Micro-flow based photoisomerization and in-flow separation process

Micro-Flow based Photoisomerization and In-flow Separation Process

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International Micro Nano Conference Amsterdam 2015

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Where innovation starts

Outline

- Introduction
- Motivation
- Photo-micro setup
- Photo reactor study
- Packed bed study
- Conclusion & Outlook

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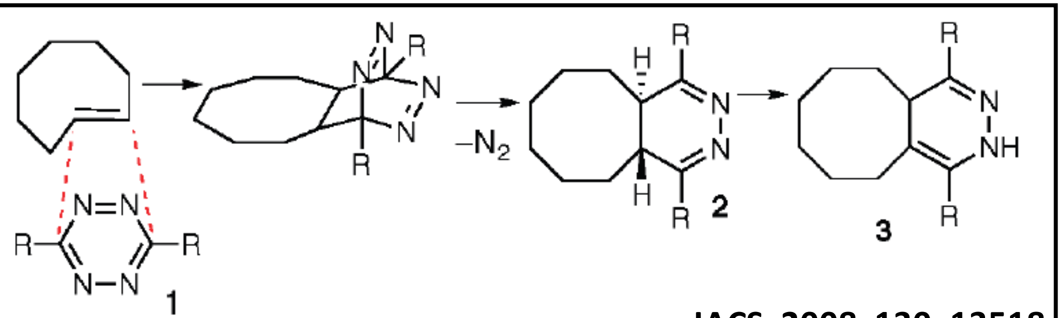
Introduction:
“Click” chemistry project - Pretargeting

The pretargeting approach:

- **Hot-topic in radiopharmaceutical research**
- **Approach that allow PET imaging of antibodies radiolabeled with fluorine-18 (antibodies and ^{18}F are otherwise not compatible in terms of pharmacokinetics)**
- **Involves a bioorthogonal reaction (inverse-electron-demand Diels-Alder reaction)**

dienophile

tetrazine

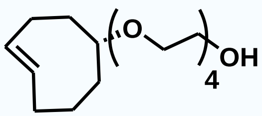


JACS, 2008, 130, 13518

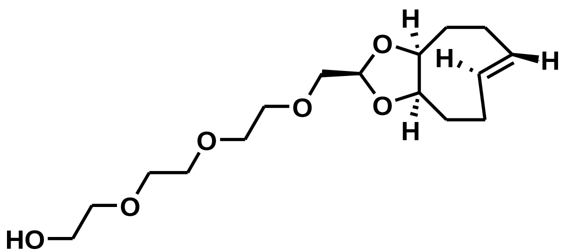
Fast kinetics, highly selective *in vivo*

Radiopharmacy lab of KU Leuven is interested in developping new dienophiles, with favorable *in vivo* properties (see next slide for structures)

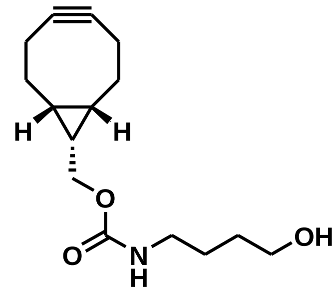
Introduction:
"Click" chemistry project - Pretargeting



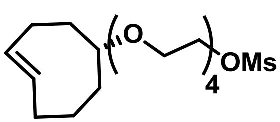
TCO-TEG-OH



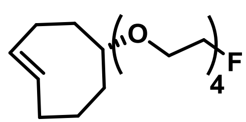
d-TCO-OH



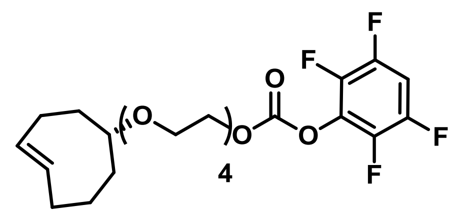
BCN-OH



TCO-TEG-OMs



TCO-TEG-F



TCO-TEG-TFP

precursor for radiofluorination

reference

conjugatable derivative

- $[^{18}F]$-dienophile + Tz-biomolecule
- $[^{18}F]$-Tz + dienophile-biomolecule
- $[^{18}F]$AlF-mHEDDA-Tz + dienophile-biomolecule

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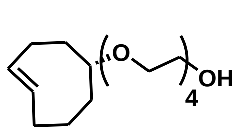
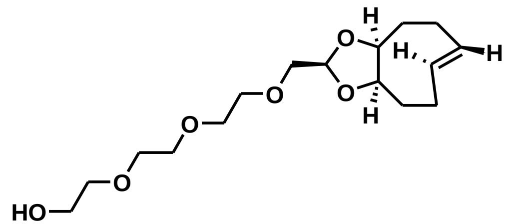
“Click” chemistry project - Pretargeting

