



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

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nova
DISCOVERY



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?

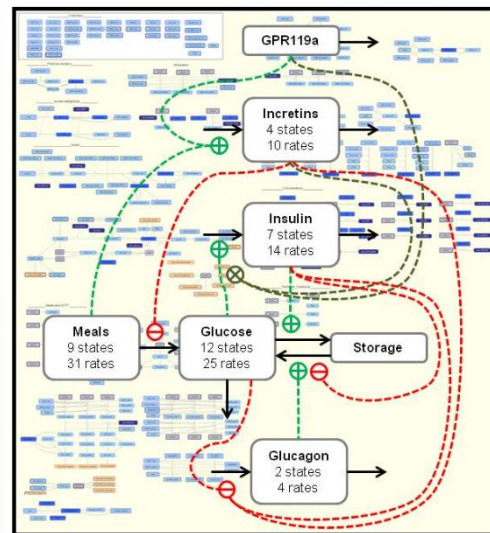
Often models are built with a focus on one set of questions

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

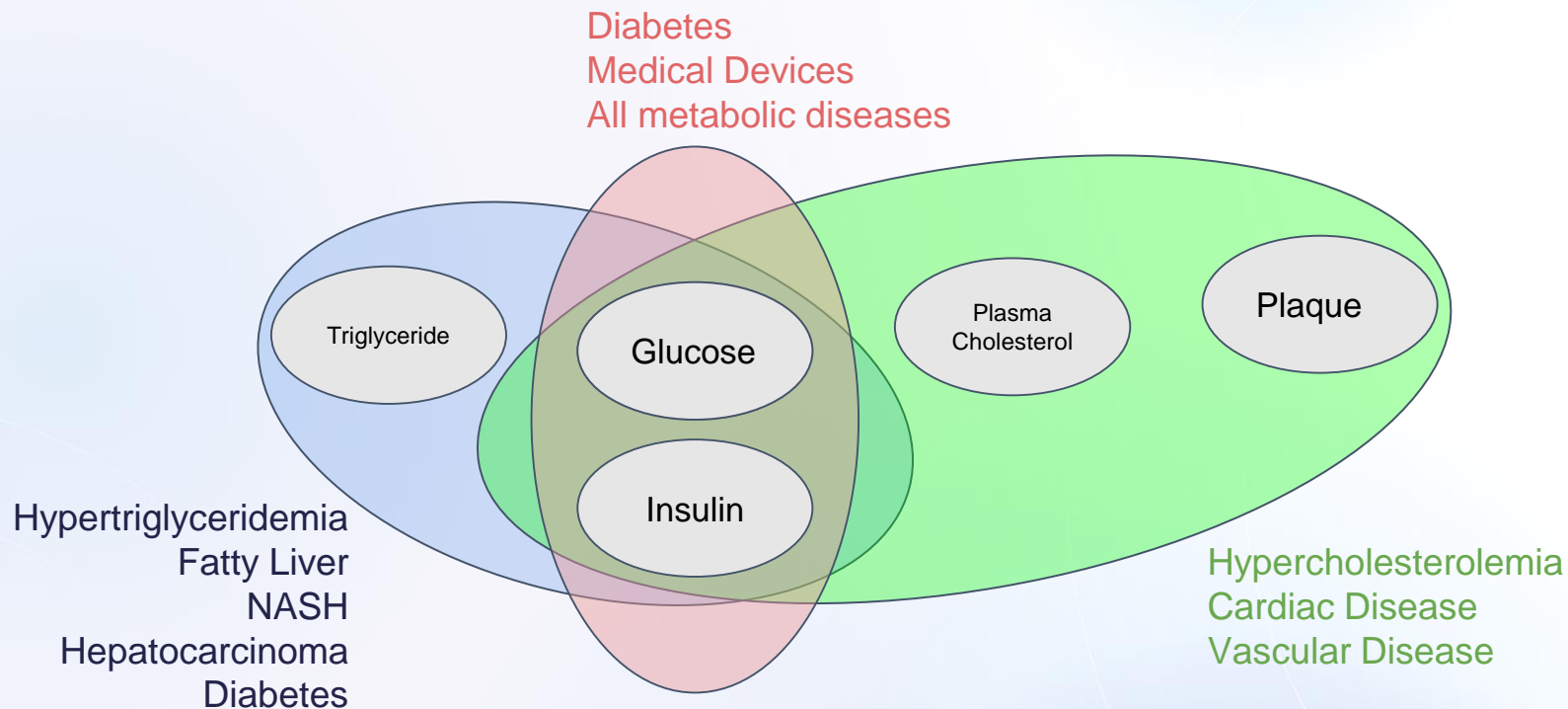
- Leveraged limited competitor data to leapfrog in understanding
- Modeling showed target not as good as other treatments (e.g. sitigliptin)
- Subsequent competitor trial confirmed model and decision
- Model not used again by Pfizer (to my knowledge)
- ⇒ Knowledge base “contributed more value than any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



