Prediction of Respimat® Inhaler Spray: Co-Flow Air Behavior

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Outline

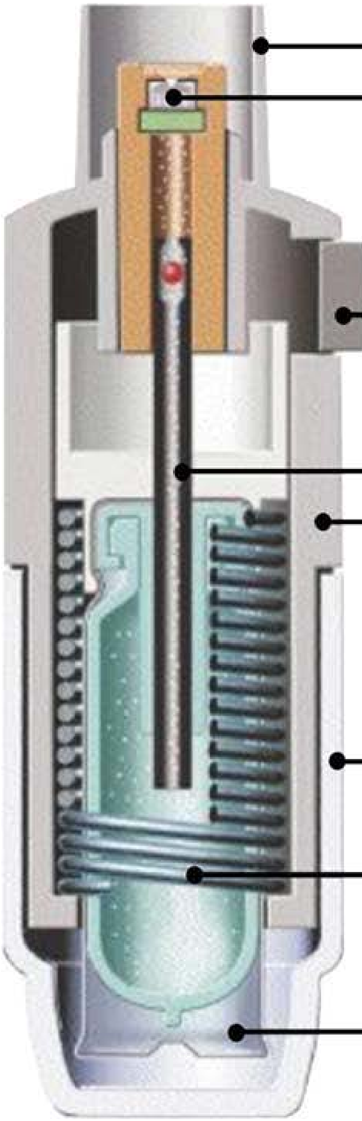
- Background
  - Respimat® Soft Mist™ Inhaler (SMI)
  - Rationale for Study
- On-Going Experimental Evaluations
  - Particle Sizing and Flow Studies to Support Modeling
- CFD
  - Prediction of Flow Field through SMI without spray injection
- Summary

Respimat SMI Drug Products

- Combivent® Respimat®
  - Approved: 10/7/2011
- Striverdi® Respimat®
  - Approved: 7/31/2014
- Spiriva® Respimat®
  - Approved: 9/24/2014
- Stiolto® Respimat®
  - Approved: 5/21/2015
- Dosage Form: Metered Spray for Inhalation
- Treatment of chronic obstructive pulmonary disease (COPD)
- Site of action: Lung airways
- Complex drug-device product

Respimat Drug Product Delivery Mechanism

- Drug product is stored in a collapsible plastic bag inside an aluminum can.
- The trigger mechanism is cocked by rotating the base a half-turn, tightening (coiling) the spring.
- The capillary tube shifts down collecting drug, that is held in place by the one way valve.
- The dose release button disengages the spring; the capillary tube shifts up propelling drug product into the "**Uniblock**".



Dalby, R., Spallek, M., & Voshaar, T. (2004). A review of the development of Respimat Soft Mist Inhaler. *Int J Pharm, 283*(1-2), 1-9. doi:10.1016/j.ijpharm.2004.06.018

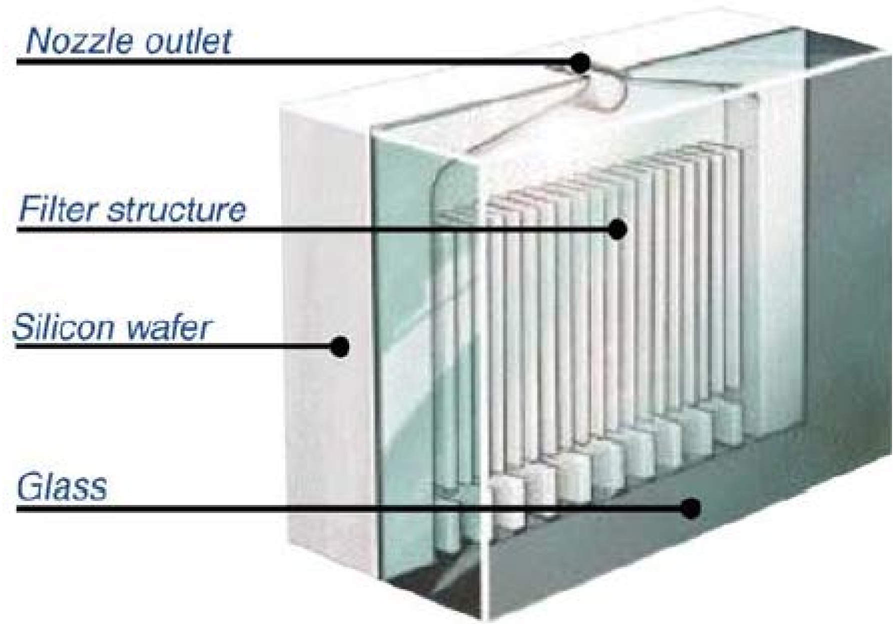
Respimat Drug Product Delivery Mechanism

- Uniblock is composed of a silicon wafer with filter channels etched onto it.
- Two liquid jets impinge at a set angle just in front of the nozzle forming the soft mist spray.

Key Inhaler Features

- No propellant.
- High fine droplet fraction (<5.8 µm) compared to pMDIs* and DPIs#.
- Initial soft mist speed ≈ tenth of aerosol cloud from pMDIs.
- Injection duration 1.5s (cf. 0.2s for pMDIs)

Uniblock



* pMDI: Pressurized metered-dose inhaler
# DPI: Dry powder inhaler

Dalby, R., Spallek, M., & Voshaar, T. (2004). A review of the development of Respimat Soft Mist Inhaler. *Int J Pharm, 283*(1-2), 1-9.

Regulatory Rationale For Study

Current Landscape

- Four approved Respimat inhaler drug products on the market.
- No generics available.
- No product-specific guidances (PSGs) for Respimat.
- Office of Generic Drugs (OGD) is currently developing PSGs for Respimat.

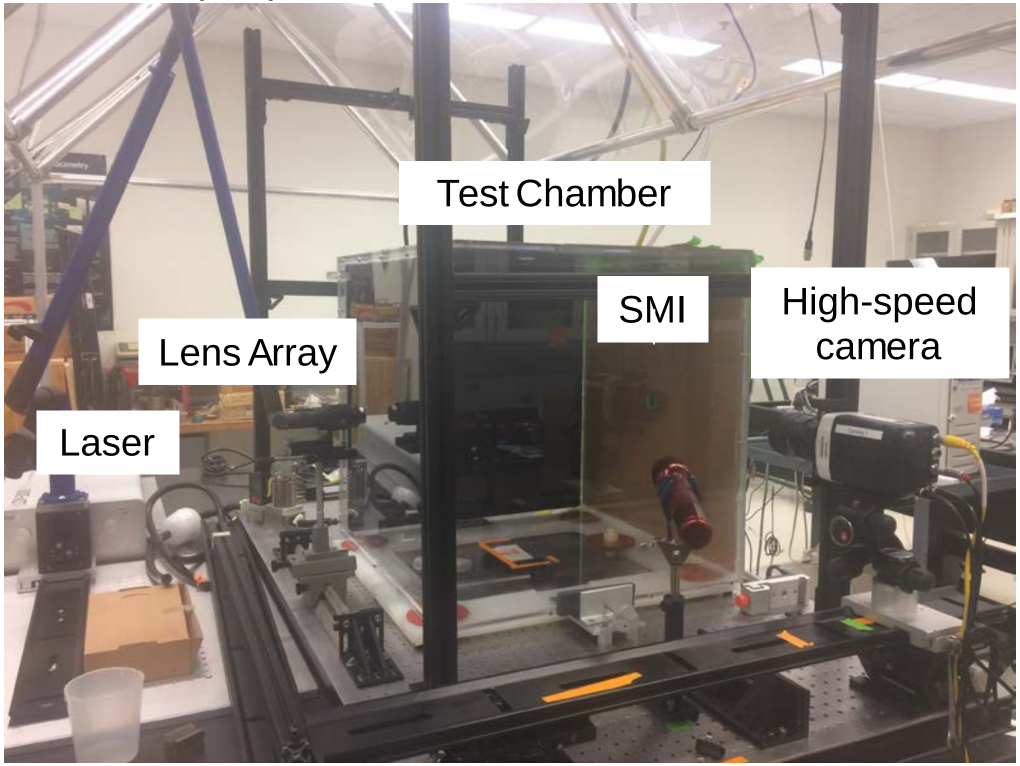
Desired Outcomes

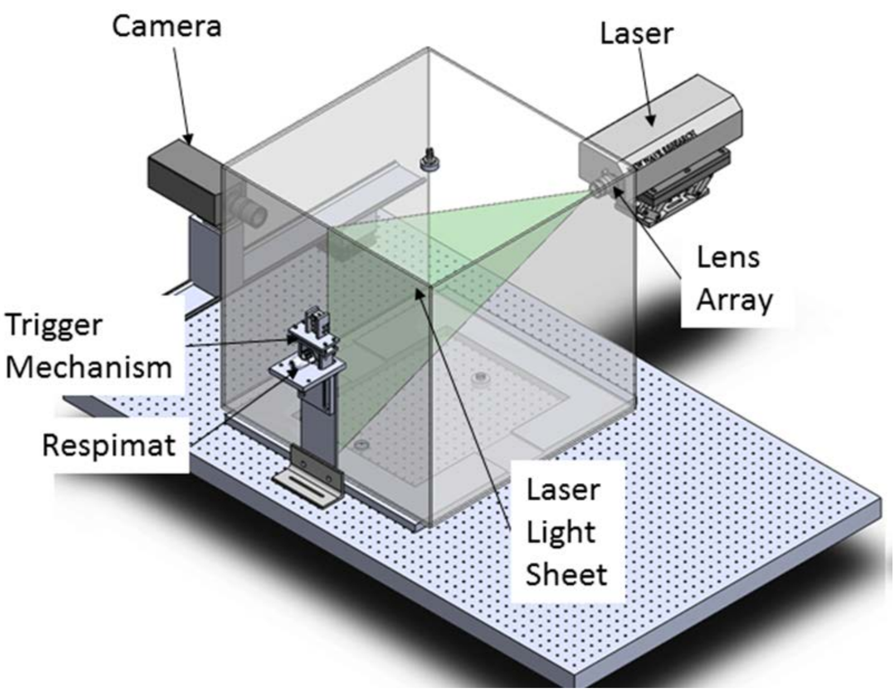
- Study aims to leverage experimental and modeling approaches to:
  - Gather physiologically-relevant data on the soft mist spray.
  - Predict sensitivity of regional deposition fraction of drug to certain spray and device characteristics.
  - Inform SMI-related PSG development.
  - Inform FDA's future SMI-related review efforts.
  - Generate credible data which may streamline bioequivalence recommendations.

