FUTURE GENERATIONS
Centre for Human Reproductive Science
Part of the integrated fertility services at Birmingham Women's NHS
NHS Foundation Trust

Birmingham Science City
ideasforlife

UNIVERSITY OF BIRMINGHAM

100 million to 1!
What can Maths tell us about the Great Sperm Race?

Dr Dave Smith

School of Mathematics

University of Birmingham

ASE Annual Conference 2014

Physiology

The number of sperm cells that can be found in semen is between **50 and 400 million**, but the amount of cells that actually complete the journey until the oviduct is incredibly low.

A ‘numbers game’

1. What is the world’s population?

2. How many people have ever lived?

3. How many people have walked on the moon?

Sperm numbers

1. How many sperm does the ‘average man’ generate every day?

2. …how many in a lifetime?

3. How many of a man’s sperm result in a new person?

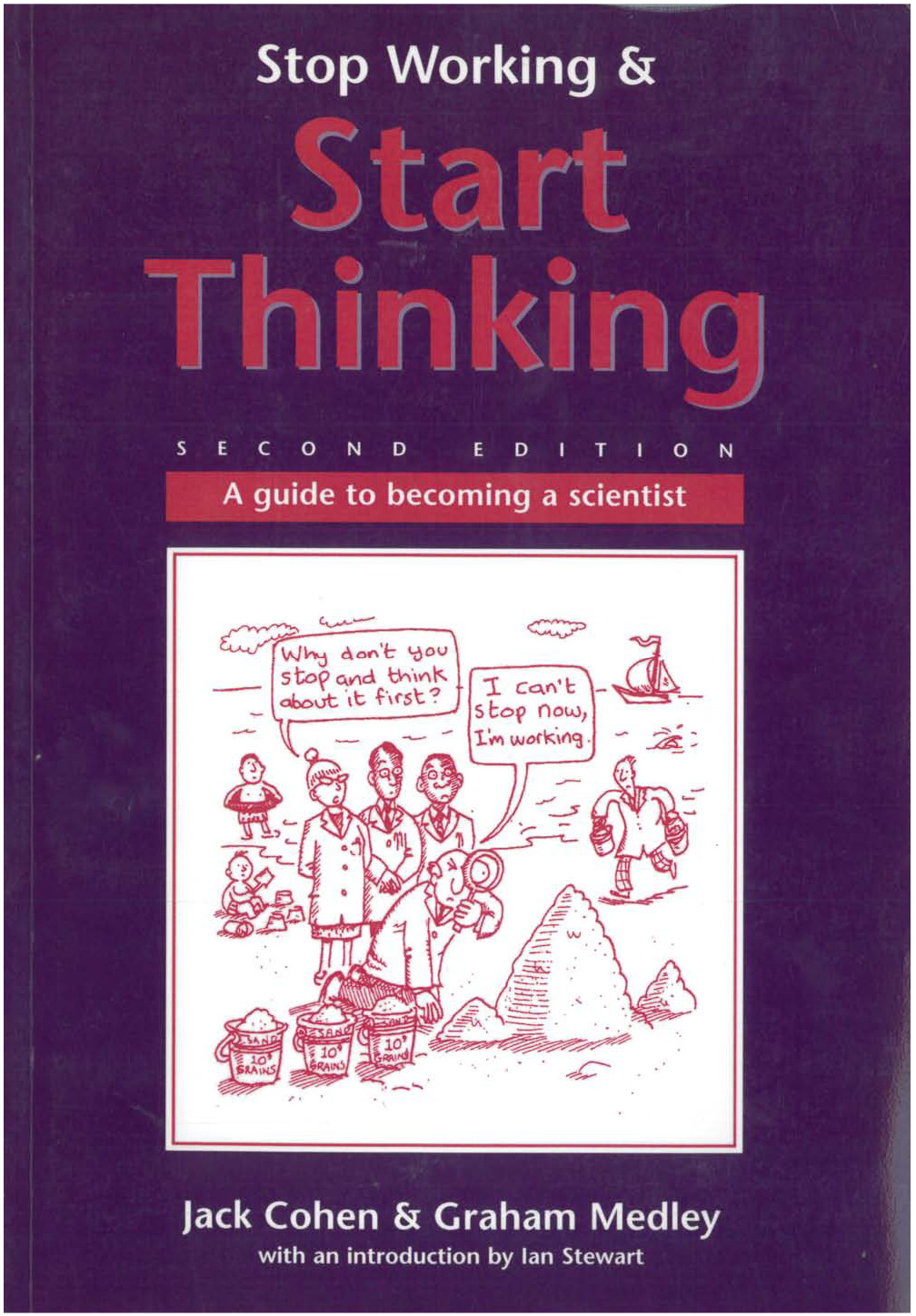
What are the chances?!

- About 1 : 10^{10} people who have ever lived have walked on the moon.

- About 1 : 10^{12} sperm who have ever 'lived' result in a new person.

(Dr Jack Cohen)

Highly recommended!



Correction

UNIVERSITY OF BIRMINGHAM

1 in a trillion!
What *else* can Maths tell us about the Great Sperm Race?

