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Do you need a life scientist for QSP modeling?

Katherine Kudrycki, PhD

October 14th 2020

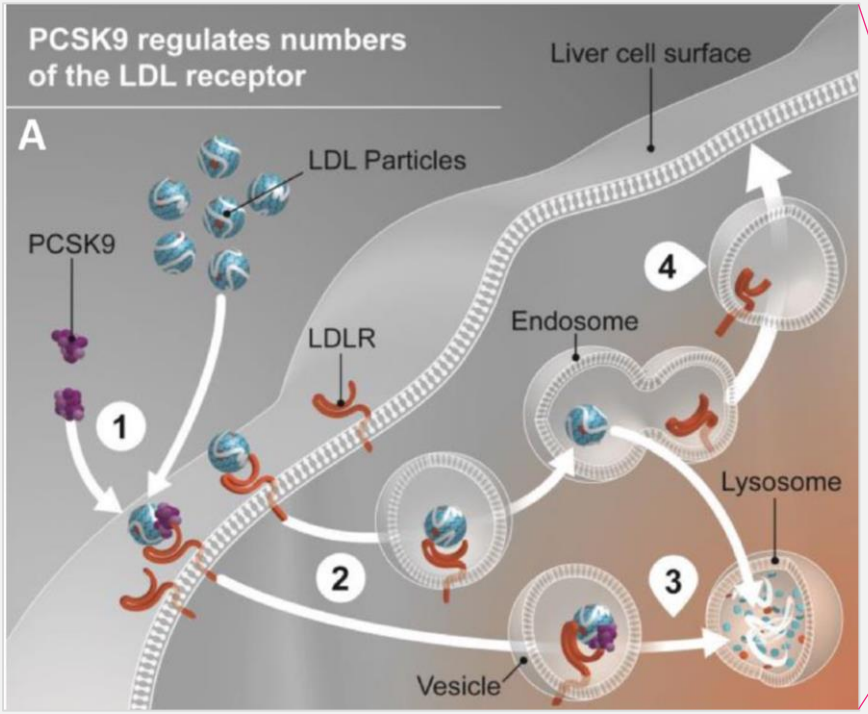
Yes! This is why…..

- Quantitative systems pharmacology (QSP) “uses mathematical computer models to characterize biological systems”

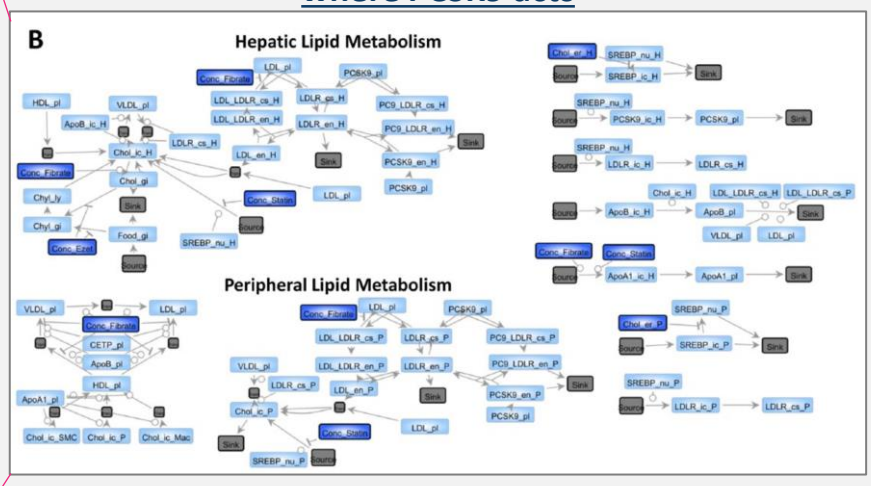
- Life scientists on the team will help with
  - A better understanding of the disease pathology and physiology
  - Data collection and interpretation
  - Interpretation of results

Biologists bring more value to a modeling project
than just adding numbers and citations.

Quantitative systems pharmacology models are models of biology.



Hepatic and peripheral subsections of the model where PCSK9 acts



A Quantitative Systems Pharmacology Platform to Investigate the Impact of Alirocumab and Cholesterol-Lowering Therapies on Lipid Profiles and Plaque Characteristics

Gene Regulation and Systems Biology
Volume 11: 1–15

DOI: 10.1177/1177625017710941
SAGE

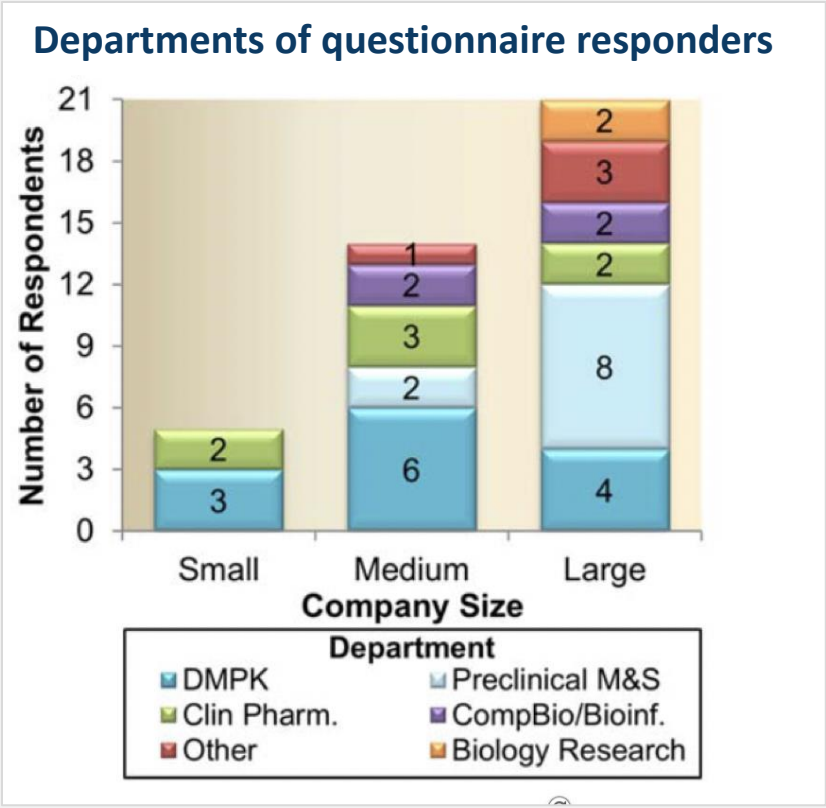
Jeffrey E Ming[1], Ruth E Abrams[1], Derek W Bartlett[2], Mengdi Tao[1], Tu Nguyen[1], Howard Surks[1], Katherine Kudrycki[2], Ananth Kadambi[2], Christina M Friedrich[2], Nassim Djebli[1], Britta Goebel[1], Alex Koszycki[1], Meera Varshnaya[1], Joseph Elassal[3], Poulabi Banerjee[3], William J Sasiela[3], Michael J Reed[2], Jeffrey S Barrett[1] and Karim Azer[1]

[1]Sanofi, Bridgewater, NJ, USA; Frankfurt Am Main, Germany, and Montpellier, France.
[2]Rosa & Co, San Carlos, CA, USA. [3]Regeneron, Tarrytown, NY, USA.

