HPC needs for product and process development in pharmaceutical R&D

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Chiesi
People and ideas for innovation in healthcare

My personal experience with HPC

With almost 10 years of academic research in the field of material science and non-equilibrium phenomena at the nano-scale I had the opportunity to deepen my knowledge in several different simulation techniques:

- Quantum mechanical calculations (DFT) + little experience in MPI parallel programming (Quantum Espresso)
- Non-equilibrium MD, Green function MD for friction, wear and lubrication modelling (LAMMPS + self-developed codes)
- Classical Montecarlo simulation of phase transitions (self-developed codes)

After joining Chiesi almost 2 years ago I started working on:

- DEM modelling of granular material flows (LIGGGHTS)
- CFD simulation of nitrogen in milling circuits (Comsol, OpenFoam)

Largest calculation ever performed:

Classical MD simulation of AFM tip sliding on a substrate undergoing a phase transition

Running on 4096 cores @ Supermuc (LRZ)

Through a PRACE project.

HPC infrastructures used:

CSCS
Centro Svizzero di Calcolo Scientifico
Swiss National Supercomputing Centre

CINECA

ZIH
Zentrum für Informationsdienste und Hochleistungsrechnen

lrz Leibniz Supercomputing Centre
of the Bavarian Academy of Sciences and Humanities

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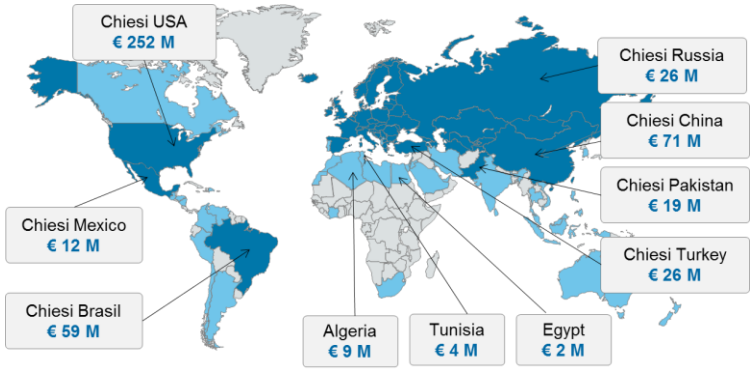
Chiesi in a nutshell



Investments in Research and development:

- 1st among Italian pharmaceutical companies
- 4th among Italian manufacturing Companies
- 17th among the European Pharmaceutical companies

More than >4000 employees worldwide

In 2016 **Chiesi** is the 1st Italian pharmaceutical company in Europe for patent deposits

- More than 2900 Worldwide patents in the portfolio Chiesi (12.31.2016)

FOSTER BUDIAIR Peyona ATIMOS BRAMITOB BREXIN
FOSTER NEXThaler HOLOCLAR Envarsus Clenil clipper CUROSURF Glybera

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Why modelling in pharma industry

Three reasons for adopting modelling in pharmaceutical industry:

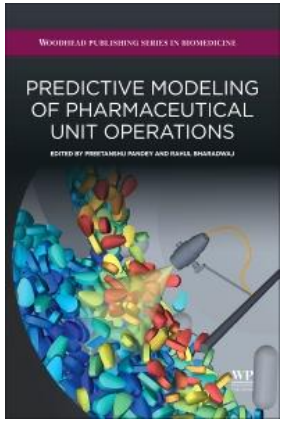
- Increasing complexity of the drug products in terms of design, development and production
- Regulatory authorities (FDA, EMA and IAFA) mandates the use of Quality by Design principles in the process design and manufacturing of drug products.

Guidance for industry PAT (2004) FDA
https://www.fda.gov/downloads/drugs/guidances/ucm070305.pdf

