Race to the Bottom:
Competition and Quality in Science

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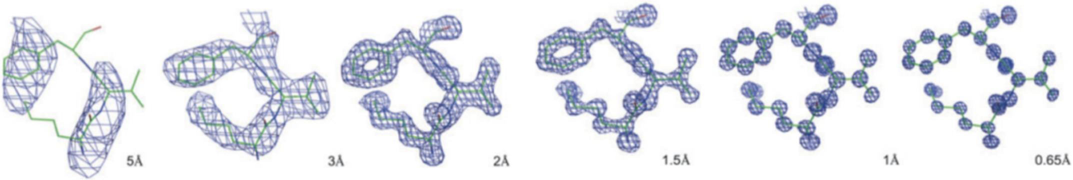
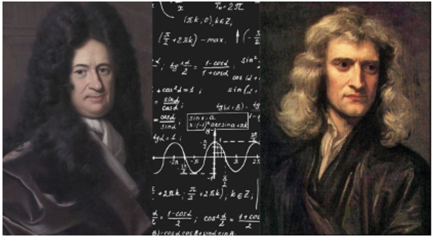
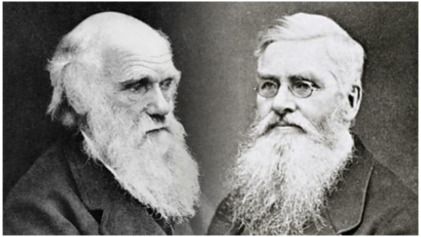


Incentives in Basic Science

- Basic scientific research advances our fundamental understanding of the world, but is not directly marketable
  - However, advances in basic research often serve as a key input in applied science (Nelson 1959, Arrow 1962)
- Therefore, credit is the currency of scientific careers
  - Credit comes from disclosing findings first
  - Leads to priority races and fierce competition to be first





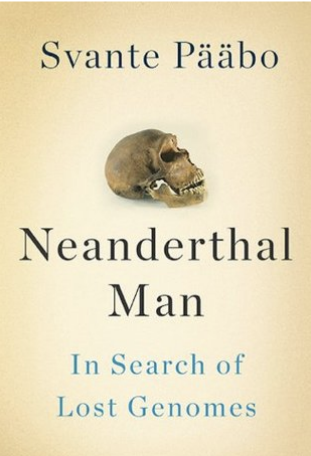
Competition in Science is a Double-Edged Sword

- Scientists compete to publish their findings first and establish priority. This competition can be good for science and society:
  - It can increase the pace of innovation
  - It induces scientists to disclose their work in order to get credit
- On the other hand, competition may have a dark side:
  - **Scientists may cut corners and reduce quality in their pursuit to publish first**

Example: Sequencing the Neanderthal Genome

"Hendrik's paper also illustrated a dilemma in science: doing all the analyses and experiments necessary to tell the complete story leaves you vulnerable to being beaten to the press...Even when you publish a better paper, you are seen as mopping up the details after someone who made the real breakthrough"

– Svante Pääbo, *Neanderthal Man: In Search of Lost Genomes*



This Project

Our goal is to answer two related questions:

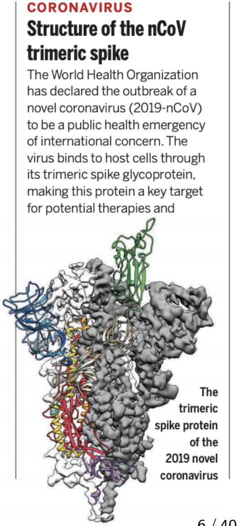
1. Does competition in science lead to lower quality research?
2. If yes, what are the implications from a welfare and policy perspective?

We do this by:

- Developing a model of competition and racing in science
- Testing the predictions of this model in the field of structural biology
- Exploring the welfare and policy implications of the priority premium in science

Why Structural Biology?

- Structural biology is the study of the three-dimensional structure of biological macromolecules (proteins)
- Important field of science!
- Uniquely detailed project-level data in the Protein Data Bank (PDB)
  - Objective measures of project quality
  - Project timelines
  - Links to publications
  - Other project details



CORONAVIRUS

Structure of the nCoV trimeric spike

The World Health Organization has declared the outbreak of a novel coronavirus (2019-nCoV) to be a public health emergency of international concern. The virus binds to host cells through its trimeric spike glycoprotein, making this protein a key target for potential therapies and

The trimeric spike protein of the 2019 novel coronavirus

Preview of Results

- Model predicts:
  - Most (ex-ante) important projects are more competitive, rushed, and lower quality
- Empirical results:
  - High-potential projects are more competitive (multiple researchers working simultaneously)
  - High-potential projects are completed faster and are lower quality
  - Follow-on work ameliorates but does not eliminate the negative relationship between potential and quality
  - Quality magnitudes large enough to impact usefulness of projects for drug development
- Welfare implications:
  - Negative relationship between potential and quality is inconsistent with idealized first best
  - Reducing competition by reducing the priority premium does not necessarily improve welfare

