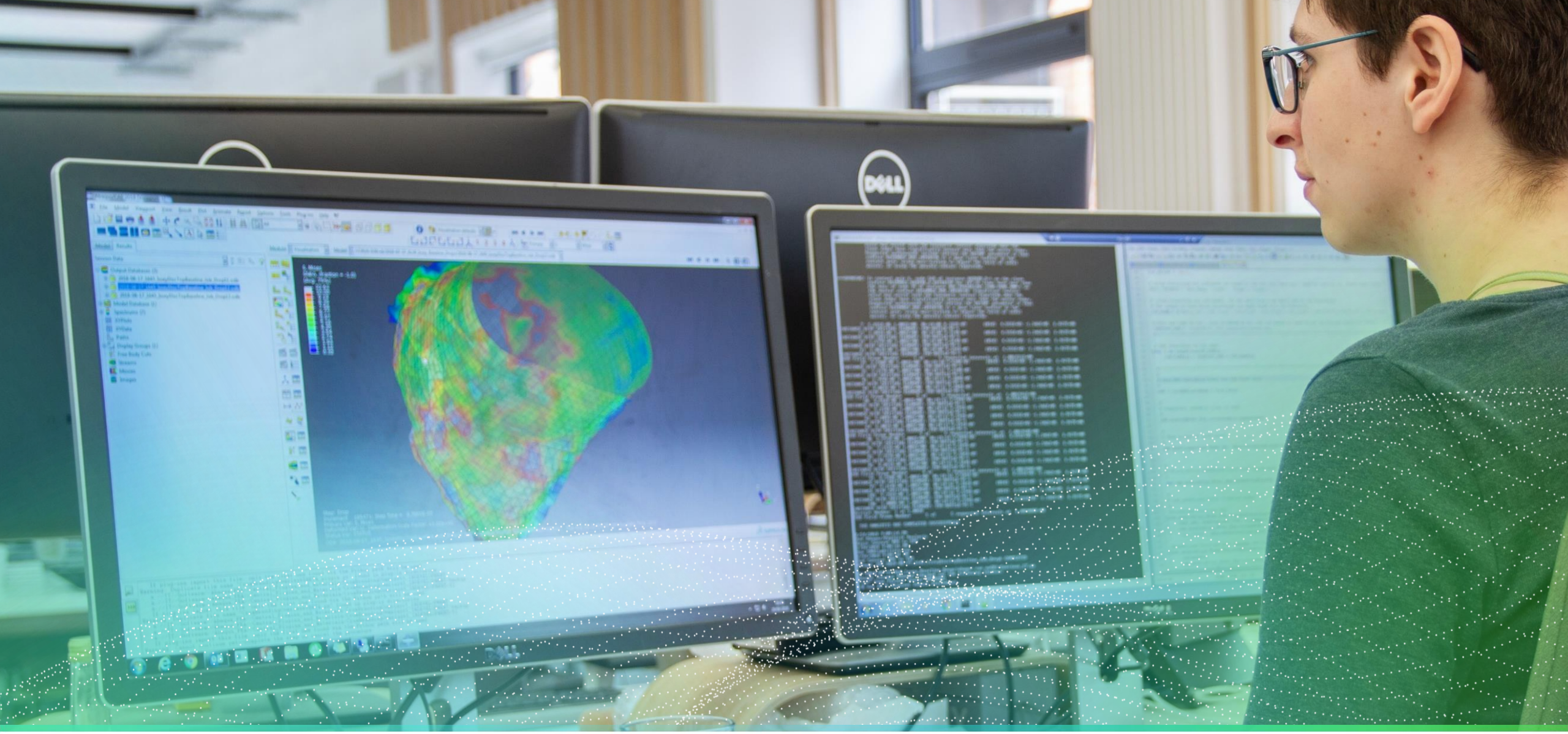
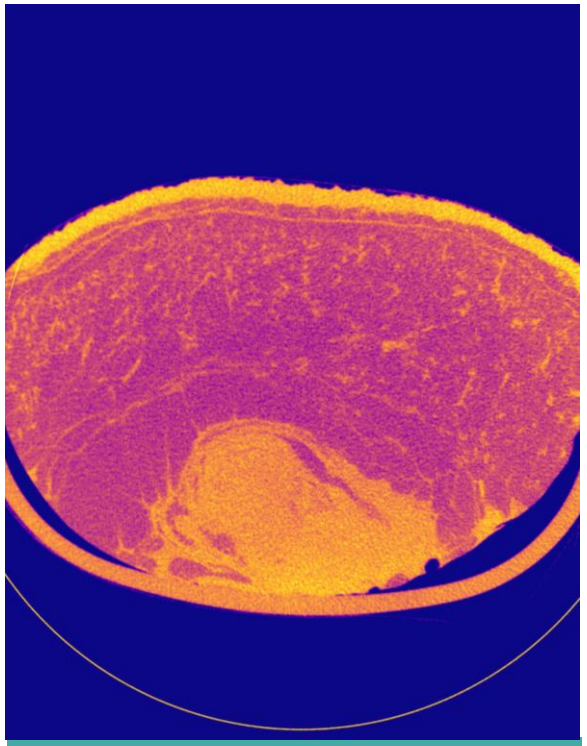


Modelling of Subcutaneous Injection & Bioavailability to Bridge IV/SubQ

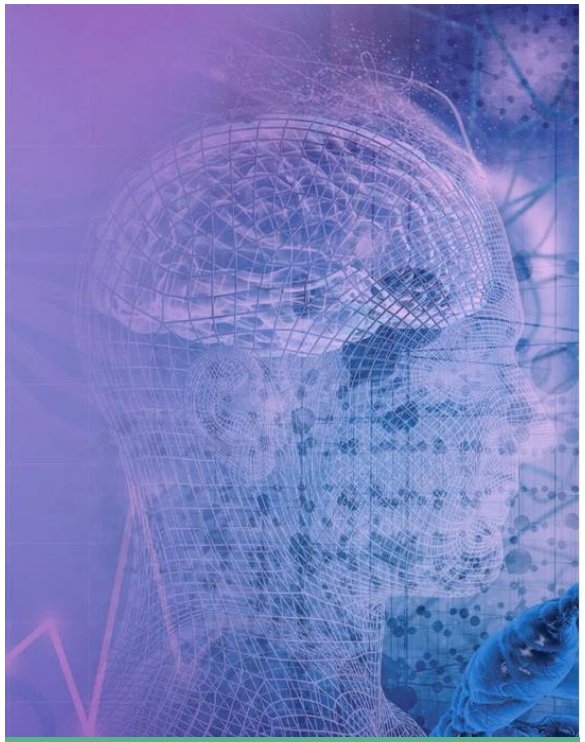
Crux Product Design

Discussion topics

CM&S for Med Devices
10 minutes



Injection Modelling at Crux
5 minutes



Questions & Answers
5 minutes

Digital Transformation

> The strategic adoption of digital technologies to improve **processes & productivity**, manage **business risk** and improve **customer service**

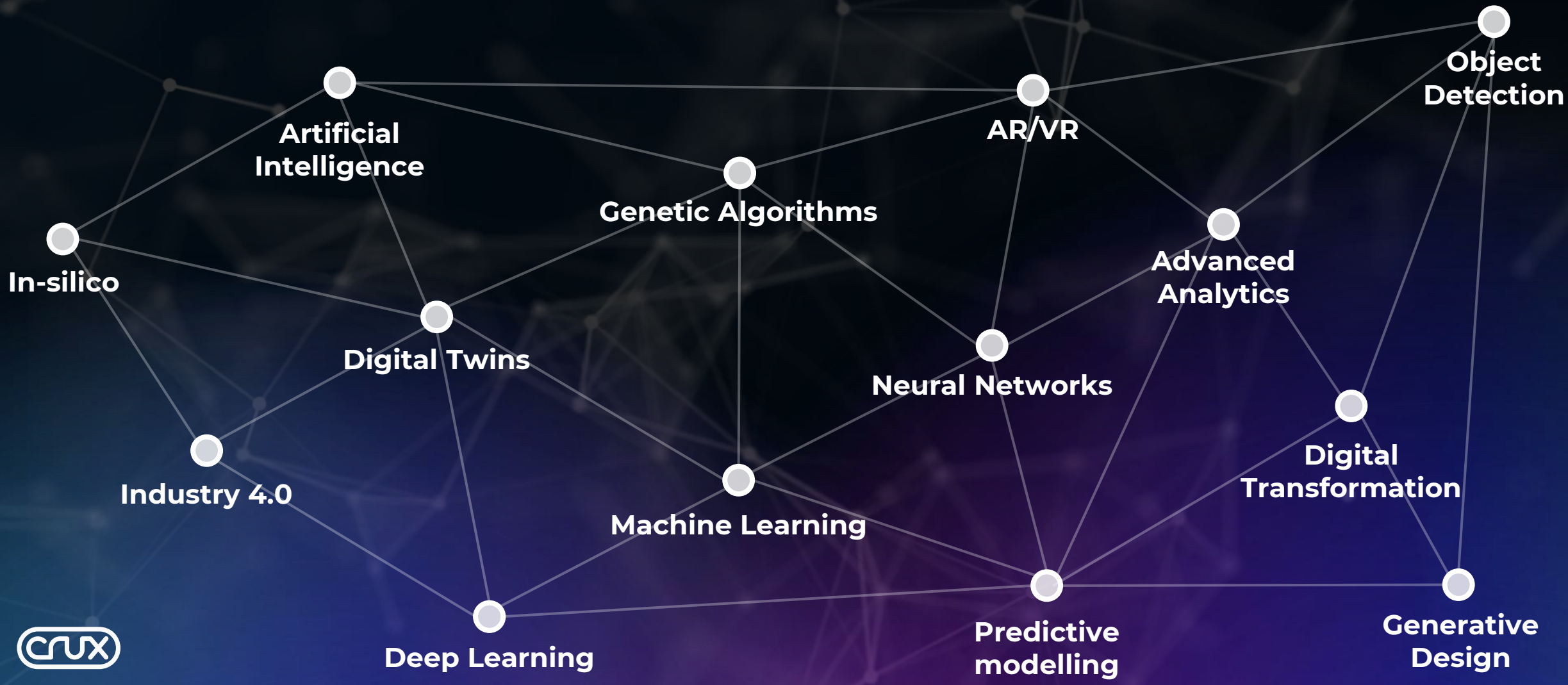
Citrix, 2018

Digital Assets

> A digital asset is **anything** that is **stored digitally** and is **uniquely identifiable** that organizations can **use to realize value**

