Mathematical Physiology

Ian Griffiths

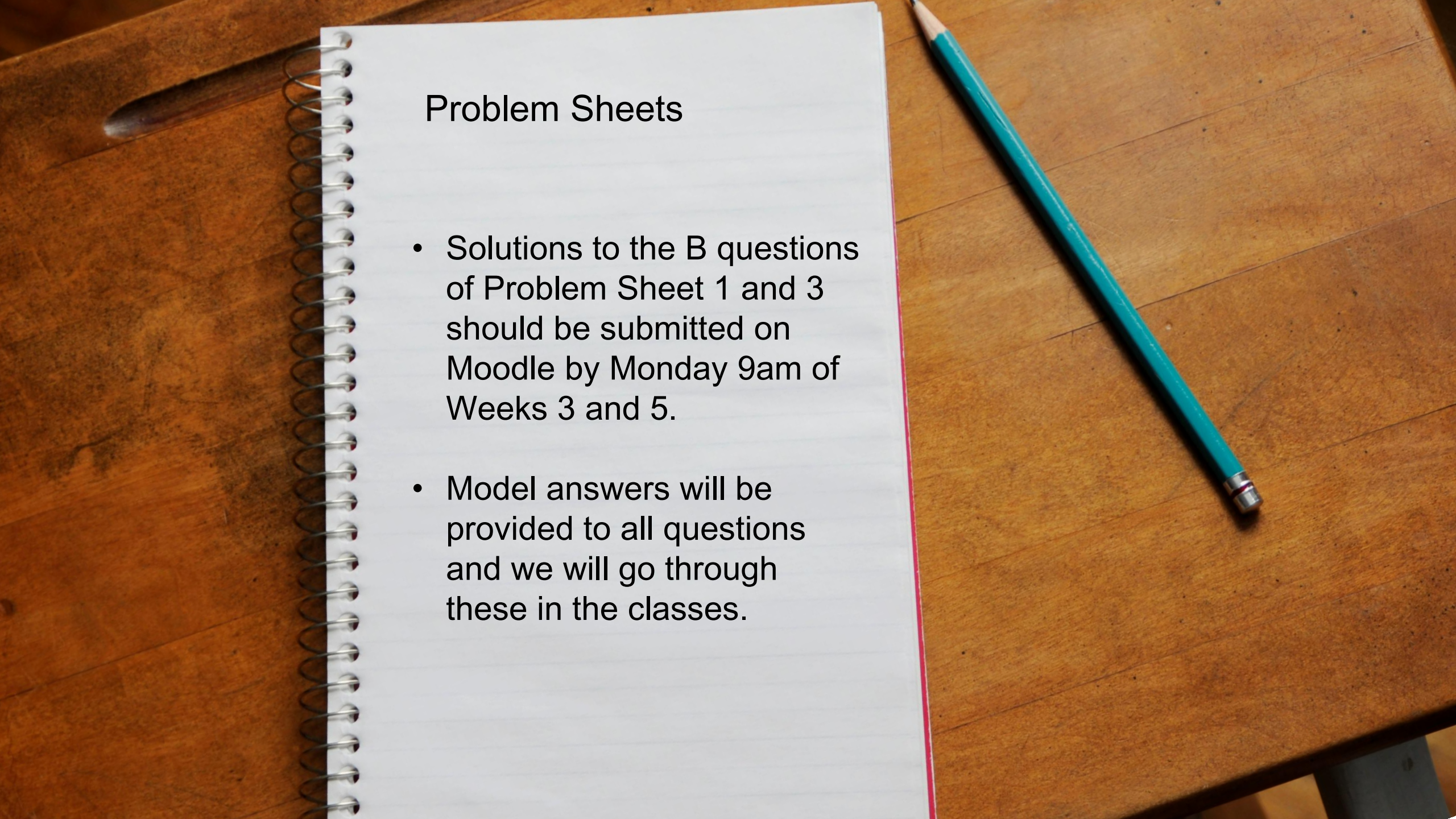
ian.griffiths@maths.ox.ac.uk

Problem Sheet Classes

Class option 1:
Thursday 10:30–12, Weeks 3, 5, 7 and Week 1 Hilary Term classroom C1.

Class option 2:
Friday 11–12:30 Weeks 3, 5, 7 and Week 1 Hilary Term, classroom C6.

Class option 3: Monday 1:30–3 in weeks 4,6,8 and Week 1 Hilary Term, classroom C5.



Problem Sheets

- Solutions to the B questions of Problem Sheet 1 and 3 should be submitted on Moodle by Monday 9am of Weeks 3 and 5.
- Model answers will be provided to all questions and we will go through these in the classes.

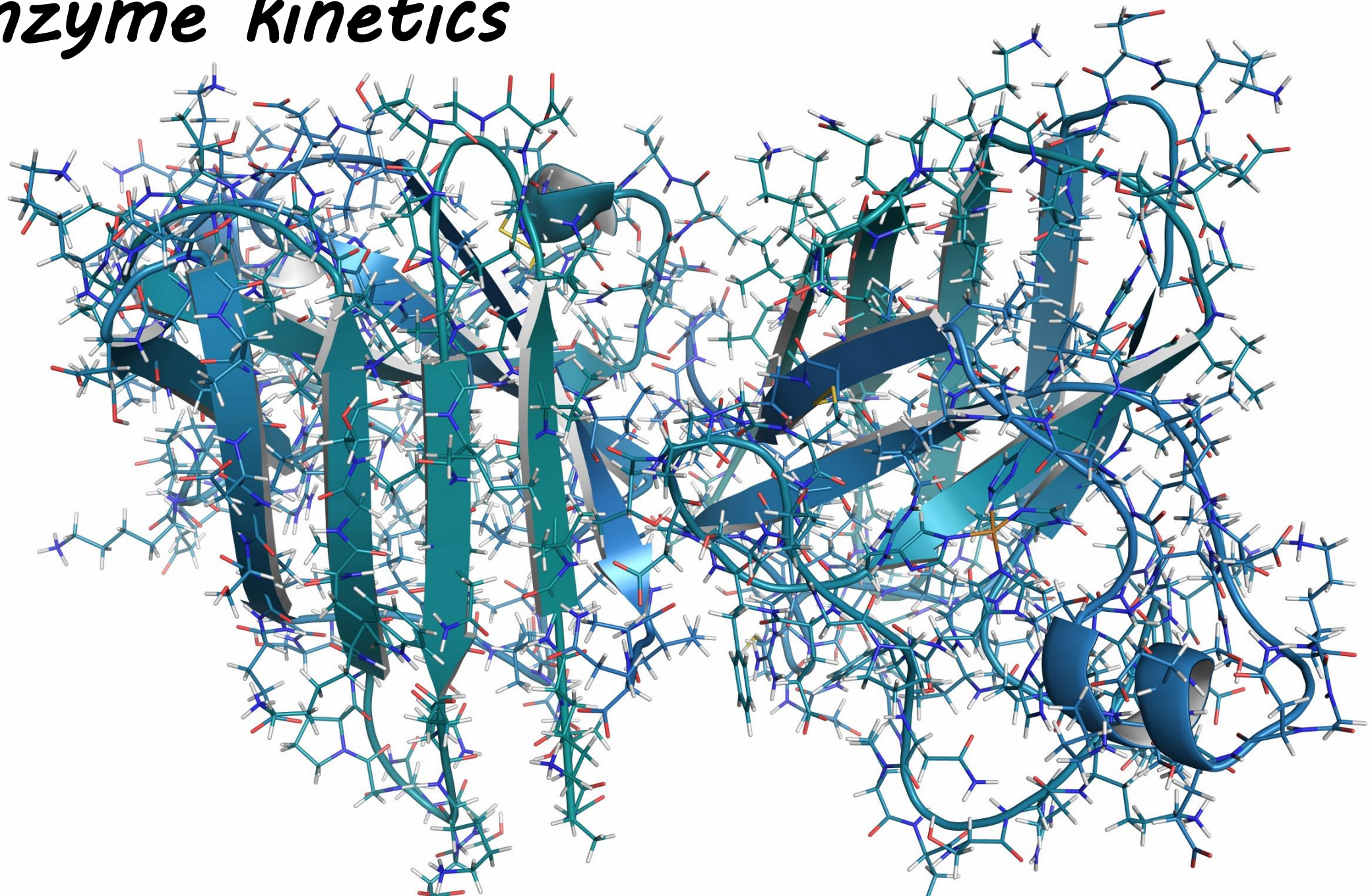
Special Topics

- For those who are attending and need to write a special topic on this course, I have uploaded a list of possible topics.

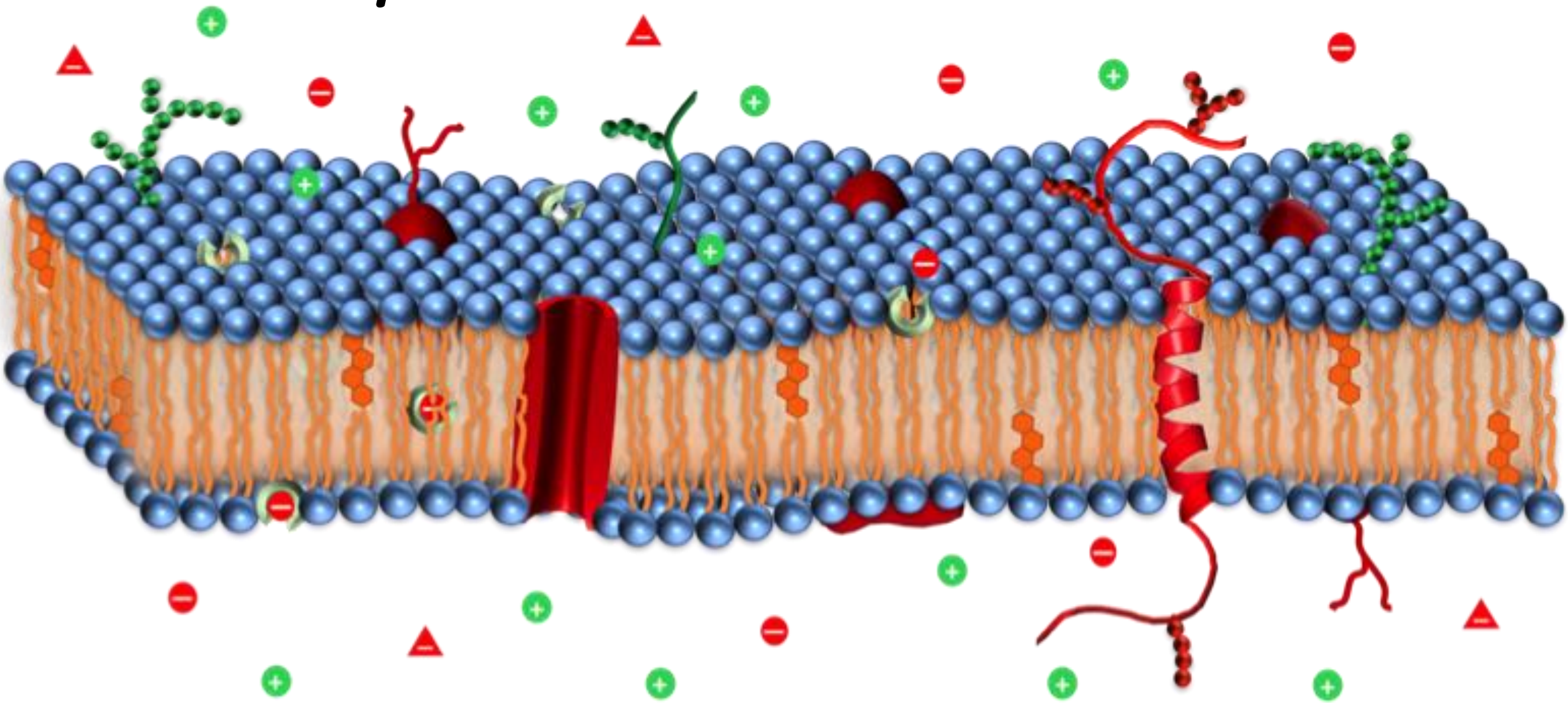
Lectures

- The typeset lecture notes are detailed. But, everything you need will be covered in the lectures. (Sometimes I will point to the lecture notes for an additional proof.)
- The course is a little different to other mathematical courses. Here there will be just as much emphasis on coming up with the appropriate mathematical models as there is on solving them.
- To add a little interest and relevance, we will have some guest appearances from research experts in the field (in brain modelling, calcium dynamics,…).
- I will use a mixture of Powerpoint slides (which will be available on the course website) and writing on the whiteboard.