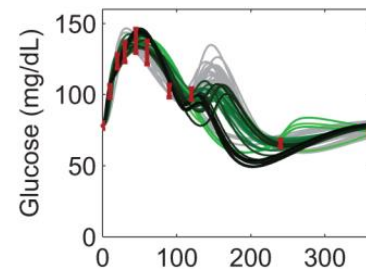
A modular approach allows flexible scope and content



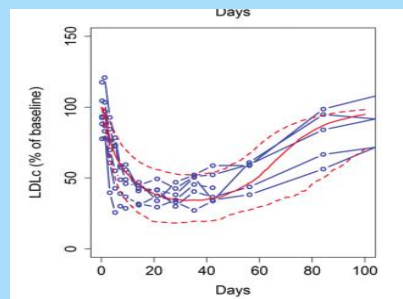
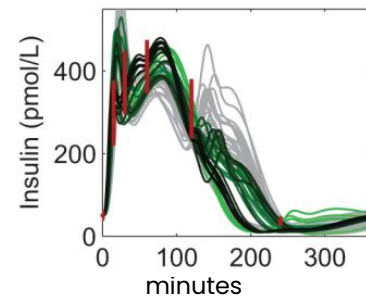
Q: Would it be useful to include in a diabetes modeling platform testable submodels?

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



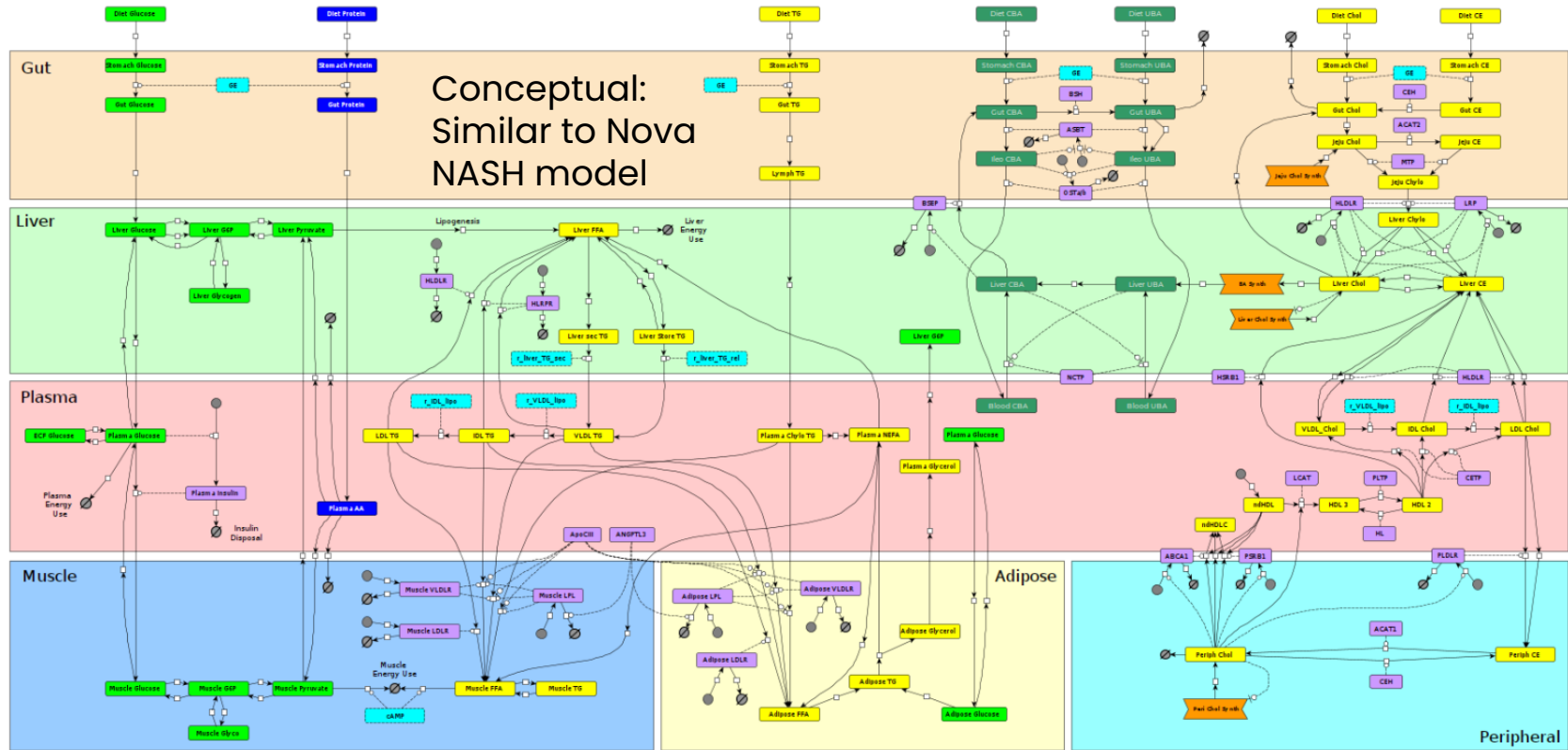
Pratt, glucose and insulin (short term)