Gartner, 2022

Digital Threads



01

02

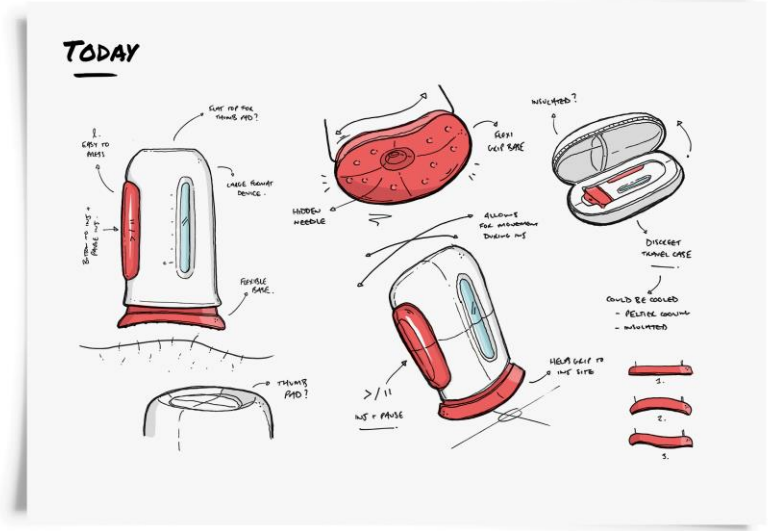
Full device digital twin

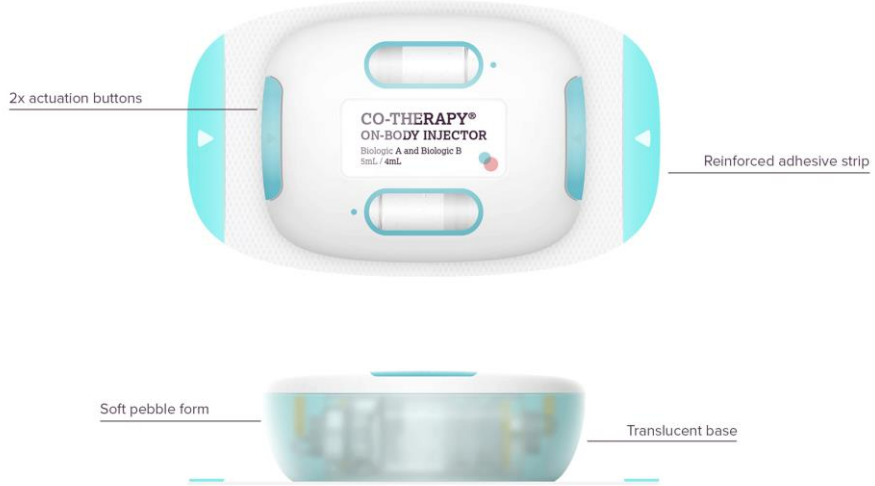
A **step** change in device development risk mitigation

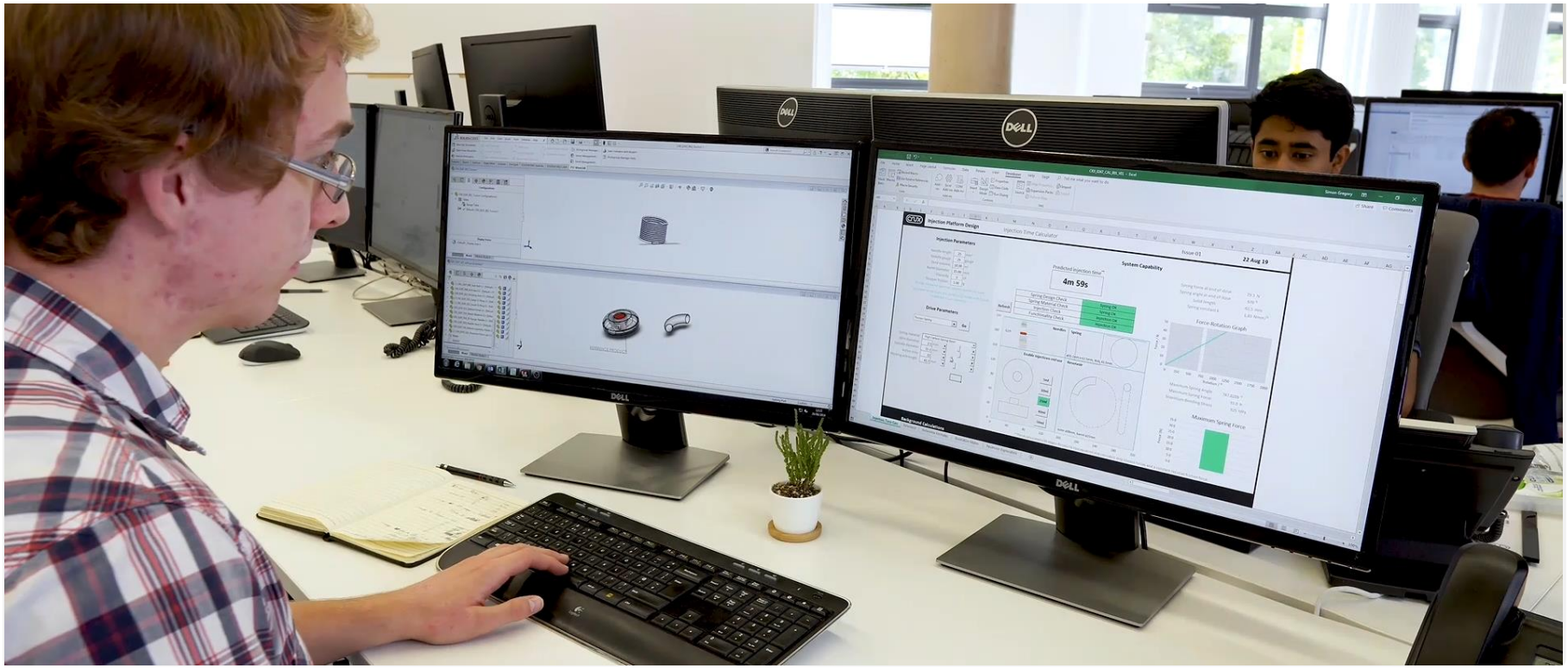
A step change in device development timeframes

