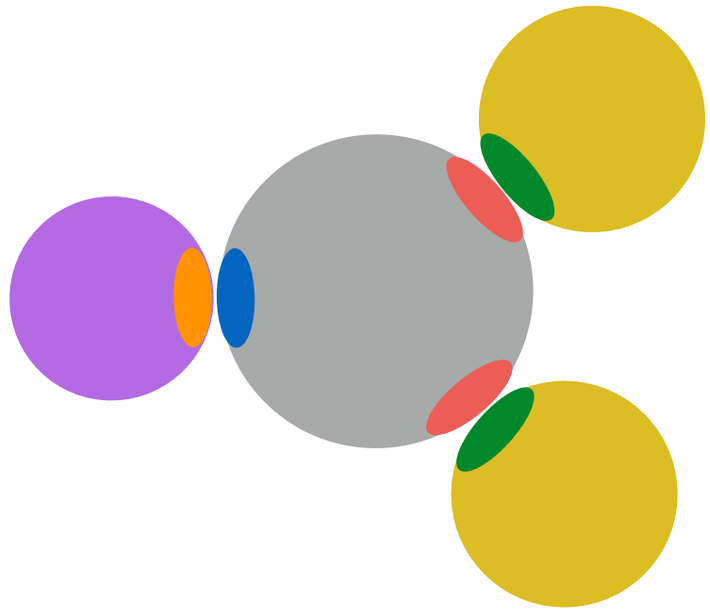


Patchy particles

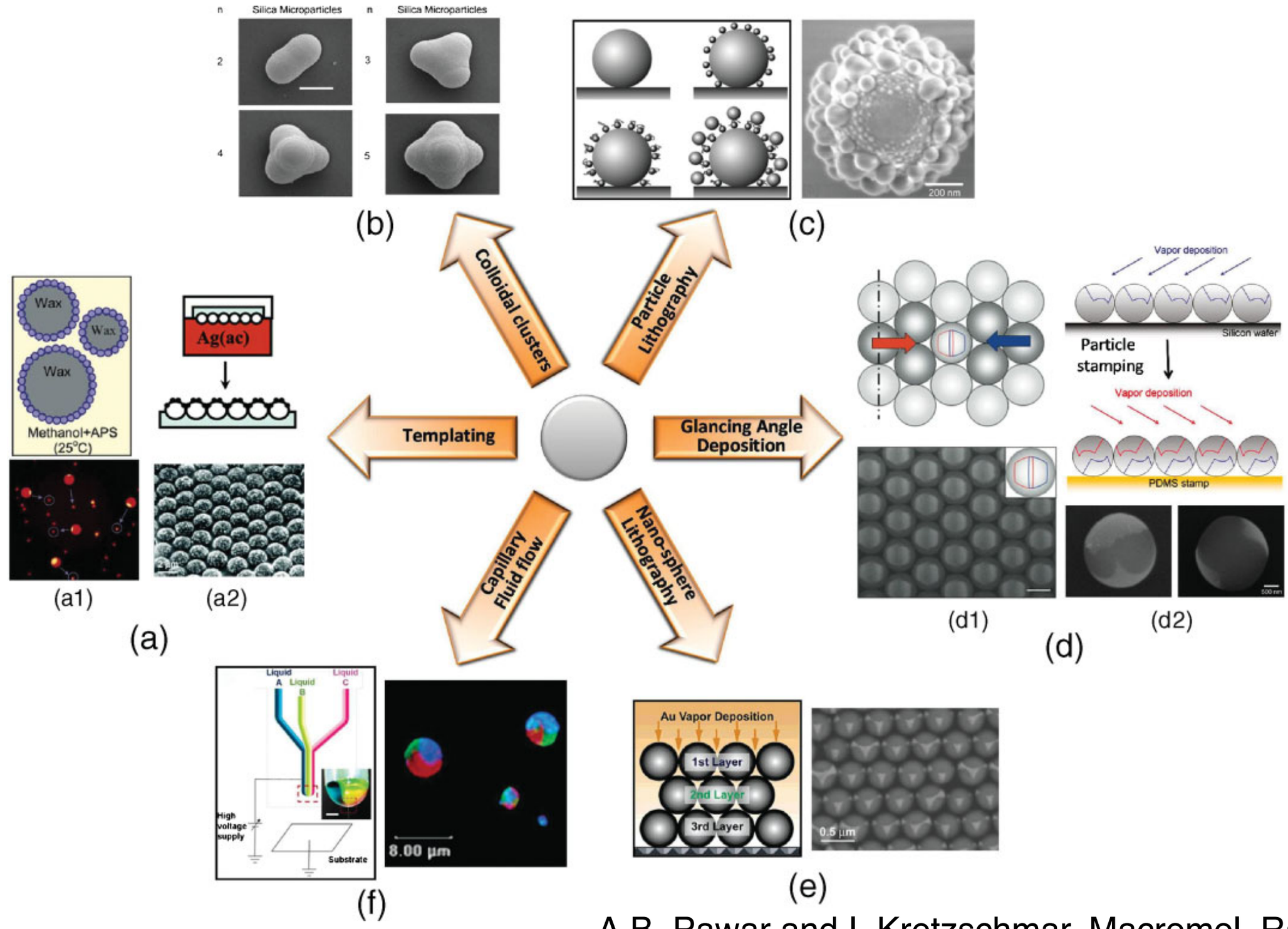


Particles with patches of different chemical/physical properties.

Patches can be designed to bind strongly only with certain partners.



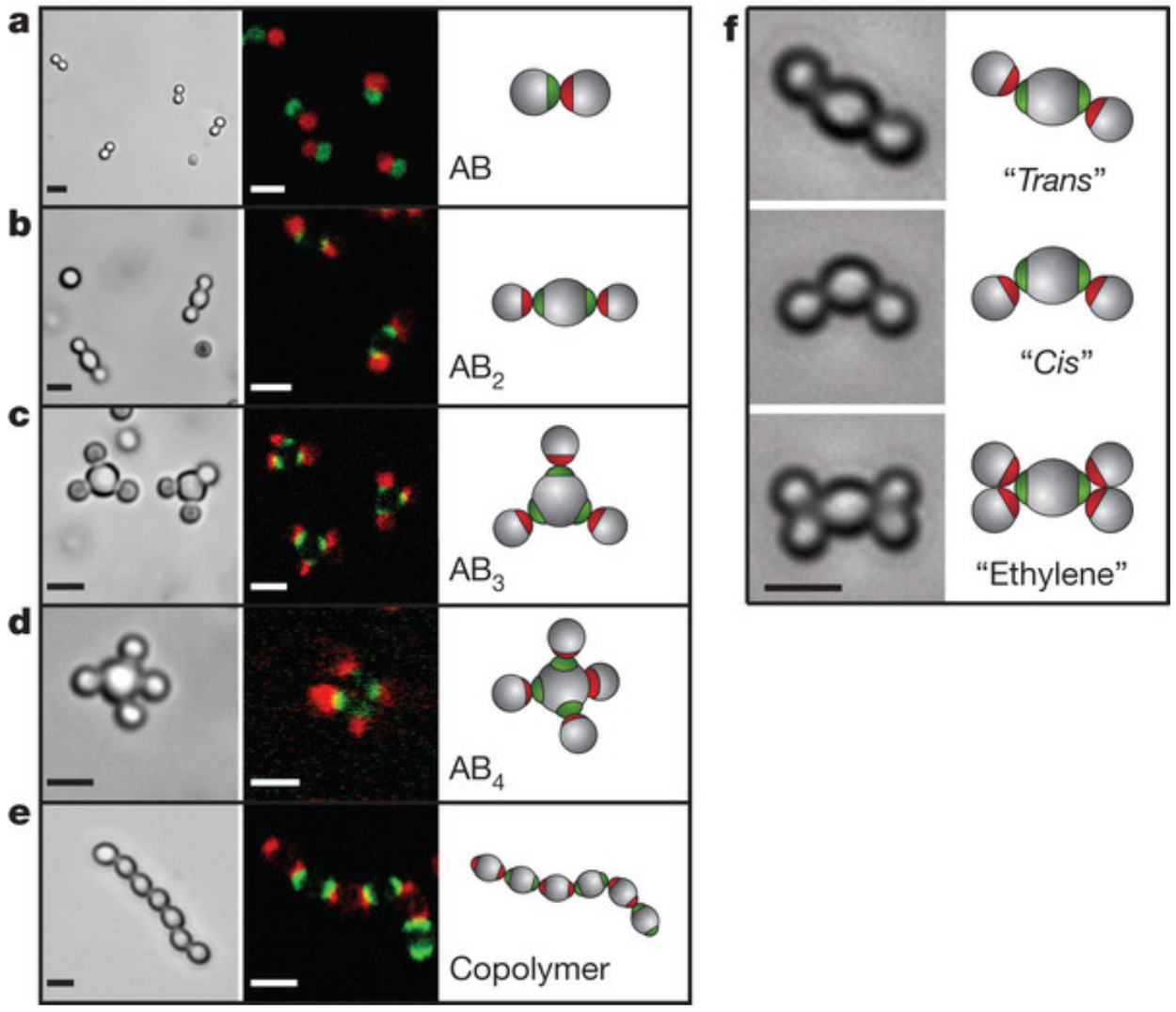
Experimental approaches for making patchy particles



