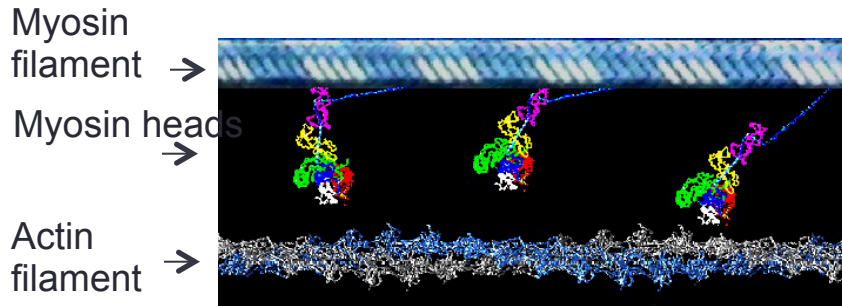
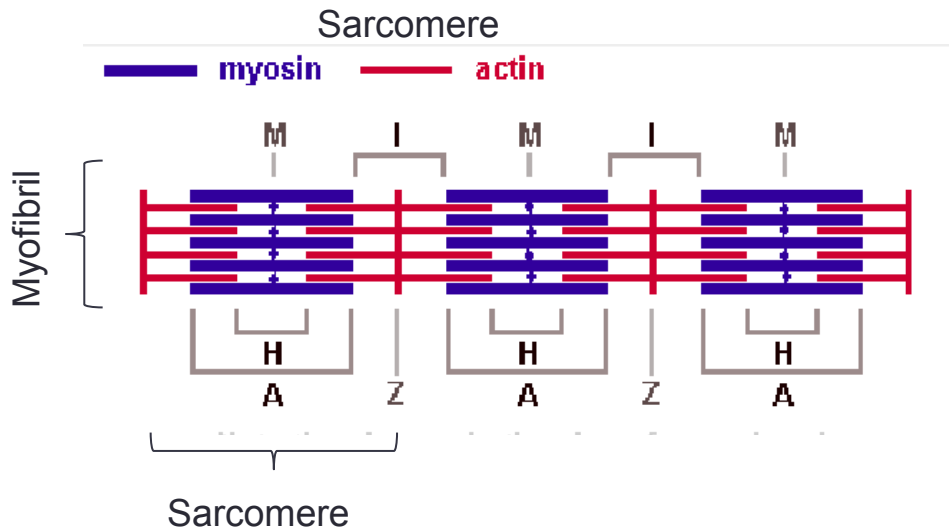
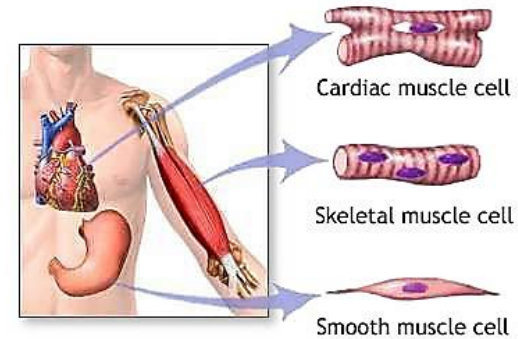


# Craig lab – regulation of muscle contraction



- Muscles (skeletal, cardiac, smooth)