Enzyme kinetics

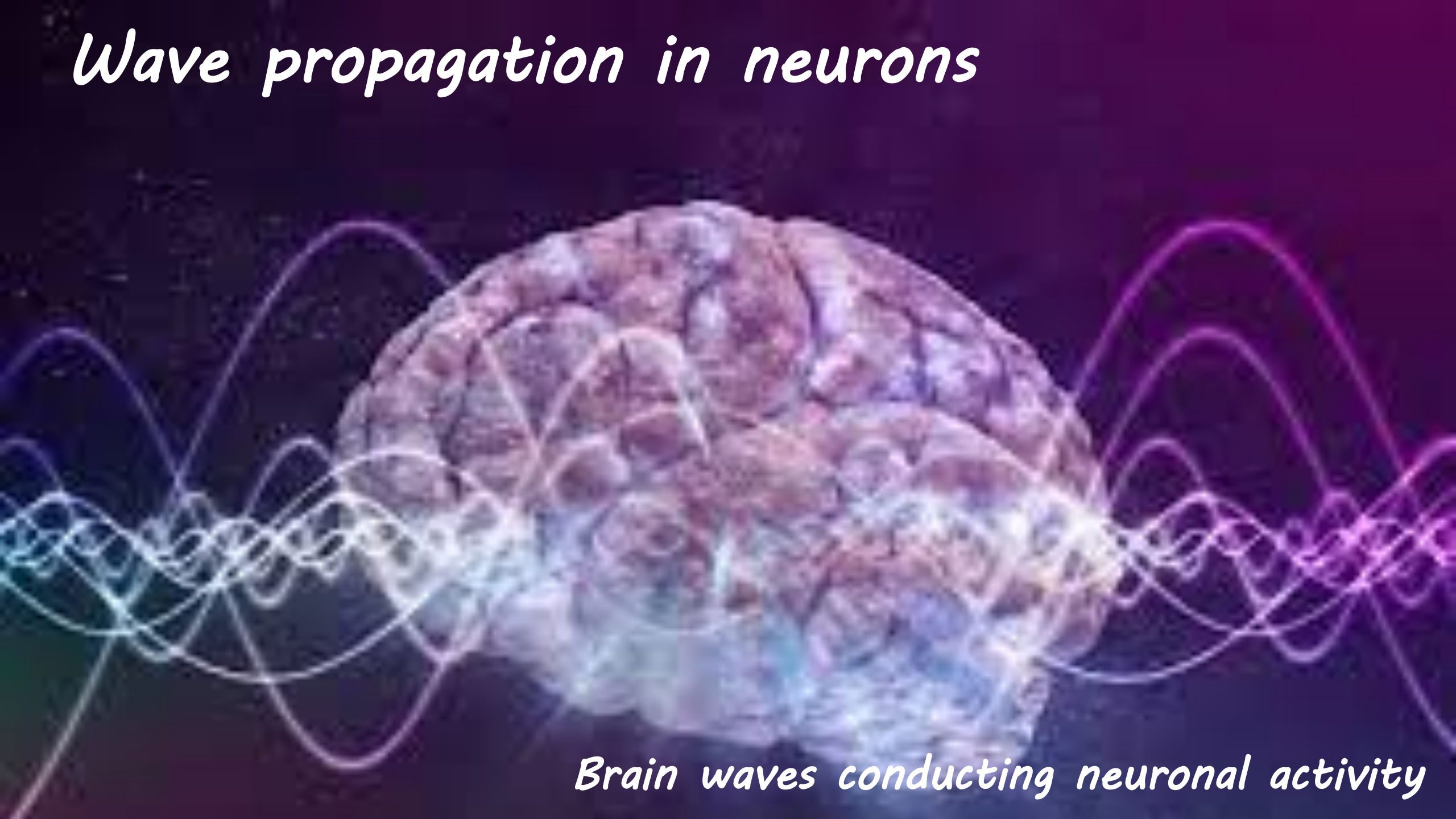


Ion transport



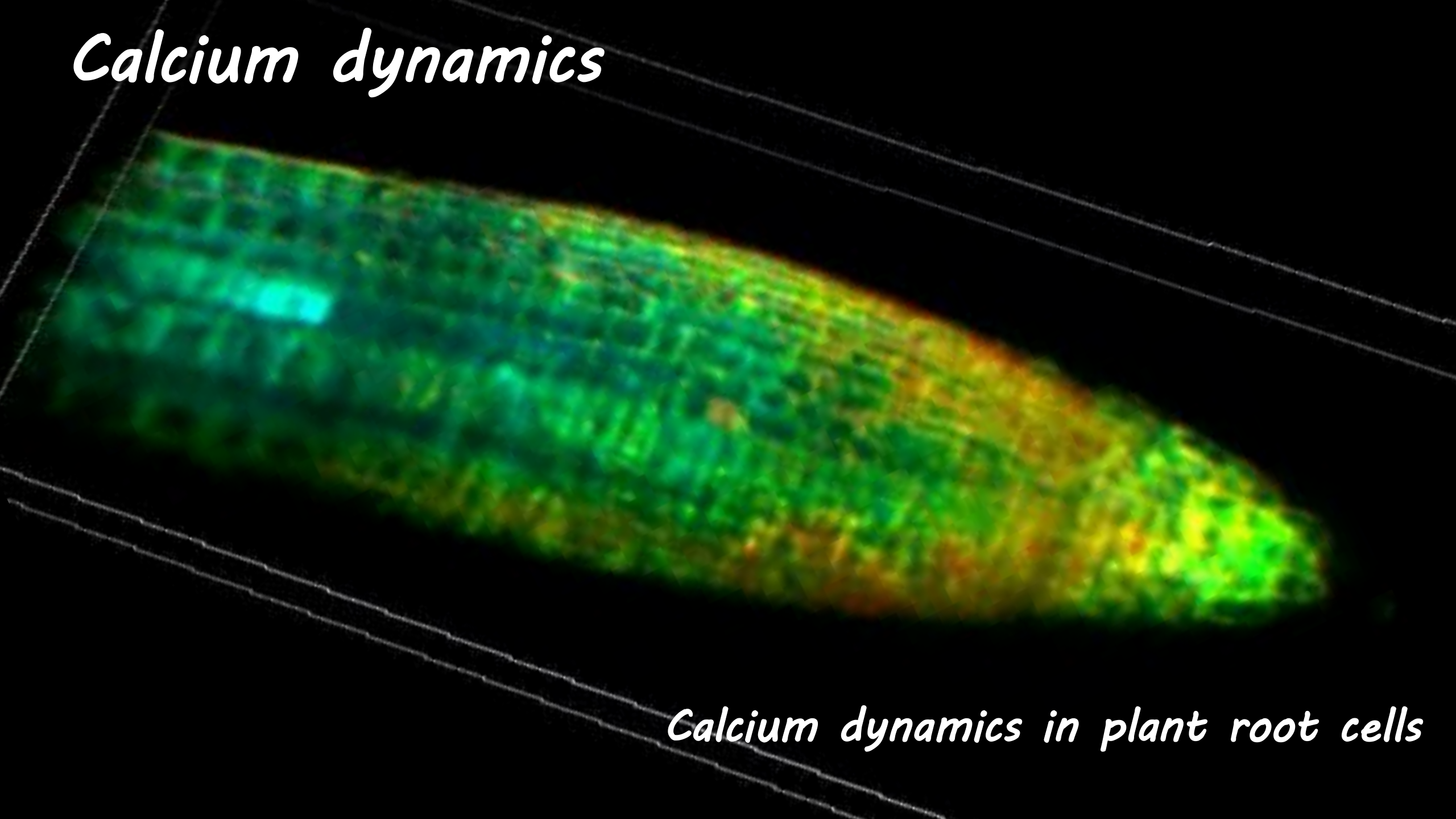
Ion transport across a lipid bilayer

Wave propagation in neurons



Brain waves conducting neuronal activity

Calcium dynamics



Calcium dynamics in plant root cells

Electrochemistry of the heart

The heart as a pump

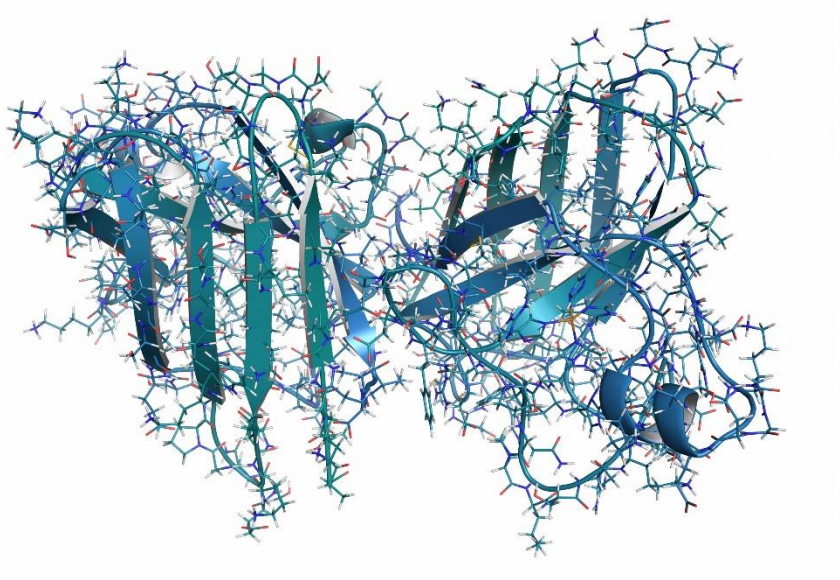
Respiration

PhD opportunity

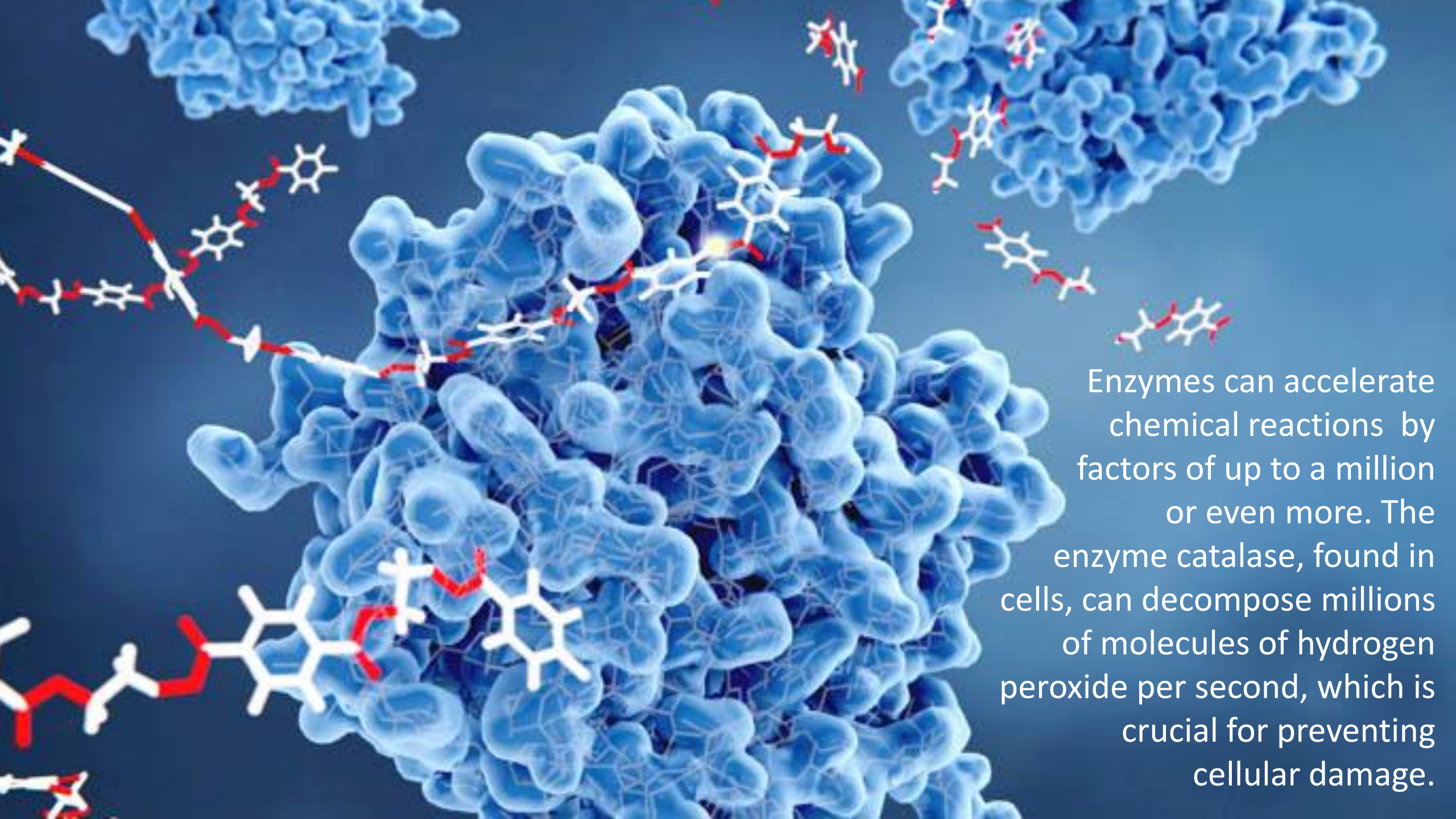
- A PhD scholarship on creating a diagnostic tool for In-Vitro Fertilization is available through the GW4 BioMed Doctoral Training Programme
- Based at Cardiff University Mathematics.
- Supervised by Dr Katerina Kaouri (Mathematics), Prof Karl Swann (Cardiff Biosciences), Prof Krasimira Tsaneva-Atanaseva (Exeter, Living Systems Institute) and Dr Cameron Hall (Bristol, Engineering Mathematics).
- Both home and international students are eligible. The funding is for four years.
- Start date: October 2025
- Deadline: 2nd November 2024.
- *More info and how to apply:* GW4 BioMed2 DTP PhD studentship - Calcium signalling in In-Vitro Fertilization: developing a non-invasive diagnostic tool at Cardiff University on FindAPhD.com
- Contact Dr Katerina Kaouri (kaourik@cardiff.ac.uk) for an informal discussion.

Enzyme kinetics

- Enzymes are catalysts – they help convert other molecules (called substrates) into products but are not used up in the reaction themselves.



- Enzymes are important in a range of biological applications, eg,
  - The digestive system where they help the body break down larger complex molecules into smaller molecules, such as glucose, so that the body can use them as fuel.
  - DNA replication where enzymes help in this process by unwinding the DNA coils.
  - Liver enzymes, which facilitate the process of destroying the toxins.



Enzymes can accelerate chemical reactions by factors of up to a million or even more. The enzyme catalase, found in cells, can decompose millions of molecules of hydrogen peroxide per second, which is crucial for preventing cellular damage.

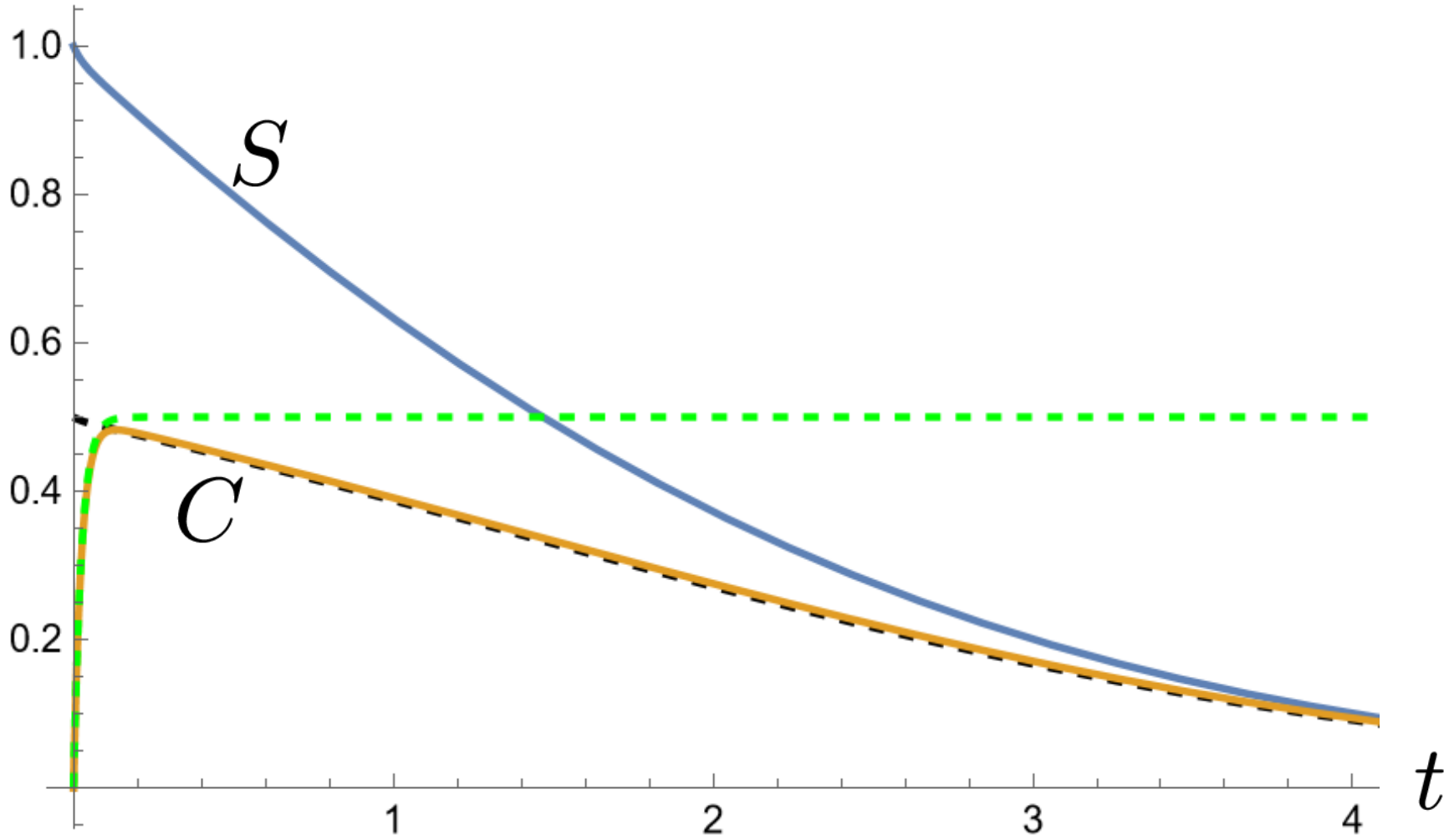
Summary of lecture 1

- An enzyme reaction: $S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + P$

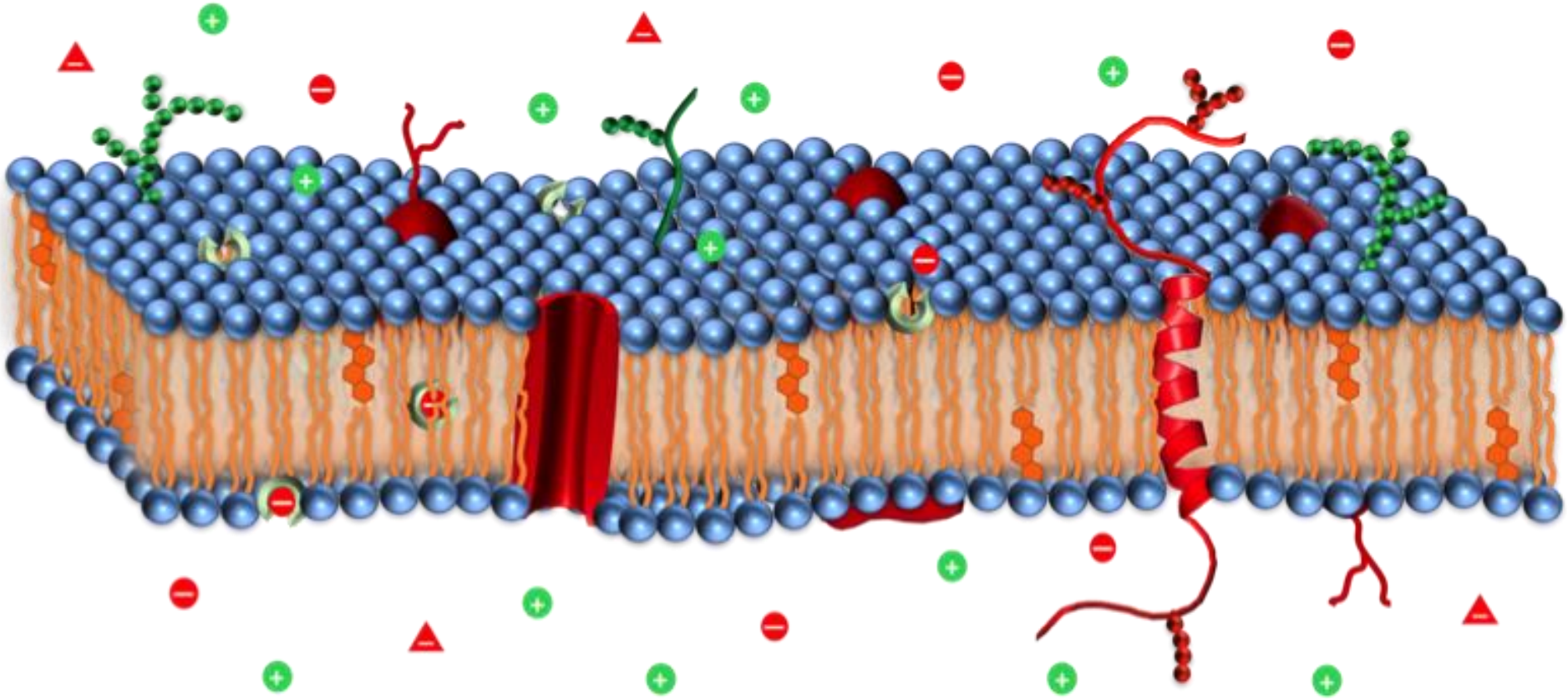
- Michaelis–Menten law: $c = \dfrac{s}{s + K'} \qquad \dfrac{\mathrm{d}s}{\mathrm{d}t} = \dfrac{-\lambda s}{s + K'}$

- Reaction rate: $R = \dfrac{\mathrm{d}P}{\mathrm{d}t} = \dfrac{k_2 E_0 S}{K + S}$

$K = \dfrac{k_{-1} + k_2}{k_1}$ Michaelis constant


1.0
0.8
0.6
0.4
0.2
S
C
1
2
3
4
t

Transmembrane ion transport



Ion transport across a lipid bilayer

- This is important for
  - cellular communication
  - homeostasis
  - energy production

Transmembrane ion transport

- Cells are effectively bags of water.
- The water contains dissolved salts: NaCl and KCl, which dissolve into Na^+, K^+ and Cl^- ions.
- They exist both inside and outside the cell, creating a potential difference.
- The cell walls are permeable – ions may be transported through the cell membrane, passing through pores called channels or gates.
- Osmosis is the mechanism by which water is transported across the cell membrane.

Transmembrane ion transport

- Carrier mediated diffusion – a molecule hitches a lift by binding to a carrier molecule that is lipid soluble and can move through the membrane.

