White paper

In silico clinical trials



nova DISCOVERY

Introduction

Modeling and simulation of clinical trials has become a key strategic area of development over the past two years, especially since the US FDA received a congressional mandate in 2018 to promote the use of *in silico* approaches in clinical trials to improve R&D outcomes. *In silico* clinical trials simulate the same conditions as *in vivo* (same endpoints, clinical outcomes on a virtual population). *In silico* trials meet the needs of the industry, which is looking for more efficient, less expensive drug development approaches as well as de-risking trials for patients.

The COVID-19 crisis is accelerating the adoption of new technologies and the pandemic is likely to change the face of human clinical trials: the time is right for biotechs and pharma companies to adopt clinical trials simulation. Running *in silico* clinical trials with virtual patients is an opportunity for the industry to drive its R&D programs forward, unleash the power of better decision-making and help bring to market life-changing therapies for patients.

How do *in silico* clinical trials work?

In silico is emerging as the 3rd pillar of the drug R&D paradigm, in support of - not a full substitute to - more conventional *in vitro* and *in vivo* exploration and evidence-generation techniques.

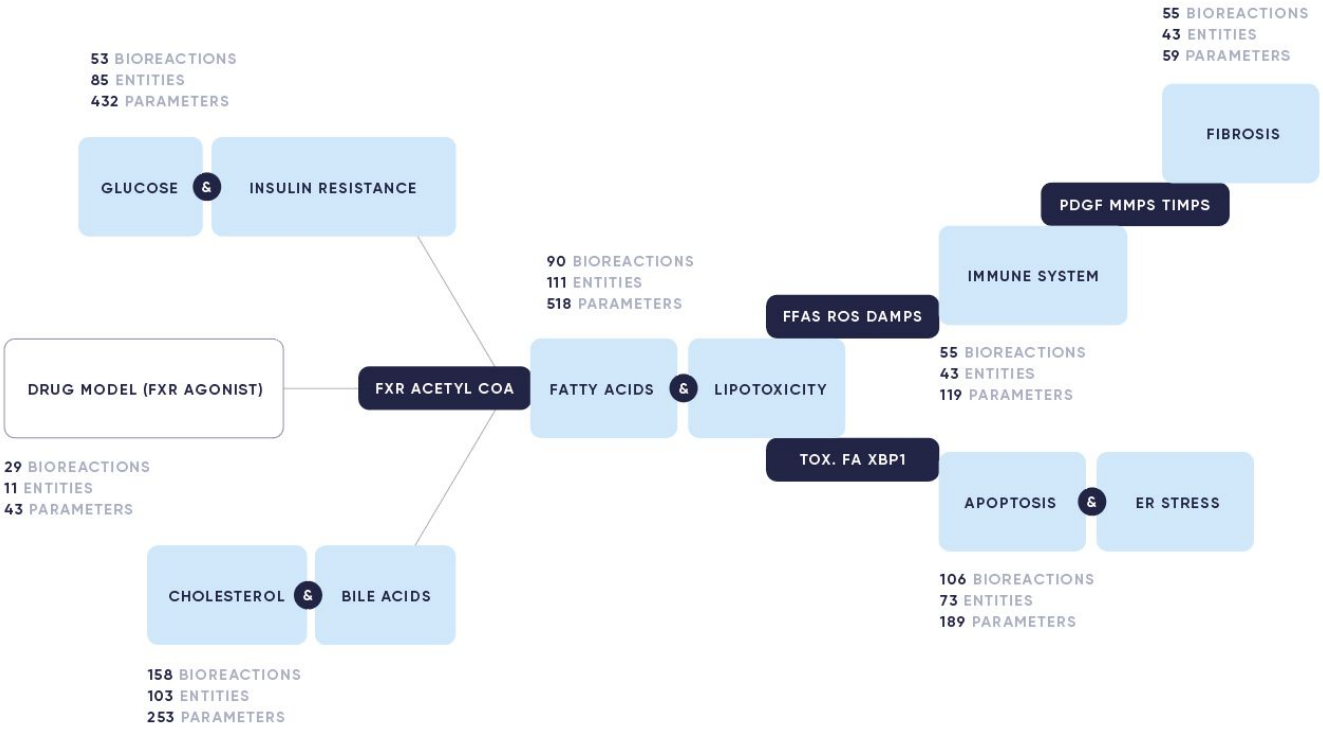
> Biotech & pharma companies are leveraging *in silico* modeling to **accelerate time to treatment** and **reduce costs** of drug development, **de-risk trials** for patients, help **better understand biology** and **increase chances of success** .

NOVA's modeling expertise combines mathematical models of diseases and treatments with virtual patients into an integrated clinical trial simulation platform called **Jinkō®**.

Disease and treatment computational models are built based on knowledge extracted from literature and data. To simulate a trial, these models are run on virtual patients to predict the clinical efficacy of new drugs at population level before trials on human subjects take place.

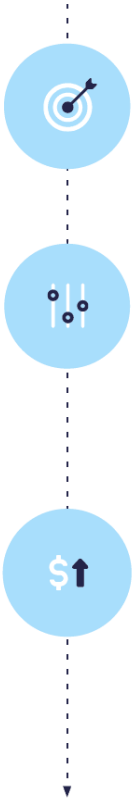
The disease model itself is a combination of various interrelated pathophysiological sub-models. They are constructed by mapping all the biological phenomenon known to be involved in the corresponding processes and characterizing the functional relationships (mostly biochemical reactions) linking these phenomenon. In practice, first the normal biology is modeled, then the perturbations leading to the disease state are introduced, and finally the treatment model is plugged in the disease model to simulate the action of the drug candidate on the system.

Example : NASH Computational Model



Applications

A computer modeling & simulation approach yields applications spanning the entire R&D spectrum, from the systematic exploration of target combinations to the demonstration of value in terms of public health to payers.



- Discovery (streamline target identification & secure proof of concept)
  - Explore efficacy between various targets
  - Explore efficacy of various combinations of targets/treatments
  - Explore transability from animal models to humans
- Clinical development
  - Explore various regimens (dose, number of administration(s) per day, time between administrations, duration of treatment)
  - Identify subgroups of optimal responders/theranostics biomarkers
  - Optimize trial design
  - Reduce sample size and follow-up duration
- Market access
  - Demonstrate value to payers by predicting the real life drug related benefit and the optimal target population
  - Transpose Phase 3 trial results into a virtual population representative of specific geographies and context
  - Benchmark competing treatments

Firstly, the use of *in silico* clinical trials is a discovery solution to broadly explore potential drug combinations and identify those worthy of being progressed into clinical development.

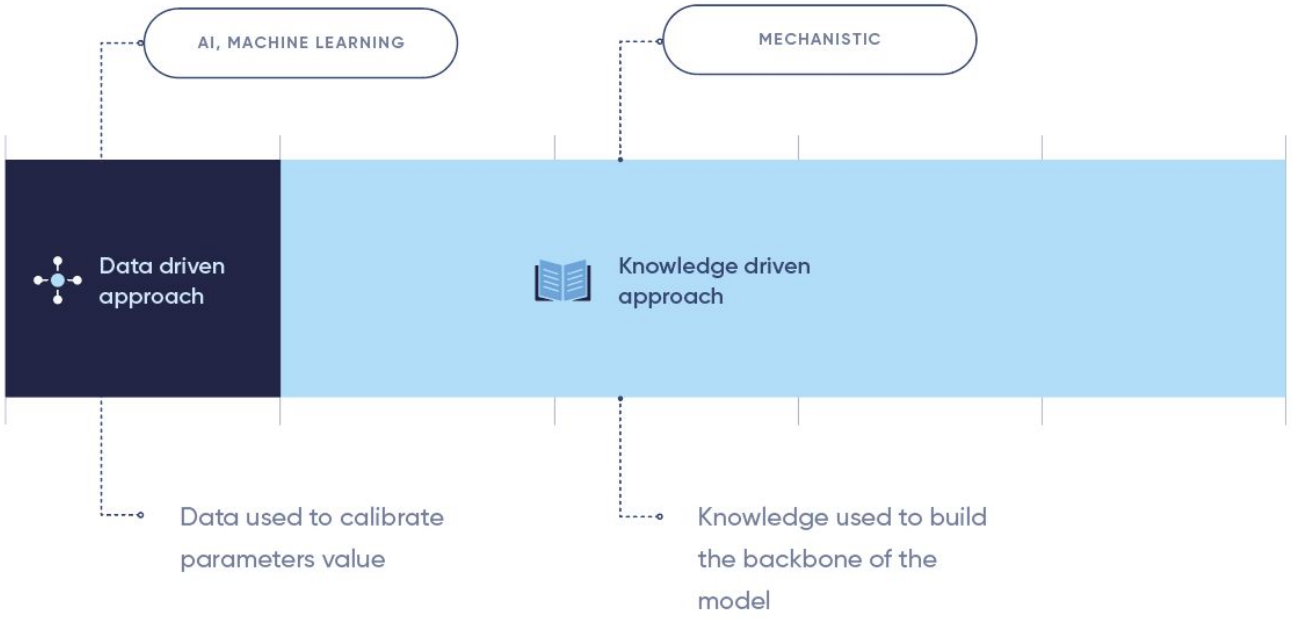
Secondly, *in silico* clinical trials are intended to be conducted prior to each *in vivo* clinical trial in order to optimize the design of "real-life" clinical trials. For example, right after a Phase 1 clinical trial, you can run a Phase 2 *in silico* to test all the hypotheses you have in mind for the design of your Phase 2 clinical trial. You will be able to test different doses, find the best treatment combinations and find the best responders for patient stratification.

There is a constant back and forth between *in vitro/in vivo* experiments and *in silico* simulations (the "learn & confirm" paradigm). Any new questions that may arise as your program progresses within your pipeline is first addressed through simulation to identify the best possible option and then confirmed by *in vitro* or *in vivo* experiments.

> Exploring hypotheses with *in silico* simulations is much faster and less costly than traditional in vitro or in vivo experiments. The added benefit is that a much larger number of hypotheses can be tested at no additional cost (e.g. testing 10 different doses on 2,000 patients costs about the same as testing 20 doses on 10,000 patients).

How do we build models?

At NOVA we build models by combining the use of knowledge and data.



On the one hand, a piece of "Knowledge" or "assertion" refers to a relationship between biological entities which is extracted from a scientific article. For example, "protein A phosphorylates protein B" is an assertion. This knowledge is used to build the scaffolding of our disease models. Biomodelers (experts in modeling of biology) analyze and curate hundreds of articles to build a "Knowledge Model" in which they list all the biological entities and their relationships within a targeted biological system of interest.

On the other hand, the term "data" refers to all client-generated clinical and non-clinical data that will be used to calibrate and validate the model, not to train an AI algorithm.

Simulation results

Complexity, the signature of life, can be defined as a mixture of redundancy and feedback. The mechanisms of disease present and exhibit complexity at each layer (molecular, cellular, organ-level) and in all interactions between these layers, making it impossible to construct "perfect" mathematical and computational models such as those found in the physical sciences.

That being said, some uncertainty in predictions is acceptable to regulatory agencies, provided the model has been properly validated. Validation is carried out by reproducing available *in vitro* or *in vivo* experiments whose corresponding data were not used in the model design.

In silico & regulatory agencies

In 2018, the US Congress voted a full paragraph on *in silico* clinical trials, giving a mandate to the US FDA to promote and expand the use of *in silico* approaches in clinical trials. Since then, the FDA has been committed to the adoption of *in silico* trials to improve R&D outcomes. Among the FDA's top 8 strategic priorities, 4 are related to modeling and simulation. In April 2018, the FDA launched a pilot program for Model-Informed Drug Development (MIDD) to foster the adoption of such techniques.

> In 2019, NOVA was selected for the US FDA's MIDD pilot program. The same year, NOVA was invited by both the FDA and EMA to discuss validation guidelines of computational models for drugs.

On March 31st 2020, the EMA published its "Regulatory Science Strategy to 2025" in which Modeling & Simulation plays an important role. It responds to the significant acceleration in the pace of innovation in recent years and the need for regulators to be ready to support the development of increasingly complex human medicines that combine different technologies. In April 2020, NOVA published an article on regulatory science for *in silico* clinical trials (Verifying and Validating Quantitative Systems Pharmacology and In Silico Models in Drug Development: Current Needs, Gaps, and Challenges) co-authored by the EMA.

As part of this strategy several key goals will accelerate the adoption of *in silico* evidence in the regulatory context of drug development:

- Encourage innovation in clinical trials
- Optimize modeling, simulation and extrapolation capabilities
- Harness digital technology and artificial intelligence in decision making

NOVA's hybrid mechanistic modeling approach

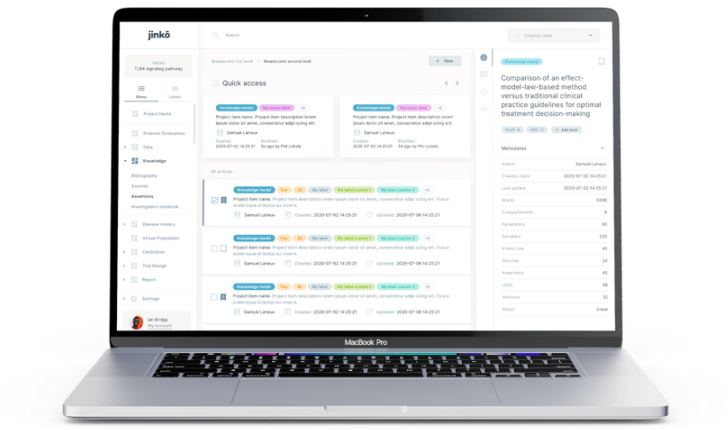
NOVA's unique positioning relies mainly on being able to simulate *in silico* clinical trials in the same conditions as in vivo (same endpoint, clinical outcome, virtual population) and offering a tool that breaks the internal silo between modeling experts and R&D teams. This uniqueness has to be reinforced by user-friendly tools, such as through the **Jinkō®** platform.

Over the past 10 years, NOVA has worked on a dozen diseases including lung cancer, hepatitis B, NASH, stroke, lymphomas, lung graft rejection, hypoparathyroidism and ischemic reperfusion injury, and is continually expanding its disease library in Jinkō® Knowledge.

A team of experts

The interdisciplinary team at NOVA includes 39 individuals (33% with PhDs) with combined expertise in biology, medicine, clinical pharmacology, applied mathematics, data science, artificial intelligence and software development. NOVA's team relies on the expertise of two internationally recognized researchers (Pr. Jean-Pierre Boissel, Co-founder and Chairman of the Scientific Advisory Board & Pr. Marc Hommel, SVP of Medicine) and Jim Bosley (SVP, Modeling & Simulation), a internationally-recognized systems biology modeler with strong expertise in QSP modeling.

Jinkō®, best-in-class clinical trial simulation and disease modeling platform



Biomodeling, artificial intelligence and virtual populations are at the heart of NOVA's innovative approach and NOVA's platform takes its name from the fortunate homonymic collision of the Japanese words for 'artificial' (人工, jinkō) and 'population' (人口, jinkō).

Jinkō® offers an integrated suite of applications, from discovery to market access, to handle complex multi-scale models in a fully whitebox environment, to facilitate model auditing. Each model component is seamlessly traceable from the model documentation back to each primary source of information to ensure full auditability. Jinkō®'s modular design allows for a number of distinct use-case-oriented workflows, ranging from the in-house model design to the client-side interaction with the simulator.

The workflows of Jinkō®'s are designed to closely resemble those of real-life clinical studies. Scenarios represent variations in disease, treatment options, and other study-related factors that, combined with the virtual unique characteristics of the virtual patient, form the input to a model simulation. Each branch of a scenario corresponds to what would be an arm of a real-life clinical trial (including a potential control arm, where no modifications are applied).

Conclusion

Learn more about *in silico* clinical trials and our Jinko® platform: contact Julie