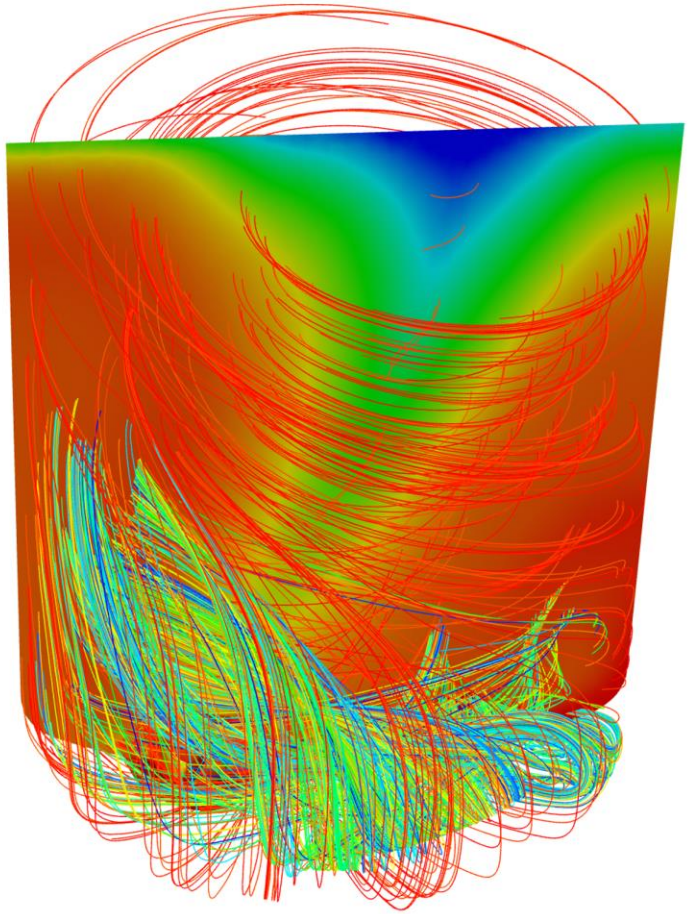
Web Metamodel for Pharma Stirring Tanks Applications Based on Novaseptic® mixers



MSc. Phys. Cosmin Vatra

15.06.2023

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Presentation content:

1. About pharma stirring tanks applications (mixing processes).
2. Mixing processes problems involved by nonlinear phenomenon.
3. Computational Fluid Dynamics (CFD), a solution for mixing processes problems.
4. Sometimes, CFD simulations could be too expensive.
5. Metamodel: what it is and how can solve the problems when CFD simulations are too expensive?
6. Metamodel for Novaseptic® mixers.

Web Metamodel for Pharma Stirring Tanks Applications Based on Novaseptic® mixers

About pharma stirring tanks applications (mixing processes).

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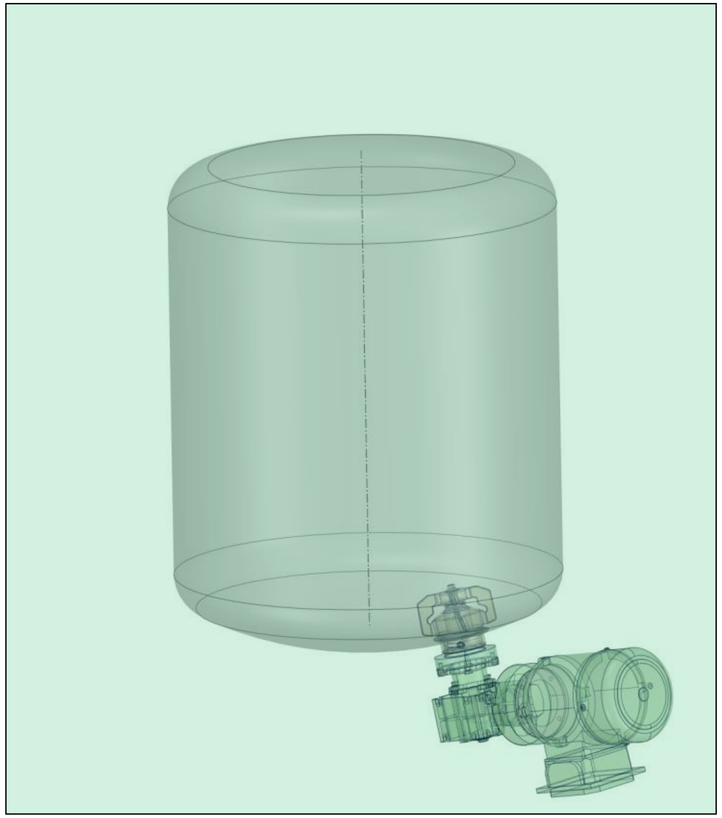
- Pharma stirring tanks are used for the preparation of liquid formulations such as suspensions, emulsions, and solutions.
- They are a critical component in the pharmaceutical manufacturing process and play a crucial role in ensuring the safety and efficacy of pharmaceutical products.
- The stirring function of the tank is important for ensuring that the formulation is homogenous, meaning that all the components are well dissolved or suspended in an optimum time and evenly distributed throughout the liquid.
- This is important for ensuring that the medication is effective and that each dose contains the appropriate amount of active ingredient.