- Carrier mediated transport – a molecule binds to a protein that has an active site that may be exposed to the interior or exterior of the cell (e.g., glucose or amino acid transport).

- Pumps – these exchange one ion for another, e.g., Na^+ for K^+ or Na^+ for Ca^{2+}.

A model for carrier mediated transport

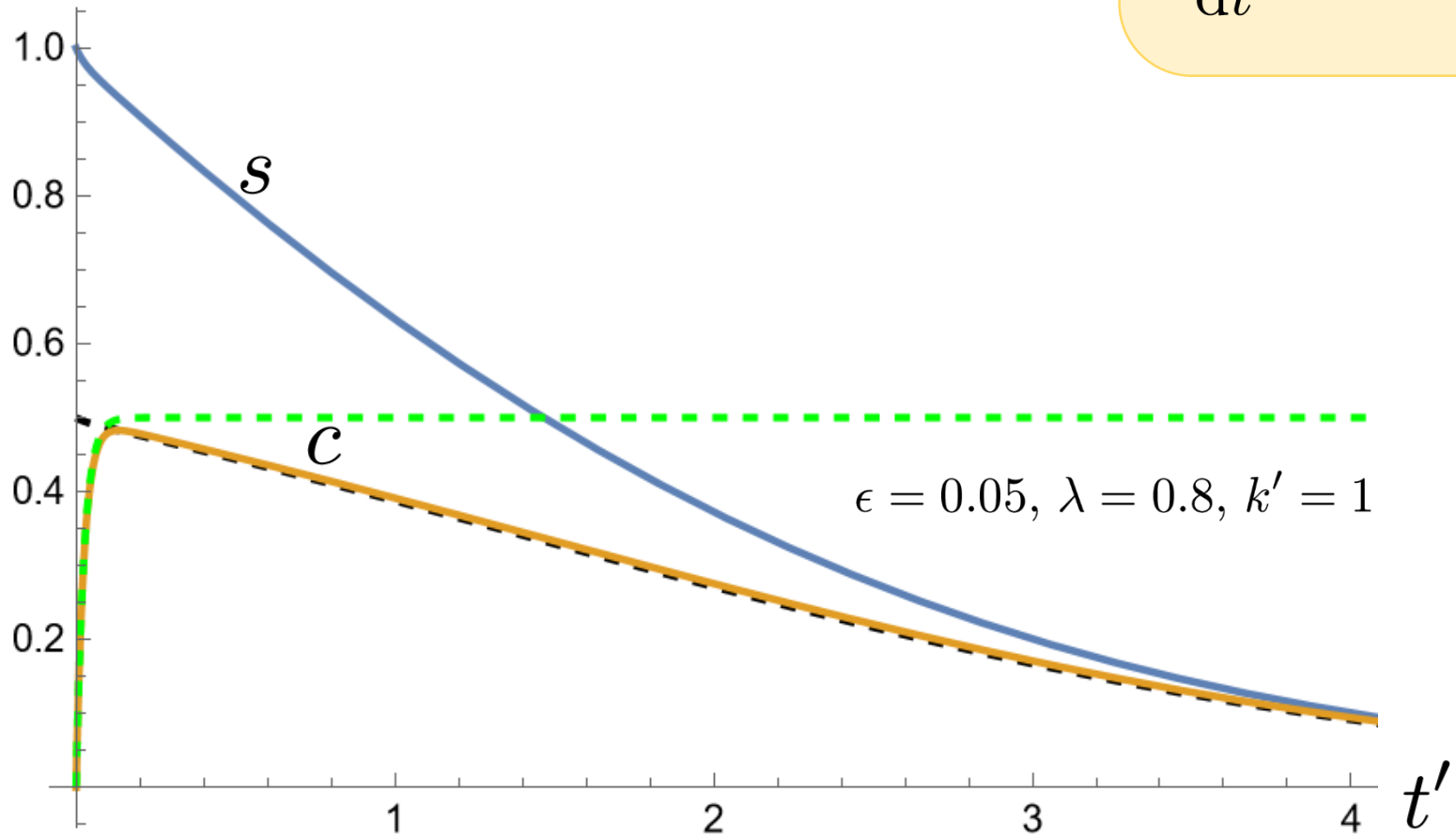
- C_i = a state with a binding site exposed to the interior.
- C_e = a state with a binding site exposed to the exterior.
- C_e can bind with a substrate molecule in the exterior S_e to make a product P_e.
- C_i can bind with a substrate molecule in the interior Si to make a product P_i (with the same rates as the exterior).
- P_i can turn into P_e . This is the carrier doing its ‘rotation’.
- C_i can turn into C_e. This is the carrier site rotating without any substrate on it. We assume this occurs at the same rate as the rotation with substrate on it.

Summary of lecture 2

- An enzyme reaction: $S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + P$

$$\frac{\mathrm{d}s}{\mathrm{d}t'} = -s + c(s + k' - \lambda)$$

$$\epsilon \frac{\mathrm{d}c}{\mathrm{d}t'} = -s - (s + k')c$$



Carrier-mediated transport

An ODE model for carrier-mediated transport tells us the rate at which ions can be transferred from the outside of the membrane to the inside in steady state.

Proteins in carrier-mediated transport are so selective they can distinguish between almost identical molecules: the glucose transporter can transport glucose but not fructose. This high level of selectivity is critical in ensuring that essential molecules are transported accurately to support physiological processes.

20–40% of all energy expended by the human brain is used to operate the sodium–potassium pump. This makes it one of the most energy-consuming processes in the body and highlights its importance for brain function.

Summary of lecture 3

- Active transport involves moving molecules against concentration gradients. This requires energy.

- Ions will move across a membrane wall to balance concentration. However, this might lead to a difference in charge. The system reaches an equilibrium when the diffusive flux balances the ionic flux.

- This occurs at the Nernst potential:

$$V_S = \frac{RT}{zF} \ln\left(\frac{c_e}{c_i}\right)$$

- We can write an equation for ionic currents:

$$C\frac{dV}{dt} + I = 0.$$

- The current is given by a sum of the individual ionic currents, I_S:

$$I = \sum_S I_S \qquad\qquad I_S = g_S(V - V_S)$$

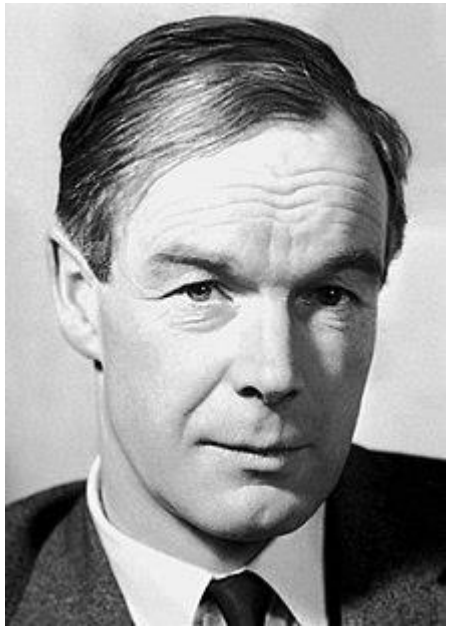
- The conductivities g_s are related to the fraction of gates that are open, n:

$$g_s = n g_{s,max}$$

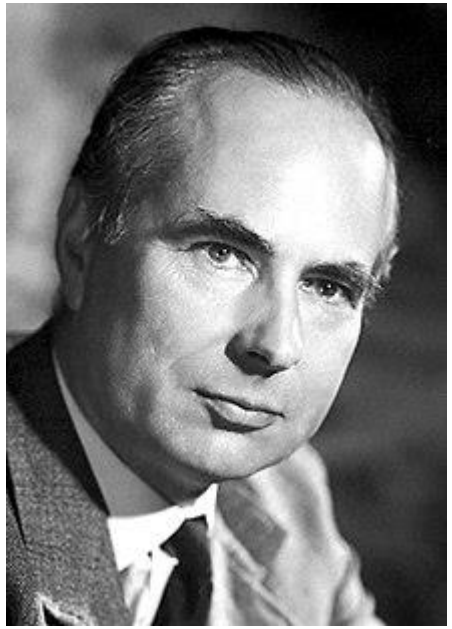
- n satisfies a gate equation:

$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n$$

The Hodgkin–Huxley model



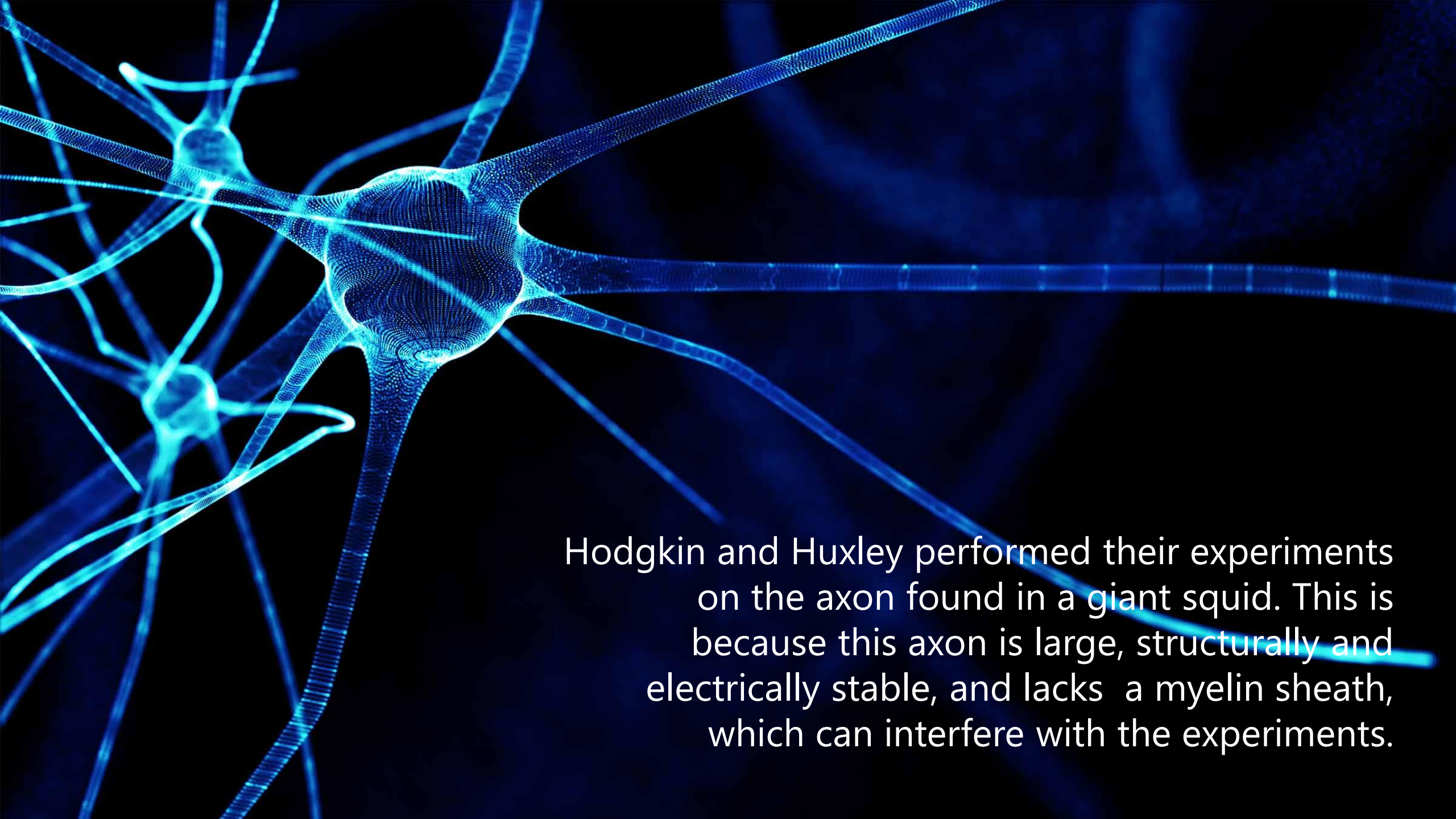
Alan Lloyd Hodgkin
1914–1998



Andrew Huxley
1917–2012

The Hodgkin–Huxley model

- The nervous system is a communication system formed by nerve cells or neurons.
- Information is propagated along long cylindrical segments called axons by electrochemical signals.
- Communication between cells occurs at junctions between synapses to the dendrites.
- If a small current is applied for a short time the membrane potential simply returns to its resting potential when the current is removed.
- But for a sufficiently high current, the membrane potential undergoes a large excursion – an action potential – before returning to its resting value.
- Signals are transmitted by the propagation of these action potentials.



Hodgkin and Huxley performed their experiments on the axon found in a giant squid. This is because this axon is large, structurally and electrically stable, and lacks a myelin sheath, which can interfere with the experiments.

Some ion channel gates
can open and close incredibly quickly,
with time scales measured in microseconds
(millionths of a second) or even faster. This
rapid gating is particularly important in
muscle contractions.

Summary of lecture 4

- The Hodgkin–Huxley model is

$$C_m \frac{dV}{dt} = I - I_i$$

$$\tau_n(V) \frac{dn}{dt} = n_\infty(V) - n$$

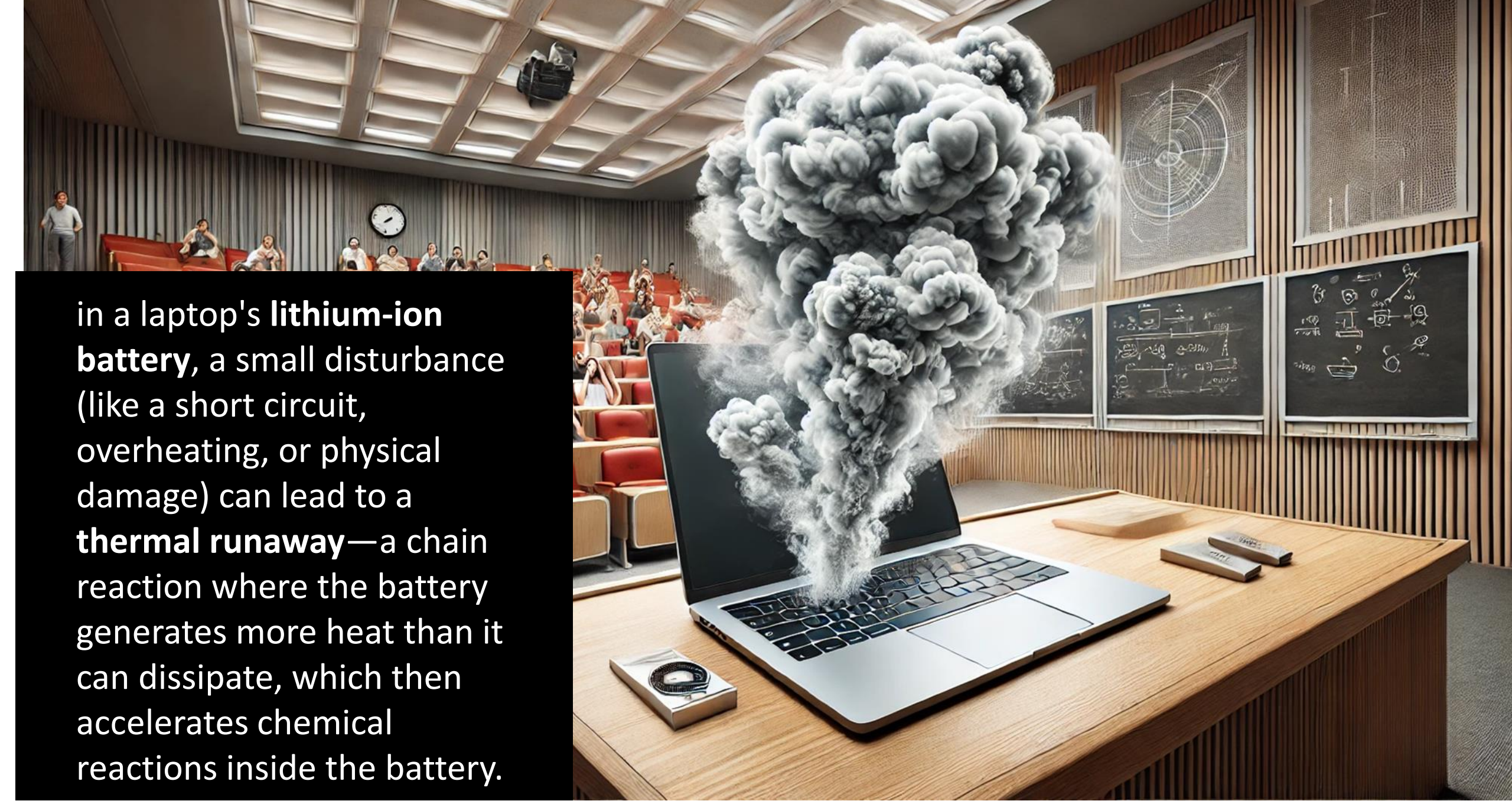
$$\begin{aligned} \tau_m(V) \frac{dm}{dt} &= m_\infty(V) - m, \\ \tau_h(V) \frac{dh}{dt} &= h_\infty(V) - h. \end{aligned}$$

$$I_i = \underbrace{g_{\mathrm{Na}} m^3 h (V - V_{\mathrm{Na}})}_{\mathrm{Na}^+ \text{ current}} + \underbrace{g_{\mathrm{K}} n^4 (V - V_{\mathrm{K}})}_{\mathrm{K}^+ \text{ current}} + \underbrace{g_L (V - V_{\mathrm{L}})}_{\text{leakage}},$$

- This allows for excursions – the action potential.

Happy Halloween!

When you get a fright during Halloween, your brain's neurons release dopamine. This surge in dopamine is part of the brain's response to stress and can contribute to the exhilaration and adrenaline rush that many people enjoy during spooky Halloween events.



in a laptop's **lithium-ion battery**, a small disturbance (like a short circuit, overheating, or physical damage) can lead to a **thermal runaway**—a chain reaction where the battery generates more heat than it can dissipate, which then accelerates chemical reactions inside the battery.

