CFD DEM Analysis of a Dry Powder Inhaler with containerization MFiX on Cloud

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Outline

- Introduction
  - DPI
  - MFiX
  - Dakota
- Framework to implement MFiX in Dakota
- Verification and Validation
- Results
Introduction

• Inhalation Therapy refers to direct delivery of the medications to/via the lungs by inhalation
  ◦ Regional Therapeutic Effect
    ◦ Respiratory Disease
      ◦ Asthma and Chronic obstructive pulmonary disease (COPD)
      ◦ Pulmonary Hypertension
  ◦ Advantages of Inhalation Therapy
    ◦ Delivery of the Medications Directly to the Action Site
    ◦ Rapid Onset
    ◦ Enhanced Bioavailability by Avoiding First Pass Effect

Introduction

Inhaler Considerations

Types of Inhaler

- Dry Powder Inhaler (DPI)
- Pressurized Metered Dose Inhaler (pMDI)

Formulation:
- Can be efficiently aerosolized?
- Stability
- Safety
- Cost

Efficient delivery to site of action: Consistent doses

Patient:
- Socioeconomic situation
- Age
- Condition
- Personal training

Device:
- Design
- Ease of use

Image sources: http://www.whitehousepharmacy.co.za/medicine-usage-guides/breath-actuated-inhalers/
Introduction

- Most common form of inhalers.
- Medication stored in solution in a pressurized canister.
- Propellants should be nontoxic, nonflammable, and compatible with drugs

- Breath-activated inhaler
- Works immediately
- DPI does not contain a propellant

- Strong inhalation is required
- Drug in loose powder form
  - Micronized drug particles (1-5µm)
Introduction

Types of DPI

- Dry powder inhalers
  - Nonreusable dry powder inhalers
    - Single dose systems
    - Multiple dose systems
  - Reusable dry powder inhalers
    - Single dose systems
    - Multiple dose systems

SD: singledose
Introduction

Working principle of a DPI
## Future Challenges of DPI

<table>
<thead>
<tr>
<th>Challenge/objective</th>
<th>Solution</th>
</tr>
</thead>
</table>
| Reducing patient errors                          | Simple self-intuitive DPI design  
Minimal number of handling steps  
The same inhaler for all inhaled medication |
| Improving patient compliance with the inhalation instruction | Simple, self-intuitive DPI design  
Feedback on inhalation performance |
| Improving patient adherence to the therapy       | Minimizing the number of inhalations per dose  
Simple, compact DPI design  
Minimal number of handling steps |
| Improving safety                                 | No unnecessary excipients  
Disposal inhalers for special applications e.g. hygroscopic drugs, vaccines, antibiotics (when the risk of bacterial resistance development in the DPI) |
| Improving efficacy                               | More powerful inhaler design (balancing between inter particulate, dispersion, and disposition forces) |
| Specialized inhalation                           | Patient (group) tailored DPI design |
| Reducing the costs of inhaled therapy            | Simple and cheap (but effective) DPI design  
Simple drug formulation technologies |
MFiX

MFiX is
• a multiphase CFD software
• developed by NETL (Opensource)
• a legacy code written in Fortran

Provides a suite of models that treat the carrier phase (gas phase) and disperse phase (solids phase) differently.
• MFiX-TFM (Two-Fluid Model)
• MFiX-DEM (Discrete Element Model)
• MFiX-PIC (Multiphase Particle in Cell)
Dakota has grown significantly beyond an optimization toolkit.

- state-of-the-art optimization methods,
- methods for sensitivity analysis, parameter estimation, uncertainty quantification, and verification

The toolkit provides a flexible and extensible interface between simulation codes and iterative analysis methods.
Consider variable characterizations, model properties, ultimate UQ goal to choose a method

Sampling (Monte Carlo, LHS)
- Robust, understandable, and applicable to any model
- Slow to converge
- Moments, PDF/CDF, correlations, min/max

Stochastic Expansions
- Surrogate models tailored to UQ for continuous variables
- Highly efficient for smooth model responses
- Moments, PDF/CDF, Sobol indices

Reliability
- Goal-oriented; target particular response or probability levels
- Efficient local (require derivatives) / global variants
- Moments, PDF/CDF, importance factors

Epistemic
- Non-probabilistic methods
- Generally applicable, can be costly when no surrogate
- Belief/plausibility, intervals, probability of frequency
A Practical Process for UQ

1. Identify uncertain input parameters
2. Characterize input uncertainties and map them into Dakota variable specifications
3. Select a method appropriate to variables, goal, and problem
4. Set up Dakota input file and interface to simulation
5. Run study
6. Interpret the results