EARLY ASSESSMENTS

REGULATORY SUBMISSIONS



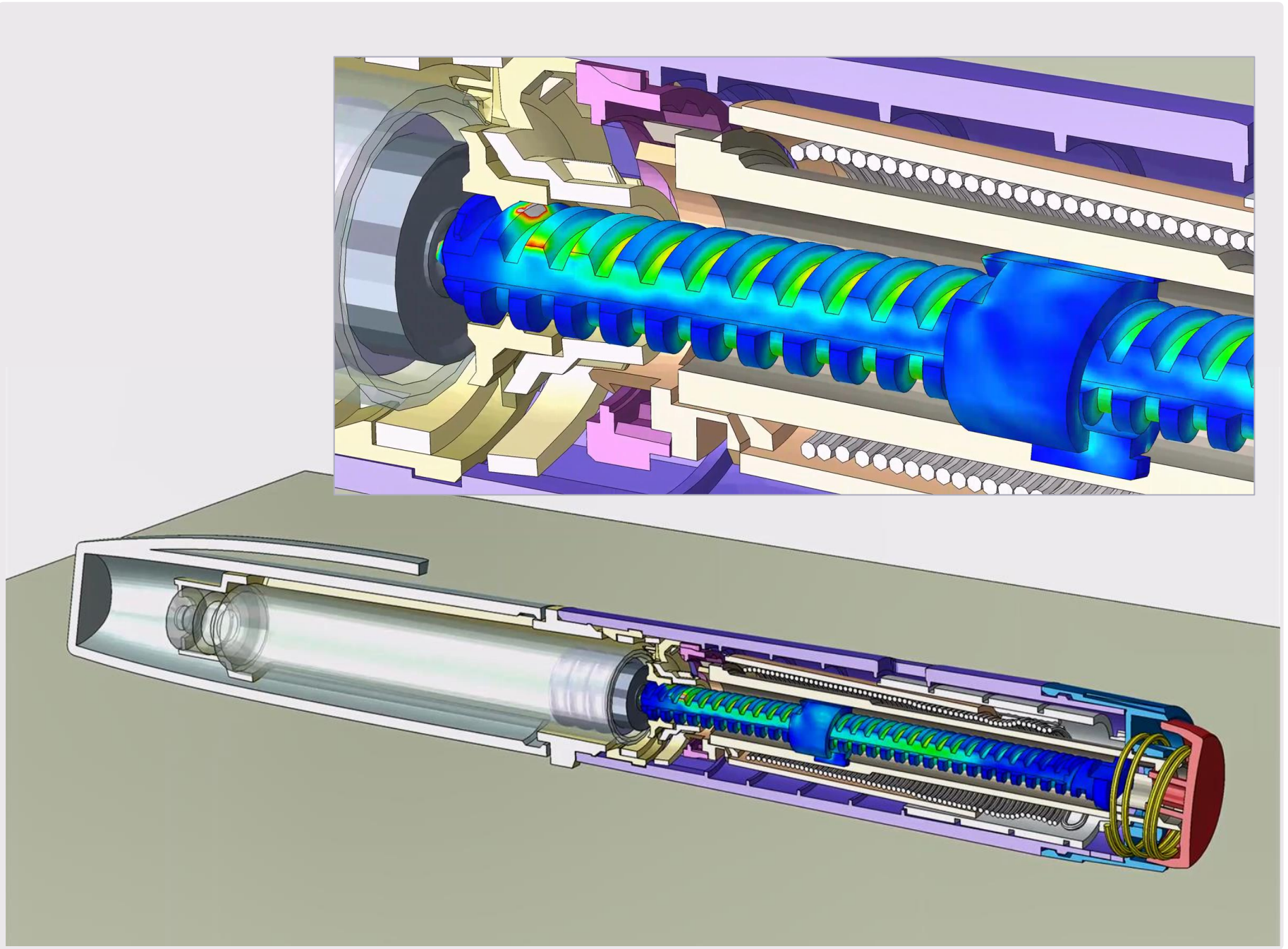




A step change in device development timeframes

EARLY ASSESSMENTS

REGULATORY SUBMISSIONS



A step change in device development timeframes

EARLY ASSESSMENTS

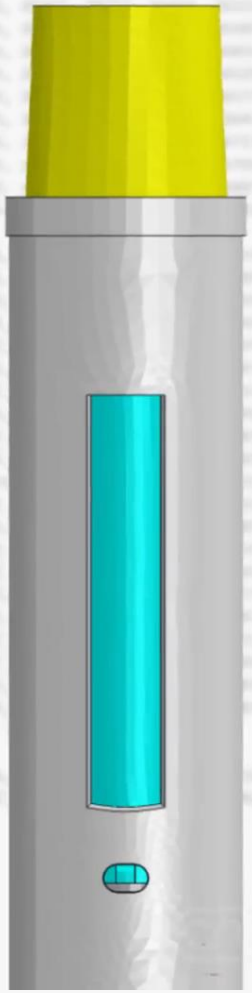
REGULATORY SUBMISSIONS

100,000 Finite Elements

600,000 Degree of Freedom Model

Simulation runtime: 4 hours

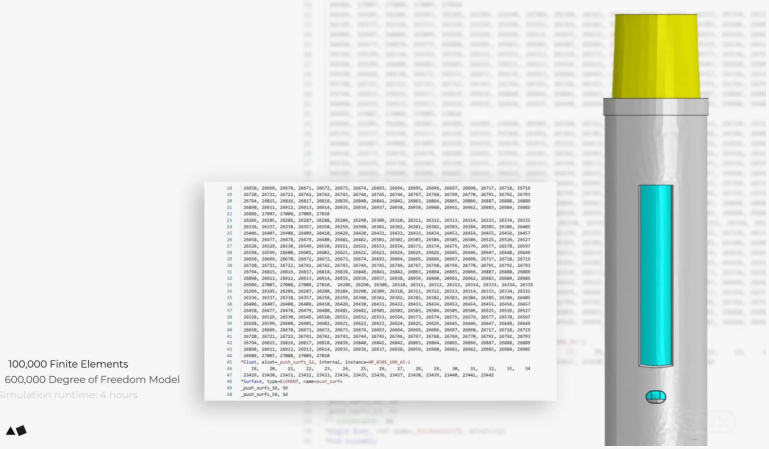
```
26650, 26669, 26670, 26671, 26672, 26673, 26674, 26693, 26694, 26695, 26696, 26697, 26698, 26717, 26718, 26719
26720, 26721, 26722, 26741, 26742, 26743, 26744, 26745, 26746, 26767, 26768, 26769, 26770, 26791, 26792, 26793
26794, 26815, 26816, 26817, 26818, 26839, 26840, 26841, 26842, 26863, 26864, 26865, 26866, 26887, 26888, 26889
26890, 26911, 26912, 26913, 26914, 26935, 26936, 26937, 26938, 26959, 26960, 26961, 26962, 26983, 26984, 26985
26986, 27007, 27008, 27009, 27010
26266, 26285, 26286, 26287, 26288, 26289, 26290, 26309, 26310, 26311, 26312, 26313, 26314, 26333, 26334, 26335
26336, 26337, 26338, 26357, 26358, 26359, 26360, 26361, 26362, 26381, 26382, 26383, 26384, 26385, 26386, 26405
26406, 26407, 26408, 26409, 26410, 26429, 26430, 26431, 26432, 26433, 26434, 26453, 26454, 26455, 26456, 26457
26458, 26477, 26478, 26479, 26480, 26481, 26482, 26501, 26502, 26503, 26504, 26505, 26506, 26525, 26526, 26527
26528, 26529, 26530, 26549, 26550, 26551, 26552, 26553, 26554, 26573, 26574, 26575, 26576, 26577, 26578, 26597
26598, 26599, 26600, 26601, 26602, 26621, 26622, 26623, 26624, 26625, 26626, 26645, 26646, 26647, 26648, 26649
26650, 26669, 26670, 26671, 26672, 26673, 26674, 26693, 26694, 26695, 26696, 26697, 26698, 26717, 26718, 26719
26720, 26721, 26722, 26741, 26742, 26743, 26744, 26745, 26746, 26767, 26768, 26769, 26770, 26791, 26792, 26793
26794, 26815, 26816, 26817, 26818, 26839, 26840, 26841, 26842, 26863, 26864, 26865, 26866, 26887, 26888, 26889
26890, 26911, 26912, 26913, 26914, 26935, 26936, 26937, 26938, 26959, 26960, 26961, 26962, 26983, 26984, 26985
26986, 27007, 27008, 27009, 27010, 26289, 26290, 26309, 26310, 26311, 26312, 26313, 26314, 26333, 26334, 26335
26266, 26285, 26286, 26287, 26288, 26289, 26290, 26309, 26310, 26311, 26312, 26313, 26314, 26333, 26334, 26335
26336, 26337, 26338, 26357, 26358, 26359, 26360, 26361, 26362, 26381, 26382, 26383, 26384, 26385, 26386, 26405
26406, 26407, 26408, 26409, 26410, 26429, 26430, 26431, 26432, 26433, 26434, 26453, 26454, 26455, 26456, 26457
26458, 26477, 26478, 26479, 26480, 26481, 26482, 26501, 26502, 26503, 26504, 26505, 26506, 26525, 26526, 26527
26528, 26529, 26530, 26549, 26550, 26551, 26552, 26553, 26554, 26573, 26574, 26575, 26576, 26577, 26578, 26597
26598, 26599, 26600, 26601, 26602, 26621, 26622, 26623, 26624, 26625, 26626, 26645, 26646, 26647, 26648, 26649
26650, 26669, 26670, 26671, 26672, 26673, 26674, 26693, 26694, 26695, 26696, 26697, 26698, 26717, 26718, 26719
26720, 26721, 26722, 26741, 26742, 26743, 26744, 26745, 26746, 26767, 26768, 26769, 26770, 26791, 26792, 26793
26794, 26815, 26816, 26817, 26818, 26839, 26840, 26841, 26842, 26863, 26864, 26865, 26866, 26887, 26888, 26889
26890, 26911, 26912, 26913, 26914, 26935, 26936, 26937, 26938, 26959, 26960, 26961, 26962, 26983, 26984, 26985
26986, 27007, 27008, 27009, 27010
*Elset, elset=_push_surfs_S2, internal, instance=HP_0305_108_A5-1
   19,   20,   21,   22,   23,   24,   25,   26,   27,   28,   29,   30,   31,   32,   33,   34
23429, 23430, 23431, 23432, 23433, 23434, 23435, 23436, 23437, 23438, 23439, 23440, 23441, 23442
*Surface, type=ELEMENT, name=push_surfs
_push_surfs_S6, S6
_push_surfs_S4, S4
```

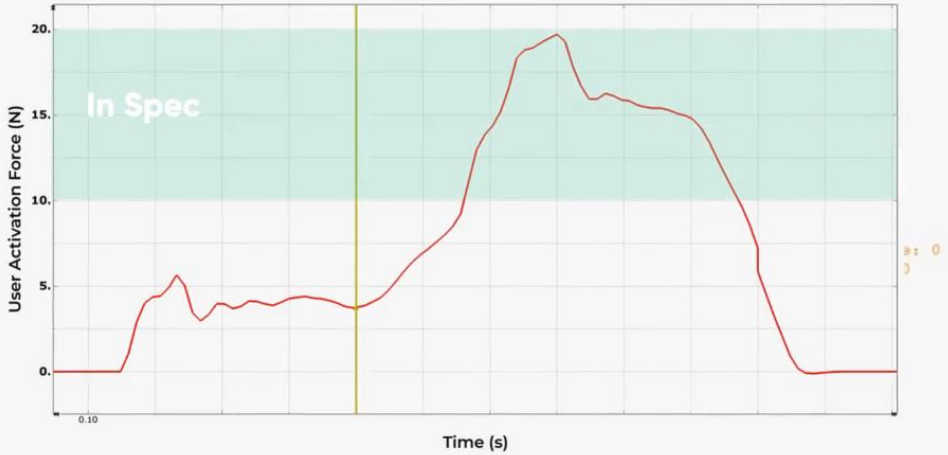


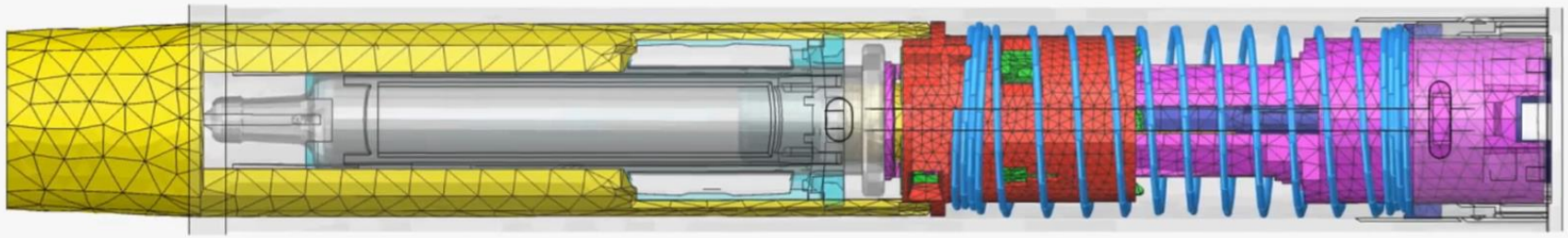
A step change in device development timeframes