A.B. Pawar and I. Kretzschmar, Macromol. Rapid Common. **31**, 159 (2010)

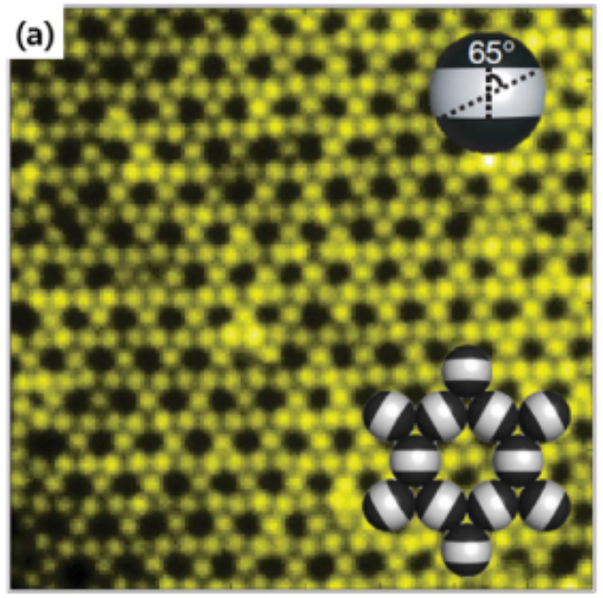
Self-assembly of patchy particles

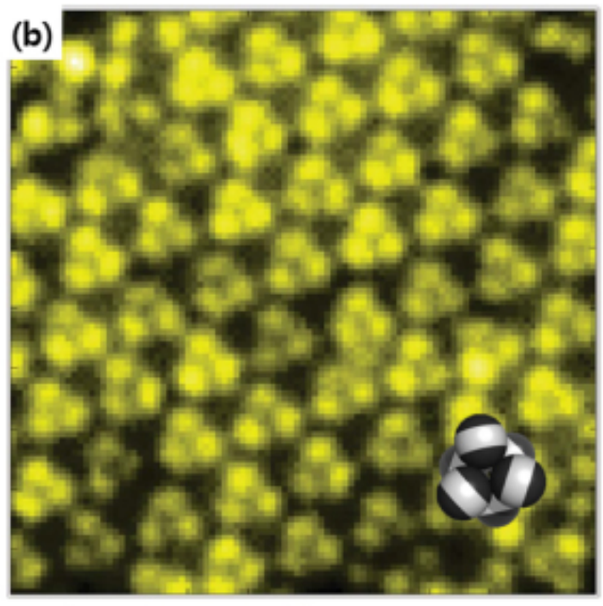
simple molecule-like structures



Y. Wang et al., Nature **491**, 51 (2012)

crystal structures

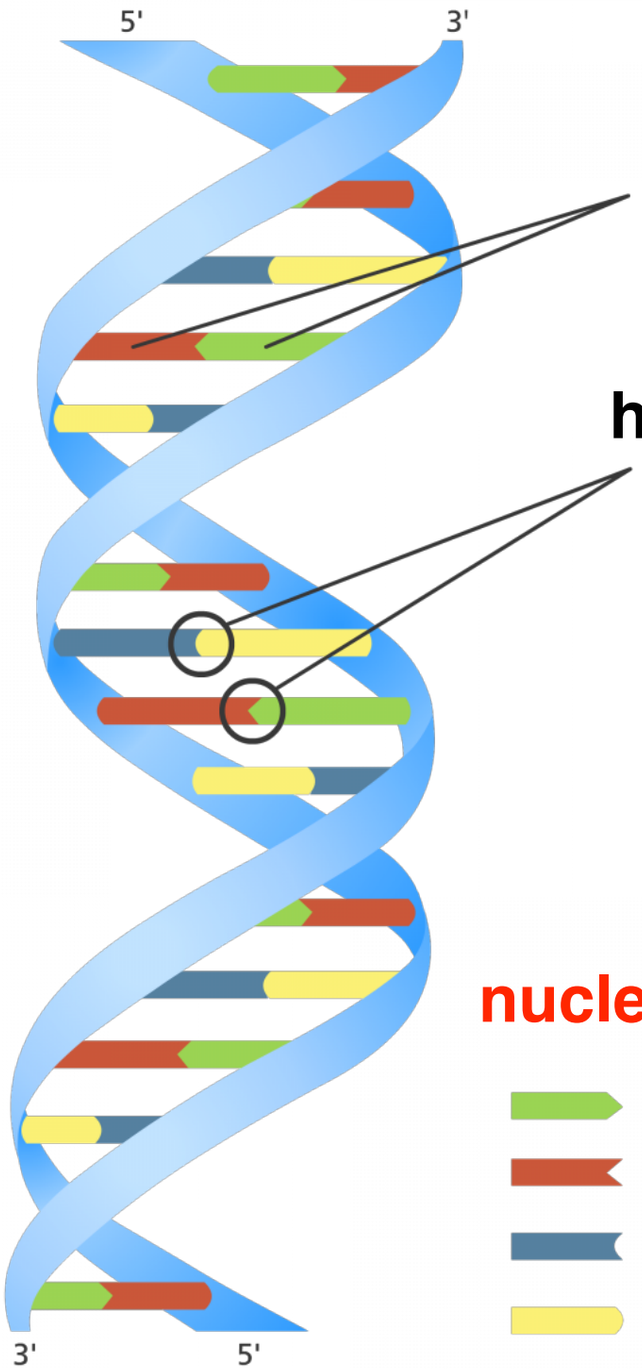




G.-R. Yi et al., J. Phys.: Condens. Mat. **25**, 193101 (2013)

DNA

Double stranded DNA forms, when the opposite strands are complementary (A-T, G-C)



Binding energy between two DNA strands *a* and *b* with sequences *s* of length N.

$$E_{\text{int}}\left(\{s_i^a\},\{s_i^b\}\right) \approx \sum_{i=1}^{N} M(s_i^a, s_i^b)$$

