Mathematical Modelling explains Heterogeneity and Variability in Sickle Cell Disease

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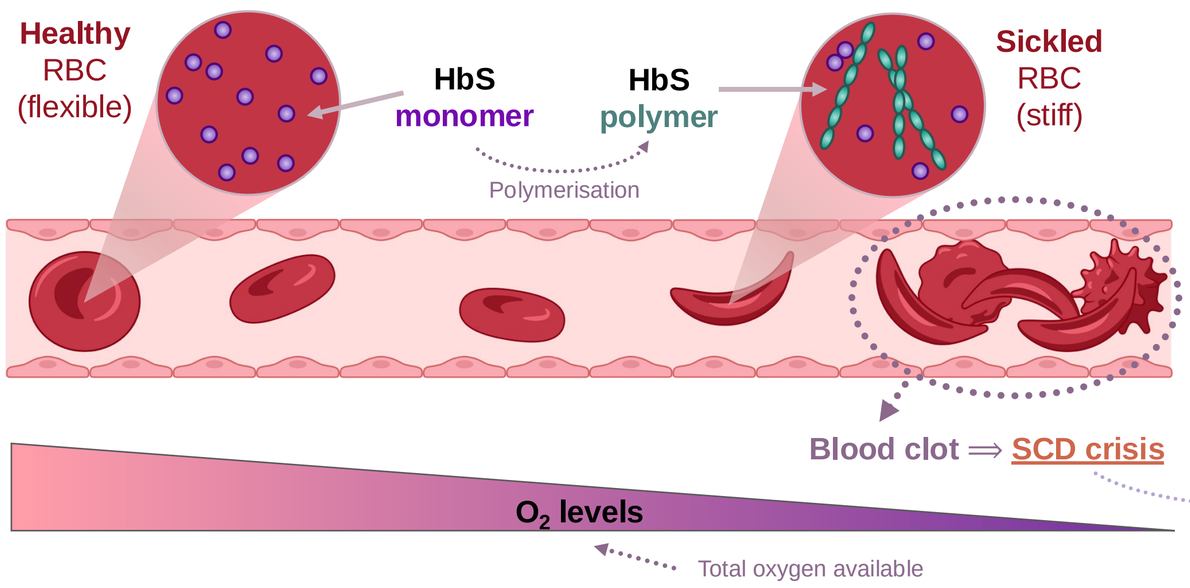
What is Sickle Cell Disease?

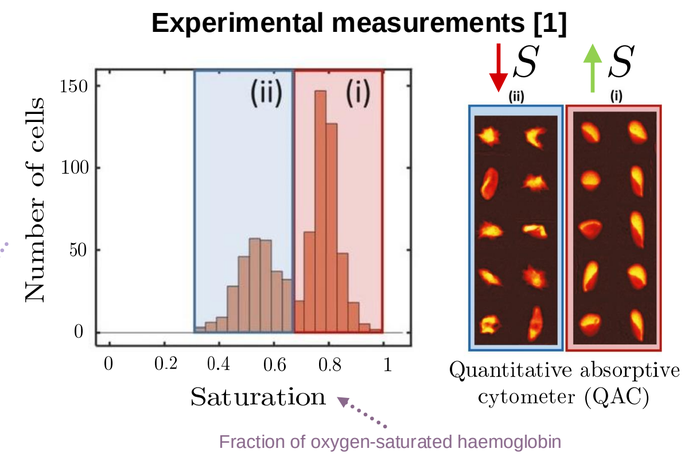
Sickle Cell Disease (SCD) is a genetic blood disorder induced by the polymerisation of sickle haemoglobin (HbS) in reduced oxygen tension inside red blood cells (RBCs).

- Millions affected worldwide
- Shorter life expectancy
- Infections & complications



Research Questions

Recent measurements on RBCs suggest the existence of two subpopulations of RBCs in SCD patients.



Q1 Why are there both **sickle** and **healthy** RBCs within the same SCD blood sample?

Q2 Is there something we can measure *(biomarker)* across all patients to predict SCD crises?

Mathematical Model – The Ingredients

Governing equations

1 Polymerisation kinetics

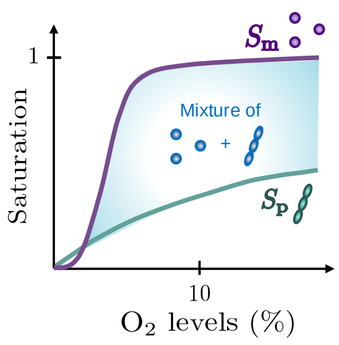
Eaton and Ferrone's moment equations [2] describe how **monomer** and **polymer** concentrations vary inside each RBC.

$$\frac{\mathrm{d}\mathscr{P}(t)}{\mathrm{d}t} = \text{Primary nucleation} + \text{Secondary nucleation} + \text{Elongation} - \text{Dissociation}$$

Time evolution of polymer mass

2 Saturation curves

Polymers have lower O_2 saturation than **monomers** because their oxygen binding sites are already occupied by other monomers. **Hill equations** describe the relation between O_2 levels and O_2 saturation.



