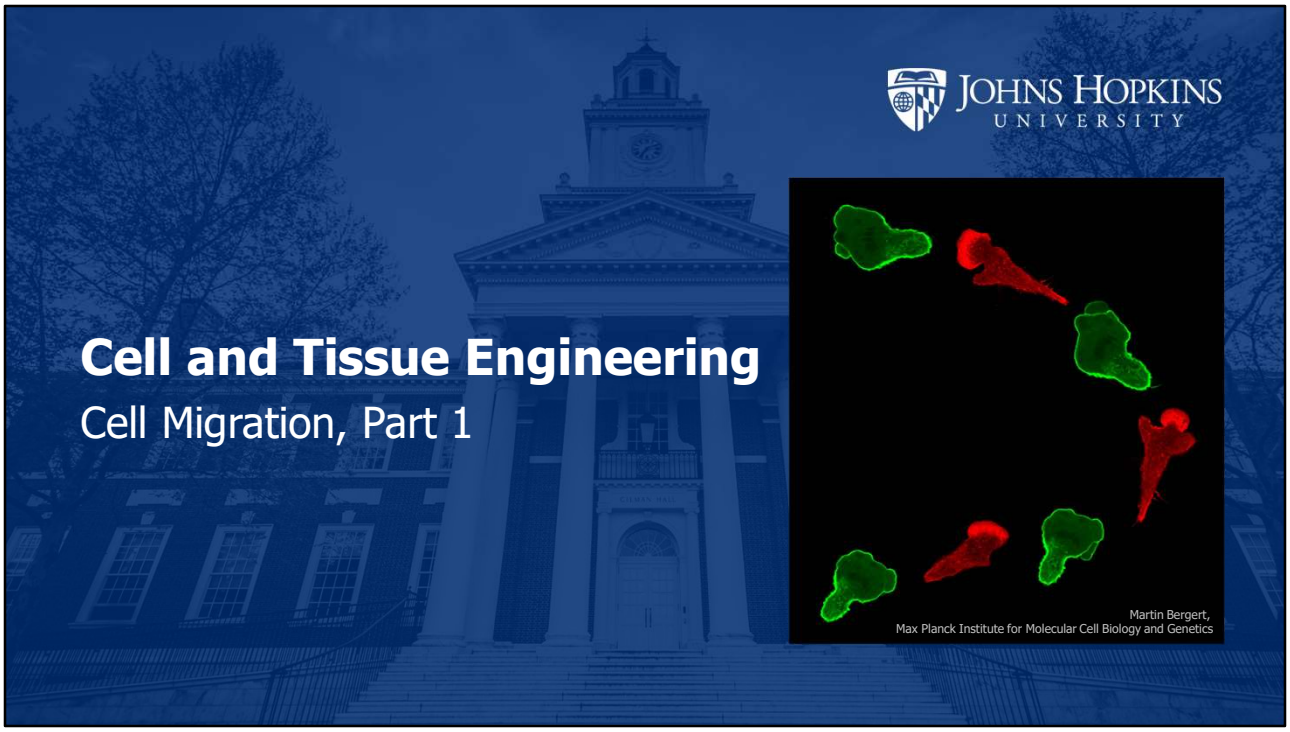

Welcome to cell and tissue engineering – Cell Migration Part 1. Cell migration is one way that cells move in our bodies – in vivo, and in the lab -- in vitro.

In this time-lapse image you can see two cells, one red and one green, as they move from the bottom left, counterclockwise around the field of view.

Cell migration

Cell Type	Why migrate?
Neutrophil	Phagocytosis bacteria
Lymphocyte	Destroy infected cells
Macrophage	Antigen presentation
Endothelial cell	Angiogenesis
Epidermis cell and fibroblast	Would healing
Tumor cell	Metastasis
Neurons and axons	Development and regeneration
Embryonic stem cell	Embryogenesis

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Adapted from Tissue Engineering, Saltzman; Reading.ac.uk

Cells can have a number of different reasons to migrate.

Now this quote says that “cell migration is an essential part of embryo development, blood vessel formation, the immune response, and cancer metastasis.