On-Going Experimental Evaluations

Imaging

- High-speed (500 fps) videography and PIV to measure:
  - Plume front velocity
  - Spray duration
  - Spray angle (cone angle)
  - Spray width
  - Spray direction
  - Transient plume velocity



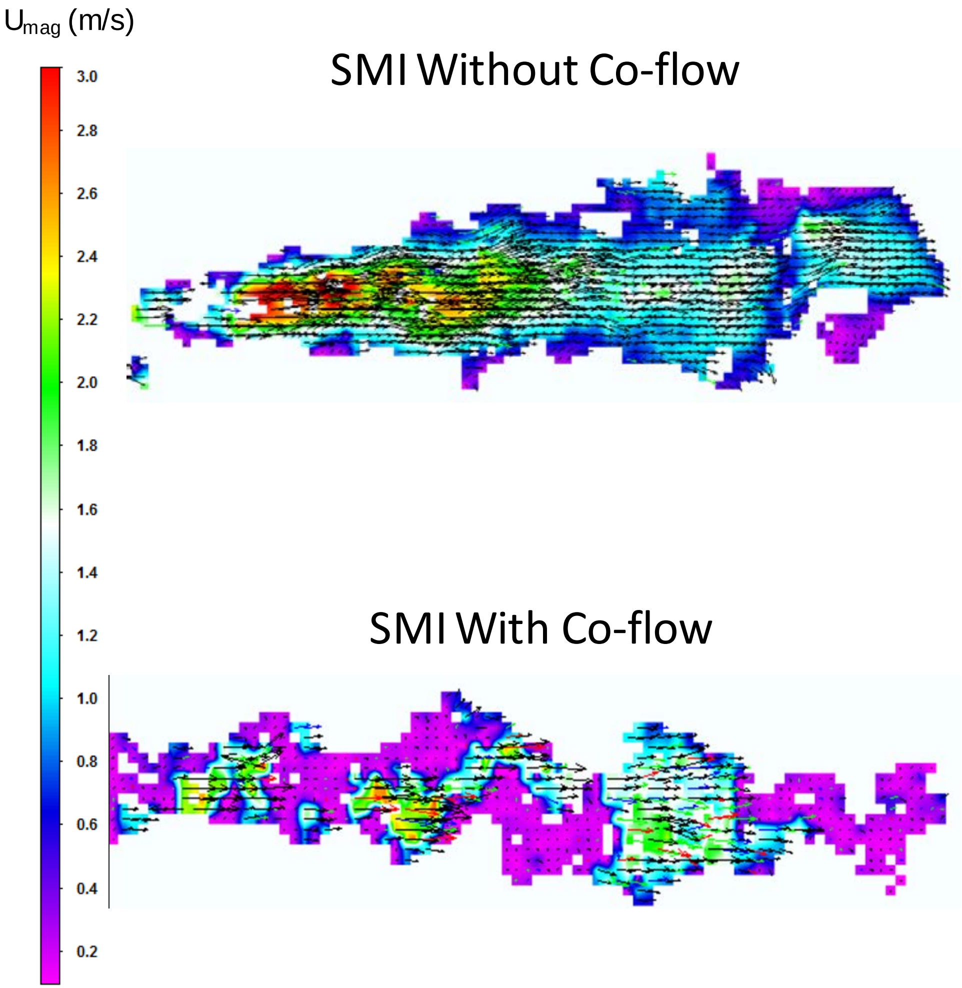


On-Going Experimental Evaluations

Imaging

PIV protocol:

- 2D co-flow of air (@ 28.3 L/min) emerging from Respimat inhaler mouthpiece without spray actuation.
  - Smoke particles (≈3µm) are used as PIV-seed
  - Validation of CFD single-phase model.
- With spray actuation (Striverdi & Spiriva) involving co-flow and quiescent air.
  - SMI particles are used as PIV-seed
  - Validation of CFD-DPM (Euler-Lagrange) two-phase model.



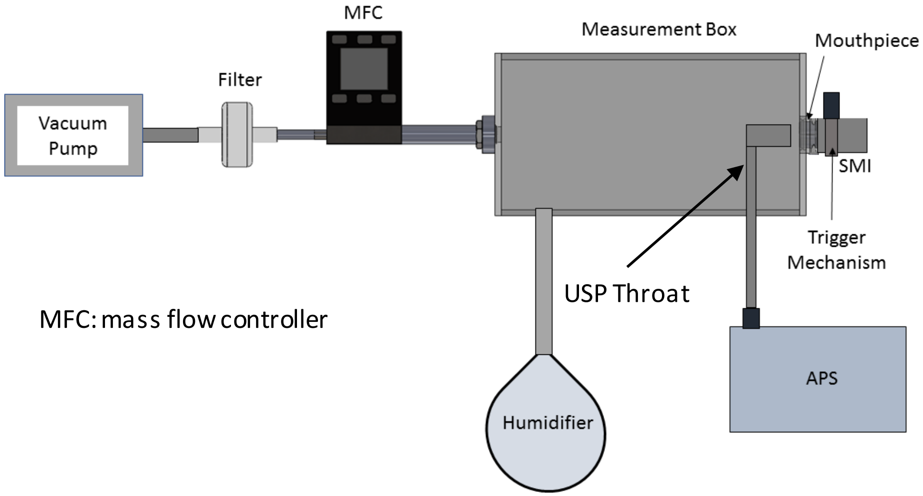
PIV Instantaneous velocity images

On-Going Experimental Evaluations

Particle Sizing

Measurements will support initialization of spray size distribution for simulations:

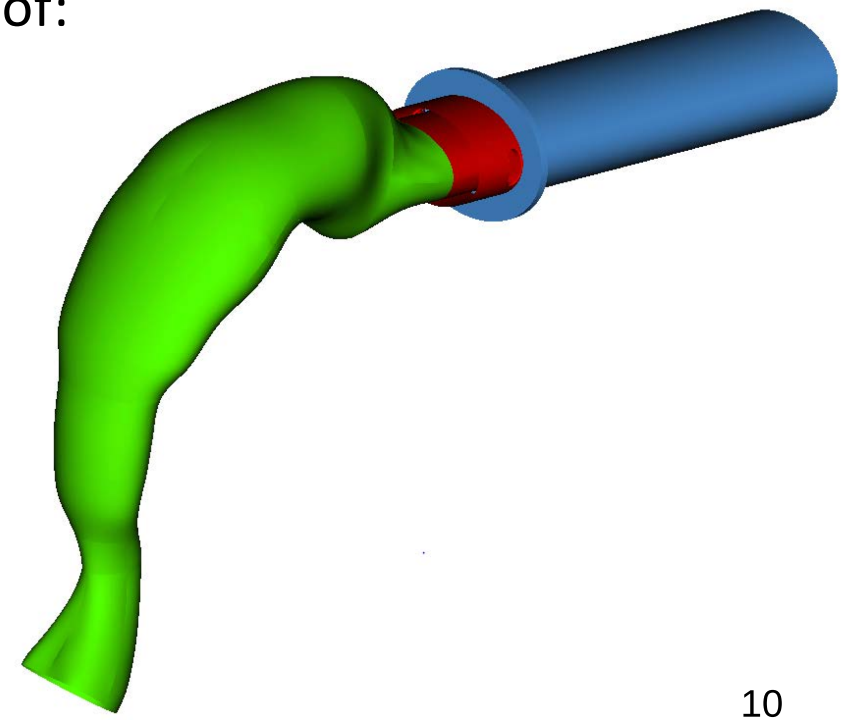
- Aerodynamic particle diameter being measured using a TSI 3321 aerodynamic particle sizer (APS)
  - measures the particle diameter using time of flight of the spray
- Volume-weighted particle diameter using laser diffraction
- APS and laser diffraction being used to study effect of:
  - Co-flow/quiescent air
  - Ambient and high relative humidity



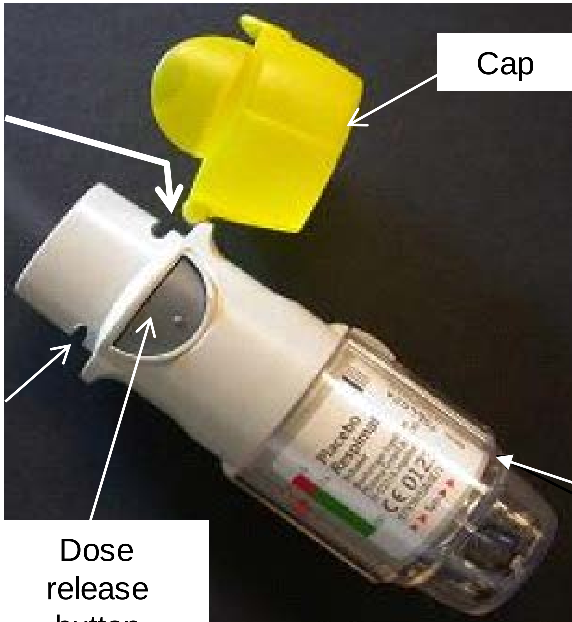
CFD: Goals

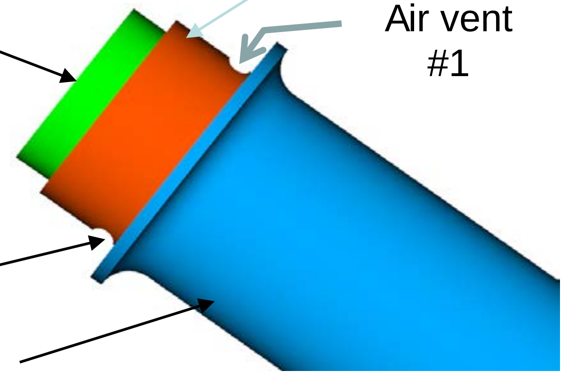
- **Validate single-phase simulation using PIV of smoke-laden co-flow air.**
- Validate two-phase simulation (with SMI actuation):
  - Particle sizing measurements → particle size distribution (PSD).
  - High speed videography → spray cone angle & injection velocity.
  - PIV measurements → discrete phase velocity field.
- Apply CFD model to predict influence of:
  - spray PSD,
  - spray angle,
  - spray velocity,
  - spray duration

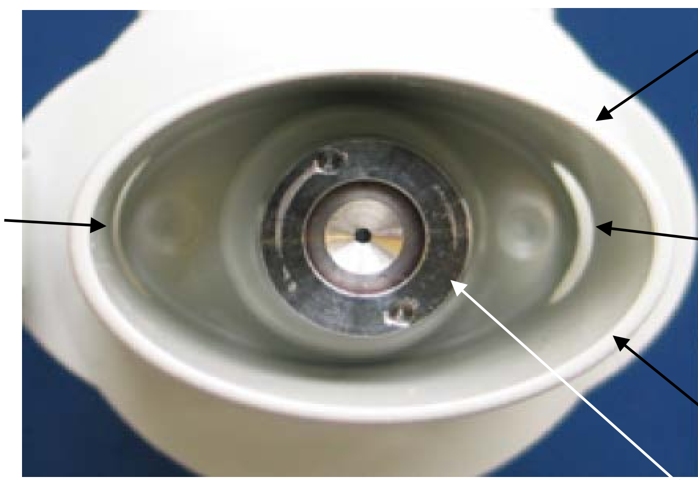
  on deposition in a mouth-throat geometry

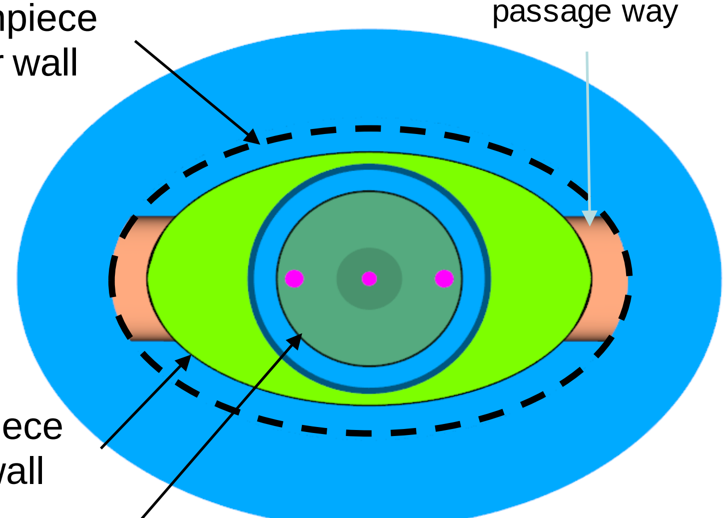


Geometry Generation (ANSYS SpaceClaim)

