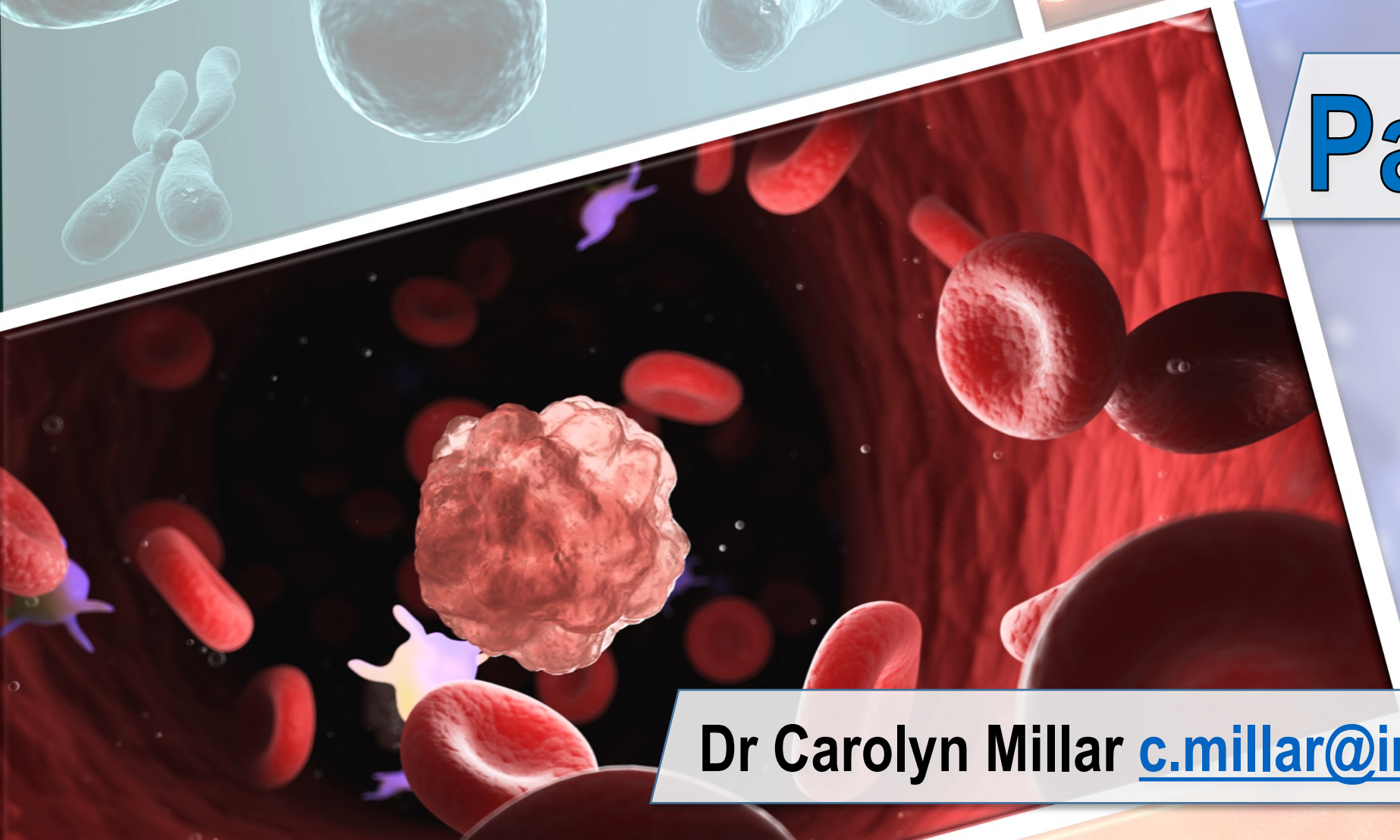
Imperial College London

Haemostasis & thrombosis

Parts 4 & 5



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Session Plan

Part 1 –Overview of Haemostasis

- Primary Haemostasis
- Secondary Haemostasis (Coagulation)
- Fibrinolysis

Part 2 –Primary Haemostasis

- Platelets
  - Adhesion
  - Release reaction
  - Thromboxane A2 synthesis
  - Platelet aggregation
- Antiplatelet drugs
- Von Willebrand factor

Part 3 – Coagulation (Secondary Haemostasis)

- Clotting factor synthesis
- Cellular base model of coagulation
  - Initiation
  - Amplification
  - Propagation
- Coagulation inhibitory mechanisms
  - - Anticoagulant Pathway
  - Anticoagulant Drugs