Contributions to the Literature

- Sociology and economics of science
  - Merton (1957); Merton (1961); Hagstrom (1974); Dasgupta and Maskin (1987); Dasgupta and David (1994); Stephan (1996)
- Strategic behavior in patent and R&D races
  - Loury (1979); Lee and Wilde (1980); Dasgupta and Stiglitz (1980); Reinganum (1982); Fudenberg et al. (1983); Harris and Vickers (1985); Harris and Vickers (1987); Grossman and Shapiro (1987); Hopenhayn and Squintani (2016); Bobtcheff, Bolte, and Mariotti (2017)
- Scientific literature / concern about the impact of competition on science
  - Brown and Ramaswamy (2007); Fang and Casadevall (2005); Alberts et al. (2014)
- **Our (primary) contribution:** bring empirics to a largely theoretical literature

Agenda

1. Introduction
2. A Model of Competition and Quality in Science
3. Structural Biology and the PDB
4. Empirical Results
5. Welfare Considerations

Summary of the Model

- Projects vary in their ex-ante potential (P)
- Scientists decide how long to work on a project (m), trading off improving the quality of their work (increasing $Q(m)$) against the threat of being scooped
- **Key ingredient:** entry into projects is endogenous → there is more likely to be competition in high potential projects
  - Operationalize this by letting scientists choose costly I, probability of entry is $g(I)$
- **Key result:** high potential projects will be executed with lower quality

more detail

Key Propositions

- **Proposition 1.** $\frac{dI^*}{dP} > 0$ and $\frac{dg(I^*)}{dP} > 0$
  "high-potential projects generate more investment → are more competitive"
- **Proposition 2.** $\frac{dm^*}{dg} < 0$ and $\frac{dQ(m^*)}{dg} < 0$
  "competitive projects completed faster → are lower quality"
- **Proposition 3.** $\frac{dm^*}{dP} < 0$ and $\frac{dQ(m^*)}{dP} < 0$
  key model prediction: "high-potential projects completed faster → are lower quality"
  (comes directly from the chain rule)

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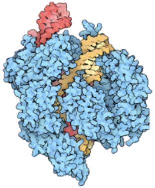
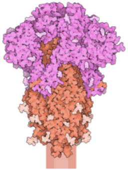
What is Structural Biology?

- The study of the molecular structure of macromolecules, especially proteins

HIV reverse transcriptase



CRISPR Cas9 protein



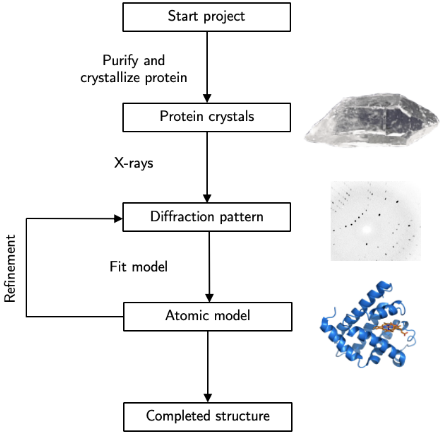
SARS-CoV-2 spike protein

- An important field of science, with applications in genetic diseases and drug development

How do Scientists Solve Protein Structures?

About 90% of proteins are solved using X-ray crystallography. This involves three steps:

1. First, proteins are purified and crystallized
2. Next, the crystals are placed in an x-ray beam, which produces a diffraction pattern
3. Finally, the diffraction data is used to infer the structure. Biologists will "refine" their structure by comparing their model to the diffraction data, trying to minimize any discrepancies. Process is more "art than science" and luck plays a role



Start project

Purify and crystallize protein

Protein crystals

X-rays

Diffraction pattern

Fit model

Atomic model

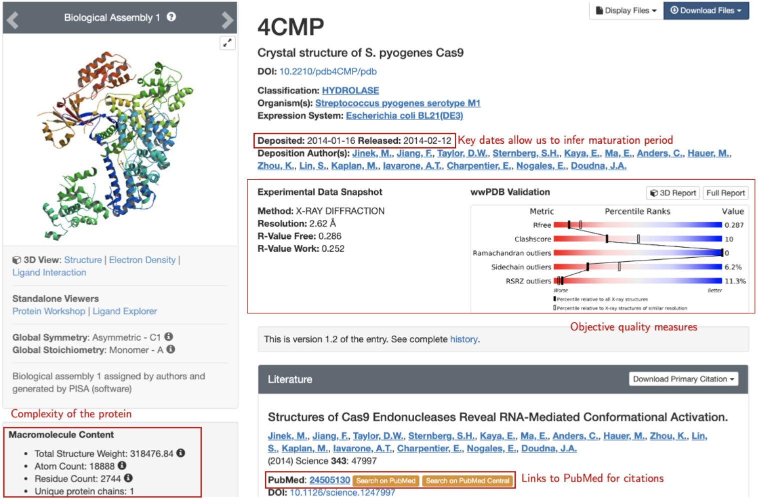
Refinement

Completed structure

What is the Protein Data Bank?