Dr Dave Smith

School of Mathematics

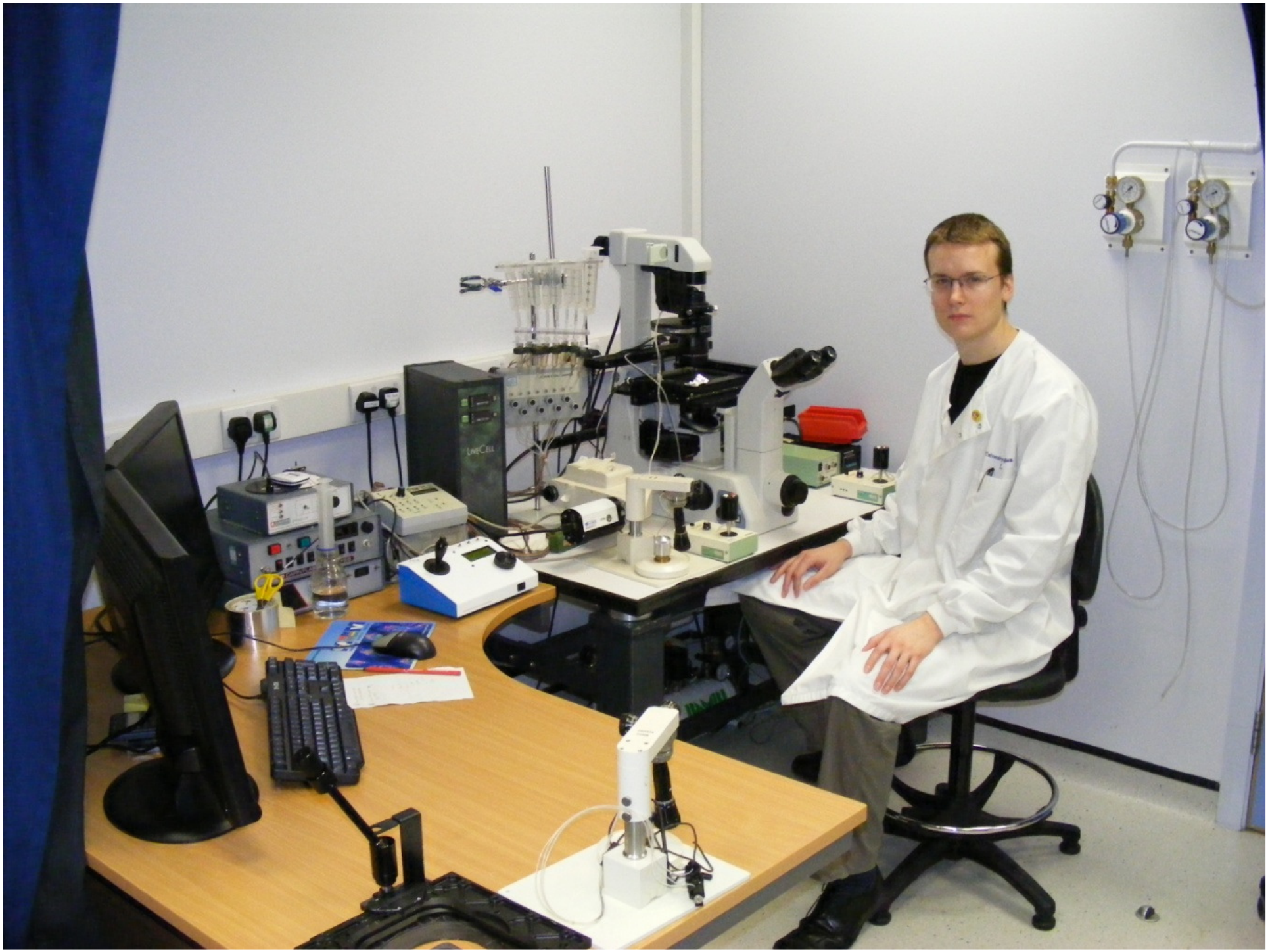
University of Birmingham

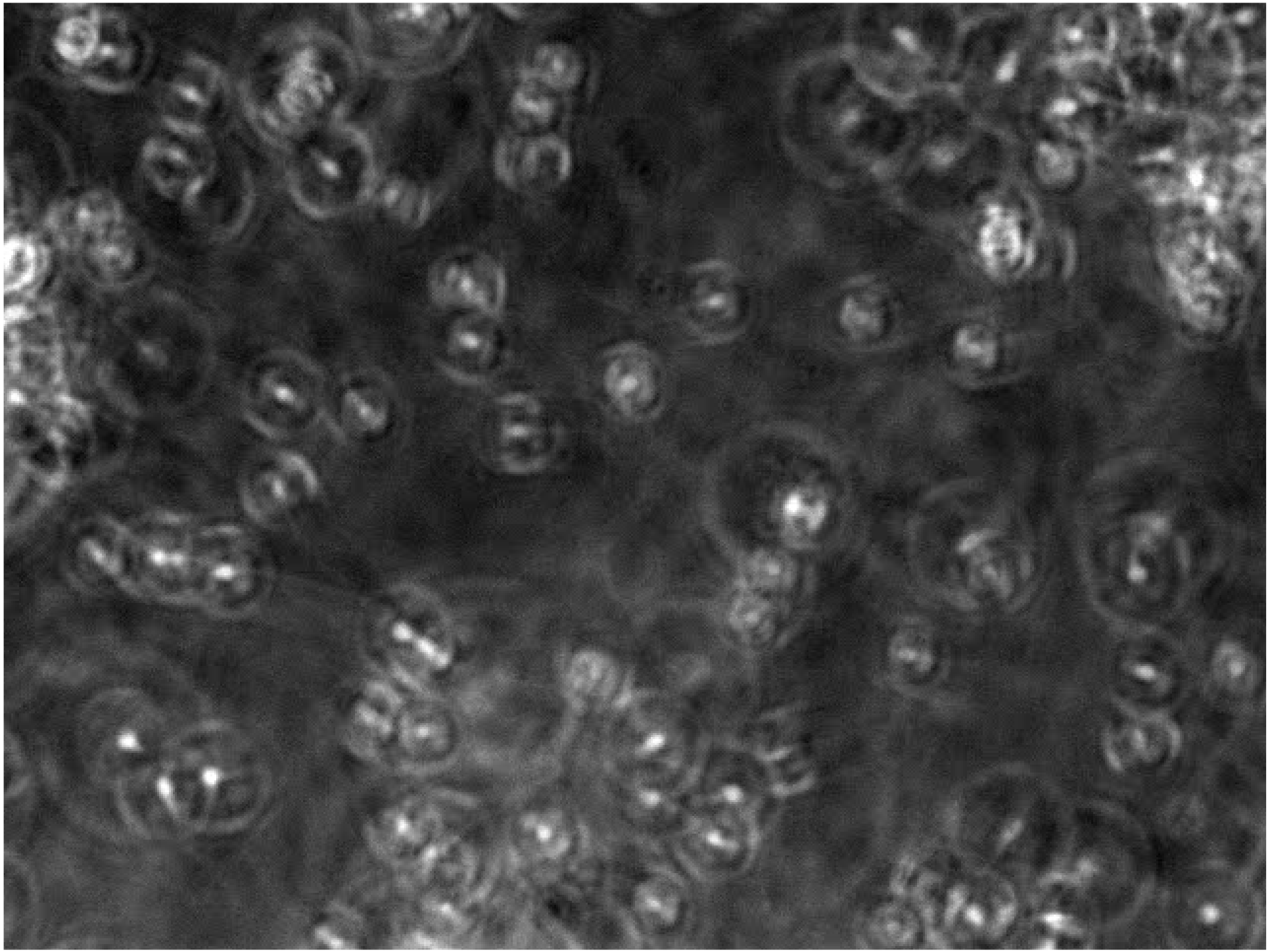
ASE Annual Conference 2014

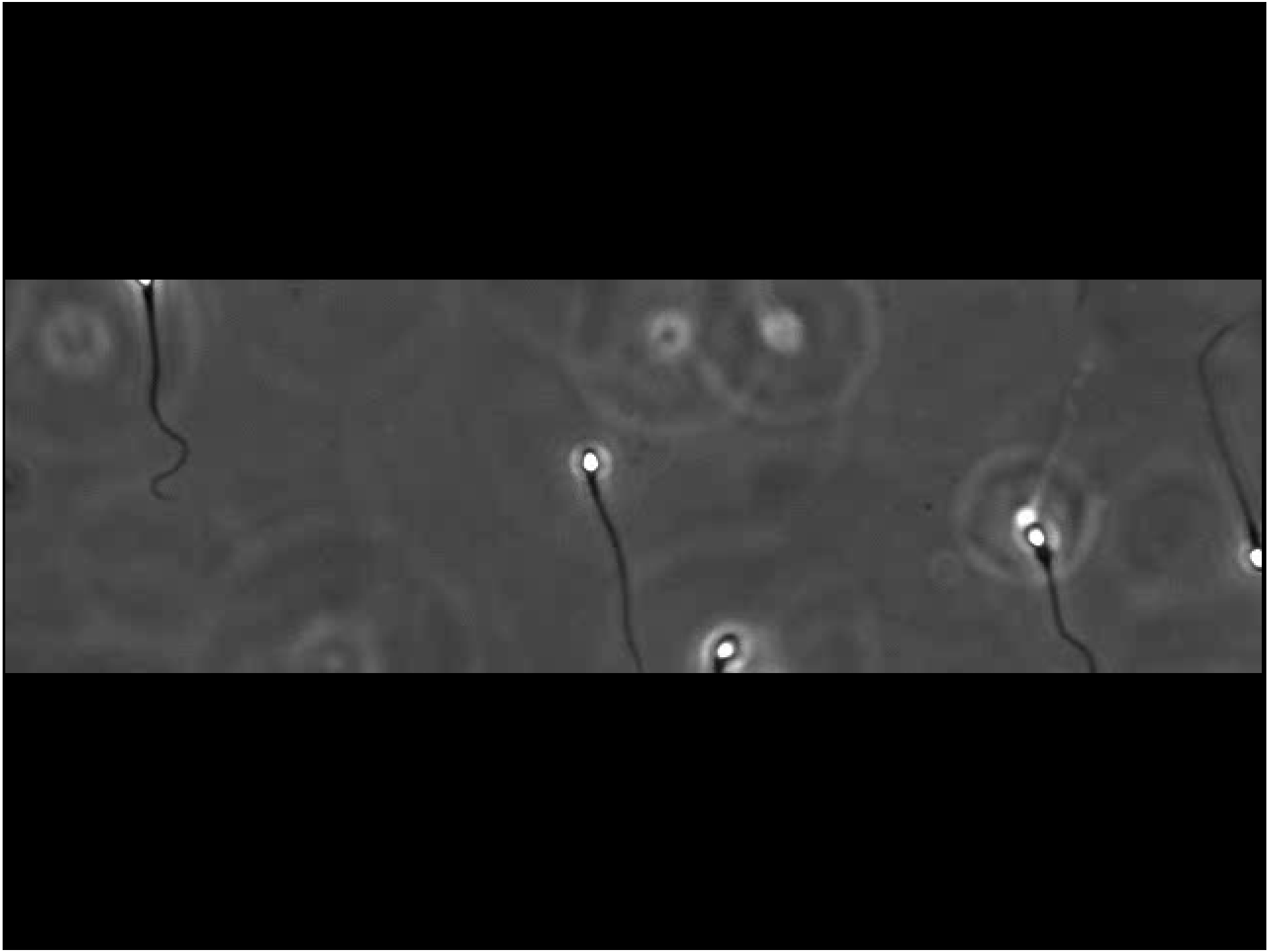
A potted history

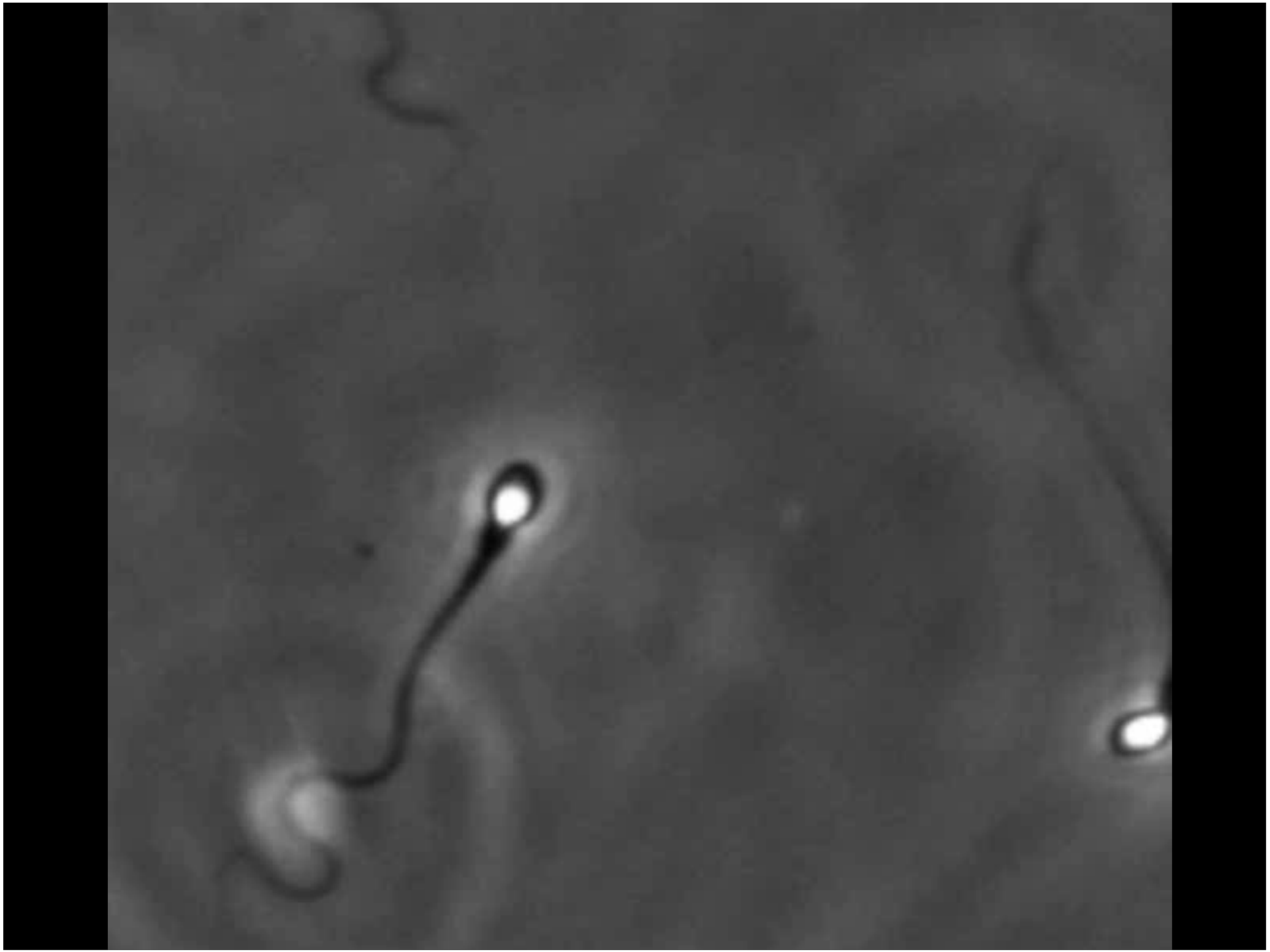
- Sperm were discovered in the late 17th Century by Antonie van Leeuwenhoek, a pioneer of microbiology.
- The internal active structure of the sperm tail *(flagellum)* was discovered via electron microscopy in the mid-1950s by B. Afzelius.
- Also in the mid 1950s, the first studies of flagellar motion and the fluid mechanics of sperm motility began, here in the UK (M.J. Lighthill, J. Gray, G. Hancock).
- In 1978, the first baby conceived in vitro was born at Oldham General Hospital, the result of a technique developed by R. Edwards and P. Steptoe.
- In 2006, the world's first home sperm test *Fertell*, developed in Birmingham, was released.

Let’s have a closer look!


LiveCell







However…

- Despite decades of intensive research around the world, we are only beginning to understand the mysteries of internal fertilisation.
  - What does a sperm have to do? And how does it do it?
  - What (if anything) determines the winning sperm? Can we tell which sperm have the ‘right stuff’?
  - What goes wrong in subfertility? What can we do about it?

Sperm motility and imaging research – joint with Birmingham Women's Hospital Fertility Centre

FUTURE GENERATIONS
Centre for Human Reproductive Science
ChRS
Part of the integrated fertility services at
Birmingham Women's NHS
NHS Foundation Trust

Dr Jackson Kirkman-Brown MBE

Scientific groups working on sperm

- Reproductive Biology and Genetics group, Clinical and Experimental Medicine, UoB
- John Blake, Daniel Loghin, UoB, Tom Montenegro-Johnson (formally UoB, now Cambridge)
- Steve Publicover's research group, Biosciences, UoB *(speaking in WG5 at 15:30)*
- Petr Denissenko, Vasily Kantsler, Warwick
- Eamonn Gaffney, Hermes Gadêlha, Oxford

The Great Sperm Race: marathon or sprint?