Part 4: Fibrinolytic system

- Fibrinolysis
- Antifibrinolytic drugs

Part 5: Tests of Coagulation

- Prothrombin time (PT)
- Activated Partial Thromboplastin Time (APTT)

Part 6 – Bleeding and Thrombosis

- The Balance Model of Coagulation and its Application

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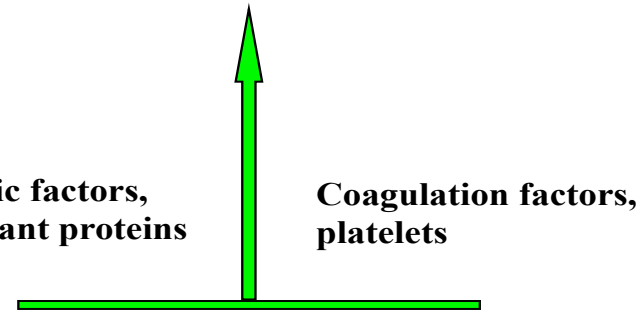
Overview of Haemostasis

Functions of Haemostasis
1. Prevention of blood loss from intact vessels
2. Arrest of bleeding from injured vessels

Normal haemostasis: a state of equilibrium



Vessel constriction

↓

Formation of an unstable platelet plug

-platelet adhesion