$$M(C,G) = M(G,C) \approx -4k_BT$$

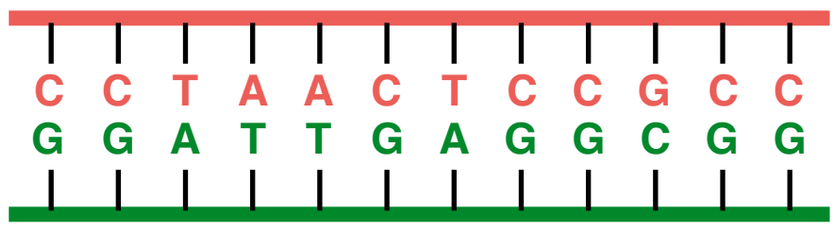
$$M(A,T) = M(T,A) \approx -2k_BT$$

$$M(A,C) = M(C,A) \approx 0$$

$$M(G,T) = M(T,G) \approx 0$$

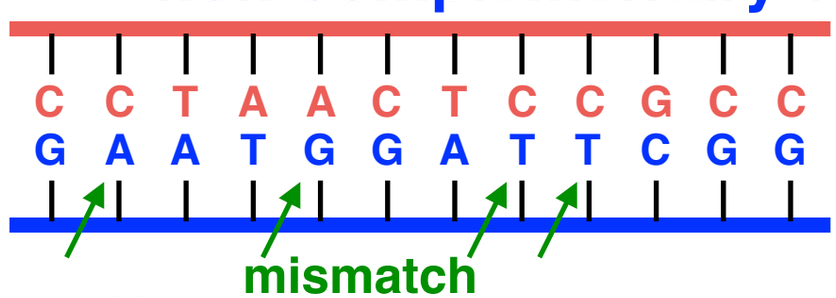
room temperature

Strong binding between complementary sequences



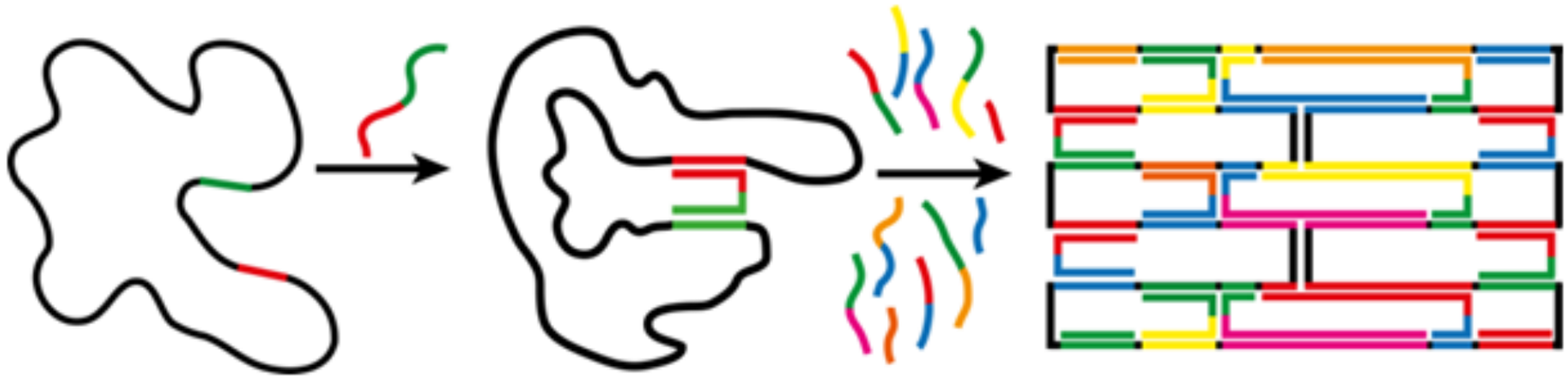
$$E_{\text{int}} \approx -40k_BT$$

Weaker binding between non-complementary sequences



$$E_{\text{int}} \approx -26k_BT$$

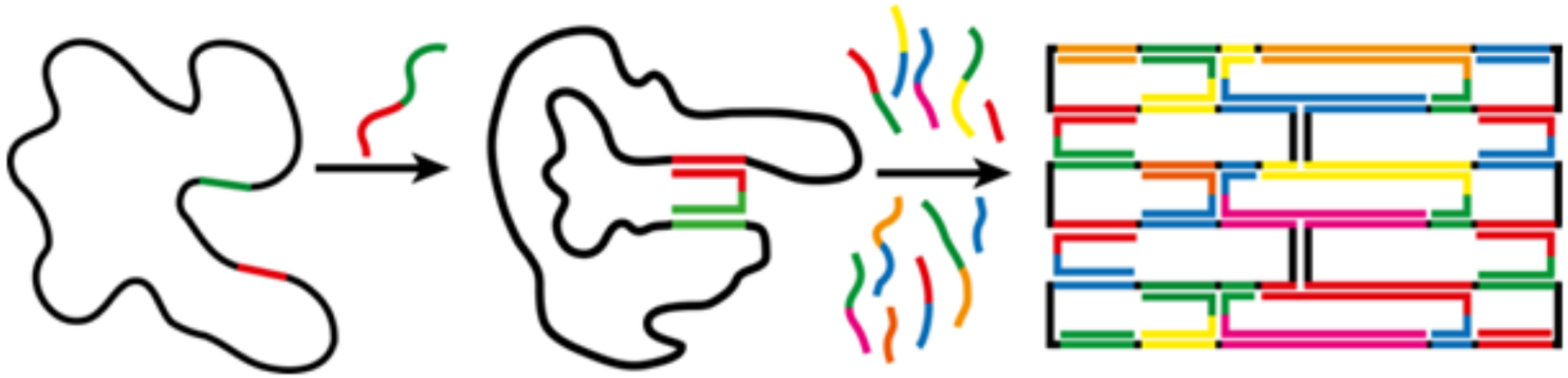
Scaffold DNA origami



Short strands (synthetic DNA) act like staples that fold the scaffold (virus DNA) into desired structure.

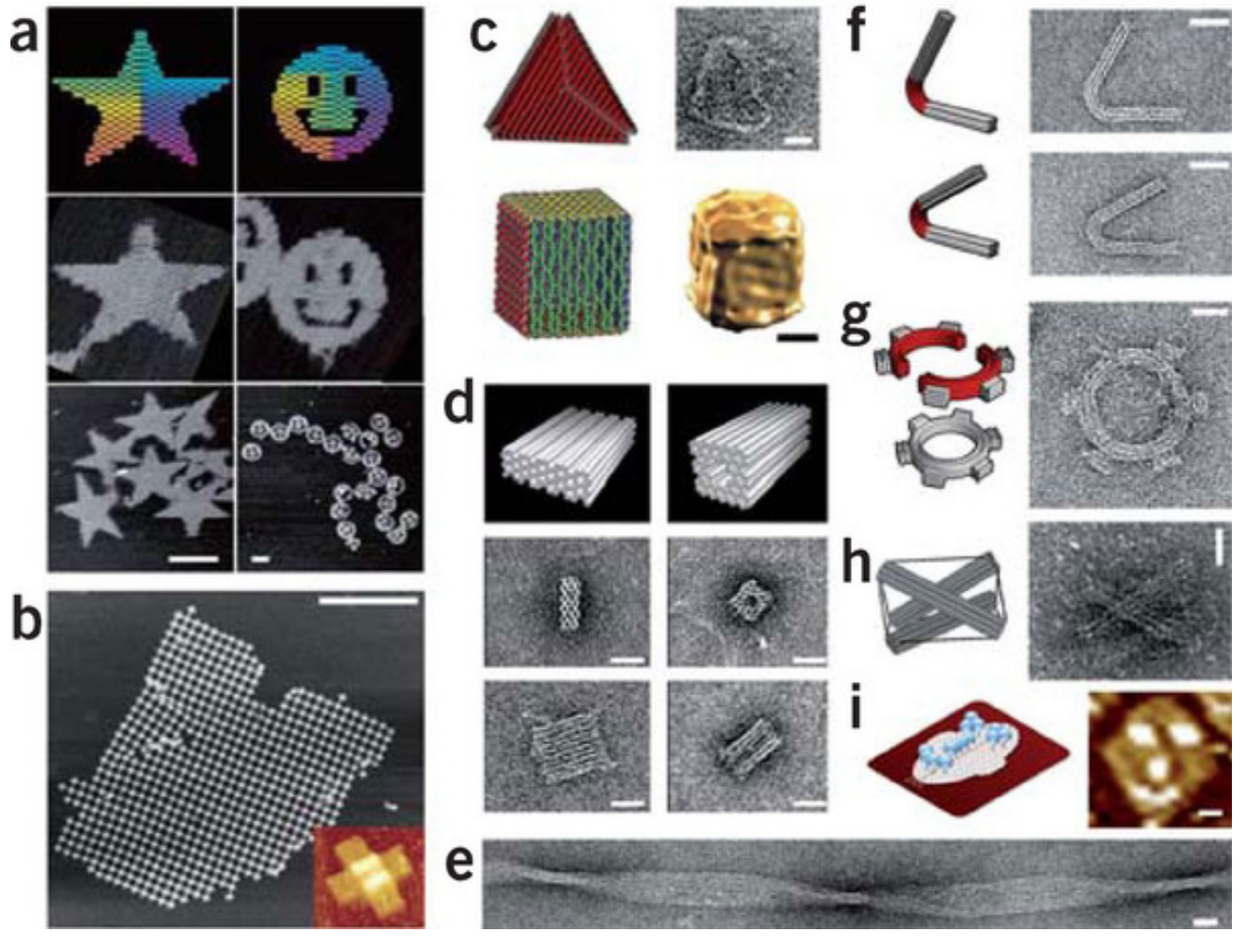
Different colors of staples correspond to different complementary sequences.