In this course we’ve already seen examples of migration including -- Embryogenesis, development and regeneration, would healing, angiogenesis, and a little bit of the leukocyte adhesion cascade.

Cell migration

Cell Type	Why migrate?
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Endothelial cell	Angiogenesis
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Tumor cell	Metastasis
Neurons and axons	Development and regeneration
Embryonic stem cell	Embryogenesis

Build replacement tissues and get into biomaterial scaffolds!

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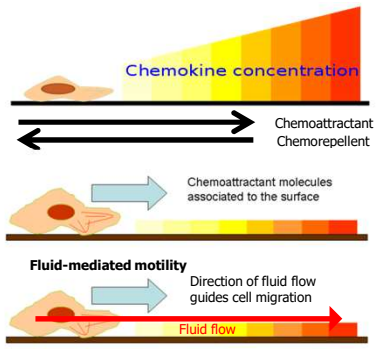
Adapted from Tissue Engineering, Saltzman Reading.ac.uk

In this course there are some OTHER reasons we care about cell migration…. Because this is one way to get cells to organize into new tissues --- and inside our tissue engineered constructs – such as porous scaffolds.

To do these things cells need to both migrate **individually** and as a **collective mass.**

Modes of cell migration



Chemotaxis
Soluble gradient

Haptotaxis
Bound gradient

Mechanotaxis
Mechanical force

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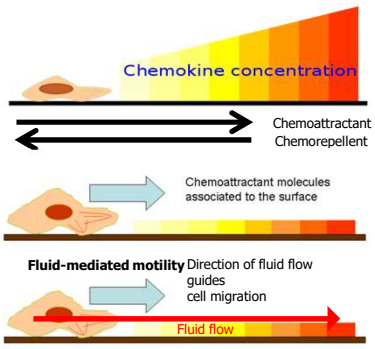
In module 5 we talked about things that stimulate and regulate migration – soluble gradients, bound gradients and mechanical forces.

Modes of cell migration



Chemotaxis
Soluble gradient

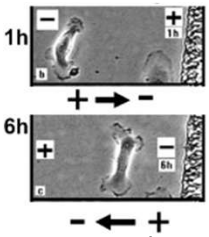
Haptotaxis
Bound gradient

Mechanotaxis
Mechanical force

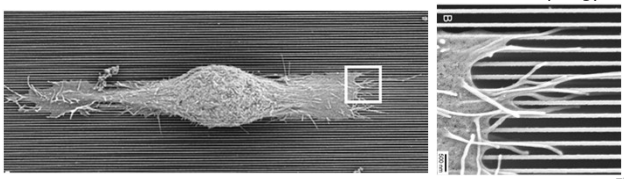
Durotaxis
Substrate mechanics

Phototaxis
Light

Galvanotaxis/Electrotaxis
Electrical currents



Contact guidance
Surface topology



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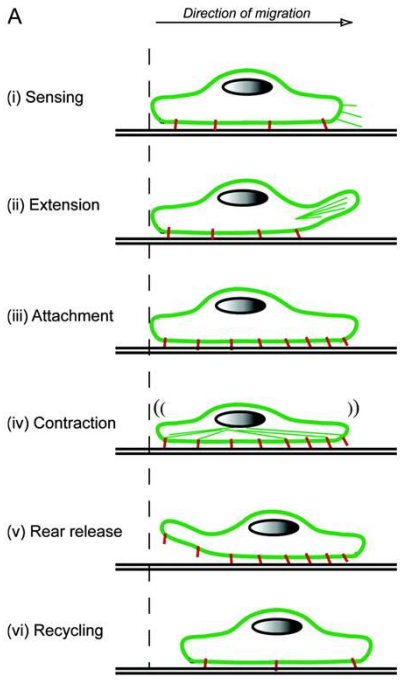
Zhao, 2009; Tiexera et al 2003

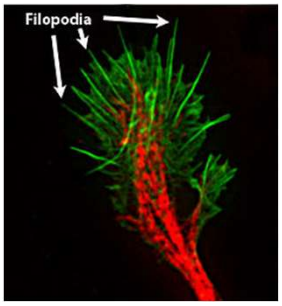
However, There are additional other modes of migration – these include:
Substrate mechanics - **Durotaxis**,
Light induced movement – **Phototaxis** ,
Movement induced by electrical currents – **Electrotaxis**. (*electrical mediated migration which involves polarization of ion channels to direct migration in the cathode direction*)
And finally **contact guidan**ce where surface topography directs migration through orientation of the cytoskeleton and focal adhesions.

