In Silico clinical trials for treatment of acute Ischemic Stroke

In Silico Models for thrombosis and thrombolysis
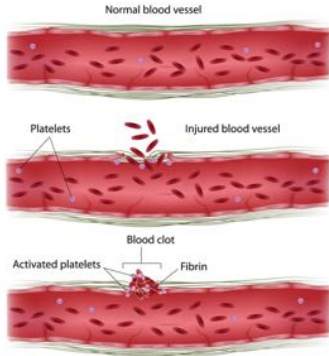
Remy Petkantchin, Franck Raynaud, Bastien Chopard
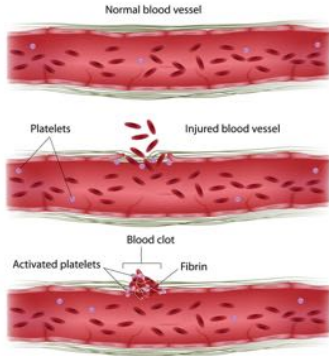
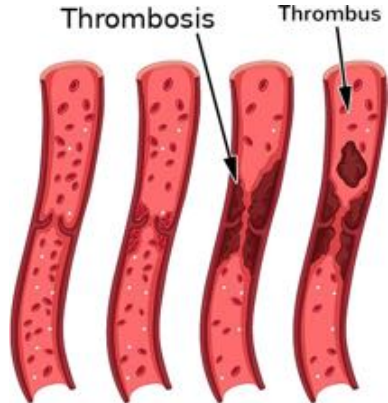University of Geneva, Switzerland.

September 25th 2019

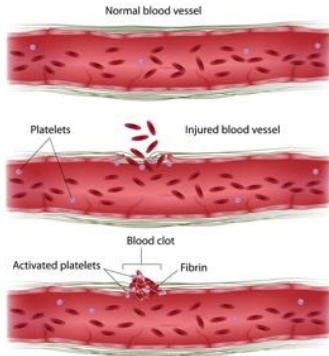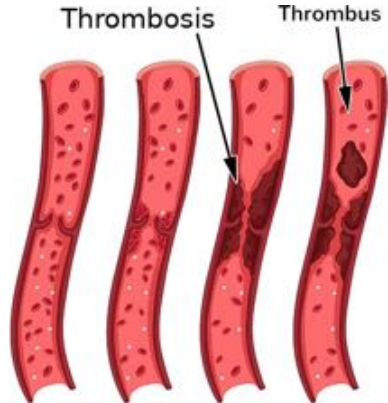# Blood clot formation

Normal blood vessel

Platelets — Injured blood vessel

Blood clot

Activated platelets — Fibrin

Blood clot formation

Normal blood vessel

Platelets   Injured blood vessel

Blood clot

Activated platelets   Fibrin

Blood clot formation

Source: https://www.blutwert.net
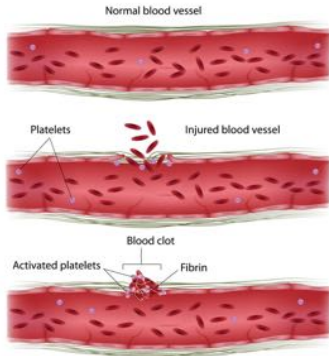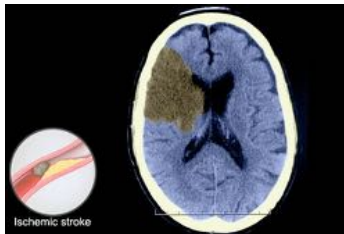
Blood clot formation

Thrombosis   Thrombus

Source: https://www.blutwert.net
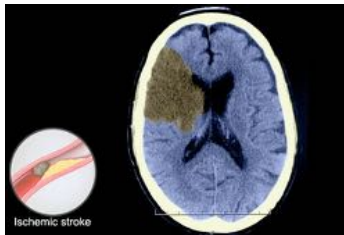
Stroke

Source: https://www.webmd.com

- ▶ 1st cause of disability and 3rd cause of death in the West
- ▶ 1+ M Europeans have a first stroke/year
- ▶ 1/3 die, 1/3 permanently disabled
- ▶ $\sim 2/3$ of treated patients become functionally dependent
- ▶ $\sim$ €27 billion/year in Europe
- ▶ Numbers rising due to population ageing