EARLY ASSESSMENTS

REGULATORY SUBMISSIONS



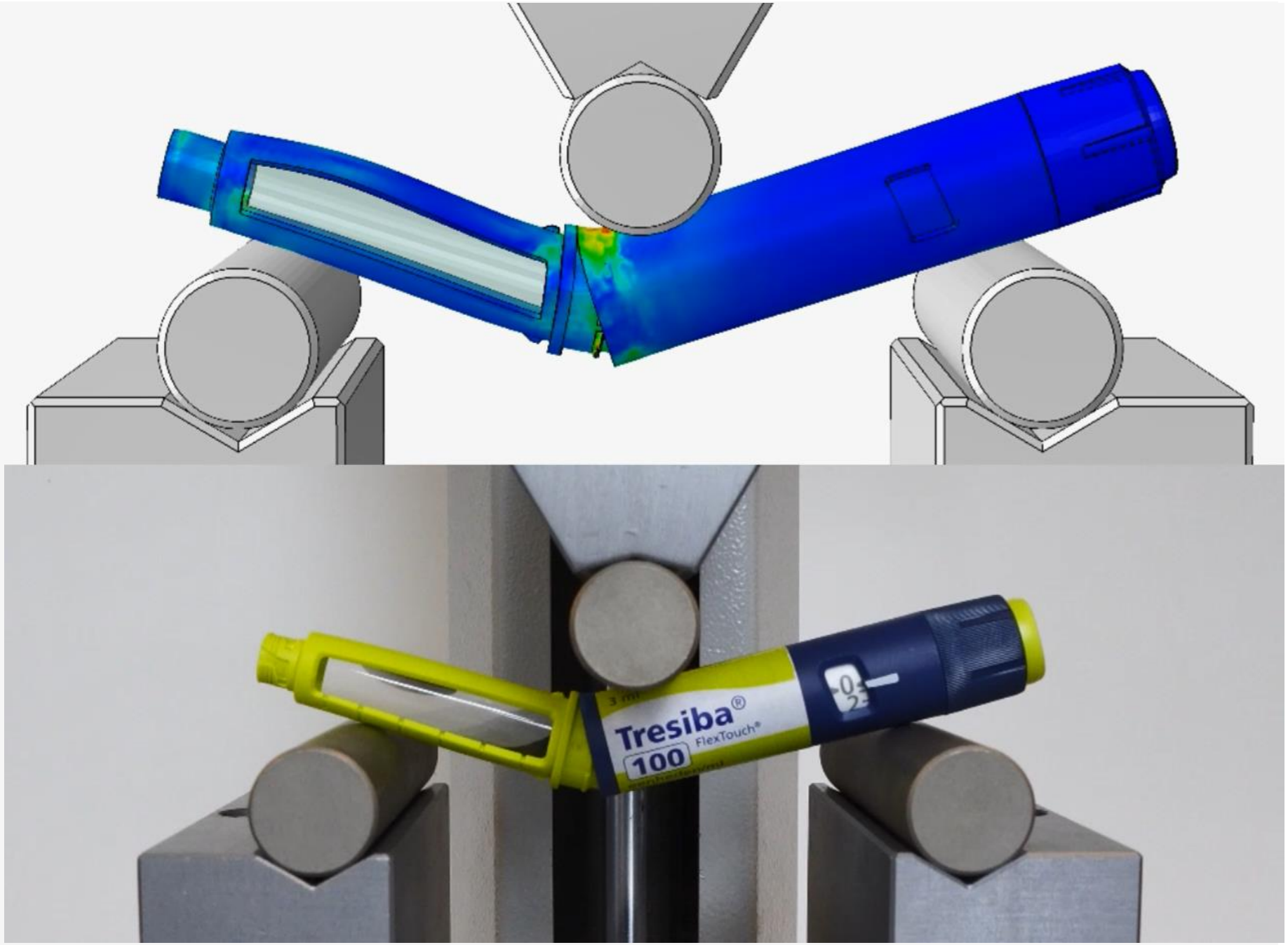




A step change in device development timeframes

EARLY ASSESSMENTS

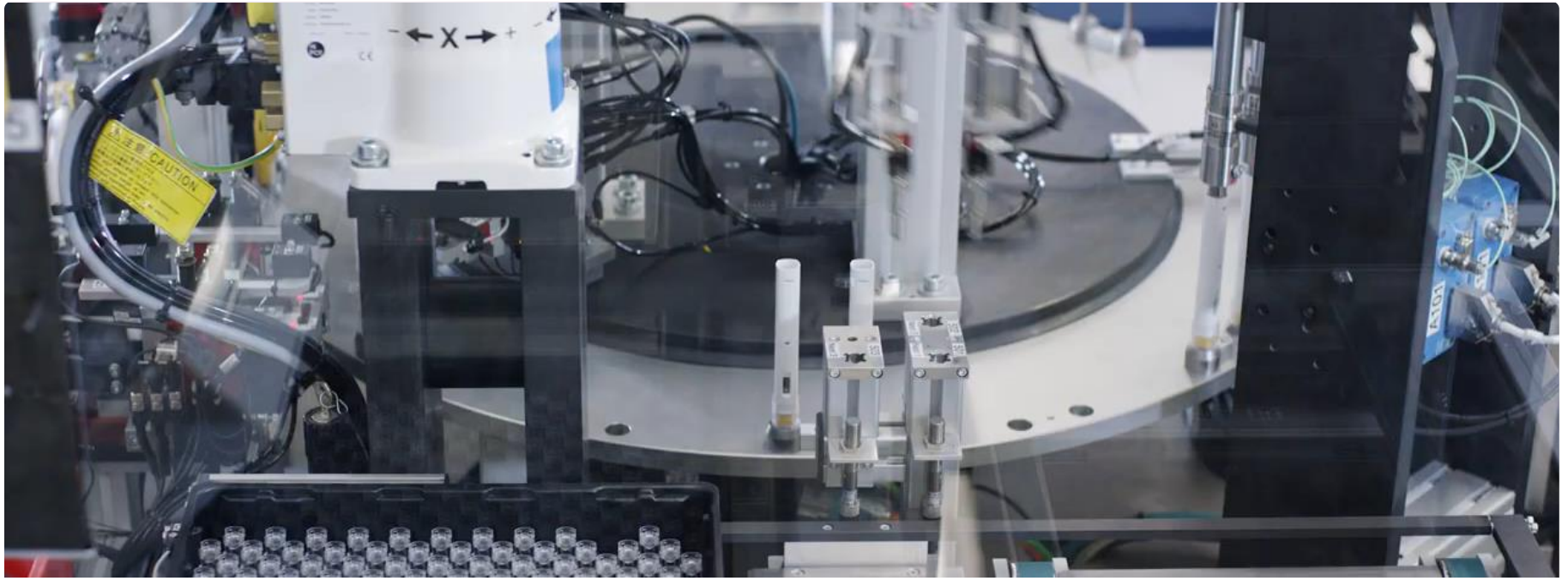
REGULATORY SUBMISSIONS

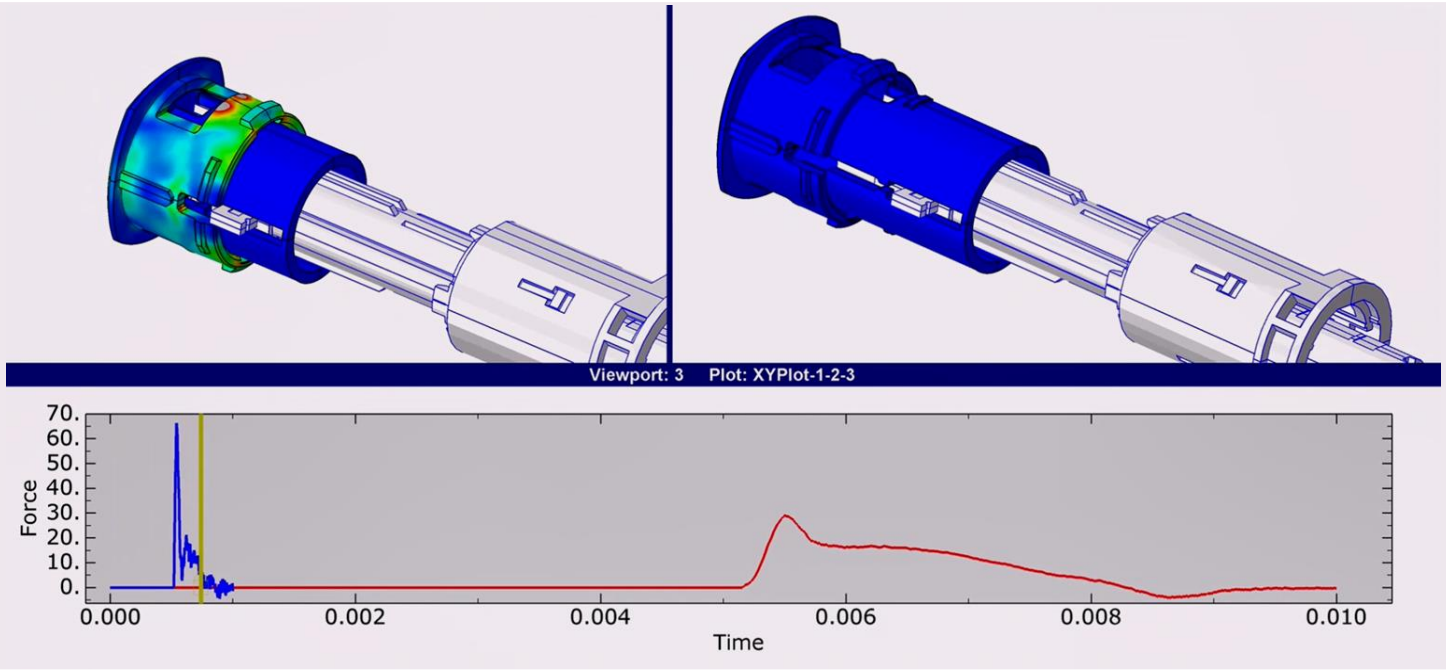


A step change in device development timeframes

EARLY ASSESSMENTS

REGULATORY SUBMISSIONS

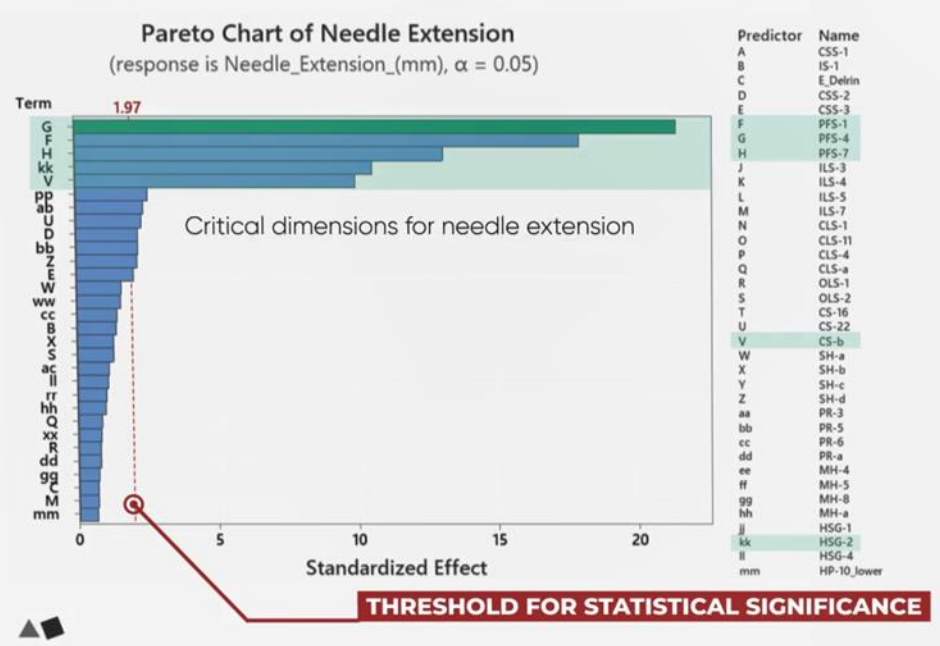


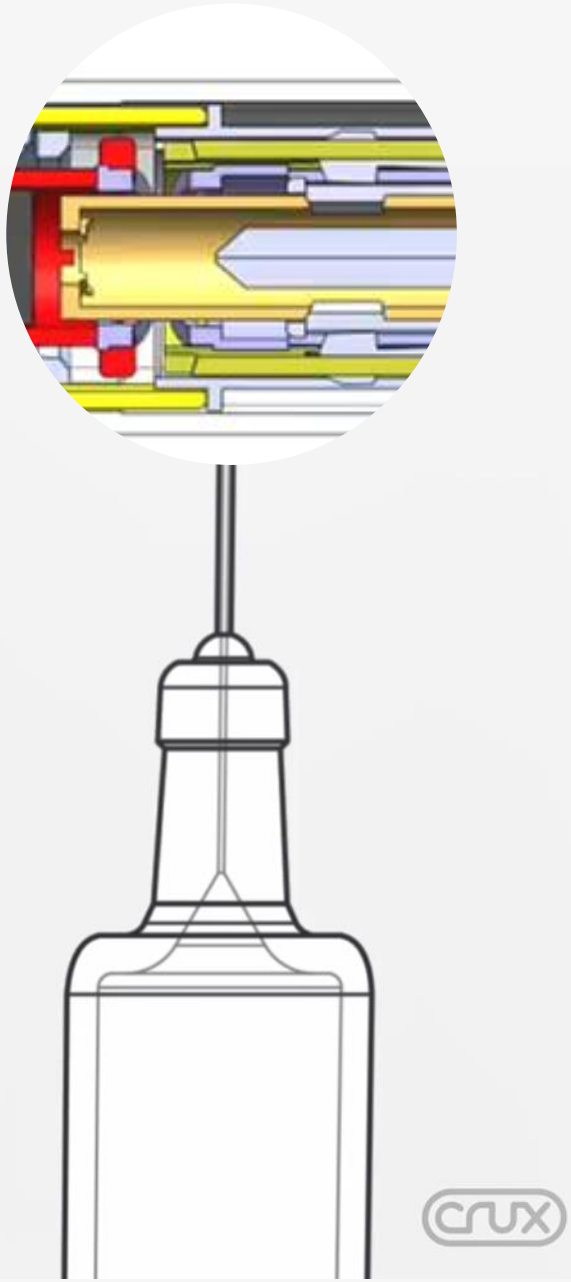


A step change in device development timeframes

EARLY ASSESSMENTS

REGULATORY SUBMISSIONS





A step change in device development timeframes

EARLY ASSESSMENTS

REGULATORY SUBMISSIONS

Can simulation replace EVT/DVT?

Can simulation become widely accepted as regulatory evidence?

A step change in device development timeframes

EARLY ASSESSMENTS

REGULATORY SUBMISSIONS

Reporting Computational Modelling Studies in Medical Device Submissions

CONFIDENTIAL: Controlled Document, Uncontrolled if printed or copied electronically

Goals: Minimal (avoid duplication), Modular (add new studies from template), Modifiable (easy to insert new information)

Document	Section.Subsection	Description	Detail
Total: 36			
Main	1	Executive Report Summary	Concise and complete overview of the study report. All items here are elaborated on within main body of submission
	1.1	Context Of Use (COU)	COU of this CM&S study with respect to regulatory submission, including clear identification of the quantity(s) of interest (QOIs).
	1.2	Model Summary and Scope	Specify which sizes and configurations of device are modelled. Explain hierarchical modelling approach. Explain how evidence may be shared across multiple COUs. Summarise model including geometry, material properties and boundary conditions.
	1.3	Type of analysis	e.g. FEA, CFD, heat transfer etc. State the software versions used. Provide solver details which are common to all analyses e.g. Explicit dynamic, mass scaling, automatic timestep, nonlinear geomety, contact.
	1.4	Conclusions	With respect to COU.
	1.5	Keywords	Up to five keywords or phrases.
	2	Device Background	Tie in device background to COU.
	2.1	Background	Clinical / commercial context for device or other relevant background information
	2.2	Device Description	Introductory description of device system and intended use environment including loading conditions and deformation modes.
	3	Code Verification	Establish correctness of our software code. Reference available documentation from software developer. N.B. Calculation Verification is discussed separately in the "Credibility Studies" section.
	3.1	Software Quality Assurance (SQ	
	3.2	Numerical Code Verification (NC	
	3.3	Assumptions, simplifications and	
	4	System Geometry	
	4.1	Geometry details	
	4.2	Geometry assumptions & simplif	