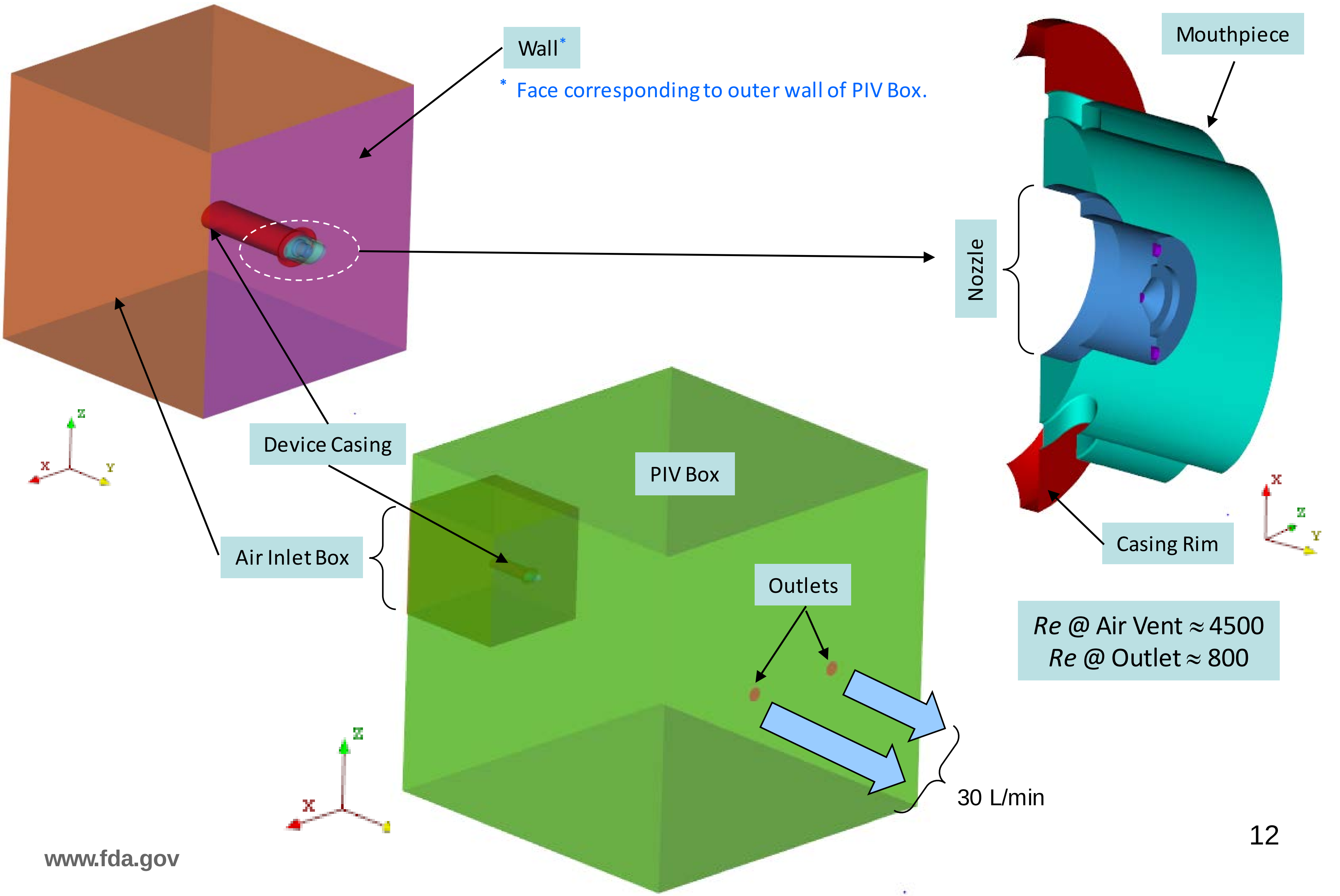








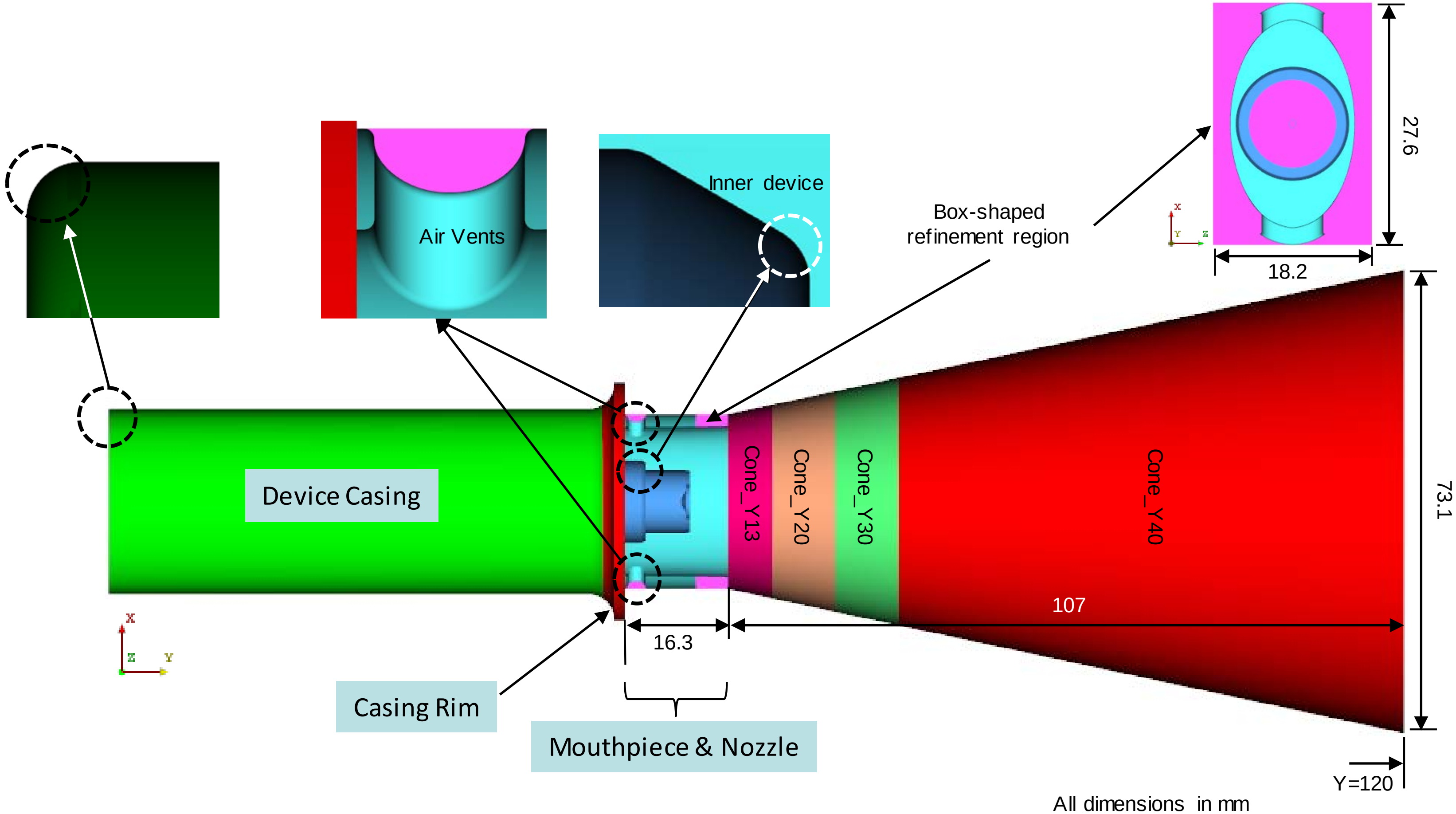
CFD: Patches



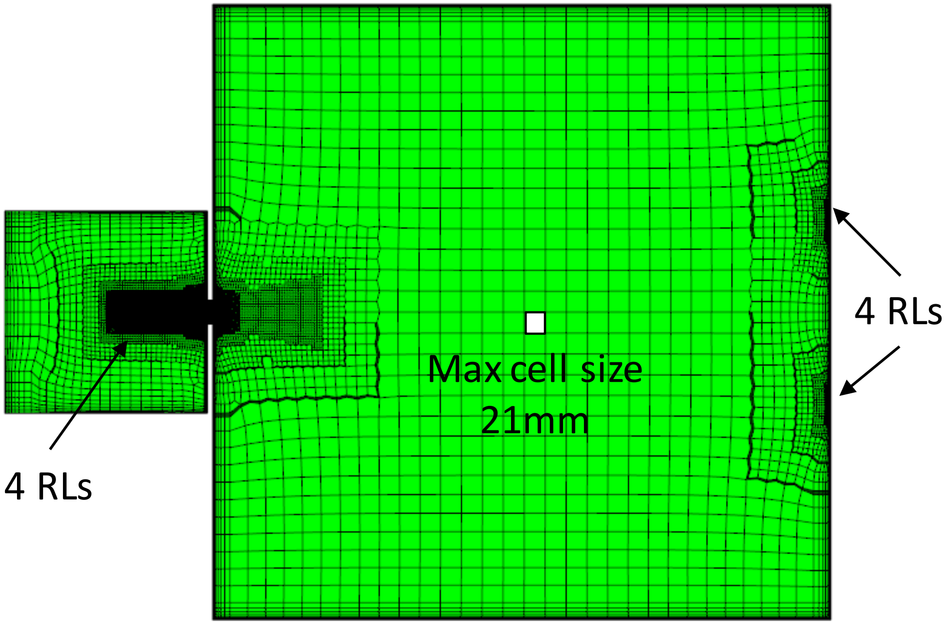
Re @ Air Vent ≈ 4500
Re @ Outlet ≈ 800

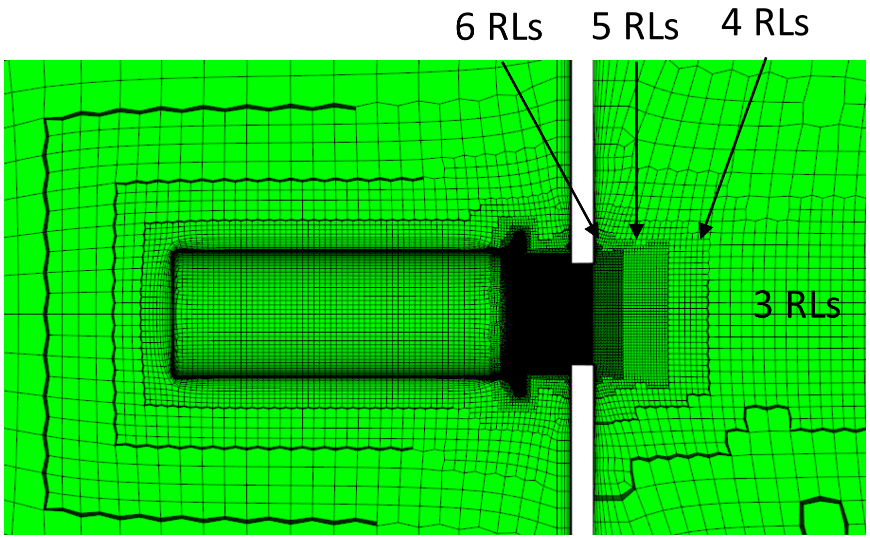
Mesh Generation (CF-Mesh+)

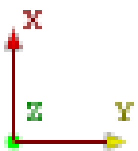
- Inclusion of fillets at air vents, inner device and bottom of device casing
- Refinement of cells at wall boundaries to ensure that $Y^+ \leq 1$.
- Mesh refinement in the mouthpiece region and downstream thereof.