- If a sperm (50×10^{-6} m) were to be scaled up to the size of a human (1.7 m), how long would the trek through the tract be?
- 6.8 km (perhaps more precision than is justified!) – the same as the Oxford-Cambridge Boat Race.

Aside: sperm in different species

The human sperm

- Sperm swim at up to 100 μm/s, the tail beat frequency is anywhere from 2-30 Hz depending on temperature, liquid properties and whether they have gone through ‘capacitation’.
- A typical ‘physiological’ capacitated cell will beat at 10-15 Hz and swim at 50 μm/s in cervical mucus substitute.

A 6.8km *swim*?

- Sperm have to travel through the cervix and the uterus, which are thin films of highly viscous fluid.
- Viscosity is the 'gloopiness' of fluid, the internal friction. Water has low viscosity (about 10^{-3} Pa.s), engine oil 0.05-0.2 Pa.s, golden syrup 10^{2} Pa.s (& glass 10^{40} Pa.s).
- Imagine trying to swim through engine oil – the resistance is around 100 times higher.

Cervical mucus

- The cervix is filled with a protective viscous mucus. The viscosity of this fluid changes with hormone levels.
- The flow properties are complex, with an effective viscosity that depends on *shear* and frequency.
- Close to ovulation, sperm encounter a viscosity around 200 times greater than water.

Viscosity: an evolutionary perspective

- We have evolved from invertebrate sea creatures which produce sperm which look similar to our own.
- The internal motor, the axoneme, is virtually identical in sea urchins and humans.
- But human sperm pull off the trick of swimming against 200 times greater resistance.
- (In fact going back further, our closest unicellular ancestors, the *choanoflagellates*, are distinctly sperm-like.)

Viscosity: clinical science perspective

- Most clinical labs around the world, and most reproductive science groups, look at sperm in low viscosity salt water solutions.

- Low viscosity changes the mechanical signals sperm encounter, changes the tail beat and cell behaviour.

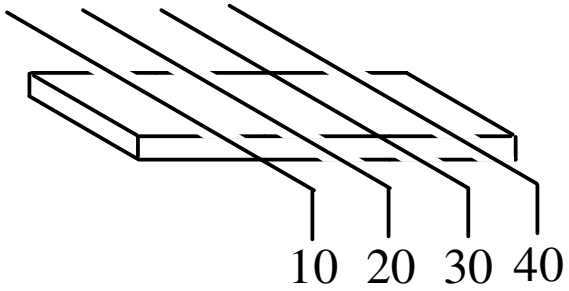
Kremer capillary

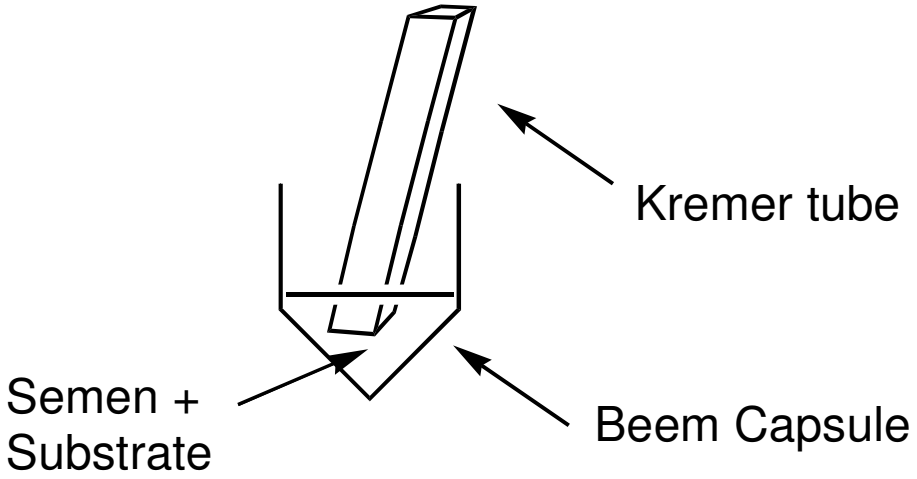
Selecting the migrating subpopulation for imaging

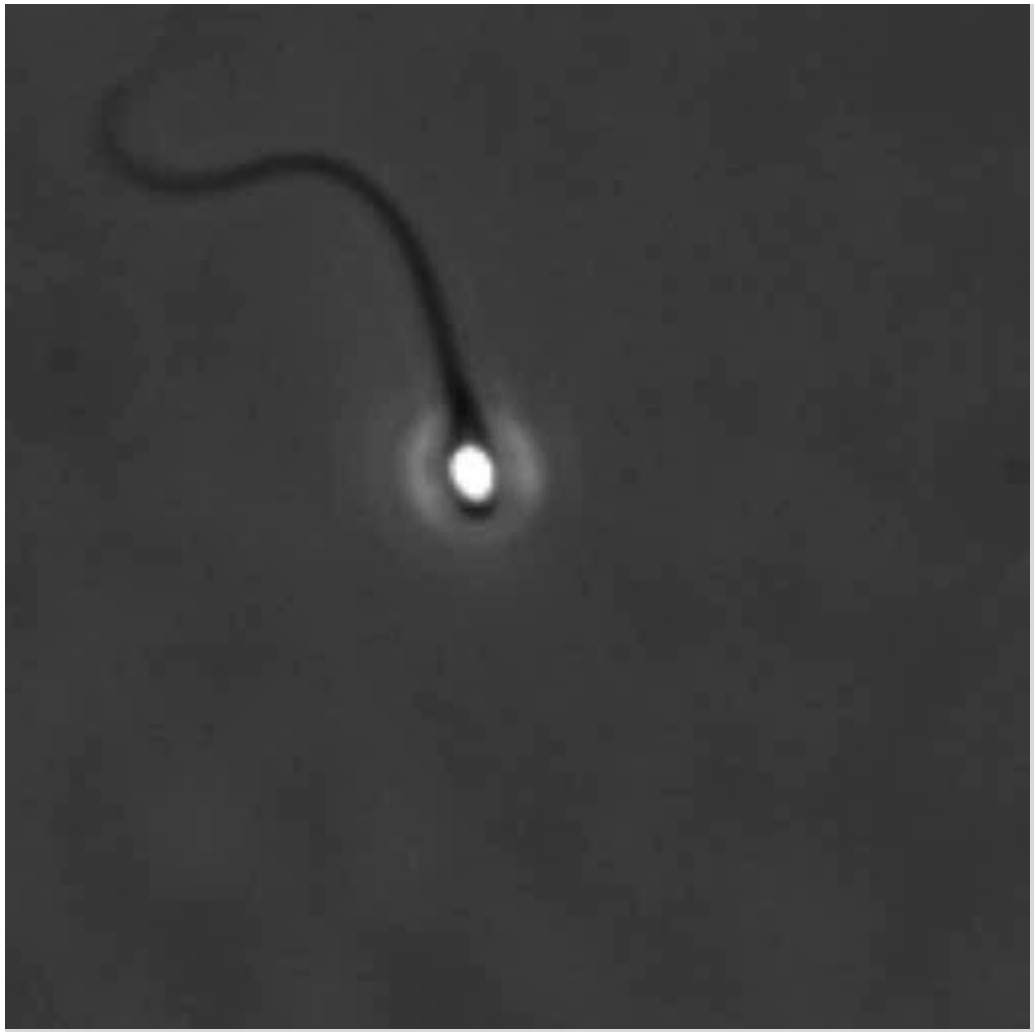
Image sperm migrating in a glass capillary (400 microns inner depth)