Source: https://insist-h2020.eu/
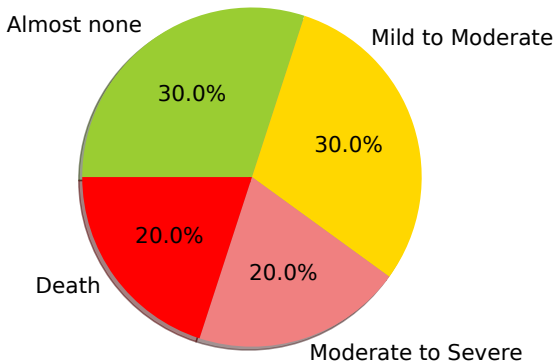
Stroke

Source: https://www.webmd.com

Treatment

- ▶ Injection of dissolving product (tPA): thrombolysis
- ▶ Mechanical removal of the clot: thrombectomy

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Source: https://insist-h2020.eu/

Neurological deficits

Almost none — 30.0%
Mild to Moderate — 30.0%
Death — 20.0%
Moderate to Severe — 20.0%

Source: https://patient.info/doctor/thrombolytic-treatment-of-acute-ischaemic-stroke

The INSIST project
In Silico Clinical Trials for treatment of Acute ischemic stroke

- ▶ European H2020 project, 9 universities + industrial partners.
- ▶ **Main purpose**: understand and predict thrombolysis and thrombectomy outcome for stroke patients.
- ▶ **Method**: generate virtual populations based on anonymous patients data, simulate treatment, and assess outcome.
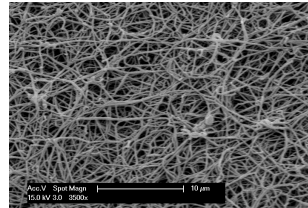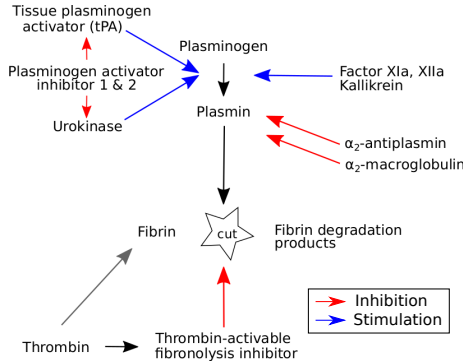
Our part in the project

UNIVERSITÉ DE GENÈVE
FACULTÉ DES SCIENCES
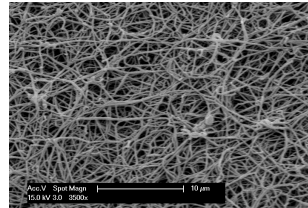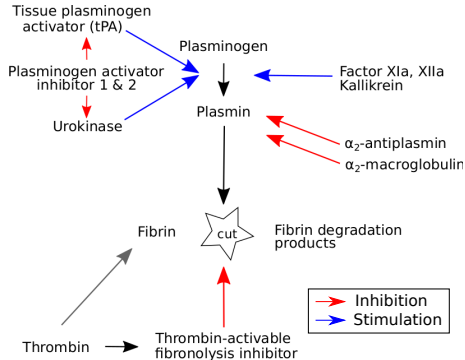
LOMONOSOV MOSCOW
STATE UNIVERSITY

▶ Thrombolysis model: why is there such variability in outcome?

▶ Thrombosis model: how and when is the clot created?

▶ Coupled thrombosis/thrombolysis model: equilibrium between clot formation and dissolution?