ICH guidelines Q8 (2004)
http://www.ich.org/products/guidelines.html

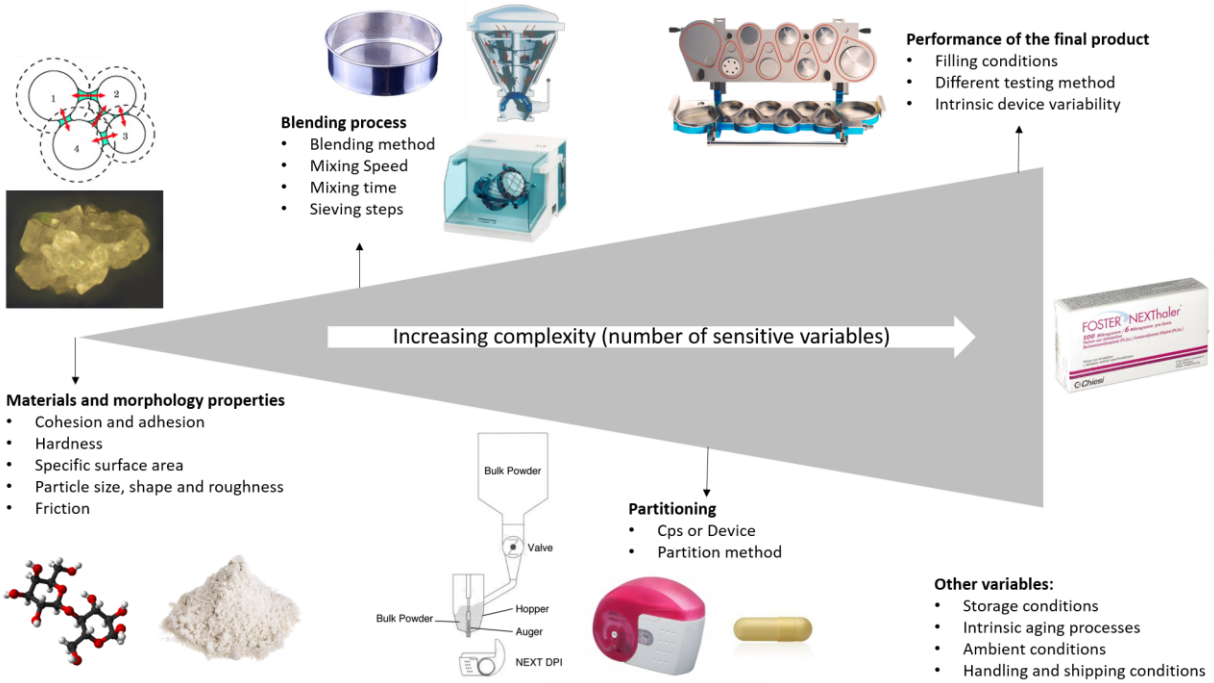
Within the QbD guidelines modelling and simulation are explicitly conceived as *a tool to foster and strengthen qualitative and quantitative prediction and understanding of the impact of process parameters and material attributes on the overall quality of the drug product*.

regulatory authorities encourage modelling and simulation to assure product quality + *high complexity of products and processes* → *HPC infrastructures will be soon necessary*



- Business (e.g. shortening of the time to market, LCL, Industrial operations)

From starting materials to finished product



- Product formulation
- Process design
- product/process interaction
- Process scale-up from lab. to pilot plant
- Process transfer to production plants

- Powder milling
- Powder mixing
- Powder dissolution

- Material characterization (chemical, physical)
- Powder rheology characterization

Current limitations and perspectives

Our current calculations are mainly based on DEM or coupled DEM-CFD algorithms. Some times we use them to have a qualitative understanding of what is going on during a unit operation, some times we would like to have some quantitative prediction, however we do see some limitations:

- The reduced particle size (1-100 µm) calls for a **small integration time-step** whilst the processes to be modelled are 10-120 minutes long;
- Long simulated time on hundreds or thousands of cpus means long simulation time;
- The total particle number to be evolved in time, for a realistic system size, can easily reach **10-50G**;
- For certain applications where poly-dispersed powders are present with a particle size ranging over 2 orders of magnitude a multiple time-step approach might be needed. **New algorithms** to deal with these challenging simulations are under development and only few prototype codes exists, are they **HPC ready**?
- **Visualizing and post-process** a simulation with 10M particle is by itself a challenge that requires HPC resources and dedicated hardware and software

Possibile future needs:

- Pay-per-use cpu time for **quick service applications**, large cps time consumption for a very limited time
- Flat HPC resources for **longer term** research activities, scouting of new possible modeling techniques and **co-development** of new algorithms and solutions.

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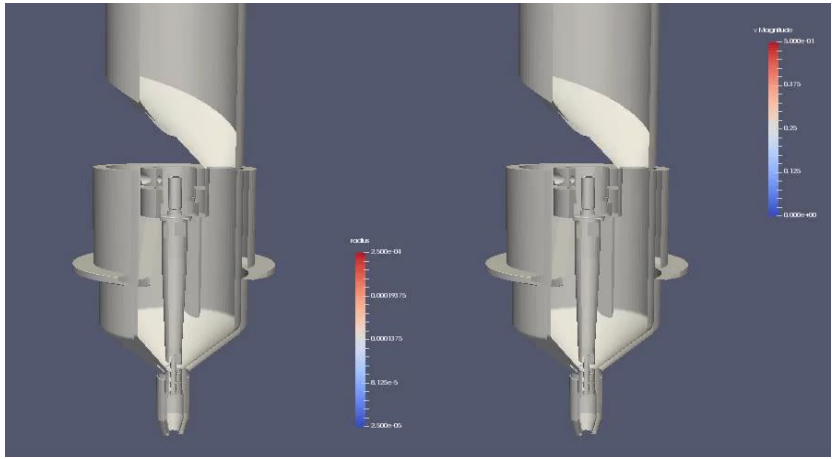
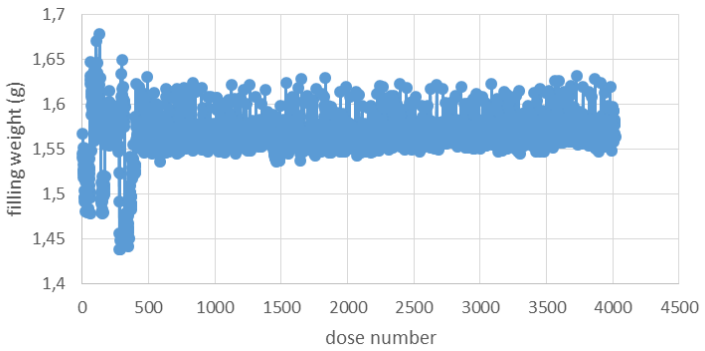
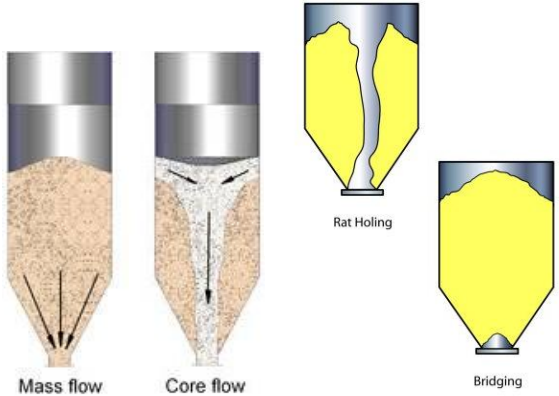
Case study: tailoring a filling system