Introduction:
Synthesis of functionalized trans-cyclooctene

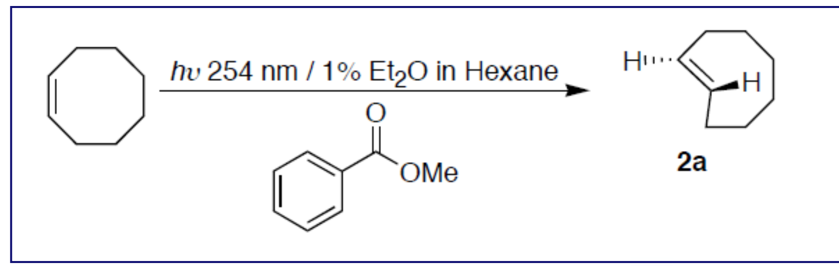


TCO-TEG-OH

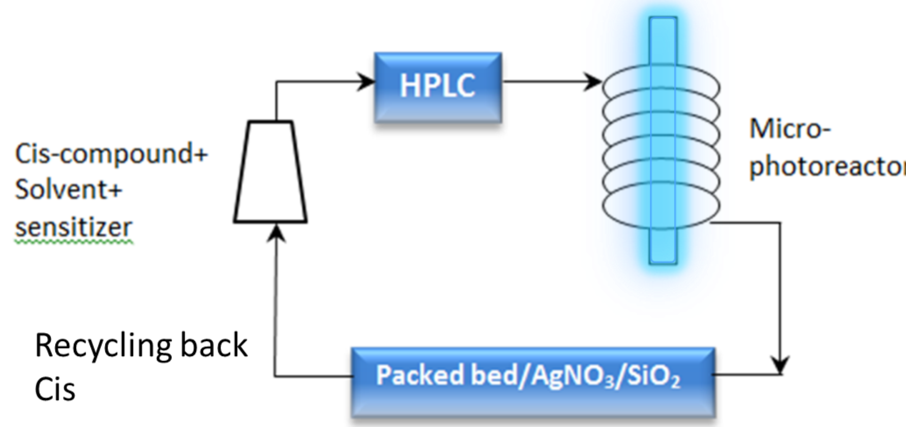


d-TCO-OH

trans **C=C**
→ photoisomerisation step



- Direct method for the synthesis of TCO
- Replacing batch reactor to microreactor
- In-flow separation process based on Ag-complexation to isolate TCO derivatives and push the equilibrium



In collaboration with Dr. Emilie Billaud, Radiopharmacy Lab, KU Leuven
Improvement of the photoreactor setup → microphotoreactor, continous-flow (at TU Eindhoven)

NOVEL PROCESS WINDOWS

- ***Process design intensifi-cation*** slow process. Thus, chemical intensification through photo-flow processing and removal of the trans isomer out of the equilibrium are required.

- ***Transport intensification*** a photo micro-flow process design with minute-range processing time and an in-flow separation process based on Ag-complexation to isolate TCO derivatives after their manufacture has been developed.

- ***New chemical transformation*** New TCO derivatives can be made by this process for in vivo pretargeted imaging

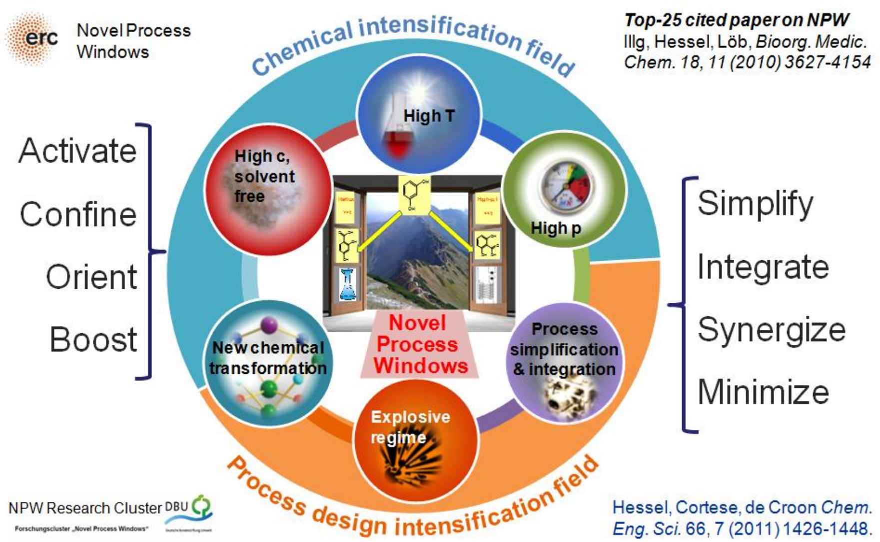
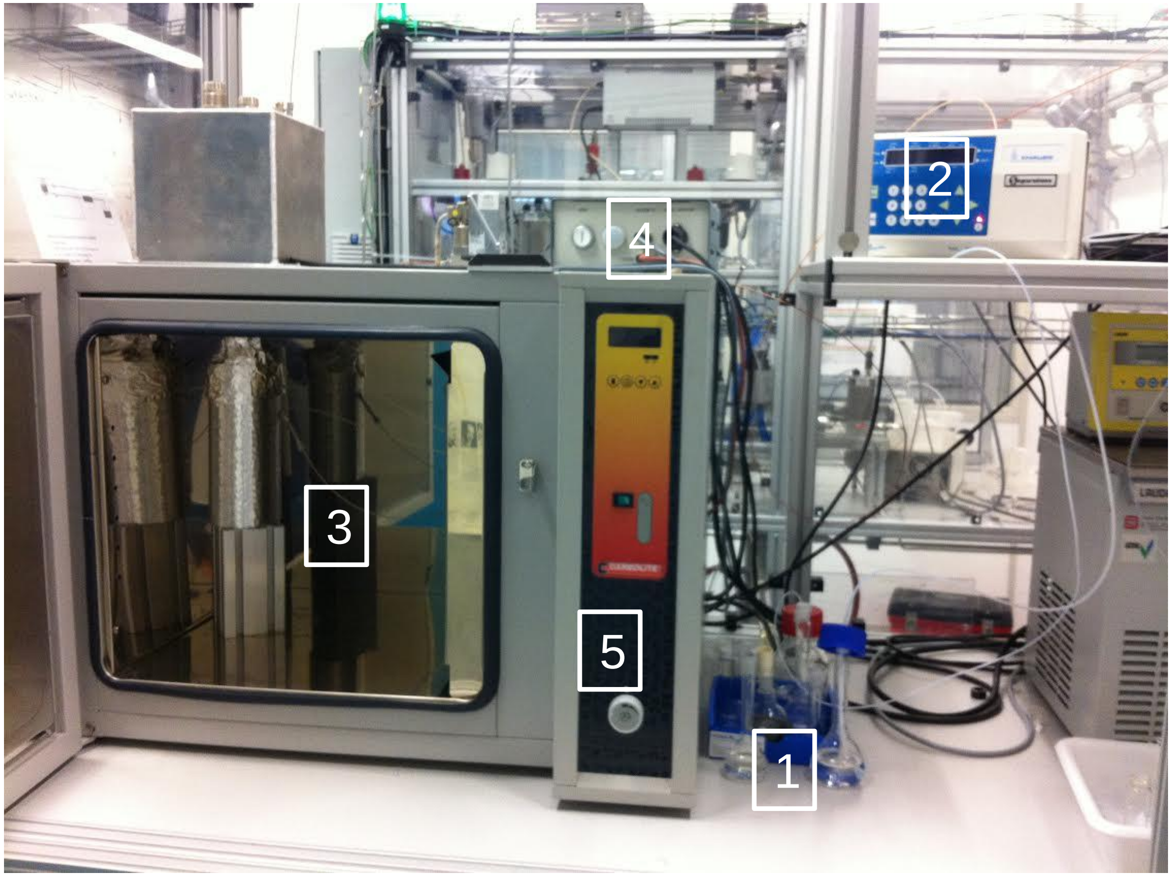