Scaffold DNA origami



Short strands (synthetic DNA) act like staples that fold the scaffold (virus DNA) into desired structure.

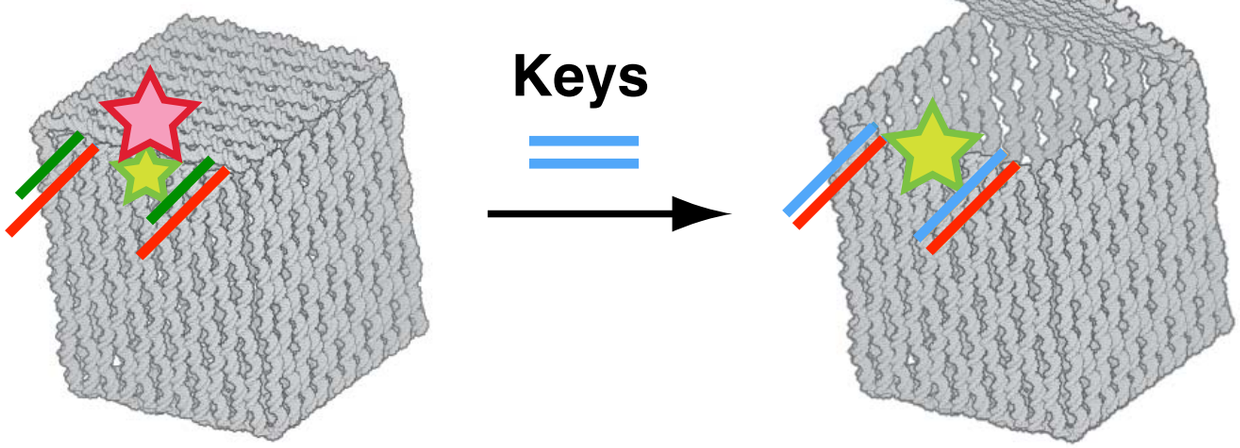
Different colors of staples correspond to different complementary sequences.



C.E. Castro et al., Nat. Methods **8**, 221 (2011)

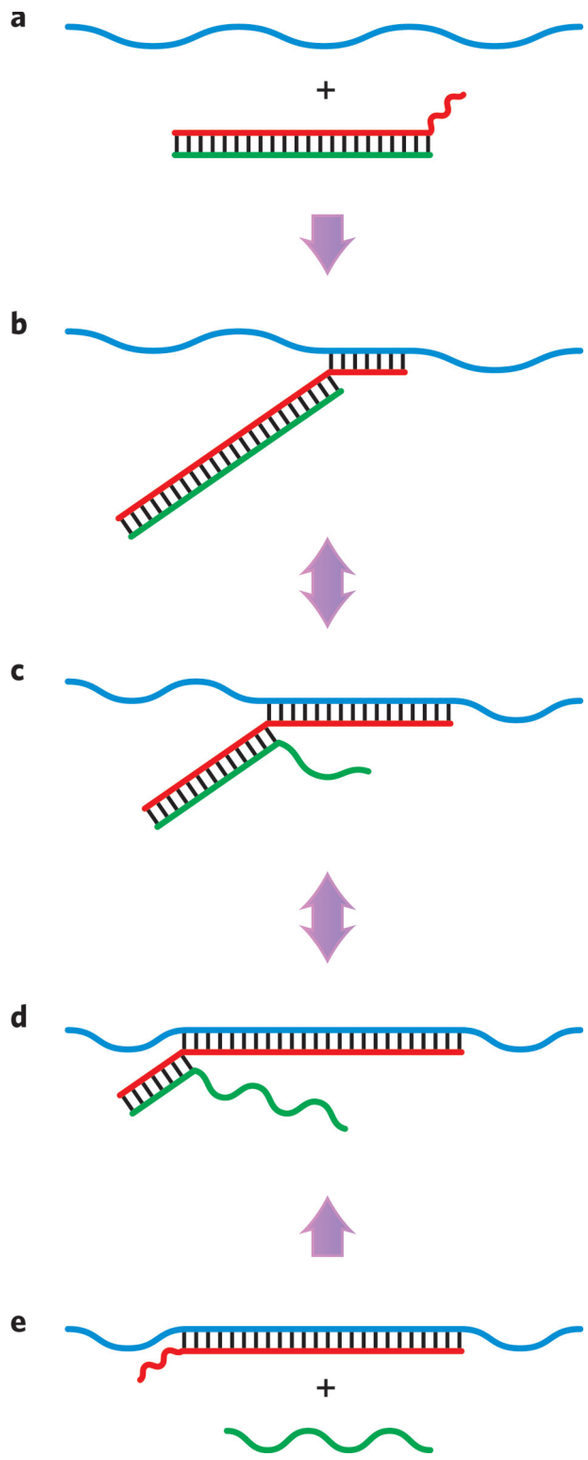
Actuation of DNA origami with a toehold exchange of DNA strands

Box is closed by binding of complementary DNA strands between the cover and the side



Longer strands (keys) bind to their complementary DNA strands on the side of the box to release the cover.

Toehold exchange

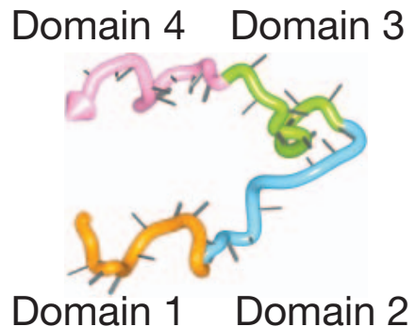


E.S. Andersen et al., Nature **459**, 73 (2009)

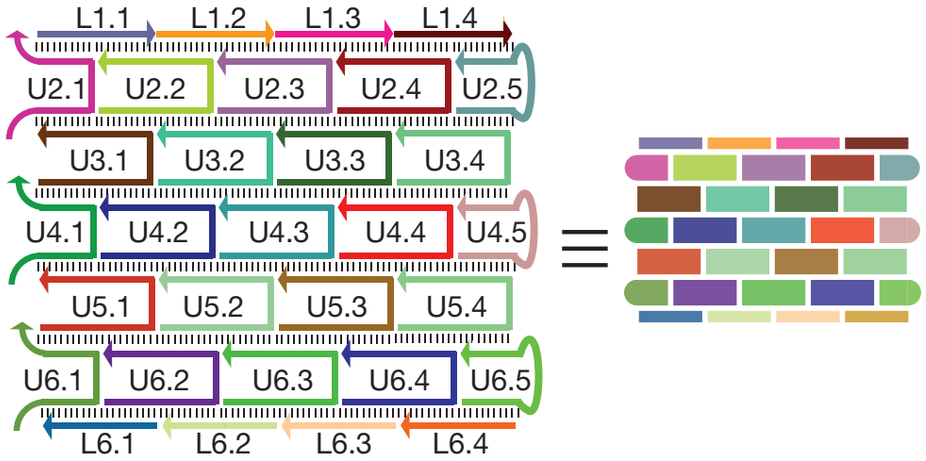
DNA brick origami

Short staple DNA strands are designed to fit like bricks in a wall.
Sequence of DNA strands determine, which “bricks fit together”.

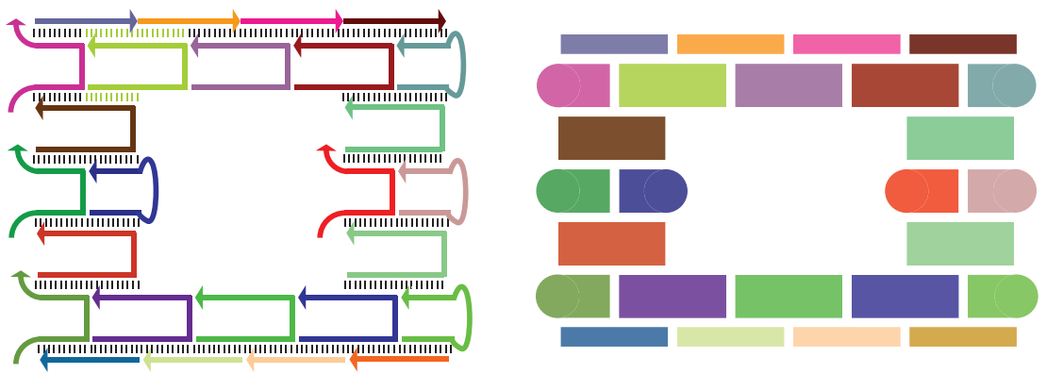
Single stranded DNA building brick (42 bases)



“Brick-wall” diagram



Design of arbitrary structure by removal of certain DNA strands (bricks) from mixture.