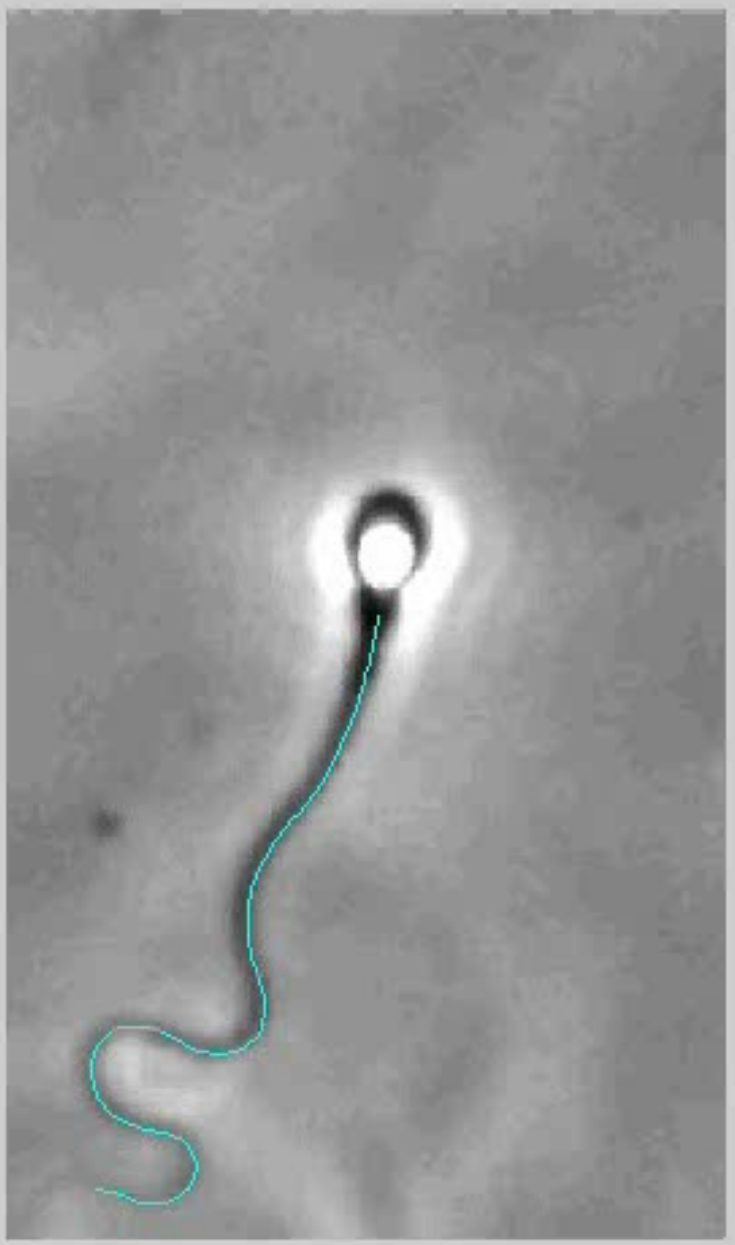
A capillary tube is filled with a carrier solution that mimics cervical mucus, usually hyaluronic acid or methylcellulose-saline (+ ions, metabolic substrates, protein...)

Incubated for 1h to allow time for sperm to swim up the tube.









Viscosity: it gets more complicated!

- This is where maths is really useful...
- ...even water behaves like a very viscous liquid to a microscopic swimmer.
- This effect is very important to understand if we want to understand what sperm have to do.
- We need to think about *viscosity* versus *inertia*.

Inertia in fluids

Steve Morris/AirTeamImages

Viscosity in fluids

Navier-Stokes: the equations of fluid dynamics

- In ‘physical variables’

$$\rho\left(\frac{\partial \boldsymbol{u}}{\partial t}+(\boldsymbol{u}\cdot\boldsymbol{\nabla})\boldsymbol{u}\right)=-\boldsymbol{\nabla}p+\mu\nabla^2\boldsymbol{u},\quad \boldsymbol{\nabla}\cdot\boldsymbol{u}=0$$

- In ‘dimensionless variables’

$$\underbrace{\left(\frac{\rho U L}{\mu}\right)}_{\text{“Re”}}\underbrace{\left(\frac{\partial \hat{\boldsymbol{u}}}{\partial \hat{t}}+(\hat{\boldsymbol{u}}\cdot\hat{\boldsymbol{\nabla}})\hat{\boldsymbol{u}}\right)}_{\text{Inertial terms, nonlinear, responsible for turbulence}}=-\hat{\boldsymbol{\nabla}}\hat{p}+\underbrace{\hat{\nabla}^2\hat{\boldsymbol{u}}}_{\text{viscous term}},\qquad \hat{\boldsymbol{\nabla}}\cdot\hat{\boldsymbol{u}}=0$$

Reynolds number

- Re is the most important number in fluid dynamics. Originally discovered in the setting of turbulence experiments by Osborne Reynolds, it gives us a way to classify any flow (of liquids or gases).

$$\mathrm{Re} = \frac{\rho U L}{\mu}$$

- U = velocity, L = length, μ=viscosity, ρ=density

Stirring tea: Re = 10^5
Ocean liner: Re = 10^9
Human swimmer: Re = 10^6
Sperm in saline: Re = 10^{-3}

Life at low Reynolds number

- Fluid mechanics at very low Reynolds number is described by the Stokes flow equations.

$$\begin{aligned} 0 &= -\boldsymbol{\nabla} p + \mu \nabla^2 \boldsymbol{u} \\ \boldsymbol{\nabla} \cdot \boldsymbol{u} &= 0, \end{aligned}$$

- An important feature you can see is that the *t* dependence (time) is missing.
- As a consequence, a swimming stroke has to be non-time-reversible to achieve propulsion.

- The movie demonstrates different balances of viscosity and inertia. In the tank of syrup, viscosity is much more important than inertia.
- The syrupy tank is a way of mimicking the microscopic world.
- *Even water behaves like syrup if you're a sperm!*
- Sperm have to do something other than flapping back and forth.
- The specific thing they do is to send a wave of bending down their tails. The movie has to look different forwards and backwards.