NovAseptic® Mixer

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Mixing processes problems involved by nonlinear phenomenon

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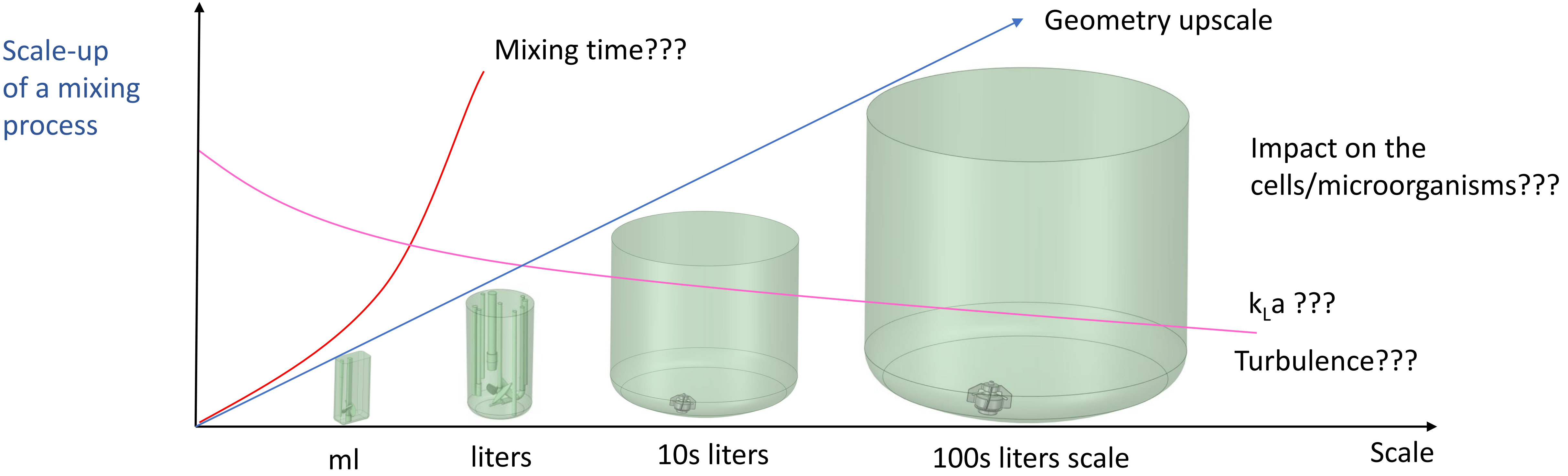
Mixing processes in stirring tanks or bioreactors are involving nonlinear phenomenon due to which the transfer or scale-up from one specific geometry (tank and one or more mixers) to another is not possible based on simple proportionality criteria. The question is how is possible to guarantee the mixing efficiency?



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Mixing processes problems involved by nonlinear phenomenon

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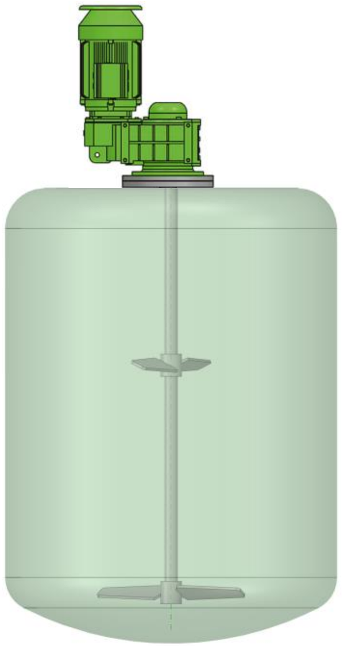
Even if we are transferring the process to a new system having the same scale, we have the same question: How can we guarantee the mixing efficiency?



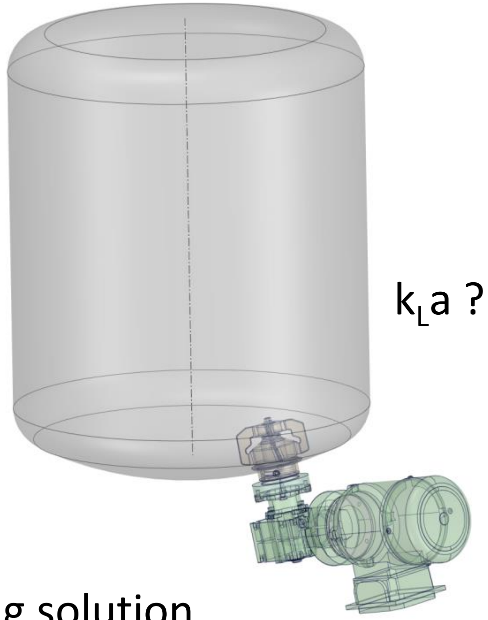
Transfer
of a mixing process

Mixing time???

Turbulence???

Impact on the cells/microorganisms???

k_La ???



NovAseptic®
Magnetic coupled mixer

Same scale, but different geometry or mixing solution.

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Computational Fluid Dynamics (CFD), a solution for mixing processes problems

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At Aseptconn, we are supporting our customers and we can guarantee the mixing process transfer and scale-up, with our expertise based on the CFD simulations!

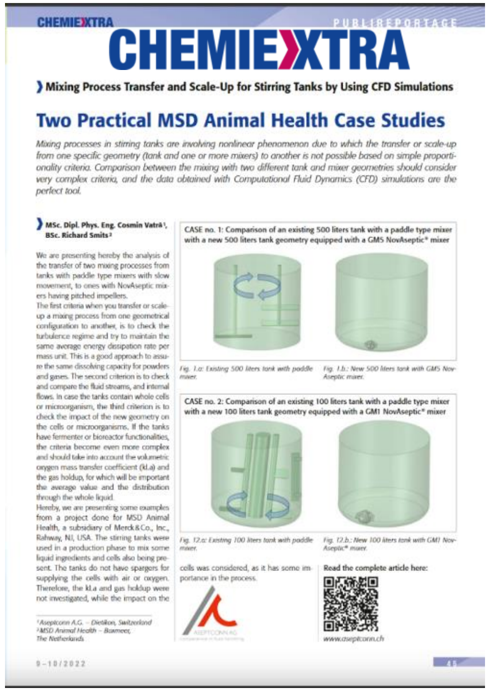
CFD simulations are a very useful tool to predict the parameters of a mixing process from a stirring tank, such as: turbulence, Reynolds number, energy dissipation rate per mass unit, mixer power number, etc.