You'll read more about contact guidance in the assigned review article

The underlying processes in migration



Cell migration happens in a six step process



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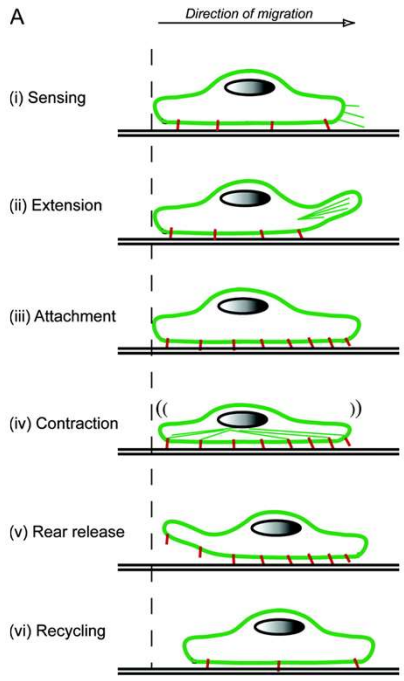
Wikipedia.org; Lamalice et al. 2007; Bio.upenn.edu

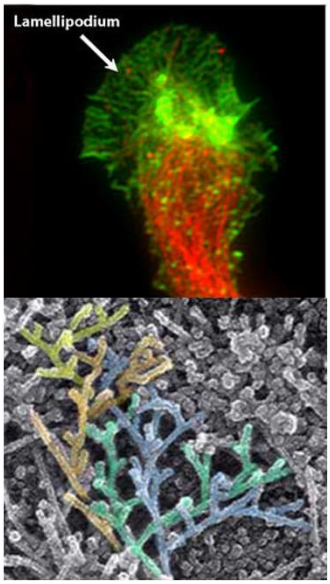
Since we know some of the stimuli for migration, let's look at the actual process for migration. Cell migration can be broken down into a SIX step process.

This process begins with cells SENSING their environment. The cell see a gradient, a topography, or an electrical current.

You may recall that one tool a cell uses to sense these signals is long, thin actin protrusions called a **filopodia**.

The underlying processes in migration





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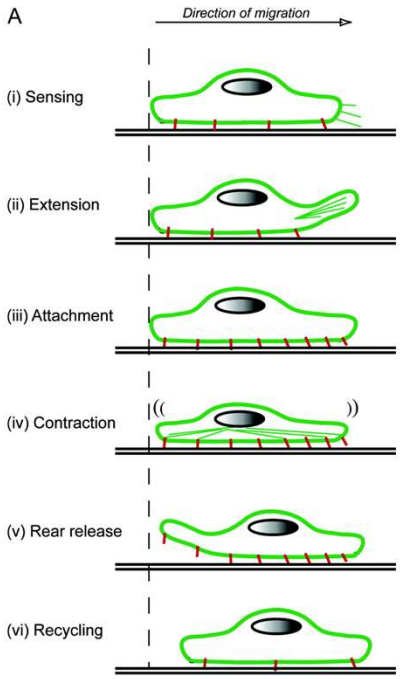
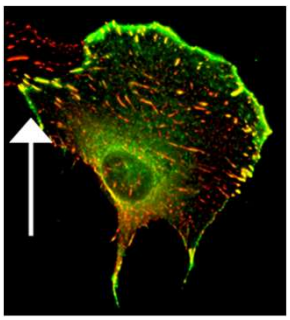
Wikipedia.org; Lamalice et al 2007

Once the direction of migration is determined by the **filapodia**, the cell moves on to step 2, EXTENSION. The cell extends a large, fan-like protrusion called a **lamellipod**

This is like a large mitt reaching out in the chosen direction. It is comprised of a dense and intricate web of actin filaments which you can see here (green image bottom right). These filaments are highly branched creating a thin fan at the leading edge of the lamellipod.

