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LTP ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Multiple Magnetic Fixed Bed Reactor for Reproducible Coating of SPIONs

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Project Goals

Superparamagnetic iron oxide nanoparticles (SPIONs) have become important for various *in-vivo* and *in-vitro* biomedical applications such as imaging, magnetic separation, biosensor devices, diagnostics, to therapeutics. For a successful applications, synthesis and coating processes has to be developed, which guarantee a high quality and reproducibility of the surface properties of the nanoparticles. **Our central goal is to develop solid phase synthesis strategies with magnetically immobilizing SPIONs for surface derivatization, using a fixed bed magnetic reactor approach with a quadrupole repulsive arrangement of permanent magnets. [1, 2] In this way, colloidal instabilities due to pH changes, washing steps and solvent exchanges are avoided. In this contribution, the layout and experimental set-up of the reactor for a fully automated surface modification of SPIONs is presented.**

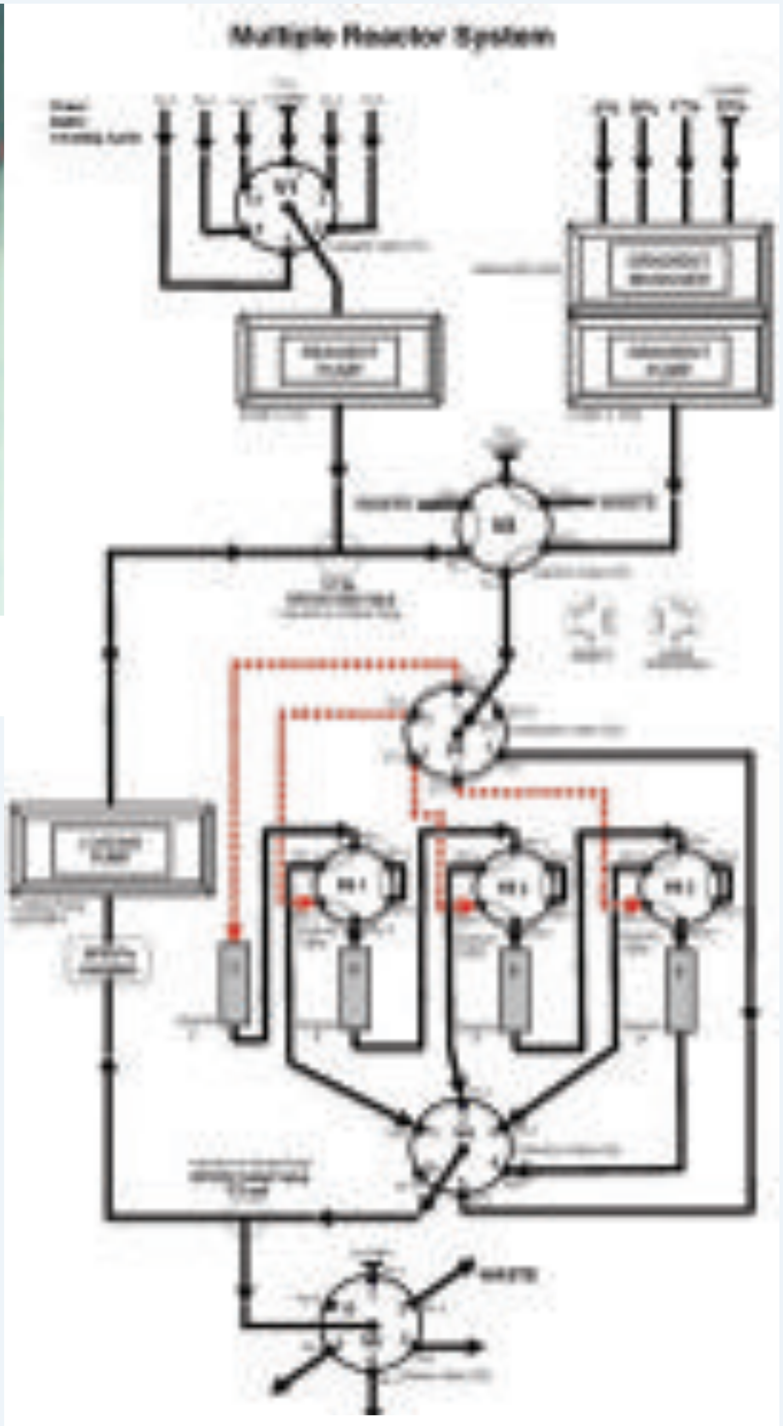
Reactor Set-up

The reactor is designed with a simple and robust hardware (valves, pumps) such to transfer the complexities of the coating process into the automation software. A *LabView* program provides a maximum of possibilities to control the different reactor units and modulate the coating process in view of final transfer of technology to the industrial partner.

Automated magnetic fix bed reactor (1 module) experimental set-up

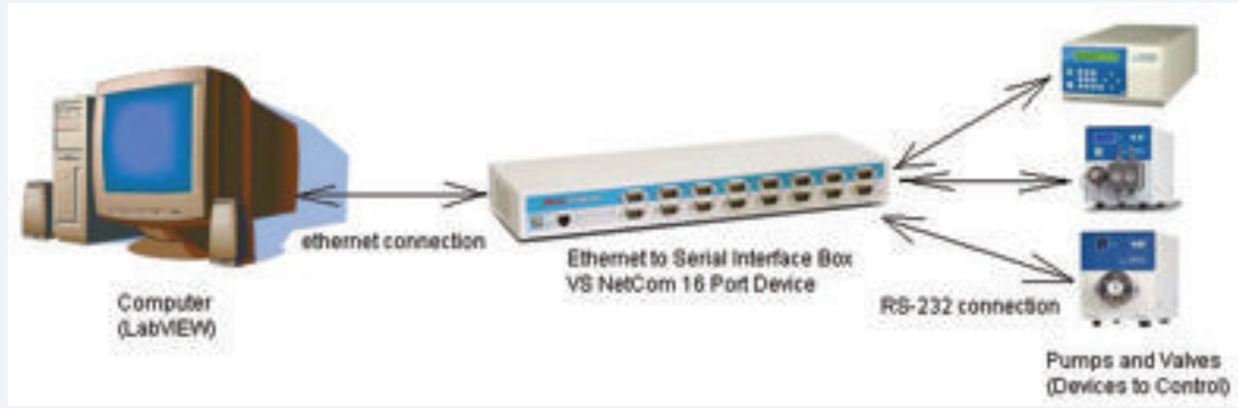
The reactor is made of modules, starting with 4 individual magnetic fixed bed units. In a later stage, the reactor will be implemented of additional modules having each 4 reactor units. The reactors can run independently, sequentially or in series.

<u>Individual Devices</u>
- 1 gradient manager
- 3 pumps
- 4 channel valves (12-16 outgoing channels)
- 4 switching valves (V2, FR1, FR2, FR3)
- 2 solenoid valves (V5)
- 4 magnetic reactors