- Established in 1971, the Protein Data Bank (PDB) is a database for 3D structural data of large biological molecules (proteins and nucleic acids)
- Most scientific journals and some funding agencies require scientists to submit their structure data to the PDB
- Today, the PDB contains 100,000+ structures, and is growing ~10% annually

Example PDB Entry - CRISPR-Associated Protein 9 (Cas9)



3D View: Structure | Electron Density | Ligand Interaction

Standalone Viewers
Protein Workshop | Ligand Explorer

Global Symmetry: Asymmetric - C1
Global Stoichiometry: Monomer - A

Biological assembly 1 assigned by authors and generated by PISA (software)

Complexity of the protein

Macromolecule Content

- Total Structure Weight: 318476.84
- Atom Count: 18888
- Residue Count: 2744
- Unique protein chains: 1

4CMP

Crystal structure of S. pyogenes Cas9

DOI: 10.2210/pdb4CMP/pdb

Classification: HYDROLASE
Organism(s): Streptococcus pyogenes serotype M1
Expression System: Escherichia coli BL21(DE3)

Deposited: 2014-01-16 **Released:** 2014-02-12 Key dates allow us to infer maturation period
Deposition Author(s): Jinek, M., Jiang, F., Taylor, D.W., Sternberg, S.H., Kaya, E., Ma, E., Anders, C., Hauer, M., Zhou, K., Lin, S., Kaplan, M., Iavarone, A.T., Charpentier, E., Nogales, E., Doudna, J.A.

Experimental Data Snapshot

Method: X-RAY DIFFRACTION
Resolution: 2.62 Å
R-Value Free: 0.286
R-Value Work: 0.252

wwPDB Validation

Metric	Value
Rfree	0.287
Clashscore	10
Ramachandran outliers	0
Sidechain outliers	6.2%
RSRZ outliers	11.3%

Percentile Ranks
Worse
Better
▮ Percentile relative to all X-ray structures
▯ Percentile relative to X-ray structures of similar resolution

Objective quality measures

This is version 1.2 of the entry. See complete history.

Literature

Structures of Cas9 Endonucleases Reveal RNA-Mediated Conformational Activation.

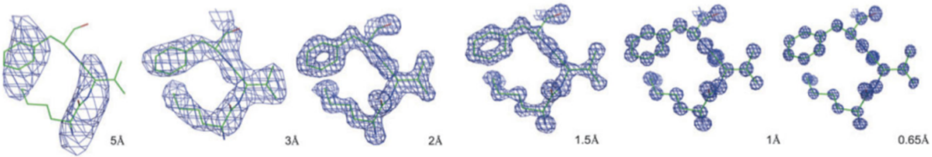
Jinek, M., Jiang, F., Taylor, D.W., Sternberg, S.H., Kaya, E., Ma, E., Anders, C., Hauer, M., Zhou, K., Lin, S., Kaplan, M., Iavarone, A.T., Charpentier, E., Nogales, E., Doudna, J.A.
(2014) Science **343**: 47997

PubMed: 24505130 Links to PubMed for citations
DOI: 10.1126/science.1247997

Mapping to the Model: Quality

A unique feature of structural biology is the objective, ex-ante measures of project quality:

1. Refinement resolution: similar to resolution of a photograph

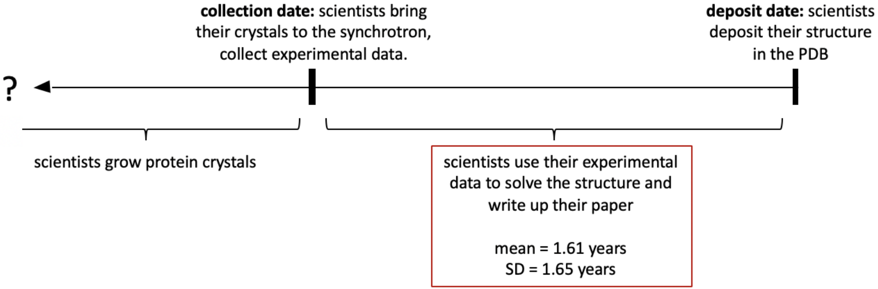


2. R-free: model fit, estimated on a holdout sample of the experimental data
3. Outliers: errors in the model based on chemical properties

Combine these outcomes into a standardized quality index (higher is better)

Mapping to the Model: Maturation

- We can actually observe time spent on project (maturation period):

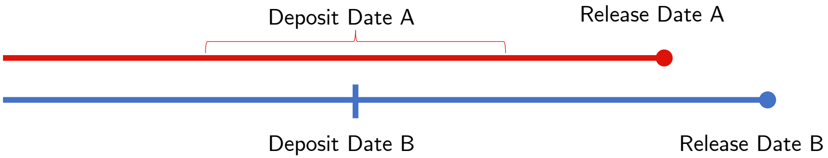

collection date: scientists bring their crystals to the synchrotron, collect experimental data.
deposit date: scientists deposit their structure in the PDB
?
scientists grow protein crystals
scientists use their experimental data to solve the structure and write up their paper
mean = 1.61 years
SD = 1.65 years

Mapping to the Model: Competition

- Use a measure developed in Hill and Stein (2022) of priority races

Rule: Winning project is released first and scooped project is deposited before winning project is released

Scenario 1: Project A scoops Project B

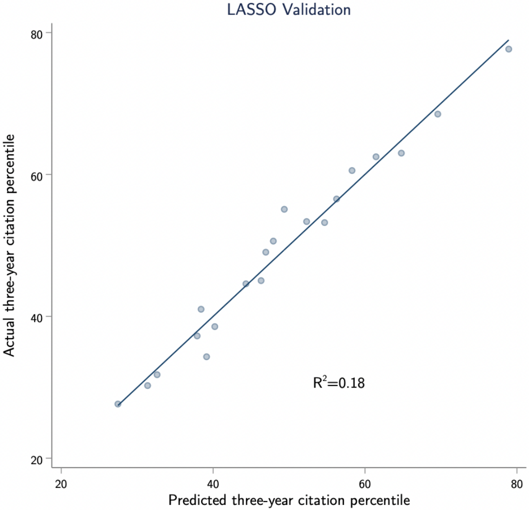


- Note that we are measuring ex-post realized competition, a noisy proxy for ex-ante competition