-platelet aggregation

↓

Stabilisation of the plug with fibrin

-blood coagulation

↓

Dissolution of clot and vessel repair

-fibrinolysis

Fibrinolysis

plasma protein, zymogen

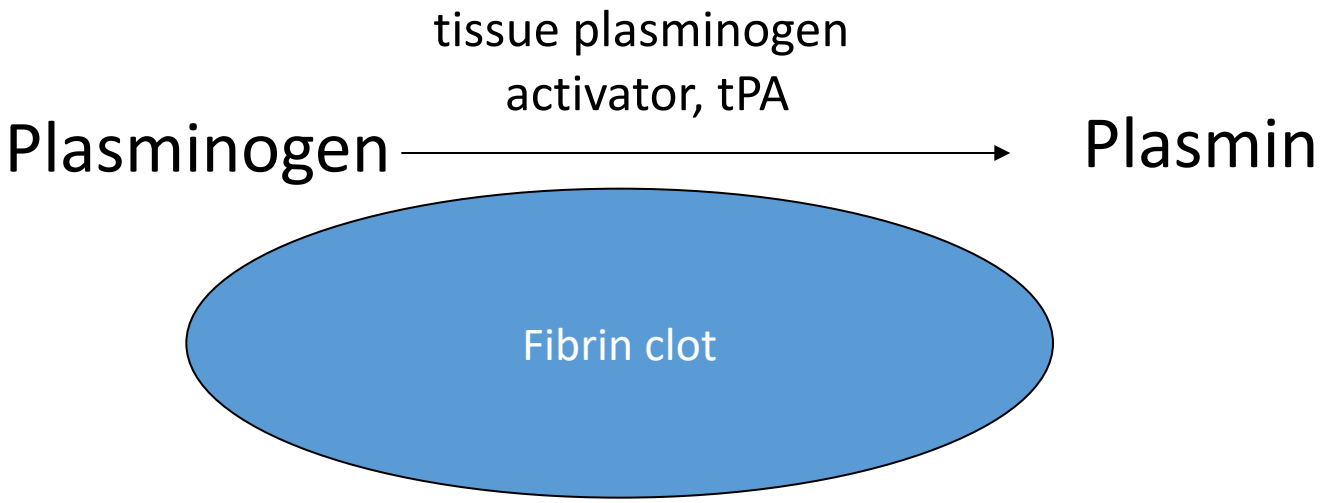
Plasminogen

tissue plasminogen activator, tPA

plasma protein, proteinase

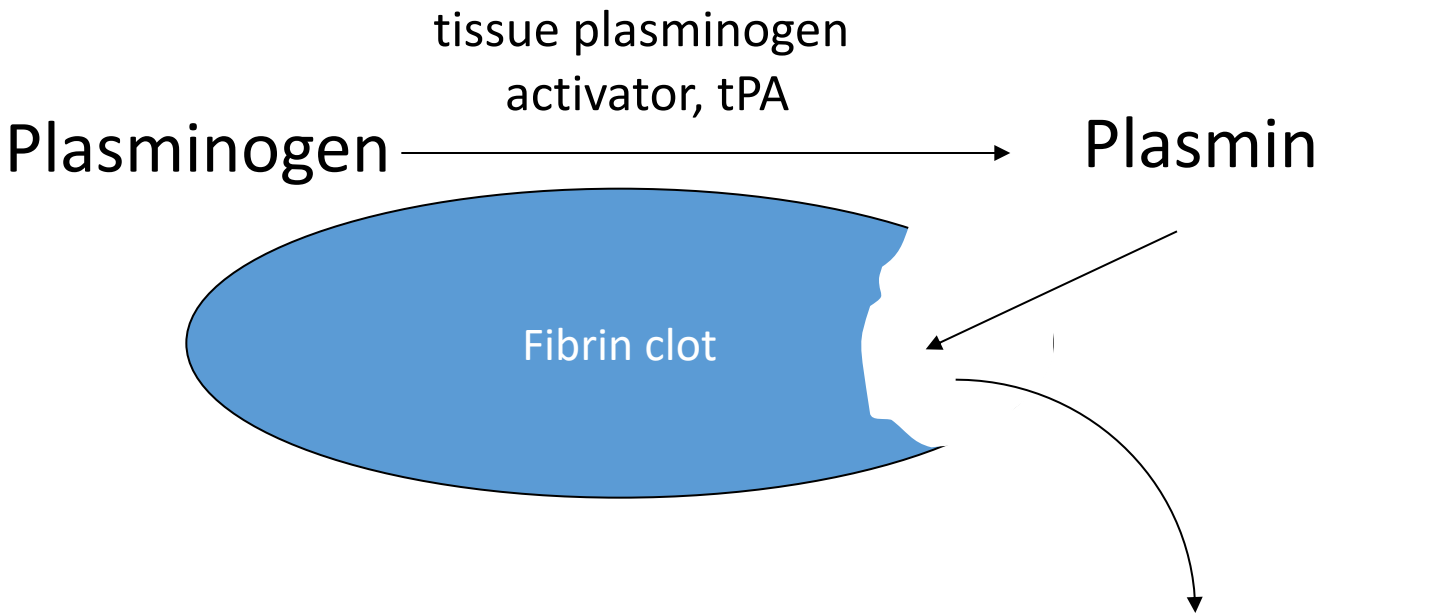
Normally, no interaction

Fibrinolysis



Plasminogen binds to the lysine residues of Fibrin

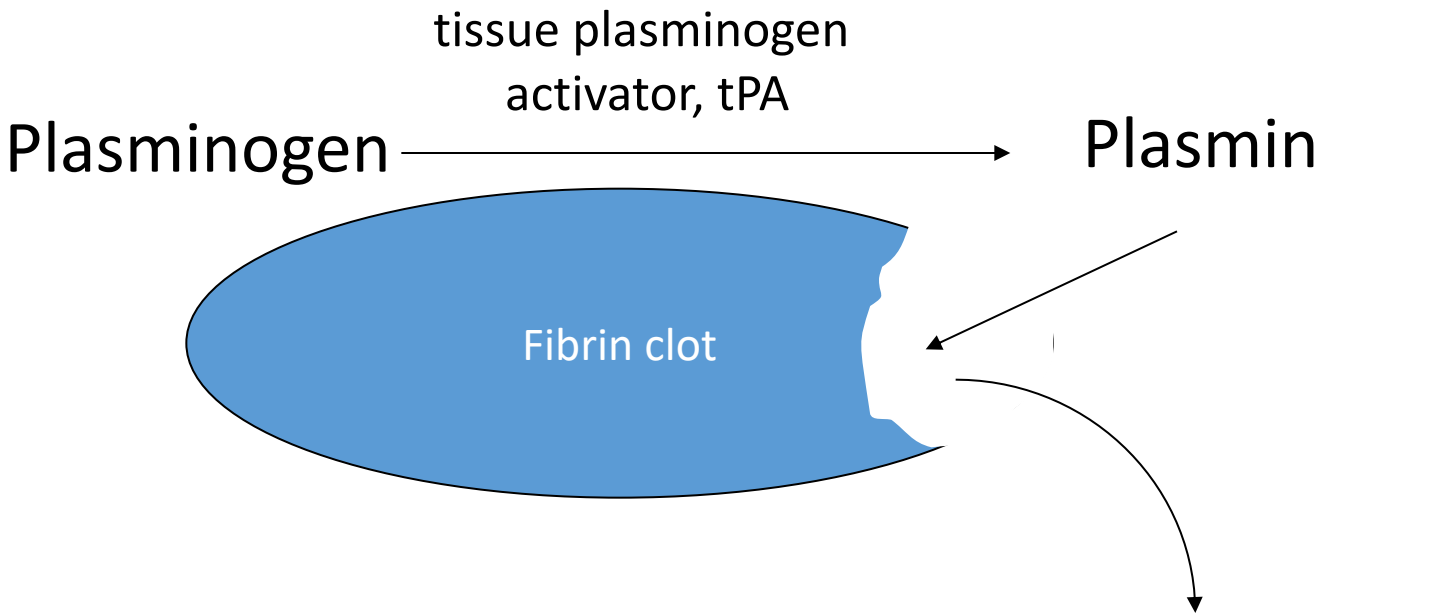
Fibrinolysis



Plasmin is inhibited by:

- Antiplasmin
- Alpha 2 macroglobulin

Fibrinolysis

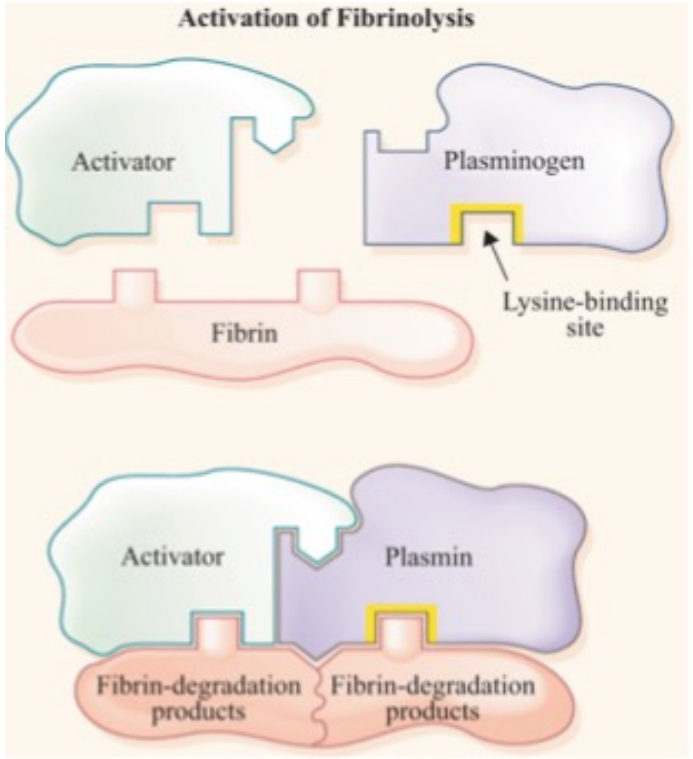


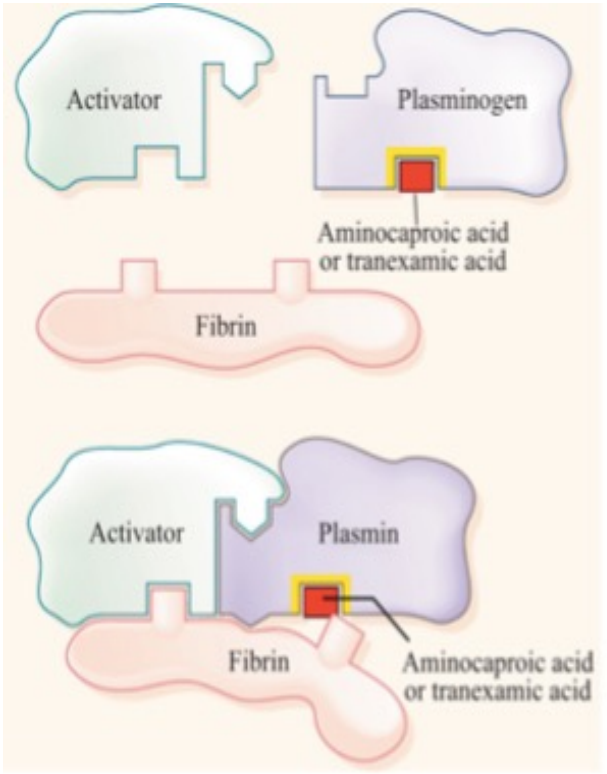
<u>tPA as Thrombolytic therapy</u>

tPA can be used in therapeutic thrombolysis for strokes and life or limb threatening venous thromboembolism
(deep vein thrombosis or pulmonary emboli)

Antifbrinolytic drugs

Activator = tPA





- Tranexamic acid is a synthetic derivative of the amino acid lysine
- It works by competitively inhibiting the binding of plasminogen to the lysine residues of fibrin
- This prevents the activation of plasminogen to plasmin, which would otherwise result in fibrinolysis
- It is used widely to treat bleeding in trauma and surgical patients as well as in patients with inherited bleeding disorders.