Photo-micro setup



1- Inlet and outlet of the microreactor

2- HPLC pump

3- Light source surrounded with microreactor, covered with aluminum sheet

4- light source power supply

5- Micro-photoreactor safety oven

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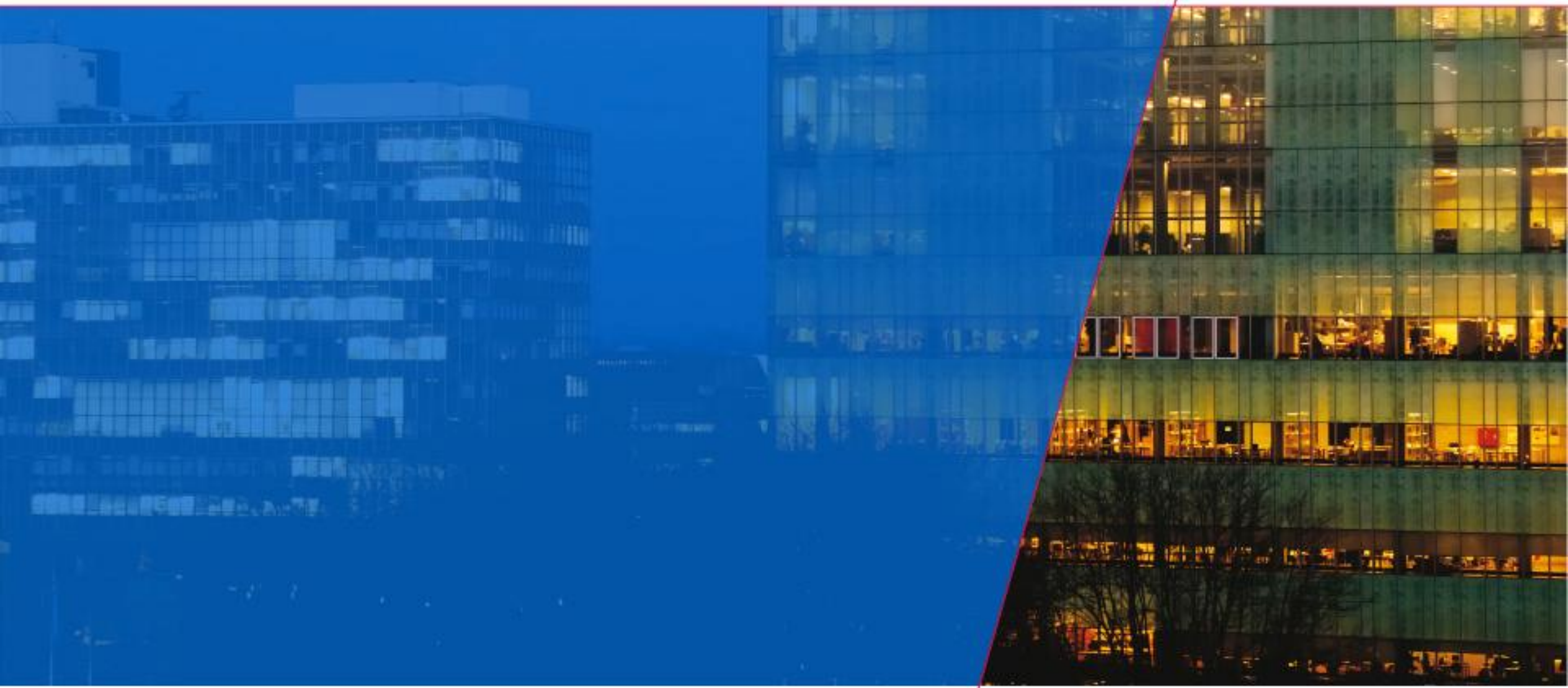

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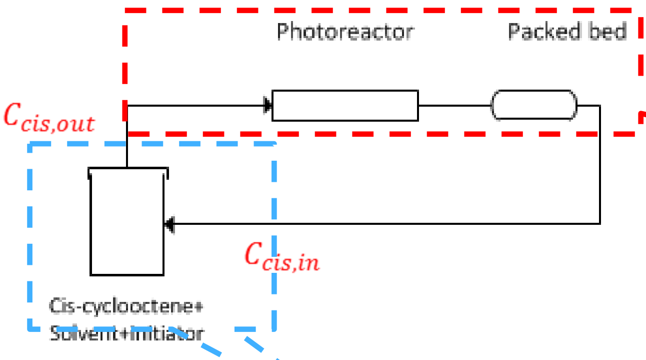
Modeling