Summary of lecture 5

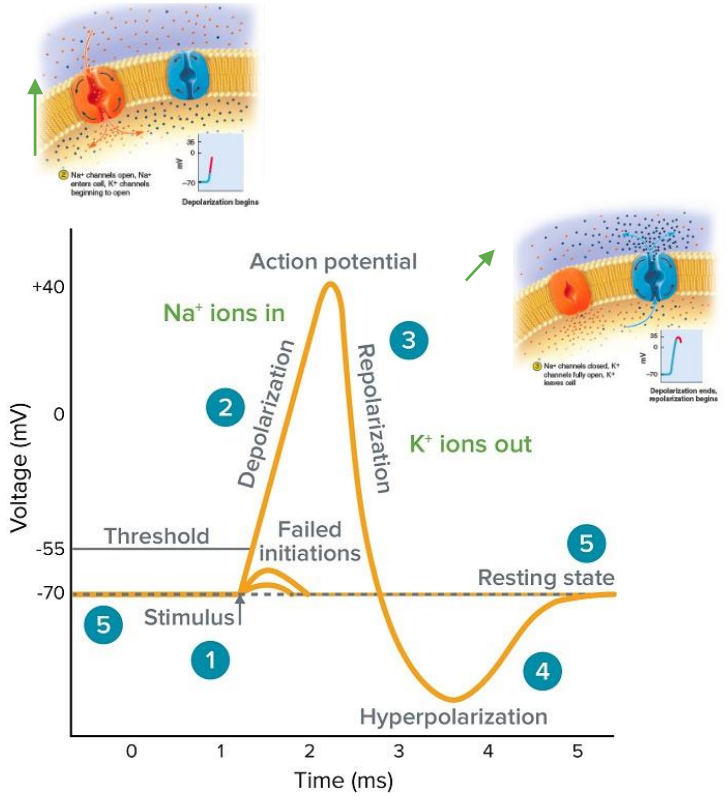
- The Hodgkin–Huxley model comprises four ODEs for four unknowns.
- This allows for excursions – the action potential.
- We may simplify the problem to two ODES for two unknowns. This is called the FitzHugh–Nagumo model.
- This enables phase-plane analysis that allows us to visualize the action potential.

From model to measurement and intervention

Malin I. Karstens (DPhil in Experimental Psychology)
Malin.karstens@psy.ox.ac.uk

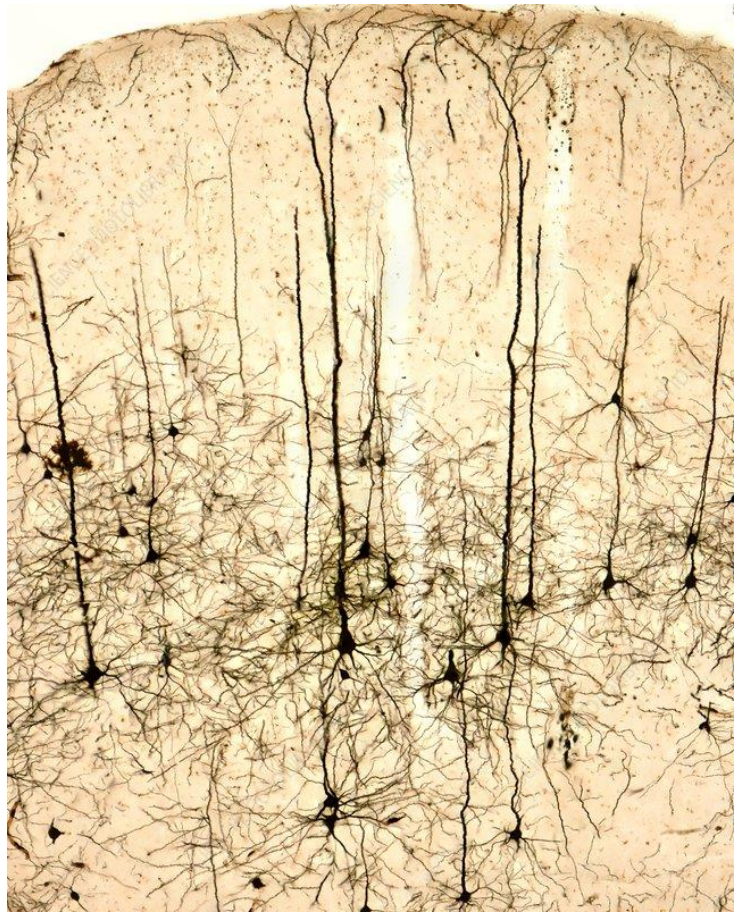
Action potentials

- Action potentials (AP's) are the rapid rise and falls of a neuron's membrane potential
- AP's travel through a neuron and cause more APs in adjacent neurons
- This happens via opening and closing of voltage gated ion channels (modelled by Hodgkin & Huxley, 1952)

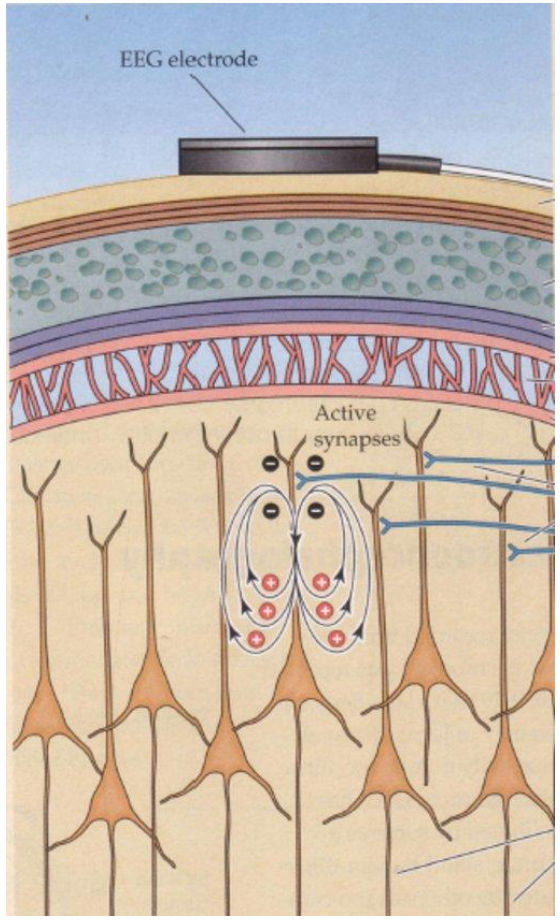


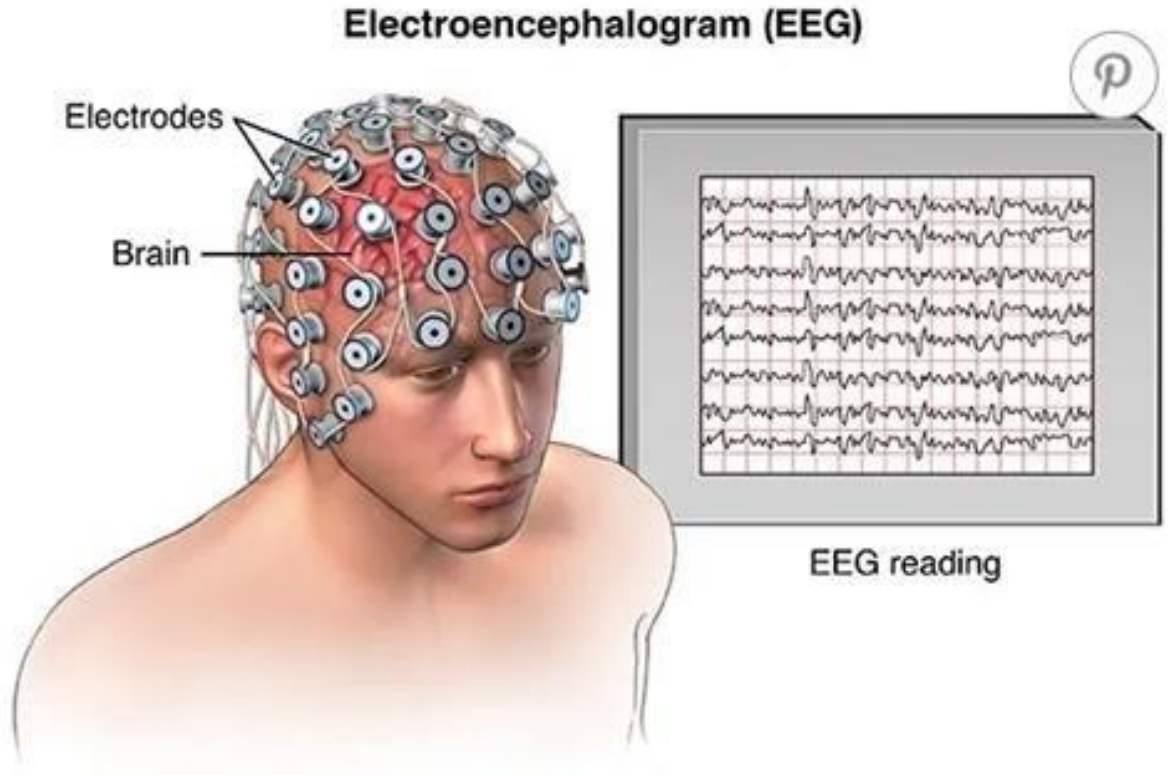
What fires together wires together

- Of particular interest are clusters of neurons
- We can measure membrane potentials when they co-occur in multiple cells close by (event related potentials)
- We can also measure periodic activity in these so-called networks (oscillations)



Electroencephalography (EEG)

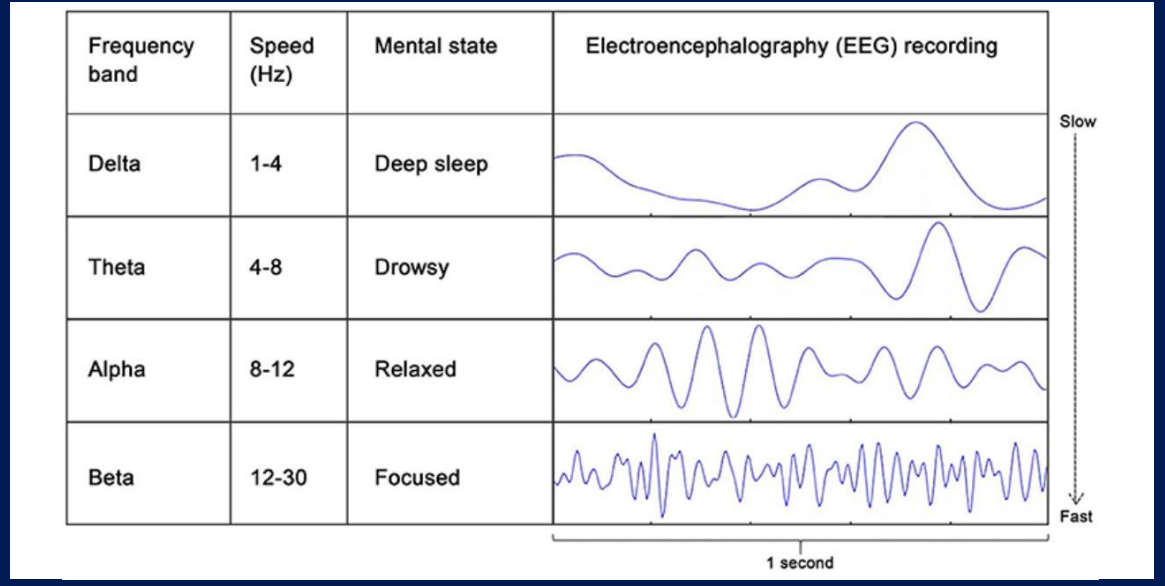


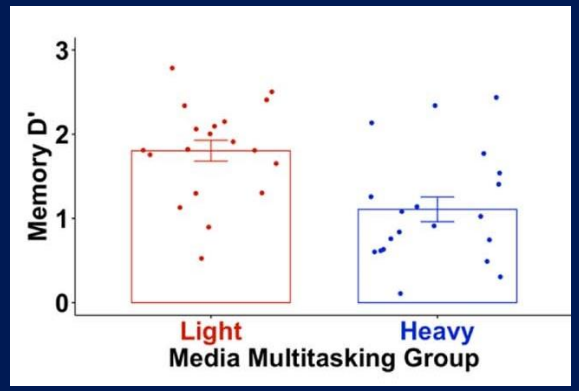


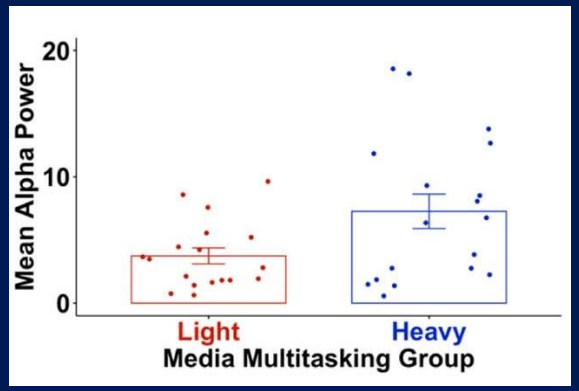
EEG measures

Oscillations

Frequency band	Speed (Hz)	Mental state	Electroencephalography (EEG) recording
Delta	1-4	Deep sleep	
Theta	4-8	Drowsy	
Alpha	8-12	Relaxed	
Beta	12-30	Focused	



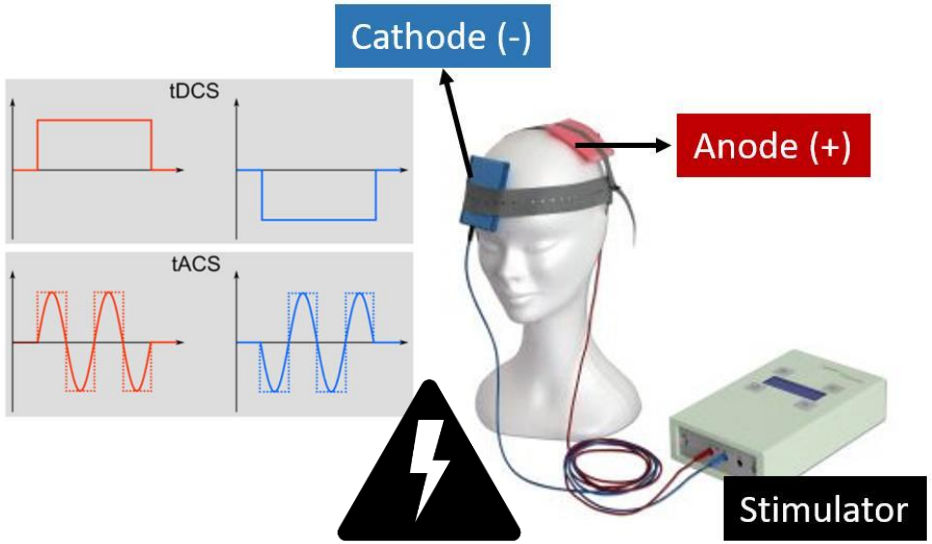




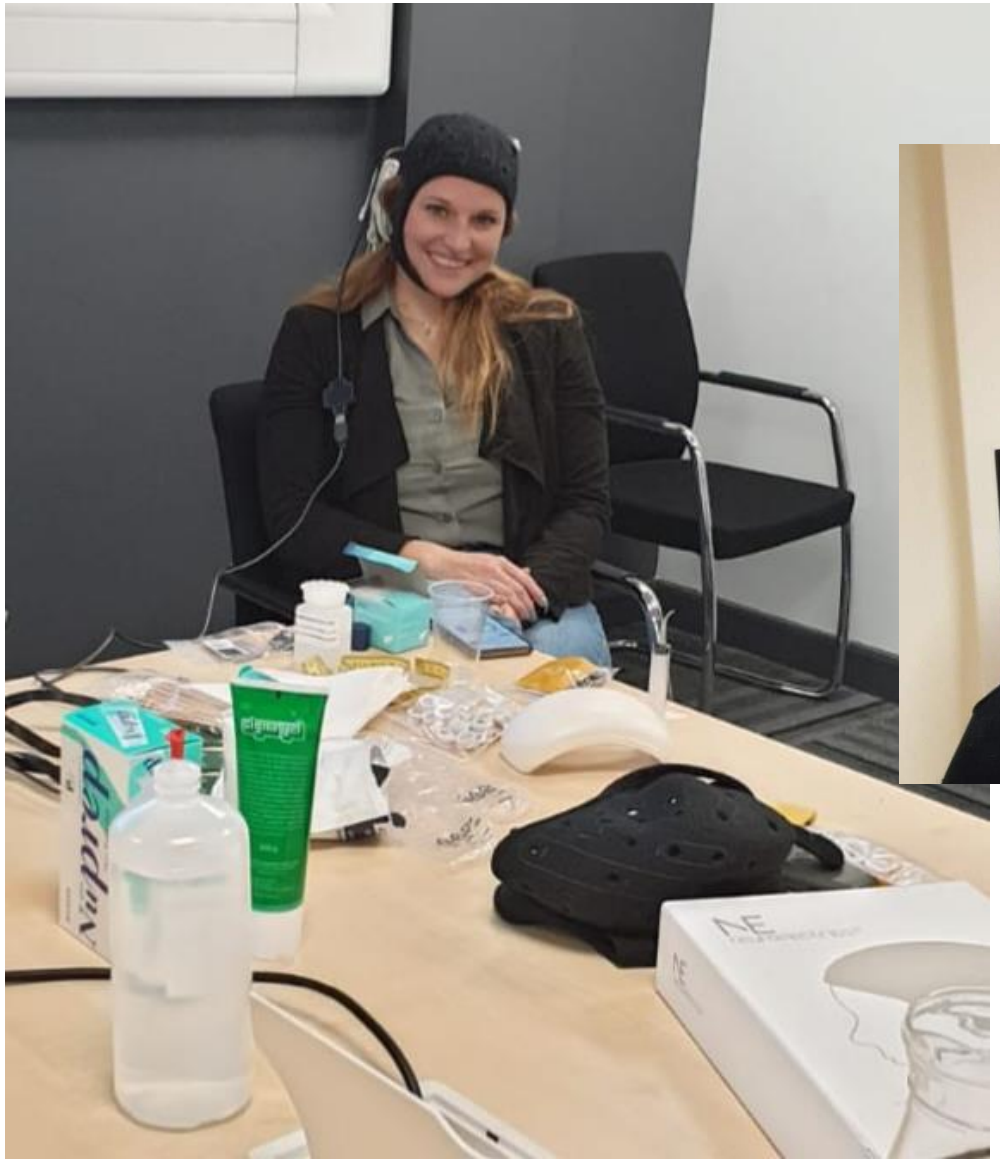
Intervention

- There are various methods for intervention of neural firing in the cortex and in deeper structures of the brain (chemical, magnetic, ultrasound, etc.)