Gray & Hancock (1955) theory

- This theory was developed by G & H while the latter was supervised by Lighthill
- It is a remarkable simplification of a 2nd rank tensorial integral equation solution of the Stokes flow equations, to a pair of algebraic relations

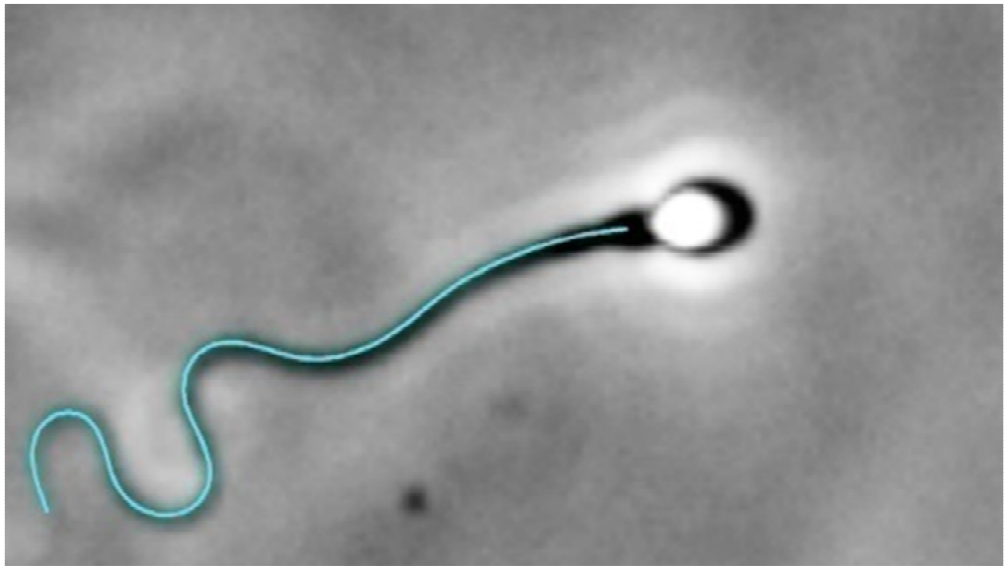
$$f_n = C_n u_n \qquad f_t = C_t u_t$$

$$\frac{C_n}{C_t} \approx 2$$

How sperm swim

- Hence oblique movements cause a thrust in one direction
- Sperm swim by propagating waves
- These waves cause oblique movements, and hence thrust

- The wavelength seems to get shorter near the end of the tail.
- *But* – what if we look at the wave as a function of arclength along the curve of the tail?
- The meandering waveform is created by an increase in curvature along the tail.
- Meandering wave / purposeful swimming?!



Subfertility

- Defined as: failure to conceive after 12 months.
- What proportion of couples in the UK experience subfertility?
- In what proportion of cases are male factors relevant?

- The most common problem observed with sperm is poor motility.

- Sperm ‘swimming’ is therefore an important target for treatment.

IVF – the numbers

1. What percentage of babies in the UK are born via IVF at present?

2. How many babies have been born from IVF in the UK? Worldwide?

3. How many IVF cycles are performed in the UK each year?

IVF

- IVF (and the related treatment, ICSI), have revolutionised treatment for both male and female factor fertility problems.

- However, the treatment is expensive (several thousand pounds per cycle), has a low success rate (about 25%) and is physically and emotionally draining, particularly for the female partner.

Contraception

- The reverse problem is contraception.

- About 550 000 pregnancies begin each day.

- Half of all pregnancies are unplanned.
- Pregnancy carries considerable risk in developing countries.
- In Niger, 1 in 7 women die from pregnancy-related causes.
- Worldwide, approximately one woman dies every minute from pregnancy related causes.

Sperm motility as a treatment target

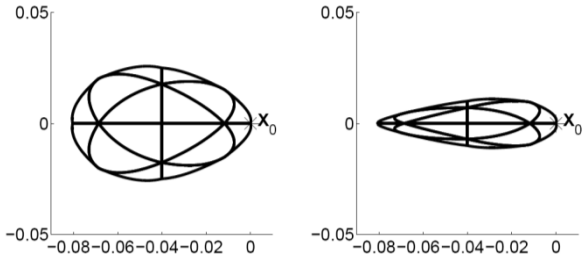
- There are no drug treatments either subfertility, or contraceptives, that directly target sperm motility.
- To find drug targets, design drugs and assess their effects, we need a better understanding of the job of a sperm, and better ways to assess how sperm motility changes under drug stimulation.
- Potential targets include metabolism, energy transport, and aspects of *capacitation* (see SJP talk at 15:30).

Fluid mechanics

- We want to understand how the flagellum interacts with fluid, and probe deeper still into the internal mechanism of the flagellum.
- Two approaches:
  1. Capture the flagellar wave from experiment, plug into a simulation. Calculate flow, forces, energy...
  2. Try to model the internal structure and motors and couple to a fluid model (more challenging).
- In both cases, cluster computing is useful.

Don’t worry about the details..!

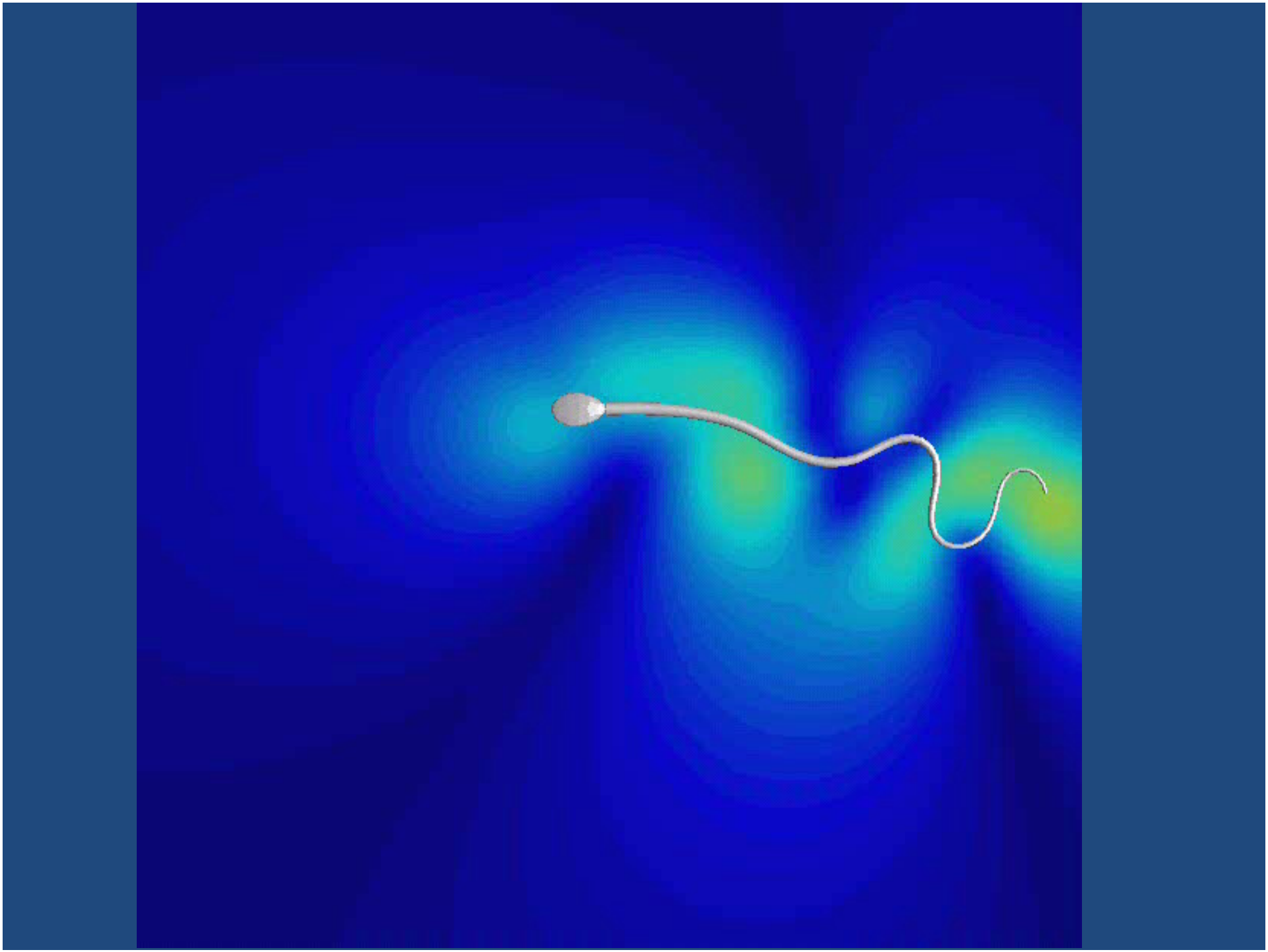
- We model:
  - flagellum (via SBT)
  - head (via BEM)
  - nearby glass surface no-slip boundary condition (by the method of images)