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

jinko

100% | Body

Jinko NSCLC

+ Create new

- Archives
- Bibliography
- NSCLC
- Simulation

+ Create folder

Settings

Trash bin

Help & feedback

Nova Admin

Schematic representation of the submodel structure

A graphical representation of the model is given in [Figure 1](#).

Legend

- Compartment
- Enzyme/ Transporters/ Peptides
- Inhibition
- Elimination
- Drug content
- Transfer

A/

Administered drug A_d $\xrightarrow{F, k_{ab}}$ Plasma C_p $\xrightarrow{k_e}$ Elimination

from ODE

B/

Plasma C_p $\xrightarrow{k_{1e}}$ Tumor tissue C_e $\xrightarrow{k_{0e}}$ Plasma

EGFR

Figure 1. Schematic representation of the submodel structure. The goal is to reproduce plasma and tumor tissue drug concentrations (respectively C_p and C_e) as a function of time. A/ C_p is described by a one-compartment PK model, where the bioavailable fraction (F) of the administered drug is absorbed with an absorption rate k_{ab} . The drug is eliminated from plasma at an elimination rate k_e . B/ C_p is input into the tumor tissue compartment, where the drug concentration C_e varies in time according to the transfer rates k_{1e} and k_{0e} respectively from and to the plasma compartment. The inhibition of EGFR in the tumor tissue depends on C_e . C_p can be modeled by solving a system of ordinary differential equations (ODEs) (as done in A/) but it is computationally expensive. Instead, an analytical function (called forcing function, $f(t)$) that uses the same parameters (F , k_{ab} and k_e) is adopted to reproduce C_p at a low computational cost and is fitted to observed plasma concentration-time data. The forcing function is inserted into the tumor tissue compartment. Note that the forcing function is only a function of time ($f(t)$) and

Document: Gefitinib

NSCLC + Add to folder

Description: Model documentation for the gefitinib submodel. This submodel aims at modeling the concentration of gefitinib in the plasma and the tumor tissue and its impact on EGFR signaling pathways.

Metadata

Created by: Jean Ponchon

Created At: 2021-10-28 08:13:48

Updated At: 2022-05-04 02:36:02





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]. Lung cancers typically start in the cells that line the bronchi and parts of the lung such as the bronchioles or alveoli   [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 DS advantages are difficult to detect due to the effects of crossover   [3].