The underlying processes in migration





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Wikipedia.org; Klemkelab.ucsd.edu

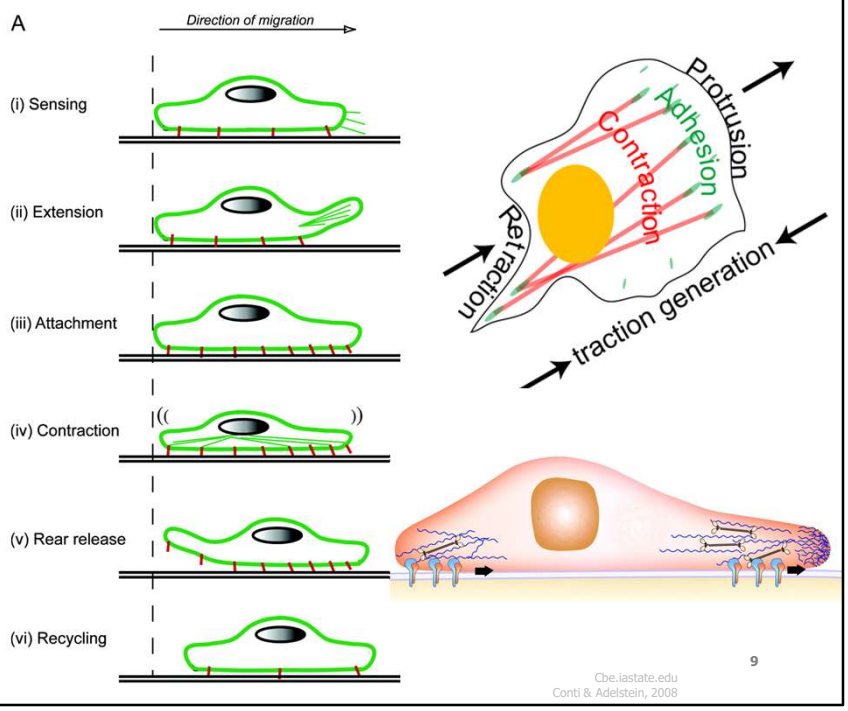
In the third step some of these actin filaments are clustered together into anchoring junctions called focal adhesions.

Imagine the cell as a mountain climber, and these adhesions are like icepicks holding the cell and giving it something to pull on in the next two steps of migration.

In this image of a migrating cell you can see punctate staining for focal adhesions along the front (top) perimeter of this cell.

Of course this cell also has adhesion in the rear (bottom) --- those are like its trailing icepicks.

The underlying processes in migration



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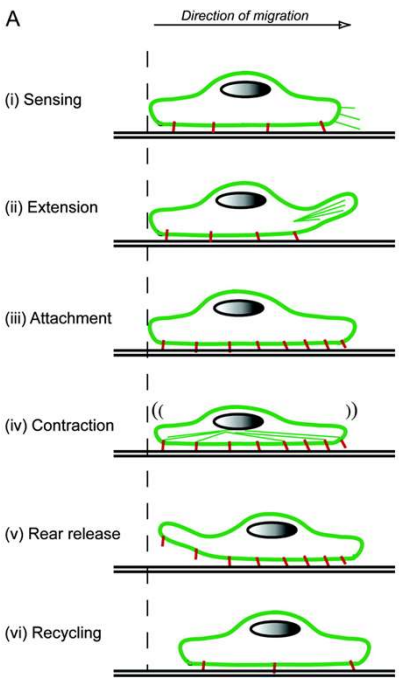
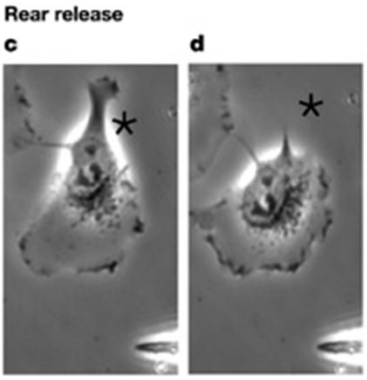
Cbe.iastate.edu
Conti & Adelstein, 2008

With firm attachments at the front of the cell, the myosin-based motors pull on the actin cytoskeleton, resulting in a contraction of the cell.