- **In order to improve the flow setup, it is important to study photoreactor and packed bed.**



One pass without considering the packed bed:

$$Cis \rightleftharpoons Trans$$

$$r_{Cis} = k_1 \times C_{cis} - k_2 \times C_{trans}$$

$$C_{trans} + C_{cis} = C_t$$

$$r_{Cis} = (k_1 + k_2) \times C_{cis} - k_2 \times C_t$$

$$-\frac{dC_{cis}}{dt} = r_{Cis}$$

$$-\frac{dC_{cis}}{dt} = (k_1 + k_2) \times C_{cis} - k_2 \times n/V$$

$$at\ t = 0 \qquad C_{cis} = const.$$

CSTR tank:

Accumulation=Input mole −Output mole

$$[n_{cis}]_{t+\Delta t} - [n_{cis}]_t = \dot{n}_{cis,in} \times \dot{n}_{cis,out}$$

$$[n_{cis}]_{t+\Delta t} - [n_{cis}]_t = Q \times C_{cis,in} \times \Delta t - Q \times \frac{n_{cis,out}}{V} \times \Delta t$$

$$\frac{[n_{cis}]_{t+\Delta t} - [n_{cis}]_t}{\Delta t} = \left(Q \times C_{cis,in} - Q \times \frac{n_{cis,out}}{V}\right)$$

$\lim \Delta t \rightarrow 0$

$$\frac{dn_{cis}}{dt} + \frac{Q}{V} n_{cis} = Q \times C_{cis,in}$$

Modeling

- **1 set of ODE:**

$$-\frac{dC_{cis}}{dt} = (k_1+k_2) \times C_{cis} - k_2 \times \frac{n_{cis}}{V}$$

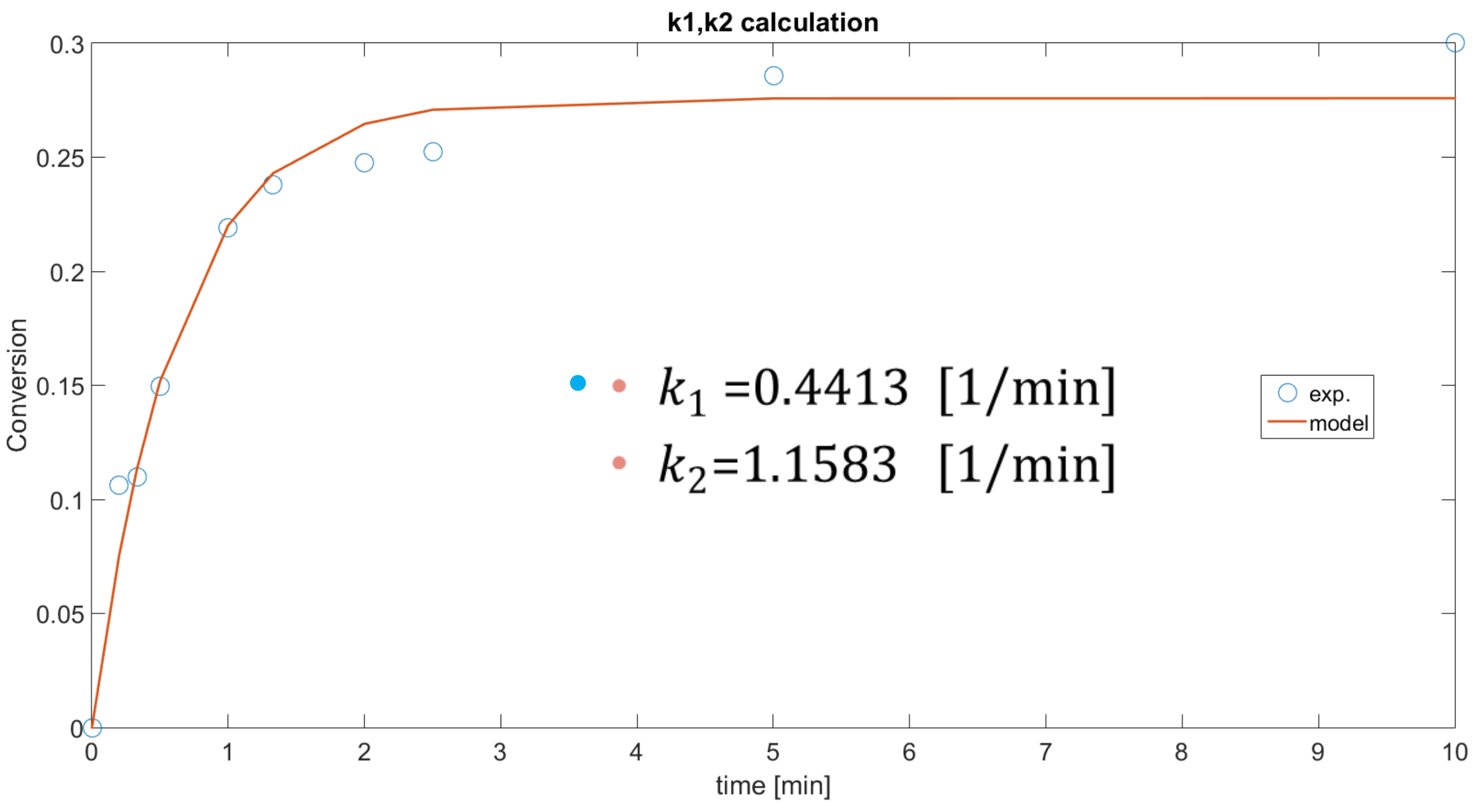
$$\frac{dn_{cis}}{dt} + \frac{Q}{V} n_{cis} = Q \times C_{cis}$$