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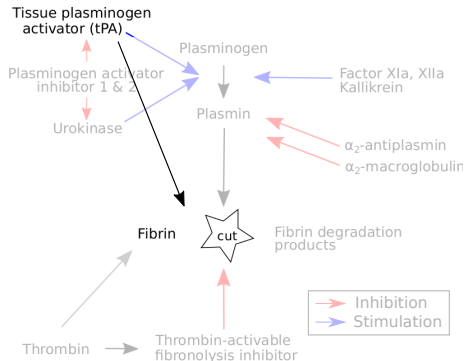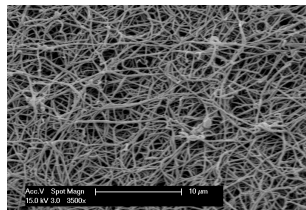
Thrombolysis

Tissue plasminogen
activator (tPA)

Plasminogen activator
inhibitor 1 & 2

Urokinase

Plasminogen

Factor XIa, XIIa
Kallikrein

Plasmin

α_2-antiplasmin
α_2-macroglobulin

Fibrin   cut   Fibrin degradation
products

Thrombin   Thrombin-activable
fibronolysis inhibitor

→ Inhibition
→ Stimulation

Inspired by:
https://en.wikipedia.org/wiki/Fibrinolysis

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M. Pantheleev's group

Model with 6 equations (6 entities).

Fibrinolysis

Tissue plasminogen activator (tPA)

Plasminogen activator inhibitor 1 & 2

Urokinase

Plasminogen

Plasmin

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Fibrin → cut → Fibrin degradation products

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Model with 6 equations (6 entities).

Simplification

Reduction to 2 entities: **Fibrin** (F_n) and **tPA**.

2-species model

Model

$$\frac{dF_n}{dt} = -k_1 F_n \cdot tPA$$

$$\frac{\partial tPA}{\partial t} = \mathcal{D}_{tPA} \frac{\partial^2 tPA}{\partial x^2} - k_2 F_n \cdot tPA$$
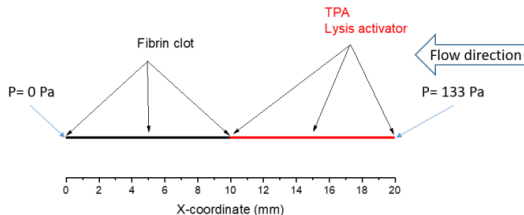
Parameters

▶ $\mathcal{D}_{tPA}$: diffusion constant.
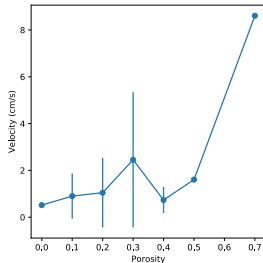
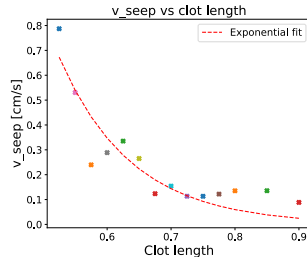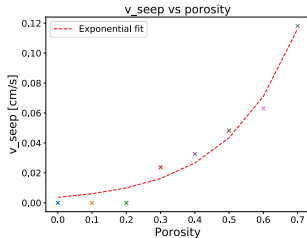▶ k_1, k_2: reaction constants.
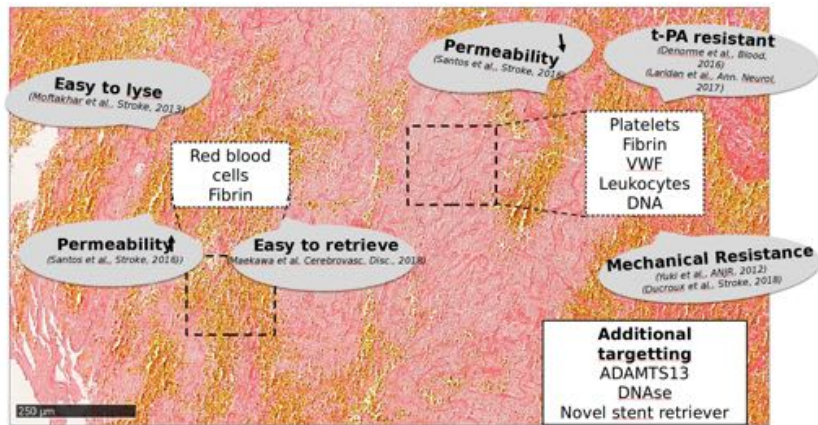
Artery model