Assumptions

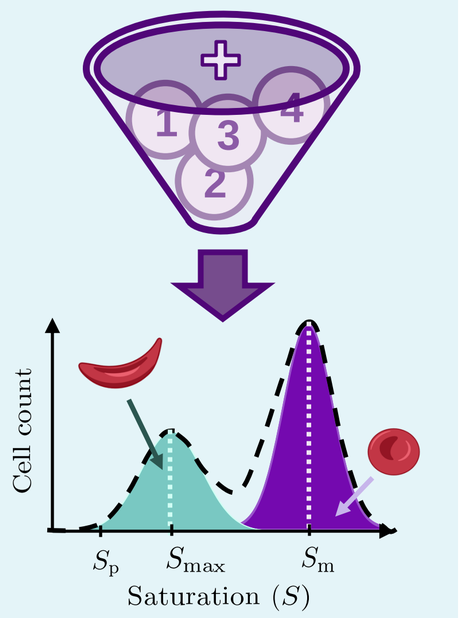
3 Steady state

Oxygen levels have stabilised by the time of the measurement.

4 Experimental error

Measurements are not completely accurate.

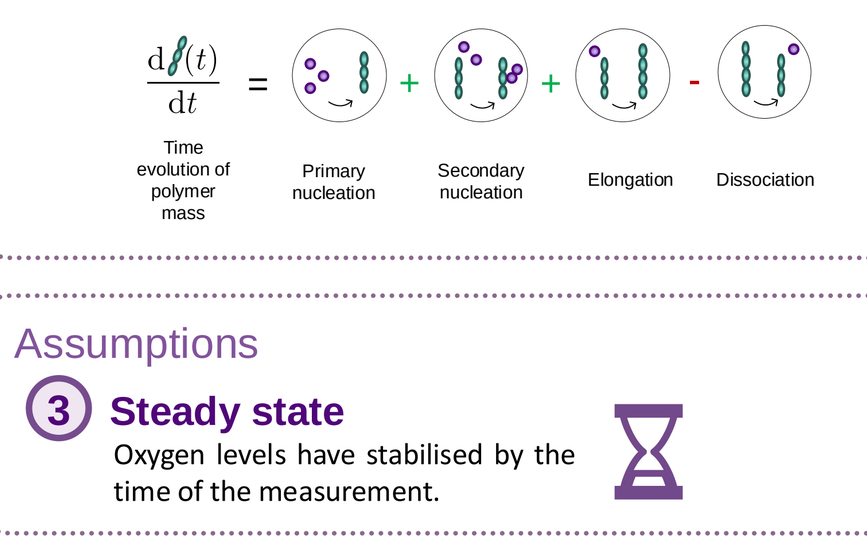
0 Each RBC has a different initial amount of monomers available for polymerisation



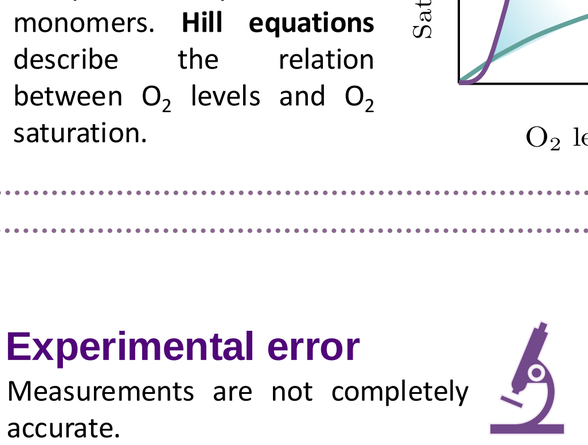
Analytical expression for saturation distribution derived mechanistically

Results – Model Fit to Patient Data

Steady state



Time dependent



A1 The model fits well to data and suggests the threshold of monomers needed for polymerisation explains heterogeneity in RBC types.

A2 We can extract patient-specific parameters such as the relevant timescale of sickling.

Discussion

Our model...

- contains the **key physics**
- is **simple** and easily reproducible
- allows to extract **patient-specific information** from data
- is a tool to probe **new biomarkers**
- can be expanded to include **drug delivery**

Acknowledgements:
Anonymised experimental data was provided by Higgins lab (Harvard Medical School) and Wood lab (University of Minnesota).

References:
[1] Di Caprio, Giuseppe *et al.*, *PNAS* (2019)
[2] Michaels & Knowles, *AJP* (2014)

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