Ming 2017 PMID: 28804243

The state-of-the-art team for QSP model development should include life scientists.

- Full incorporation of life scientists in modeling teams is not a universal practice
- Integrated teams deliver insights that would be difficult or *impossible* to achieve with a *traditional* research approach
- **To build QSP models, modelers and life scientists should closely work together to translate biological concepts into mathematical models and evaluate results**



In a cross-industry survey on QSP use conducted within pharmaceutical companies, only a small fraction of responders identified as biologists (Nijsen 2018 PMID: 29349875)

Advantages of Having a Dedicated Life Scientist on a QSP Modeling Team

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Dedicated Life Scientist as part of the modeling team	"Borrowed" Life Scientist from a research project or department
Has time to analyze the data and model	Applies a few minutes between other tasks
Has time to evaluate the model and can explain the model to others	Has only seen pictures of the model in a slide deck
Raises questions and considerations during model development	Answers questions that the modelers thought to ask
Can apply data and knowledge across multiple modeling projects	Focuses on one disease and its data
Recognizes when model/VP behavior is consistent with relevant constraints	Not familiar with model constraints, assumptions, and uncertainties

Life scientists provide valuable contributions to make QSP projects successful.

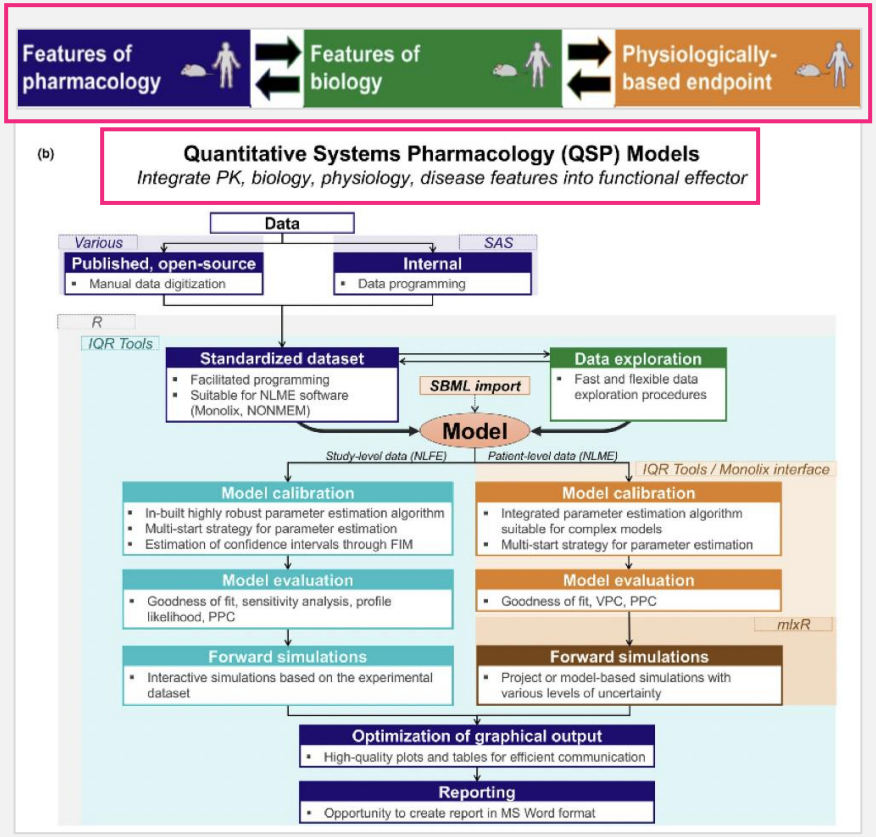
Reasons for Successful QSP Impact	Role of Life Scientists
Impacting projects with timely and sufficient modeling support	Scientific support
Addressing the clearly defined problems within the intended scope	Define, limit scope
Management or decision maker interest	Communicate w/ stakeholders
Modeling findings supported by literature and experimental data	Identify best data, test experiments
Model development/validation/uncertainty well performed or documented	Identify, document assumptions/uncertainties
Inclusion in regulatory documents and regulatory agency interest	Contribute to draft regulatory documents
Preclinical QSP work typically get presented at governance meetings	Contribute to the meetings

Nijsen 2018 PMID: 29349875

- Responders to the cross-industry survey conducted (Nijsen 2018 PMID: 29349875) identified reasons for successful QSP modeling
- Participation of life scientists can enhance all of the critical success factors
- Decision makers are often life scientist, not modelers

If the team has only mathematical modelers, the focus can be on techniques more than the biology.

