ALaSCA: A system for prioritising experimental design in early drug discovery and medical device product development, using causal analysis

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Causal analysis unlocks unknown mechanisms

What is causal analysis?
Causal analysis is a formal, hypothesis driven method for uncovering causal effects in data. Causal analysis involves building a logical framework of interactions between the system components and then applies Bayesian hypothesis testing to the network. **This is a white-box approach, which improves upon the correlative analyses of statistics and black-box approaches of AI/ML.**

What does it do?
Using established Bayesian statistical methods, the diagram is analysed to gain an understanding of **cause-and-effect relationships** appearing in measurements of and interventions in the system.

Why do we need it?

AI/ML analyses (Correlation Only)	Correlation + Causation
Difficult (to impossible) to determine which is the cause and which is the effect	It is clear which action is the cause and which is the effect, through directionality in and quantification of the relationships
Not possible to identify hidden variables/ confounders in a system	The presence of hidden variables/ confounders can be discovered and quantified
Difficult to catch spurious correlations	Easy to catch spurious correlations which may have no causality
Cascading effects across nodes and between systems cannot be understood	Quantification of upstream and cross-stream effects possible

Aeglea BioTherapeutics Receives Refusal to File Letter from FDA for Pegzilarginase for the Treatment of Arginase 1 Deficiency

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In the RTF letter the FDA requested additional data to support effectiveness, such as evidence showing that plasma arginine and metabolite reduction predicts clinical benefit in patients with ARG1-D or clinical data demonstrating a treatment effect on clinically meaningful outcomes.

Evidence gathering is accelerated with causal analysis
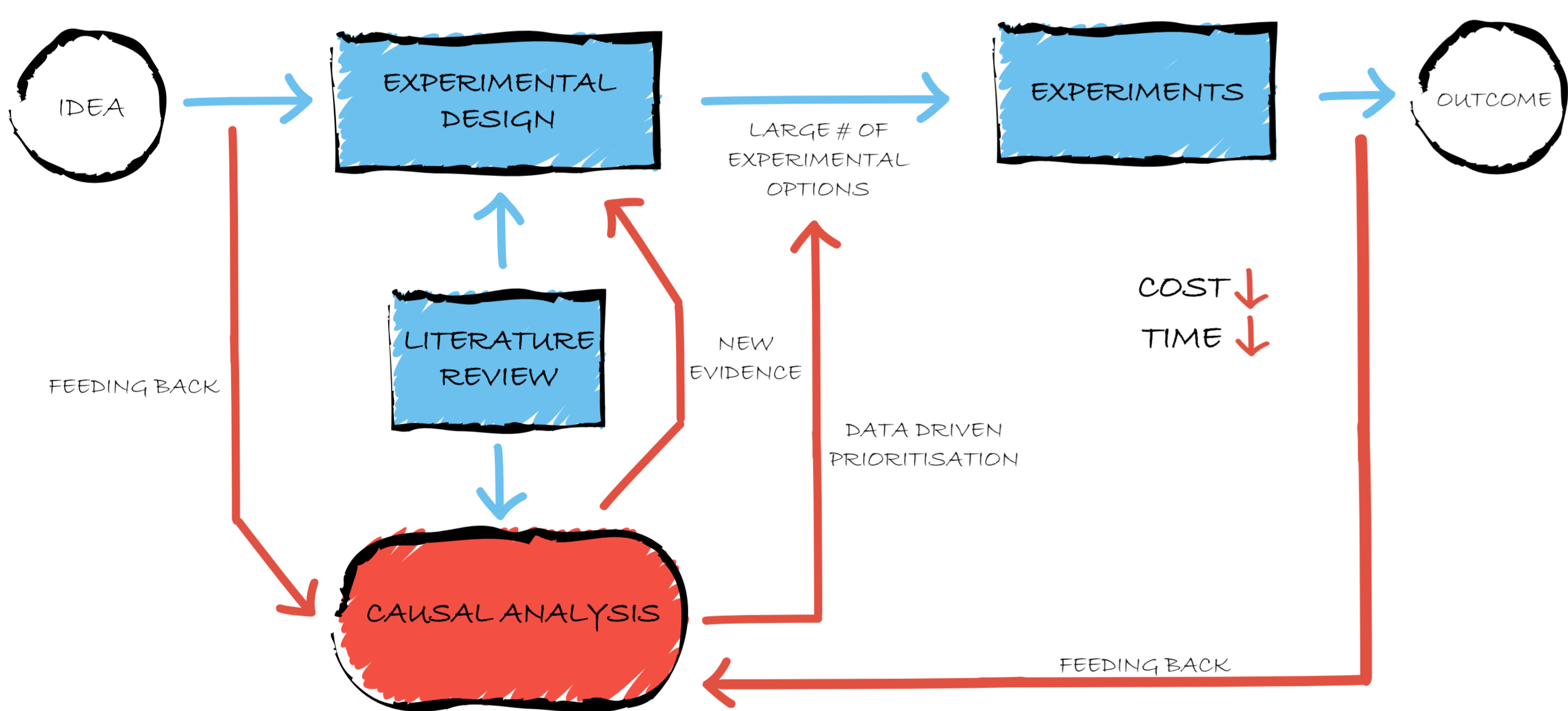
Causal analysis can work with a variety of datasets
It is not a question of "Do we have enough data?", but rather "Do we have quality data?" Causal analysis does not require the same quantity of data as one would need for other types of analysis such as ML or AI. Diversity in data is not a hurdle, it provides a basis for conditioning - a key concept of causal analysis.
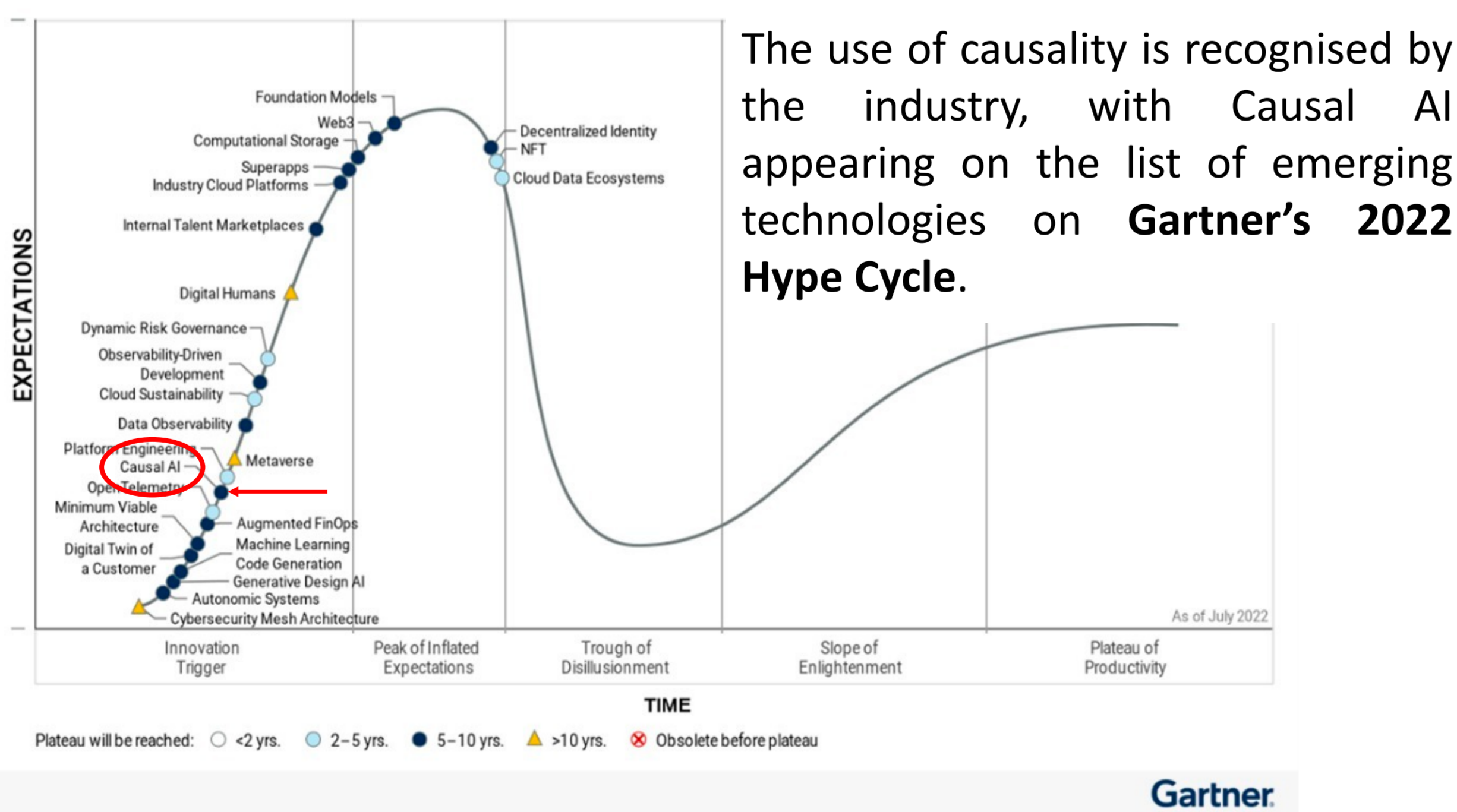

The use of causality is recognised by the industry, with Causal AI appearing on the list of emerging technologies on **Gartner's 2022 Hype Cycle**.

AMR case study demonstrating causal analysis

This case study shows how we quantified the causal effects of Cephalosporin on AMR infections in Stellenbosch, South Africa - insights that were not clear from correlative and machine learning analyses alone.
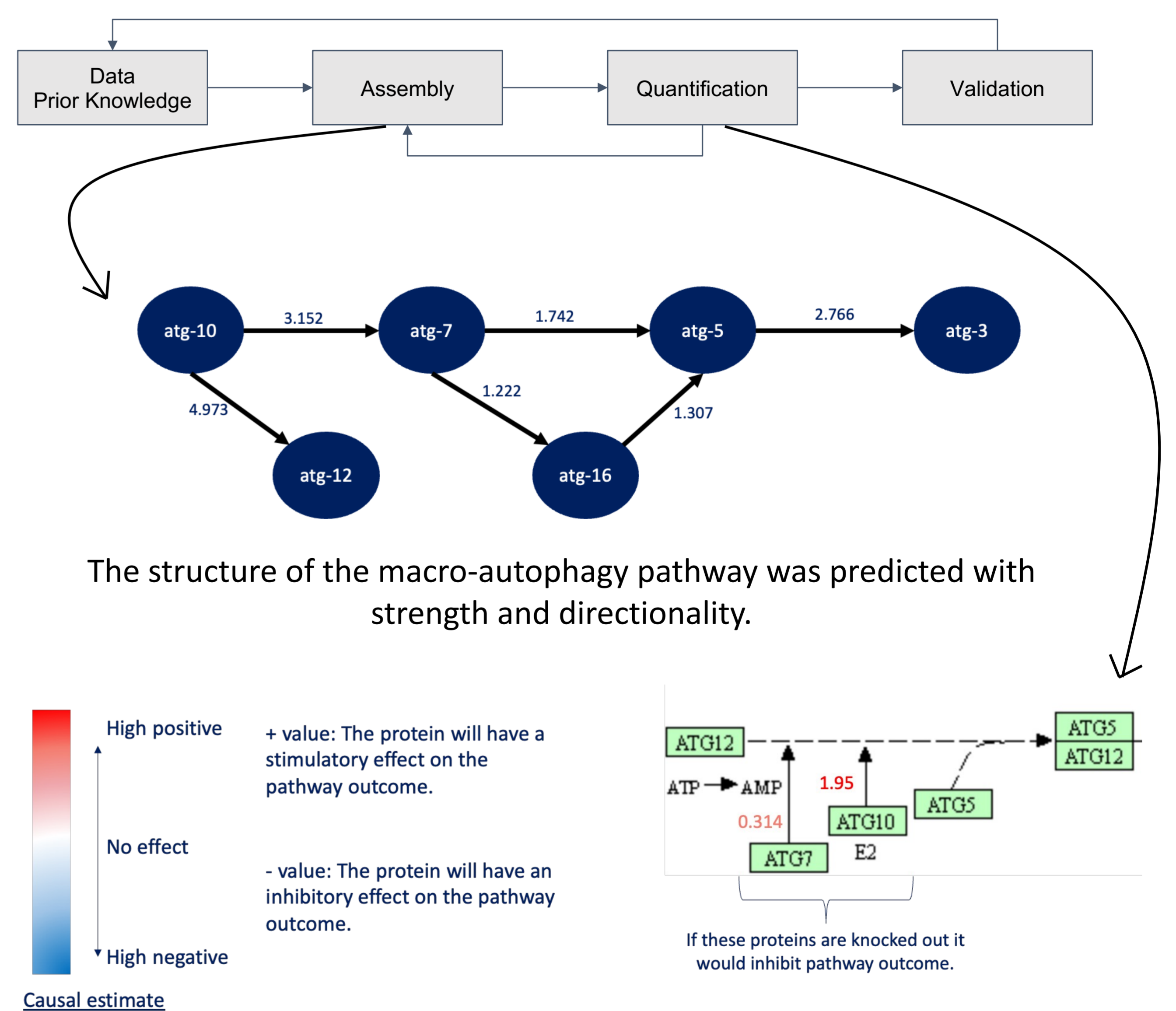
Antimicrobial resistant (AMR) infections are a global threat to public health. The use of the antibiotic, Cephalosporin, has been associated with the emergence of resistant organisms. Furthermore, the rise in resistance against Cephalosporin is of great concern to the WHO. **The aim was to determine the strength of the causal effect of Cephalosporin use on the incidence of resistant infections.**

We find that Cephalosporin use in agriculture has the strongest causal effect on the resistant infections of eight of the microbes (both figures on left). The Cephalosporin use in human healthcare has the strongest causal effect on the resistant infections of the remaining microbes, save for one, of which the strongest causal effect is re-infection (left top). This analysis shows evidence of a strong causal association between the antibiotic use in agriculture (veterinary treatment, prophylactic use, etc.) and antimicrobial resistant infections.

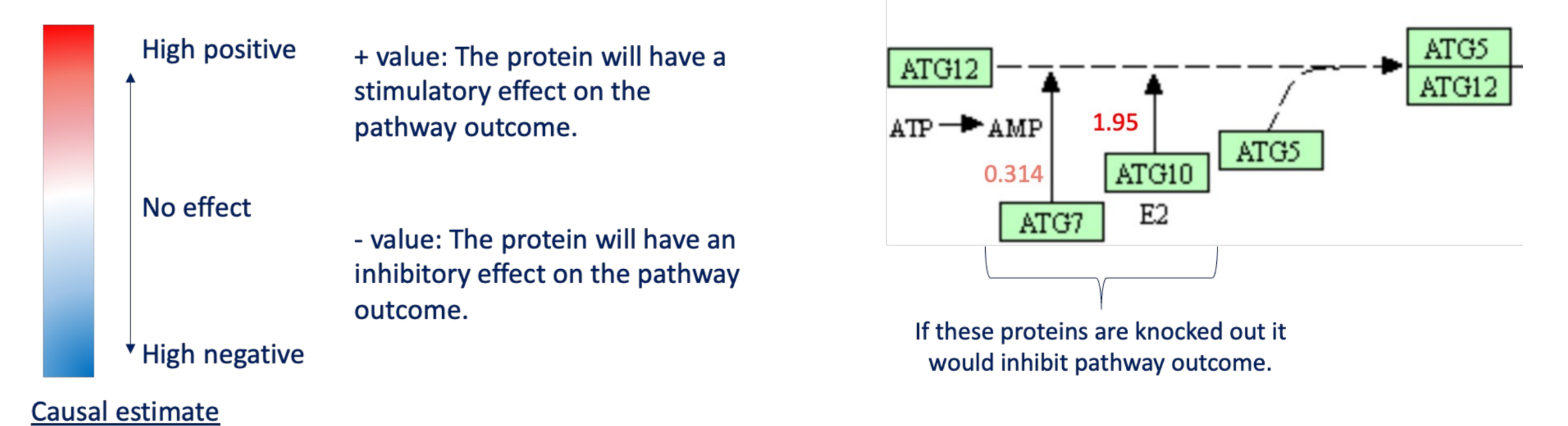Stellenbosch
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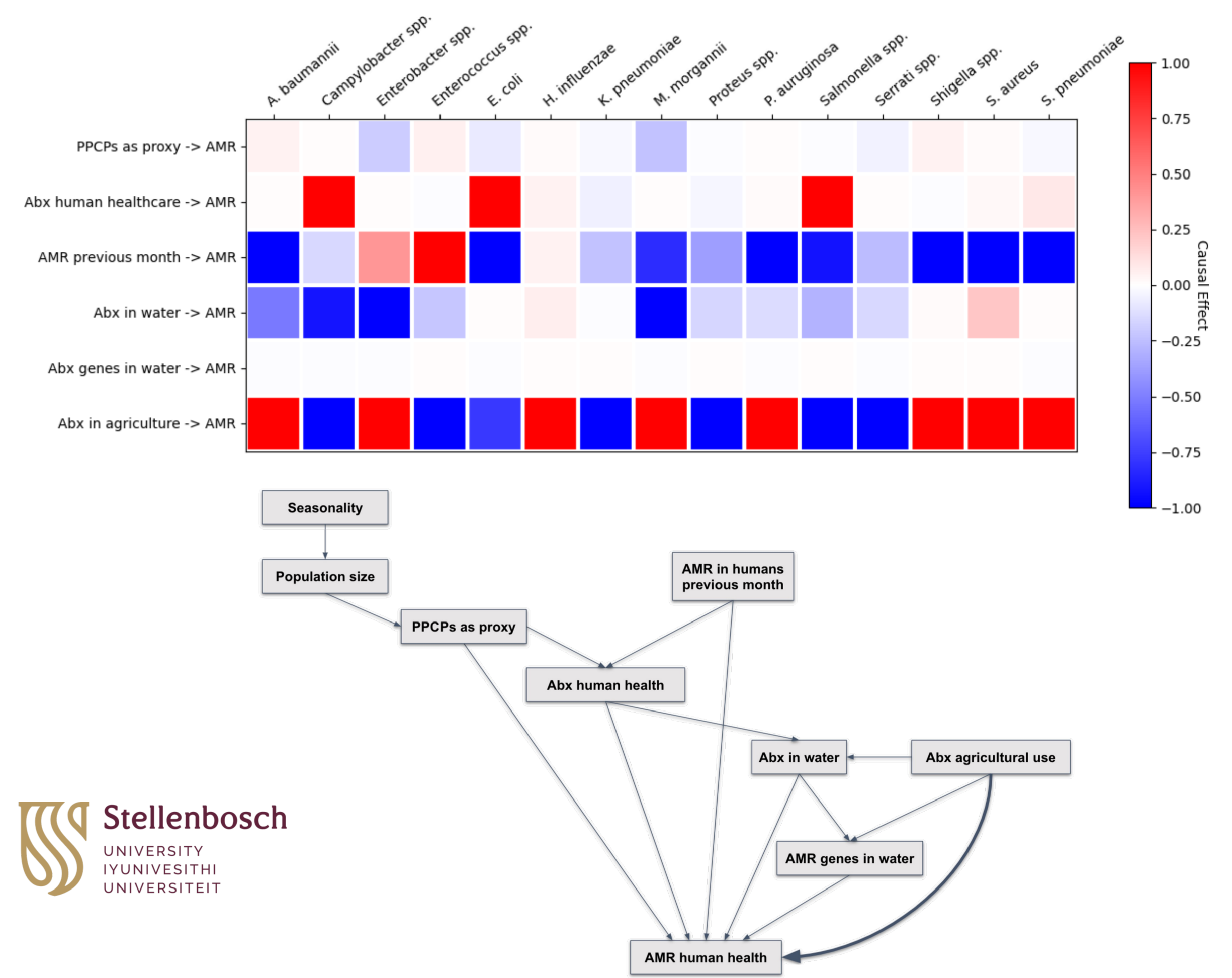
ALaSCA: Adaptable Large-Scale Causal Analysis

The ALaSCA platform enables us to infer with confidence hidden mechanisms across neuronal networks in the brain that are driving disease progression, which are otherwise impossible to see.
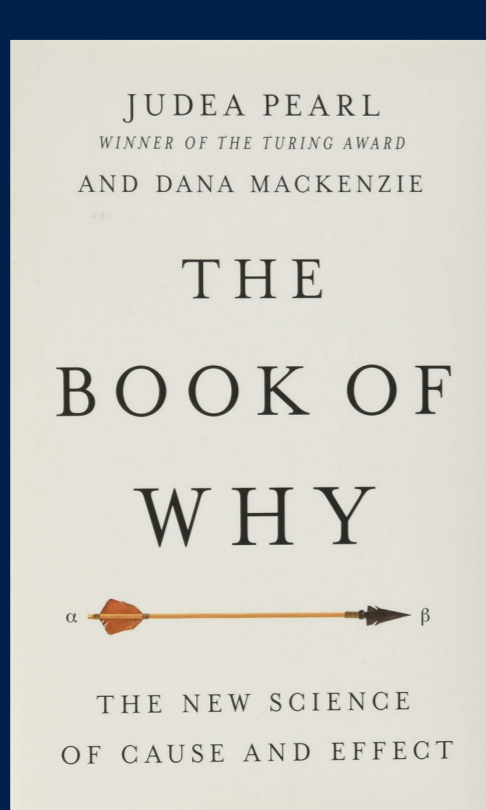

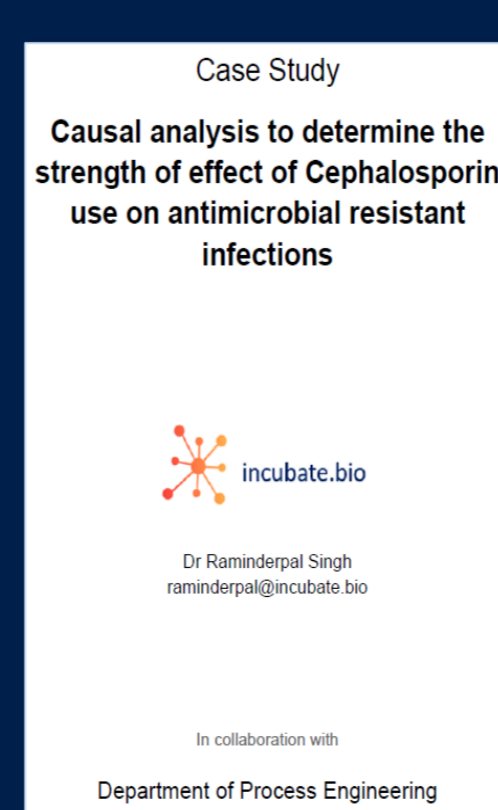The structure of the macro-autophagy pathway was predicted with strength and directionality.

+ value: The protein will have a stimulatory effect on the pathway outcome.

- value: The protein will have an inhibitory effect on the pathway outcome.

If these proteins are knocked out it would inhibit pathway outcome.

The pathway structure from KEGG was annotated with a causal strength between the known interactions.

Reference library:

JUDEA PEARL
WINNER OF THE TURING AWARD
AND DANA MACKENZIE
THE BOOK OF WHY
THE NEW SCIENCE OF CAUSE AND EFFECT
https://www.amazon.co.uk/Book-Why-Science-Cause-Effect/dp/0141982411/r

Case Study
Causal analysis to determine the strength of effect of Cephalosporin use on antimicrobial resistant infections
incubate.bio
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In collaboration with
Department of Process Engineering
Stellenbosch University
https://www.incubate.bio/causalanalysis

bioRxiv
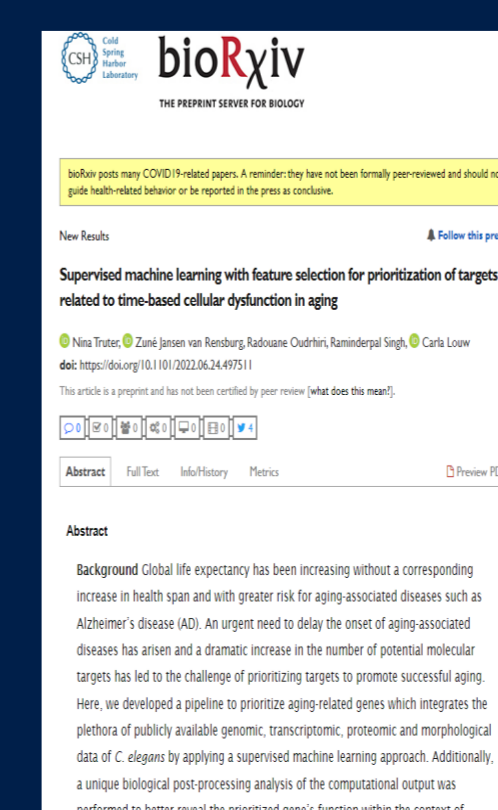https://www.biorxiv.org/content/10.1101/2022.06.24.497511v1

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