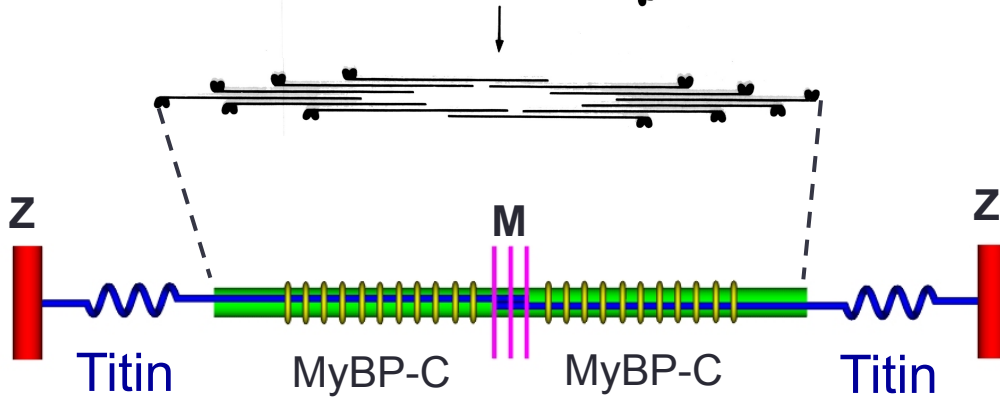
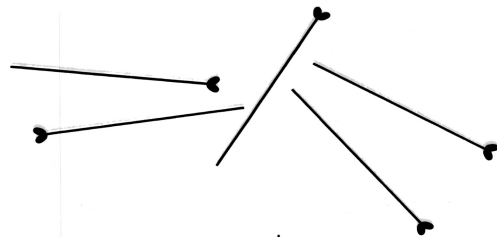
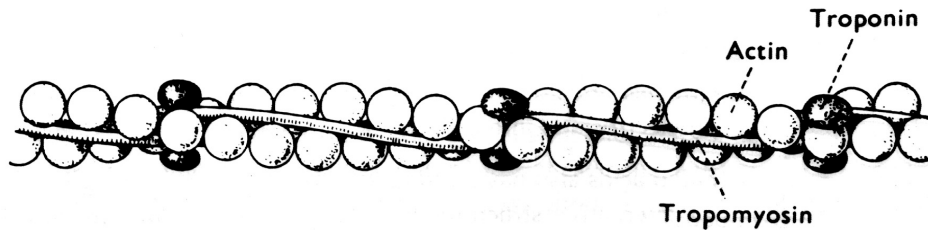
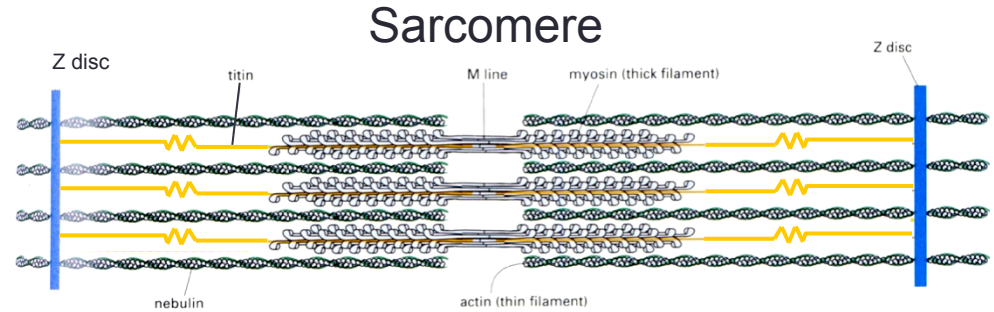


- Model systems studied
  - Invertebrates (tarantula, horseshoe crab, scallop)
  - Vertebrates (mouse, frog)



- How is contraction switched on and off?

# Proteins studied

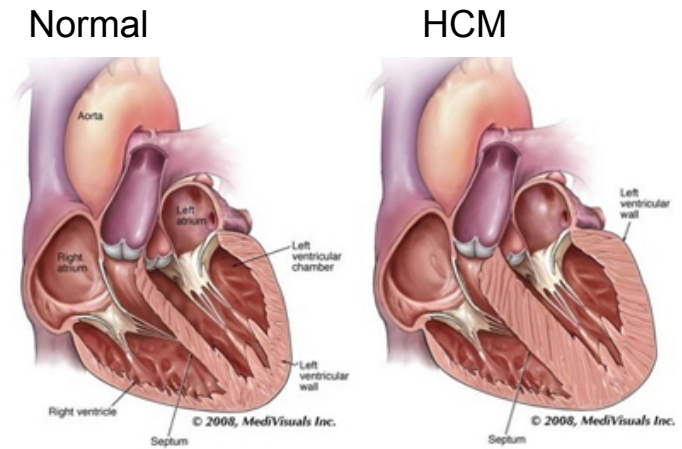


- Thin filament = actin + tropomyosin and troponin – how do Tm and Tn switch off contraction?
- Thick filaments = myosin + other proteins
- Myosin-binding protein C – modulates contraction in the heart
- How are thick filaments switched on and off?

# Disease connection

Mutations in sarcomeric proteins lead to diseases:

- Cardiac muscle – inherited hypertrophic cardiomyopathy (HCM)
- 1 in 500; sudden cardiac death; diastole impaired
- Skeletal muscle – distal arthrogryposis, Sheldon-Hall syndrome, distal myopathy



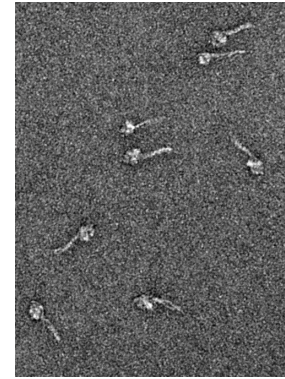
Distal arthrogryposis

# Techniques

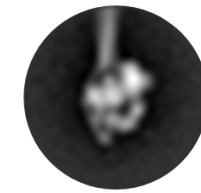
- Electron microscopy
  - Cryo-EM
  - Negative staining
  - Other molecular and tissue EM techniques
- 3D image reconstruction
  - Helical
  - Single particle
- Docking atomic structures into reconstruction



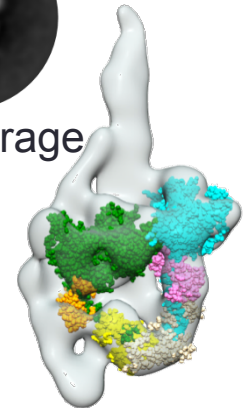
Cryo-EM (A-level)