How do we do this?

As an application example, you can read the article about the project done by us for ***MSD Animal Health***, a subsidiary of ***Merck & Co., Inc., Rahway, NJ, USA***, published in ***ChemieExtra*** magazine.

www.aseptconn.ch

By scanning the QR code, you can read the full article!



CHEMIEXTRA PUBLIREPORTAGE

CHEMIEXTRA

❯ Mixing Process Transfer and Scale-Up for Stirring Tanks by Using CFD Simulations

Two Practical MSD Animal Health Case Studies

Mixing processes in stirring tanks are involving nonlinear phenomenon due to which the transfer or scale-up from one specific geometry (tank and one or more mixers) to another is not possible based on simple proportionality criteria. Comparison between the mixing with two different tank and mixer geometries should consider very complex criteria, and the data obtained with Computational Fluid Dynamics (CFD) simulations are the perfect tool.

❯ MSc. Dipl. Phys. Eng. Cosmin Vatră[1], BSc. Richard Smits[2]

We are presenting hereby the analysis of the transfer of two mixing processes from tanks with paddle type mixers with slow movement, to ones with NovAseptic mixers having pitched impellers.

The first criteria when you transfer or scale-up a mixing process from one geometrical configuration to another, is to check the turbulence regime and try to maintain the same average energy dissipation rate per mass unit. This is a good approach to assure the same dissolving capacity for powders and gases. The second criterion is to check and compare the fluid streams, and internal flows. In case the tanks contain whole cells or microorganism, the third criterion is to check the impact of the new geometry on the cells or microorganisms. If the tanks have fermenter or bioreactor functionalities, the criteria become even more complex and should take into account the volumetric oxygen mass transfer coefficient (kLa) and the gas holdup, for which will be important the average value and the distribution through the whole liquid.

Hereby, we are presenting some examples from a project done for MSD Animal Health, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. The stirring tanks were used in a production phase to mix some liquid ingredients and cells also being present. The tanks do not have spargers for supplying the cells with air or oxygen. Therefore, the kLa and gas holdup were not investigated, while the impact on the cells was considered, as it has some importance in the process.

CASE no. 1: Comparison of an existing 500 liters tank with a paddle type mixer with a new 500 liters tank geometry equipped with a GM5 NovAseptic® mixer

Fig. 1.a: Existing 500 liters tank with paddle mixer.

Fig. 1.b.: New 500 liters tank with GM5 NovAseptic mixer.

CASE no. 2: Comparison of an existing 100 liters tank with a paddle type mixer with a new 100 liters tank geometry equipped with a GM1 NovAseptic® mixer

Fig. 12.a: Existing 100 liters tank with paddle mixer.

Fig. 12.b.: New 100 liters tank with GM1 NovAseptic® mixer.

Read the complete article here:

www.aseptconn.ch

[1] Aseptconn A.G. – Dietikon, Switzerland
[2] MSD Animal Health – Boxmeer, The Netherlands

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Sometimes, CFD simulations could be too expensive

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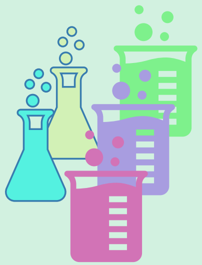
Sometimes, CFD simulations can be computationally expensive and time-consuming, especially when you need to run simulations on many combinations, to find the optimal solution.

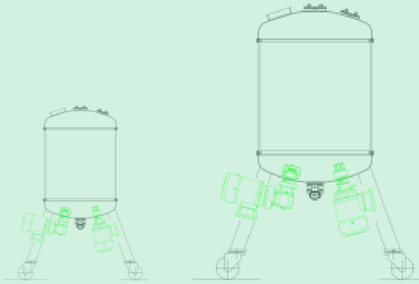
Substances



Mixers

NovAseptic® Mixers

Tanks



Too many combinations

Expensive and time consuming CFD simulations

But this problem could be solved by creating a METAMODEL!

What is a Metamodel:

- In the context of computational fluid dynamics (CFD), a metamodel is a mathematical model that is derived from a set of simulations generated by a CFD solver.
- The metamodel can then be used to predict the behavior of the fluid system under different conditions without requiring additional computational resources.
- A metamodel can be constructed by using a set of inputs and outputs from a set of simulations to train a surrogate model, such as a neural network, decision tree, or polynomial regression. The metamodel can then be used to approximate the response of the CFD simulation for new input parameters.
- The use of metamodels in CFD has become increasingly popular as they can significantly reduce the computational cost of simulations, allowing for more efficient exploration of the design space. They are particularly useful in the design optimization of complex systems, where there are many design variables and objectives to consider.

Web Metamodel for Pharma Stirring Tanks Applications Based on Novaseptic® mixers

Metamodel: what it is and how can solve the problems when CFD simulations are too expensive?