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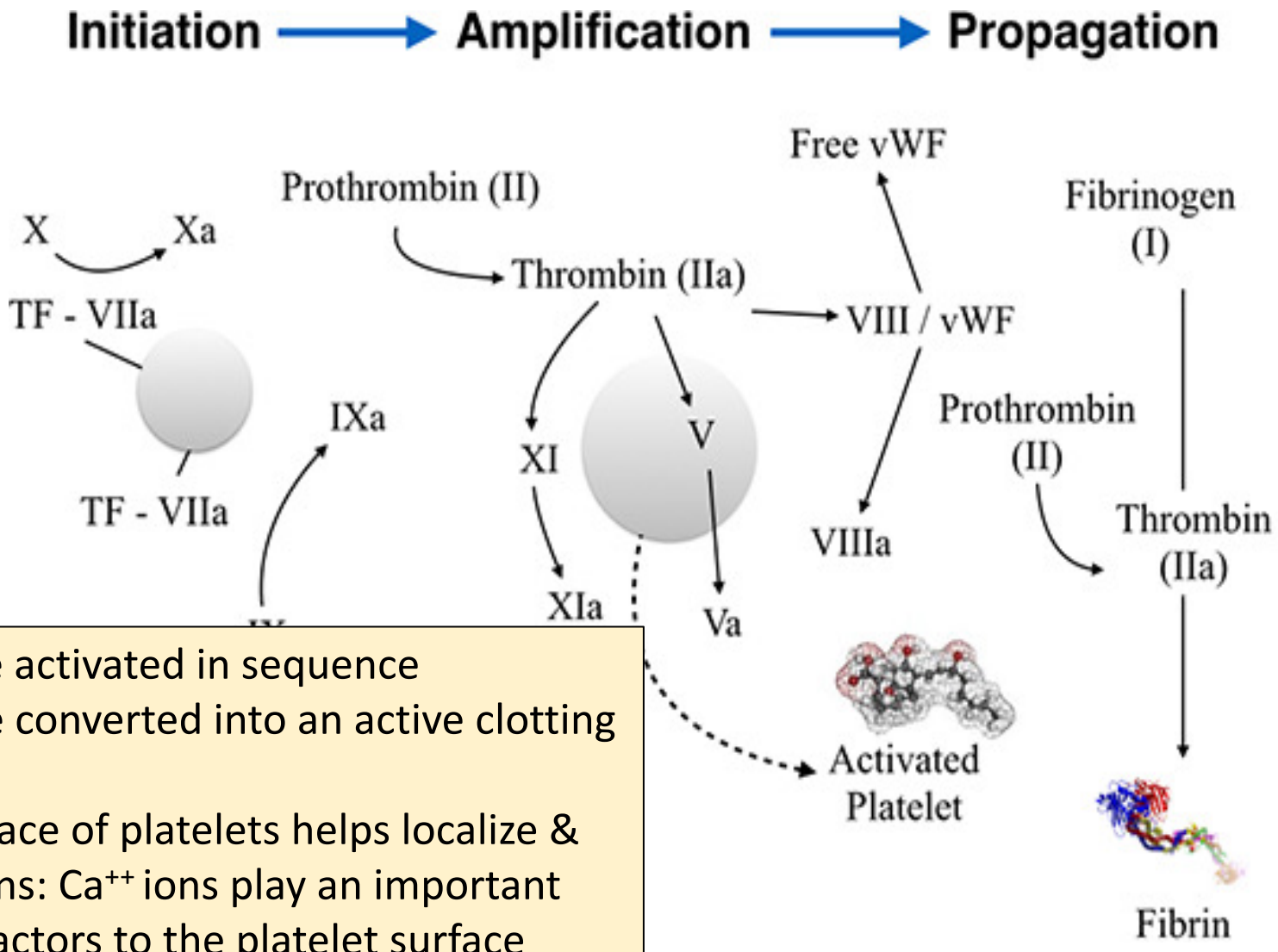