Contains Nonbinding Recommendations

Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

Guidance for Industry and Food and Drug Administration Staff

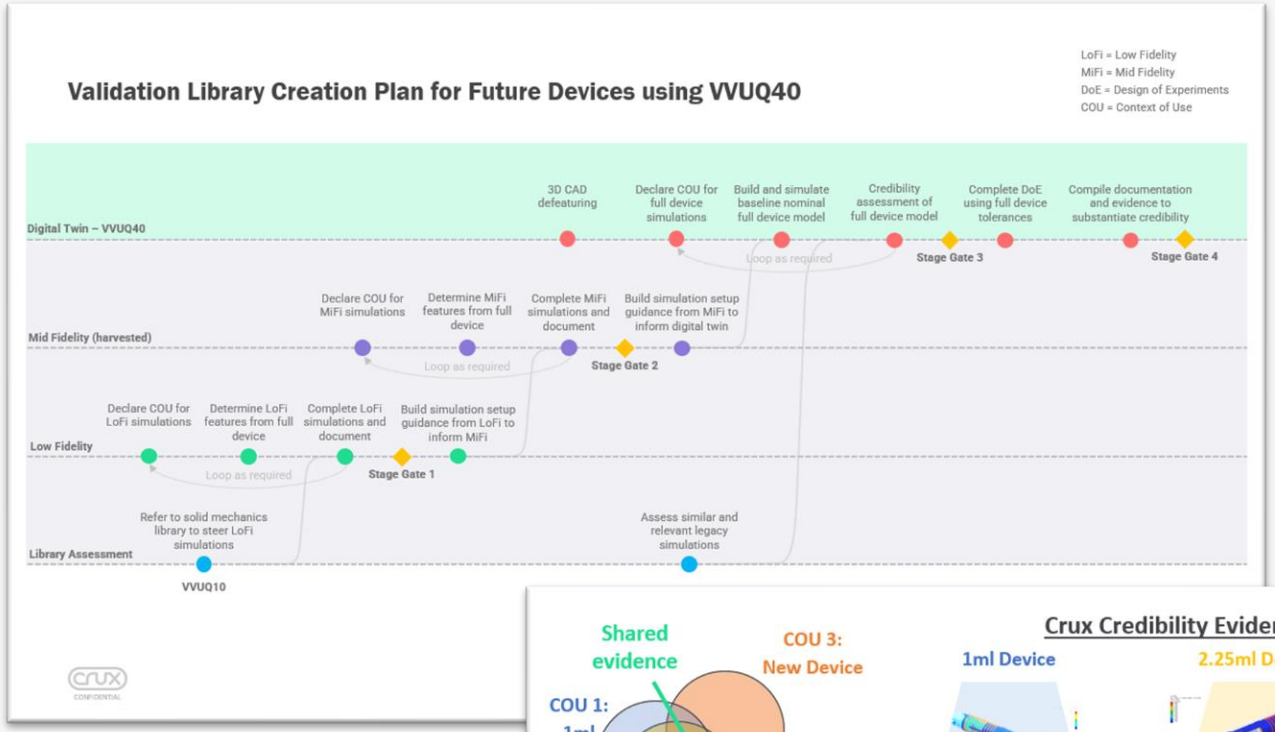
Document issued on January 6, 2021.

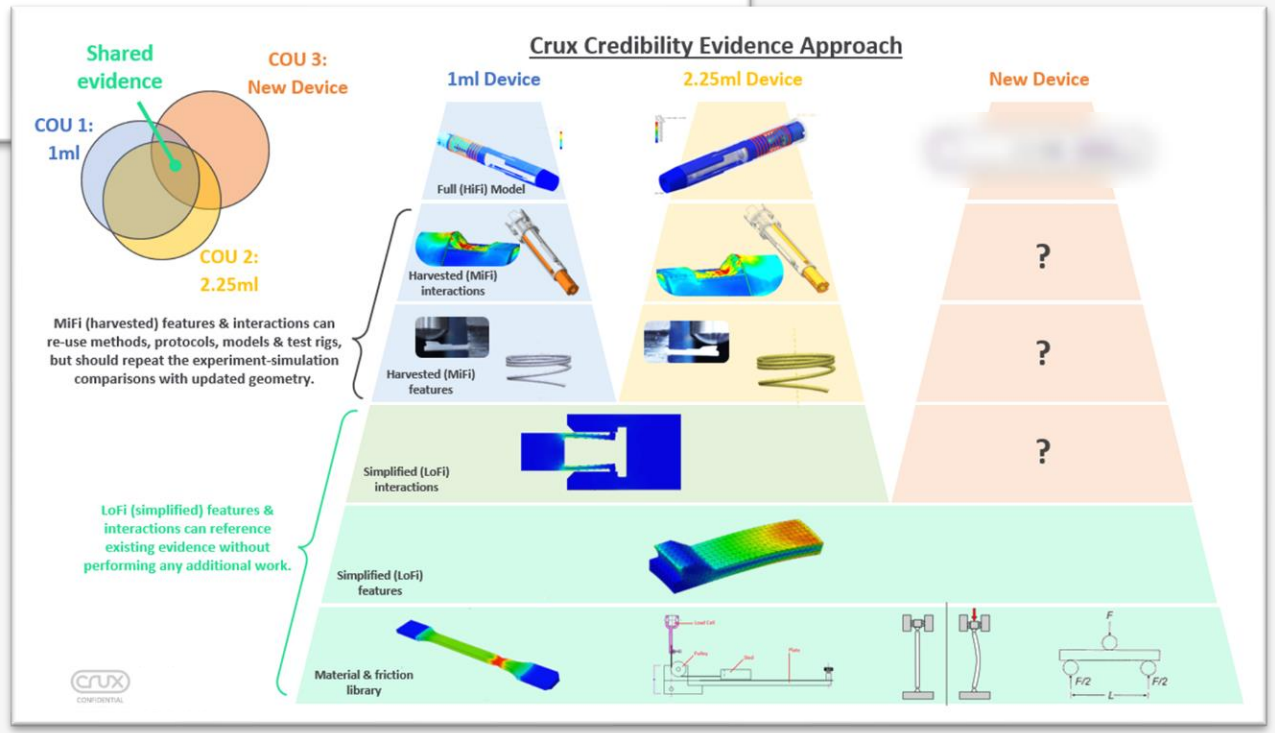
Document originally issued on May 7, 2019.

A step change in device development timeframes

EARLY ASSESSMENTS

REGULATORY SUBMISSIONS

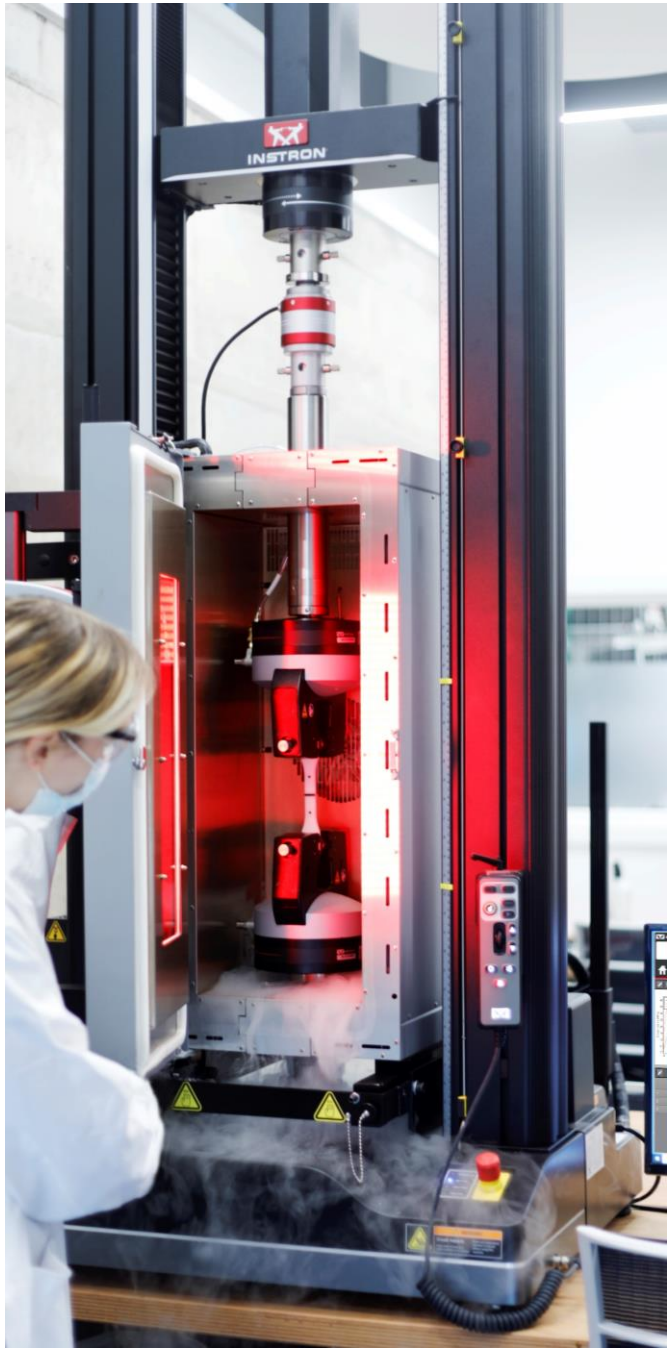




A step change in device development timeframes

EARLY ASSESSMENTS

REGULATORY SUBMISSIONS



Full device digital twin

De-risk early

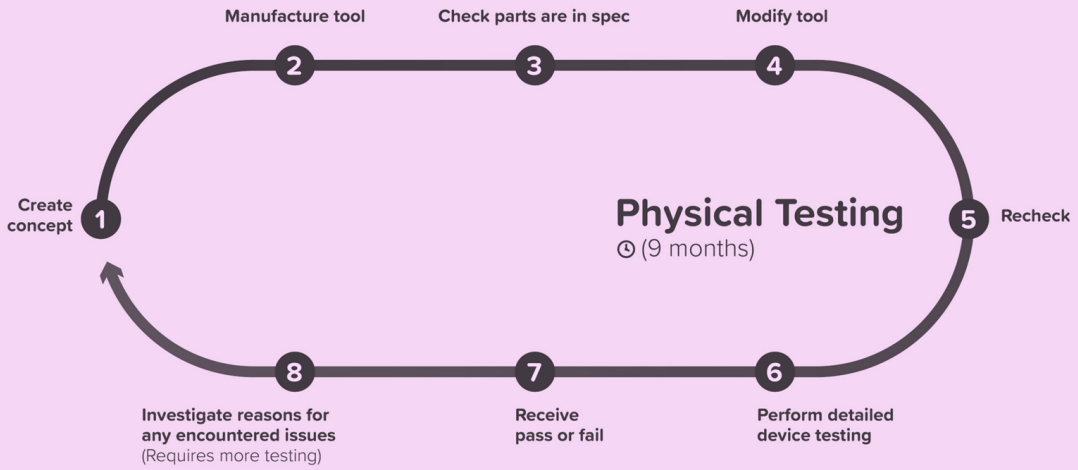
Simulation provides rapid risk assessments at all stages.

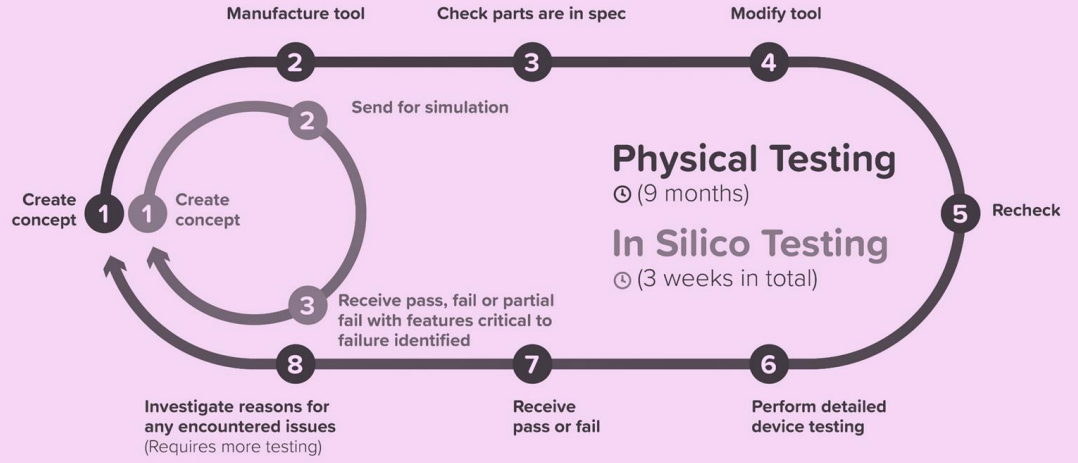
Digital evidence

An understanding of how to generate and submit digital evidence is now within reach.