At t=0 $n_{cis} = \frac{C_0}{V}$

At t=0 $C_{cis} = C_0$

In order to solve this set we need to know k_1, k_2.

k_1, k_2 calculation



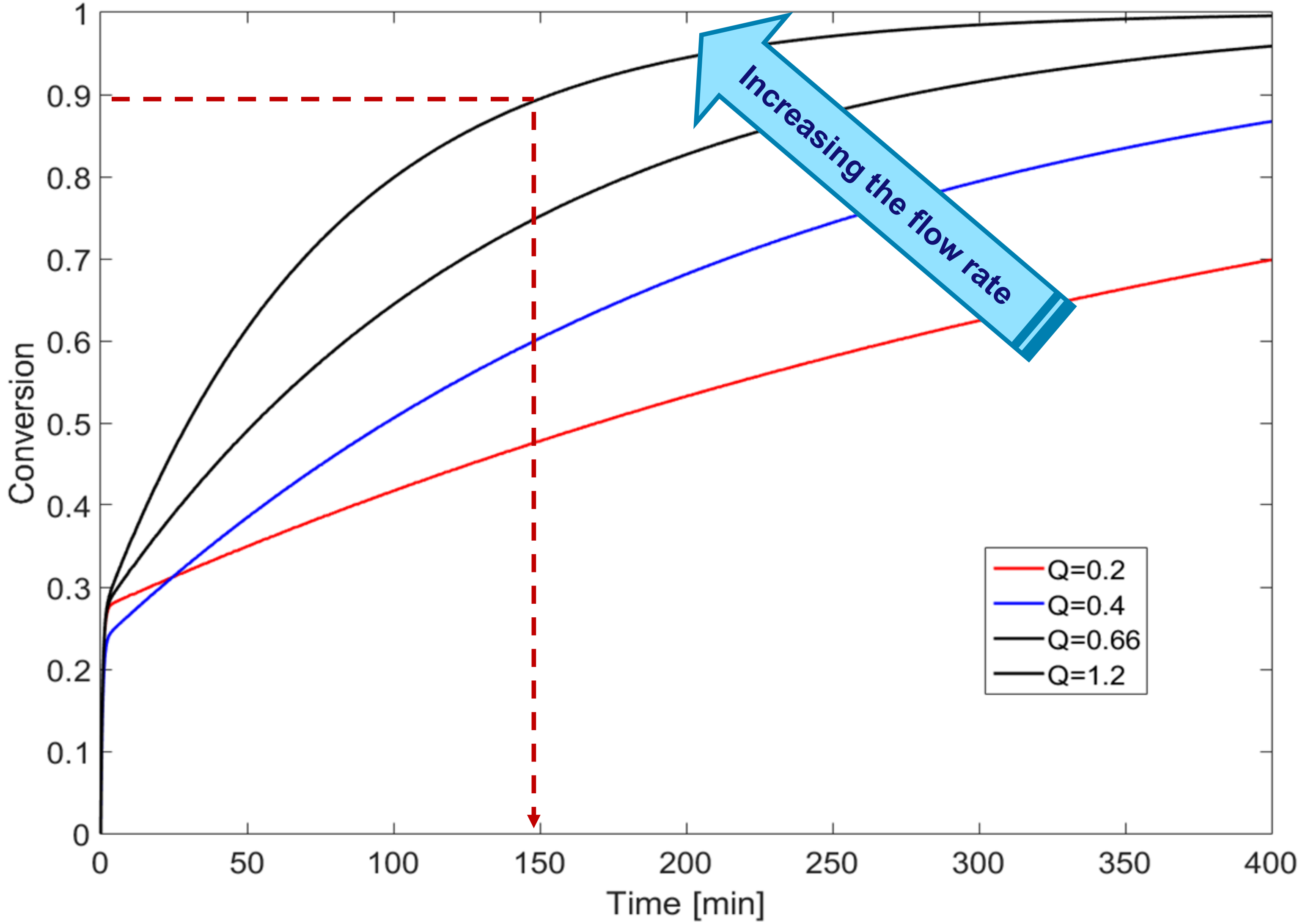
- $k_1 = 0.4413 \quad [1/\text{min}]$
- $k_2 = 1.1583 \quad [1/\text{min}]$

$$-\frac{dC_{cis}}{dt} = (k_1 + k_2) \times C_{cis} - k_2 \times C_t$$

$$at\ t = 0 \qquad C_{cis} = 0.02\ \text{M}$$

$$\Rightarrow \quad X = 1 - \left[\frac{1}{k_1 + k_2}\left(k_1 e^{-t(k_1+k_2)} + k_2\right)\right]$$