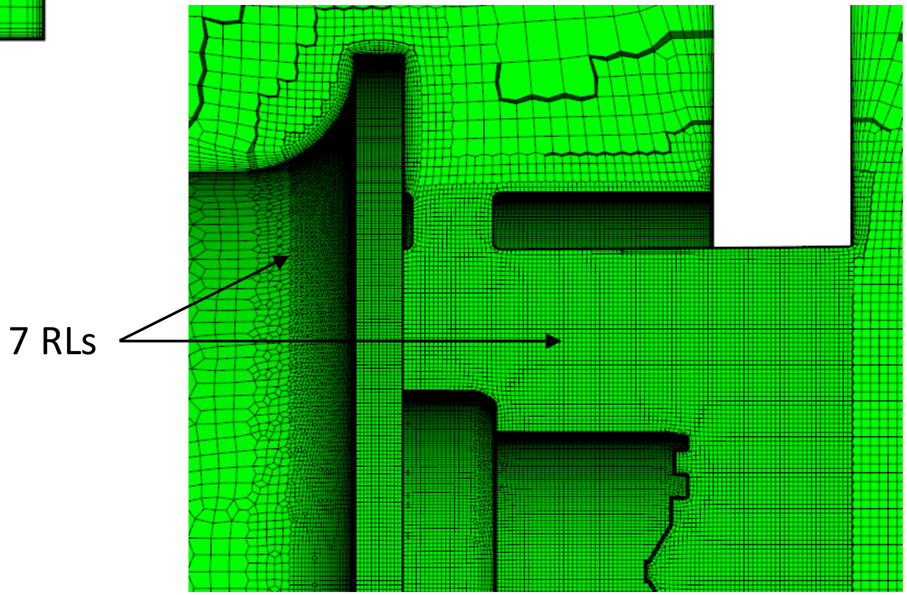
Mesh Generation (CF-Mesh+)





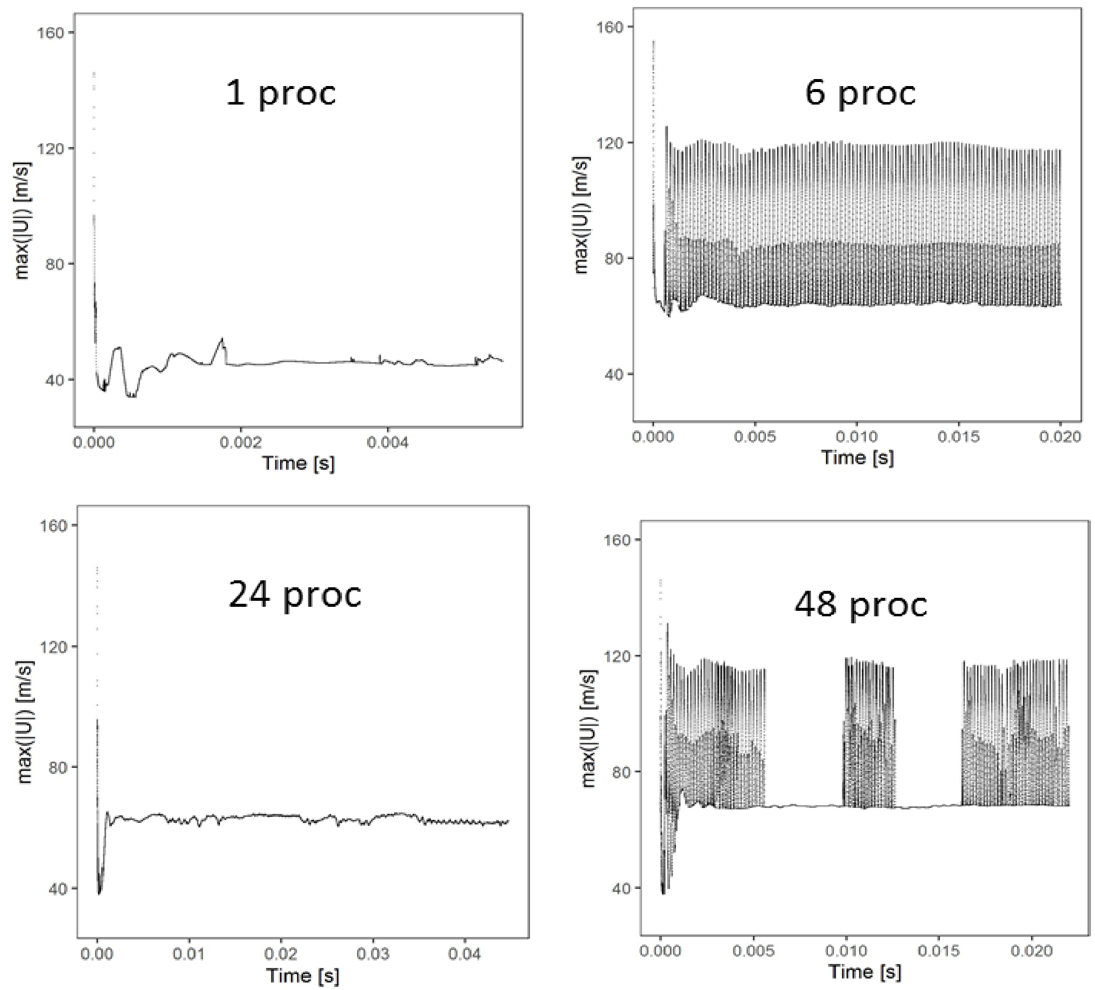


Cells: 3,598,758	
hexahedra:	3,492,869
prisms:	31,230
polyhedra:	74,659
Max aspect ratio = 7.7	
Non-orthogonality	Max: 61.6 Avg: 5.3
Max skewness = 2.5	



Effect of Processor # on $\max\left|\vec{U}_f\right|$

- 1.5M cells, max non-orthogonality 73.3°
- No fillets
- LES-WALE, max Courant # = 0.9,
- Solver: pimpleFoam
- Implausible $\max\left|\vec{U}_f\right|$ very localized.
- Lack of processor scalability.
- No improvement with use of other differencing schemes.
- OF v1906.

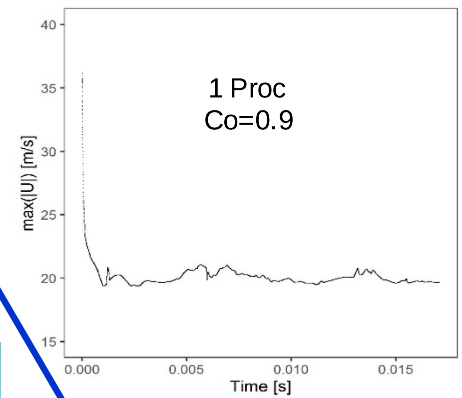


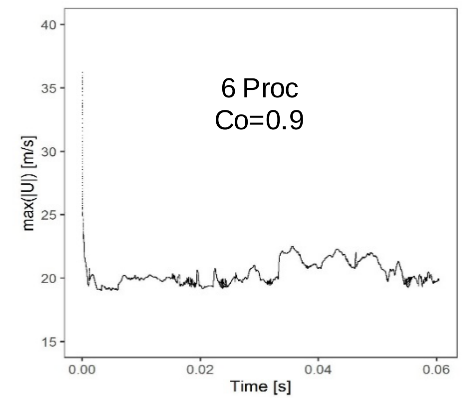
w/o FILLET

$\max\left|\vec{U}_f\right|$ (or, max(|U|) in Y-axis of plots) is the maximum of the filtered velocity magnitude.

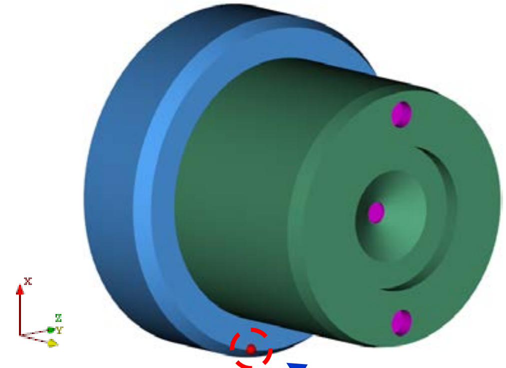
Effect of Fillets on $\max\left|\vec{U}_f\right|$

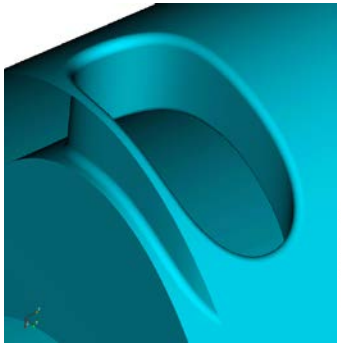
- 1.5M cells, max non-orthogonality 67.1°.
- LES-WALE
- $\max\left|\vec{U}_f\right|$ improved for C0=0.9, but …
- Choice of differencing scheme impacts $\max\left|\vec{U}_f\right|$.
- Courant # effect visible at Co=0.5.