Mapping to the Model: Measuring and Predicting Potential in the PDB

- One way to measure potential: use ex-post citations (over some time window)
    - Problems: ex-post citations different than ex-ante potential, conflates potential and quality
- Alternatively: predict citations using only ex-ante characteristics of the structure
    - To avoid over-fitting, we use LASSO to select the model

LASSO details



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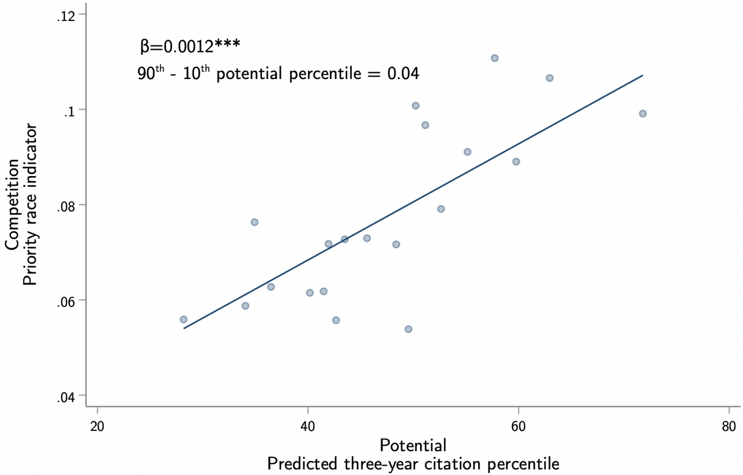
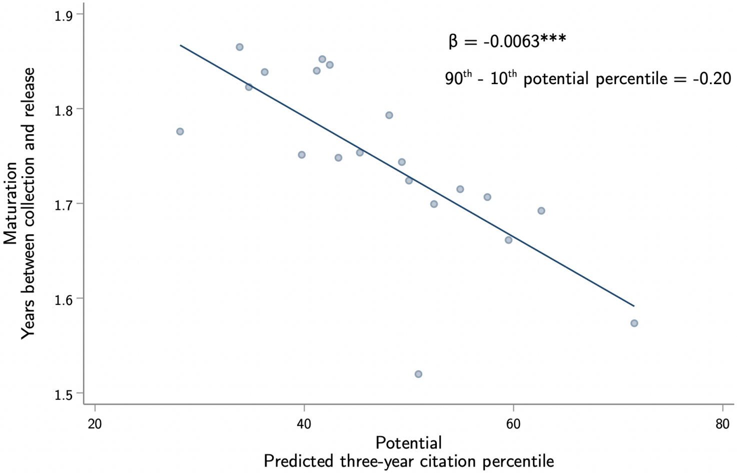
Proposition 1: High-Potential Projects are More Competitive



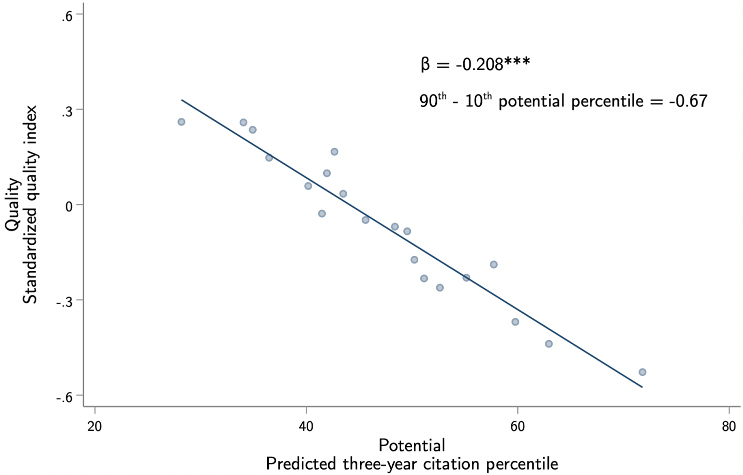
$$PriorityRace_{it} = \alpha + \beta PredictedCites_{it} + \tau_t + \varepsilon_{it}$$

Proposition 3: High-Potential Projects are Completed Faster...



$$Maturation_{it} = \alpha + \beta PredictedCites_{it} + \tau_t + \varepsilon_{it}$$

...So High-Potential Projects are Lower Quality



$$Quality_{it} = \alpha + \beta PredictedCites_{it} + \tau_t + \varepsilon_{it}$$

What About Project Complexity?