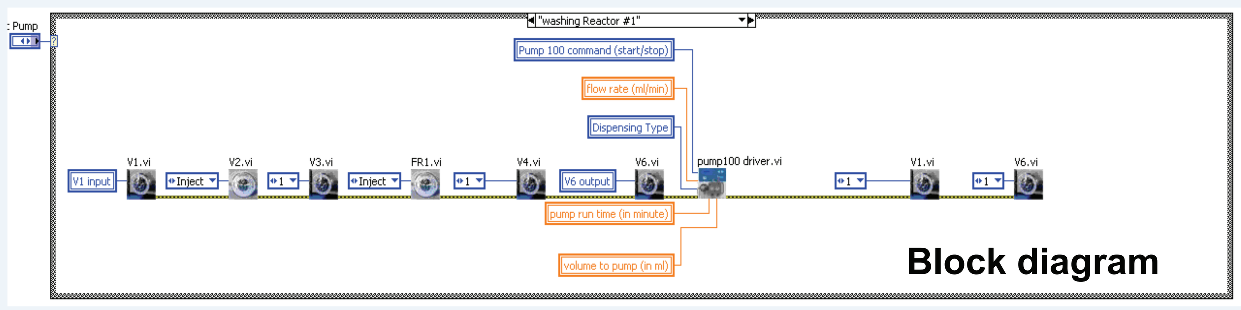


Schematic representation of the reactor individual devices and layout

Connecting hardware with software

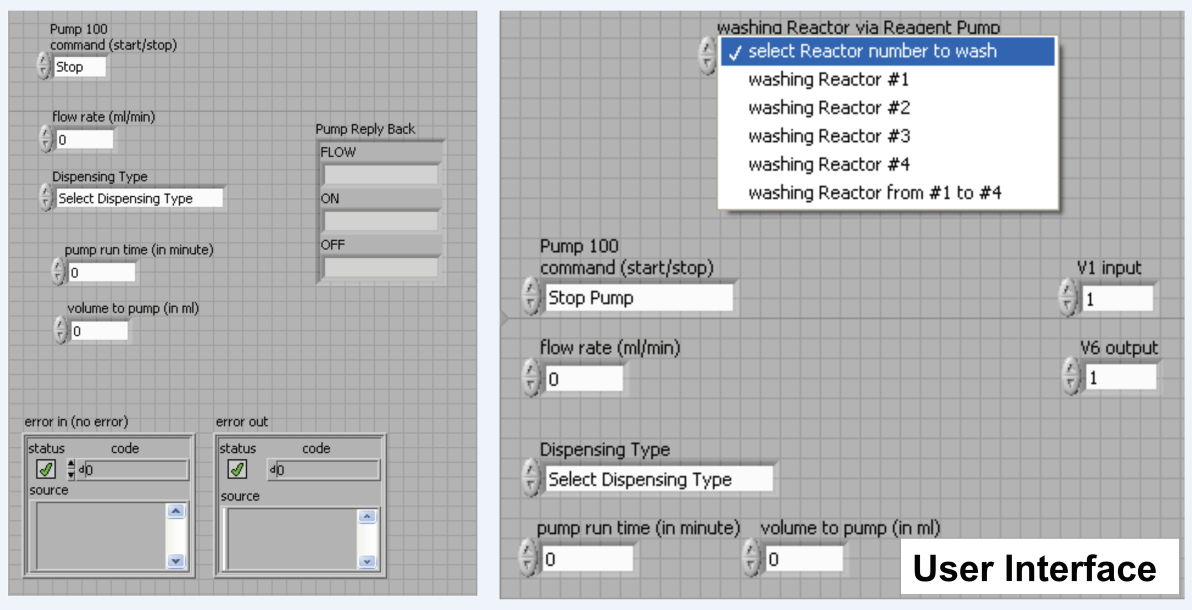


Programming Unit Operations with LabView



Block diagram

- ❑ 50 Unit Operations
- ❑ Access individual device (pumps, valves, reactors)
- ❑ Control each step, e.g. loading of particles, reactants, washing steps
- ❑ Control the coating processes (combined Unit Operations) for fully automated device and variables e.g., reactor, flow, time, valve position