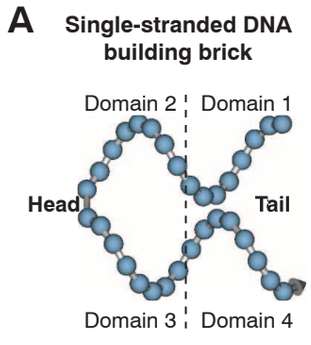
Example of generated structures

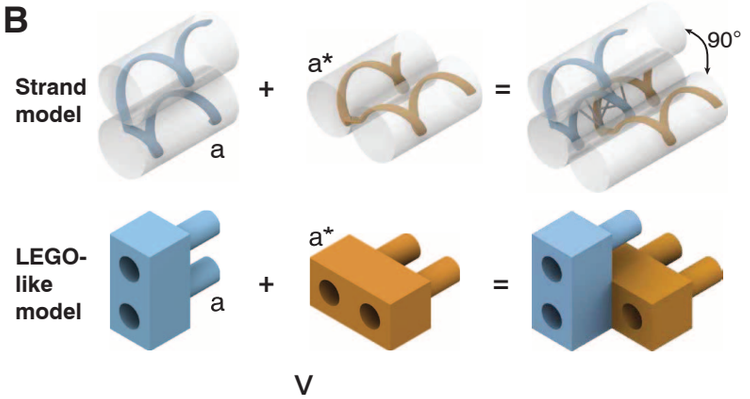
B. Wei et al., Nature **485**, 623 (2012)

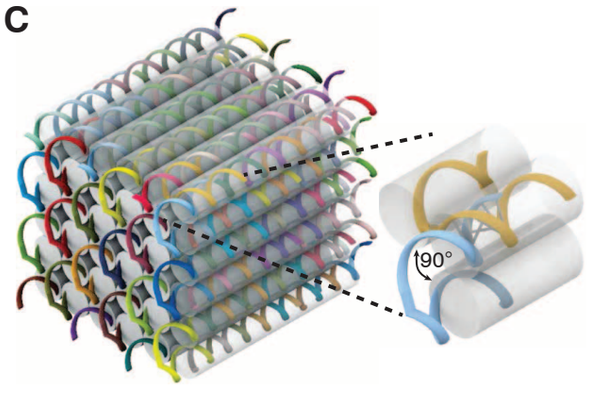
DNA brick origami

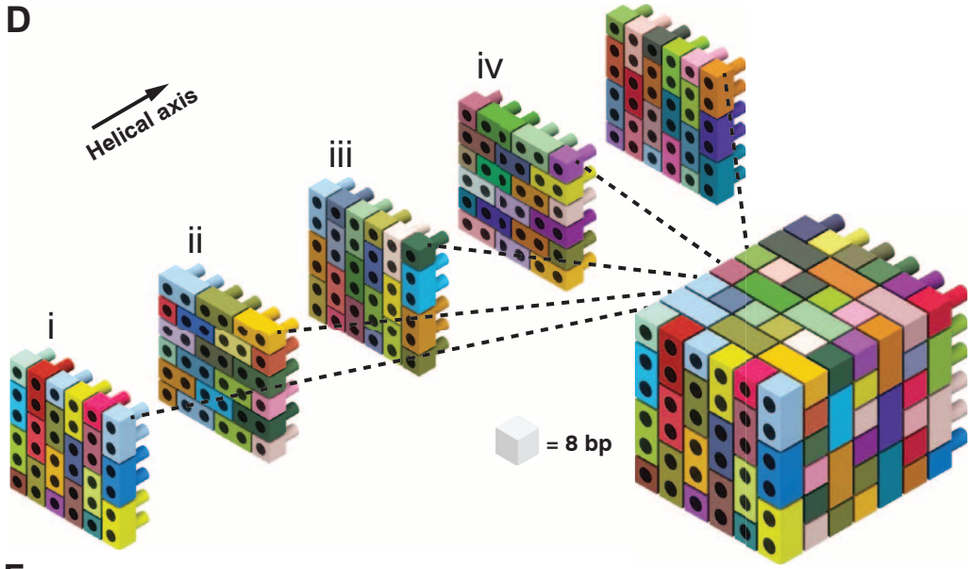
Short staple DNA strands are designed to fit together like lego blocks.
Sequence of DNA strands determine, which “lego blocks fit together”.

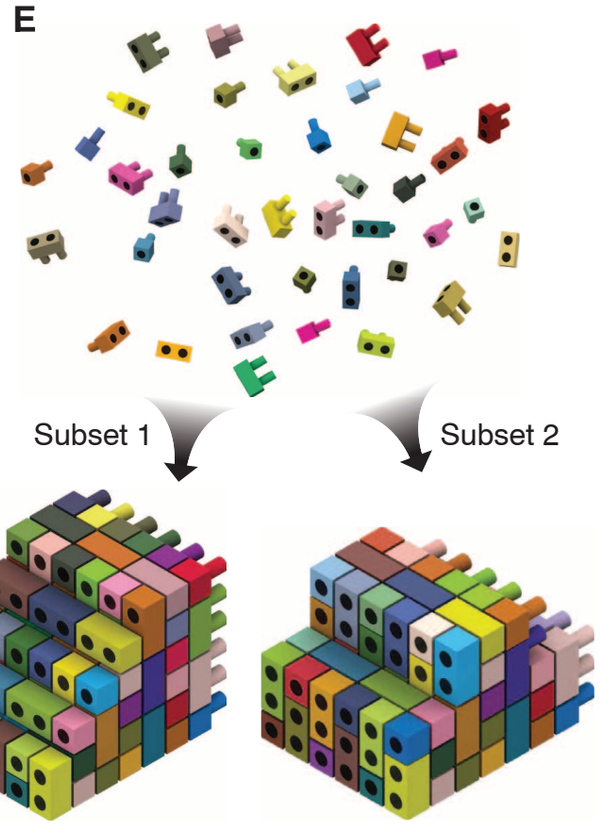
Single stranded DNA building brick (32 bases)