Transcranial Electrical Stimulation (tES)

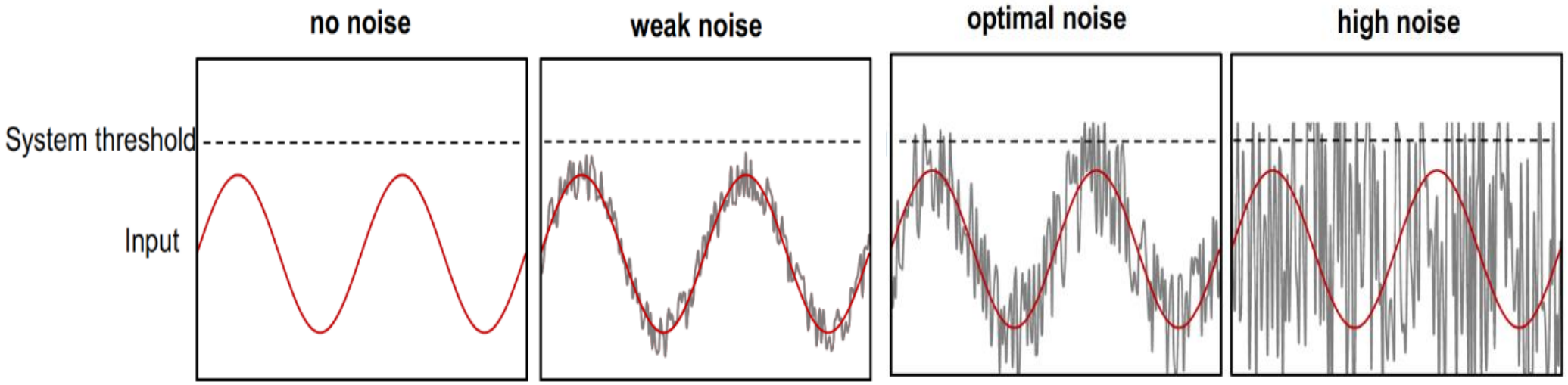


The experimental set-up



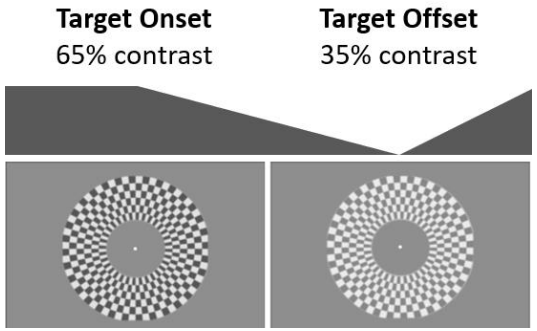
Transcranial Random Noise Stimulation (tRNS)

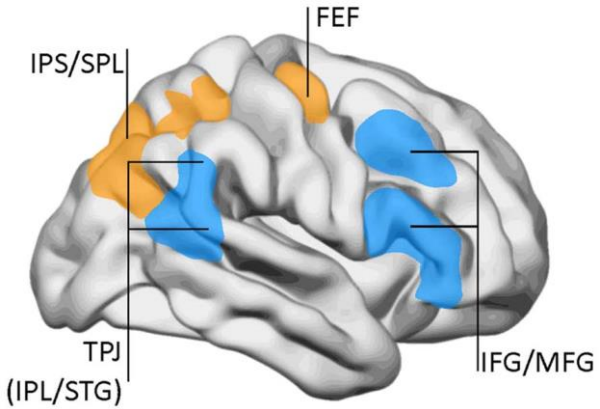
- High frequency noise (~ white noise) enhancing cortical activity in a state-dependent manner (stochastic resonance)

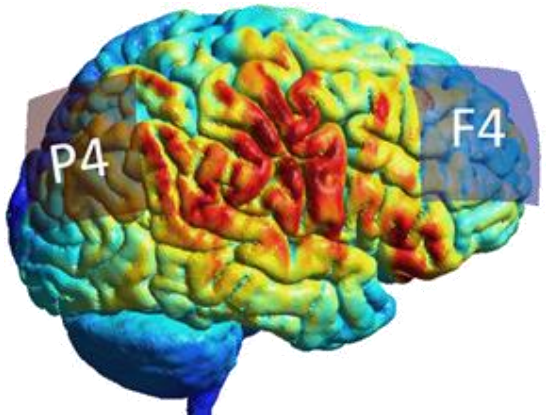


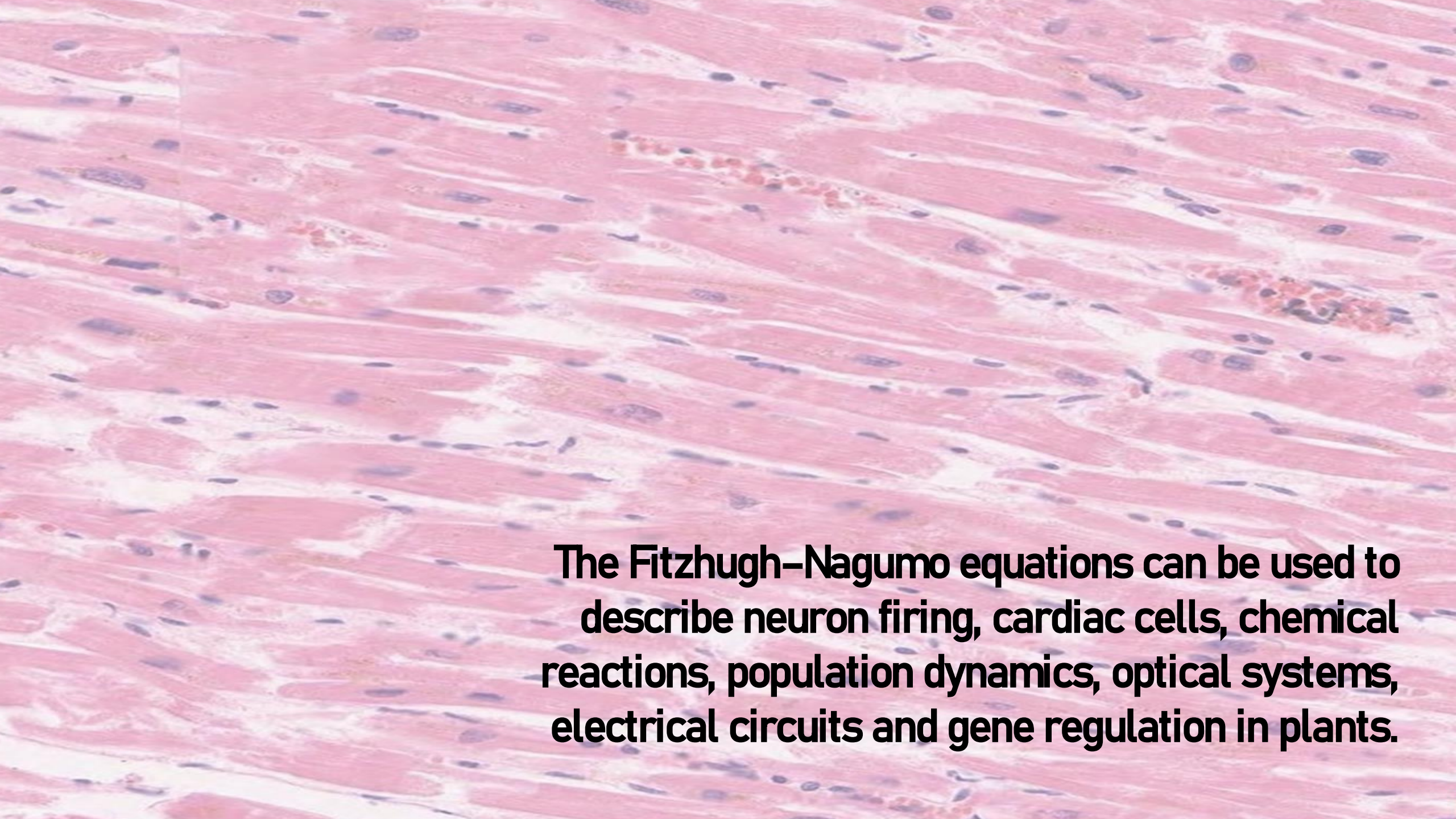
Behaviour

- Sustained attention: Maintaining attention over long periods of time associated with right frontoparietal activity








The Fitzhugh–Nagumo equations can be used to describe neuron firing, cardiac cells, chemical reactions, population dynamics, optical systems, electrical circuits and gene regulation in plants.

https://www.nikonsmallworld.com/galleries/2023-small-world-in-motion-competition/developing-neurons-connecting-the-opposite-side-of-the-central-nervous-system

Summary of lecture 6

- The FitzHugh–Nagumo model

$$\epsilon \dot{v} = I^* - g(v, n)$$

$$\dot{n} = n_\infty(v) - n$$

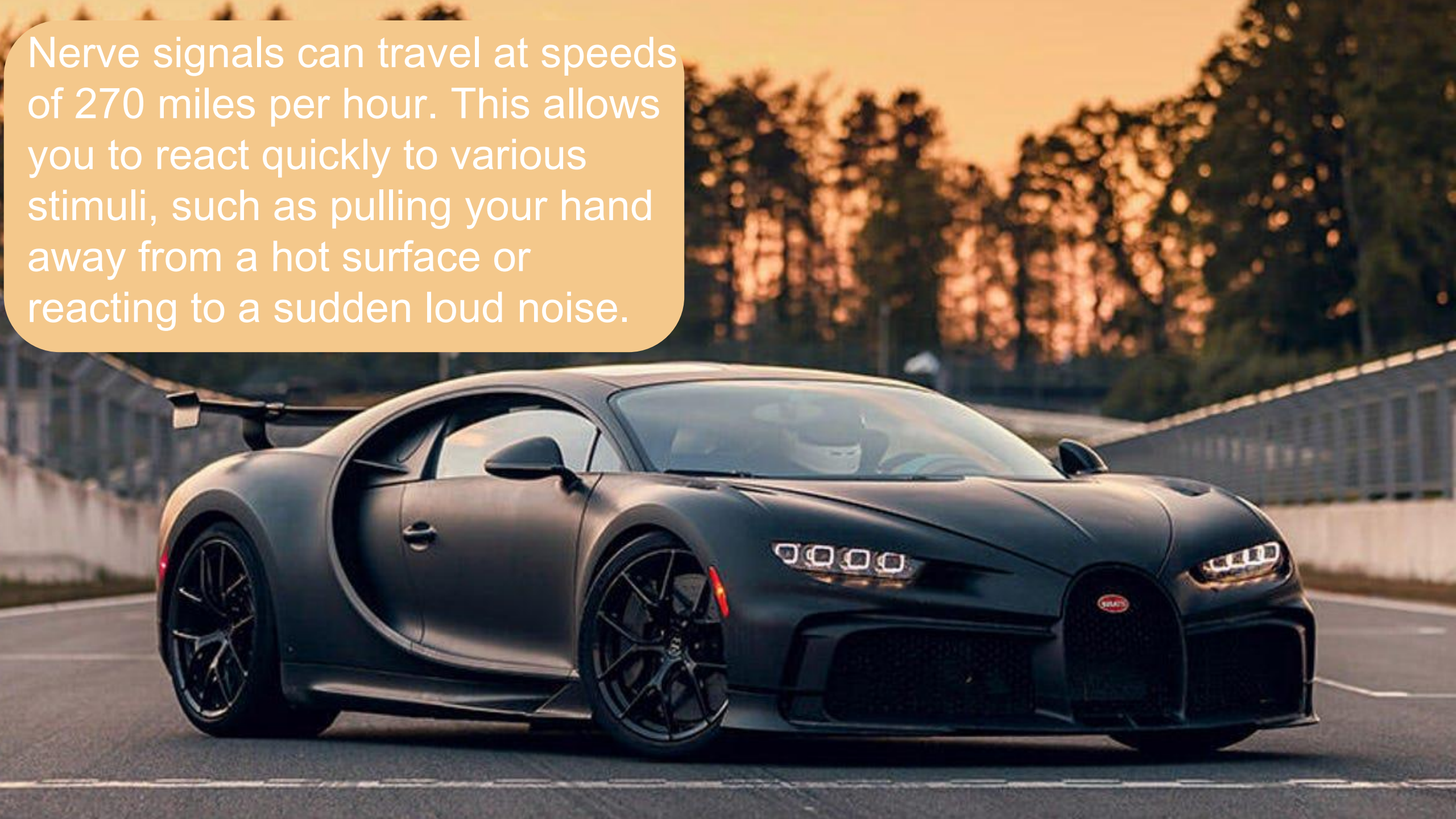
- The FitzHugh–Nagumo equations

$$\dot{w} = \gamma v - w$$

$$\epsilon \dot{v} = I^* + f(v) - w$$

$$f(v) = v(v - a)(1 - v) \qquad 0 \leq a \leq 1$$

- `Malin Karstens' talked about her work on brain stimulation and its relation to the Hodgkin – Huxley model.



Nerve signals can travel at speeds of 270 miles per hour. This allows you to react quickly to various stimuli, such as pulling your hand away from a hot surface or reacting to a sudden loud noise.

Summary of lecture 7

- We looked at the spatial version of the Fitzhugh–Nagumo equations

$$\epsilon \frac{\partial v}{\partial t} = f(v) - w + \epsilon^2 \frac{\partial^2 v}{\partial x^2} \qquad f(v) = v(v-1)(1-v)$$

$$\frac{\partial w}{\partial t} = \gamma v - w$$

- Hodgkin – Huxley video: https://www.youtube.com/watch?v=zOmhHE2xctw&ab_channel=ArtemKirsanov

Calcium dynamics

- Calcium (Ca^{2+}) is important in muscle dynamics and cell signalling.
- Ca^{2+} is stored in cells in bones and released by hormonal stimulation. The internal store is called the sarcoplasmic reticulum.
- It releases Ca^{2+} via calcium induced calcium release.
- The intracellular fluid matrix is called the sarcoplasm.
- Extracellular Ca^{2+} concentrations are higher than intracellular concentrations so Ca^{2+} must be pumped out.
- Muscle cells are bundles (fascicules) of muscle fibres (cells) each of which contains arrays of filament structures (microfibrils) which contract under the action of Ca^{2+}.

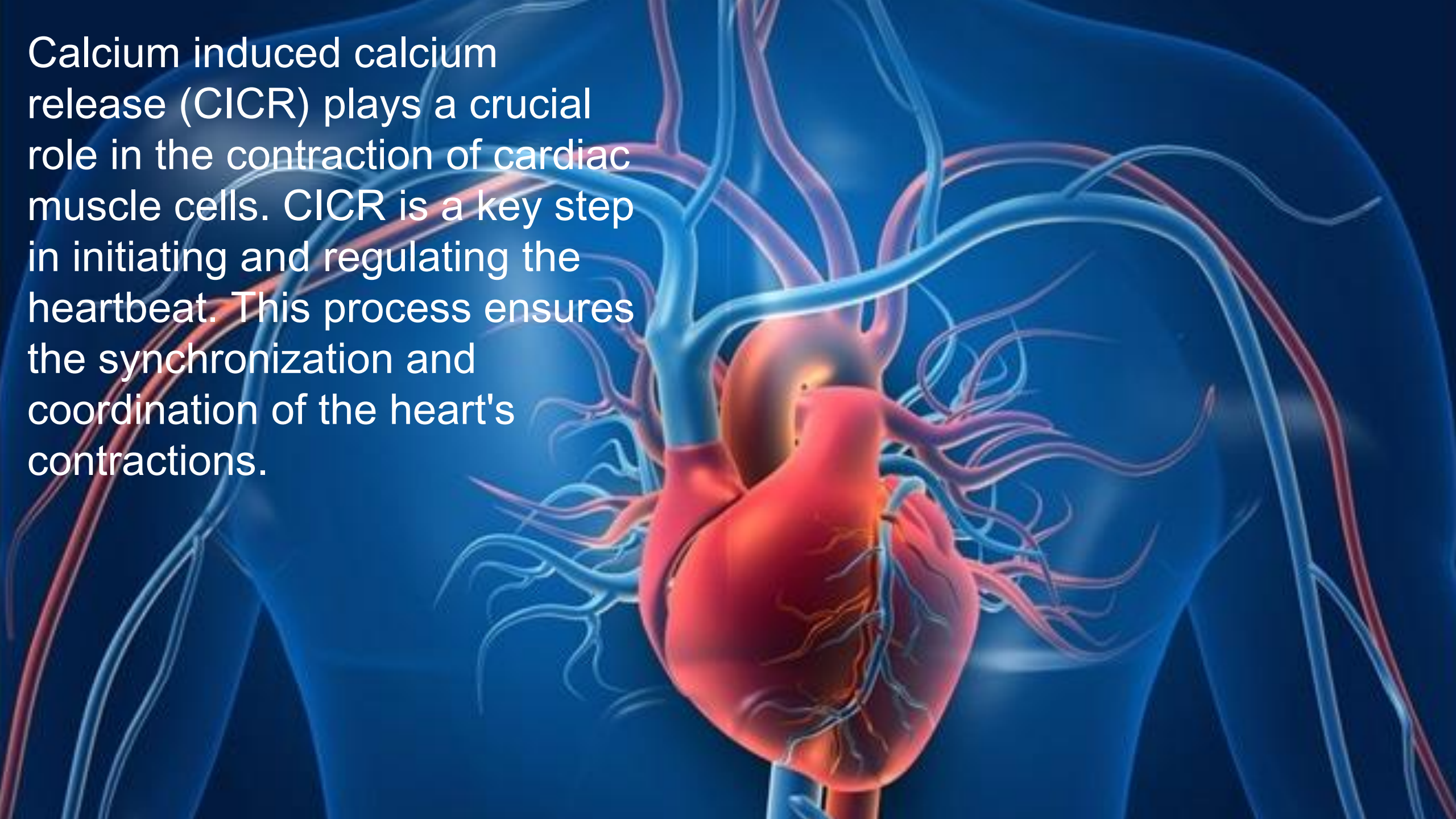
Calcium dynamics

- Under stimulation from a nerve cell, an action potential is triggered and propagates along the fibre (as we have seen last lecture).
- Na^+ floods in and this allows Ca^{2+} in too.
- The release of Ca^{2+} is quite spiky.