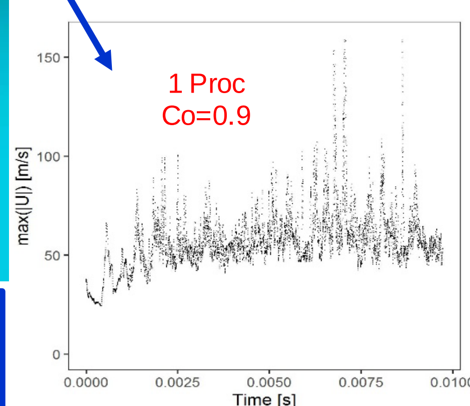


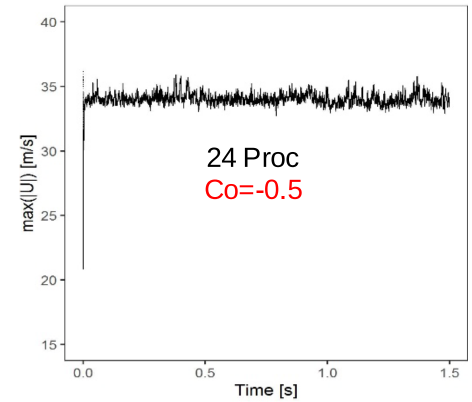


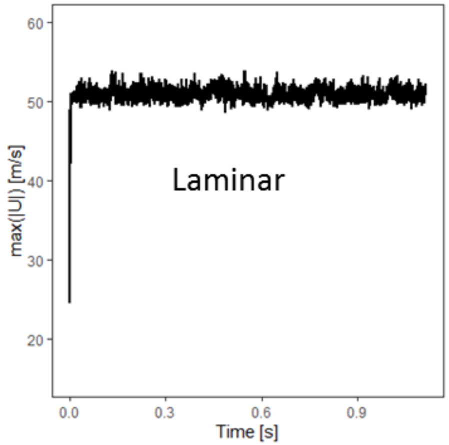
with FILLET

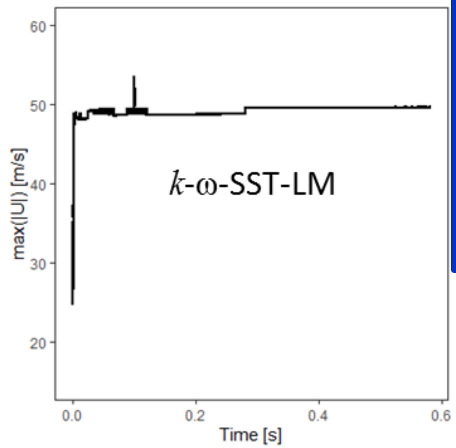






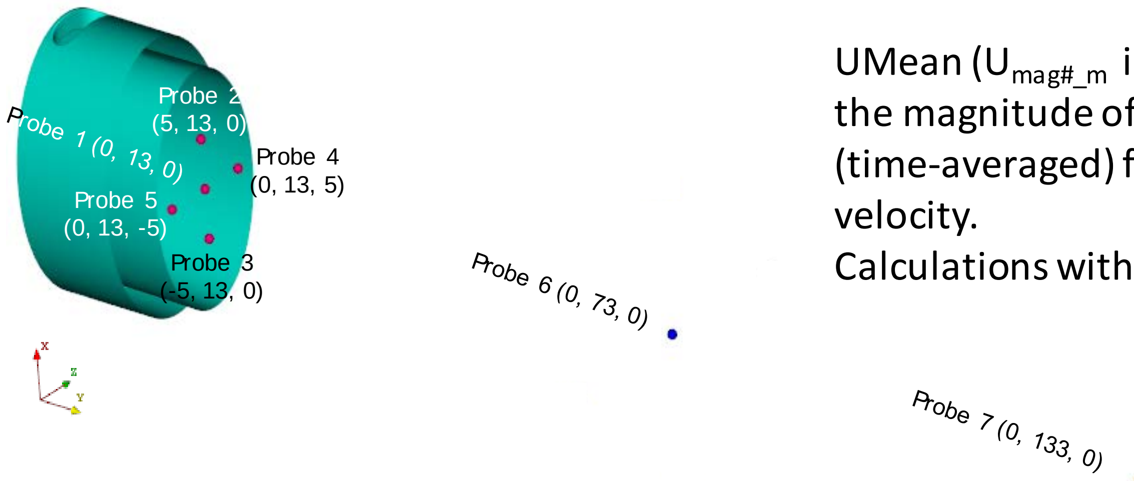






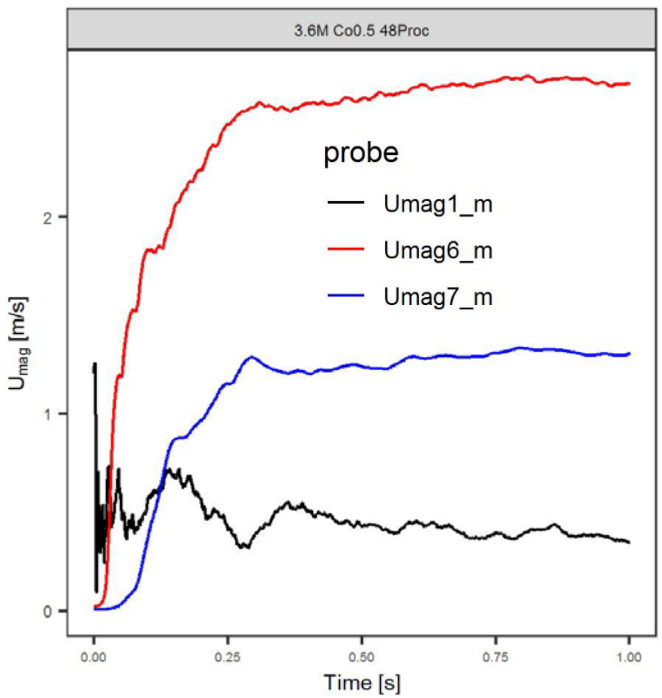
- Laminar and *k*-ω-SST-LM @ C0=0.5 show persistently high $\max\left|\vec{U}_f\right|$.
- Nearly all these were located at the same point.

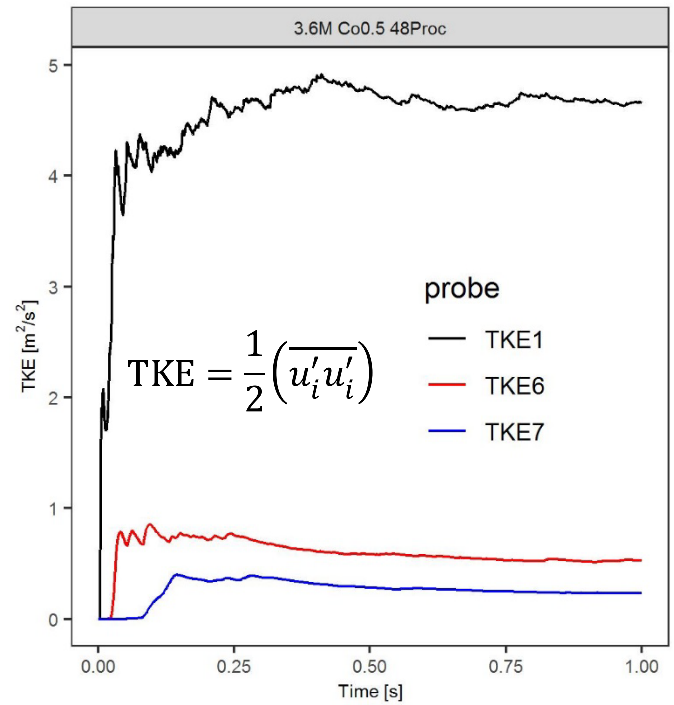
UMean and UPrime2Mean Probes (LES-WALE)



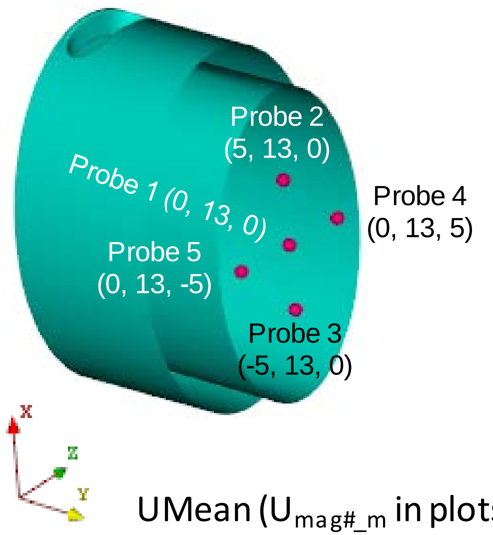
UMean ($U_{mag\#\_m}$ in plots) is the magnitude of the mean (time-averaged) filtered velocity.

Calculations with OF v1912.





UMean Laminar, LES-WALE, *k*-ω SST-LM



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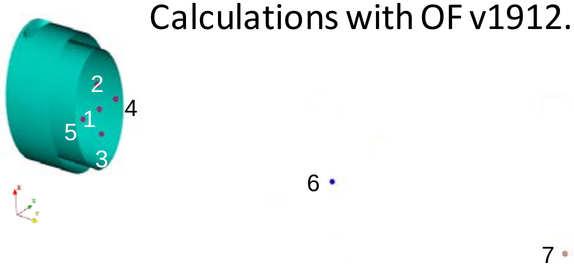
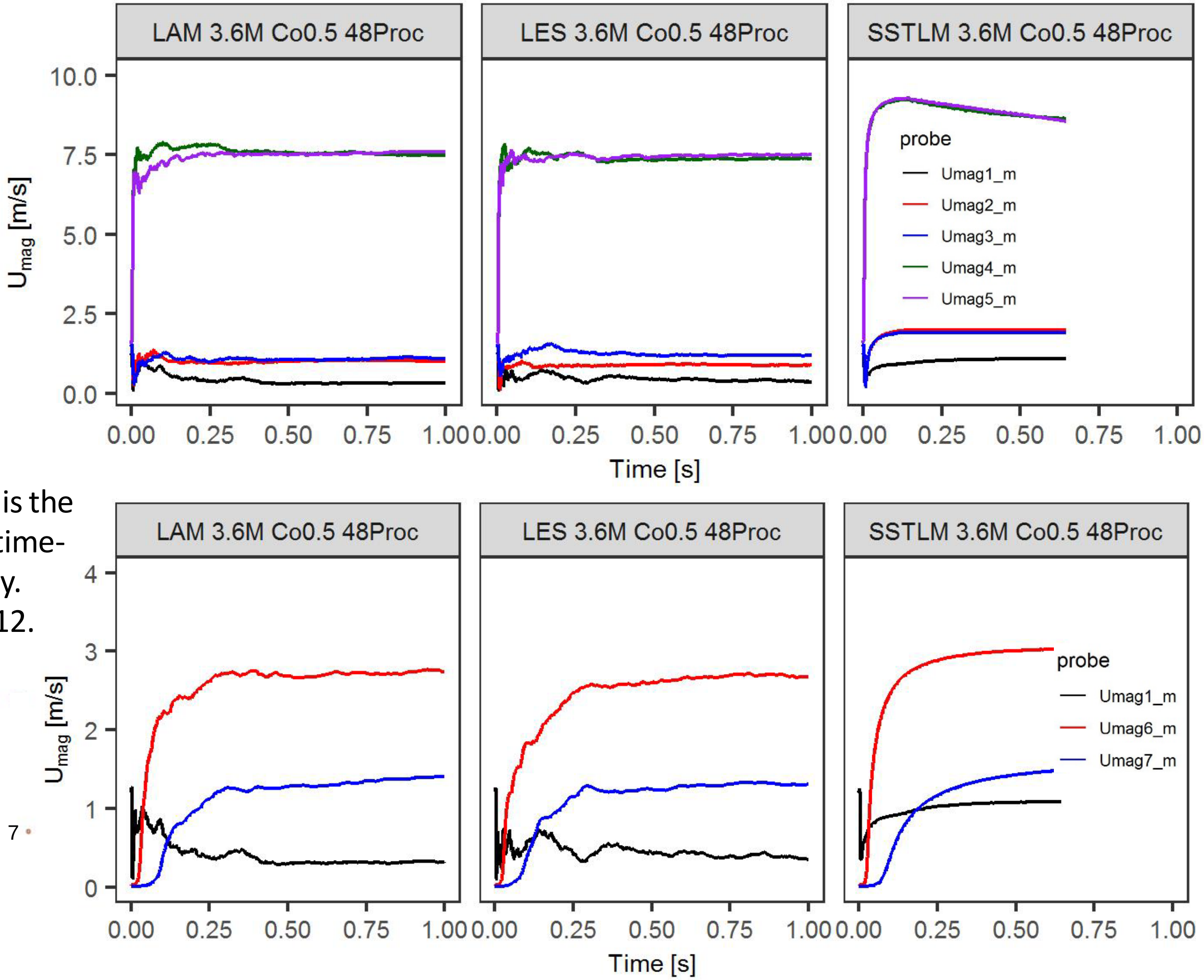




Velocity at Nozzle (LES-WALE)

Symmetrical patterns notable in overall unsteady flow behavior.

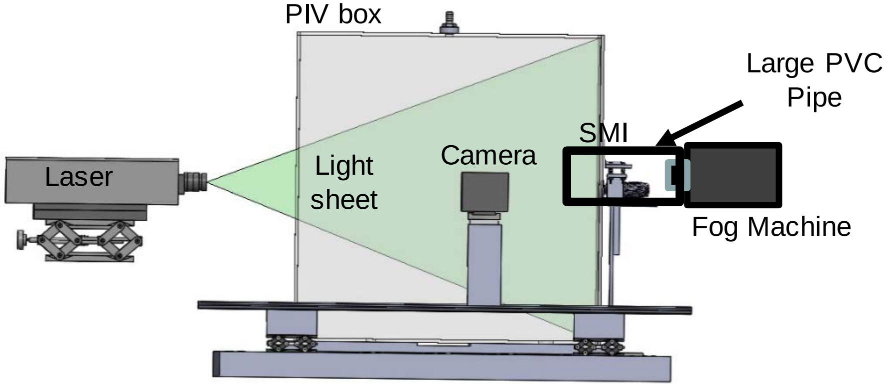
All vectors and contours are in-plane and for filtered field.