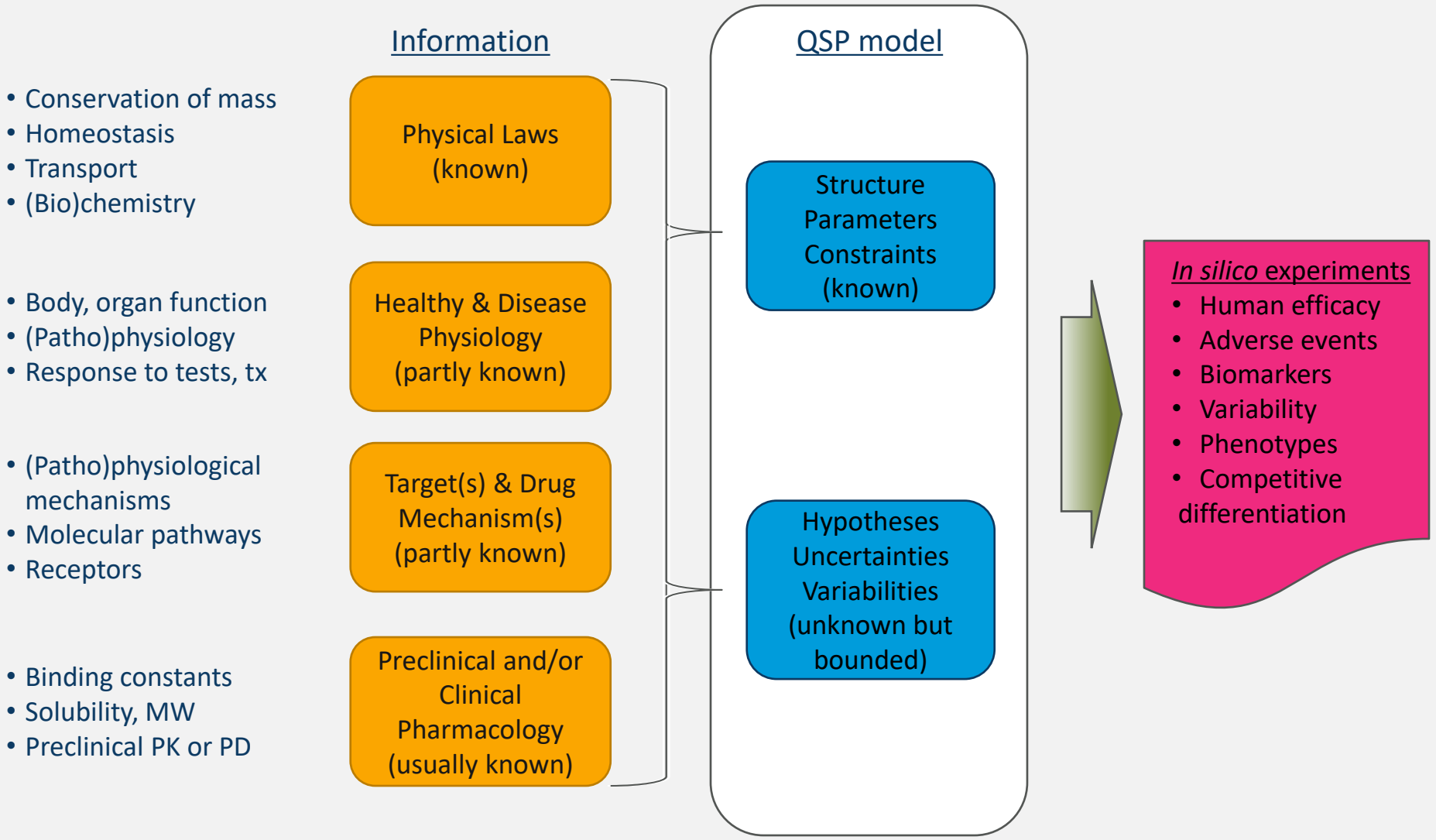
- From Helmlinger 2019 et al.
  - *"We developed best practices for QSP based on cumulative knowledge and experience in applications"*
  - Emphasizes that QSP models integrate pharmacology and biology
- Apart from parameter values, the workflows do not mention how biology is integrated into the model
- The workflows could be improved by explicitly integrating biological expertise, which plays a critical role at every step of model development



Helmlinger 2019 PMID 31087533

Life scientist and modelers working together can create a more impactful model

Life scientist participation is vital in acquiring and interpreting data incorporated in the QSP models.



Can’t the modeler just learn biology? What could go wrong?

- Why would anyone expect a modeling expert to **become a Ph.D. biologist within the time frame of a model development project**?

- It is difficult to grasp the physiology/biology from Wikipedia and review papers
  - Reviews are biased towards the author’s opinion and hypotheses
  - Reviews may have misleading or wrong information – even genius can be wrong!
  - Reviews may lack citations for the original data
  - Reviews may contain unpublished information without data or citations

Experienced life scientist judgment is critical for model scoping and data curation.

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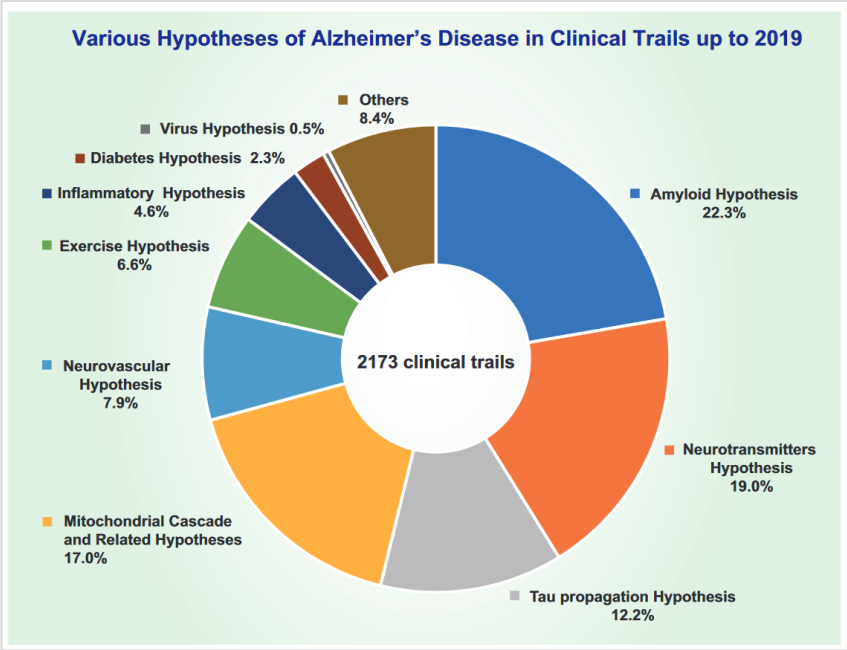
- Life scientists understand the disease pathophysiology and can provide context for setting the model scope
- Experienced life scientists are able to rapidly extract the most reliable and relevant data for the in silico development and research needs
- Life scientists provide judgment on the of quality, applicability, and usage of data to be included in the modeling process
    - Quality of data
        - Were the data obtained from one or more studies?
        - Were the methods comparable?
        - If data were obtained from only one study, was there any supporting evidence? Was the study compelling enough to accept the findings?
    - Applicability of data
        - Are the data relevant to the research question that the QSP model is supposed to address?
    - Usage of data
        - E.g., how to apply values derived from the literature to parameters/concepts in the model

Modelers may lack perspective on which aspects of biology are genuinely relevant for the project focus.