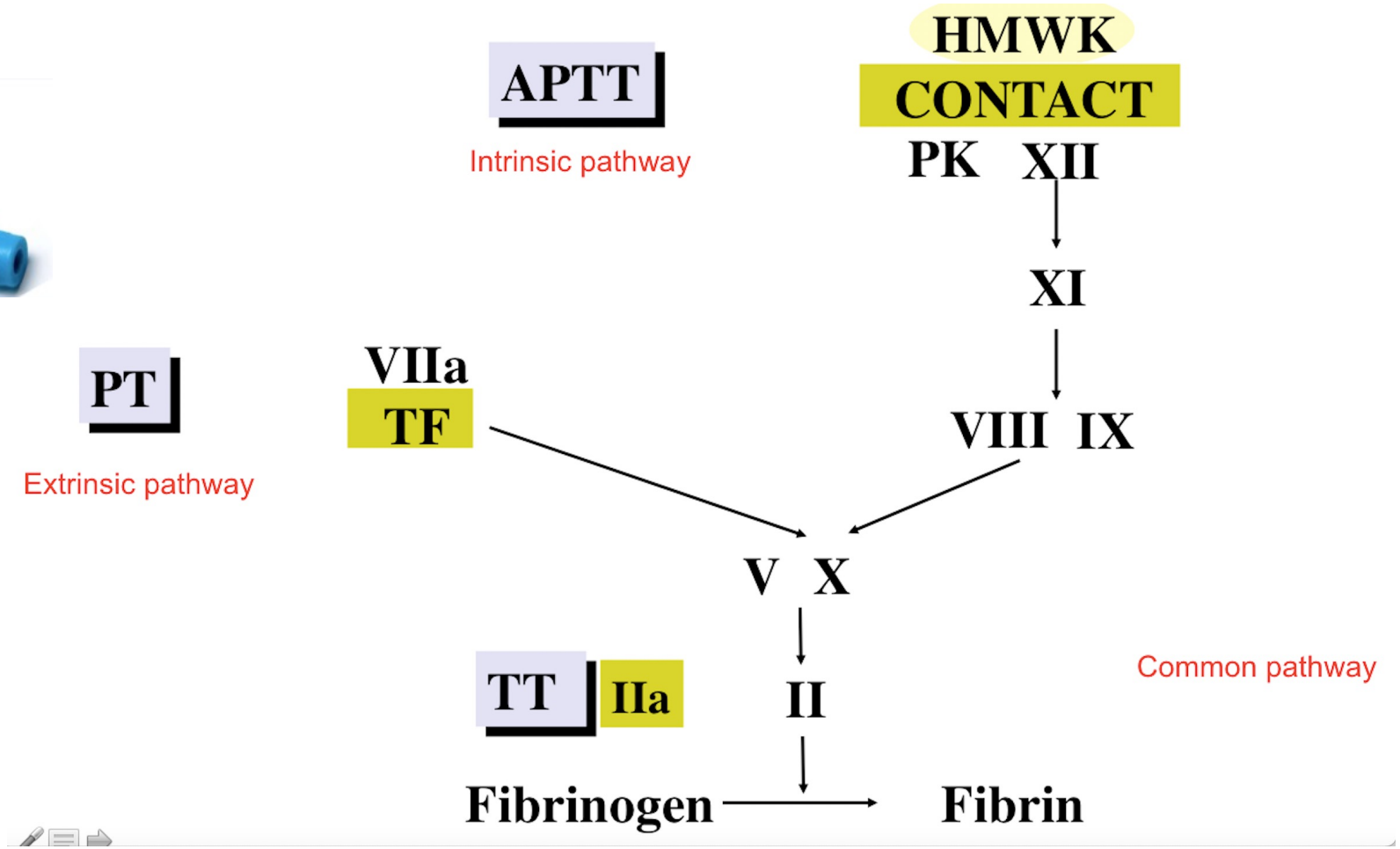
Cellular-based model of Coagulation: an accurate physiological representation