Environment
- Method: sampling
- Sample type: lhs
- Samples = 1000
- Seed = 98765
- Rng = rnum2

Variables
- Normal uncertain = 2
- Means = 0.80 0.80
- Standard deviations = 0.10 0.10
- Descriptors: ‘x1’ ‘x2’

Interface
- Fork
  - Analysis driver = ‘mfix’

Responses
- No gradients
- No hessians
- Response functions = 1
UQ results with Dakota

Flow in the fluidized bed

\[ e_{p,n} = \text{particle-particle restitution co-efficient} \]

\[ e_{w,n} = \text{Particle-wall restitution co-efficient} \]

Response function (Bed height) =

\[ 17.026 - 7.767 e_{p,n} - 0.46428 e_{w,n} + 5.6644 e_{p,n}^2 + 0.18379 e_{p,n} e_{w,n} + 0.20556 e_{w,n}^2 \]

UQ results with PSUADE

MCS with 100,000 samples

<table>
<thead>
<tr>
<th>Case #</th>
<th>Input1 ( e_{p,n} )</th>
<th>Input 2 ( e_{w,n} )</th>
<th>Bed height Sample mean</th>
<th>Bed height Sample Std deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N(0.8,0.1)</td>
<td>N(0.8,0.1)</td>
<td>14.374</td>
<td>1.7e-01</td>
</tr>
<tr>
<td>2</td>
<td>N(0.8,0.1)</td>
<td>N(0.8,0.05)</td>
<td>14.372</td>
<td>1.6e-1</td>
</tr>
</tbody>
</table>

Flow in a fluidized bed

Central jet fluidized bed

- The air is injected at a speed of 4200 cm/s through a narrow inlet having width of 1 cm and located exactly at the geometric center of the bottom wall.
- Cells size: 1 cm x 2 cm
- Number of cells: 675 (=15x45) computational cells.
- The bed is initialized with 217.15 g of particles with a diameter of 0.4 cm and density of 2.7 g/cm³, resulting in total of 2400 spherical particles.
- DEM
- Non reacting flow

Flow in a fluidized bed: parameters for UQ analysis

<table>
<thead>
<tr>
<th></th>
<th>$D_p$</th>
<th>$U_{\text{inlet}}$</th>
<th>$e_{p,n}$</th>
<th>$e_{w,n}$</th>
<th>$KN$</th>
<th>$KN_W$</th>
<th>$\mu$</th>
<th>$\mu_W$</th>
<th>$\mu_g$</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>0.34</td>
<td>4200</td>
<td>0.8</td>
<td>0.8</td>
<td>1000000</td>
<td>1000000</td>
<td>0.1</td>
<td>0.1</td>
<td>0.00018</td>
</tr>
<tr>
<td>std</td>
<td>0.0297</td>
<td>367.5</td>
<td>0.07</td>
<td>0.07</td>
<td>87500</td>
<td>87500</td>
<td>0.0087</td>
<td>0.0087</td>
<td>0.00001575</td>
</tr>
</tbody>
</table>

$D_p$ = Particle diameter
$U_{\text{inlet}}$ = Velocity of the fluidizing agent at the inlet
$e_{p,n}$ = particle-particle restitution co-efficient
$e_{w,n}$ = particle-wall restitution co-efficient
$KN$ = particle – particle normal collision spring constant
$KN_W$ = particle – wall normal collision spring constant
$\mu$ = particle - particle friction co-efficient
$\mu_W$ = particle – wall friction co-efficient
$\mu_g$ = viscosity of the fluidizing agent at the inlet

Response function

Average bed height

$$H_p(t) = \sum_{n=1}^{N_p} Y^n / N_p$$
UQ results: Flow in a fluidized bed

**Response function**

**Average bed height**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Std</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D_p) (cm)</td>
<td>0.34</td>
<td>0.0297</td>
</tr>
<tr>
<td>(U_{inlet}) (cm/s)</td>
<td>4200</td>
<td>367.5</td>
</tr>
<tr>
<td>(e_{p,n})</td>
<td>0.8</td>
<td>0.07</td>
</tr>
<tr>
<td>(e_{w,n})</td>
<td>0.8</td>
<td>0.07</td>
</tr>
<tr>
<td>(KN) (g/s²)</td>
<td>1000000</td>
<td>87500</td>
</tr>
<tr>
<td>(KN_W) (g/s²)</td>
<td>1000000</td>
<td>87500</td>
</tr>
<tr>
<td>(\mu)</td>
<td>0.1</td>
<td>0.0087</td>
</tr>
<tr>
<td>(\mu_W)</td>
<td>0.1</td>
<td>0.0087</td>
</tr>
<tr>
<td>(\mu_g) (g/cm s)</td>
<td>0.00018</td>
<td>0.00001575</td>
</tr>
</tbody>
</table>