Can we derive a mathematical model for muscle contraction with a low Ca^{2+} concentration in steady state that is excitable under stimulus?

The two pool model

- We want to derive a model to explain how Ca^{2+} moves between the sarcoplasmic reticulum (the store) and the sarcoplasm.
- C = concentration of Ca^{2+} in the sarcoplasm.
- C_s = concentration of Ca^{2+} in the sarcoplasmic reticulum (SR).
- J_+ = rate of take up of Ca^{2+} by the sarcoplasmic reticulum (by receptors) [active uptake].
- J_- = rate at which the SR releases its internal store (calcium induced calcium release) [active release].
- r = influx of Ca^{2+} into the sarcoplasm from the outside world because of an applied stimulus.
- k_sC_S = rate of leakage of Ca^{2+} from SR into the sarcoplasm [passive – proportional to concentration].
- kC = rate of leakage of Ca^{2+} from sarcoplasm to outside world [passive –proportional to concentration].



Calcium induced calcium release (CICR) plays a crucial role in the contraction of cardiac muscle cells. CICR is a key step in initiating and regulating the heartbeat. This process ensures the synchronization and coordination of the heart's contractions.

Summary of lecture 8

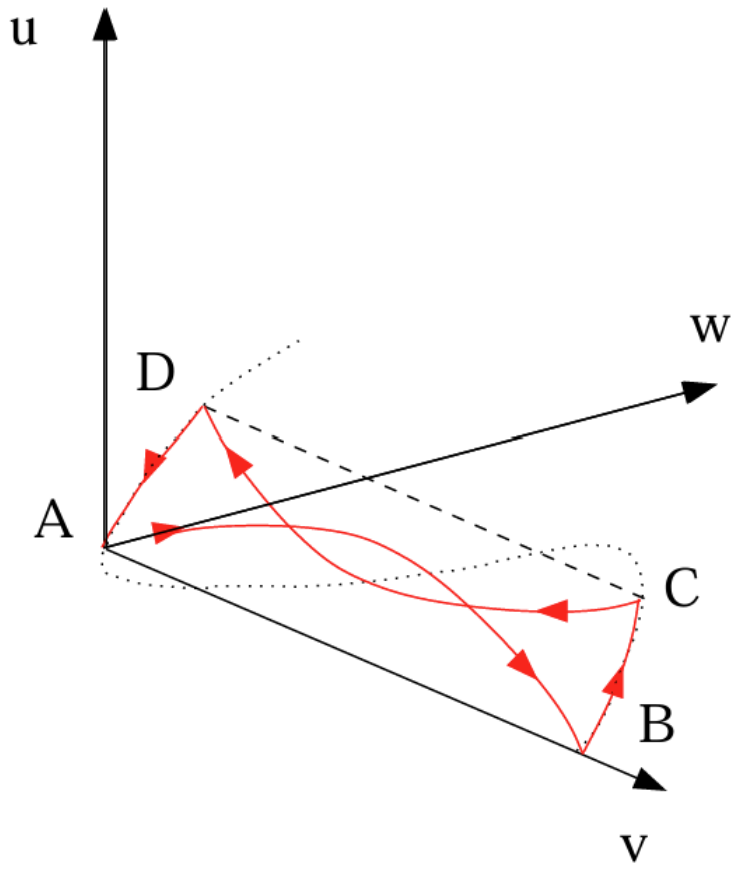
- We looked at travelling wave solutions of the Fitzhugh–Nagumo equations:

$$v = v(\xi) \qquad \xi = ct - x$$

$$cv' = f(v) - w + v''$$

$$cw' = \epsilon(\gamma v - w)$$

$$f(v) = v(v-1)(1-v)$$



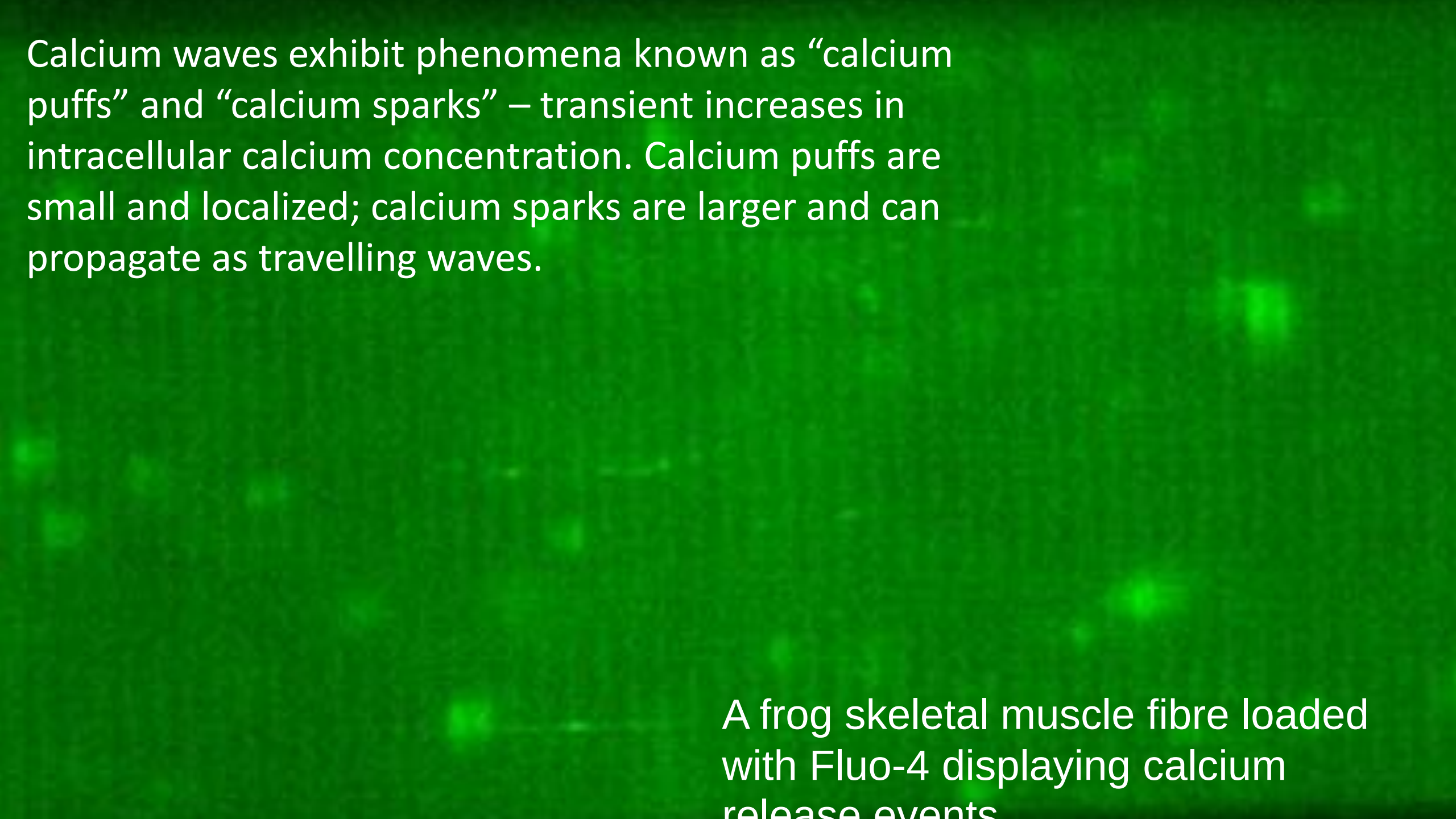
VisualPDE simulation of Fitzhugh-Nagumo excursion

- https://canary.visualpde.com/sim/?preset=FNWaves)

- Click a little bit, the peak relaxes down. Click for longer, the peak becomes an action potential that then travels through the domain.

- If you go to the top-right corner -> Domain -> Dimension 2, then you get exactly the same phenomenon in 2D, with the waves now being circular.

Calcium waves exhibit phenomena known as “calcium puffs” and “calcium sparks” – transient increases in intracellular calcium concentration. Calcium puffs are small and localized; calcium sparks are larger and can propagate as travelling waves.



A frog skeletal muscle fibre loaded with Fluo-4 displaying calcium release events

Summary of lecture 9

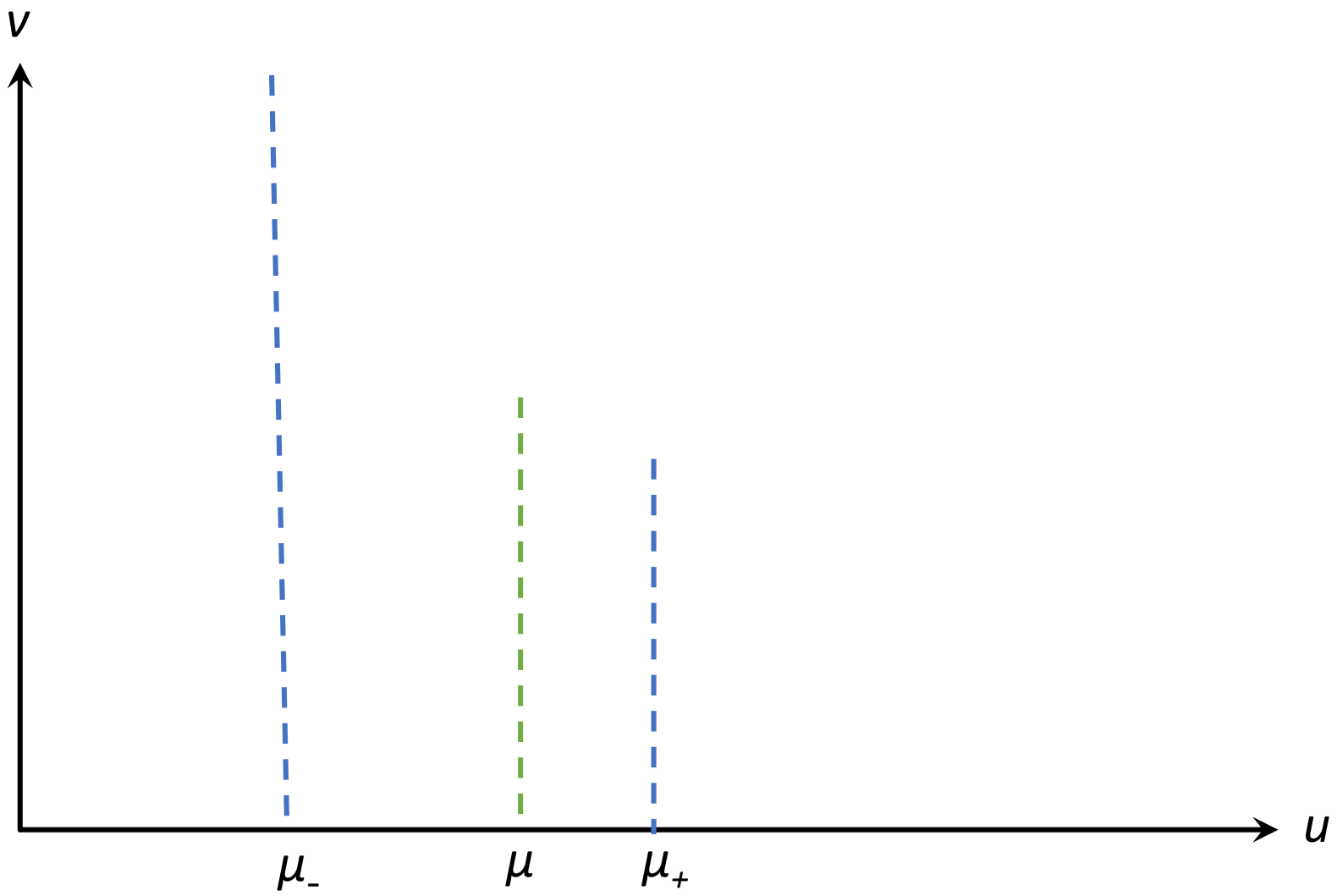
- We looked at calcium induced calcium release and found that there are three types of behaviour:

- Case (i) $\mu_- < \mu < \mu_+$

$$\frac{d}{dt}(u+\gamma v) = \mu - u$$

When $u<\mu$ we move to the right.
When $u>\mu$ we move to the left.

This leads to sustained or relaxation oscillations.



Summary of lecture 9

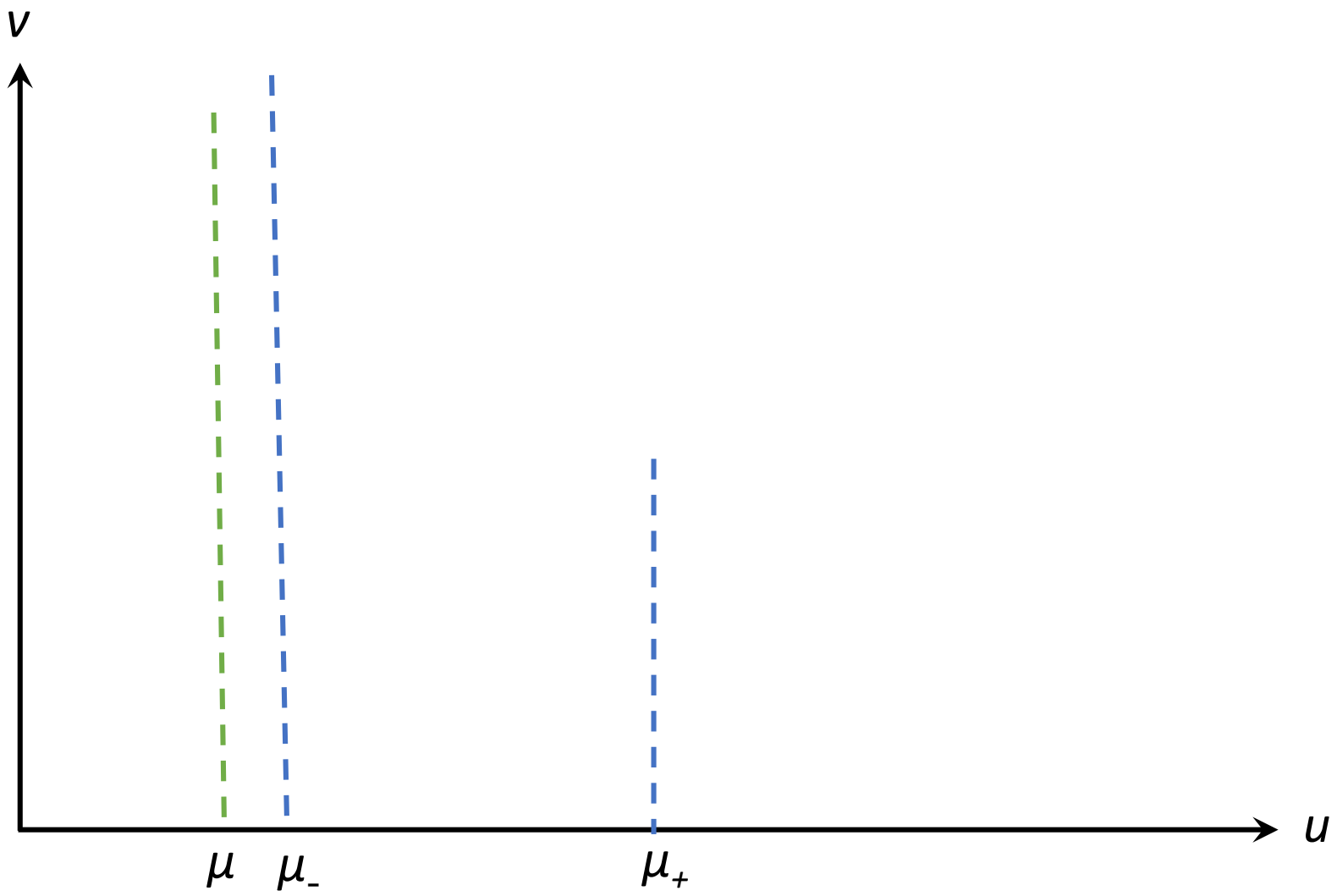
- We looked at calcium induced calcium release and found that there are three types of behaviour:

- Case (ii) $\mu < \mu_-$

$$\frac{d}{dt}(u+\gamma v) = \mu - u$$

When $u<\mu$ we move to the right.
When $u>\mu$ we move to the left.

We need to give a little energy to move away from the green equilibrium point and make an excursion.