Solving the ODE

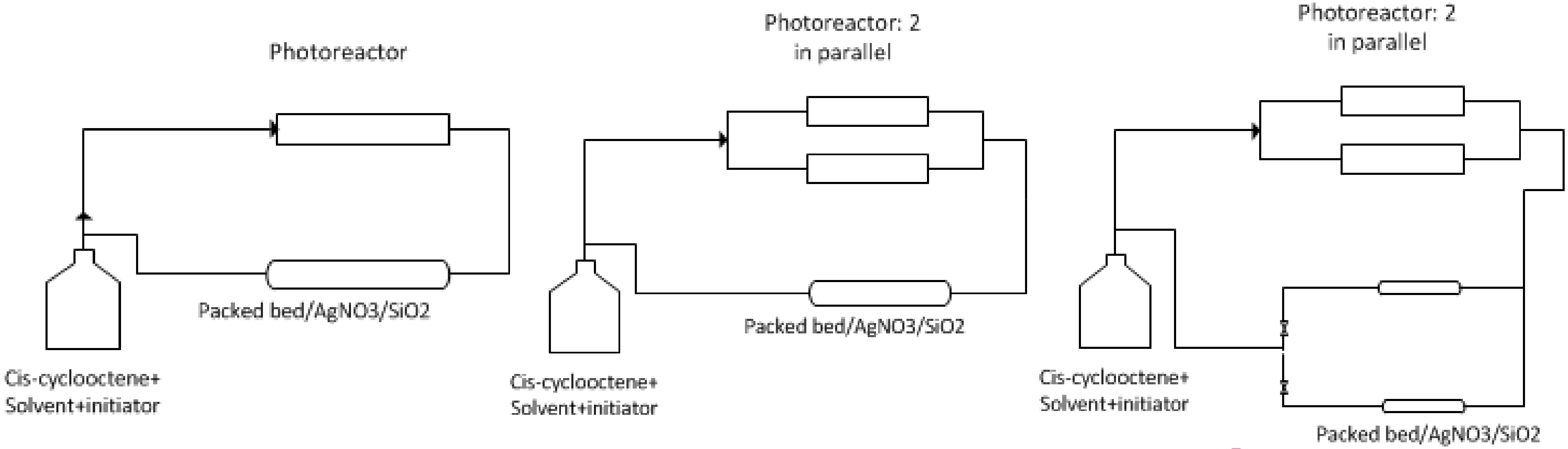


Photoisomerization

- **In order to design the photoisomerization setup, we chose as a case study to first focus on cis to trans cyclooctene since cis-cyclooceten is available commercially.**