- If high P projects are also more complicated, this could drive our observed results
- Lower quality is driven by the difficulty / complexity of the project, not rushing

Strategy #1: Control for Complexity

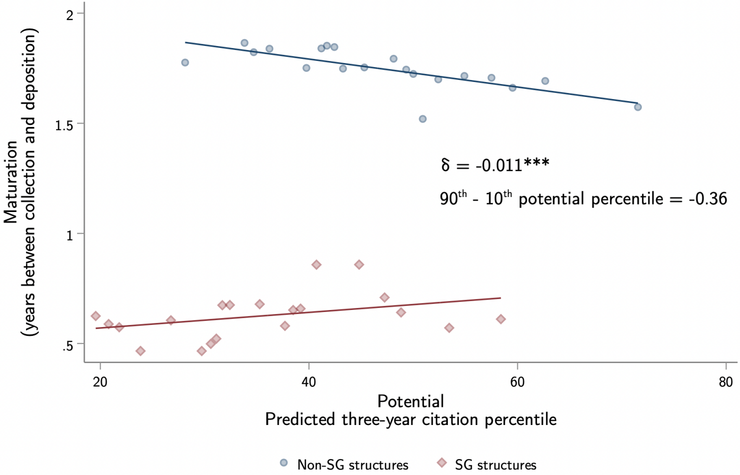
- We are able to observe measures of molecule complexity in our data:
    - Molecular weight
    - Residue count
    - Atom site count
- Include these (and their squares), coefficient on potential remains stable:

Dependent variable:	Std. resolution	Std. R-free	Std. Rama. outlieres	Std. quality index
Panel A. Without complexity controls				
Potential	-0.020***	-0.020***	-0.011***	-0.021***
	(0.001)	(0.001)	(0.001)	(0.001)
R-squared	0.049	0.082	0.064	0.068
Panel B. With complexity controls				
Potential	-0.019***	-0.018***	-0.010***	-0.019***
	(0.001)	(0.001)	(0.001)	(0.001)
R-squared	0.273	0.160	0.101	0.210
Observations	16,215	16,215	16,215	16,215

Strategy #2: Structural Genomics Consortia

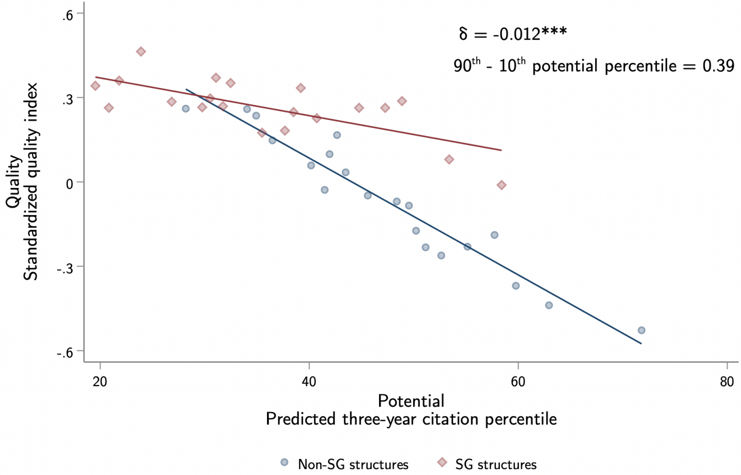
- Structural genomics consortia are publicly funded groups focused on achieving comprehensive coverage of the protein folding space
- Less focused on publishing and priority → competition is less important
- About 20% of structures in our sample were deposited by a structural genomics group

SG versus Non-SG Structures: Maturation



$$Maturation_{it} = \alpha + \beta PredictedCites_{it} + \gamma NonSG_{it} + \delta(PredictedCites_{it} * NonSG_{it}) + \tau_t + \varepsilon_{it}$$

SG versus Non-SG Structures: Quality



$$Quality_{it} = \alpha + \beta PredictedCites_{it} + \gamma NonSG_{it} + \delta(PredictedCites_{it} * NonSG_{it}) + \tau_t + \varepsilon_{it}$$

Strategy #3: A Survey Experiment

Finally, as a direct test of our model, we conducted a survey experiment of 341 structural biologists (PDB authors). We asked the following questions:

Q1: Consider the following scenario: You are working on a project and you have generated some preliminary results. Based on the research question and your results, you expect that it will publish in a high impact journal (such as Science, Nature, or the top journal in your field OR medium impact field journal. How likely is it that another research team is working on a very similar project?

A: slider bar 0 to 100%

Strategy #3: A Survey Experiment

Finally, as a direct test of our model, we conducted a survey experiment of 341 structural biologists (PDB authors). We asked the following questions:

Q2: Consider a different scenario: Suppose you have generated some preliminary results for a project. You are fairly confident that nobody else is working on a very similar project (less than a 10% chance). OR You are fairly confident that somebody else is working on a very similar project (greater than a 90% chance). Answer the following questions with this scenario in mind:

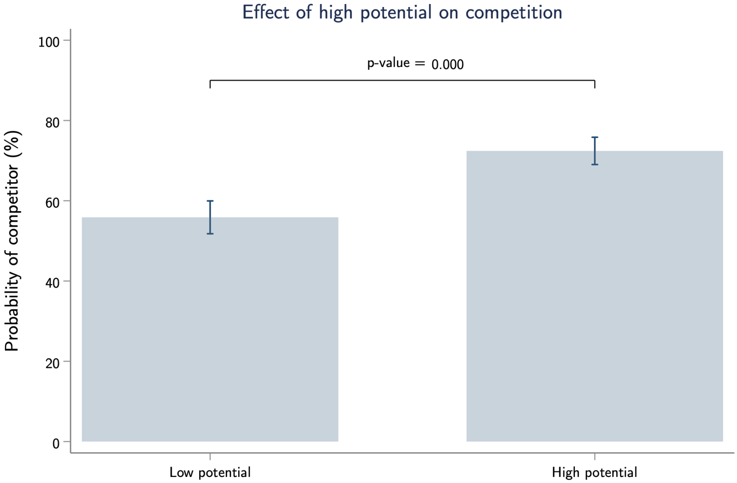
(a) How long would it take for you to complete the project and submit the paper to a journal?