Velocity downstream of Mouthpiece (LES-WALE)

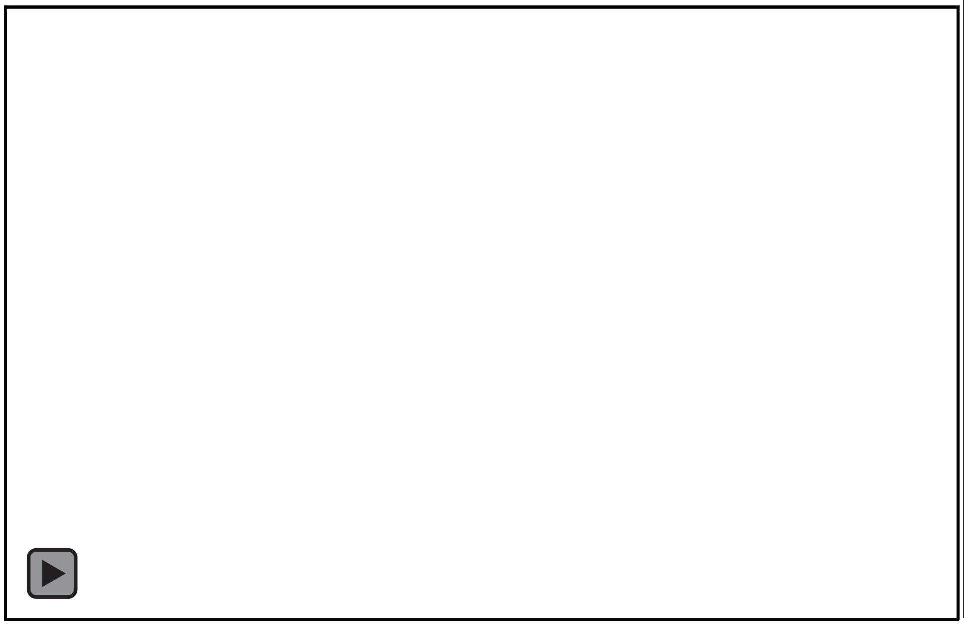
Axial drop in velocity with entrainment of surrounding air.
Flow far downstream of mouthpiece develops into classic round jet.

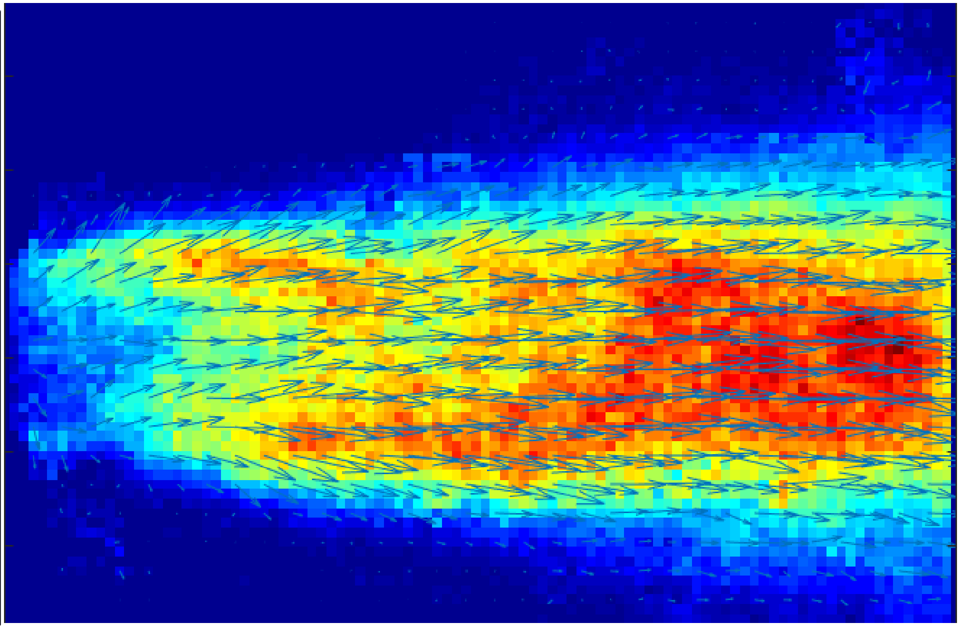
Complex jet emerges from inhaler mouthpiece with regions of backflow.

Velocity downstream of Mouthpiece (LES-WALE)



Measurement plane is downstream of mouthpiece outlet.





In-plane mean (time-averaged) filtered velocity

Time-average of 400 images of in-plane ‘preliminary’ PIV data from 4 tracer (smoke-entrained) experiments.

Summary

- Numerous experimental approaches are being pursued to support the initialization and validation of the CFD models.
- CFD models of single-phase flow indicates strong sensitivity to geometrical treatment of sharp edges and choice of differencing schemes.
- Baseline (3.6M mesh) appears to demonstrate a balance between grid-independent solution, mesh quality and manageable size.
- Future work will build on experience generated thus far to examine Euler-Lagrange simulation and mouth-throat deposition studies.

Acknowledgements

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- Geng Tian

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- Renishkumar Delvadia

CDER/OPQ/OLDP

- Dhaval Gaglani

CDRH/OSEL/DAM

- Suvajyoti Guha
- Brent Craven

Backup Slides

Initial & Boundary Conditions

Field Variable	Initialization	Surface (Patch)	Boundary Condition
p (Pa)	0	Air inlet box	Pressure inlet
		All other patches	Zero gradient
U (m/s)	0	Air inlet box	Zero gradient
		Outlet	flowRateOutletVelocity: 5×10^{-4} m^3/s (=30 L/min)
		All other patches	No slip (Fixed: 0)
$\nu_{t,WALE}$ (m^2/s)	0	All patches	Zero gradient
$\nu_{t,k\text{-}\omega}$ (m^2/s)	0	Air inlet box	Calculated from *k* and ω
		Outlet	
		All other patches	nutkWallFunction: 0
ω (s^{-1})	100	Air inlet box	Fixed: from internal field
		Outlet	Zero gradient
		All other patches	omegaWallFunction
k (m^2/s^{-2})	0.11	Air inlet box	Fixed: from internal field
		Outlet	Fixed: Zero gradient
		All other patches	Fixed: Zero
Re_θ(-)	0.64	Air inlet box	Fixed: from internal field
		All other patches	Zero gradient
γ (-)	1	Air inlet box	Fixed: from internal field
		All other patches	Zero gradient

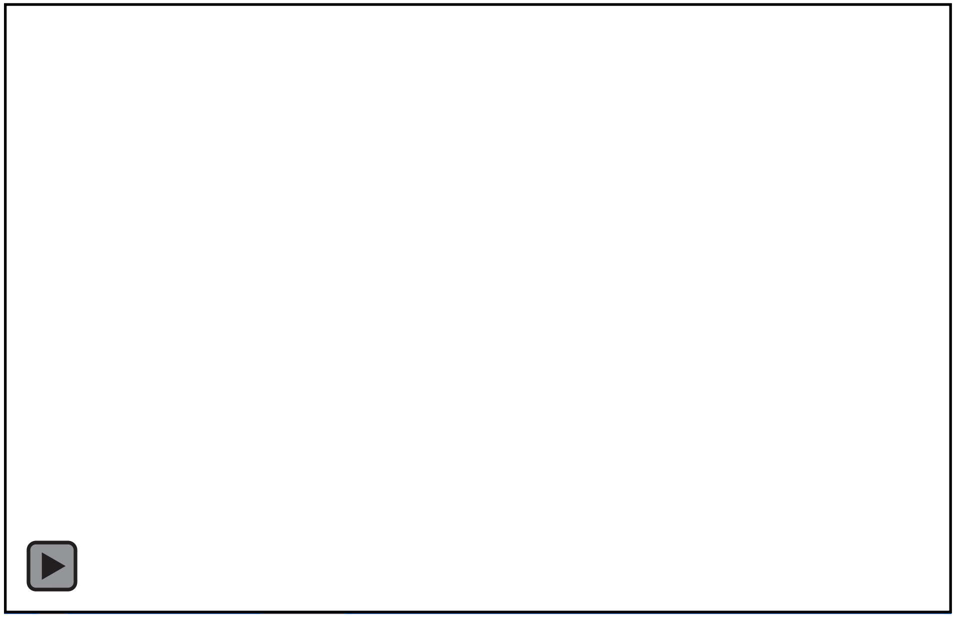
Discretization Schemes and Solution Solvers

fvSchemes	
ddtSchemes	
default	backward;
gradSchemes	
default	cellMDLimited Gauss linear 1.0;
grad(p)	cellLimited leastSquares 1.0;
divSchemes	
default	none;
div(phi,U)	bounded Gauss linearUpwindV default;
div(phi,k)	Gauss limitedLinear 1;
div(phi,omega)	Gauss limitedLinear 1;
div(phi,gammaInt)	Gauss limitedLinear 1;
div(phi,ReThetat)	Gauss limitedLinear 1;
div((nuEff*dev2(T(grad(U)))))	Gauss linear;
laplacianSchemes	
default	Gauss linear limited 0.5;
interpolationSchemes	
default	linear;
snGradSchemes	
default	limited 0.5;
wallDist	
method	meshWave;
corrected	yes;

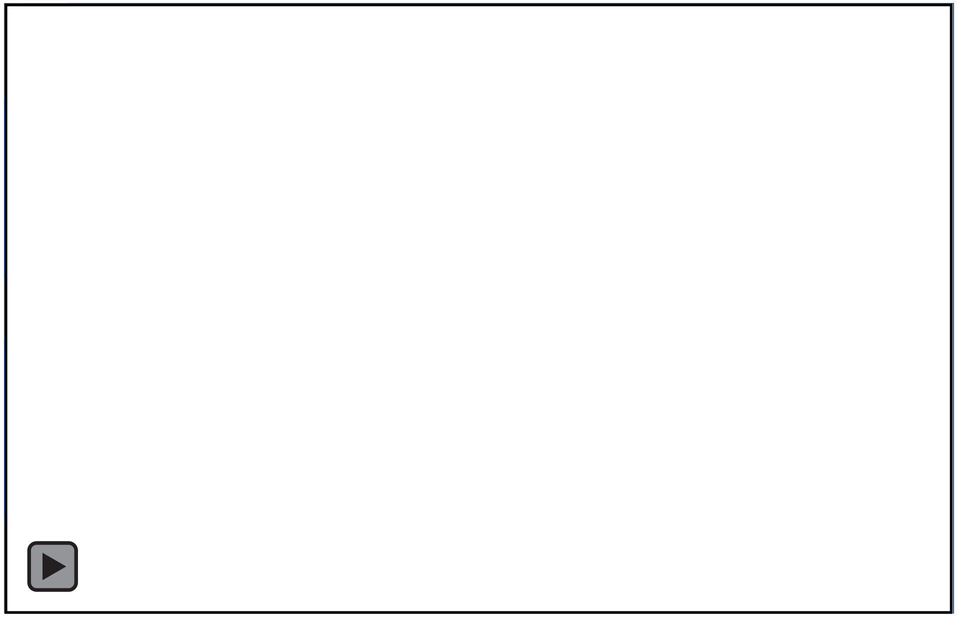
fvSolution	
solvers p	
solver	GAMG;
smoother	symGaussSeidel;
tolerance	1e-06;
relTol	0.01;
minIter 1;	
maxIter 300;	
solvers "(U|k|omega|gammaInt|ReThetat)"	
solver	PBiCG;
smoother	symGaussSeidel;
preconditioner	DILU;
tolerance	1e-05;
relTol	0.01;
minIter	1;
maxIter	100;
"(p|U|k|omega|gammaInt|ReThetat)" Final	
$"(p|U|k|omega|gammaInt|ReThetat)" ;	
relTol	0;
PIMPLE	
momentumPredictor	yes;
nOuterCorrectors	1;
nCorrectors	2;
nNonOrthogonalCorreactors	0;
turbOnFinalIterOnly	no;
relaxationFactors	
equations	
".*"	1;

Turbulence Parameters at Nozzle (LES-WALE)