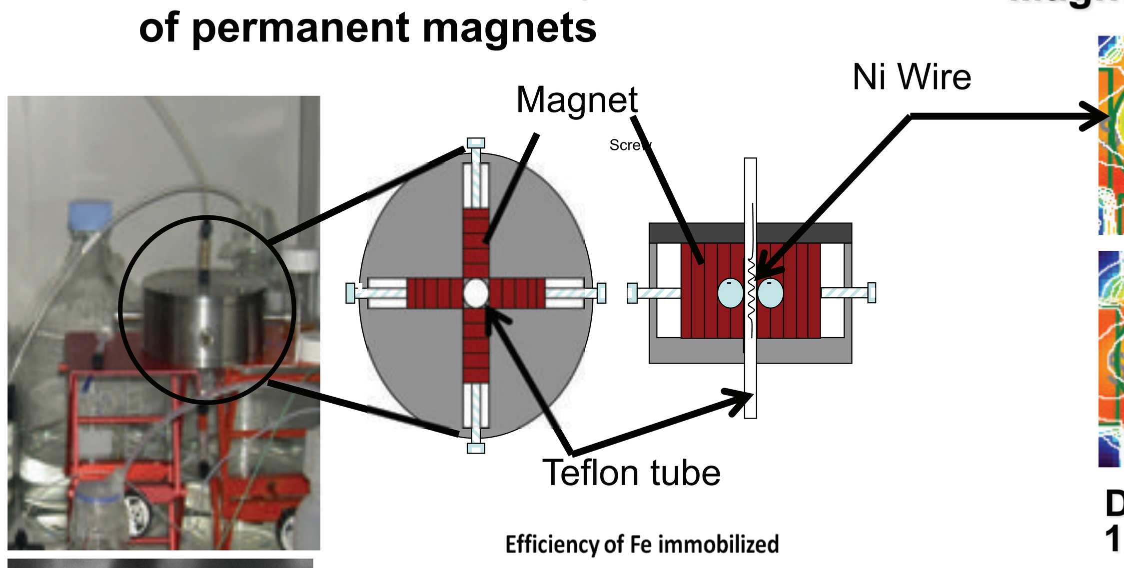


User Interface

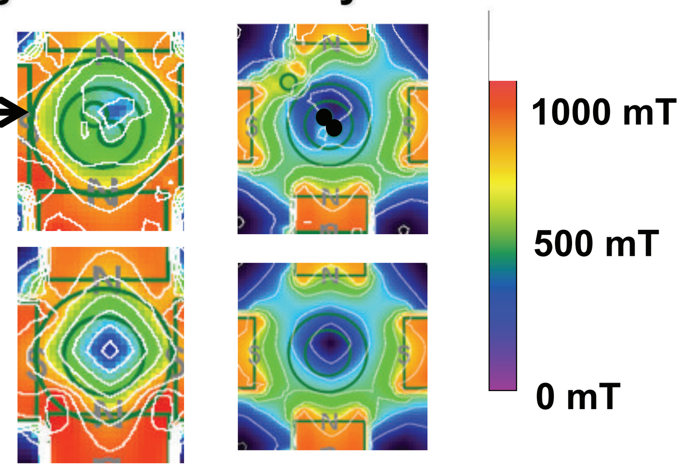
<u>Example: Wash with water in series Reactor 1-4 via Gradient Pump</u>
(gradient manager 5050) -> Pump S1000 (ml) -> V2 -> V3 out 1 -> reactor 1 -> Fr1 -> reactor 2 -> Fr2 -> reactor 3 -> FR3 -> Reactor 4 -> V4 in4 -> V6 out1

Magnetic Solid Phase Reactor

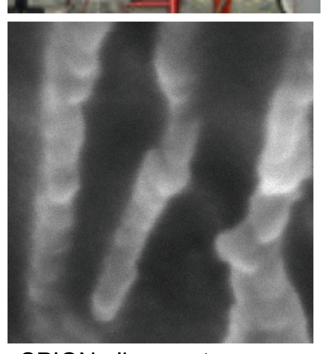
Quadrupole repulsive arrangement of permanent magnets