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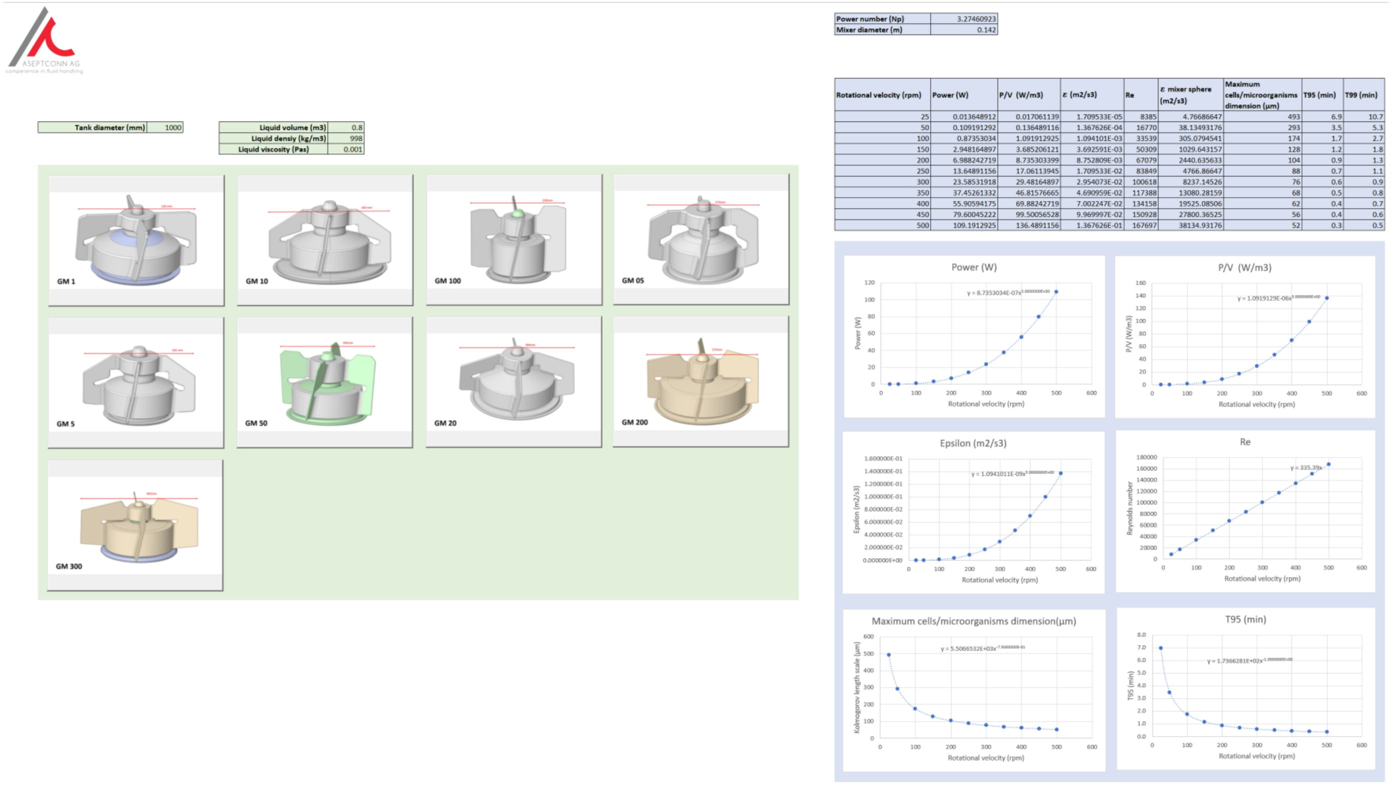
This is why we have developed an innovative metamodel for the Millipore Novaseptic® mixers, based on hundreds of simulations performed on different geometries. We have integrated this metamodel into an application, where the users could introduce the tank diameter, the liquid properties, choose the mixer model, and will obtain instantly the mixing parameters.



Tank diameter (mm)	1000

Liquid volume (m3)	0.8
Liquid densiy (kg/m3)	998
Liquid viscosity (Pas)	0.001

Power number (Np)	3.27460923
Mixer diameter (m)	0.142

Rotational velocity (rpm)	Power (W)	P/V (W/m3)	ε (m2/s3)	Re	ε mixer sphere (m2/s3)	Maximum cells/microorganisms dimension (μm)	T95 (min)	T99 (min)
25	0.013648912	0.017061139	1.709533E-05	8385	4.76686647	493	6.9	10.7
50	0.109191292	0.136489116	1.367626E-04	16770	38.13493176	293	3.5	5.3
100	0.87353034	1.091912925	1.094101E-03	33539	305.0794541	174	1.7	2.7
150	2.948164897	3.685206121	3.692591E-03	50309	1029.643157	128	1.2	1.8
200	6.988242719	8.735303399	8.752809E-03	67079	2440.635633	104	0.9	1.3
250	13.64891156	17.06113945	1.709533E-02	83849	4766.86647	88	0.7	1.1
300	23.58531918	29.48164897	2.954073E-02	100618	8237.14526	76	0.6	0.9
350	37.45261332	46.81576665	4.690959E-02	117388	13080.28159	68	0.5	0.8
400	55.90594175	69.88242719	7.002247E-02	134158	19525.08506	62	0.4	0.7
450	79.60045222	99.50056528	9.969997E-02	150928	27800.36525	56	0.4	0.6
500	109.1912925	136.4891156	1.367626E-01	167697	38134.93176	52	0.3	0.5

Web Metamodel for Pharma Stirring Tanks Applications Based on Novaseptic® mixers

Metamodels for Novaseptic® mixers

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For the METAMODEL, we have used Ansys softwares, which presents the following advantages:

- Fully integration between the softwares, which allows fully automation.
- Fully customization by using Python programming language.
- Professional support from CADFEM.