There are two main types of primary lung cancer   [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   [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**   [2]. There are three main histological subtypes of NSCLC   [4]   [2]:

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

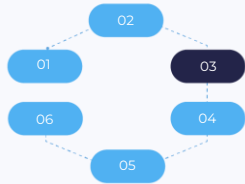
Squamous cell carcinoma (SCC): about 25–30% of all lung cancers. This type of cancer develops in cells that line the airways and is usually caused by smoking   [2]

- Large cell (undifferentiated) carcinoma: around 10–15% of all lung cancers. It gets its name from the way that the cancer cells look like when they are examined under a microscope   [2]



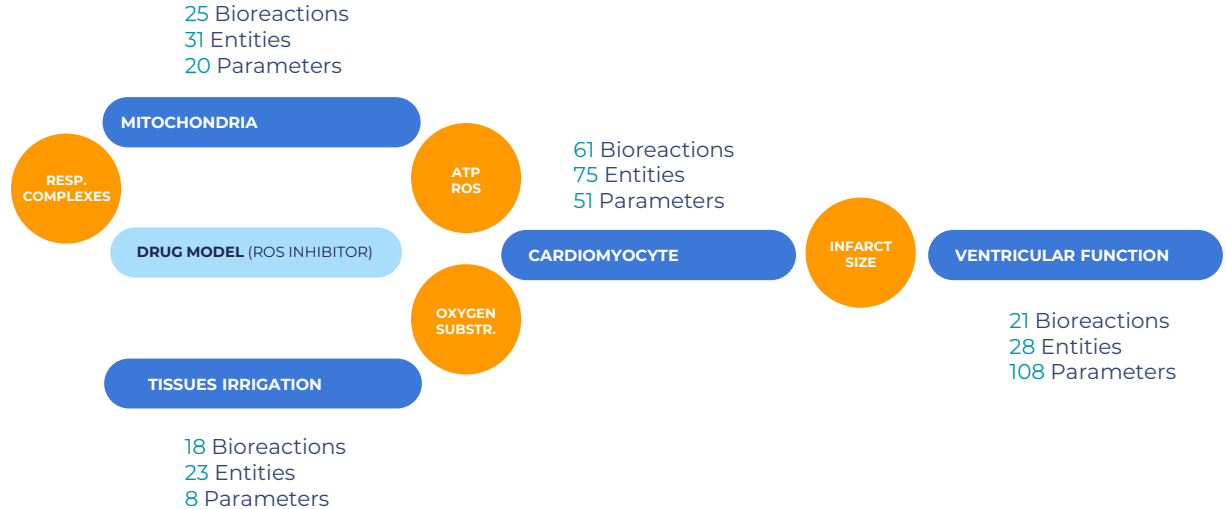
Computational disease & drug models

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



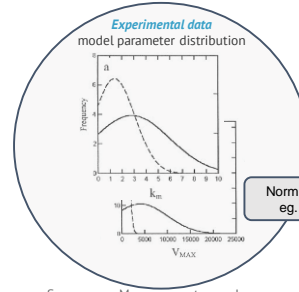
Virtual Patients

- 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.

↳ 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



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.

Normal distribution
eg. Vmax, Km

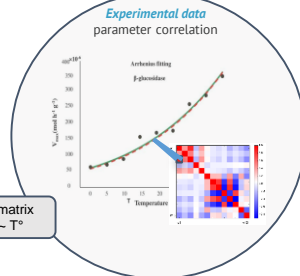
In silico
bioreaction: enzymatic activity

$$v = \frac{d[P]}{dt} = \frac{V_{max}[S]}{K_M + [S]}$$

Correlation matrix
eg. Vmax - T°

Other extracted data information

Vpop



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

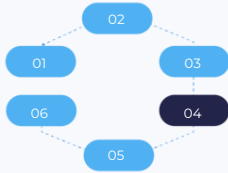
Examples of patient parameters

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



Virtual population

INTER-/INTRA-PATIENT
VARIABILITY



VpopDesign in jinkō

jinko

Search names and/or descriptions

jinko
NSCLC - Demo

+ Create new

- Archives
- Bibliography
- NSCLC
- Simulation

+ Create folder

Trash bin

Help & feedback

NOVA

+ Create a Vpop design

Vpop design
Create your vpop from a CM and update all the descriptors you want.