A: slider bar 0 to 24 months

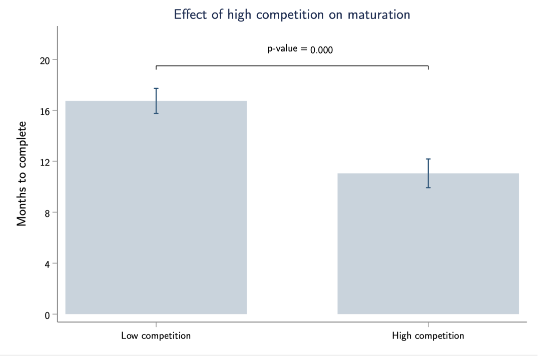
(b) Prior to publication, would re-run or replicate the key experiment?

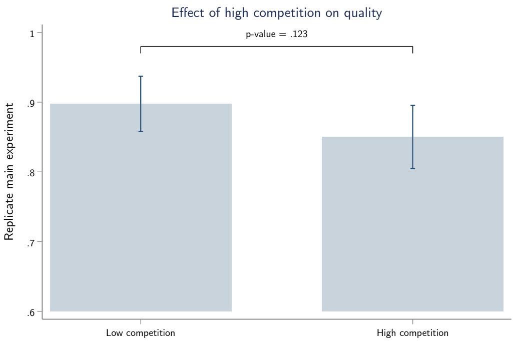
A: yes / maybe / no / NA

Survey Experiment Results: Potential and Competition



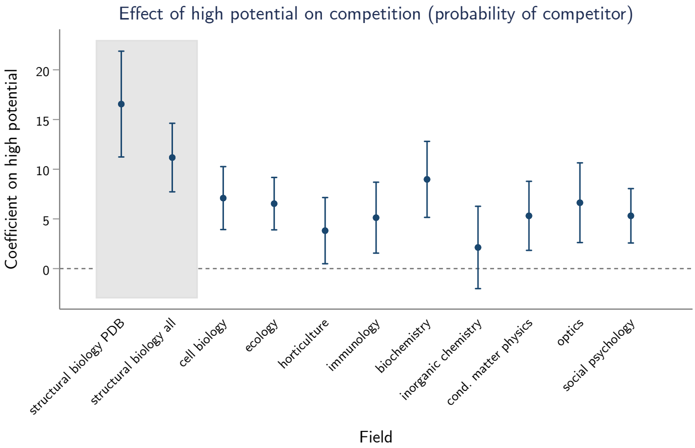
Survey Experiment Results: Competition and Maturation, Quality



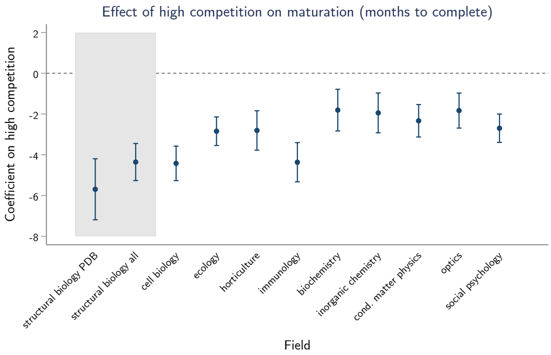


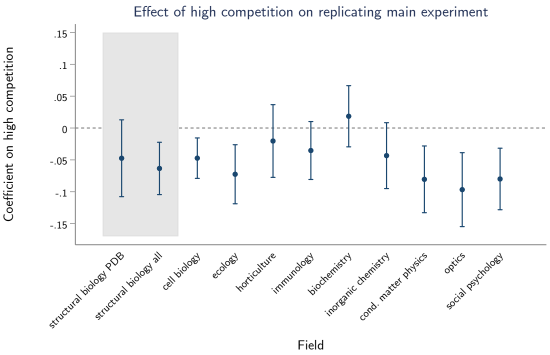
External Validity: Potential and Competition

In addition to the PDB scientists, we survey researchers from 9 other fields of science (~1000 researchers per field)



External Validity: Competition and Maturation, Quality





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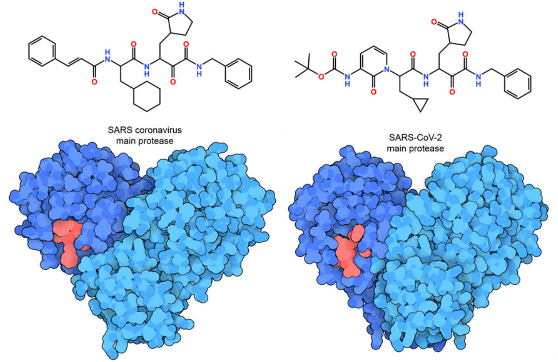
Does Quality Matter for Structure's Usefulness?