Reduce time to market

Massive time saving available on iterations aiding a ‘right first time’ approach.





01

02

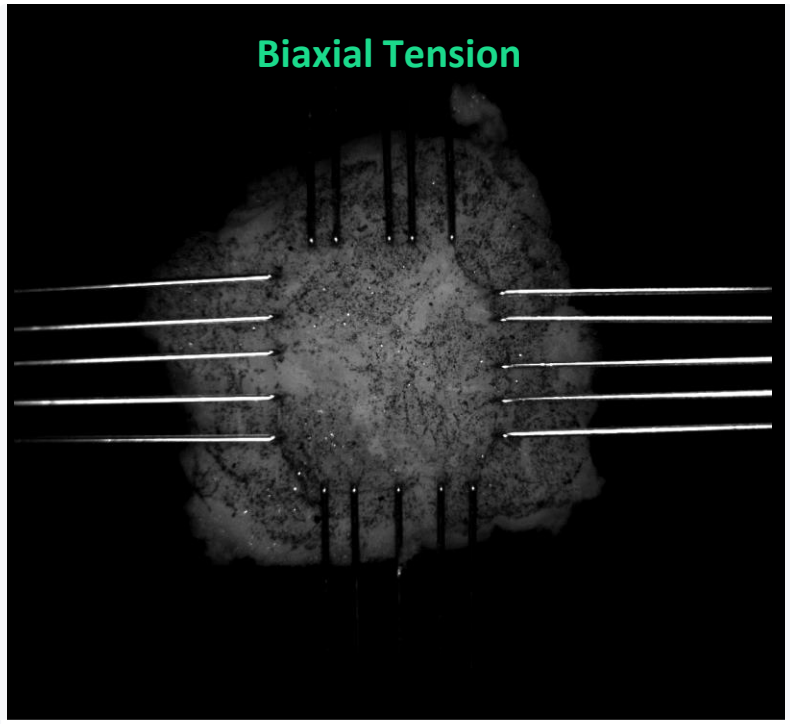
Injection Modelling at Crux

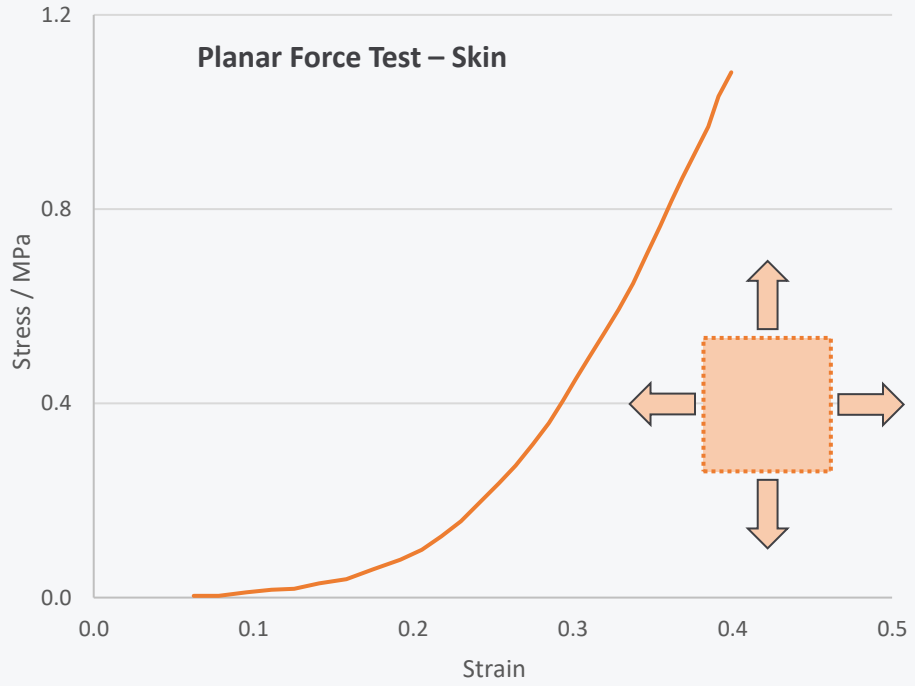
A **leap** towards drug-device-tissue interaction understanding

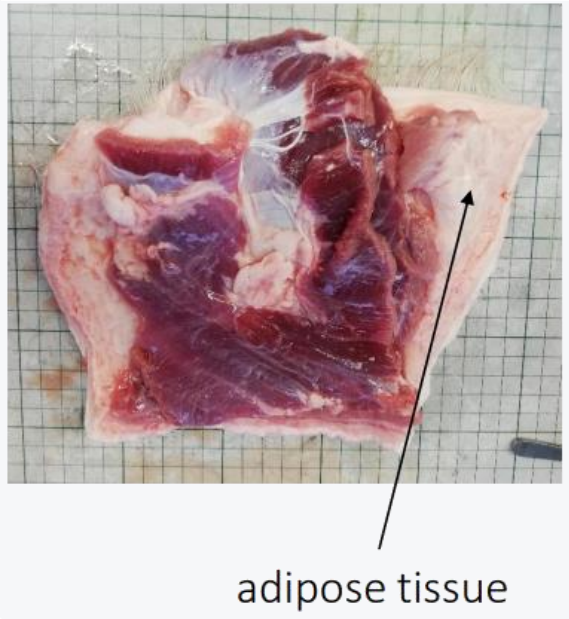
A leap towards drug-device-tissue interaction understanding

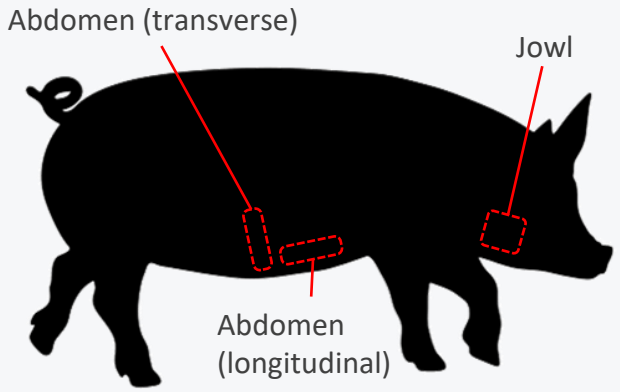
Crux have built a library of biological tissue models using minipig tissue samples, ambition to augment clinical trials in future.

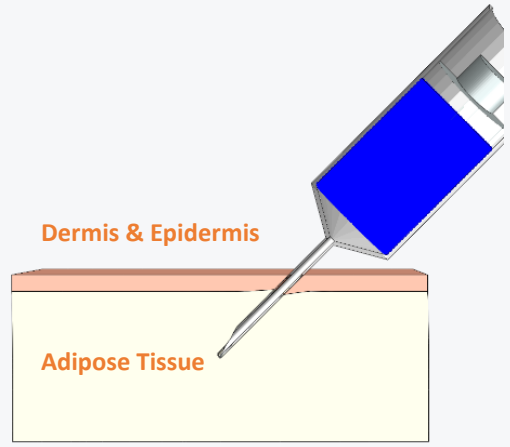
DIGITAL ANIMALS FOR SIMULATION







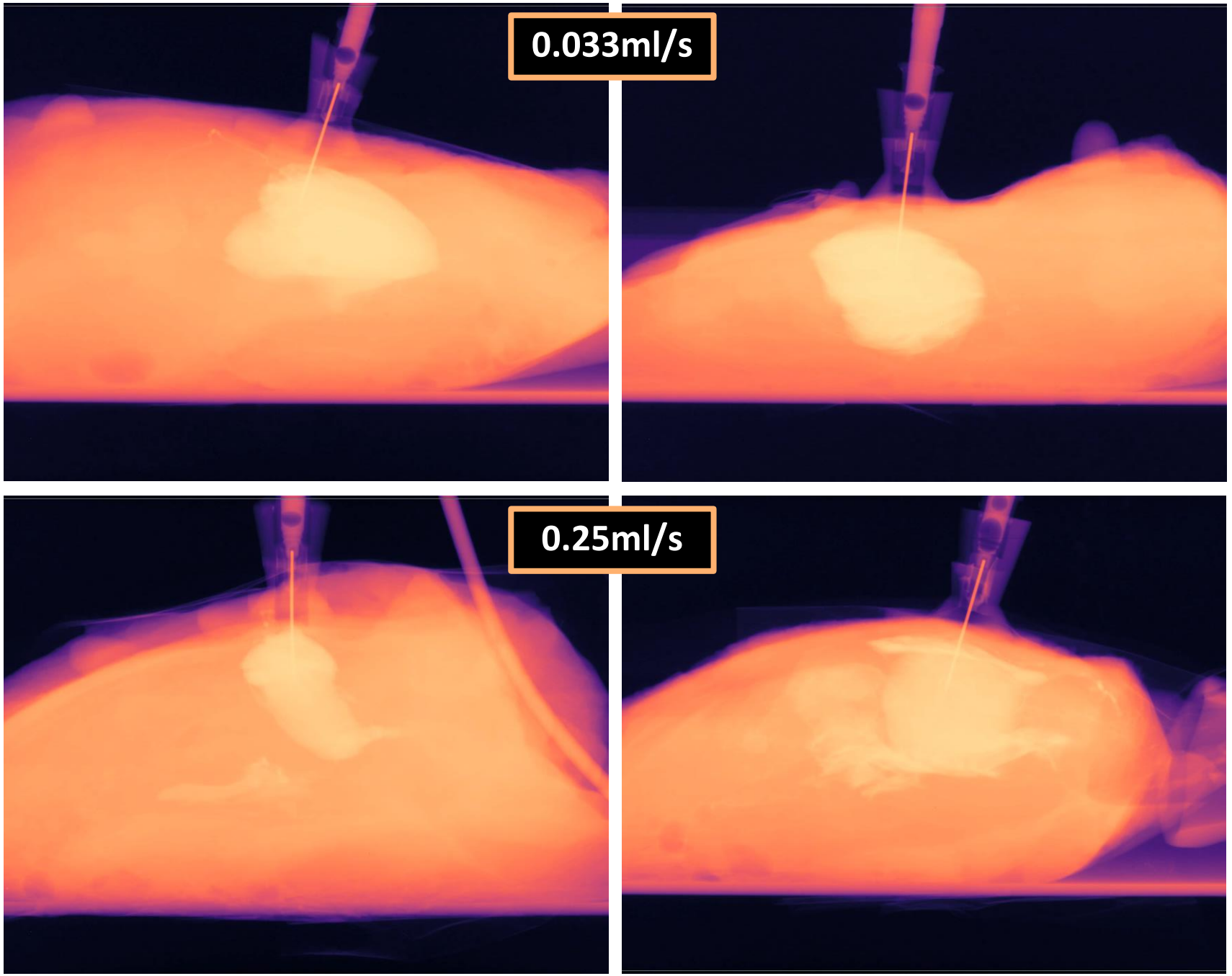




A leap towards drug-device-tissue interaction understanding

Dynamic CT scans of 10ml injections (5mins and 40secs), faster injection rates show more variability – risk of tissue damage, pain and intramuscular delivery may be higher.