CADFEM

Professional services and support for Ansys products

Ansys

complete solution:

optiSLang
Sensitivity analysis for design optimization

Workbench – Simulation Integration Platform

SpaceClaim
CAD software for building the geometry for the CFD

Fluent
CFD meshing and solving

Web Metamodel for Pharma Stirring Tanks Applications Based on Novaseptic® mixers

Metamodel for Novaseptic® mixers

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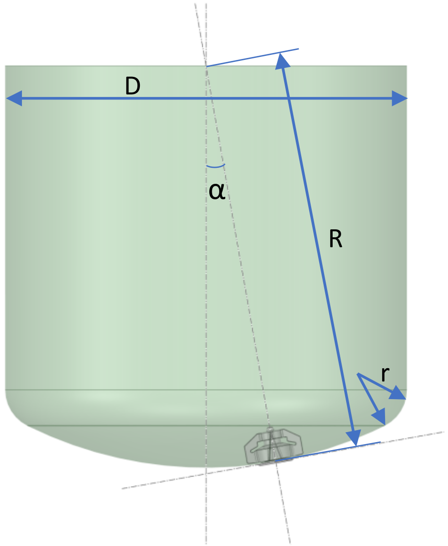
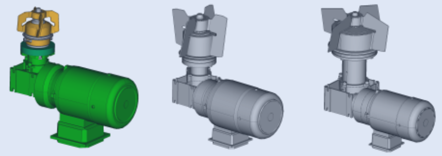
First, we have defined the input & output data for the metamodel.
We have used the most common tank type, which is Klopper, according to the norm DIN 28011

According to DIN 28011:
R=D
r = R/10



INPUT DATA

Mixer type selection:



Tank geometry parameters:

- Diameter (D)
- Mixer angle (α)

Liquid parameters:

- Liquid volume
- Density (ρ)
- Viscosity (μ)

OUTPUT DATA

- Mixer torque as a function of mixer speed (rpm)
- Mixer power as a function of mixer speed (rpm)
- Power per volume as a function of mixer speed (rpm)
- Power number
- Reynolds number function of mixer speed (rpm)
- Average energy dissipation rate per mass unit as a function of mixer speed (rpm)
- Average energy dissipation rate per mass unit in the mixer region as a function of mixer speed (rpm)
- Mixing time (T95 and T99) for a passive tracer as a function of mixer speed (rpm)
- Maximum dimension of the cells and microorganisms that could live in the tank without being affected, as a function of rotational speed

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Metamodel for Novaseptic® mixers

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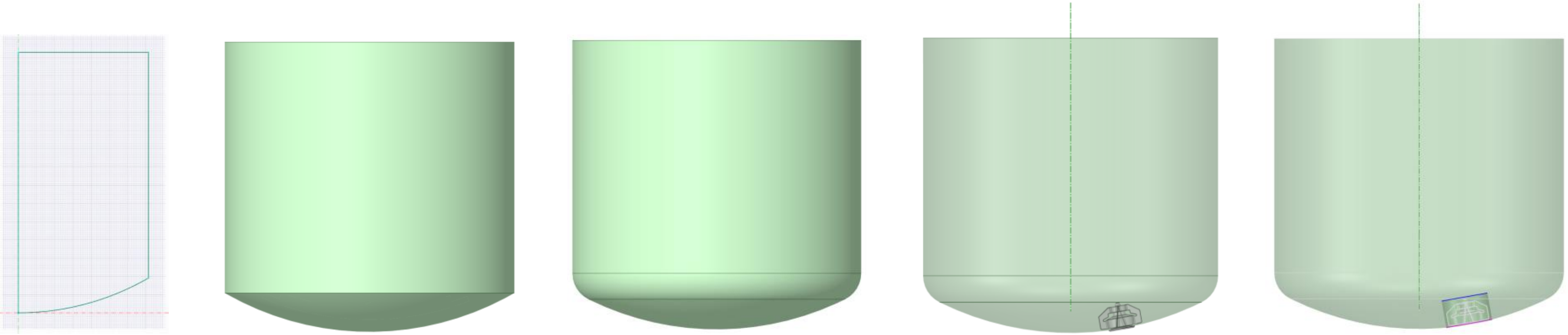
Second, we have written Python subroutines for SpaceClaim, for automatic generation of the geometry for CFD:



Fully automatic geometry generation

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We have written Python subroutines to generate automatically the setup files for Fluent meshing and solver.

Ansys 2022 R2

Script Editor

API: V22

```
#---------------------------------------------------------------------\
#                                                                     |
#              Mesh Sizings                                           |
#                                                                     |
#---------------------------------------------------------------------/


#==============================================================================
#              Meshing parameters
#
#---------------------------------------------------------------------
global_max_size = tank_diameter/30
global_min_size = mixer_diameter / 280
global_prox_min_size = global_min_size * 5
global_GW = 1.2
global_Prox = 2
global_Curv = 15

body_size = mixer_diameter/20
body_size_GW = 1.2



#==============================================================================
#              Create size control
#
#---------------------------------------------------------------------

f_siz =  open(path_userfiles + "mesh_sizing.szcontrol",'w')

f_siz.write(";; Scoped Sizing                                    \n")
f_siz.write(";; Name Type Parameters Scope                            \n")
f_siz.write("(                                                  \n")
f_siz.write("(\"body_size_rotor\" \"boi\" "+str(global_min_size)+" "+str(body_size)+" "+str(body_size_GW)+" 18 1 12 \"Face Zone Labels\" \"ge
f_siz.write("(\"global_curvature\" \"curvature\" "+str(global_min_size)+" "+str(global_max_size)+" "+str(global_GW)+" "+str(global_Curv)+" "+
f_siz.write("(\"global_proximity\" \"proximity\" "+str(global_prox_min_size)+" "+str(global_max_size)+" "+str(global_GW)+" "+str(global_Curv)-
f_siz.write(")                                                  \n")
f_siz.write(";; Global Parameters                                 \n")
f_siz.write(";; Min Max Growth Ref                                 \n")
f_siz.write("("+str(global_min_size)+" "+str(global_max_size)+" "+str(global_GW)+" "+str(global_Prox)+")
```