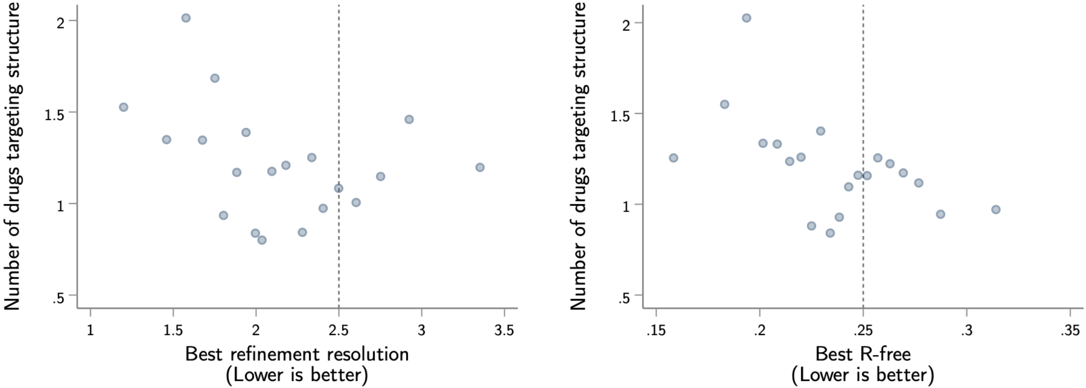
- Short answer: depends on the structure's use case
- For structure-based drug design, quality is important (Anderson 2003):
  - Resolution should be 2.5 Å or better (35% of non-SG structures don't meet this cutoff)
  - R-free should be 0.25 or better (45% of non-SG structures don't meet this cutoff)
- We will demonstrate that these thresholds appear to matter

Linking Target Protein Structures and Drugs

- A drug target is the protein that the drug binds to, in order to have its effect
- Use data from DrugBank to link drugs to their targets, and targets to their PDB ID(s)



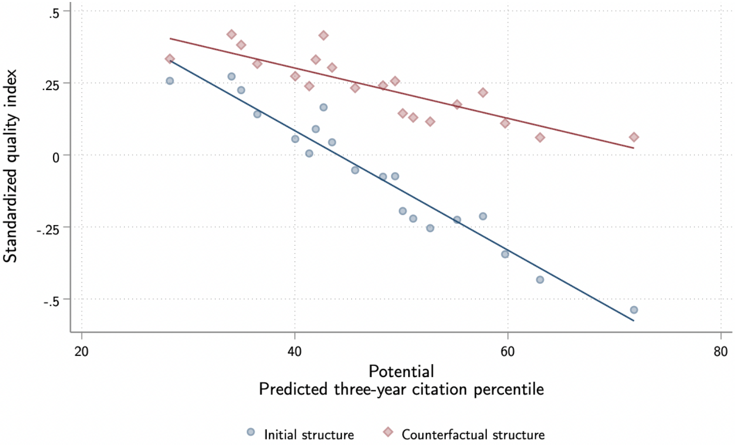
More Drug Development when Structures Exceed Quality Thresholds



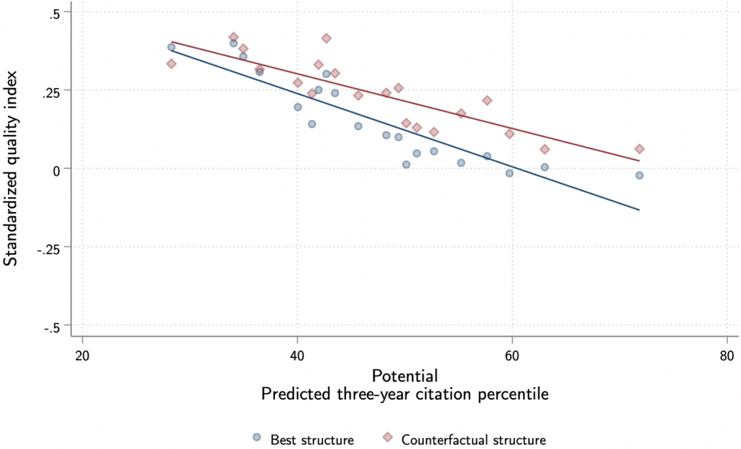
Will Follow-on Work Fix the Problem?

- In a standard quality ladder model, researchers could costlessly build on rushed, lower quality structures
- In our setting, making a marginal quality improvement requires re-sinking all the same costs (typically over a year of time and $100K)
    - Only worth fixing particularly bad / important structures
    - More efficient to do it well the first time
- Two potential sources of welfare loss:
    - Missing quality
    - Costs of re-solving structures to gain residual quality

Using SG Researchers as a Counterfactual Shows Missing Quality Initially



But Repeated Deposits Recover the Majority



Suggests the main welfare loss is the cost of repeated deposits (est. $1.5 to 8.8 billion)

Alternative Policy: Ending Races Early

- If races ended when the first team successfully entered the project, there would be no maturation distortion (no competition → no need to rush)
- In fact, in the 1970s researchers used to publish their protein crystals, which signaled that other teams should "back off"
  - "There was a tradition that if someone had produced crystals of something, they were usually left alone to solve the problem" (Ramakrishnan, 2018)
- This norm collapsed once the field became too large, but still interesting to note that the field "organically" solved this problem at one point

Conclusions and Future Work

- Calibration of the optimal priority rewards is beyond the scope of this project
- Competition likely affects science in ways we have not considered here:
  - May reduce collaboration and free sharing of ideas
  - Impacts who enters certain fields and who is deterred
- Brings up questions of alternative models of science:
  - More collaborative models: Protein Structure Initiative, Human Genome Project