Summary of lecture 9

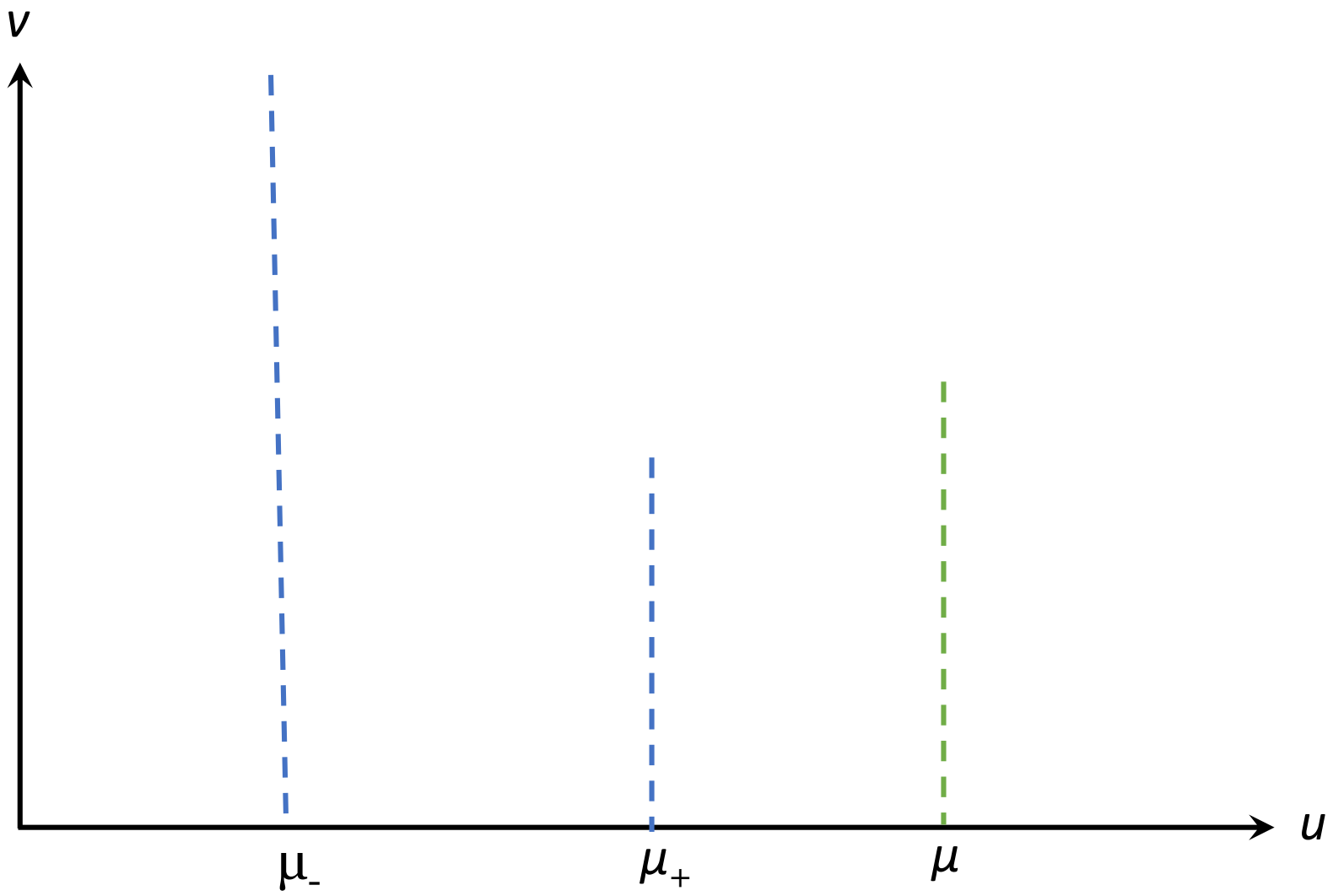
- We looked at calcium induced calcium release and found that there are three types of behaviour:

- Case (iii) $\mu > \mu_+$

$$\frac{d}{dt}(u+\gamma v) = \mu - u$$

When $u<\mu$ we move to the right.
When $u>\mu$ we move to the left.

The equilibrium lies at $u > \mu_+$ which is high.
This leads to cramps and rigor mortis.



Mid-Term Questionnaire – C5.12 Mathematical Physiology (2024-25)

Hilary Term 2024

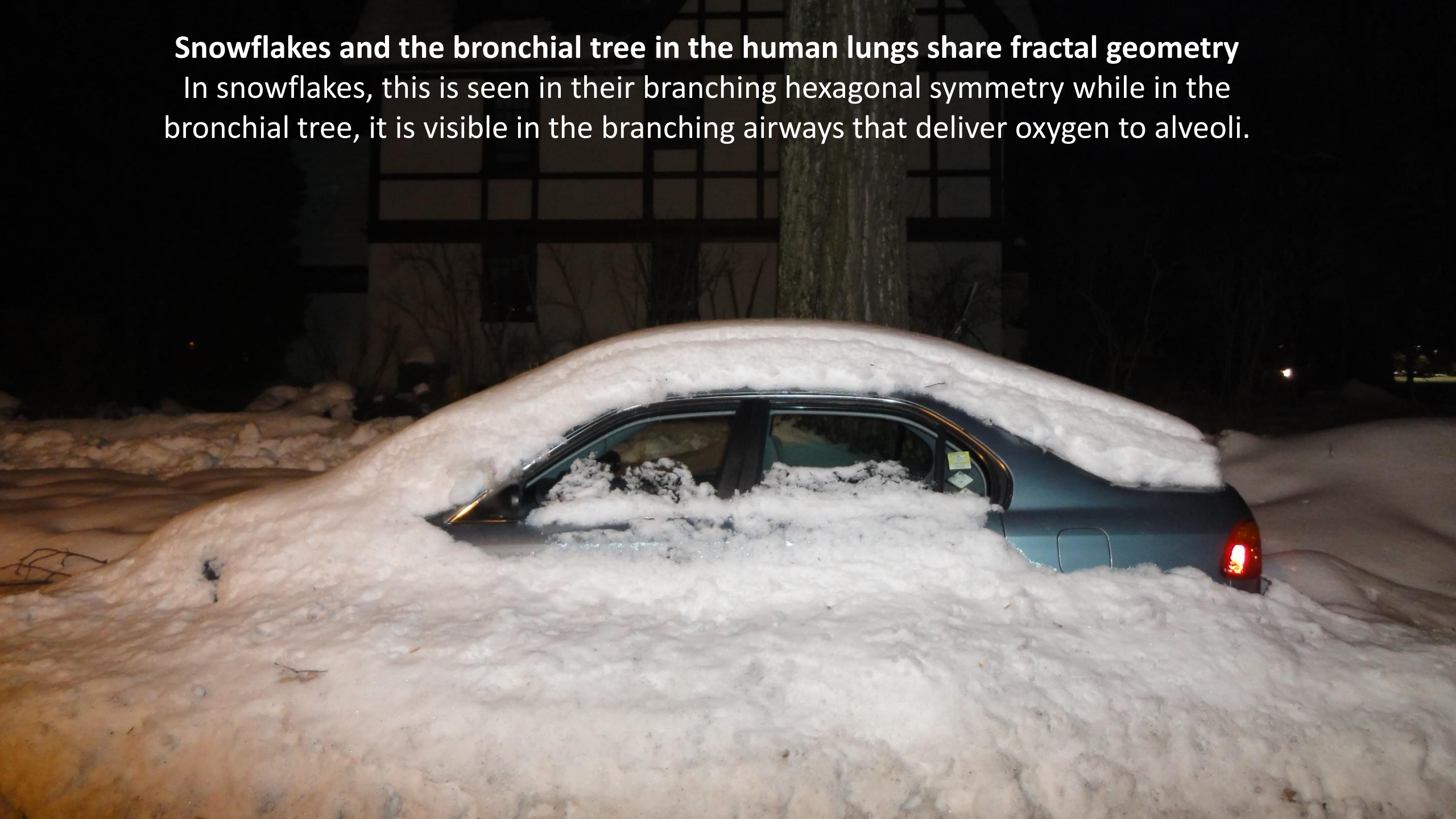
	Too Fast	Just Right	Too Slow	No Response
The pace of the course is	0%	100%	0%	0%

	Agree	Disagree	No response
When I attend in person, I find that the lecturer uses visual aids (boards, slides, ...) effectively	100%	0%	0%

Total number of questionnaires received: 2

Snowflakes and the bronchial tree in the human lungs share fractal geometry

In snowflakes, this is seen in their branching hexagonal symmetry while in the bronchial tree, it is visible in the branching airways that deliver oxygen to alveoli.



Summary of lecture 10

- Katerina Kaouri (Cardiff University) talked about current research in calcium dynamics and its relation to spina bifida and IVF.

- We saw how the space-dependent model for calcium-induced calcium release admits periodic travelling wave solutions.

$$
\begin{aligned}
u_t + \gamma v_t &= \mu - u + \nu u_{xx}, \\
\varepsilon v_t &= f(u, v),
\end{aligned}
$$

The heart

- There are two parts to the heart function.

1) Electrochemical action – causes muscle contraction to pump blood around the body.

2) Mechanical action – enables unidirectional circulation via a system of valves.

The electrochemical action of the heart

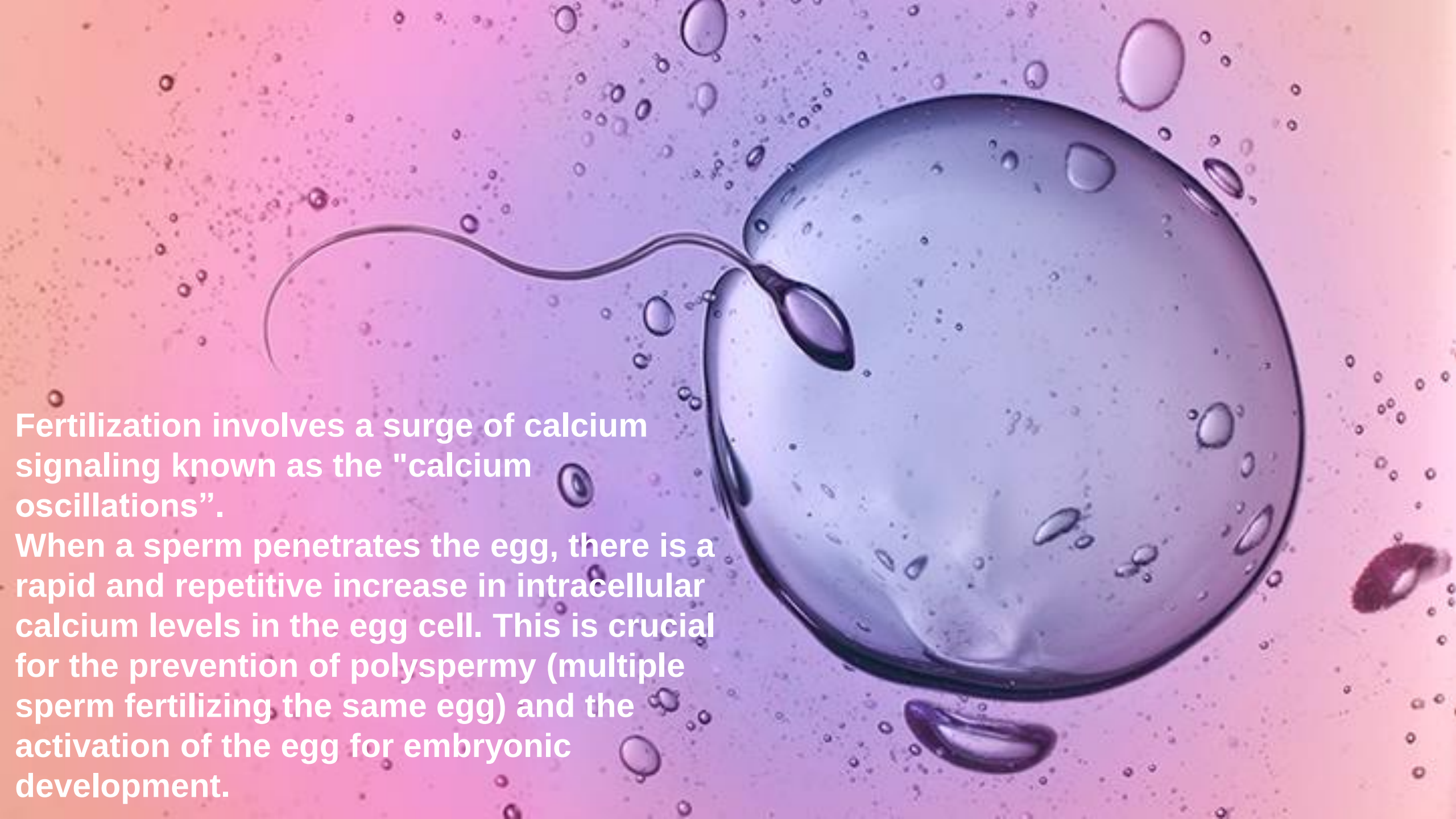
- The heart has four chambers: the right atrium (RA), the right ventricle (RV), the left atrium (LA) and the left ventricle (LV).

- Blood flows into the RA from the venous system to the RV, perfuses through the lungs where it gains oxygen, moves to the LA then to the LV and then to the arteries.

- In the RA is the sino-atrial (SA) node, whose cells act as pacemakers with a periodic action potential.

The echocardiogram (ECG)

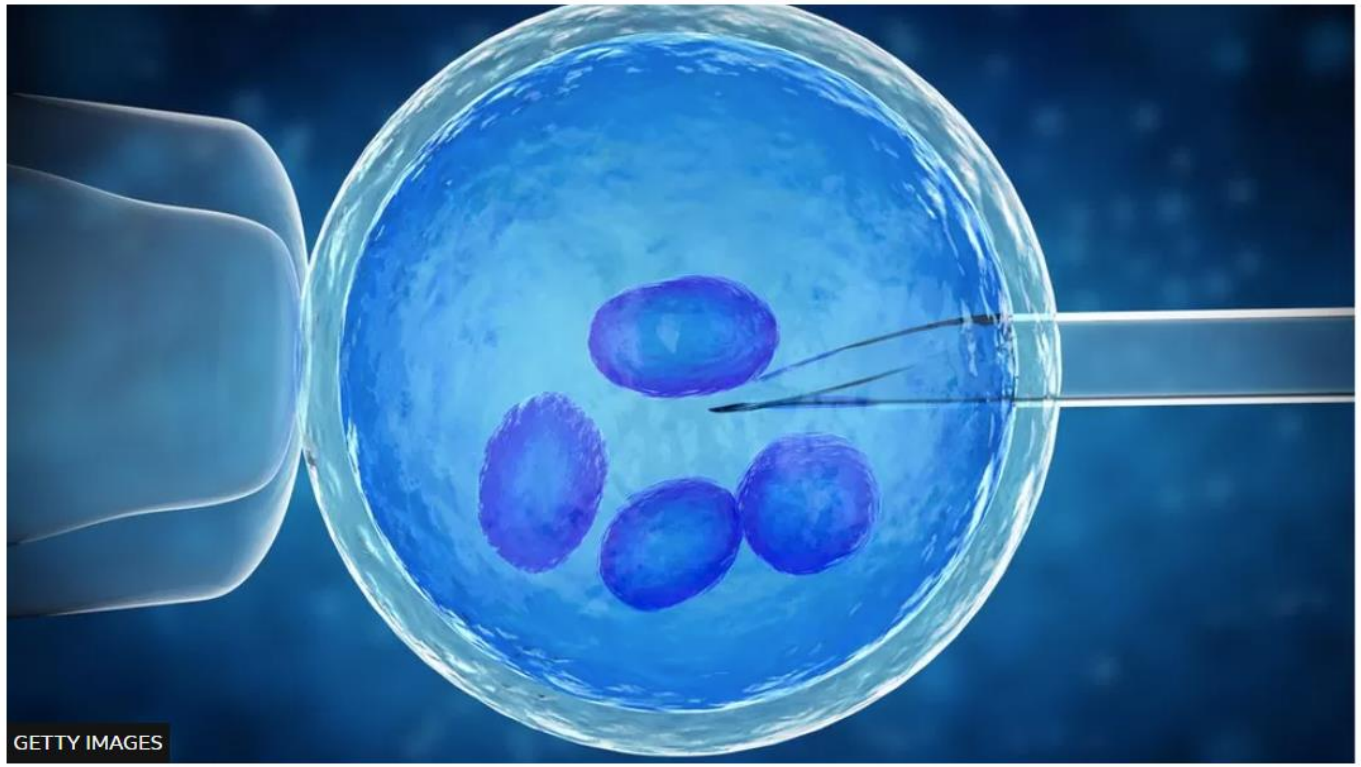
- Approximately 2D waves propagate through the heart from the SA.
- Blockage of conduction paths can lead to ‘re-entrant’ spiral waves, which cycled round the diseased tissue. This causes ventricular tachycardia.
- In the diseased heart, spiral waves can become chaotic. This causes ventricular fibrillation.



Fertilization involves a surge of calcium signaling known as the "calcium oscillations”.
When a sperm penetrates the egg, there is a rapid and repetitive increase in intracellular calcium levels in the egg cell. This is crucial for the prevention of polyspermy (multiple sperm fertilizing the same egg) and the activation of the egg for embryonic development.