- Modelers may opt for inclusion of too many components or omit crucial aspects of biological functions
  - Without proper biological perspective of life scientists, it is easy to include the "**sexy molecule of the day**" in the model or a "**pet hypothesis,**" which may not be relevant for the model context, and for which there may be not much verifiable data available
- And it is critically important to select **Good Data**

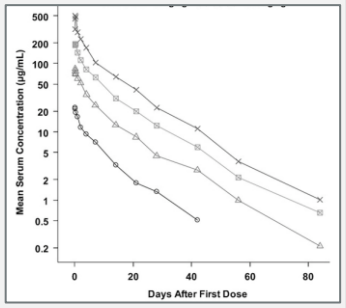


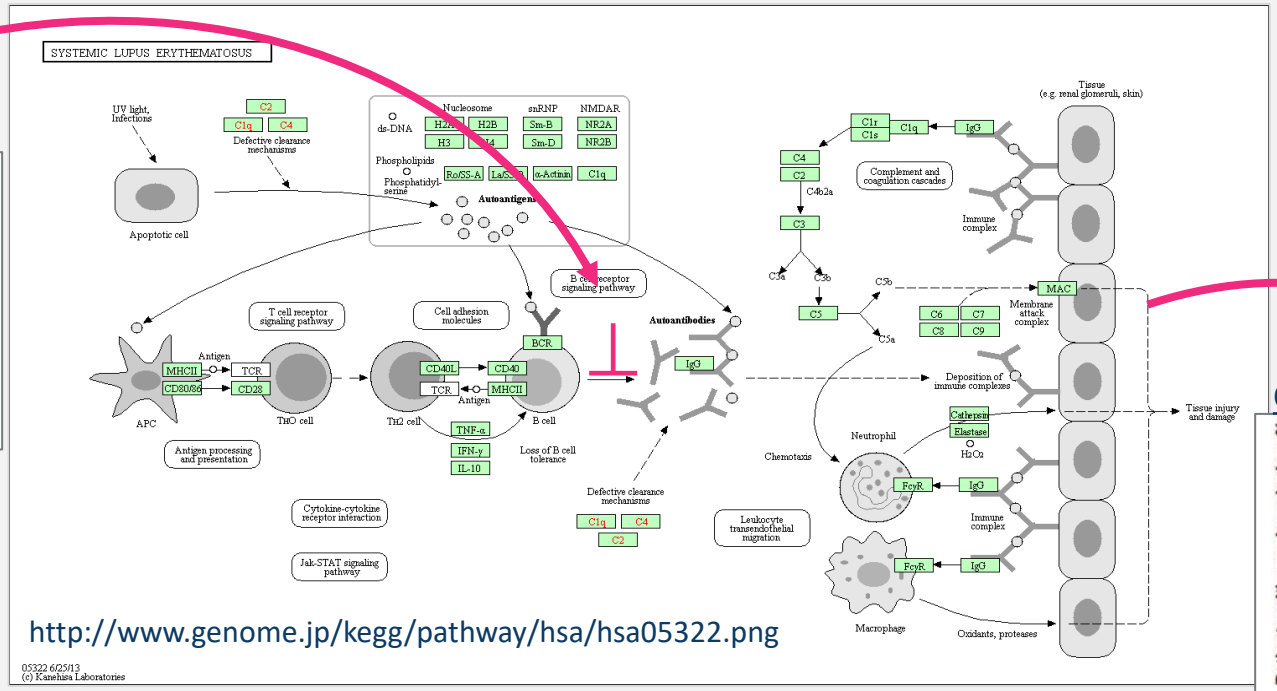
Liu 2019 PMID: 31637009

How to ensure that the model scope is “right”?

Schematics of Pathophysiology of the Disease

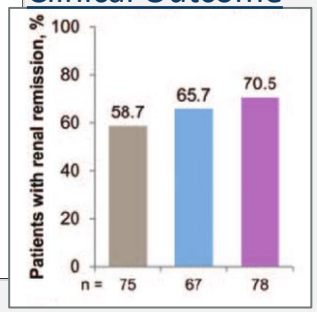
Preclinical Evidence





http://www.genome.jp/kegg/pathway/hsa/hsa05322.png

Clinical Outcome



- With the preclinical data, defined clinical outcomes, and pathways involved in the disease pathophysiology outlined in the latest review paper, it should be easy to determine the model scope. However…
  - It is necessary to know which mechanism/components/pathways are critical: this ensures that the model responses will be appropriate to answer a research question
- Life scientists are critical to addressing these questions

Can there be “too many nodes” in the model?

Herr Mozart, too many notes!

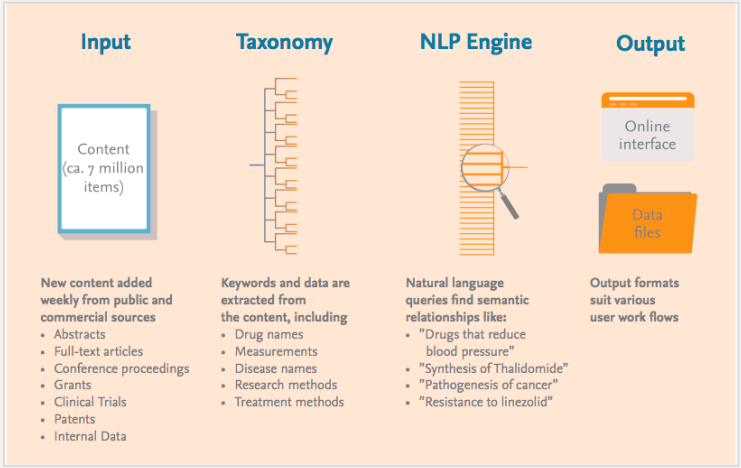
- The goal of the model is the answer specific **scientific question in a reasonable amount of time**
- There is often a temptation to build large, overly complex models based on the assumption a comprehensive model will be more robust and more predictive. **But is this true?**
- Often, overly complex representations of biological processes can result in modeling redundancies, which obscure instead of clarifying biological behavior
- Experienced life scientists familiar with functional biological redundancies can recommend which biological entities should be explicitly and implicitly included

How do you find Good Data?

- QSP requires specific information about topics such as disease mechanisms, compound bioactivities, drug efficacies, and competitor product performances
- The traditional approach is to manually review 100s of papers, extract the relevant data for model structure and parameter values
- Data mining tools such as Elsevier Text Mining Tool can help with data retrieval
- **Regardless how the data are obtained, the life scientist's judgment is necessary to make final decisions about the data to be included**

Literature survey via PubMed and Google

Data Mining Tools



https://www.elsevier.com/solutions/professional-services/text-mining

Interpreting data may also include interpreting authors and co-authors.