1. A number of steps are activated in sequence
2. Inactive zymogens are converted into an active clotting factor
3. The phospholipid surface of platelets helps localize & accelerate these reactions: Ca^{++} ions play an important role in binding clotting factors to the platelet surface

Coagulation Screen:
‘Cascade’ based on Intrinsic/Extrinsic model (old)



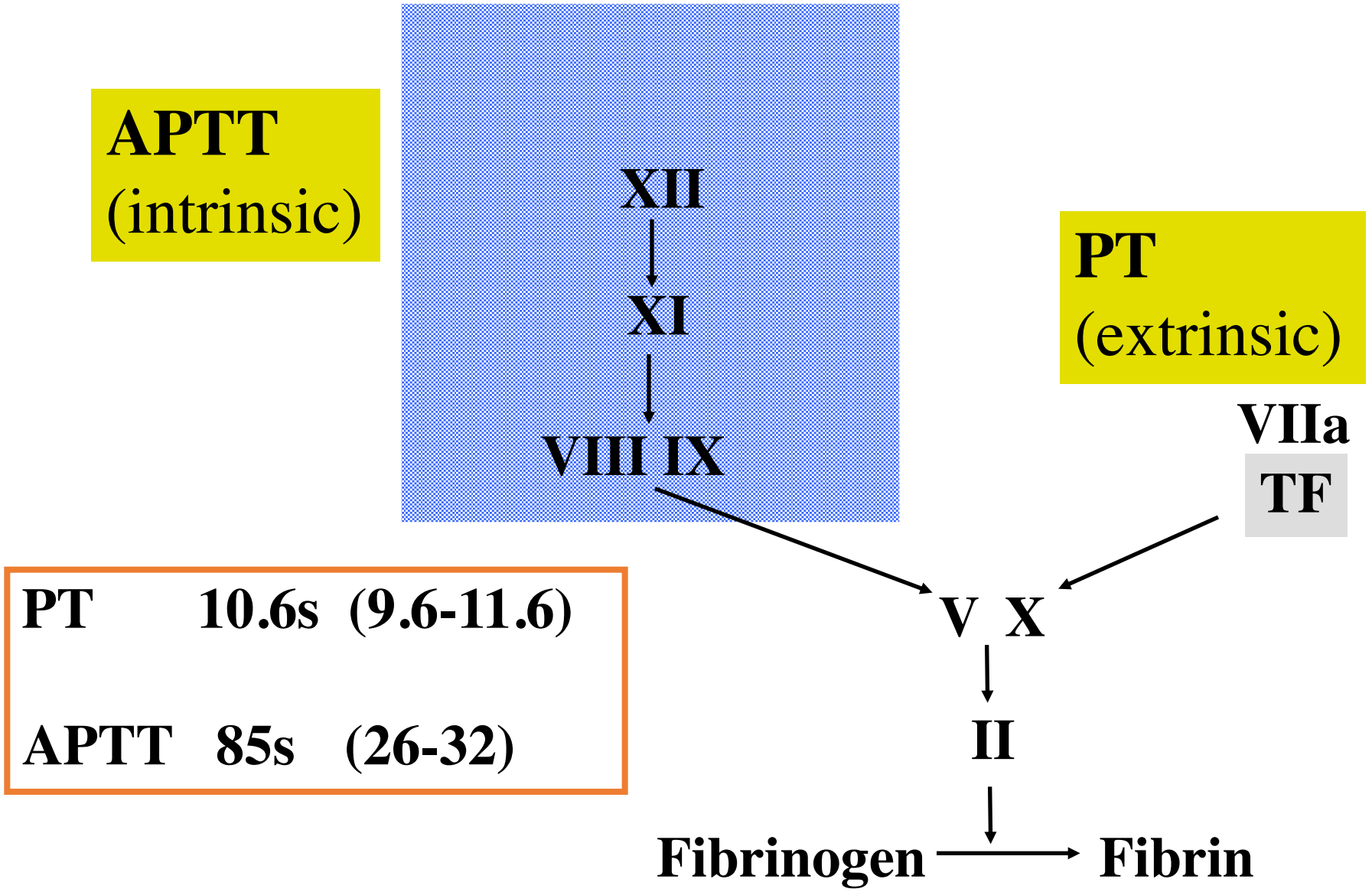
Prothrombin Time

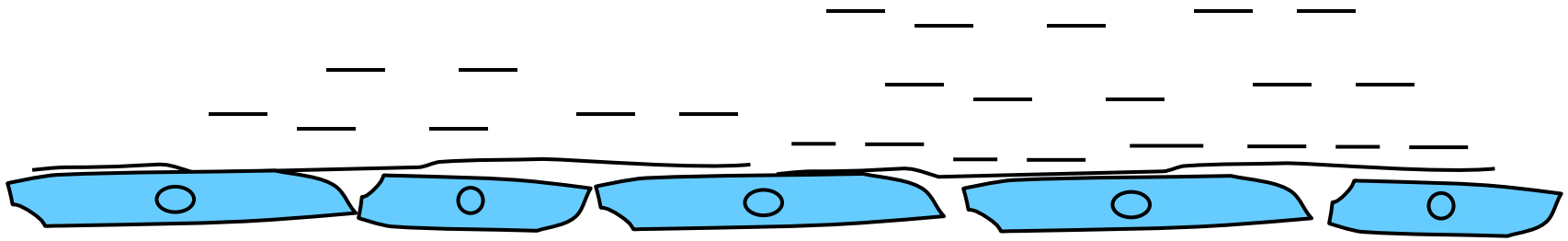
- Measures the integrity of the ‘extrinsic’ pathway (and common pathway)
- Patient’s blood is collected into a bottle containing sodium citrate, which does not contain calcium thus preventing the blood from clotting in the bottle
- The sample is spun to produce platelet-poor plasma
- A source of TF and phospholipid is added to the citrated plasma sample, together with calcium to start the reaction; the length of time taken for the mixture to clot is recorded.
- The PT estimates the activity of factors VII, X, V, II (prothrombin) and fibrinogen i.e. (‘prothrombin’ is a misnomer).
- Nowadays recombinant thromboplastin is often used as the source of TF and phospholipid
- When the PT is used for the control of vitamin K antagonist anticoagulant therapy such as warfarin, the results are expressed as the international normalised ratio (INR). This involves a correction for the different thromboplastin reagents used by different laboratories and means that the same therapeutic ranges apply to patients taking warfarin irrespective of the source of thromboplastin.