Hopes for IVF boost from University of Warwick maths doctor's idea

1 day ago



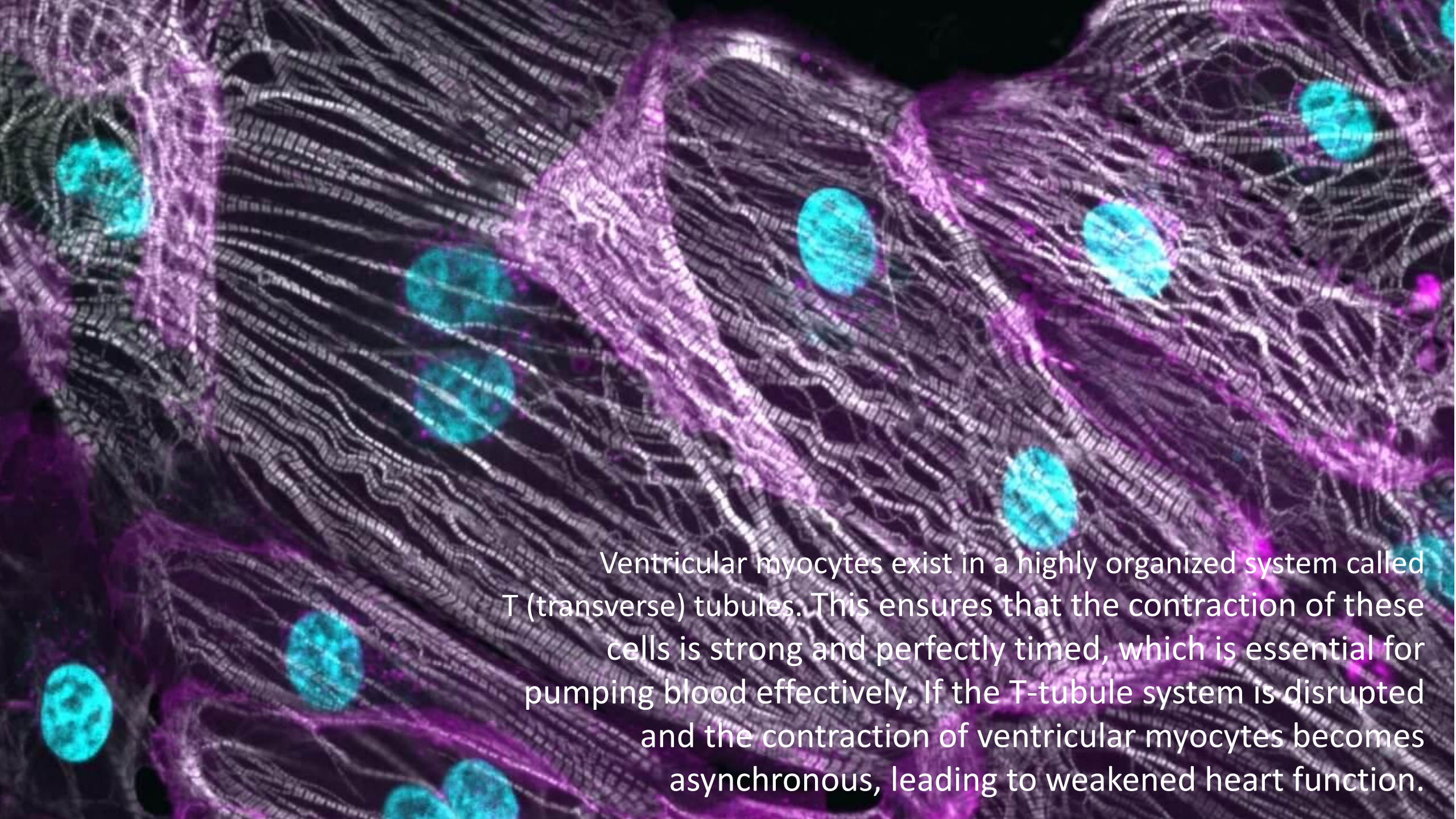
Doctors have to collect eggs from women for IVF cycles

https://www.bbc.co.uk/news/uk-england-coventry-warwickshire-67498261


After the cardiac muscle cells fire, they become completely unresponsive to additional stimuli. This is essential for preventing chaotic or premature contractions to ensure stability and reliability of the heart's rhythm.

Summary of lecture 11

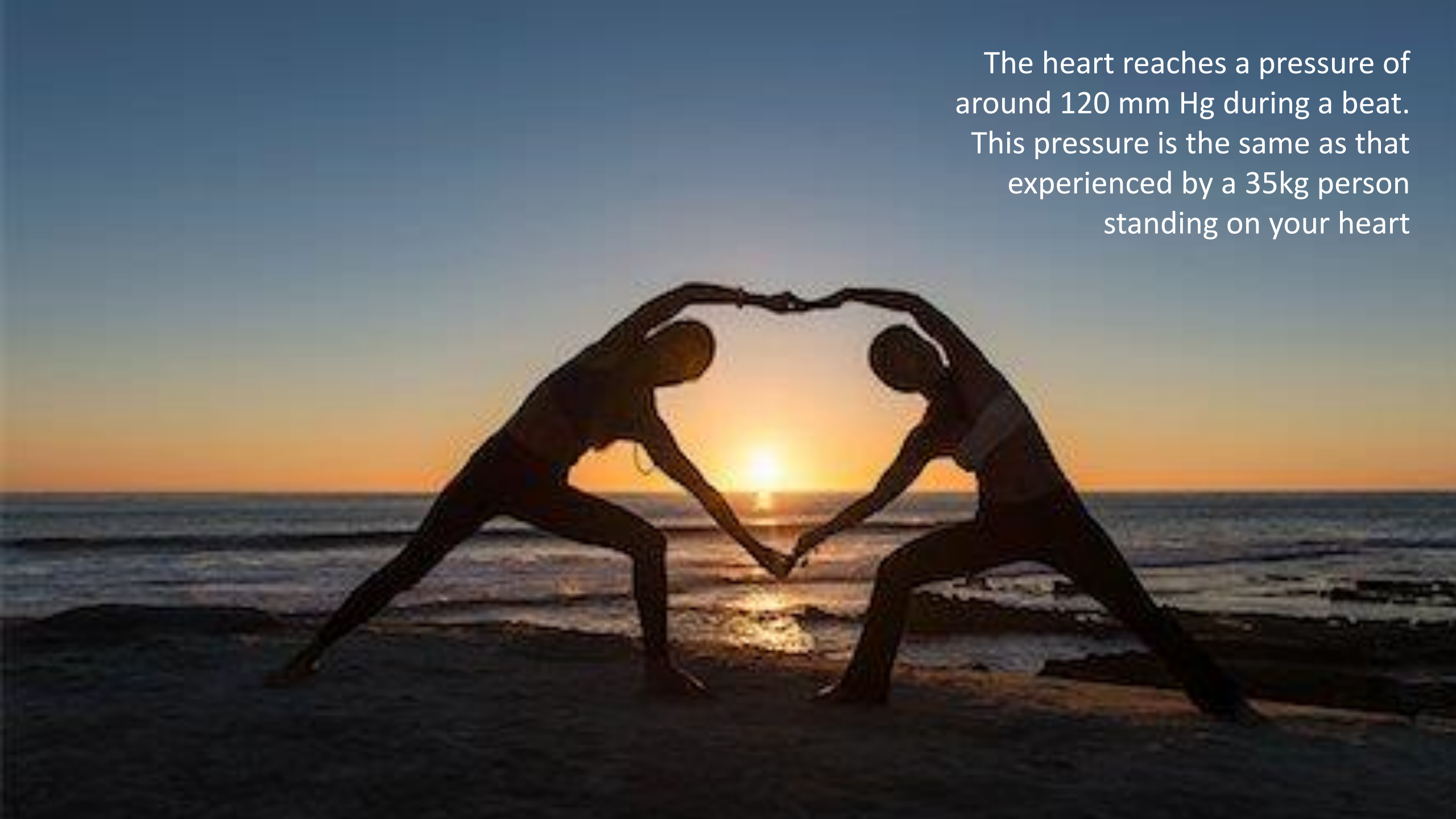
- The Noble model describes the electrochemical action of the heart.
- This explains the action potential of ventricular myocytes.



Ventricular myocytes exist in a highly organized system called T (transverse) tubules. This ensures that the contraction of these cells is strong and perfectly timed, which is essential for pumping blood effectively. If the T-tubule system is disrupted and the contraction of ventricular myocytes becomes asynchronous, leading to weakened heart function.

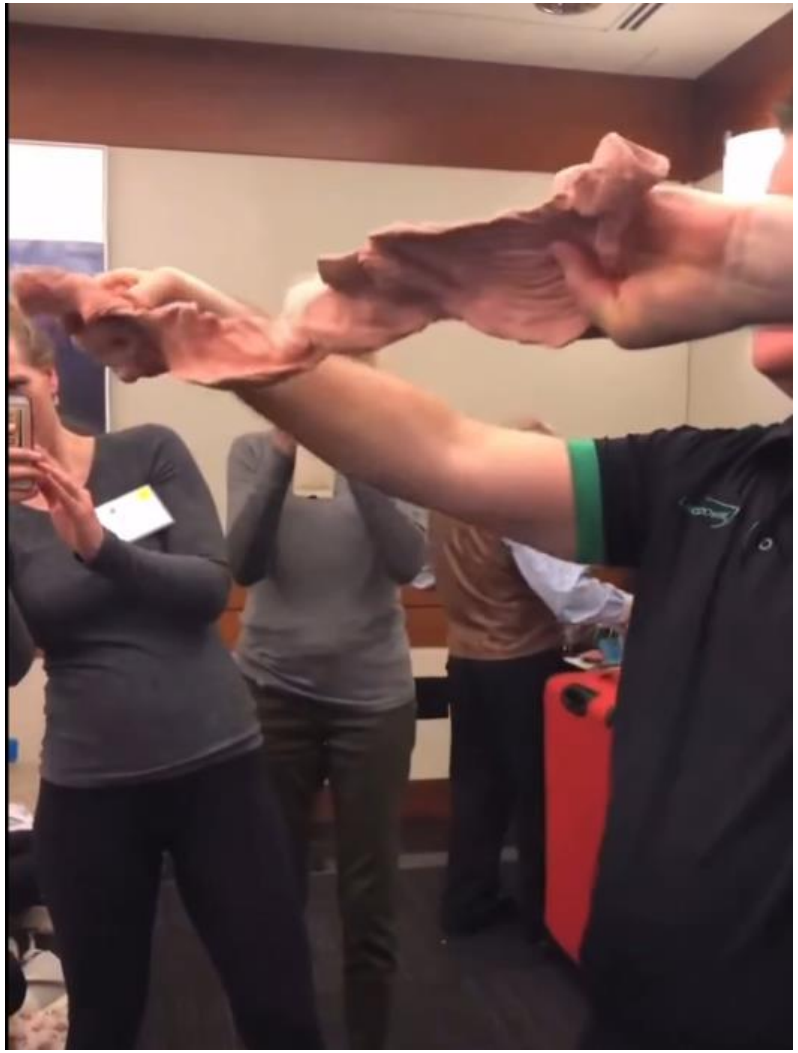
Summary of lecture 12

- The Noble model gives rise to a new type of periodic wave pattern:
  - The order-one time evolution is described by the phase plane.
  - Over the long time, the phase plane, in particular the nullclines, evolve, leading to disappearance and formation of steady states.


The heart reaches a pressure of around 120 mm Hg during a beat. This pressure is the same as that experienced by a 35kg person standing on your heart

Summary of lecture 13

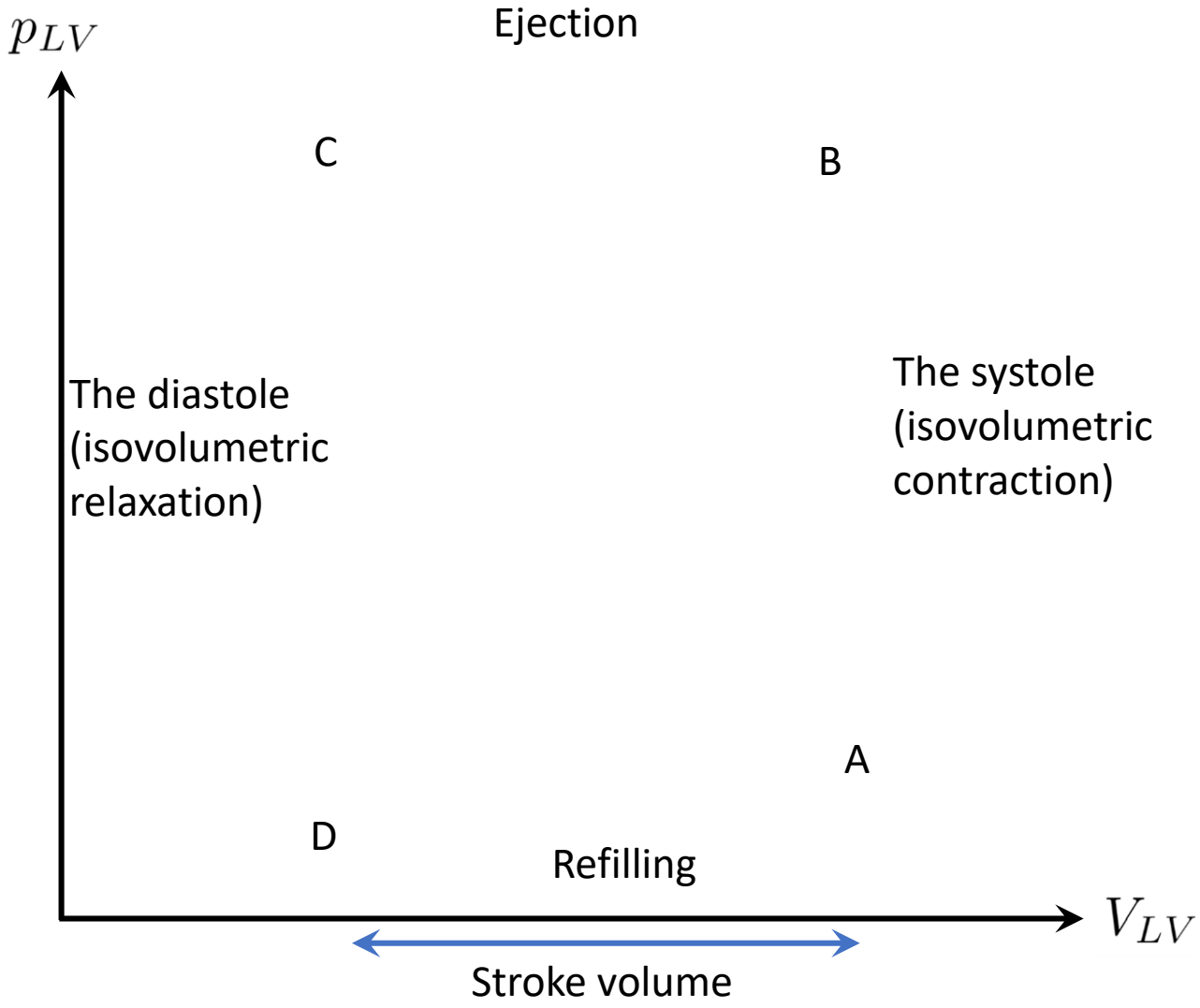
- Periodic wave propagation explains two types of behaviour:
  - Target patterns – circularly radiating waves that are observed in the heart and generated by pacemaker cells.
  - Spiral waves –when electrical signals propagate unevenly through heterogeneous heart tissue.
  - Both of these are seen in atrial or ventricular fibrillation.



When the heart contracts, it doesn’t just squeeze the blood out of the ventricle; it twists on a longitudinal axis, much like wringing out a washcloth.

Summary of lecture 14

- The pressure–volume cycle of the heart consists of four stages:



Nervous control of the heart

- Controls heart rate, stroke volume and arterial blood pressure.
- There are two parts to the nervous system: the sympathetic and parasympathetic systems:
    - The sympathetic system releases noradrenaline and adrenaline. This acts slowly (over around 10s) and increases blood pressure through vasoconstriction and increases heart rate.
    - The parasympathetic system releases acetylcholine which reduces blood pressure through vasodilation and reduces heart rate. This acts quickly.
- Baroreceptors control the blood flow and blood pressure. They are located in the aortic arch and the carotid sinus in the chest. The control response is called the baroflex.

Summary of lecture 14

- Nervous control of the heart includes heart rate regulation, stroke volume and arterial blood pressure.

- There are two parts to the nervous system: the sympathetic and parasympathetic systems.

- The sympathetic system releases noradrenaline and adrenaline. This acts slowly (over around 10s) and increases blood pressure through vasoconstriction and increases heart rate.

- The parasympathetic system releases acetylcholine which reduces blood pressure through vasodilation and reduces heart rate. This acts quickly.

- A typical blood pressure reading is 120/80 mmHg.
- The higher number is the systolic pressure and is the pressure in your arteries when your heart's **ventricles contract** and pump blood into the arteries.
- The lower number is the diastolic pressure and is the pressure in your arteries when the heart is **relaxed** between beats and filling with blood.

Summary of lecture 15

- Isovolumetric contraction:
  - $C_{LV}p_{LV}$=constant. C_{LV} falls so p_{LV} rises
- Ejection:
  - C_{LV}=constant. p_{LV} falls exponentially to a value 0.87 times that at the start of this phase.
- Isovolumetric relaxation
  - $C_{LV}p_{LV}$=constant. C_{LV} rises so p_{LV} falls.
- Refilling
  - C_{LV}=constant. p_{LV} falls exponentially to a value 0.76 times that at the start of this phase.

Why do we study mathematical physiology?

1) **Quantitative Understanding.** Mathematical models provide a way to describe complex biological phenomena, which can lead to precise predictions and insights. This allows researchers to explore fundamental questions about life processes and the principles that govern them.

2) **Prediction and Simulation.** Mathematical models enable us to predict the behaviour of physiological systems under different conditions. This is particularly valuable for simulating experiments and testing hypotheses.

3) **Clinical Applications.** Models can aid in the diagnosis and treatment of diseases by providing insights into the underlying physiological mechanisms.

Why do we study mathematical physiology?

4) **Drug Development.** Mathematical models can help predict the effects of drugs on physiological systems, optimize dosage regimens, and understand how drugs interact with biological pathways.

5) **Optimizing Therapies.** This includes designing personalized treatment plans, predicting patient responses to interventions, and identifying optimal conditions for medical procedures.

6) **Advancing Basic Science.** By providing a quantitative framework, it allows researchers to explore fundamental questions about life processes and the principles that govern them.