You can see in this lower image that antiparallel myosin will slide actin filaments in opposing directions, resulting in a net contraction of the cell.

The underlying processes in migration





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Hood & Cheresh, 2002

Following contraction the cell needs to release the rear attachments.

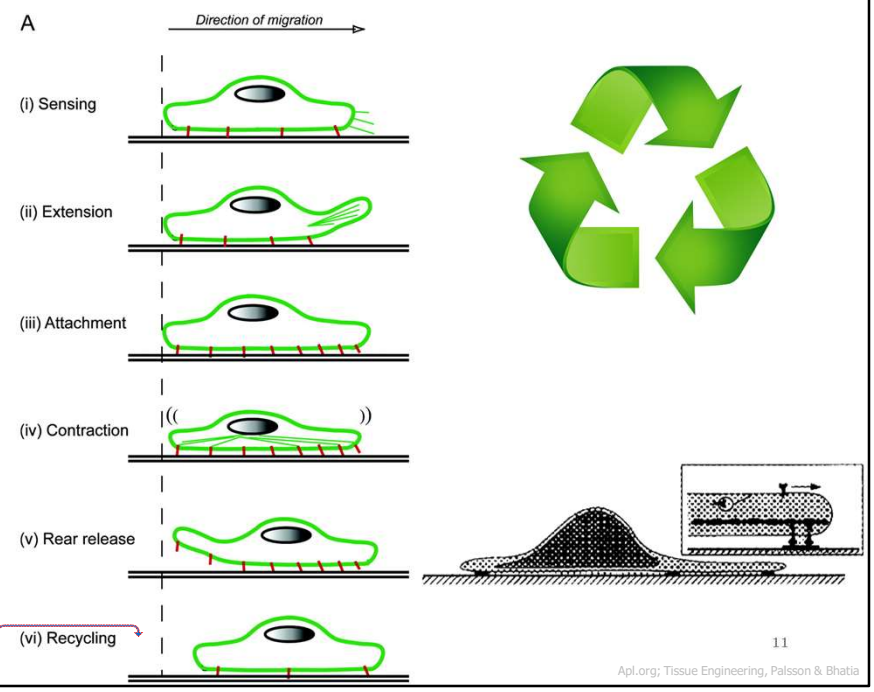
It has been proposed that fewer contacts in the rear of the cell results in preferential release of attachments at the trailing edge following contraction.

Other hypotheses include differences in calcium availability at the front and rear of the cell, and calcium being required for integrin attachments.

In any event, the release of these attachments results in the movement of the back in the direction of migration.

In the time lapse images on the right, you can see the release of the back end (top) and movement towards the center of the cell.

The underlying processes in migration



In the last step, integrin receptors at the rear for the cell are **recycled** to the front of the cell.

The cell saves both resources and time by simply moving receptors instead of **degrading** and **reproducing** them .

In this process integrin receptors at the rear of the cell are either **endocytosed** into vesicles and moved internally, or moved through the cell membrane via **directed transport**.

Rewind and review

Modes of directed migration

Chemotaxis
Soluble gradient

Haptotaxis
Bound gradient

Mechanotaxis
Mechanical force

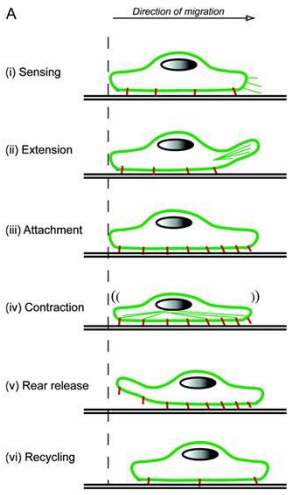
Galvanotaxis/Electrotaxis
Electrical currents

Contact guidance
Surface topology

Durotaxis
Substrate mechanics

Phototaxis
Light

Migration steps



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In this lecture we've covered a lot of ground – let's quickly look back at what we've been through.

We stared by looking at modes of directed migration which you'll cover in more depth in your homework assignment.

From there we discussed the six detailed steps of cell migration


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