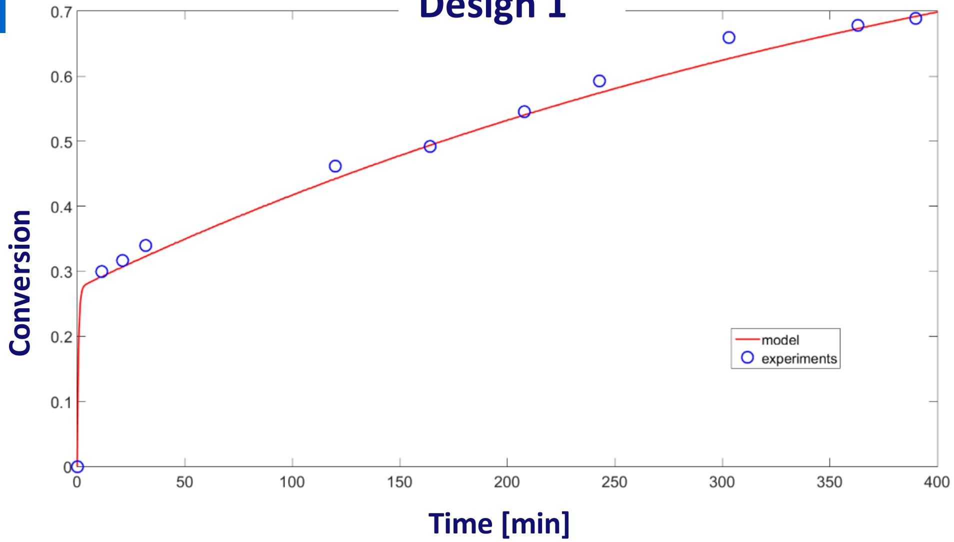
Different designs

Design 1 | Design 2 | Design 3

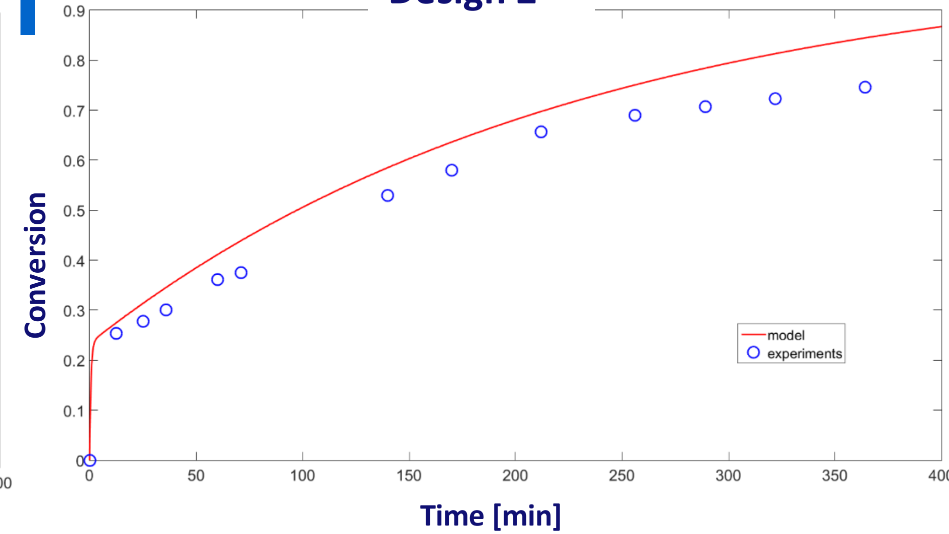


Solving the ODE

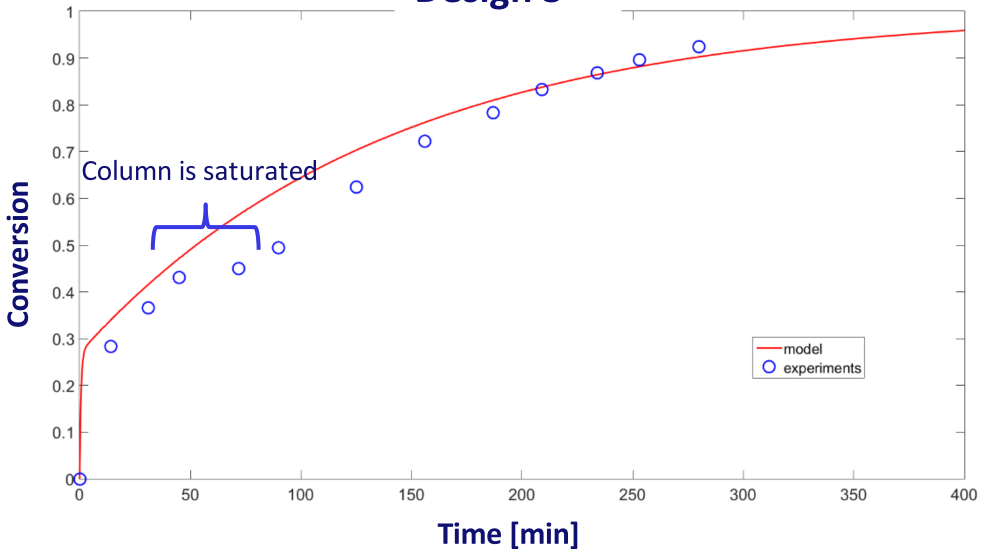
Design 1



Design 2



Design 3



- In order to complete the design it is important to know about the saturation time of the packed bed.

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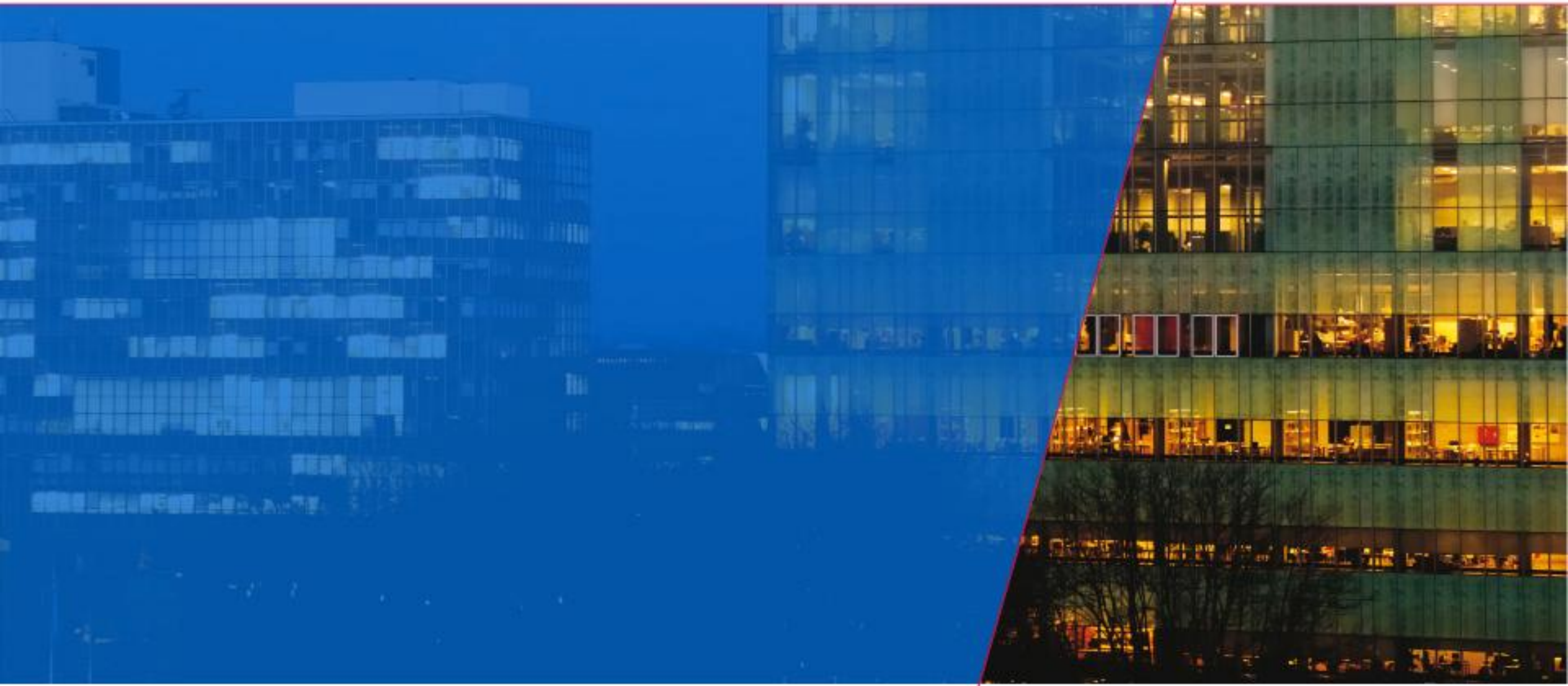

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Packed bed: Breakthrough curve

