Dynamics of molecular motors (continued)

Touring patterns

DNA origami
Molecular motors are fueled by ATP

How is ATP produced?

Regulation of blood sugar levels

- **Glycogen** (polysaccharide of glucose)
- **Glucose** (blood sugar)
- **Liver**
- **Stomach**
- **Pancreas** (behind stomach)
- **Small intestine**

Stimulates formation of glycogen
Stimulates glucose uptake from blood
Lowers Blood Sugar
Promotes insulin release
Promotes a high blood sugar level

Tissue cells (muscle, kidney)
Regulation of blood sugar levels

- **Liver**
  - Converts glucose to glycogen
  - Releases glucose when blood sugar is low
- **Stomach**
- **Pancreas** (behind stomach)
  - Releases insulin and glucagon
- **Small intestine**

**Glycogen** (polysaccharide of glucose)
**Glucose** (blood sugar)

- **Insulin**
  - Promotes glucose uptake by tissue cells (muscle, kidney)
  - Increases blood sugar levels
- **Glucagon**
  - Stimulates breakdown of glycogen
  - Lowers blood sugar levels
  - Increases blood sugar levels

**Blood sugar**

4 Regulation of blood sugar levels
Conversion of blood sugars to ATP

Blood glucose → Glucose → Glycolysis → ATP, Pyruvate

Aerobic respiration

O₂: C₆H₁₂O₆ + 6O₂ → 6CO₂ + 6H₂O + 36ATP

Anaerobic respiration

no O₂: C₆H₁₂O₆ → 2 Lactic Acids + 2ATP (muscle fatigue)

Note: Citric acid cycle = Krebs cycle
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.
Energetics of ATP hydrolysis

How much energy is released during ATP hydrolysis?

\[
\Delta G = \mu_{\text{ADP}} + \mu_P - \mu_{\text{ATP}}
\]

\[
\Delta G = \mu^0_{\text{ADP}} + \mu^0_P - \mu^0_{\text{ATP}} + k_BT \ln \left( \frac{[\text{ADP}][\text{P}_i]}{[\text{ATP}]c_0} \right)
\]

\[\sim -12.5k_BT\]

Under physiological conditions: \[\Delta G \sim -20k_BT\]

([ATP], [ADP], [P_i] \sim 1\text{mM})

Chemical potentials are typically defined relative to concentration \(c_0 \sim 1\text{ M}.

\[
\mu_s(c_s) = \mu_s(c_0) + k_BT \ln \left(\frac{c_s}{c_0}\right)
\]
Crawling of cells

Actin

**Immune system:** neutrophils chasing bacteria

<table>
<thead>
<tr>
<th>Neutrophil Chasing Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Image of neutrophil chasing bacteria" /></td>
</tr>
<tr>
<td>David Rogers (1950s)</td>
</tr>
</tbody>
</table>

**Migration of skin cells during wound healing**

**Spread of cancer cells during metastasis of tumors**

**Amoeba searching for food**

\[ v \sim 0.1 \mu m/s \]
roughly 10 nm

This tells us that the area per protein is

\[ m \approx 6 \]

can be carried out for the cell membrane as well. To see this, we

reveal a mean spacing comparable to protein size, similar estimates

proteins are reported in Mitra et al. (2004).

measurements of the relative mass of phospholipids and membrane

than 50% of the membrane mass is donated by proteins. Interesting

membrane proteins. Indeed, in the case of the mitochondria, more

the electron micrograph of freeze-fractured membranes. This image

proteins in mitochondria can be manipulated by the application of an

...diffusive processes are altered as a result of the tight packing

erent from the dilute and homogeneous environments of

usive processes are altered as a result of the tight packing

ronment of cells. We have seen that this crowded structure that serves

14.1.4

occupied by proteins.

with a crude estimate being that roughly half of the membrane area is

of the order of 3 nm. The cell membrane is tightly packed indeed,

Fish skin cell

\[ v = 0.2 \mu m/s \]

