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Article

Biotech's Mirrored Universe: Predictive Engineering and Digital Twinning

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Biotech's Mirrored Universe: Predictive Engineering and Digital Twinning

The biotechnology industry now can harness advanced engineering techniques that have helped save astronauts, save energy, and save countless millions of dollars.

The biotechnology industry is cautious about innovation: Change does not take place for its own sake, and it does not happen overnight. Indeed, some therapies remain on the market after 20 years because they have established safety and efficacy, and change could conceivably put patients at risk. It is with this wary eye that pharmaceutical companies may view digital twinning and predictive engineering — modern engineering tools considered disruptive techniques and technologies in healthcare. However, Kindeva already is successfully applying these methods to complex drug delivery device development and is among the few companies in this industry to completely integrate these tools into its product development stream. Our approach offers product developers a greater understanding of product performance variables based on fundamental science. It also enables organizations to be more agile in their decision making — versus following a specific, lengthy product development process — saving money, de-risking cutting-edge design innovations, and expediting product market launch timelines. Whether you need to test a design's physical integrity (i.e., drop test) or predict its therapeutic performance, Kindeva has established techniques for every product development step. This article defines and examines digital twinning as well as techniques that support it, like predictive engineering and predictive analytics. We also look at real-world examples of these techniques benefiting pharmaceutical organizations and detail Kindeva's expertise in this arena.

"Twins" Working Toward a Single Goal

Digital twinning has many definitions, but for purposes of this article, consider this relatively new concept in engineering and innovation a digital representation of a physical asset (i.e., the physical twin). A digital twin is not just a picture or a graph of a physical entity; it is a dynamic model of that physical entity, changing over time as the physical entity changes over time.

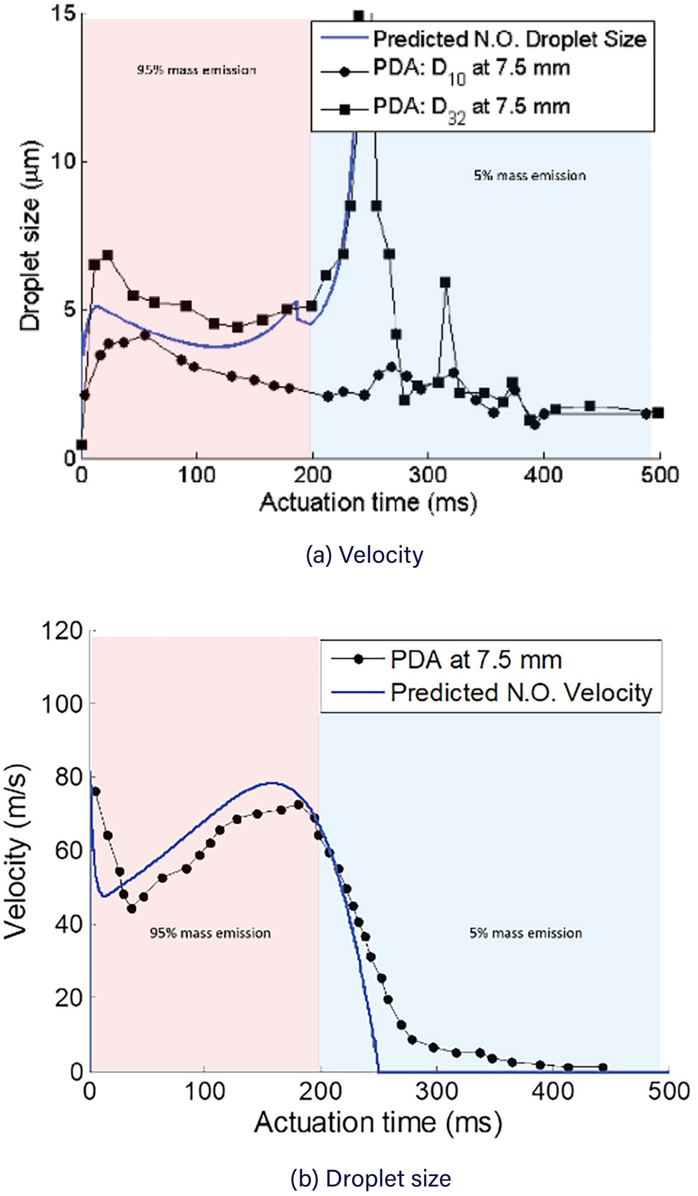
Crafting an Object's Digital Twin Requires Three Elements:

1. Represent in the digital realm, as accurately as possible, each system component. The necessary knowledge can be gained through historical system performance data and real-time system data, applying fundamental physics via predictive engineering techniques to fill gaps in that performance data.
2. Define the interactions between each system component, as well as those components' interactions with the product's likely use environments, as part of this digital realm.
3. Embed continuous improvement and learning. Transfer data from the physical twin (product), during its life cycle, to the digital twin. The digital twin then can analyze the data and apply findings to improve/maximize product performance. Kindeva is working to streamline real-time data transfer between digital and physical twins.

In part, Kindeva has been able to leverage predictive engineering and digital twinning in complex drug delivery device development by examining their efficacy in other industries. For example, in its infancy, NASA adopted pairing technology — the precursor to digital twin technology — to aid in the operation, maintenance, and repair of systems that were not physically nearby. NASA currently applies digital twinning to explore next-generation vehicles and aircraft.[1] Multinational conglomerate General Electric Co. also was an early adopter of digital twinning and currently maintains more than 1.2 million digital twins of its physical assets (up from 660,000 at the end of 2016). Additionally, Chevron is applying digital twinning to predict maintenance problems in its oil fields and refineries; the oil and gas giant intends to connect sensors to most of its high-value equipment by 2024.[2] Returning to delivery device development, this combination of analytics and engineering techniques also builds confidence in designs before clinical trials and patient tolerability studies. Ultimately, each method is founded in fundamental science, making them applicable across all disciplines. Consider, for example, Kindeva’s effort to create its intelligent control inhaler (a pressurized metered-dose inhaler, or pMDI): computational fluid dynamic (CFD) techniques were used to predict key spray characteristics — such as droplet size, droplet velocity, and the interaction between a patient’s airflow and a drug sprayed from the delivery device. The resulting data were used to optimize spray force and spray temperature, which may help ensure patients take their medications in an efficient and comfortable manner (and, by extension, encourage uptake/use of the device). The intelligent control inhaler is in late-stage development and not currently available for commercial sale. First, Kindeva created a digital twin system (virtual model) of the device and defined different optimization criteria for its virtual domain. Kindeva applied predictive engineering, coupled with state-of-the-art mathematical representation of multi-component medical propellants’ material properties, to predict, control, and optimize the device’s issued droplet size, spray velocity, spray force, and spray temperature to acceptable standards.

In optimizing spray temperature, it is well understood that propellants used in pMDI products have subzero boiling points. Large droplets can deposit in the mouth and throat and lead to patient discomfort (“cold Freon effect”). This was particularly problematic for CFC pMDIs, but can still be an issue with some HFA pMDI configurations.[3] Additionally, HFA134a and HFA227ea are considered gases with high Global Warming Potential (GWP), leading Kindeva to consider other propellants, such as HFA152a, to improve product sustainability, as well as alternative device designs based on predictive models’ outcomes, to improve patient comfort. Optimizing the device’s spray force involved a similar approach in which Kindeva experts evaluated the physics governing the device’s spray to determine whether it’s comfortable. Designers used their findings

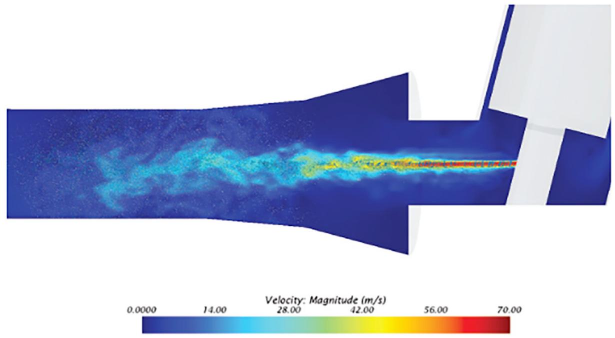
FIGURE 1. Time-dependent predicted near-orifice (N.O.) pMDI spray characteristics validated by phase Doppler anemometry (PDA) measurements.



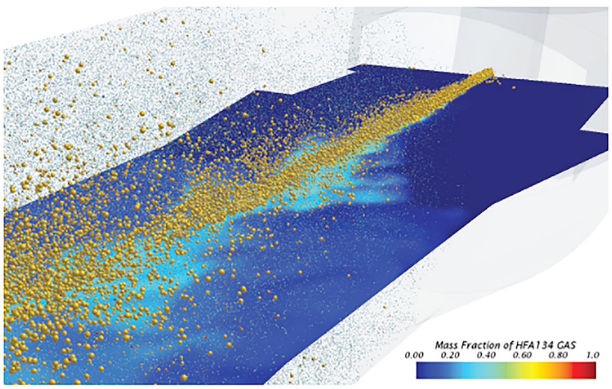
(a) Velocity

(b) Droplet size

FIGURE 2. Evolution of pMDI spray inside a USP-induction port rendered on various section planes, color-coded by spray characteristics, using high-fidelity CFD models.



(a) Velocity magnitude



(b) Mass fraction of HFA134a and dispersed droplets

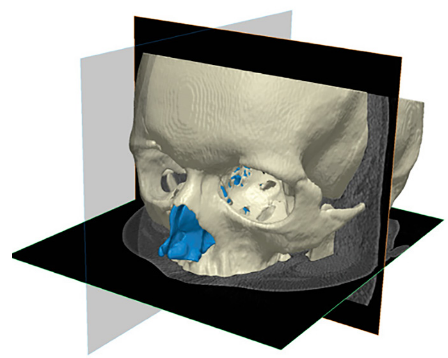
to come up with a "safe zone," just as they did for spray temperature. Only after researchers were comfortable with the simulated outcome — here, favorable interaction between the device, spray characteristics, and patient inhalation — did development move to prototyping and manufacturing. Another example of Kindeva's leadership in the application of predictive engineering and digital twinning is a nose-to-brain drug-delivery platform. Novel modeling techniques had to be developed to represent a patient's nasal cavity geometry based on CT scans.

Specifically, Kindeva developed an artificial intelligence algorithm that could detect and quantify nasal cavity region variability between different patients using the CT scan data. That variability was averaged to model an "average" human nasal cavity. Based on this model, the drug delivery device was designed to maximize driveline delivery of the drug to the higher regions of the nasal cavity, where it will be absorbed by the olfactory nerves.

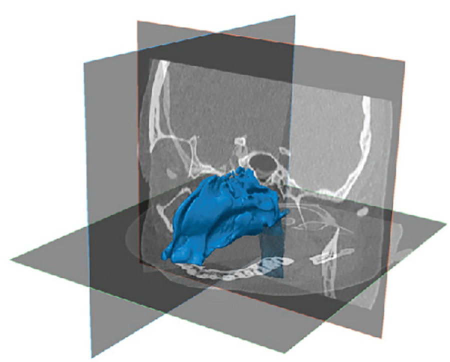
How Kindeva Can Help Your Organization

As stated earlier, Kindeva has shaped and validated these models, from scratch, to perform optimally in pharmaceutical product development applications. We apply novel processes to each stage of product development — specific frameworks using predictive engineering, predictive analytics, and digital twinning. This templatization allows us to effectively automate many of our processes: each time we apply the same input or similar inputs into a framework, we can generate consistent, reliable results, culminating in optimized product design capable of meeting the highest standard. Projects often are a combination: techniques applied in a way we have done before, plus techniques reshaped to fit new challenges. By not committing to a more specific, lengthy product development process, Kindeva can be very agile in our approach, collaborating with customers to experiment with new ideas or alter design course in a de-risked environment, effectively.

FIGURE 3. Construction of patient-specific nasal cavity geometry from CT-scans and analysis of anthropomorphic landmarks' variability, via Kindeva's bespoke image analysis routine, leading to the development of an averaged human nasal cavity.

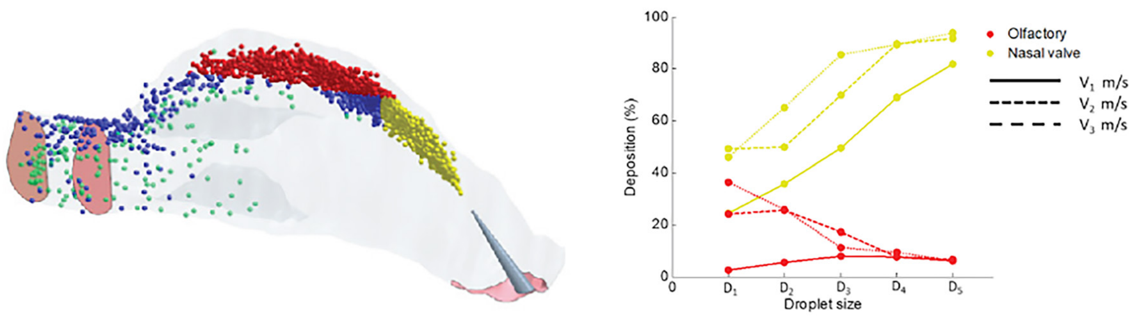


(a) Skull and nasal cavity



(b) Nasal cavity

FIGURE 4. CFD-based prediction of the effect of spray velocity and droplet size to maximize drug delivery to the olfactory region.[4]



Conclusions

Digital twinning and predictive engineering have historically been considered disruptive techniques and technologies in healthcare but have been applied effectively in other industries. Predictive engineering techniques are based on well-understood, if complex, data analytics algorithms, and sophisticated mathematical routines. However, the pharmaceutical industry will benefit, as will patients, from a more serious-minded approach to these techniques and their applications. Even in times of "normalcy" (versus the current pandemic climate), individuals or groups involved in a product's development may be spread out across a state or the globe. In such scenarios, it is difficult to overstate the value of being able to complete critical design tasks digitally. You can still crank the handle of innovation by virtually representing different segments of your product development stream. Is your product development encountering challenges that could be overcome with predictive engineering and digital twinning techniques? Reach out to Kindeva at contactus@kindevadd.com to find answers. We look forward to hearing from you!

1. Marr, B. "7 Amazing Examples of Digital Twin Technology In Practice." Forbes, Forbes Magazine, 23 Apr. 2019, *www.forbes.com/sites/bernardmarr/2019/04/23/7-amazing-examples-of-digital-twin-technology-in-practice/*.
2. Eshkenazi, A. "Real Benefits from Digital Twins." APICS Blog, Association for Supply Chain Management, 21 Sept. 2018.
3. Gabrio, B.J., Stein, S.W., & Velasquez, D.J. "A new method to evaluate plume characteristics of hydrofluoroalkane and chlorofluorocarbon metered dose inhalers." Int J Pharm. 1999 186:1, 3-12. doi:10.1016/s0378-5173(99)00133-7.
4. The nasal cavity geometry is adopted from — Liu, Y., Johnson, M.R., Matida, E.A., Kherani, S., Marsan, J. "Creation of a standardized geometry of the human nasal cavity." Journal of Applied Physiology 2009 106:3, 784-795. *https://doi.org/10.1152/japplphysiol.90376.2008*