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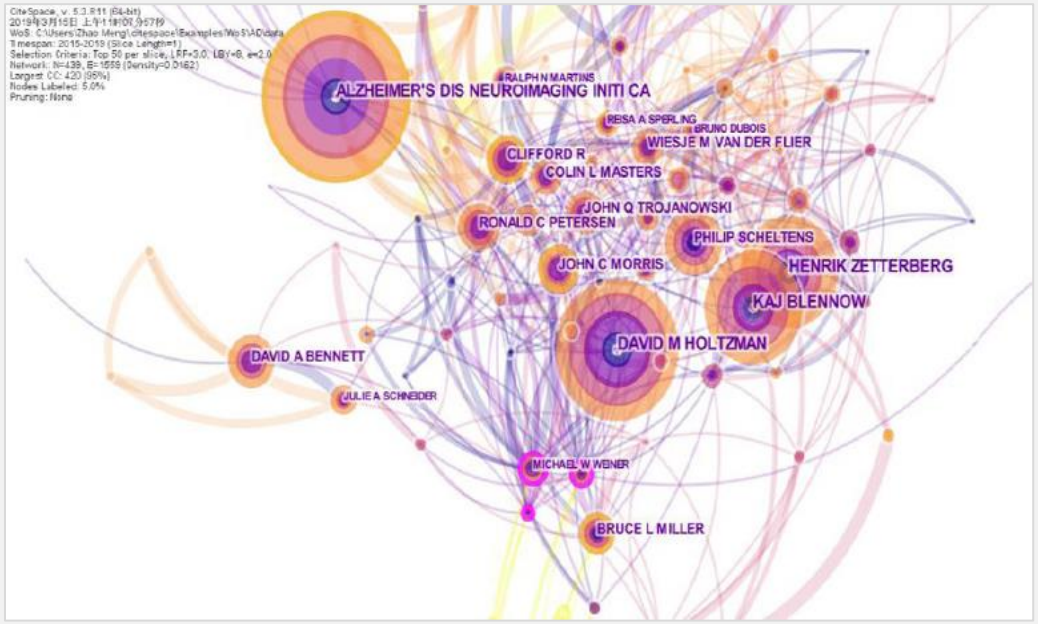
Co-authorship of Alzheimer's disease research



Liu 2019 PMID: 31089065

- Does the publication report new data or a remix of previous work?
  - Have the data been replicated by someone who is not a co-author?
- Is the review heavily cited because the author has a lot of friends/co-authors?
- Knowing who is who in the field can help with interpreting publications
  - Life scientists working in a research area can help

When science is exciting, data may be overinterpreted.

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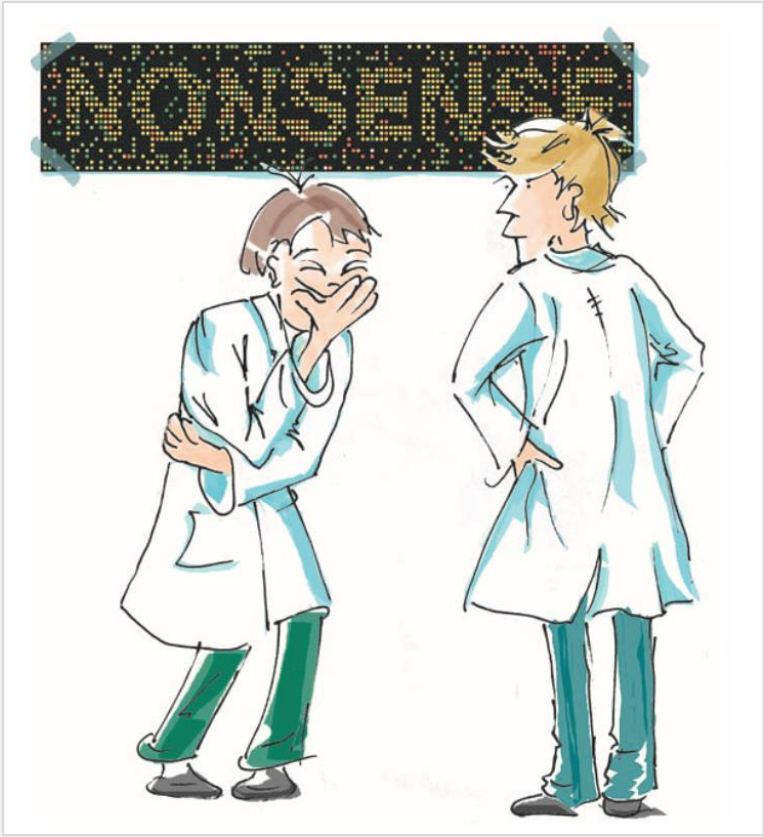
- Many published reports contain scientific errors and unresolved uncertainties that may substantially impact the quality of model building and in silico research results
  - Negative results are rarely published
  - Small background fluctuations can be misinterpreted as meaningful due to wishful thinking
  - A plausible hypothesis which confirms common prejudice is likely to be accepted without adequate verification

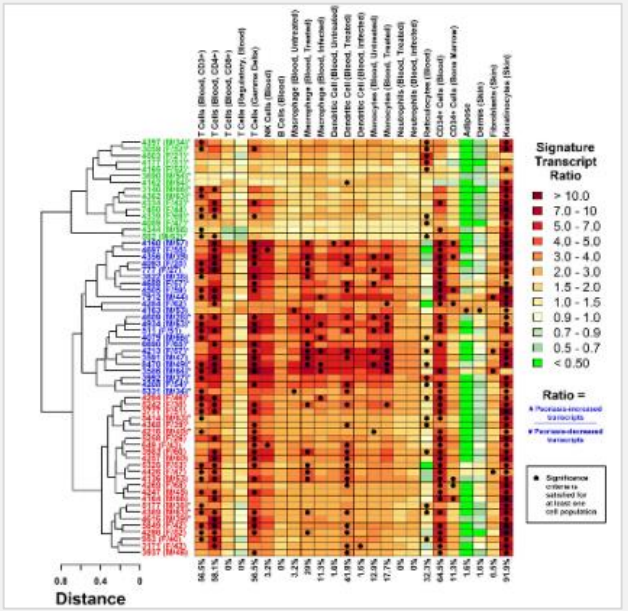
Robust scientific discussion should question dogma

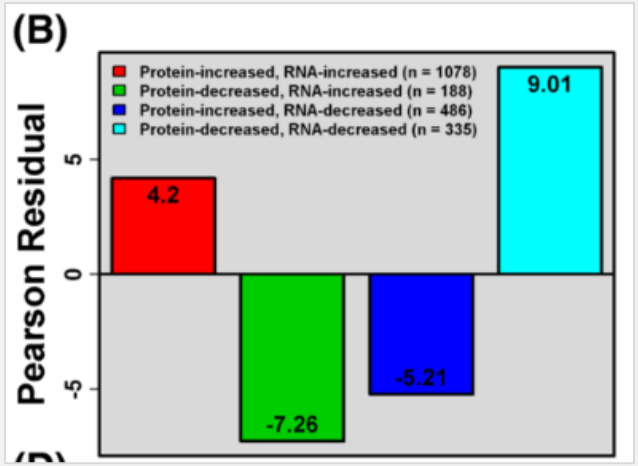


Weigmann 2005 PMID: 15809657

Life scientists can help to determine the appropriate use of data in model development.