Vpop
Import your own Vpop from a json or csv file

Select a Computational Model
NSCLC_model4

Name
VpopDesign

Description

Add to folder(s)
NSCLC

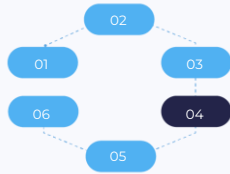
Cancel Validate

35
items

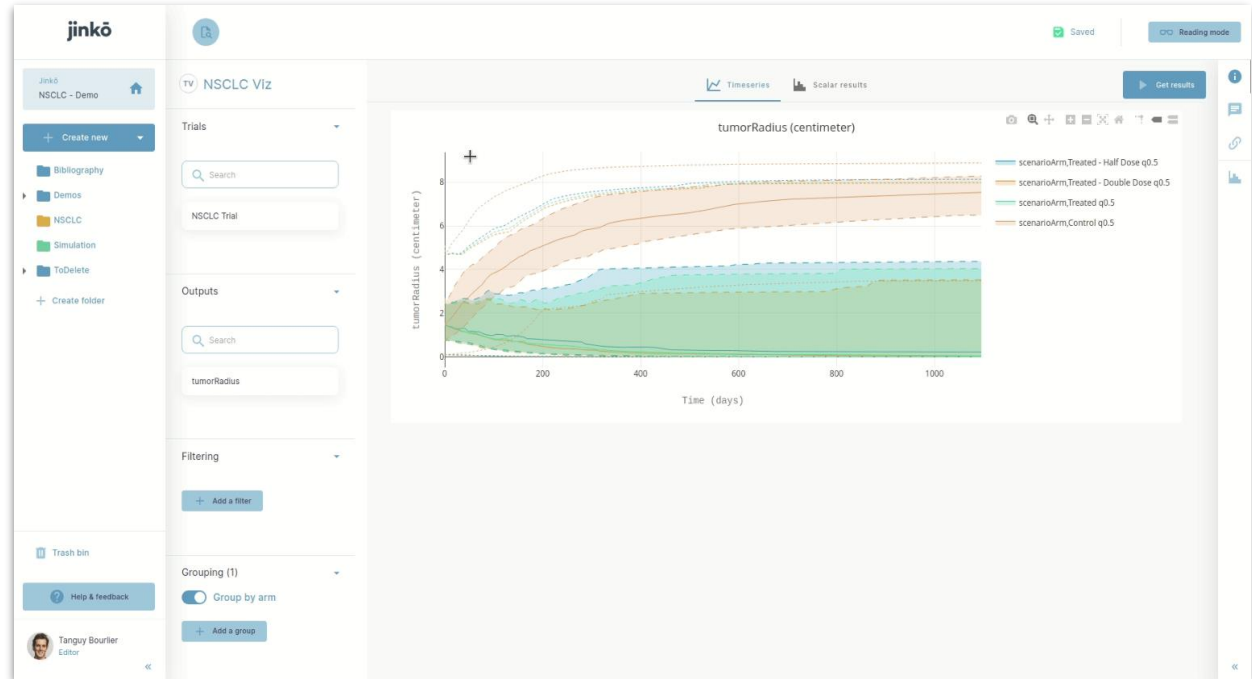


Virtual population

INTER-/INTRA-PATIENT
VARIABILITY

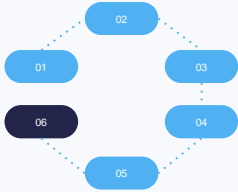


results visualization in jinko

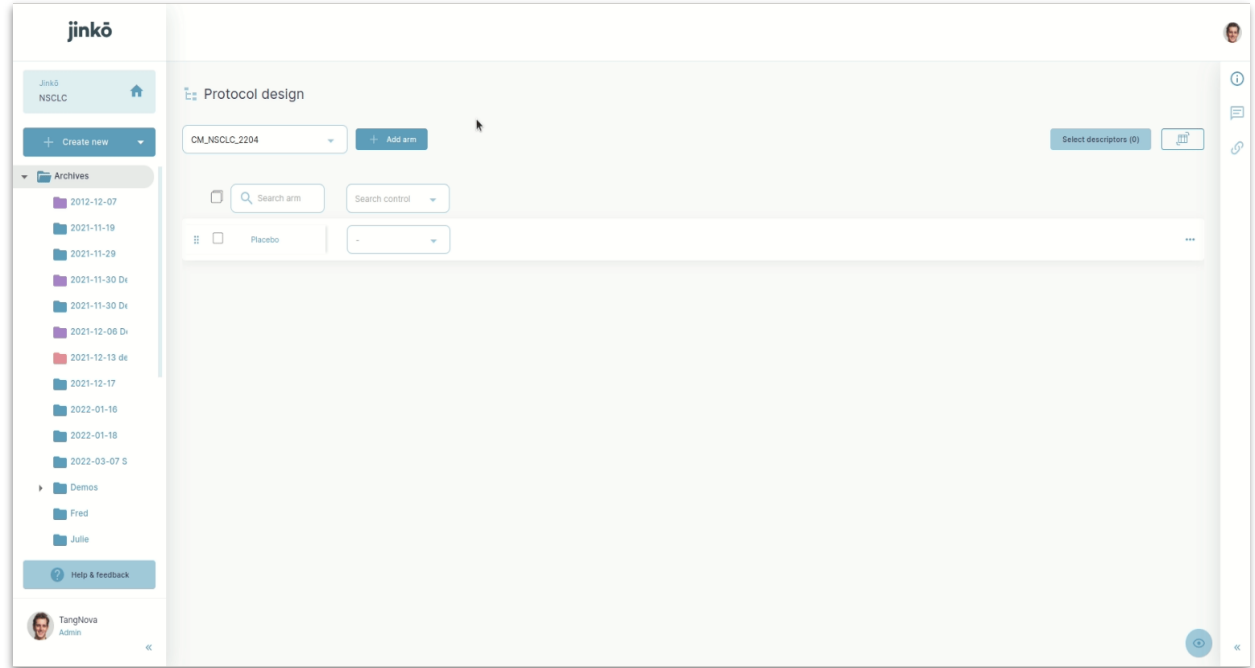




Simulations



ProtocolDesign in jinko

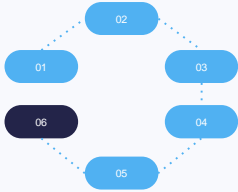


The screenshot displays the jinko Protocol design interface. The sidebar on the left contains the following elements:

- Jinko NSCLC (Home icon)
- + Create new (Dropdown arrow)
- Archives