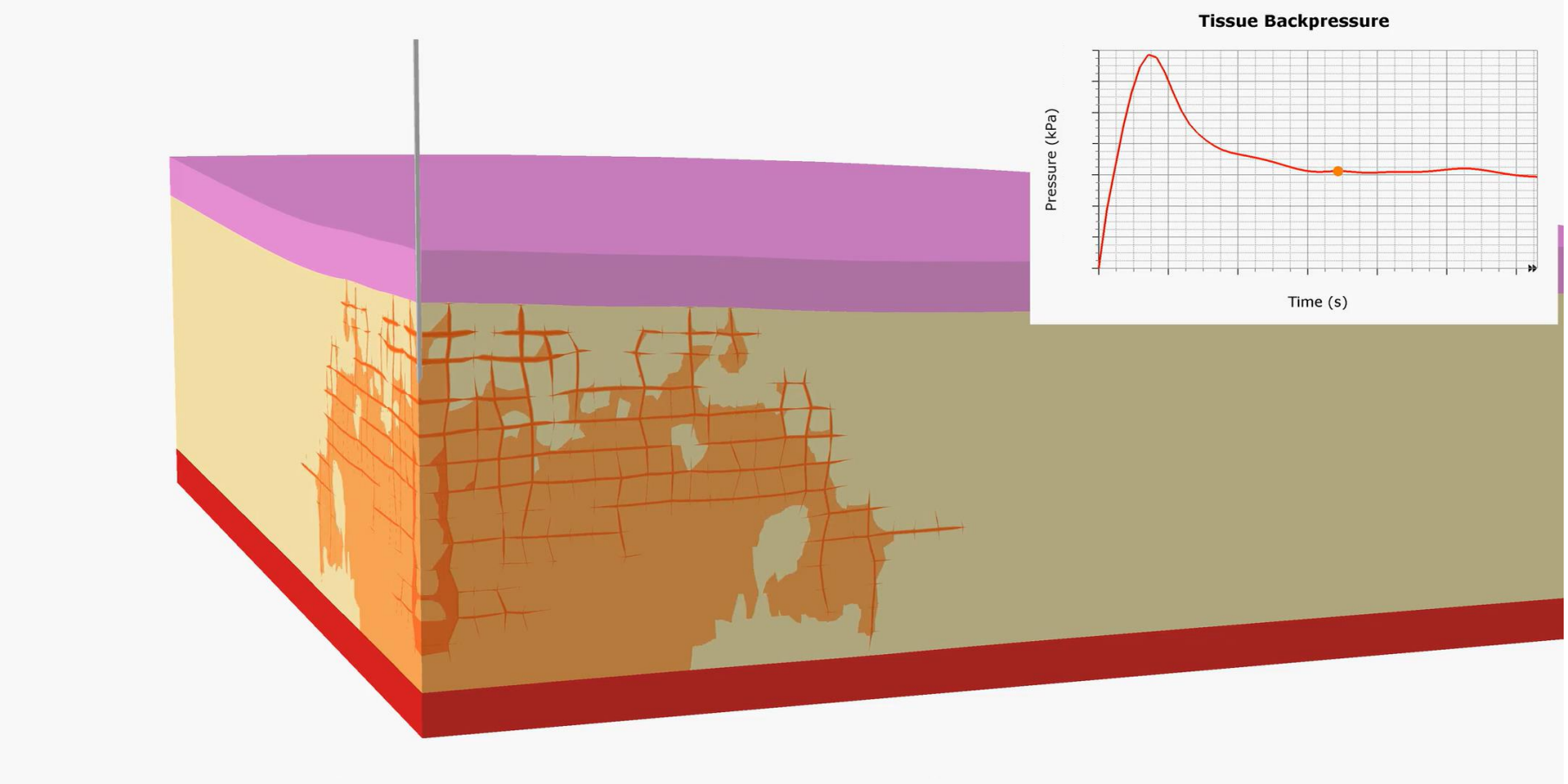
DIGITAL ANIMALS FOR SIMULATION



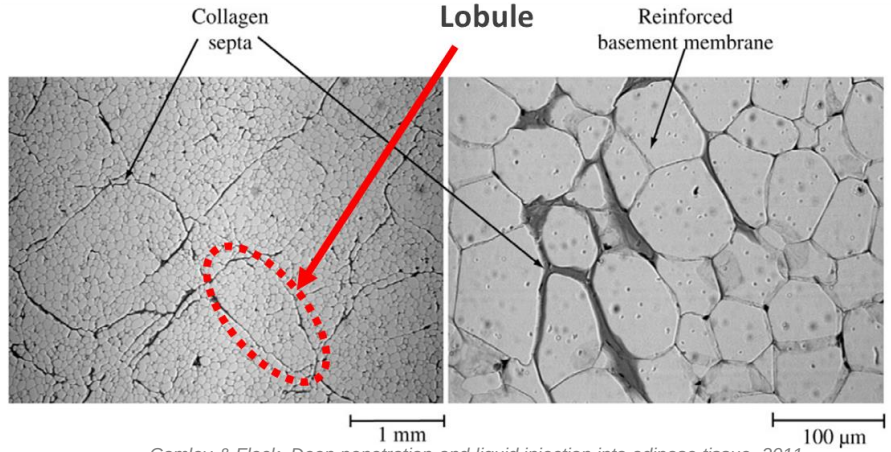
A leap towards drug-device-tissue interaction understanding

Technique translated from fracking simulation technology; uniform tissue stretch applied.

DIGITAL ANIMALS FOR SIMULATION



Maria Thomsen, Subcutaneous injections: Visualising and optimising device-tissue interactions, PhD thesis, 2015

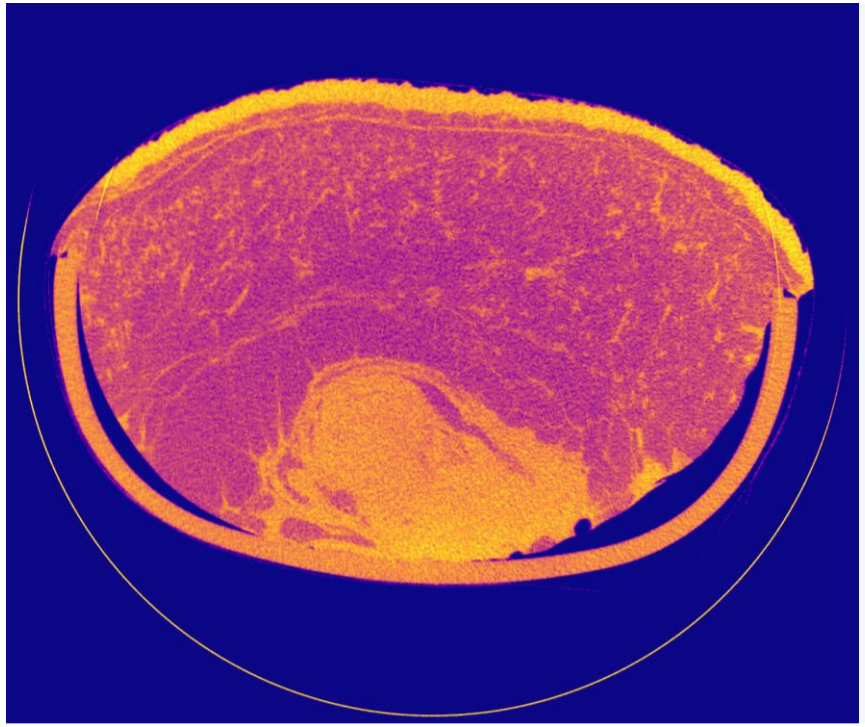


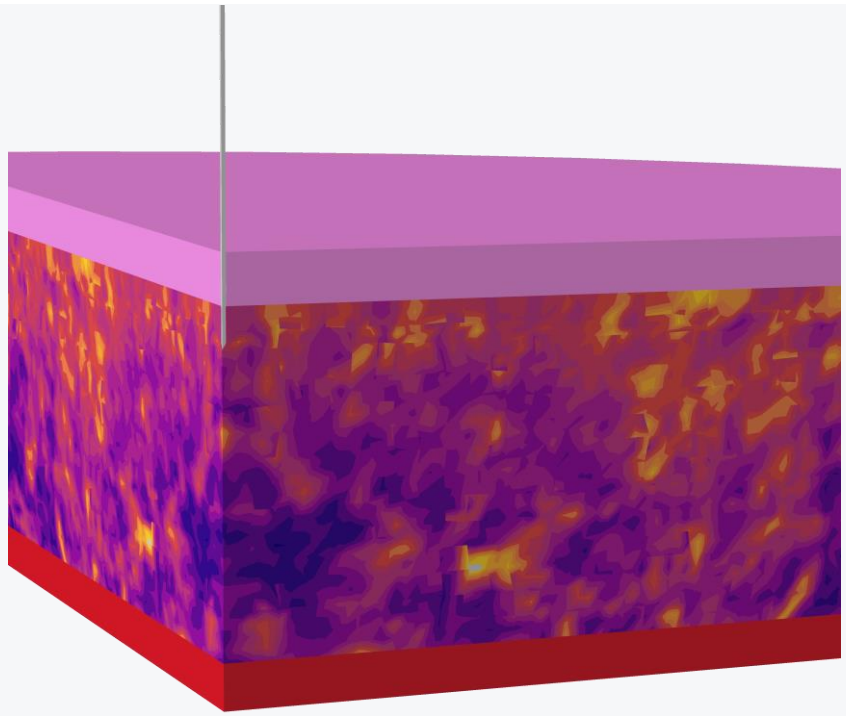
Comley & Fleck, Deep penetration and liquid injection into adipose tissue, 2011

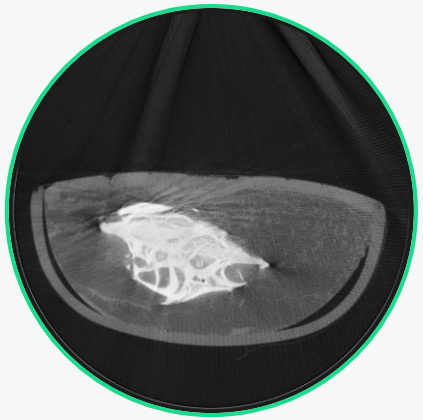
A leap towards drug-device-tissue interaction understanding

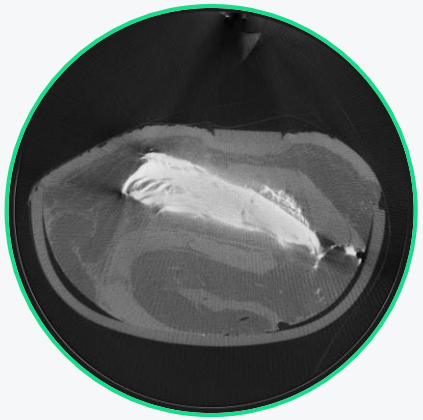
Biological tissue density variability can be extracted from CT scans and has a significant impact on drug dispersion; this can be mapped into the model to simulate variable material properties.