Bed height at \(t=40\) is 9.86838 cm

Number of samples = 500

Mean: 9.6826836828
Std: 1.9528769373

Partial Correlation Matrix between inputs and output

Bed height:
- \(D_p\): 9.87853e-01
- \(U_{inlet}\): 7.65915e-01
- \(e_{p,n}\): 1.26841e-03
- \(e_{w,n}\): -2.19558e-02
- \(KN\): -5.4467e-02
- \(KN_W\): -4.08984e-02
- \(\mu\): -1.03671e-02
- \(\mu_W\): 6.74702e-02
- \(\mu_g\): -1.76986e-02

Mean:
- \(D_p\): 9.6826836828
- \(U_{inlet}\): 7.65915e-01
- \(e_{p,n}\): 1.26841e-03
- \(e_{w,n}\): -2.19558e-02
- \(KN\): -5.4467e-02
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- \(\mu\): -1.03671e-02
- \(\mu_W\): 6.74702e-02
- \(\mu_g\): -1.76986e-02

Std:
- \(D_p\): 0.8
- \(U_{inlet}\): 0.8
- \(e_{p,n}\): 87500
- \(e_{w,n}\): 87500
- \(KN\): 0.0087
- \(KN_W\): 0.0087
- \(\mu\): 0.00018
- \(\mu_W\): 0.00001575
- \(\mu_g\): 0.000018

**Bed height (cm)**

- Instantaneous
- Averaged
DPI: Problem definition

- 20 equi-spaced discretized cells in the axial direction
- 10 equi-spaced discretized cells in the normal direction
- 500 drug particles
  - Size: 3.2 \( \mu m \)
  - Density: 1520 kg/m\(^3\)
- 500 carrier particles
  - Size: 52.5 \( \mu m \) and
  - Density: 2.650 kg/m\(^3\)
- Velocity of air: 3.0 m/s,
- Density of air: 1.205 kg/m\(^3\)
Results

Velocity fields along the x-direction

Velocity (y-direction) fields along the y-direction
Results: Effect of particles diameter

$V_{inlet} = 1.32 \text{ m/s}$
$D_{P1} = 3.17 \times 10^{-5} \text{ m}$
$\rho_{p1} = 2344.94 \text{ kg/m}^3$

$D_{P2} = 3.41 \times 10^{-6} \text{ m}$
$\rho_{p1} = 1562.45 \text{ kg/m}^3$

$V_{inlet} = 1.35 \text{ m/s}$
$D_{P1} = 3.89 \times 10^{-5} \text{ m}$
$\rho_{p1} = 2867.71 \text{ kg/m}^3$

$D_{P2} = 4.63 \times 10^{-6} \text{ m}$
$\rho_{p1} = 1489.88 \text{ kg/m}^3$

axial velocity (y-direction) fields
Results: Effect of velocity at the inlet

$t=0.0\ s$  
$t=3.0\ s$  
$t=0.0\ s$  
$t=2.0\ s$

$V_{\text{inlet}} = 2.64\ \text{m/s}$  
$D_{p1} = 5.6\times10^{-5}\ \text{m}$  
$\rho_{p1} = 2694.64\ \text{kg/m}^3$  
$D_{p2} = 3.11\times10^{-6}\ \text{m}$  
$\rho_{p1} = 1731.72\ \text{kg/m}^3$

$V_{\text{inlet}} = 5\ \text{m/s}$  
$D_{p1} = 5.6\times10^{-5}\ \text{m}$  
$\rho_{p1} = 2694.64\ \text{kg/m}^3$  
$D_{p2} = 3.11\times10^{-6}\ \text{m}$  
$\rho_{p1} = 1731.72\ \text{kg/m}^3$

axial velocity (y-direction) fields  
axial velocity (y-direction)
Summary

- A framework is used to implement MFiX in Dakota-UQ toolkit
- The framework has been validated on various test cases.
- 2D simulations are carried out with MFiX to simulate flow in an inhaler.
- Particles residence time increases with the particle diameter
- Particle residence time decreases with an increase in the inflow velocity.
Multi-physics & scale
Computational Lab

Uncertainty quantification

Exa-scale Pore Network Simulator (EXPNS):
High viscosity fluid invading through porous media

Fluidized Bed (TFM, gas-solid)
With Trilinos
Sandia

MFIX
NETL

~50% faster

With Trilinos
Sandia

MFIX
NETL

>50% faster

Wrapped(Phase), Rylov=0.2

Unwrapped(Phase), Rylov=0.2

Uncertainty quantification

PoreFracDepth E/D [um]

Time (s)
THANK YOU ..........................