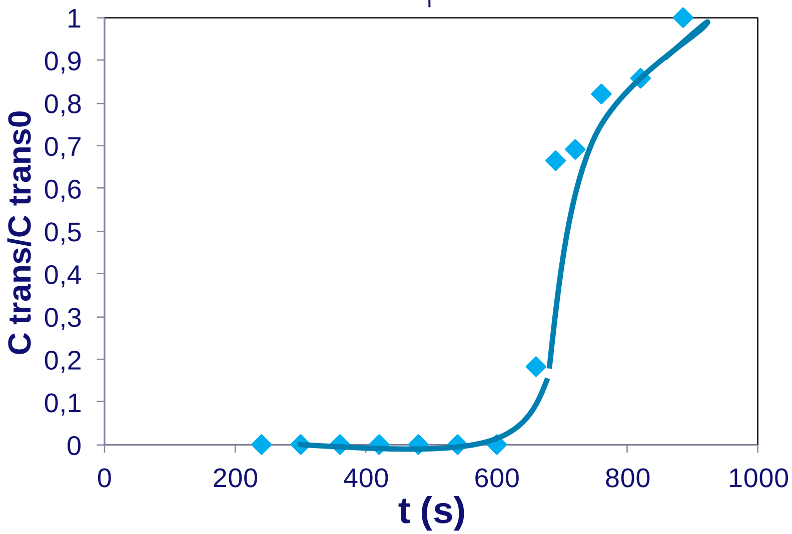
Model

Experiment

We could prove that mass transfer limitation is negligible : Intrinsic process

$$\frac{1}{k_{ads}} \gg \frac{1}{k_{mass\ transfer} \cdot a}$$

- **Local equilibrium theory:** This model is based on the equilibrium between solid and fluid concentration (Langmuir isotherm).
- **Local kinetic theory:** This model is based on the non-equilibrium surface reaction.



- Flow rate = 1 (ml/min)
- $AgNO_3$ = 200 (mg)

Conclusion & outlook

- ✓ Above **90%** conversion could be achieved within **less than 3 hrs**. In batch process 66% conversion was achieved within 12 hrs [*].
- ✓ Process integration and chemical intensification (NPW): By theoretically studying and modelling the whole process and validating with the experimental results with different process conditions, it is possible to give a methodology for scaling up the photo-microreactor with in-flow separation process.
- ✓ We already have made similar study (separation in flow) for high temperature for acid base resin (kilo-lab process) [**].

[*] M. Royzen, G. P. A. Yap & J. M. Fox, J. Am. Chem. Soc. 2008, 130, 3760-37
[**] E. Shahbazali, M. Spapen, T. Noel, V. Hessel, Chem. Eng. J. 2018, 281, 144-154

Contact me on
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Thank you

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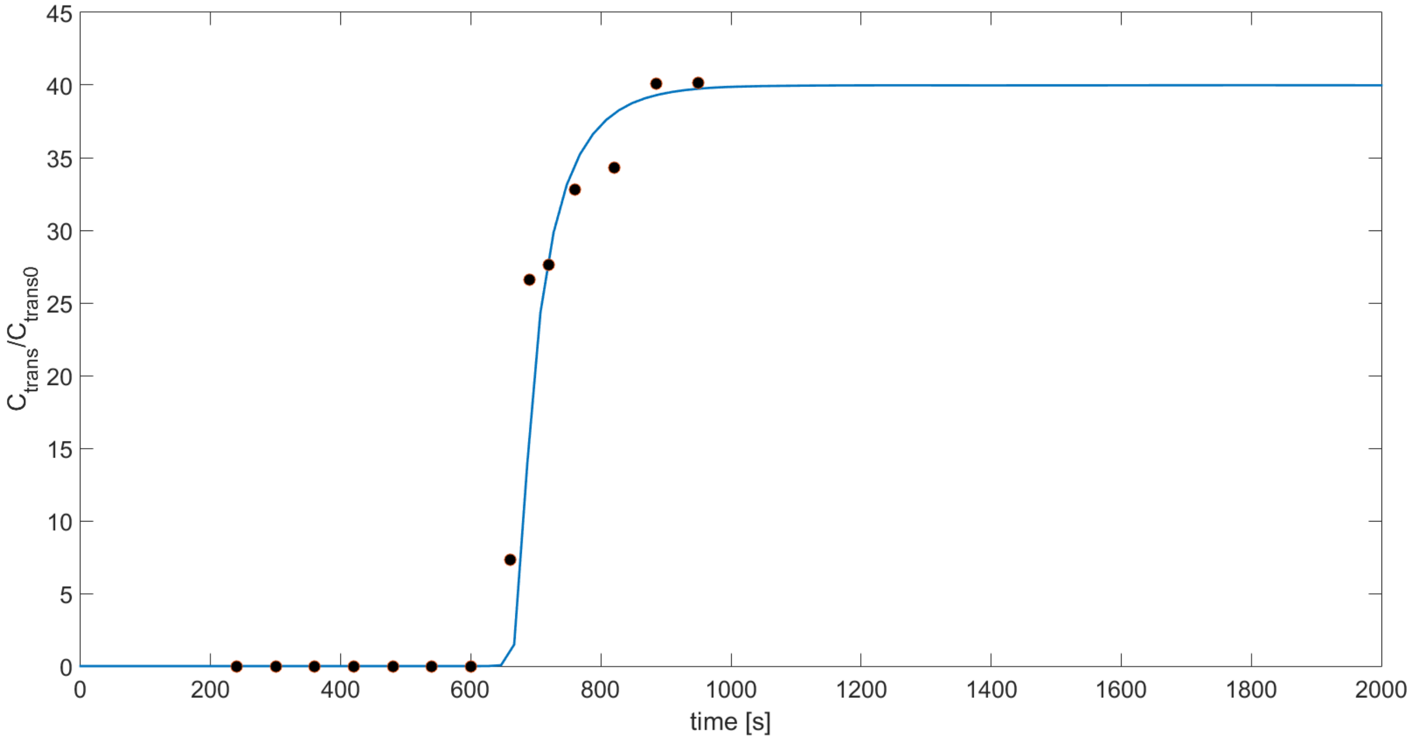
Backup slide

- **Local equilibrium theory:**



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