 - 2012-12-07
 - 2021-11-19
 - 2021-11-29
 - 2021-11-30 Dr
 - 2021-11-30 Dr
 - 2021-12-06 Dr
 - 2021-12-13 de
 - 2021-12-17
 - 2022-01-16
 - 2022-01-18
 - 2022-03-07 S
- Demos
 - Fred
 - Julie
- Help & feedback (Info icon)
- User profile: TangNova Admin

The main content area is titled "Protocol design" and includes:

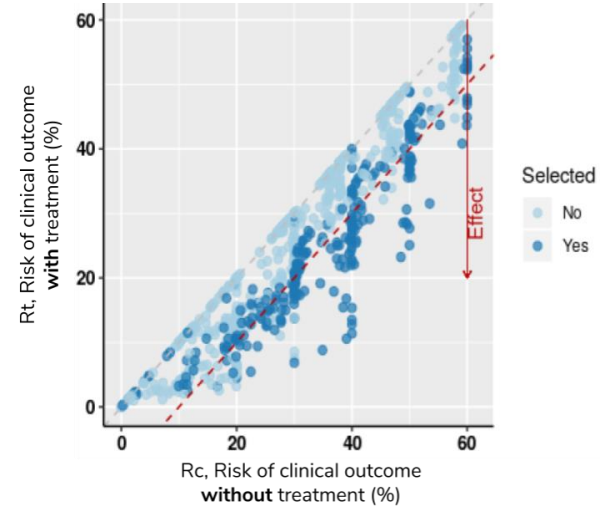
- Protocol ID: CM_NSCLC_2204
- + Add arm (Button)
- Select descriptors (0) (Button)
- Search arm (Input field)
- Search control (Dropdown menu)
- Placebo (Dropdown menu)



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

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

Thank you!



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