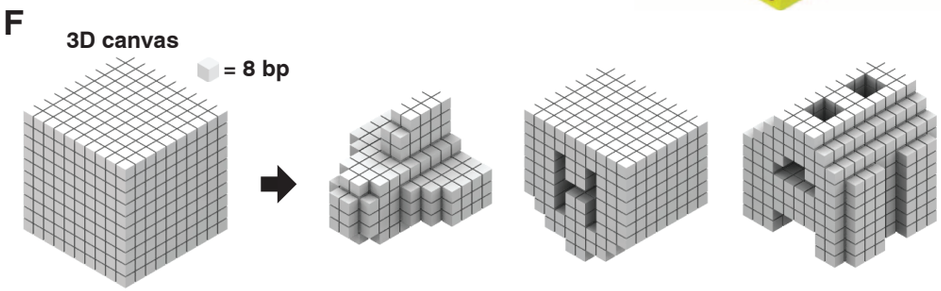








10x10x10 canvas

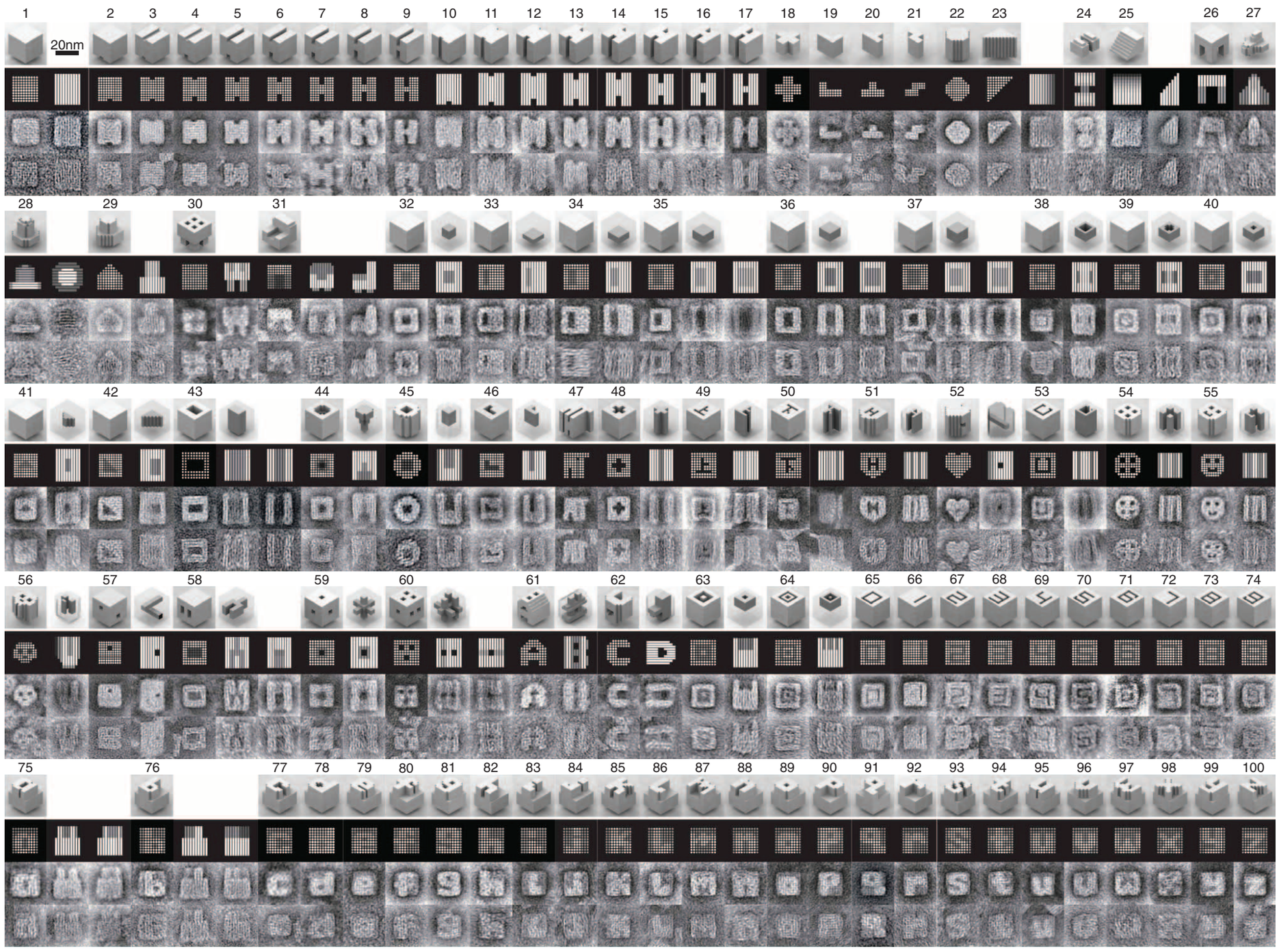


Design of arbitrary structure by removal of certain DNA strands (bricks) from mixture.

Y. Ke et al., Science **338**, 1177 (2012)

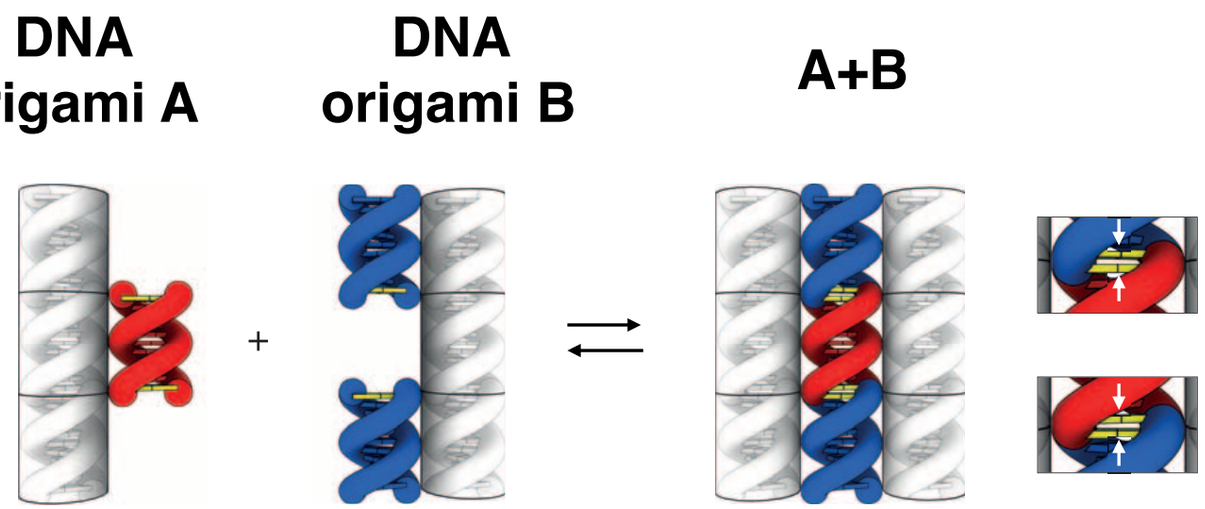
DNA brick origami

Example of generated 3D structures

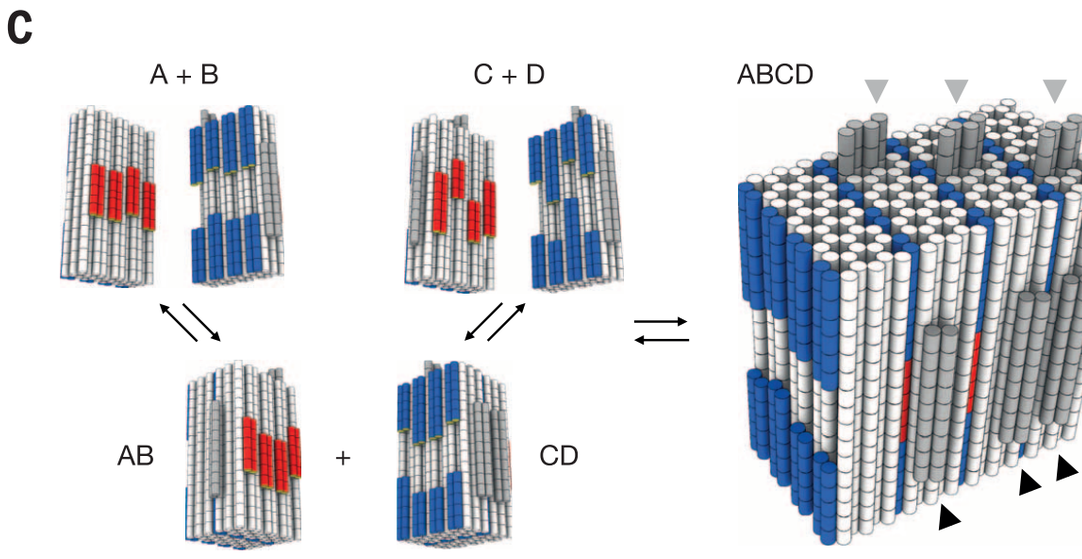


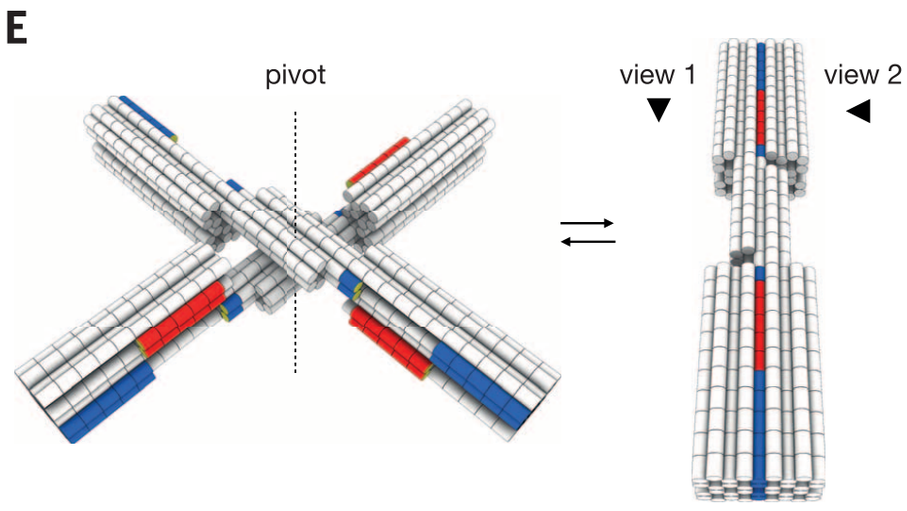
Y. Ke et al., Science **338**, 1177 (2012)