- Genome-Wide Association Studies (GWAS), proteomics, and metabolomics, etc. data can influence the design and quantification of a model
  - Various data sources, including GWAS can identify critical drivers of disease pathophysiology
- Gene expression data is typically considered **qualitatively**, to confirm or suggest mechanistic pathways which may be involved in the disease
- **Such data should be used with caution** since actual protein levels and enzymatic activity vary from GWAS results (Swindell 2015 PMID: 26251673)

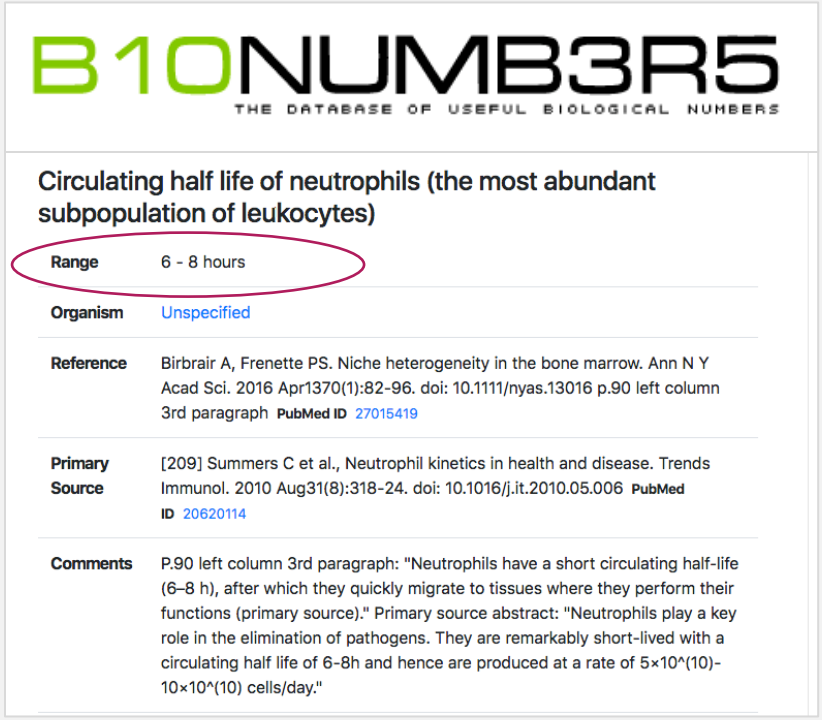




Swindell 2012 PMID: 22479649

Parameter selection is not always straightforward.

Example: Neutrophils half-life



B10NUMB3R5
THE DATABASE OF USEFUL BIOLOGICAL NUMBERS

Circulating half life of neutrophils (the most abundant subpopulation of leukocytes)

Range	6 - 8 hours
Organism	Unspecified
Reference	Birbrair A, Frenette PS. Niche heterogeneity in the bone marrow. Ann N Y Acad Sci. 2016 Apr1370(1):82-96. doi: 10.1111/nyas.13016 p.90 left column 3rd paragraph **PubMed ID** 27015419
Primary Source	[209] Summers C et al., Neutrophil kinetics in health and disease. Trends Immunol. 2010 Aug31(8):318-24. doi: 10.1016/j.it.2010.05.006 **PubMed ID** 20620114
Comments	P.90 left column 3rd paragraph: "Neutrophils have a short circulating half-life (6–8 h), after which they quickly migrate to tissues where they perform their functions (primary source)." Primary source abstract: "Neutrophils play a key role in the elimination of pathogens. They are remarkably short-lived with a circulating half life of 6-8h and hence are produced at a rate of 5×10^(10)-10×10^(10) cells/day."

- In healthy conditions, neutrophils circulate in the blood for just a few hours (Summers 2010 PMID: 20620114)
  - **6-8 h** is often used as a parameter value
  - Recent data suggest the half-life may be approximately 17 hours (Lahoz-Beneytez PMID: 27136946)
  - The range in the literature for humans is 4-153 hours (Tak 2013 PMID: 23625199, Pillay 2010 PMID: 20410504)
- Which half-life is appropriate for the pathophysiology represented in the model?

Reported parameter values can differ depending on pathophysiology and experimental conditions.

TABLE 2. Neutrophil Half-Life under Nonhomeostatic Conditions

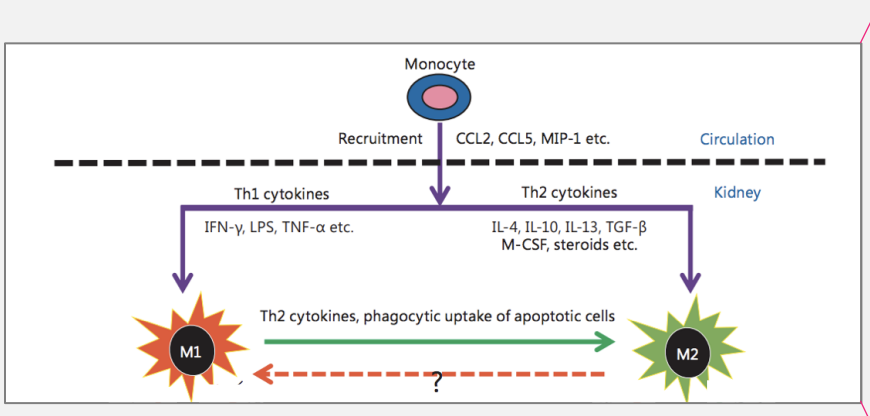
Disease/pharmaceutic	Labeling method	Half-life (non-homeostatic)	Half-life (control)
Neutropenia	Transfusion of ^{3}H-DFP-labeled, isolated neutrophils from volunteers receiving G-CSF and dexamethasone	20.3 h	9.6 h
GM-CSF	Transfusion of autologous ^{3}H-DFP-labeled blood	13.1 h	
Prednisone	Transfusion of autologous, ex vivo DF^{32}P-labeled blood	10.3 h	6.8 h
Excercise		6.7 h[a]	
Adrenalin		5.8 h[a]	
G-CSF	Transfusion of autologous, ex vivo ^{3}H-DFP-labeled blood	13.5–15.9 h[a]	10.4 h
DFP injection	Ex vivo ^{51}Cr-labeling of isolated neutrophils	9.4 h	17.5 h
Rheumatoid arthritis	Ex vivo ^{99m}Tc-HMPAO labeling of isolated white blood cells	4.2 h	4.3 h
Suspected inflammatory disease[b]	Ex vivo ^{111}In-tropolonate	5.8 h	6.3 h
	Ex vivo ^{99m}Tc-HMPAO	4.5 h	4.2 h
CML	Transfusion of autologous, ex vivo ^{3}H-DFP-labeled blood	82–140 h	7.6 h
Sarcoidosis		17 h	
Liver cirrhosis		15 h	
Drug-induced neutropenia		8.4, 13.2 h	
Other neutropenia		2.3–7 h	
Infection		4–12 h	
Splenectomy		22.2 h	