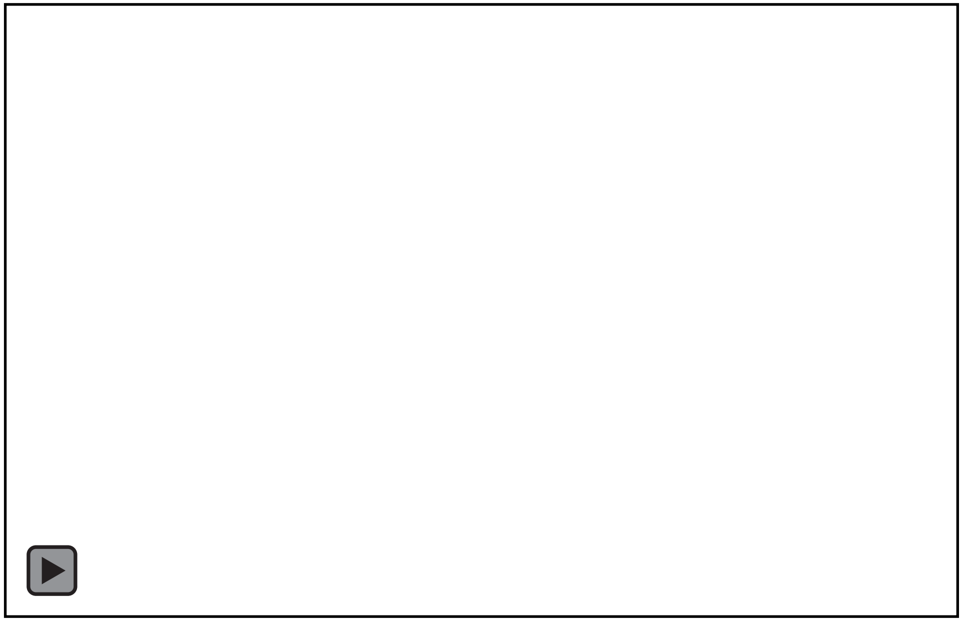
$$k = \frac{1}{2}\left(\overline{u_i' u_i'}\right)$$

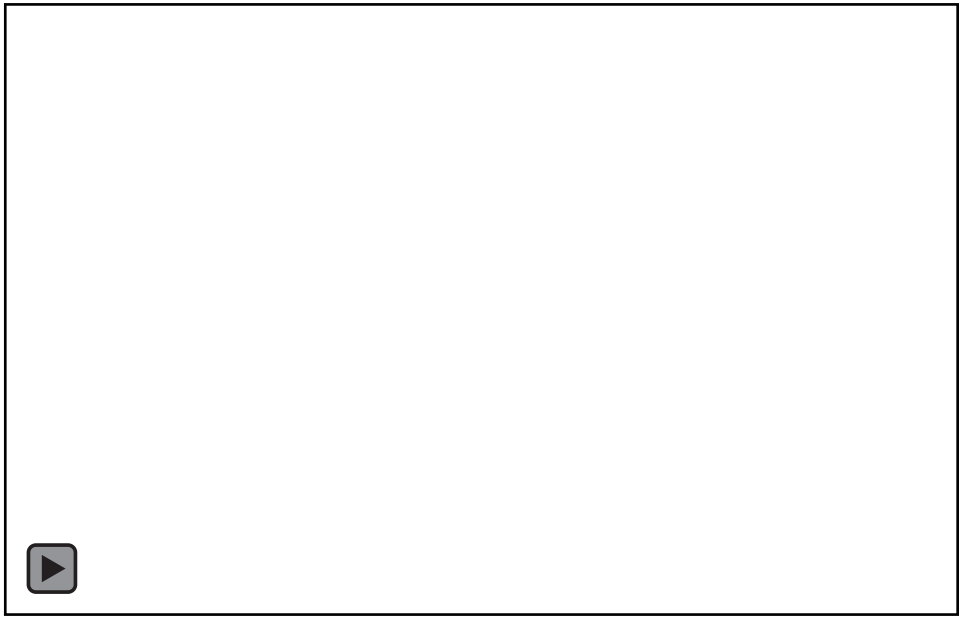


$$\nu_t$$

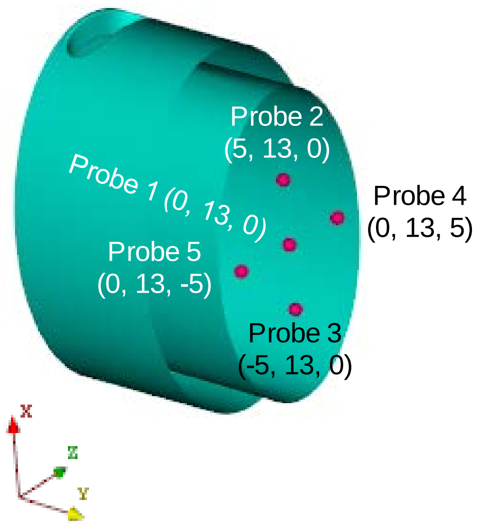


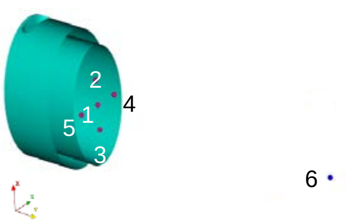
Velocity downstream of Mouthpiece (LES-WALE)