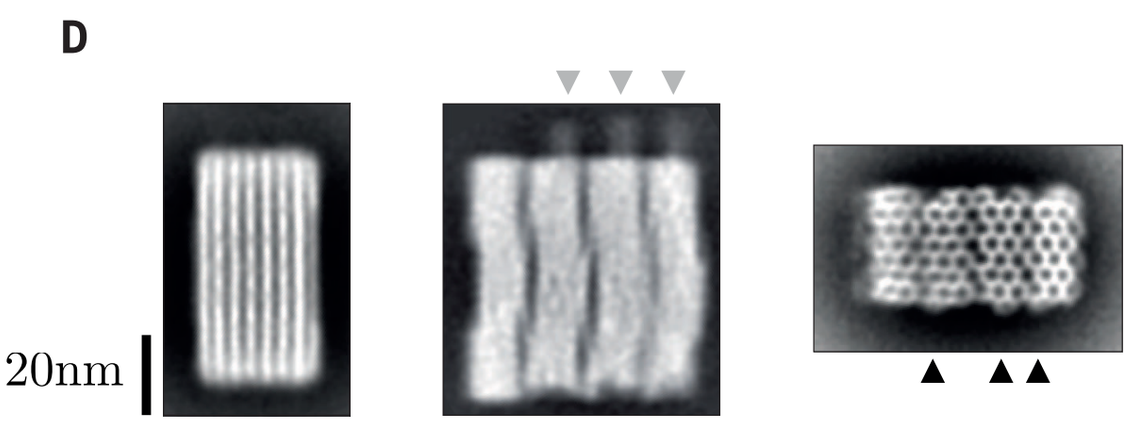
Shape complementarity with DNA origami

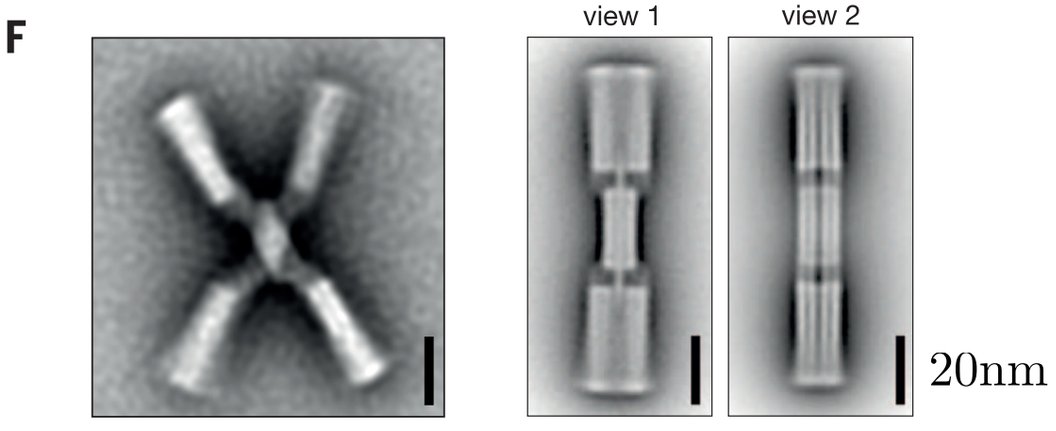


binding can be strengthened by additional complementary nucleotides (yellow)







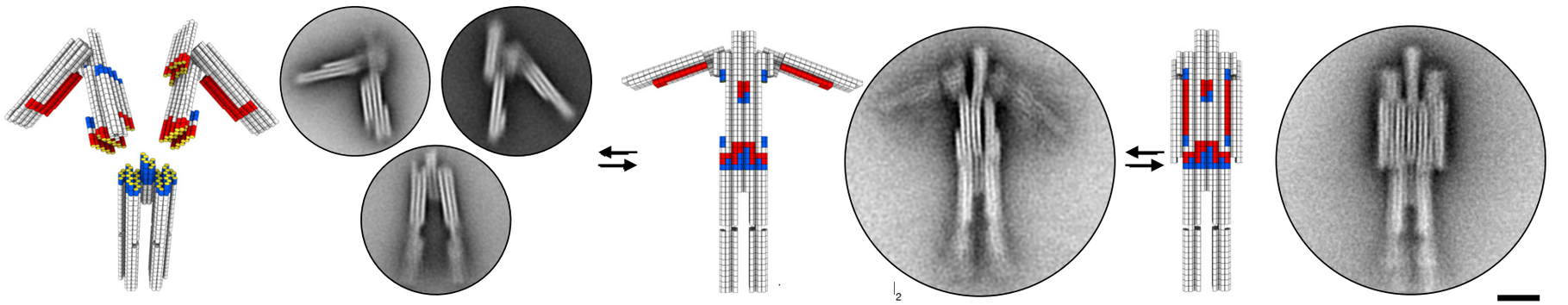


T. Gerling et al., Science **347**, 1446 (2015)

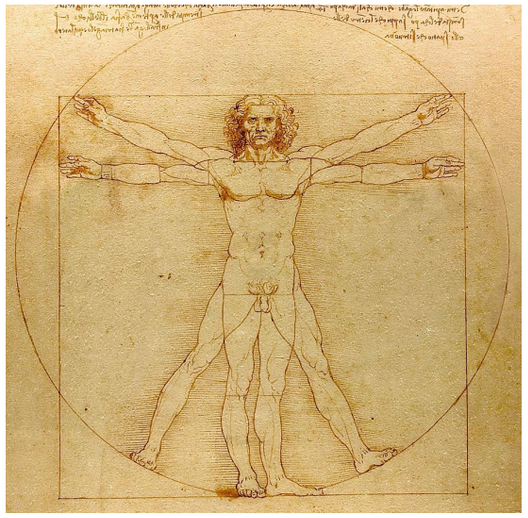
Actuation of DNA origami

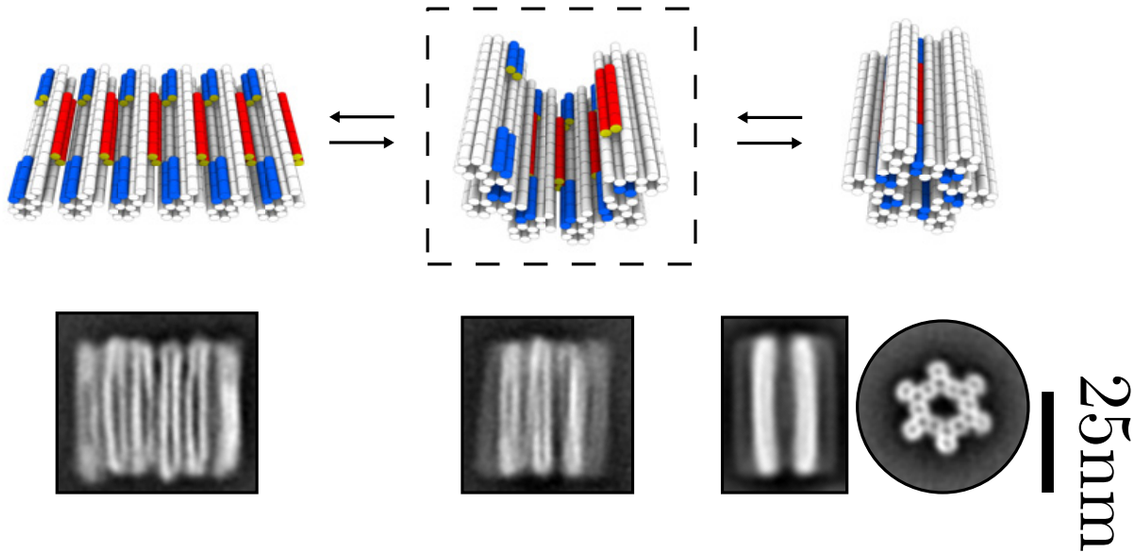
Assembly of structures is controlled by temperature and external salt, which screens the electrostatic interaction between charged DNA strands.