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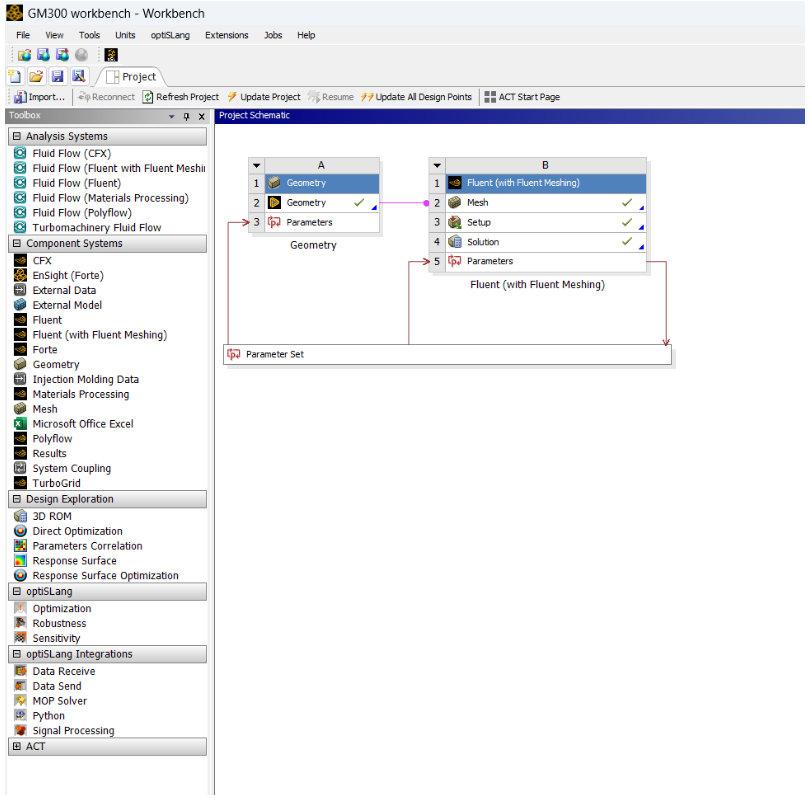
We have configured the automatic workflow in Workbench:



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Metamodel for Novaseptic® mixers

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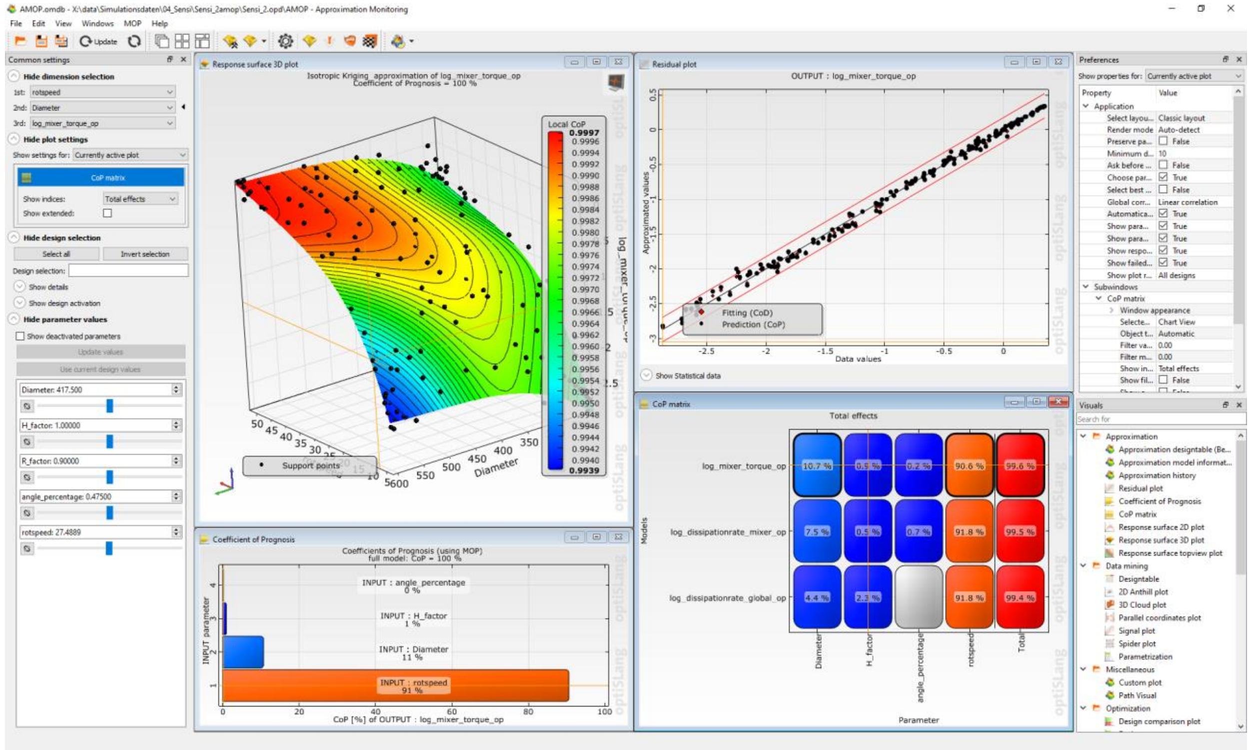
We have used OptiSLang to generate the design points and make the sensitivity analysis for one of the mixer models. OptiSLang generated approximatively 150 design points for which Workbench generated the geometries and performed the CFD simulations.