$$\boldsymbol{U}(\boldsymbol{X}) = \int\int_H \mathbf{S}(\boldsymbol{X};\boldsymbol{\xi}^H)\cdot\boldsymbol{\phi}(\boldsymbol{\xi}^H)\,\mathrm{d}\boldsymbol{\xi}^H + \int_0^1 \mathbf{S}(\boldsymbol{X};\boldsymbol{\xi}(\sigma))\cdot\boldsymbol{f}(\sigma)\,\mathrm{d}\sigma$$

(+ dipoles)

- We also need to take into account the fact that the cell is subject to zero inertia



Sperm power estimates

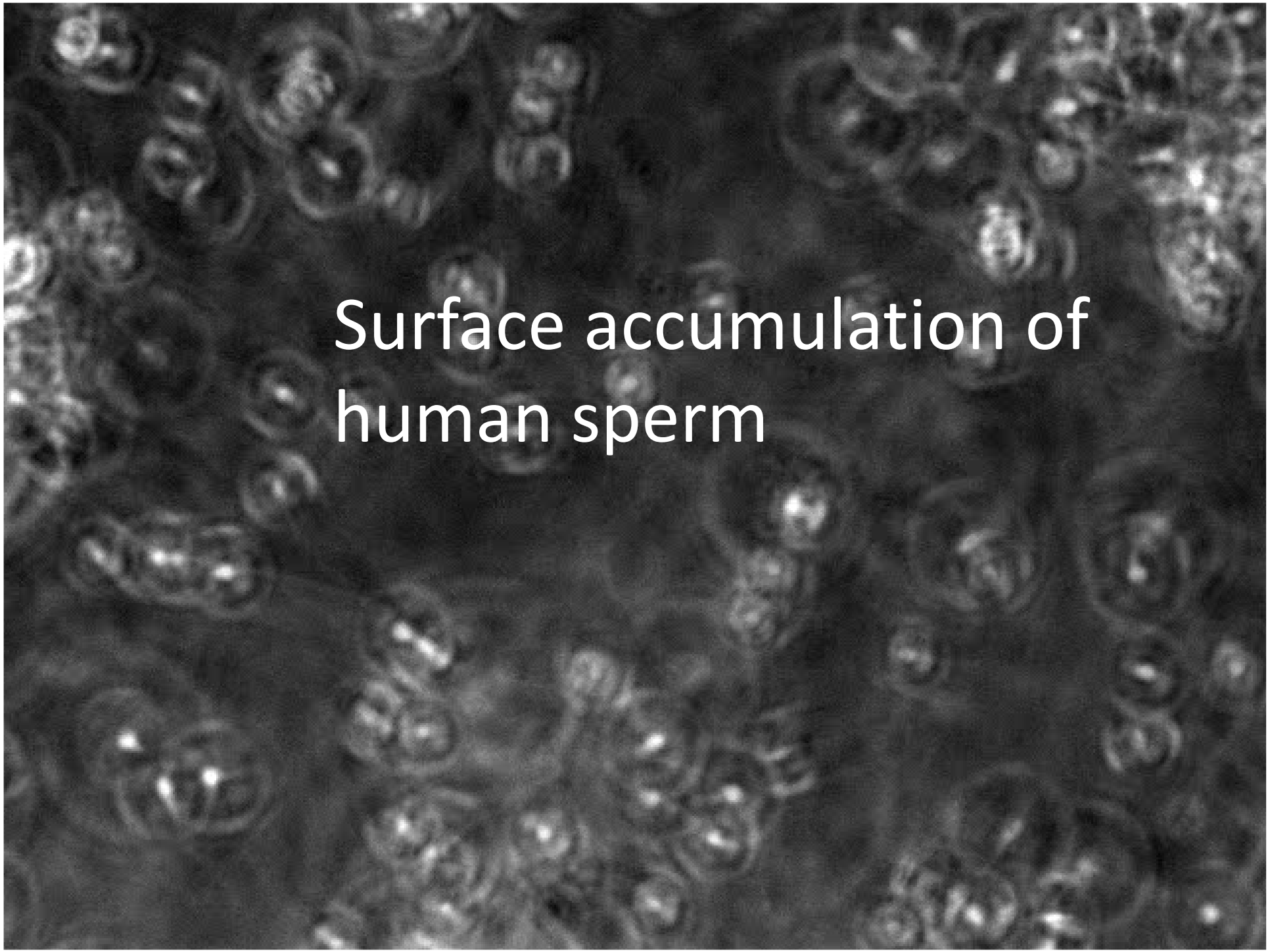
- Low viscosity cell, mean velocity 64 µm/s, power 9.9 x 10^{-15} W
- High viscosity cell, mean velocity 49 µm/s, power 3.1 x 10^{-13} W

Nondimensional ‘expenditure’/inverse efficiency

- Consider the following measure, which takes into account viscosity and velocity (L is just sperm length to give a nondimensional number)