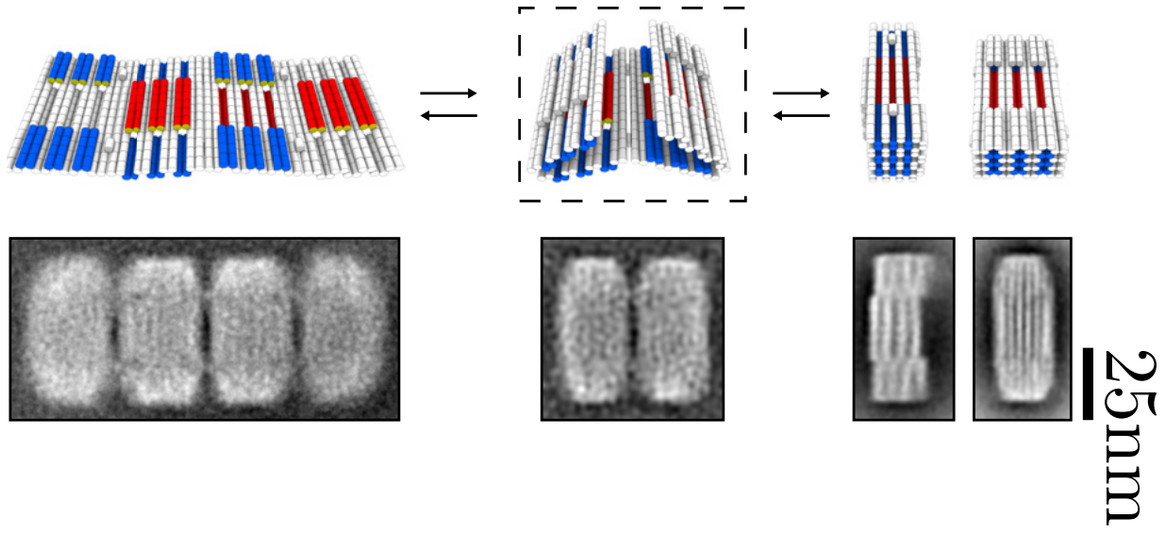
5 mM $MgCl_2$ **12.5 mM $MgCl_2$** **30 mM $MgCl_2$**



Vitruvian man by da Vinci

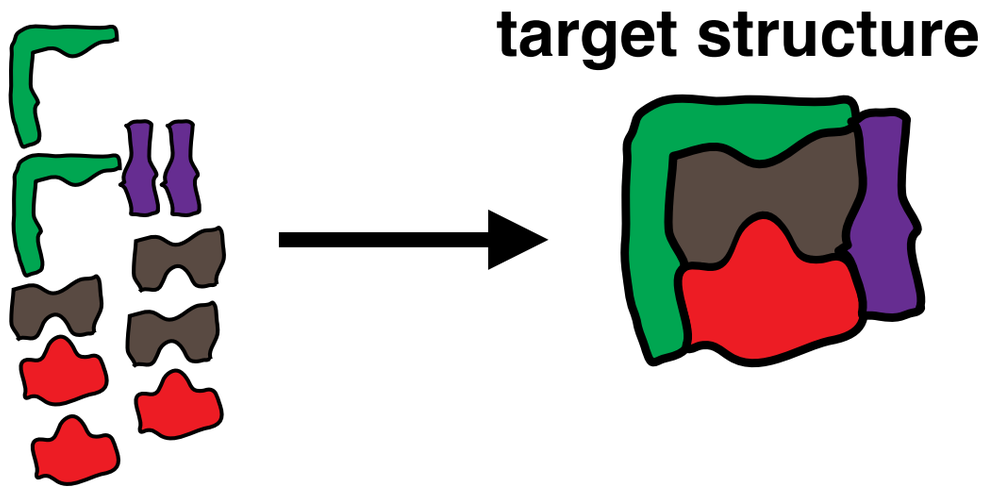




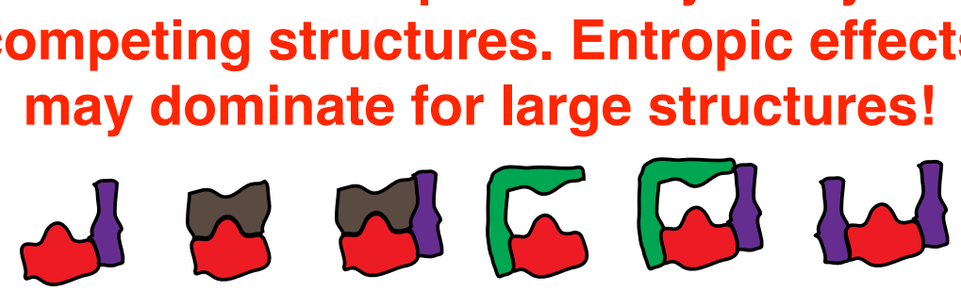


T. Gerling et al., Science **347**, 1446 (2015)

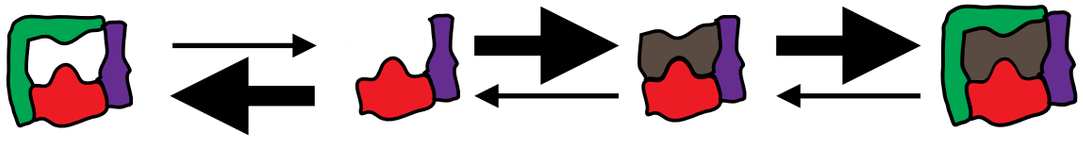
Potential issues with self-assembly



There are exponentially many competing structures. Entropic effects may dominate for large structures!

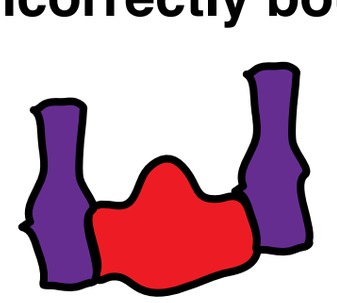


If specific interactions are too strong, we may get trapped in incomplete structures. E.g. green piece has to unbind, before the brown piece can bind correctly, but this unbinding is exponentially slow!



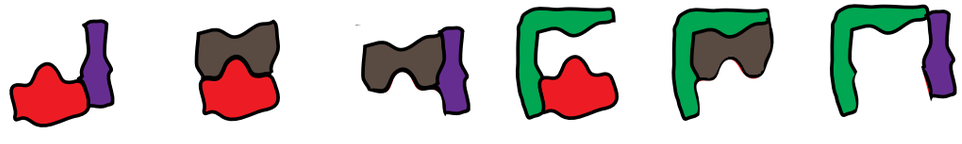
A. Murugan et al., Nat. Comm. **6**, 6203 (2015)

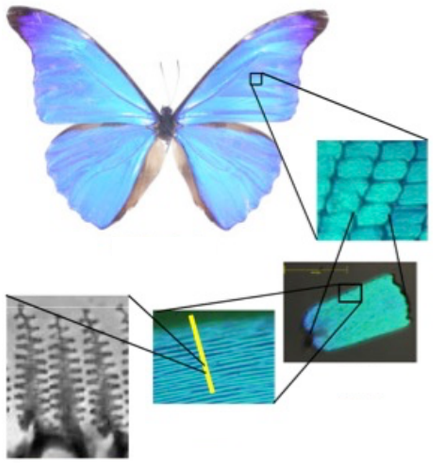
If non-specific interactions are too strong, we may get incorrectly bound structures.

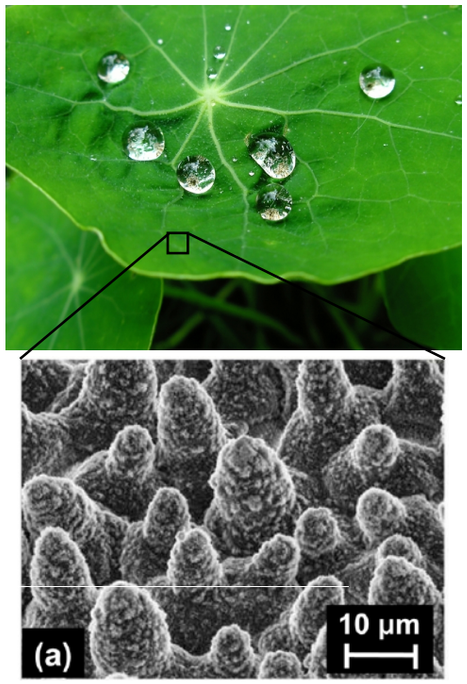


Kinetic arrest: target structure can be self-assembled in many different ways. All components may be used up before generating target structures! This may result in many incomplete structures.

Solution: nonuniform concentrations of components may guide certain assembly pathways.







Biology is cool!