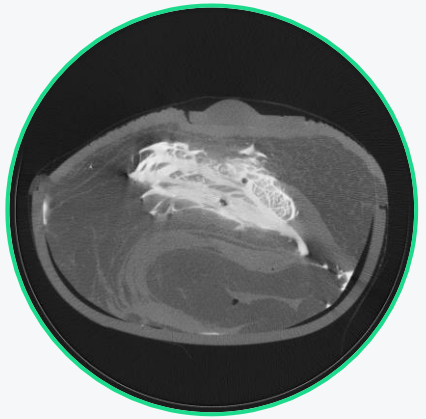
DIGITAL ANIMALS FOR SIMULATION

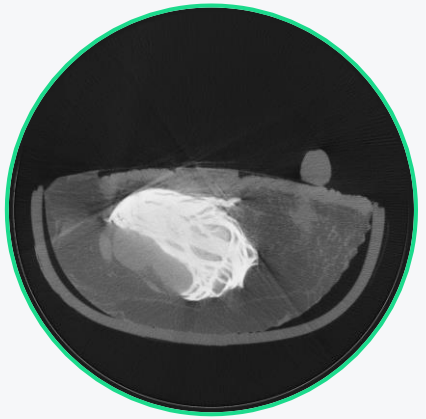








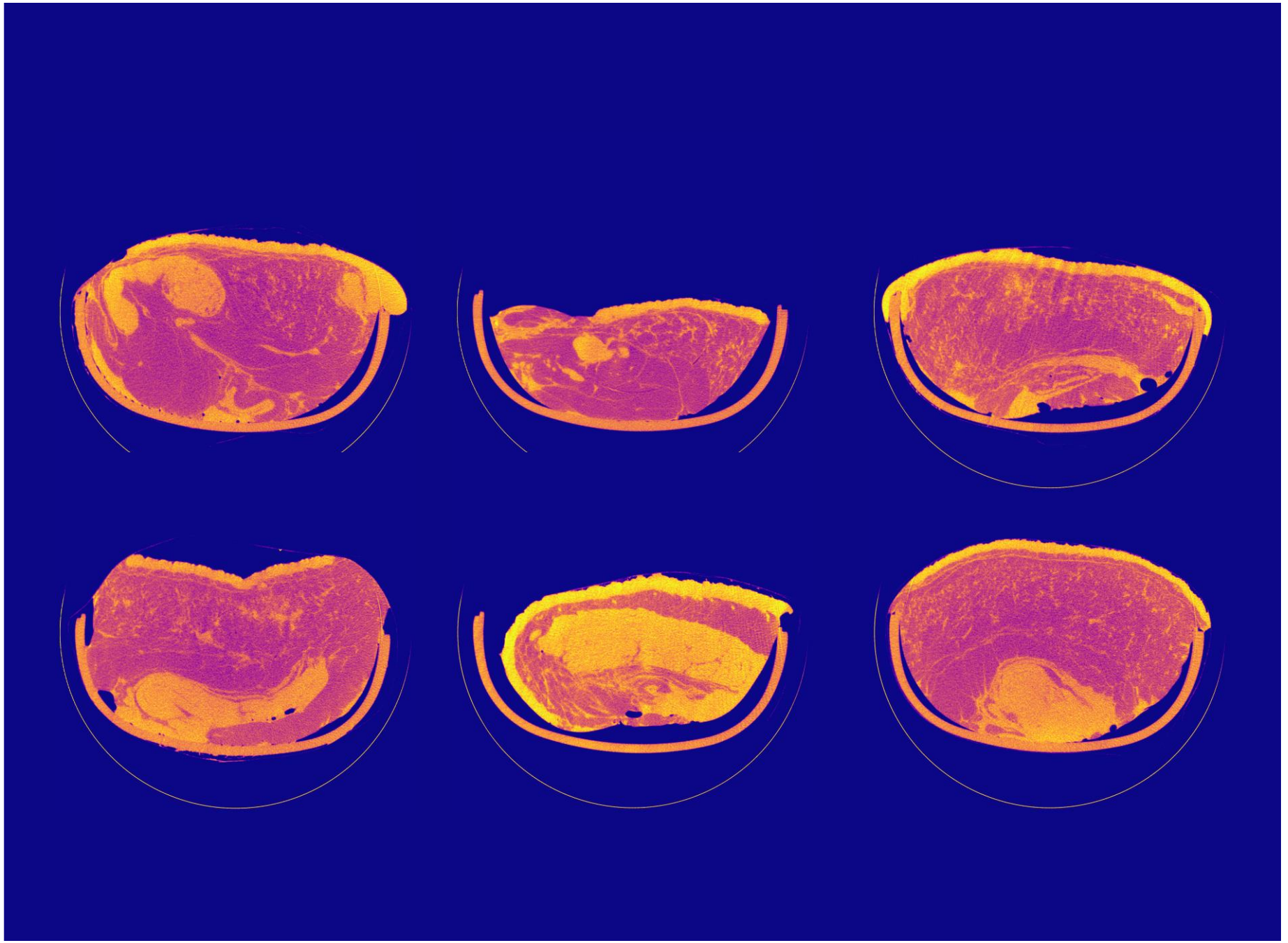




A leap towards drug-device-tissue interaction understanding

Biological variation is prolific across samples even for similar injection sites.

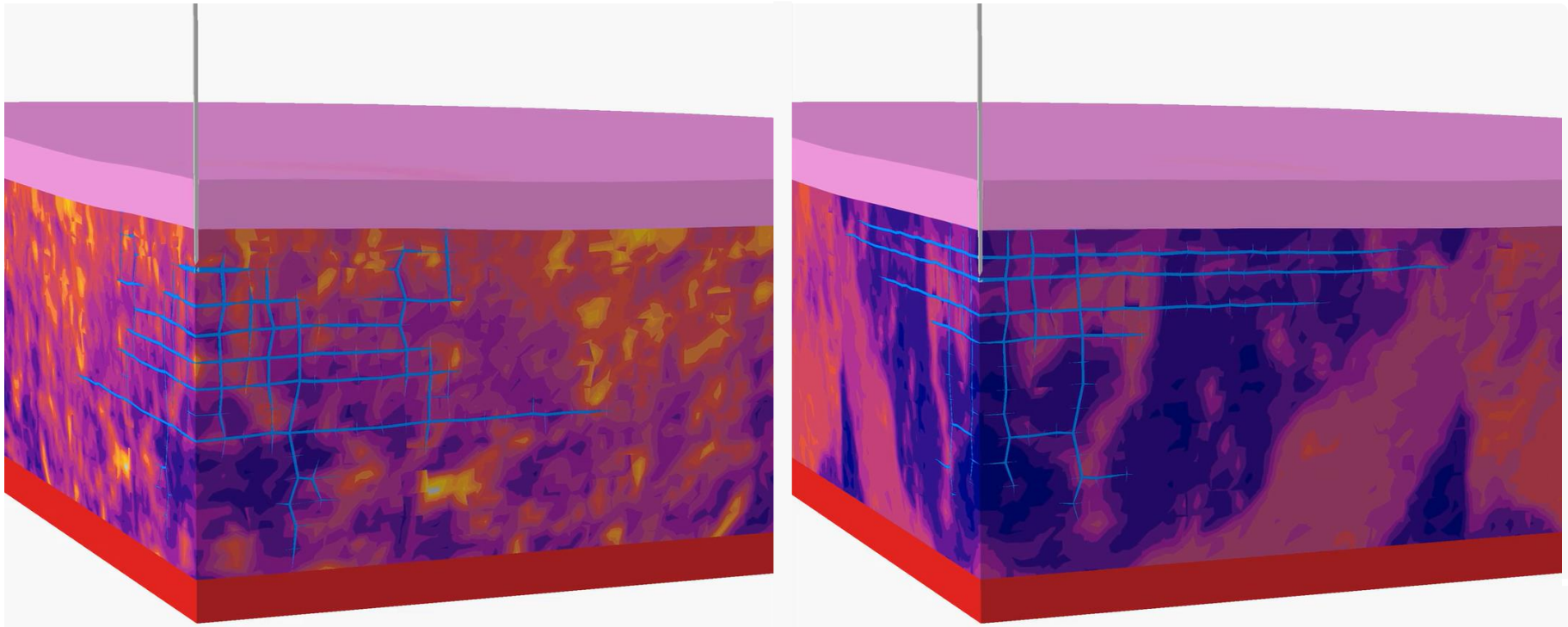
DIGITAL ANIMALS FOR SIMULATION

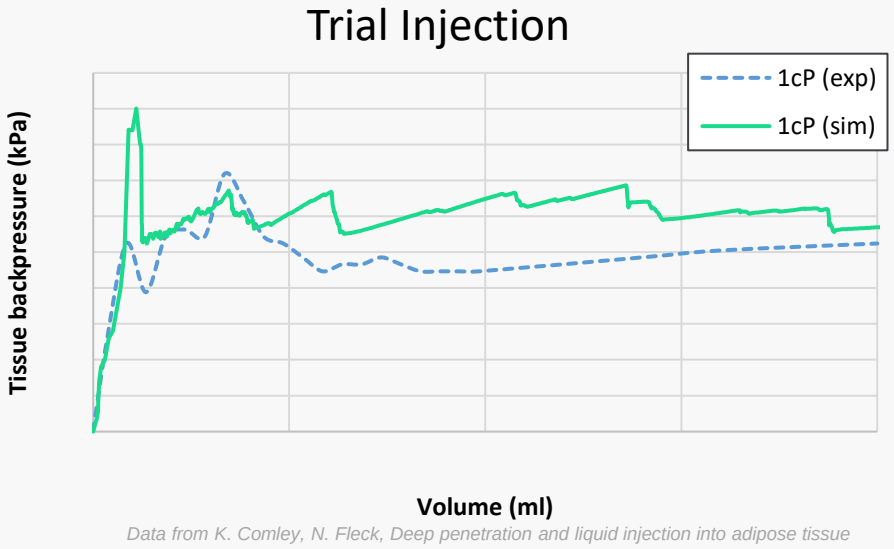


A leap towards drug-device-tissue interaction understanding

Crux virtual minipig injection model already operation as a technical capability.

DIGITAL ANIMALS FOR SIMULATION





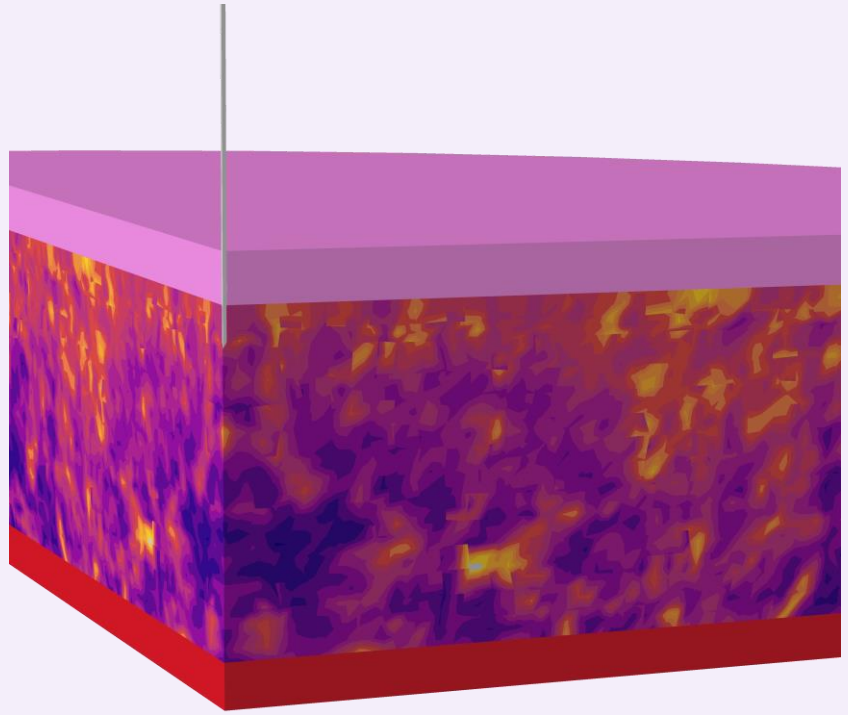
Data from K. Comley, N. Fleck, Deep penetration and liquid injection into adipose tissue

Future digital threads

Sustainable engineering approaches
Re-using experimental and simulation databases for rapid future decision making.

Digitising tissues is here
Mechanical characterisation of animal tissue and inclusion in simulation is now available.

Future injection technologies
Simulation capabilities are now accessible to do early risk assessments on next-gen injection tech.



What can we develop together?

Joel Gresham
Life Sciences Engineering Lead
joel.gresham@cruxproductdesign.com