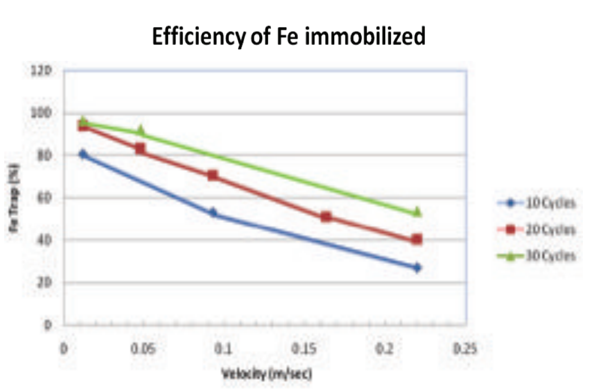
Magnetic flux density in the reactor tube



Distance of magnetic poles: 11 mm 22 mm



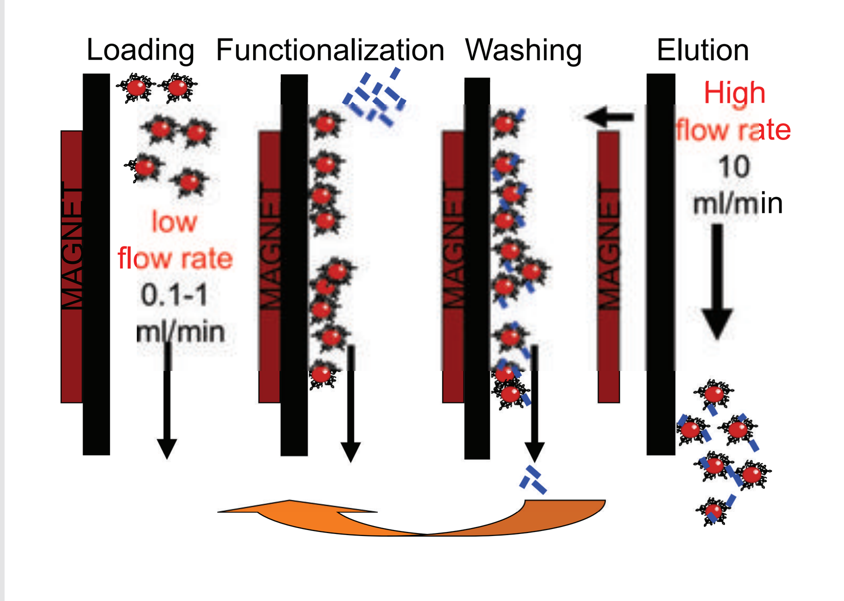
SPION alignment : mean relative distance 100 nm



- ❑ To immobilize particles within the reactor tube, it is necessary to arrange the magnets as close as possible, e.g. shortest possible distance between the magnets is 11 mm. Ni/Fe wires induce an inhomogeneous field with high magnetic gradient promoting particle immobilization in high yield
- ❑ Maximum loading: 3-5 mg calculated for SPION (4 ml of 2 mg) circulation 20 min at 0.5 mg/ml

Outlook

Surface Derivatization of SPION



- ❑ Control volume and flow rate of elution step
- ❑ Reduce solution contamination during the process
- ❑ Reduce colloidal instabilities due to pH changes, washing steps and solvent exchanges
- ❑ Fast and efficient purification steps performed by a continuous washing at high flow rate

- ❑ **Reactor validation with increased loading to 10 ml/reactor**
- ❑ **Surface derivatization with biomolecules, e.g. peptides**
- ❑ **Labeling with fluorophores, e.g. Cy5,5 for dual mode detection**
- ❑ **Protein separation**
- ❑ **High quality and reproducibility of the surface properties**

Publications

- [1] Benedikt Steitz, Jatuporn Salaklang, Andrija Finka, Conlin O'Neil, Heinrich Hofmann, Alke Petri-Fink, Bioconjugate Chem. 2007, 18, 1684
- [2] Jatupron Salaklang, EPFL thesis n° 4539 (2009) "Advanced surface derivatization of supermagnetic iron oxide nanoparticles in a fixed bed magnetic reactor for bio-application