Activated Partial Thromboplastin Time

- Measures the integrity of the ‘intrinsic’ pathway (and common pathway)
- Performed by the contact activation of factor XII by a surface such as glass, or using a contact activator such as silica or kaolin.
- Contact activator, together with phospholipid, is added to the citrated plasma sample followed by calcium; the time taken for this mixture to clot is measured
- Prolongation of the APTT is seen in a variety of situations where there is a reduction in a single or multiple clotting factors; in the the latter there may also be an associated prolonged PT
- An isolated prolonged APTT (i.e. normal PT) is seen in patients with haemophilia A (factor VIII deficiency), haemophilia B (factor IX deficiency) and factor XI deficiency.
- However this may also be caused by factor XII deficiency which does not result in bleeding. (Note that FXII does not appear in the cell-based model described in 'Coagulation (secondary haemostasis): formation of the stable fibrin clot' and is not important for clotting *in vivo*).

e.g. APTT is PROLONGED in HAEMOPHILIA





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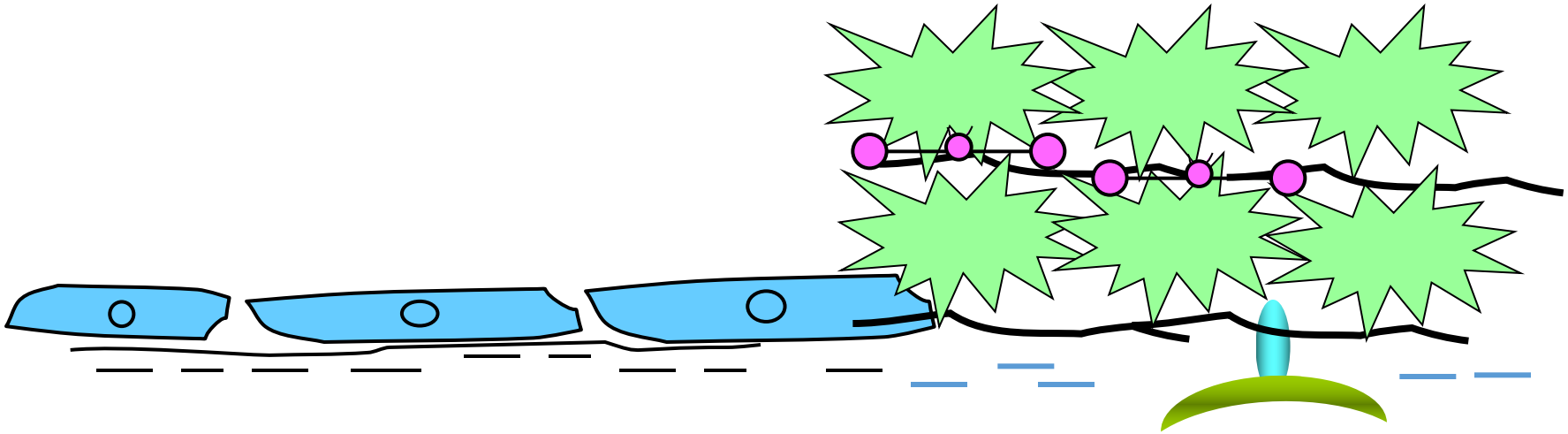

Haemophilia: failure to generate fibrin to stabilise platelet plug

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Part 6 – Bleeding and Thrombosis: READING

- The Balance Model of Coagulation and its Application: