Towards a platform of diabetes systems biology models and submodels - Nova's Jinkō

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nova DISCOVERY

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Systems models are used to lower cost, speed up development, and support more confident decisions

In two basic ways:

1. Decision Analytics (go/nogo, target selection)
High return (compared to standard practice) in early decisions
Underused, because early programs have low budgets limiting application

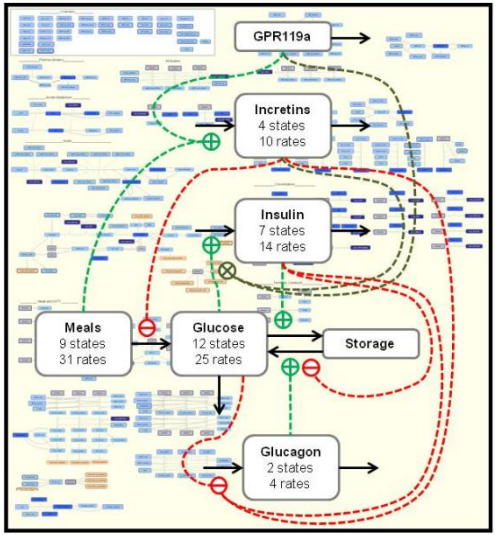
2. Trial Design and Optimization
Return realized in later stages (dose, protocol in Phase I, understanding later phases)
Trial stages have bigger budgets, justifying modeling
Examples: Identifying responders and non-responders for upcoming trial, or providing a better **synthetic control arm** using more subjects and an exact protocol match

Q: Would it make sense to have a platform that many programs could use?

Often models are built with a focus on one set of questions

Pfizer: How does a GPR119 agonist compare to standards of care?

- Leveraged limited competitor data to leapfrog in understanding
- Modeling showed target not as good as other treatments (e.g. sitigliptin)
- Subsequent competitor trial confirmed model and decision
- Model not used again by Pfizer (to my knowledge)
- ⇒ Knowledge base “contributed more value than any CRO” (T. Maurer, personal communication)

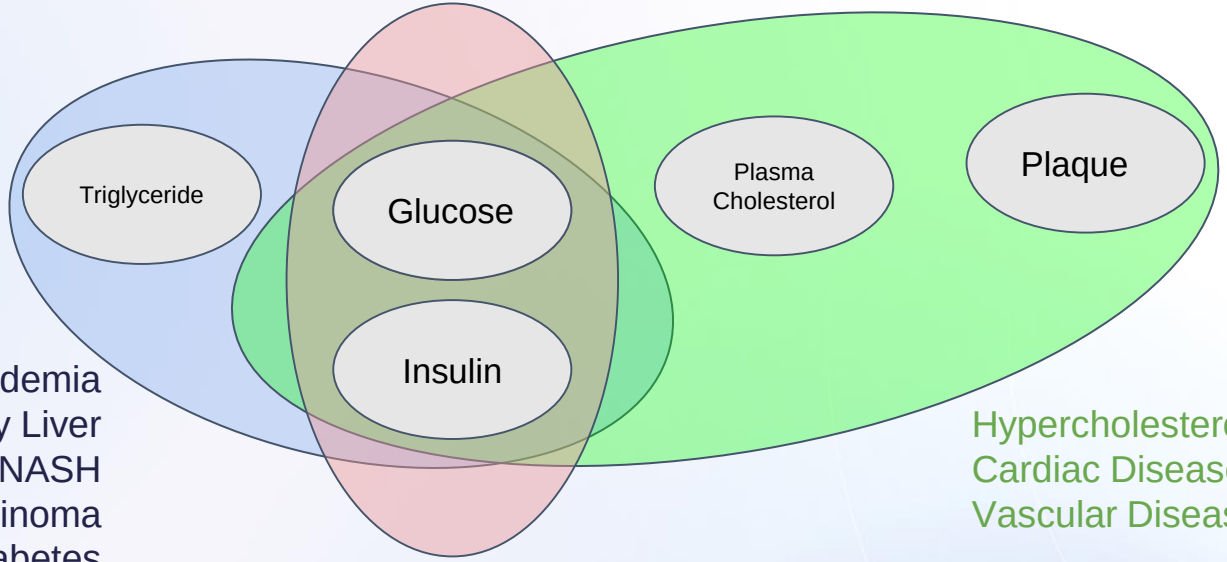


Q: Shouldn’t we preserve these models as platforms providing durable competitive advantages?

Reference: T. Maurer, “Model-Based Discovery & Development of Novel Therapies for Type-2 Diabetes Mellitus”, 2012, NYAS

A modular approach allows flexible scope and content

Diabetes
Medical Devices
All metabolic diseases



Hypertriglyceridemia
Fatty Liver
NASH
Hepatocarcinoma
Diabetes

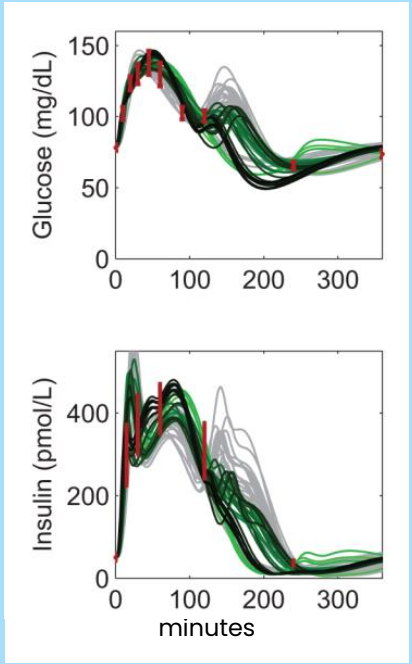
Hypercholesterolemia
Cardiac Disease
Vascular Disease

Q: Would it be useful to include in a diabetes modeling platform <u>testable submodels</u>?

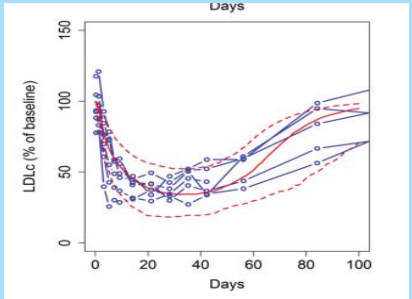
Metabolic models are available

- Dalla Man et al., 2007-22
  - Short term - glucose and insulin
  - Included glucose meals
- Pratt et al. 2014
  - Short term - TG, glucose and insulin
- Gadkar et al. 2015
  - Longer term
  - LDL-C and glucagon - no glucose/insulin
- Sips et al. 2015
  - Short term post prandial focus
  - Fatty acids and detailed insulin!
- O'Donovan et al. 2019
  - Short term postprandial adipose lipid focus
  - no insulin!
- Morgan et al. 2020, MacAuley 2015
  - Cholesterol focus, analysed aging
  - TG-rich particles but no glucose or insulin!
- Khaksar-Toroghi et al. 2021
  - Longer term
  - TG particles, glucose, insulin
- Bosch et al. 2022
  - Focus on GLP1 and glucagon
  - Used NONMEM - pharmacometric model

Pratt, glucose and insulin (short term)

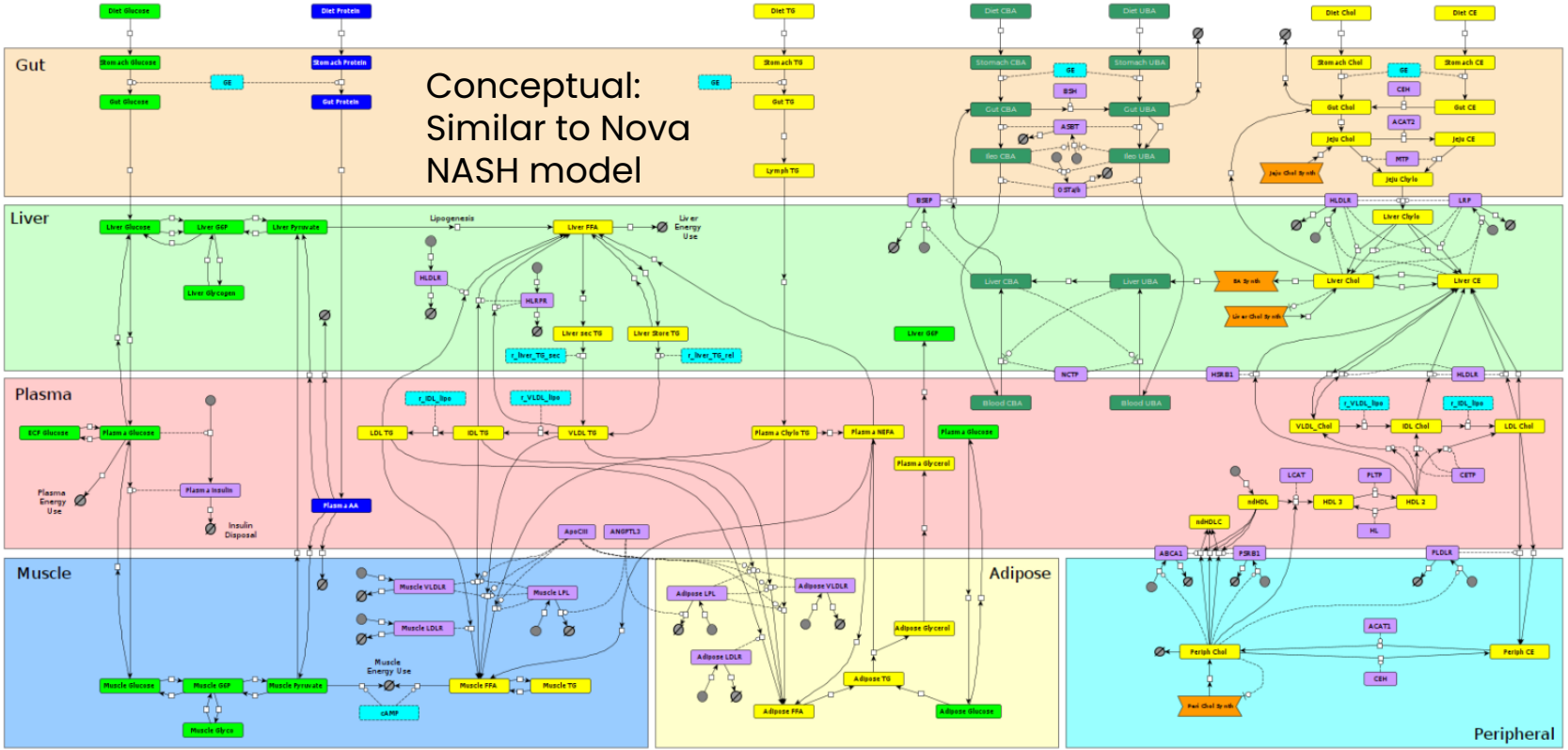


Khaksar-Toroghi, LDL (long term)



Q: Would it be useful to integrate different published models with different strengths?

Integrating several models suggests a basis for a platform model



Q: What would be best practice for creating and preserving a comprehensive modeling platform?

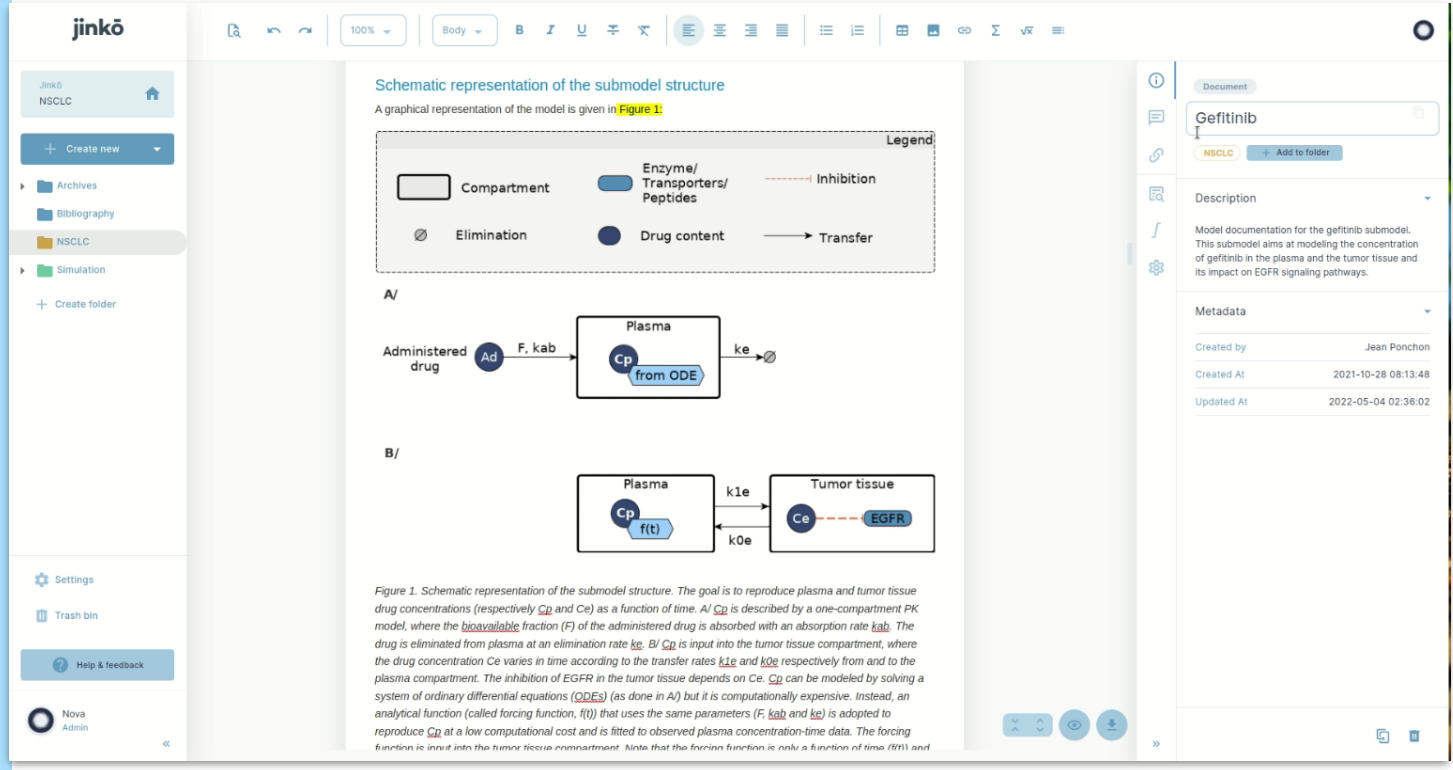
A model implemented in a platform makes sense

- ➔ Applicable to many programs, either early or late
- ➔ A permanent, evolving scientific tool (including a Knowledge Model)
- ➔ A durable competitive advantage
- ➔ A library of reusable submodels
- ➔ A way to integrate many publicly available models

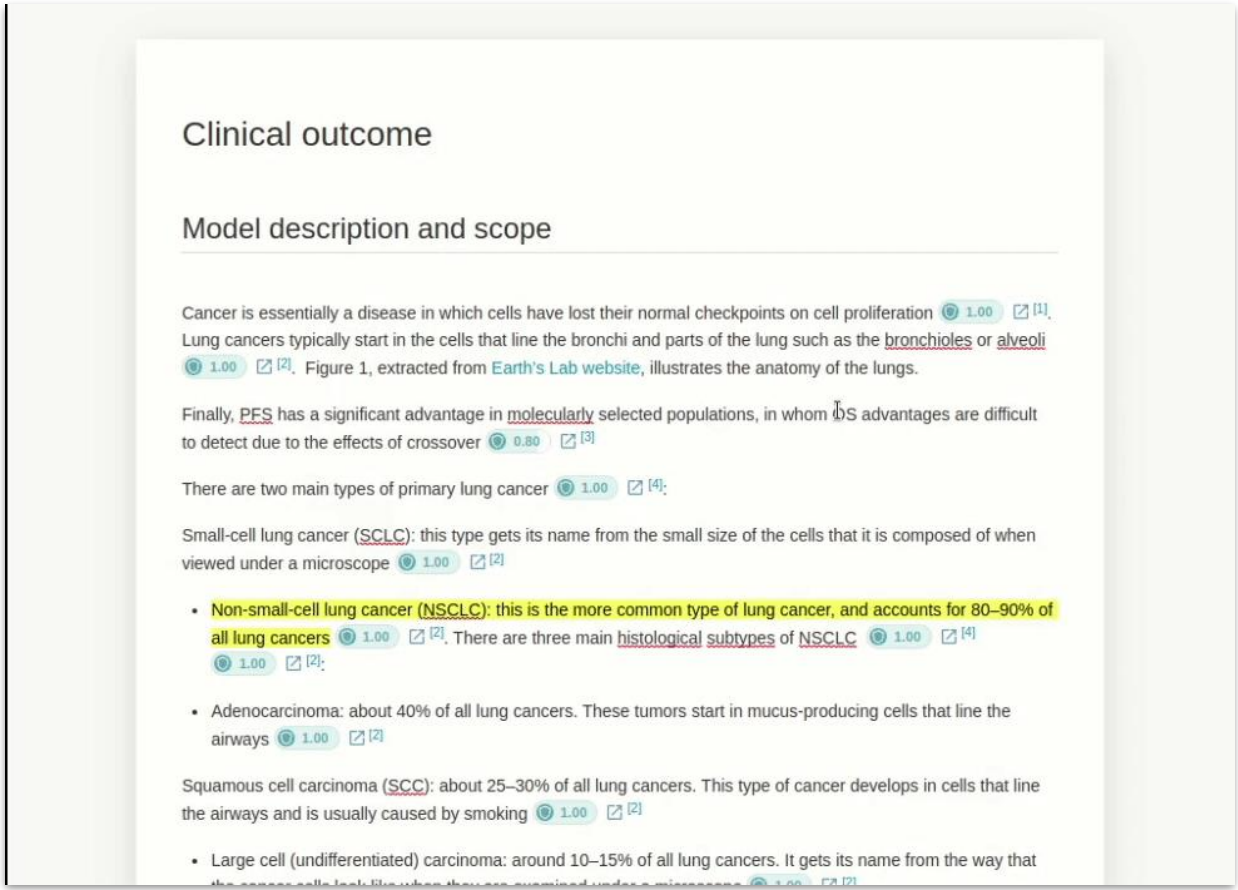
Novadiscovery has created a software platform, Jinkō, to provide these benefits

Project workflow

Knowledge Management



Knowledge Management



Clinical outcome

Model description and scope

Cancer is essentially a disease in which cells have lost their normal checkpoints on cell proliferation 1.00 [1]. Lung cancers typically start in the cells that line the bronchi and parts of the lung such as the bronchioles or alveoli 1.00 [2]. Figure 1, extracted from Earth's Lab website, illustrates the anatomy of the lungs.

Finally, PFS has a significant advantage in molecularly selected populations, in whom OS advantages are difficult to detect due to the effects of crossover 0.80 [3]

There are two main types of primary lung cancer 1.00 [4]:

Small-cell lung cancer (SCLC): this type gets its name from the small size of the cells that it is composed of when viewed under a microscope 1.00 [2]

- Non-small-cell lung cancer (NSCLC): this is the more common type of lung cancer, and accounts for 80–90% of all lung cancers 1.00 [2]. There are three main histological subtypes of NSCLC 1.00 [4] 1.00 [2]:

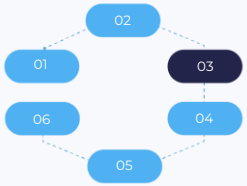
- Adenocarcinoma: about 40% of all lung cancers. These tumors start in mucus-producing cells that line the airways 1.00 [2]

Squamous cell carcinoma (SCC): about 25–30% of all lung cancers. This type of cancer develops in cells that line the airways and is usually caused by smoking 1.00 [2]

- Large cell (undifferentiated) carcinoma: around 10–15% of all lung cancers. It gets its name from the way that

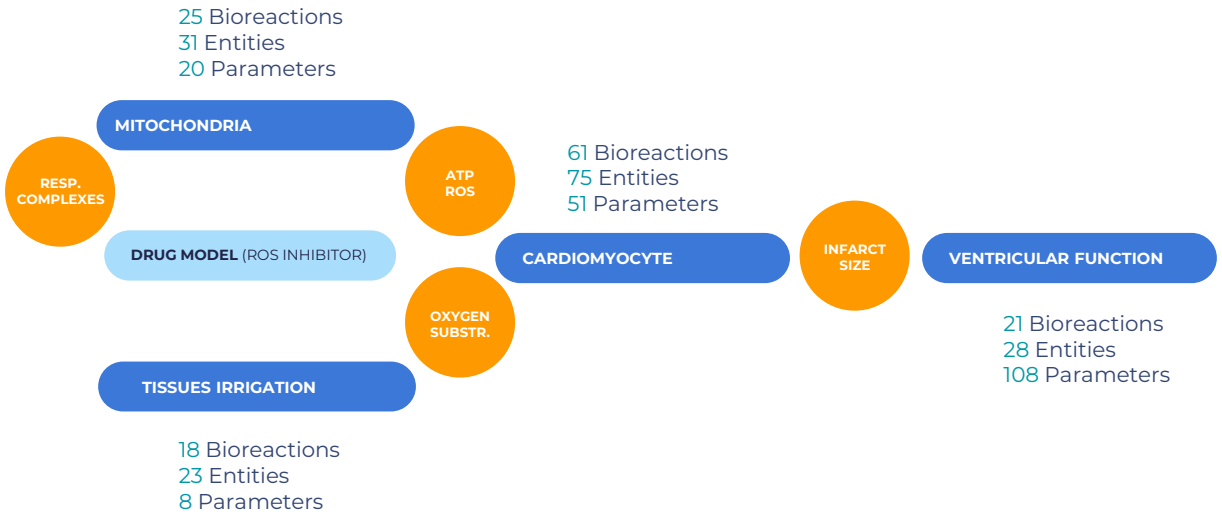
Computational disease & drug models

COMPUTATIONAL MODEL



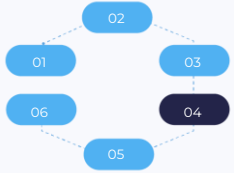
Convert what was previously described in graphical and textual form into mathematical equations and computer code

I/R Injury Computational Model



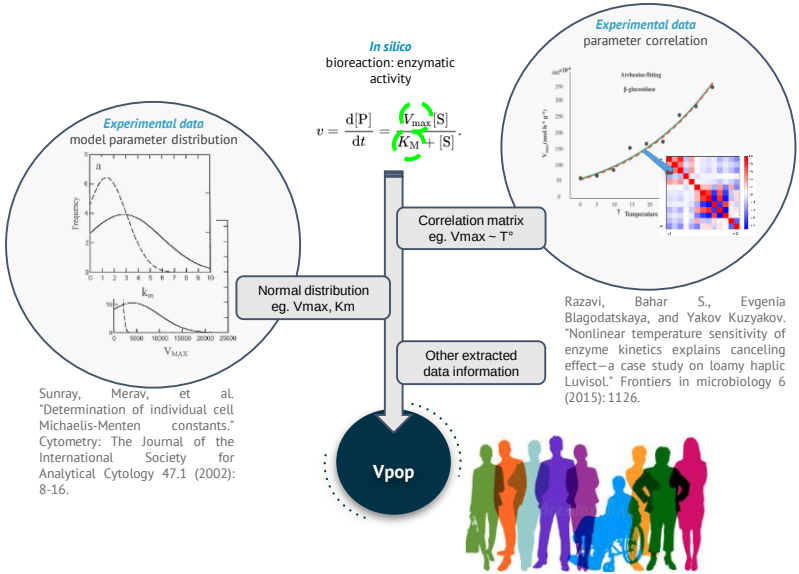
Virtual population

INTER-/INTRA-PATIENT VARIABILITY



Virtual Patients

- Each virtual patient takes a value in the distribution of each parameter of the disease model to represent the inter-/intra-patient variability.
- The virtual population (Vpop) is the total cohort of virtual patients.



Sunray, Merav, et al. "Determination of individual cell Michaelis-Menten constants." Cytometry: The Journal of the International Society for Analytical Cytology 47.1 (2002): 8-16.

Razavi, Bahar S., Evgenia Blagodatskaya, and Yakov Kuzyakov. "Nonlinear temperature sensitivity of enzyme kinetics explains canceling effect—a case study on loamy haplic Luvisol." Frontiers in microbiology 6 (2015): 1126.

↘ No limitation in the number of virtual patients (rare diseases)

↘ No limitation in the duration of the in silico study
(long term benefit)

↘ The patient serves as own control, which allows the perfect comparison of the efficacy of various treatments, everything else being equal

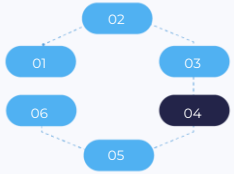
Examples of patient parameters

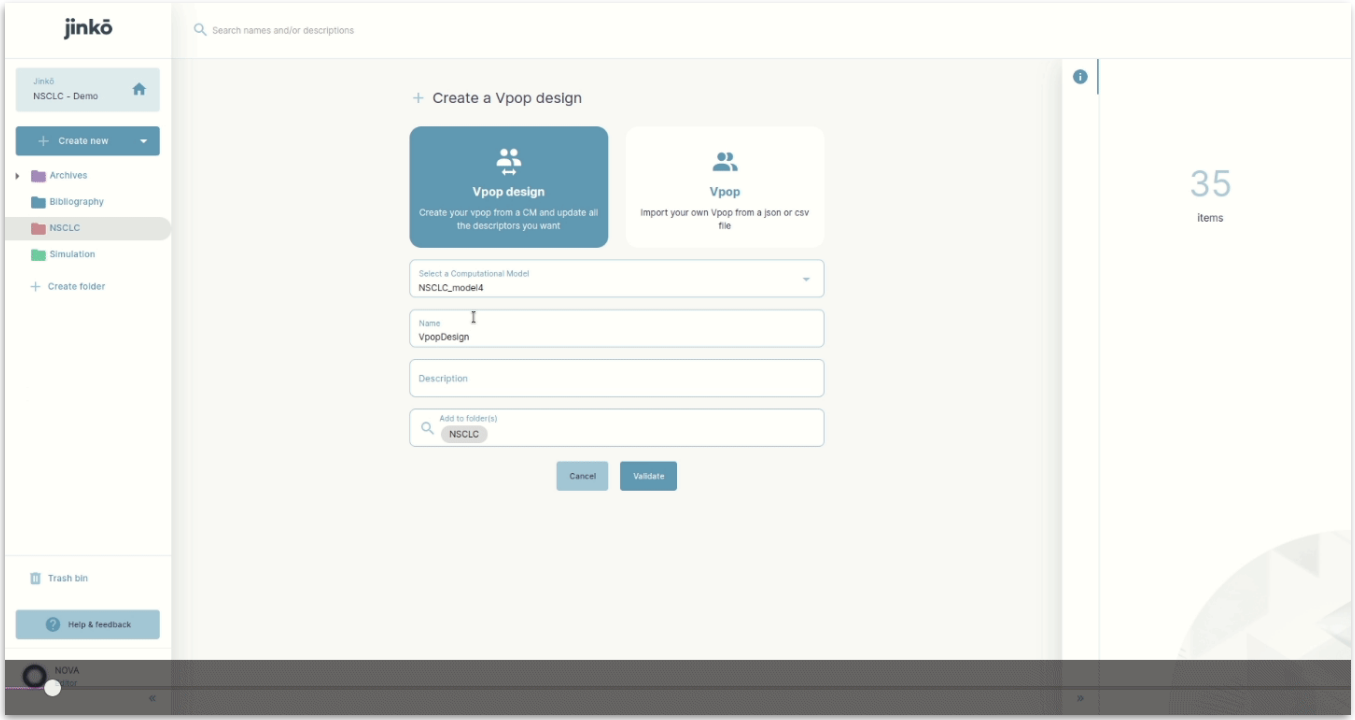
- sex
- age
- weight
- initial TIMI flow grade
- final TIMI flow grade
- LAD lesion location
- LAD diagonality
- ischemia duration,
- left ventricular mass
- ...

VpopDesign in jinkō

Virtual population

INTER-/INTRA-PATIENT VARIABILITY

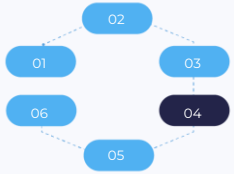


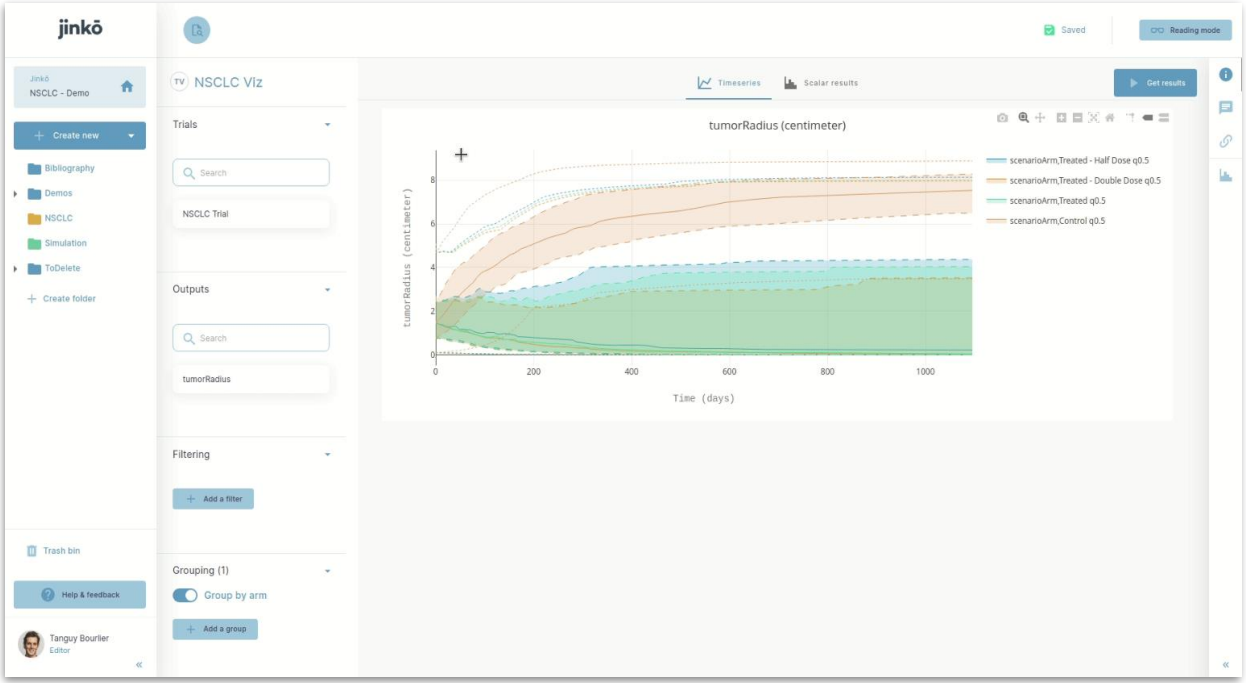


results visualization in jinkō

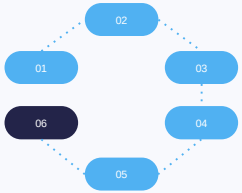
Virtual population

INTER-/INTRA-PATIENT VARIABILITY

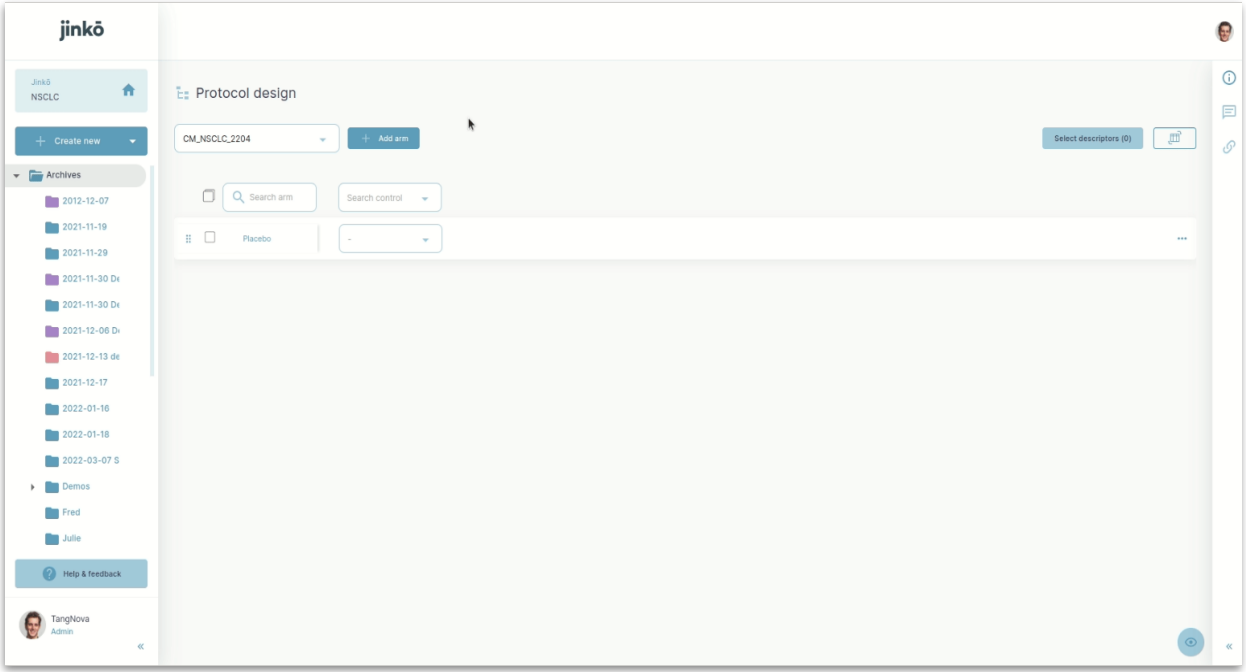




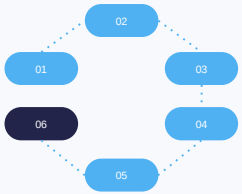
Simulations



ProtocolDesign in jinkō



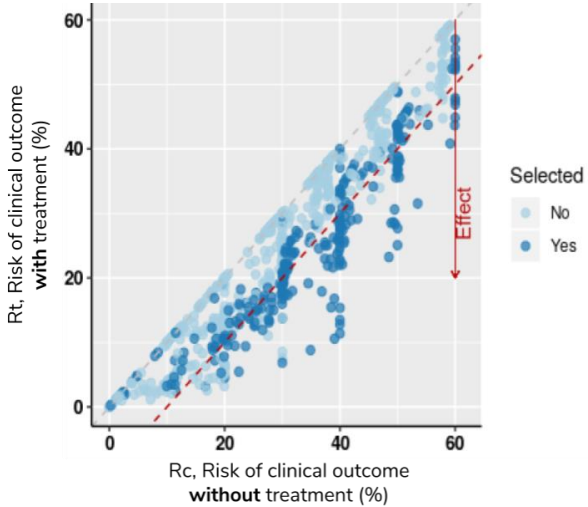
Simulations



Responder characterization

Clinical trial simulation
to optimize CT design

- The Effect Model establishes a functional connection between the drug effect on a biological system and its efficacy on clinical outcome
- Optimal responders are patients with the highest expected clinical benefit (ABi= Rc,i – Rt,i)



Takeaway messages

A comprehensive platform model of diabetes supports better decisions and design and is:

- ➔ Applicable to many programs, either early or late
- ➔ A permanent, evolving scientific tool (including a Knowledge Model)
- ➔ A durable competitive advantage
- ➔ A library of reusable submodels
- ➔ A way to integrate many publicly available models
- ➔ Creates protocols and simulates trials easily and efficiently
- ➔ A way to communicate model results to internal clients
- ➔ A way to incorporate new science and data
- ➔ A basis for education, showing impact of different factors on individuals
- ➔ A tool using proper modern agile programming tools and languages

Novadiscovery has created a software platform, Jinkō, to provide these benefits

Thank you !

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