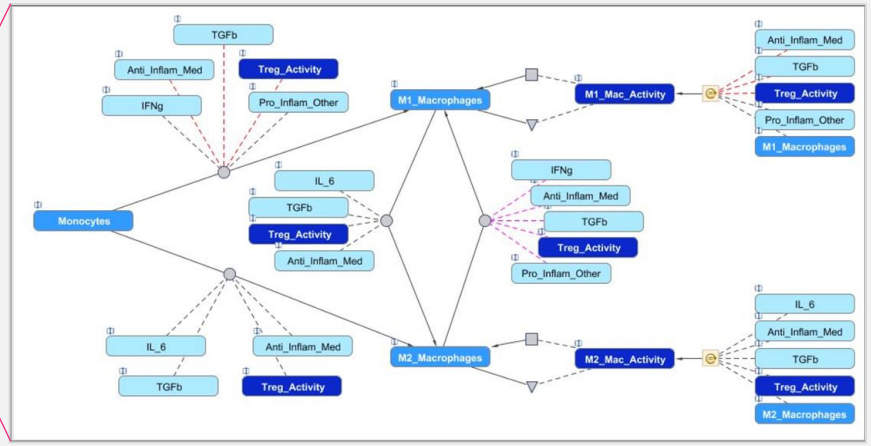
Tak 2013 PMID: 23625199

- Which value to chose?
  - The pro-inflammatory environment can prolong neutrophil survival
  - Clearance can be affected by, e.g., formation of NETs, rate of macrophage activity, etc.
- Life scientists provide scientific judgment and justification to select the most appropriate parameter values

How and when to implement alternative hypotheses?

Dynamics of M1 and M2 macrophages in disease



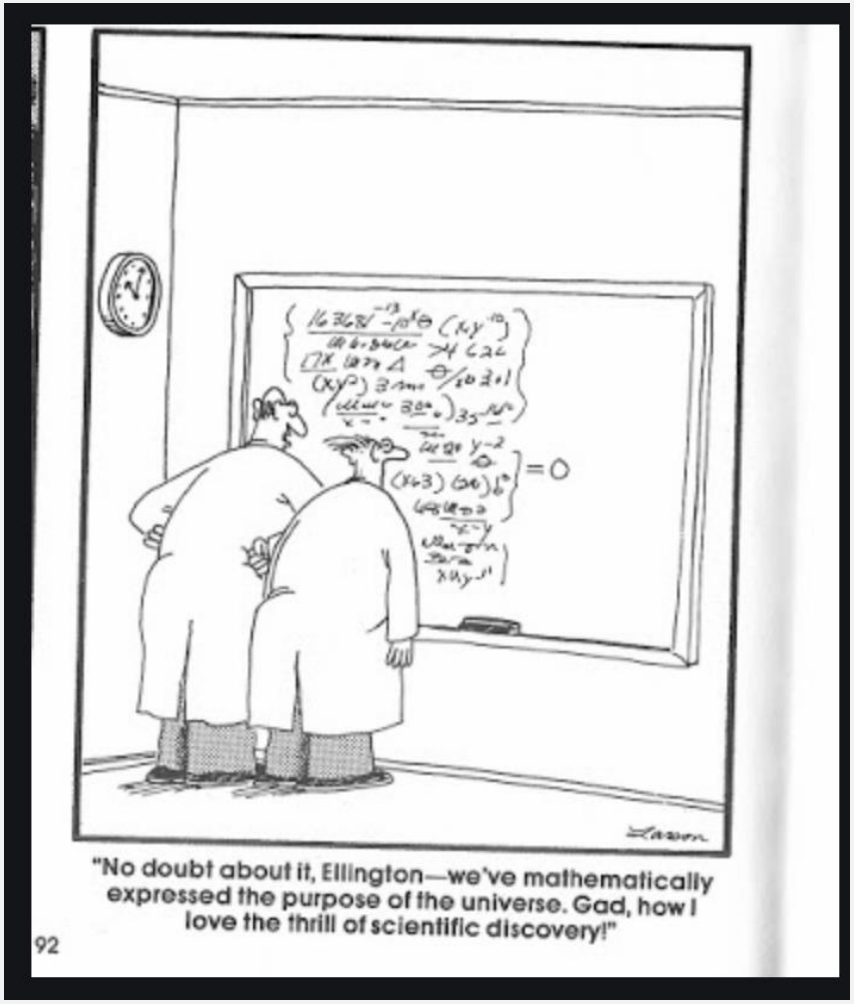


Meng 2015 PMID: 27536674

- Literature suggests an increase in pro-inflammatory M1 or anti-inflammatory M2 macrophage populations in tissue is achieved by **recruitment** from blood and **polarization** in situ. It is uncertain which pathways predominate in a given pathology
- Do all alternatives need to be represented in the model to answer the scientific question?
  - Solution 1: Represent all hypothesized pathways in the model, test as the alternative hypothesis
  - Solution 2: Represent selected pathway(s) most relevant to the scope of the model and research question