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

Alberts et al., Molecular Biology of the Cell

actin cortex

lamellipodium

substratum

actin polymerization at plus end protrudes lamellipodium

cortex under tension

movement of unpolymerized actin

myosin II

contraction

focal adhesions (contain integrins)

ATTACHMENT AND TRACTION

Figure 16–75

Fig 16–76

PROTRUSION

attachment and traction

Figure 16–75

Fig 16–76

Crawling of cells

Alberts et al., Molecular Biology of the Cell

R. Phillips et al., Physical Biology of the Cell
Swimming of sperm cells

Sperm flagellum is constructed from microtubules

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

Jeff Guasto

\[ v \approx 50 \mu m/s \]
Further reading
Patterns in nature

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

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

\[ c_i(\vec{r}, t) = C_i(\vec{r}, t) - C_i^* \]

\[ M_{ij}^0 = \frac{\partial F_i}{\partial C_j} \bigg|_{C_i^*} \]

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

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

\(\lambda\) 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:

\[
\text{Re}(\lambda_{\alpha}) < 0
\]
Reaction-diffusion equations

Assume linearly stable fixed point in the absence of diffusion

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

\[\text{Re}(\lambda_\alpha) < 0\]

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

\[c_i(\vec{r}, t) = \int d\vec{k} \tilde{c}_i(\vec{k}, t) e^{i\vec{k} \cdot \vec{r}}\]

How are eigenvalues of the system affected due to diffusion?
One component system \((N=1)\)

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

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 \((N=2)\)

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

Relation between eigenvalues and trace of the matrix

\[
\lambda_1(0) + \lambda_2(0) = M_{11}^0 + M_{22}^0 < 0 \\
\lambda_1(k) + \lambda_2(k) = M_{11}^0 + M_{22}^0 - k^2(D_1 + D_2) < 0
\]

Therefore we must have one positive and one negative eigenvalue for Turing instability! No temporal oscillations are possible! \(\text{Im}(\lambda_1) = \text{Im}(\lambda_2) = 0\)

Stability in the absence of diffusion
\(\text{Re}(\lambda_1), \text{Re}(\lambda_2) < 0\)

What are the conditions for matrix \(M_{ij}^0\) 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 $k^* \in (k_-, k_+)$. 

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

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

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

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

$$M_{12}^0 M_{21}^0 < 0$$
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 $M_{11}^0 < 0$, $M_{22}^0 > 0$

\[
M_{11}^0 + M_{22}^0 < 0 \quad \Rightarrow \quad |M_{11}^0| > |M_{22}^0|
\]

\[
\frac{M_{11}^0 D_2 + M_{22}^0 D_1}{2 D_1 D_2} > 0 \quad \Rightarrow \quad D_1 > \frac{|M_{11}^0|}{|M_{22}^0|} D_2 > D_2
\]

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

Ribosome
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

Self-assembly of patchy particles

simple molecule-like structures

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

crystal structures

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

**DNA**

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

\[
E_{\text{int}}\left(\{s^a_i\}, \{s^b_i\}\right) \approx \sum_{i=1}^{N} M(s^a_i, s^b_i)
\]

\[
M(C, G) = M(G, C) \approx -4k_B T
\]

\[
M(A, T) = M(T, A) \approx -2k_B T
\]

\[
M(A, C) = M(C, A) \approx 0
\]

\[
M(G, T) = M(T, G) \approx 0
\]

**Strong binding between complementary sequences**

\[
E_{\text{int}} \approx -40k_B T
\]

**Weaker binding between non-complementary sequences**

\[
E_{\text{int}} \approx -26k_B T
\]
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.
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

Keys

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

Example of generated structures

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

**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”.

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

DNA brick origami

Example of generated 3D structures

Shape complementarity with DNA origami

DNA origami A

DNA origami B

A+B

binding can be strengthened by additional complementary nucleotides (yellow)

C

A + B

C + D

ABCD

E

pivot

view 1

view 2

AB

CD

20nm

20nm

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 MgCl₂

12.5 mM MgCl₂

30 mM MgCl₂

Vitruvian man by da Vinci

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!

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.

A. Murugan et al., Nat. Comm. 6, 6203 (2015)
Biology is cool!