<u>We discovered that:</u>

- some input parameters have a very small influence on the output and could be neglected.
- the output parameters have precise algebraical dependence on some input parameters.

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Metamodel for Novaseptic® mixers

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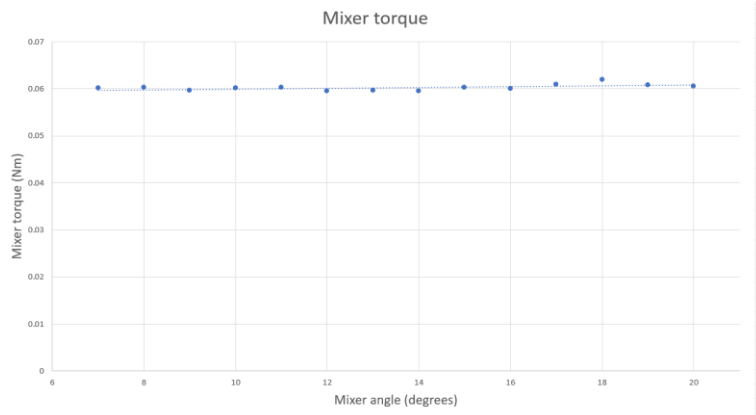
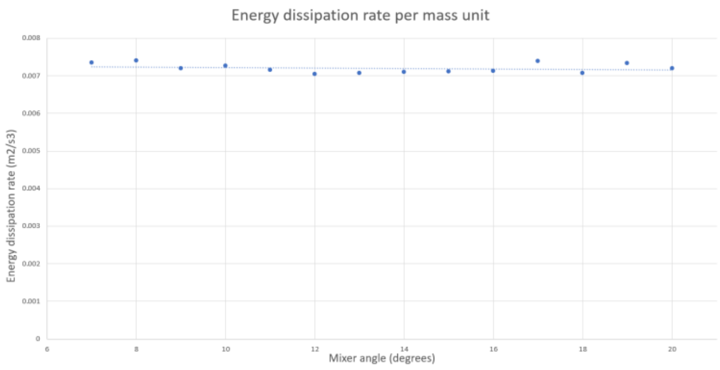
After the sensitivity analysis we have done the following simplifications:

- We renounced to the mixer angle input parameter, because it has a negligible influence on the output parameters.
- We decided to perform the simulations on a fixed mixer rotational velocity. For other rotational velocities, we decided to use algebraical formulas to obtain the output values.





Output parameters have a negligible dependence on the mixer angle

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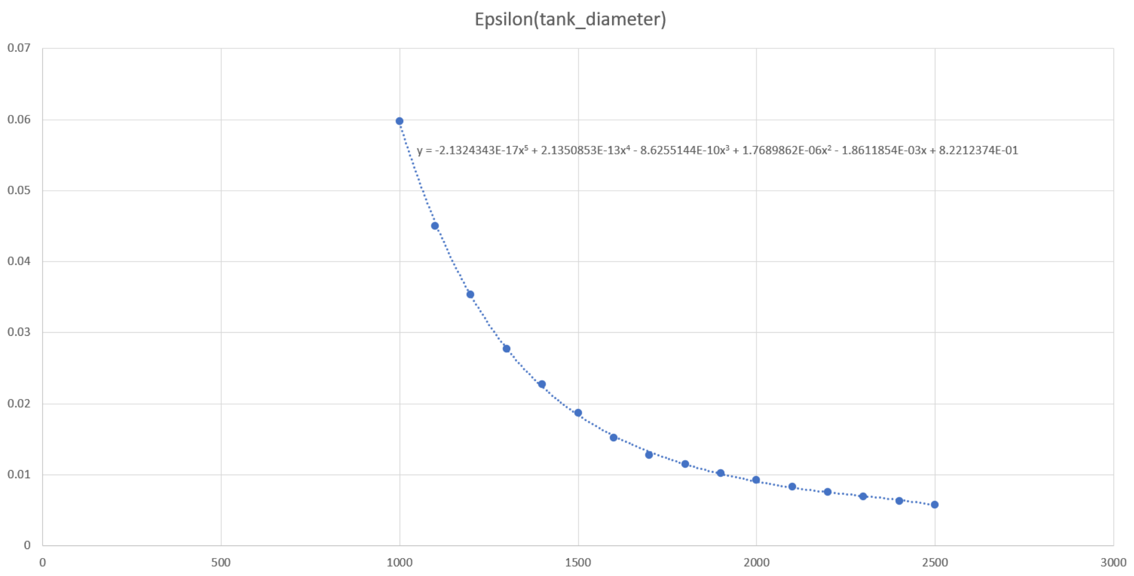
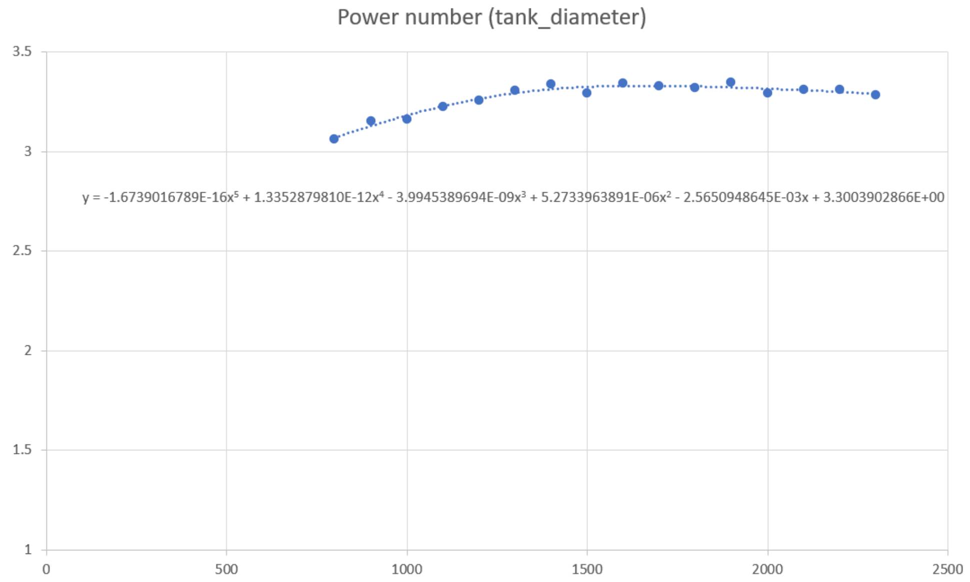
After the sensitivity analysis we decided to create the mixer's metamodels based on polynomial regression models. Due to this big simplification, the number of the design points decreased 10 times and we developed the mixer's metamodels without using OptiSLang. We used only Workbench with a fixed number of design points.