Source: https://www.thingiverse.com/thing:1233389

Thrombolysis
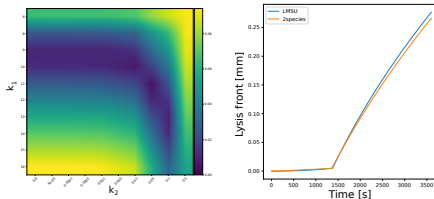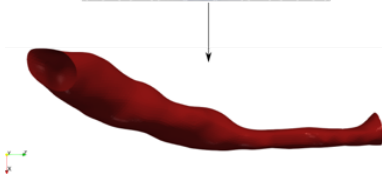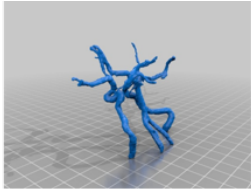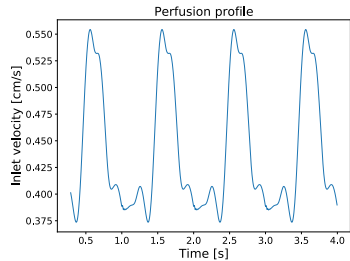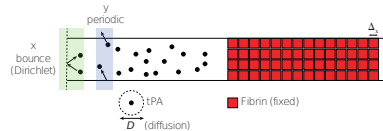
$v_{seepage}$ vs porosity and length

v_seep vs porosity
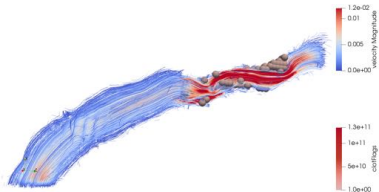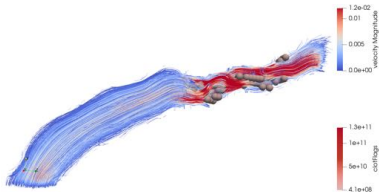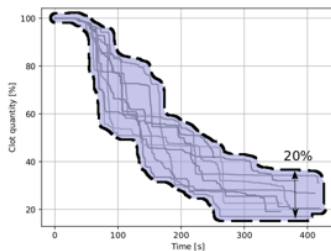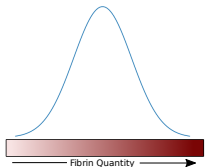

v_seep vs clot length

- ▶ Upper panel: simulation data
- ▶ Lower panel: data from 44 patients

Clot heterogeneity

Source: S. De Meyer et al. (KUL)

Clot heterogeneity

Clot heterogeneity
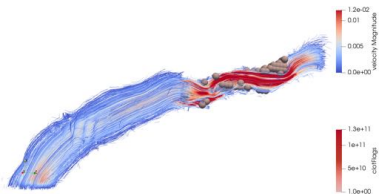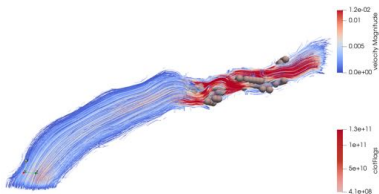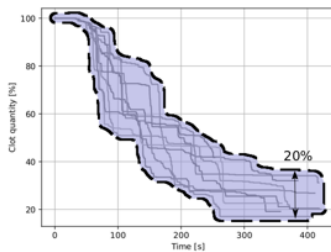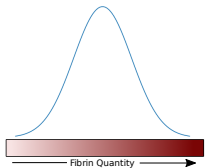
Does it explain treatment outcome? Clot representation OK?

Conclusion

Takeaway

- ▶ Phenomenology not fully grasped.
- ▶ In silico trials to optimize treatment, patient-based.
- ▶ High societal stakes.

Thank you!