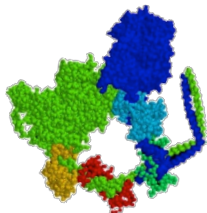
Negative stain – myosin molecules



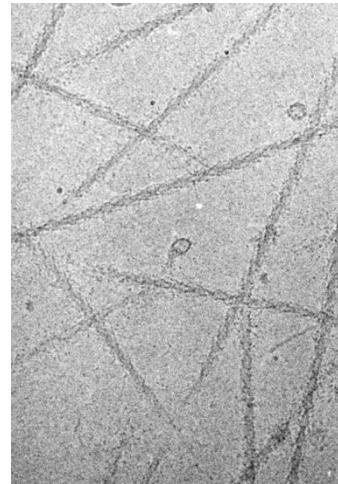
2D average



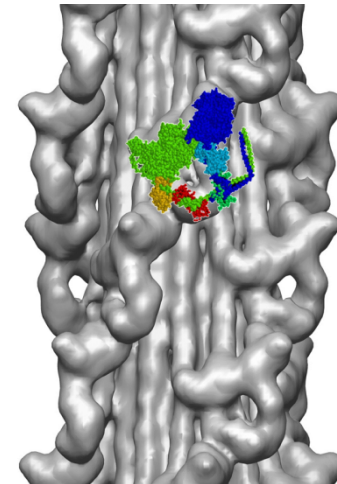
3D recon



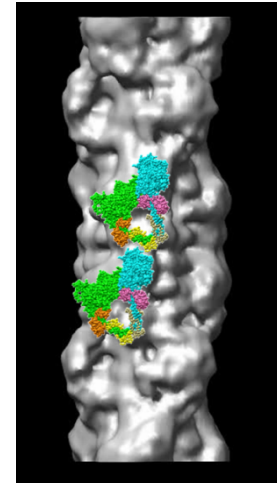
Interacting heads motif



Cryo – myosin filaments



Tarantula – 3D recon



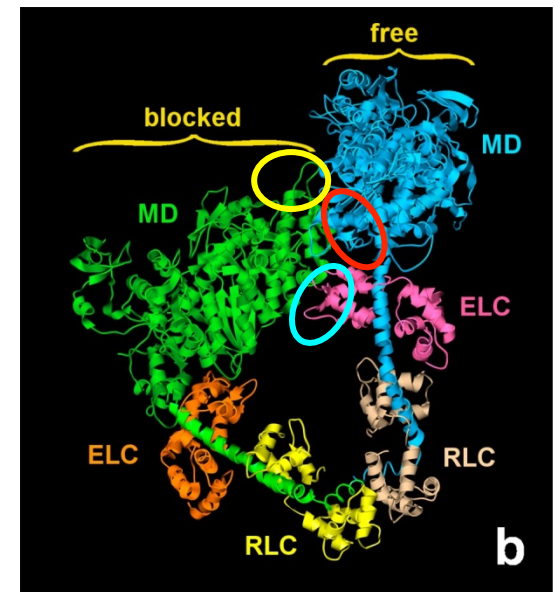
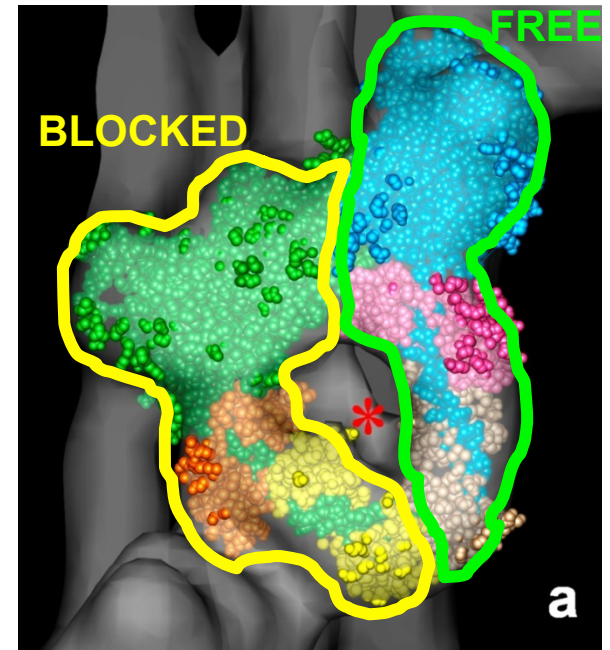
Mouse – 3D recon





# Why is the IHM important?

- Head-head interaction switches heads off by inhibiting actin interaction and ATPase – would switch filament OFF → relaxation
- Is fundamental – has been present from the origin of animals
- Is the state heads return to as part of the relaxation process – saves energy
- In single molecules is used as storage or transport form
- Disruption of interactions in diseases such as HCM or DA may be the cause of hypercontractility



# Future directions

- Structure of IHM at high resolution – cryo-EM
- Structure of thick filaments at high resolution
- How do mutations affect IHM structure/stability
- Do HCM drugs stabilize the IHM?