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Metamodel for Novaseptic® mixers

At the end, we have created the graphical user interface (GUI).

The user will set:

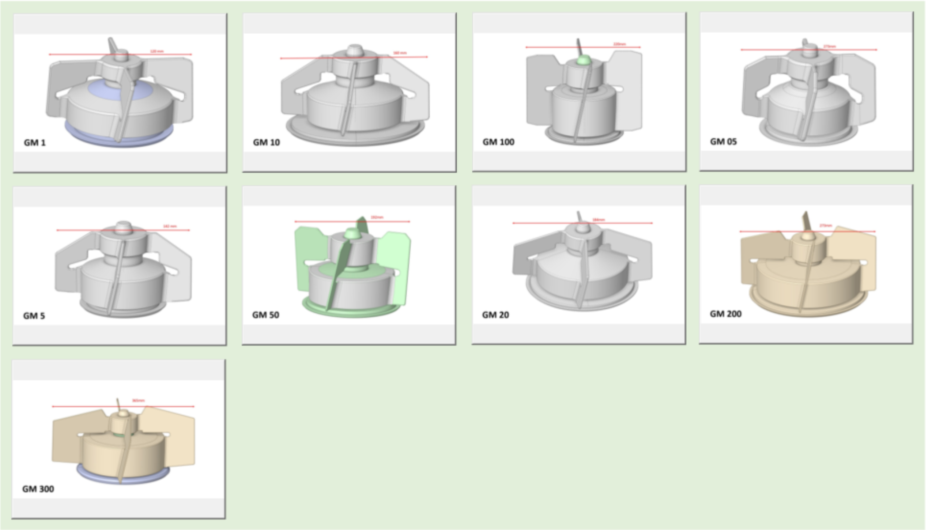
- tank diameter
- liquid properties
- mixer model

The GUI will return the following:

- Power number
- power
- P/V
- Averaged dissipated energy per mass unit (ε)
- Averaged dissipated energy per mass unit (ε) for the mixer region
- Reynolds number
- Maximum cells/microorganism dimension
- T95, T99

Tank diameter (mm)	1000

Liquid volume (m3)	0.8
Liquid densiy (kg/m3)	998
Liquid viscosity (Pas)	0.001



Power number (Np)	3.27460923
Mixer diameter (m)	0.142

Rotational velocity (rpm)	Power (W)	P/V (W/m3)	ε (m2/s3)	Re	ε mixer sphere (m2/s3)	Maximum cells/microorganisms dimension (µm)	T95 (min)	T99 (min)
25	0.013648912	0.017061139	1.709533E-05	8385	4.76686647	493	6.9	10.7
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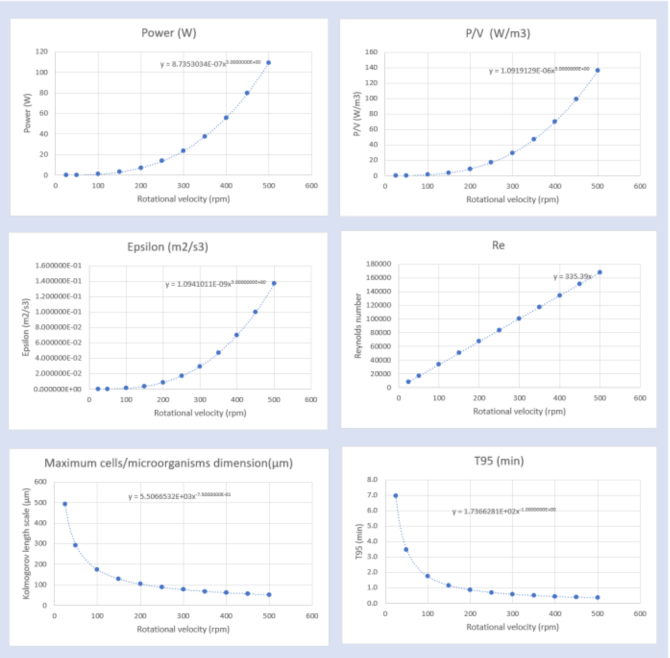

Thank you for your attention!

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