Choosing Maturation

After entering the project, researcher i chooses maturation:

$$\max_{m_i} \underbrace{e^{-rm_i} PQ(m_i)}_{\text{PDV of project}} \left[\underbrace{\pi(m_i, m_j)\overline{\theta} + (1 - \pi(m_i, m_j))\, \underline{\theta}}_{\text{expected credit share}} \right]$$

where

- r is the discount rate
- $\pi(m_i, m_j)$ is probability i publishes first
- $\overline{\theta}$, $\underline{\theta}$ are first, second place credit shares

First-order condition:

$$\frac{Q'(m^*)}{Q(m^*)} = r + \frac{g(I^*)(\overline{\theta} - \underline{\theta})}{\Delta \left(2\overline{\theta} - g(I^*)(\overline{\theta} - \underline{\theta})\right)}$$

back

Choosing Investment

When deciding how much to invest in entry, researcher i solves:

$$\max_{I_i} \quad \underbrace{g(I_i)}_{\text{Pr(enter)}} \; \underbrace{e^{-rm_i} PQ(m_i^*)}_{\text{PDV of project}} \left[\underbrace{\overline{\theta} - \frac{1}{2} g(I_j)(\overline{\theta} - \underline{\theta})}_{\text{expected credit share}} \right] - \underbrace{I_i}_{\text{cost}}$$

where

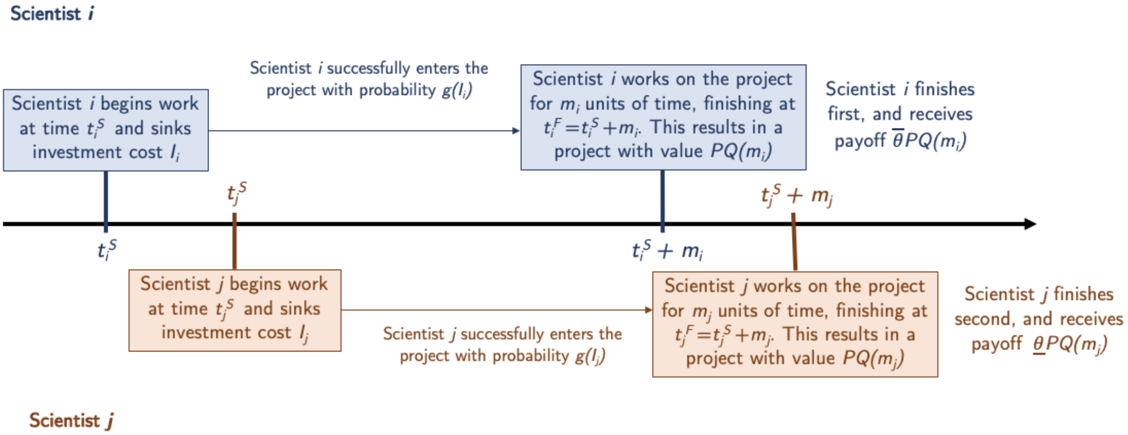
- r is the discount rate
- $\pi(m_i, m_j)$ is probability i publishes first
- $\overline{\theta}$, $\underline{\theta}$ are first, second place credit shares

First-order condition:

$$g'(I^*) = \frac{1}{e^{-rm^*} PQ(m^*) \left[\overline{\theta} - \frac{1}{2} g(I_j)(\overline{\theta} - \underline{\theta}) \right]}$$

back

Timing



Scientist *i*

Scientist i begins work at time t_i^S and sinks investment cost I_i

Scientist i successfully enters the project with probability $g(I_i)$

Scientist i works on the project for m_i units of time, finishing at $t_i^F = t_i^S + m_i$. This results in a project with value $PQ(m_i)$

Scientist i finishes first, and receives payoff $\overline{\theta} PQ(m_i)$

t_j^S

$t_j^S + m_j$

t_i^S

$t_i^S + m_i$

Scientist j begins work at time t_j^S and sinks investment cost I_j

Scientist j successfully enters the project with probability $g(I_j)$

Scientist j works on the project for m_j units of time, finishing at $t_j^F = t_j^S + m_j$. This results in a project with value $PQ(m_j)$

Scientist j finishes second, and receives payoff $\underline{\theta} PQ(m_j)$

Scientist *j*

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Information

What does scientist i know about scientist j?

- Knows that j entered with probability $g(I_j)$ (known in equilibrium)
- Believes that j's start time is uniformly distributed around her own start time:

$$t_j^S \sim U[t_i^S - \Delta, t_i^S + \Delta]$$

- Implication: the value of i's start time is not informative about whether she is ahead or behind

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Sample Construction

We start with the universe of PDB x-ray structures from 1971 to 2018 (128,876 structures, 71,685 papers)

- Restrict to single structure-paper pairs (35,538 obs)
- Restrict to new structure discoveries (22,127 obs)
- Restrict to non-missing outcomes (20,434 obs)

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LASSO Details

- LASSO predictors include:
  - Macromolecule type (protein, DNA, RNA)
  - Classification (membrane protein, oxygen transport)
  - Taxonomy (homo sapiens, e. coli, influenza virus)
  - Gene linkage (gag-pol gene, CA2 gene)
  - Prior citations to protein (papers prior to structure discovery, from UniProt)
  - Publication year

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