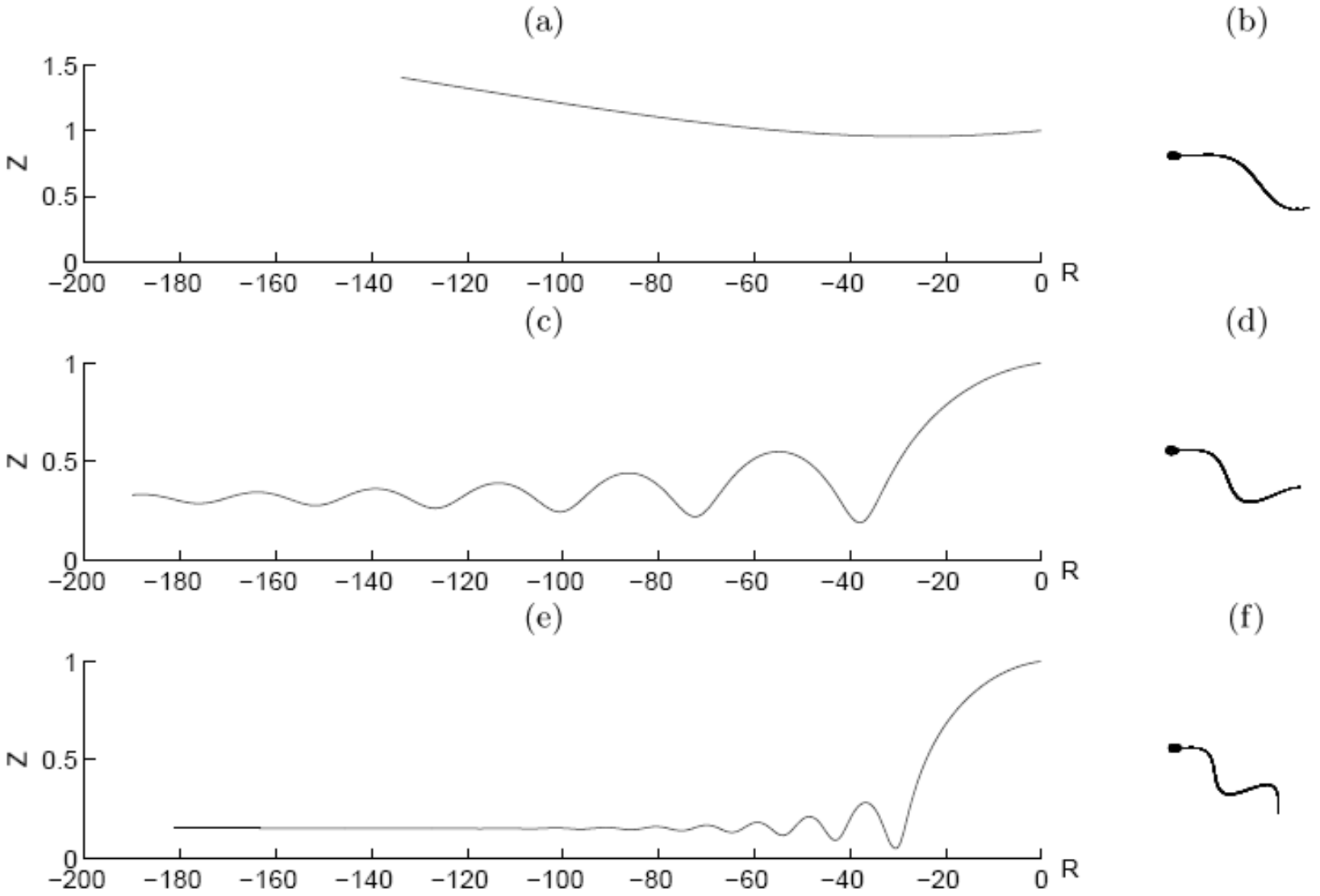
$$\frac{P}{\mu L^2 U}$$

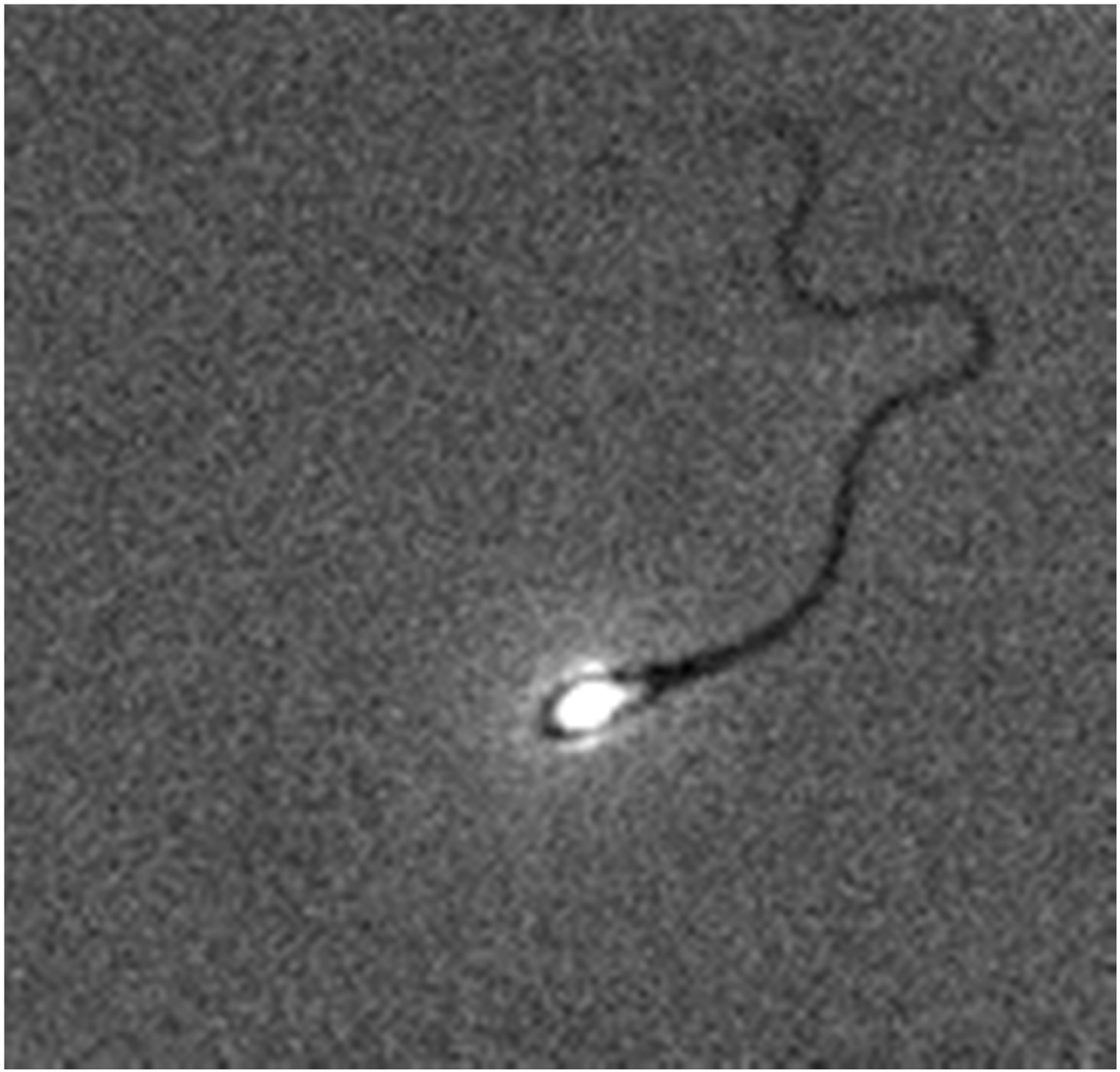
- LVM – 88.5
- HVM – 19.7 – so over 4 times more efficient


Surface accumulation of
human sperm

Surface accumulation of sperm

- Bull sperm - Rothschild, Nature 1963, **198**:1221-2.
- Human sperm are found at by far the highest concentrations at 10-20 microns from glass surfaces (Winet et al. Reprod. 1984, **70**:511-).


(a)
(b)
(c)
(d)
(e)
(f)
Z
R
1.5
1
0.5
0
−200
−180
−160
−140
−120
−100
−80
−60
−40
−20
0



Summary

- Sperm motility is a highly complex problem, and maths cannot possibly provide all of the answers.
- However, bringing a maths/ physics/ engineering perspective to the biological lab provides a lot of new information, and some powerful tools for understanding.
- In turn, the biological system encourages the development of new mathematical techniques.

Acknowledgements

- Ean Hin Ooi, Petr Denissenko, Vasily Kantsler, Tom Montenegro-Johnson
- John Blake, Eamonn Gaffney, Jackson Kirkman-Brown
- All colleagues in Reproductive Biology and Biosciences in Birmingham
- Birmingham Women's Fertility Centre
- EPSRC, MRC, Wellcome Trust, Birmingham Science City/HEFCE, Advantage West Midlands