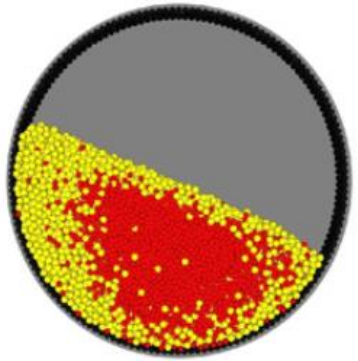


Down-scale of a factor 2 on the system size (50g simulated vs. 300g in reality) 5M poly-disperse particles with realistic particle size. Run on CINECA's Marconi on 720 CPSs for 8-10 days to simulate few tens of doses, 4K doses would be the optimal target.

- realistic dispersion of particles
- Realistic particle size
- Almost realistic plant size
- Strong computer time limitation



Plenty of possibilities for HPC applications



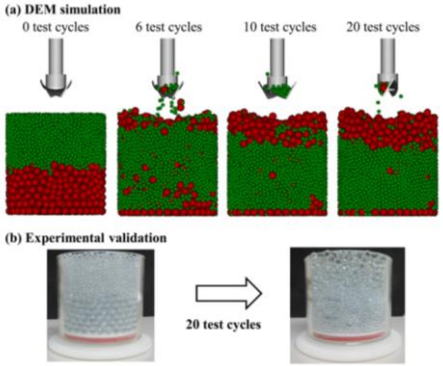


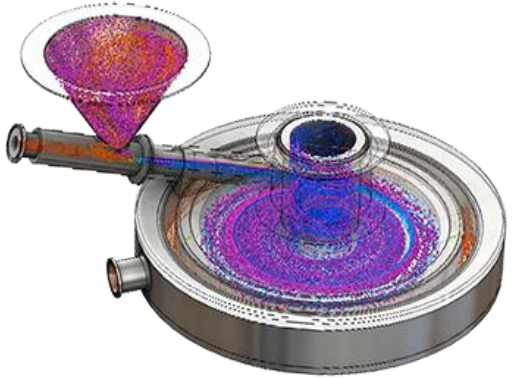
Fig. 3. Segregation observation in the calibrated DEM simulations and FT4 validation experiments using 2 mm and 4 mm glass beads.

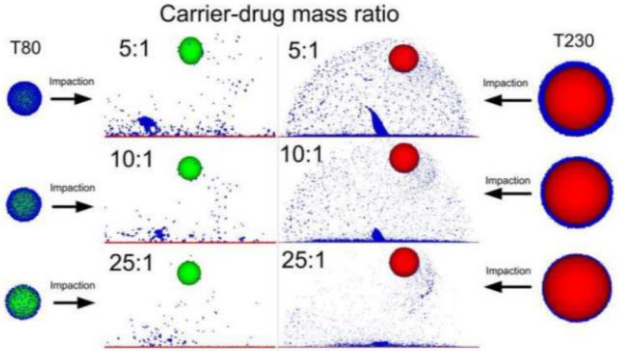
Powder mixing unit-operations

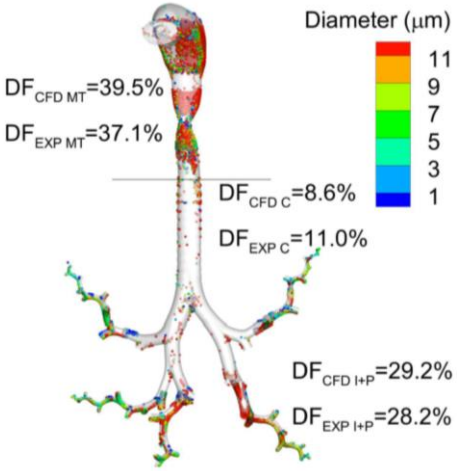
Jet milling and powder comminution

Simulation of powder rheology experiments for data interpretation

Modeling drug delivery in the patient body







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