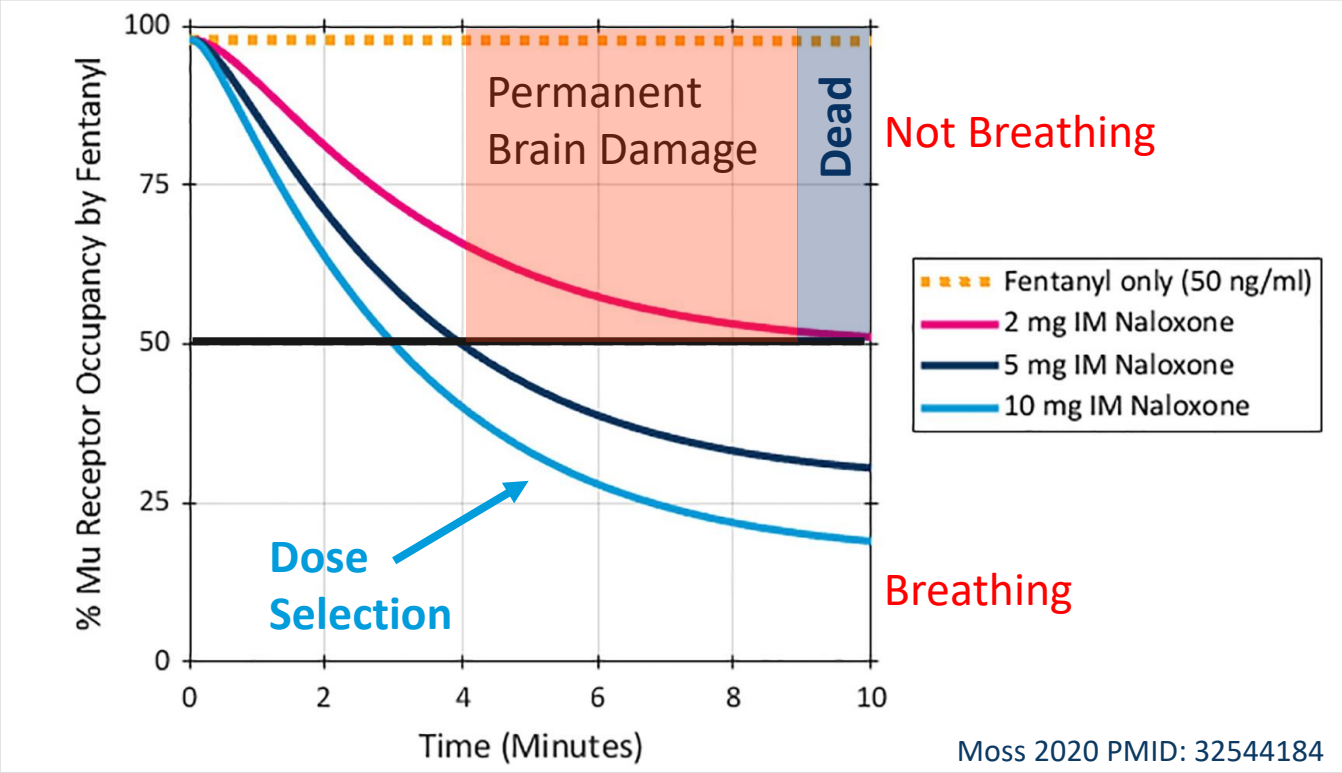
You want an expert to interpret your results.

- Life scientists can let you know whether your results make physiological sense
- Life scientists can provide an interpretation, an explanation of why the results are reasonable - or not!
- If the results are unexpected, the life scientists can formulate alternative hypotheses to be tested
  - Is it enough to test alternative hypotheses in the existing model?
  - Do we need to add additional biology to the model to get the expected results?



Life scientists can interpret simulation results to enable actionable results.

What do the simulation results mean for the development program?

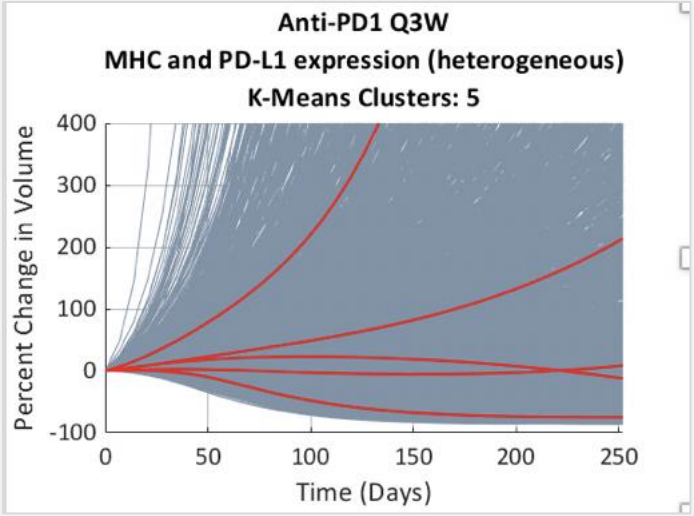


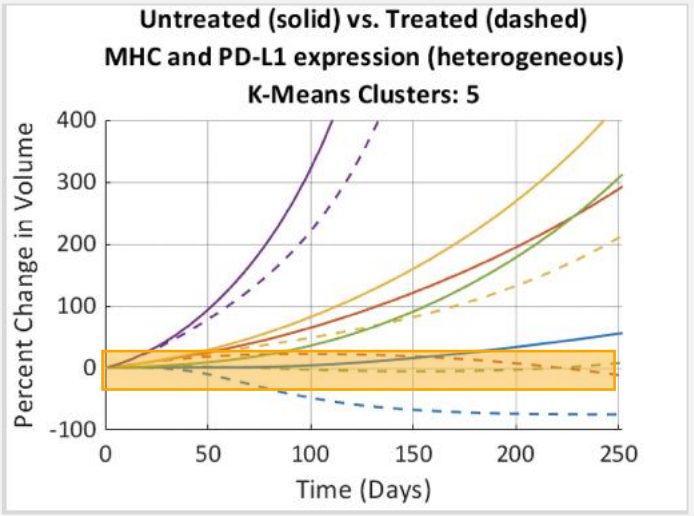
Moss 2020 PMID: 32544184

- Biological interpretation of simulation results indicate a higher dose of naloxone would be more beneficial to counteract effects of opiate overdose
  - The 50% mu receptor occupancy has been associated with clinical reversal of opiate toxicity (Melichar 2003 PMID: 12524149)

Life scientists and modelers work together to solve difficult problems.

- Problem:
  - A stable response to anti-PD-1 therapy in a solid tumor is often difficult to achieve in QSP models
- Solution:
  - Based on extensive scientific literature review, **life scientists hypothesized that that independently varying MHC and PDL-1 expression on two populations of tumor cells would help to achieve stable tumor response to the therapy**
  - This hypothesis was tested using the QSP model of solid tumor in MATLAB®
- Result:
  - All tumor responses to the therapy, including the **stable response** based on RECIST criteria, i.e., there was neither an increase in tumor size of more than 20% nor a decrease of more than 30% since the initial baseline measurement





Chung at al., presented at ACoP10 2019

What makes a good “modeling” life scientist?

- Understands modeling concepts as well as biology
  - Can evaluate the realistic model scope
  - There should be no parameter values without context
  - Computational understanding/biological dynamics
- Familiar with theory and gaps in the knowledge base
  - Willingness to trust numbers rather than dogma
  - Detailed understanding of the methods and limitations used to collect data
  - Willingness and ability to formulate alternative hypotheses
- Experienced enough to switch between therapeutic areas
  - Understand commonalities and differences for different diseases and species
  - Ability to learn quickly, adapt, and function no matter what disease area
  - Find data outside of typical search terms
  - Ability to communicate with decision-makers

Key Take Home Points

QSP models are models of biology

Life scientists on the team can improve communication and impact

Life scientists and modelers working together produce better QSP models

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