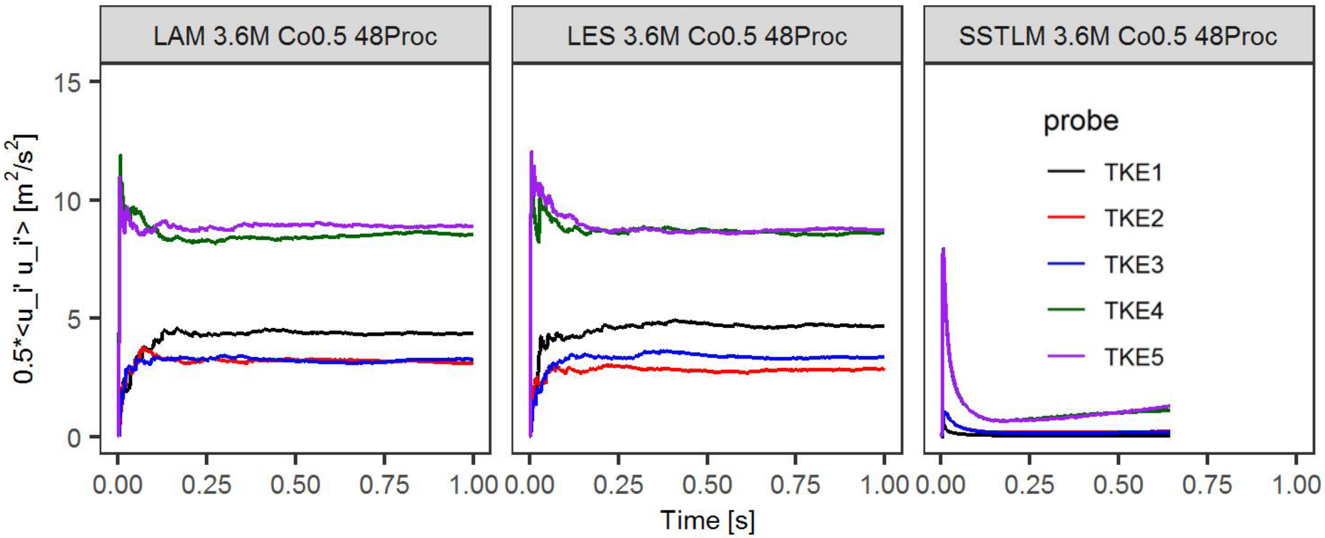


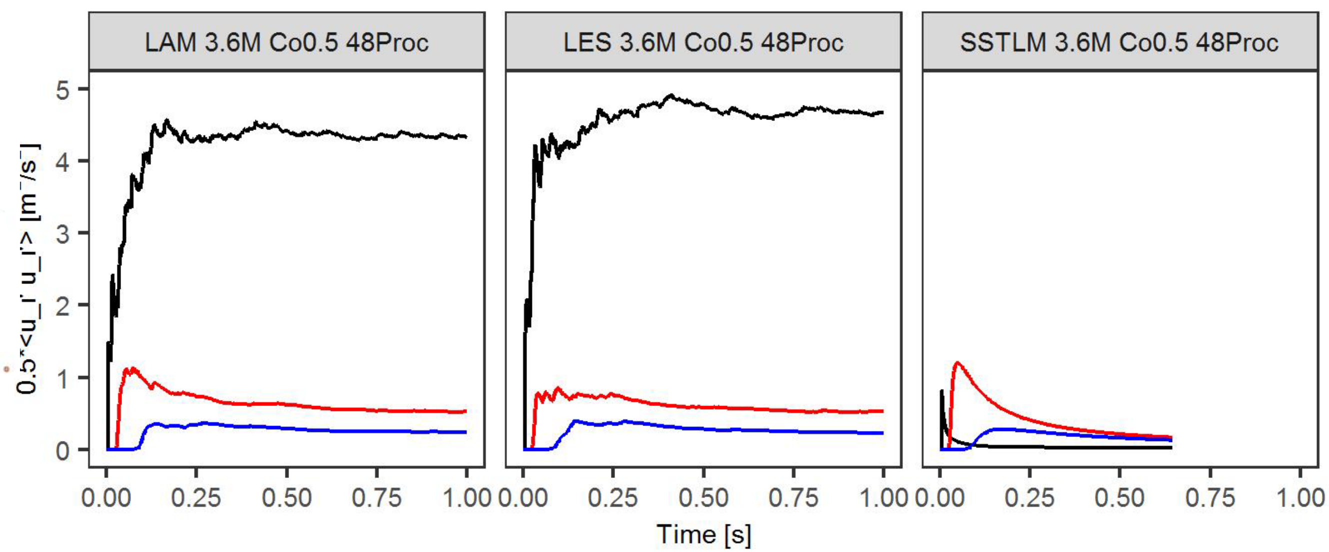


UPrime2Mean Laminar, LES-WALE, *k*-ω SST-LM

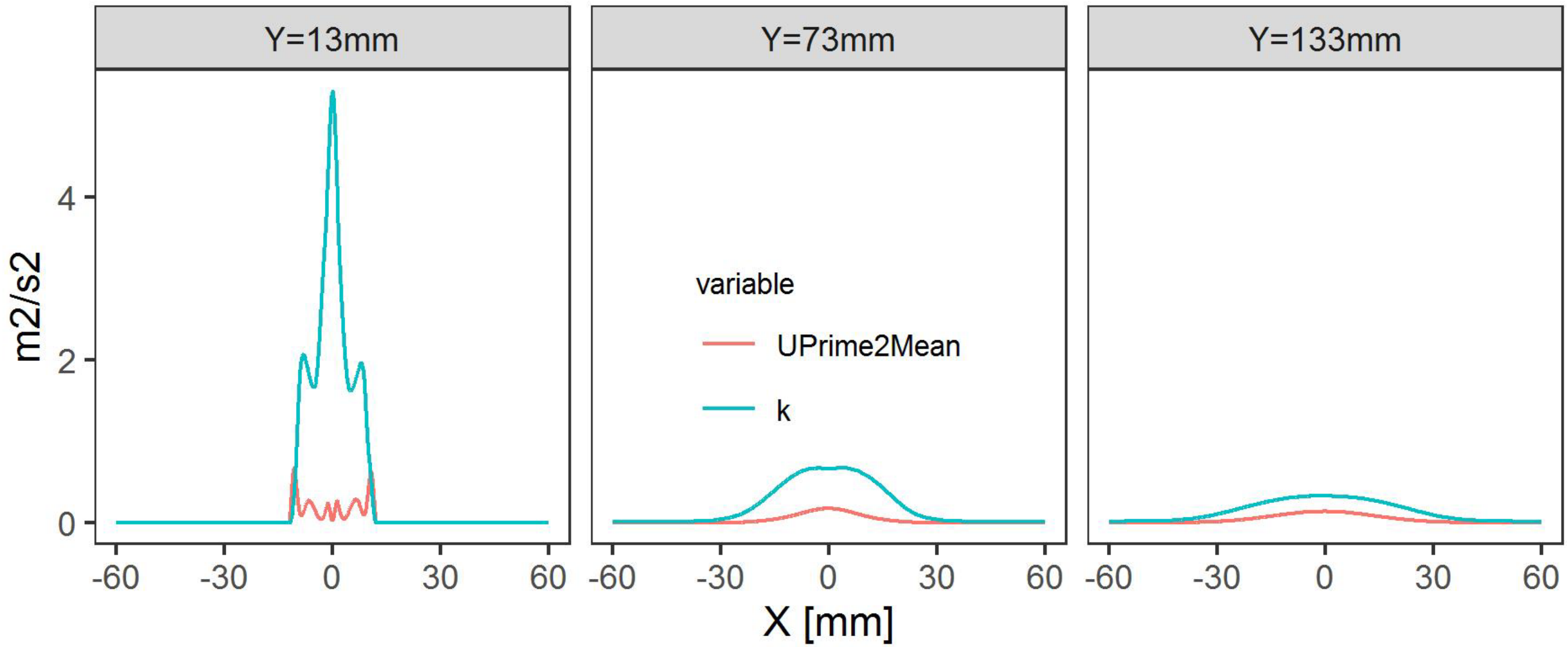






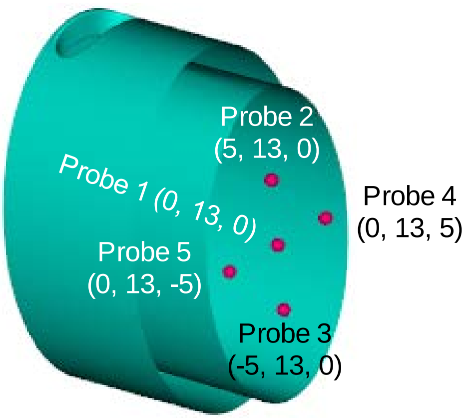


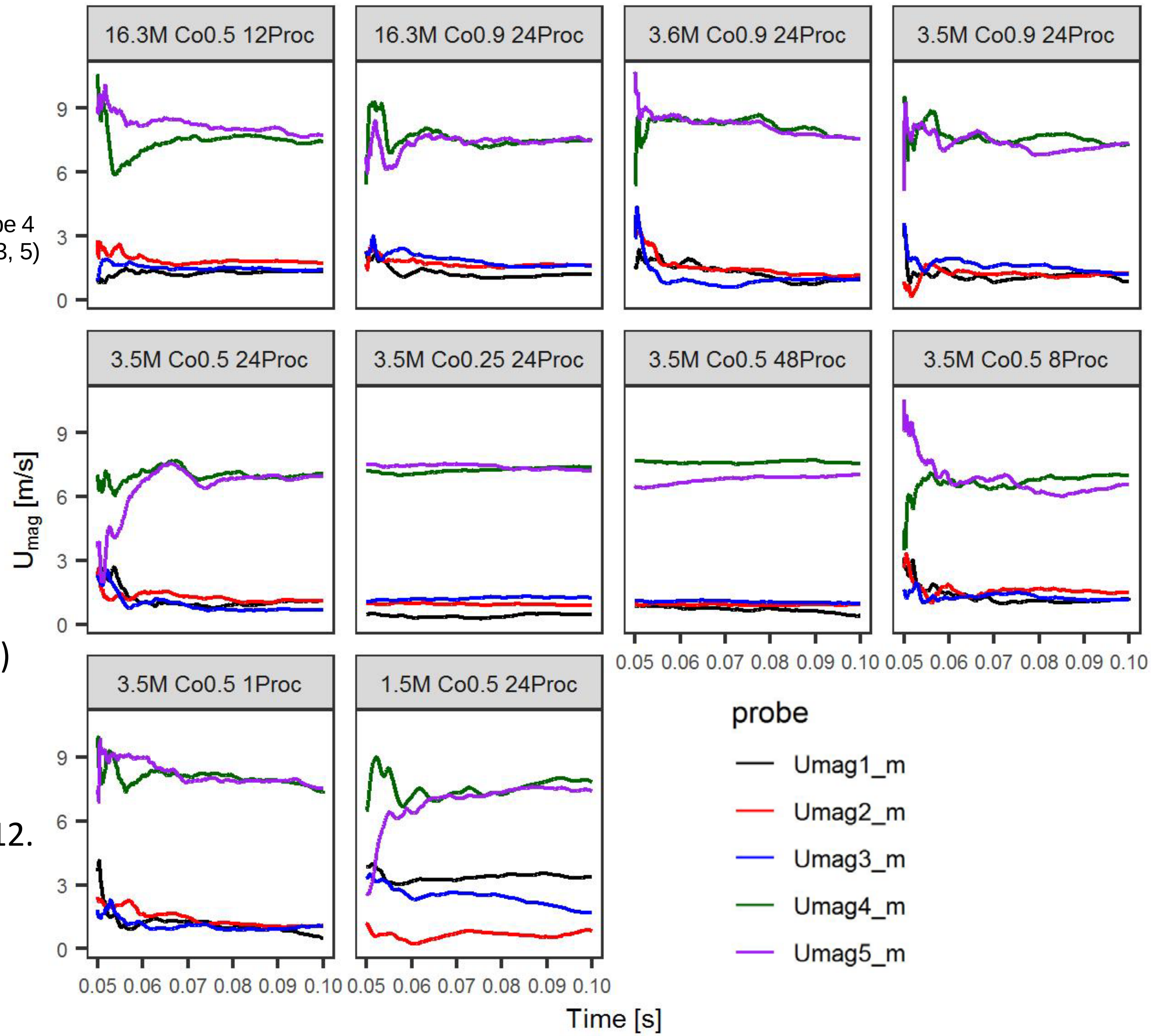
UPrime2Mean *k*-ω SST-LM



Radial Profiles of *k* and $\frac{1}{2}\left(\overline{u_i' u_i'}\right)$.

$|\vec{U}_{avg,f}|$ Probes (LES-WALE)

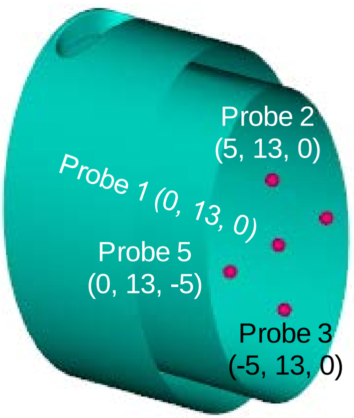




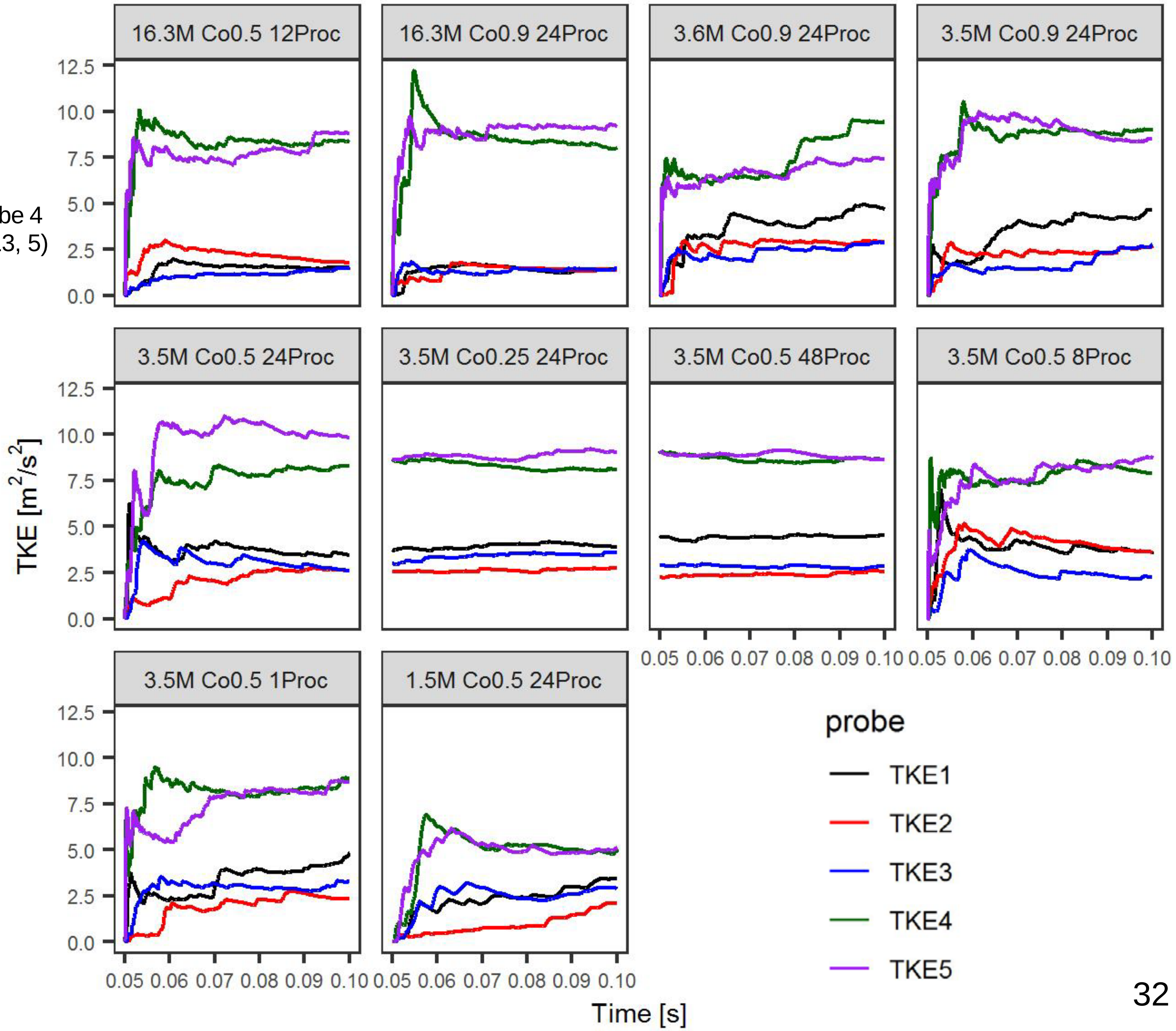
$|\vec{U}_{avg,f}|$ ($U_{mag\#\_m}$ in plots) is the magnitude of the mean (time-averaged) filtered velocity.

Calculations with OF v1912.

TKE Probes (LES-WALE)



$$k = \frac{1}{2}\left(\overline{u_i' u_i'}\right)$$



Run Times

Model	Physical Time (s)	Execution Time (h)	Clock Time (h)	Nproc* (-)	# Nodes (-)
LES-Wale	1	215	216	48	4
Laminar	1	196	197	48	4
k-ω SST-LM	0.65	212	213	48	4

* Intel(R) Xeon(R) CPU E5-2620 0 @ 2.00GHz, 15M Cache

FDA HPC Capability

Large-scale cluster

- 421 nodes with 5,720 cores
- About 53 TB of RAM 1.2 PB of storage
- 40G Infiniband & 100G OPA network

Medium-scale cluster

- 82 compute nodes with 984 cores
- 63GB RAM per node, 180 TB storage
- Infiniband-connected CPUs