

CUP 8

“Could do better”

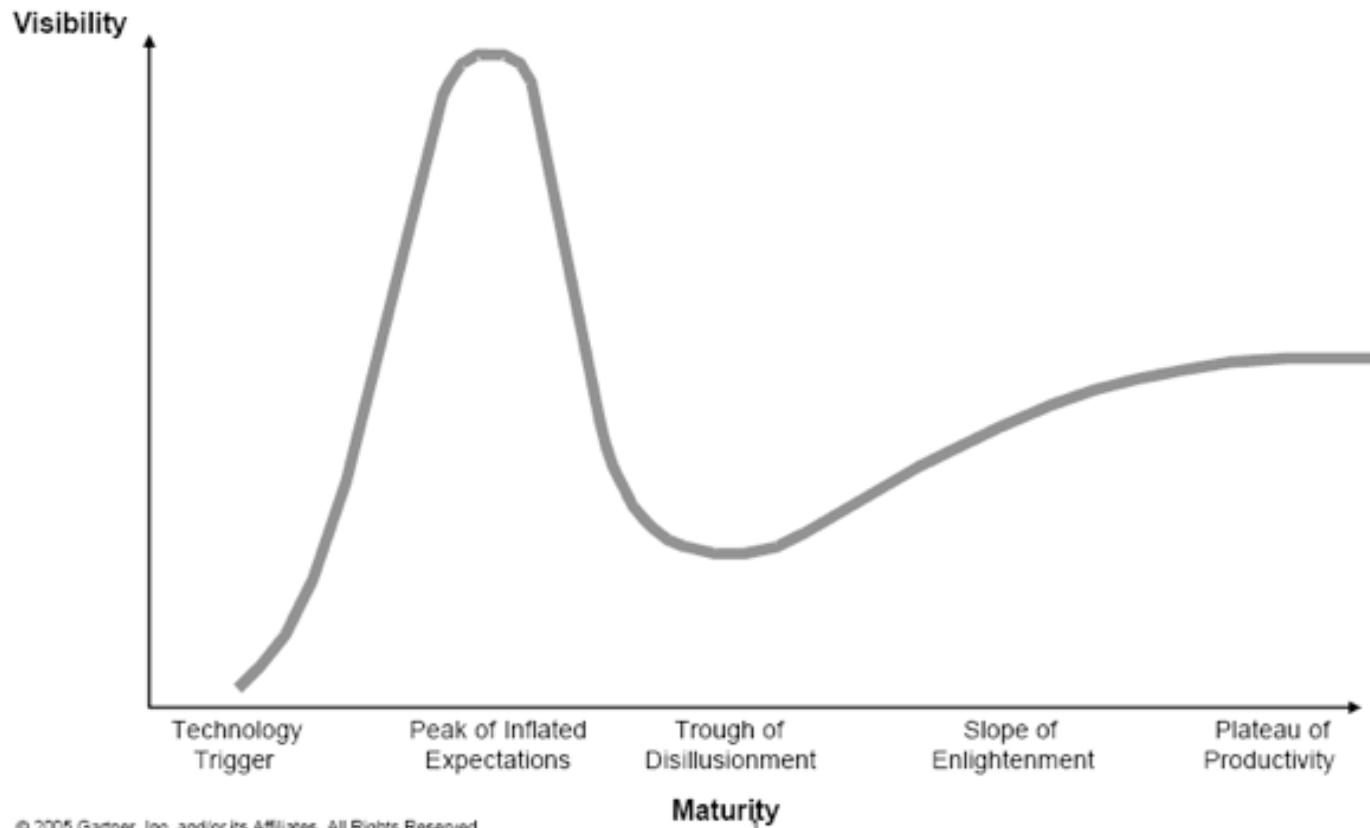
-Brian T. Hall, 1972-79

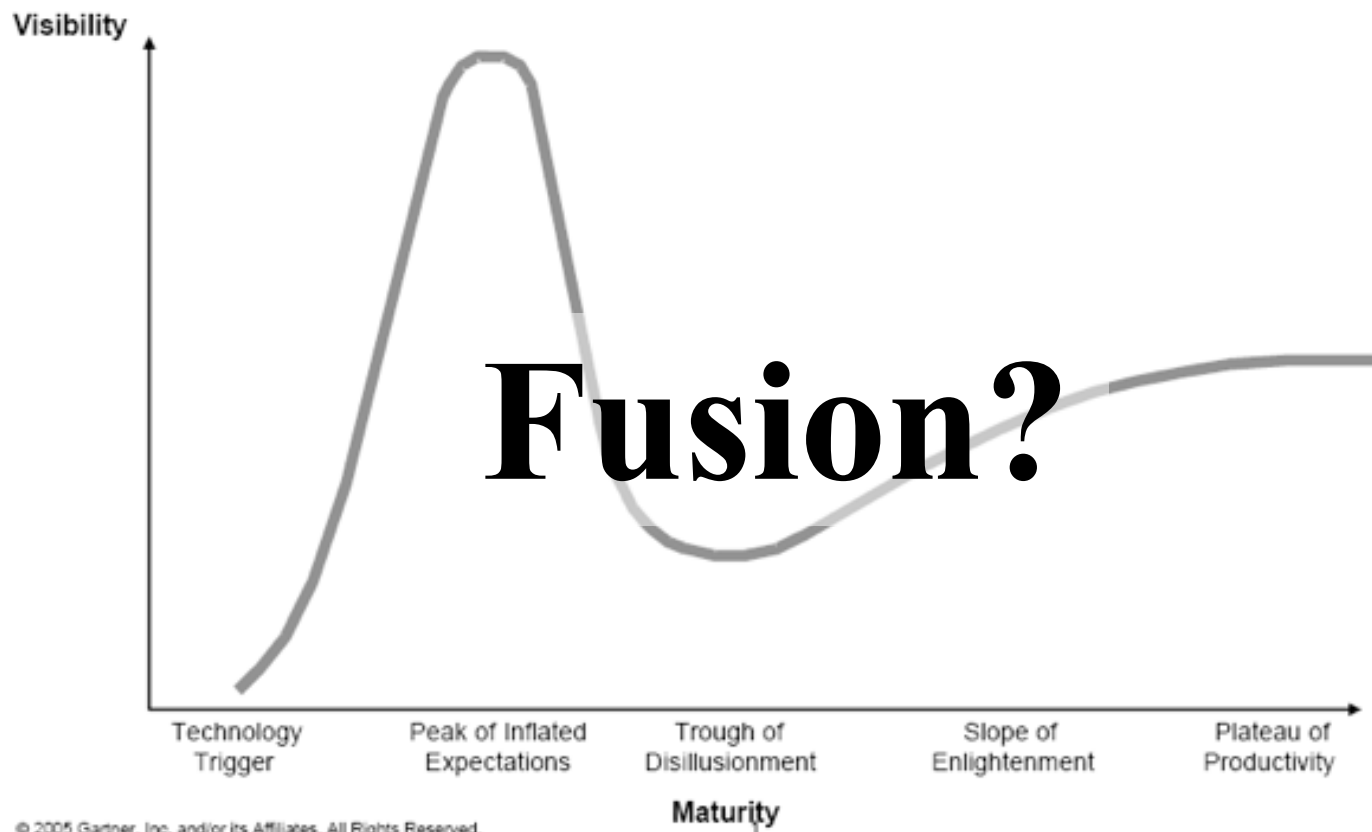
“The best place to get news is from the financial papers – Wall Street Journal, Financial Review, etc. The reason being that people who spend money need real information”

attrib. Noam Chomsky



The Gartner “Hype” Curve





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What's the problem?

Physical Properties

Physics

Bioactive conformations	ok
Transfer energies between phases	fair
pKa, tautomeric preference	poor
Solubility	v. poor
Crystal forms	v. v. poor
Binding affinity	hopeless

Who's to blame?



HARCOURT FENTON MUDD

DON'T HATE THE PLAYER, HATE THE GAME.

What's to Blame?


- Drug design is hard
 - Provenance and Paucity of **public** data
 - Pharma paranoia over **private** data
 - NIH/NSF disaster
 - Bayh-Dole act
-
- Too **little** prospective science
 - Too **much** prediction, too **little** understanding
 - The Perils of Parameters

Inoperable



Up to us

Successful (Mature) Fields

- Understanding
 - Basic principles
 - Few parameters
 - Strong error estimation
 - Examples
 - Mechanical Engineering
 - Oil Exploration
 - Stamp collecting
 - Examples of all known forms
 - Many parameters
 - Weak error estimates
 - Examples
 - Chip design
 - Natural Language Processing
 - Credit card fraud
- 

Perils of Parameterization

- Hidden Parameters
- Excess Parameters
- Implicit Parameters

Implicit Parameterization: OPLS

The N-methylamine Problem

	Molecule	Expt. (kcal)	PB (kcal)
NH_3	Ammonia	-4.29	-6.2
NH_2CH_3	Methylamine	-4.56	-4.4
NHC_2H_6	N-dimethylamine	-4.29	-3.4
NC_3H_9	N,N-trimethylamine	-3.23	-2.2

The Landscape Model

“... more than one set of non-bonded parameters may yield calculated densities and heats of vaporization in close agreement with experiment.

...Only parameter sets for ammonia were further considered if they also yielded ... a qualitatively correct free energy of hydration relative to methylamine..”

Thomas Kuhn

“No crisis is, however, so hard to suppress as one that derives from a quantitative anomaly that has resisted all the usual efforts at reconciliation”

“The function of measurement in physical science”, *Isis*, No.2, 1961

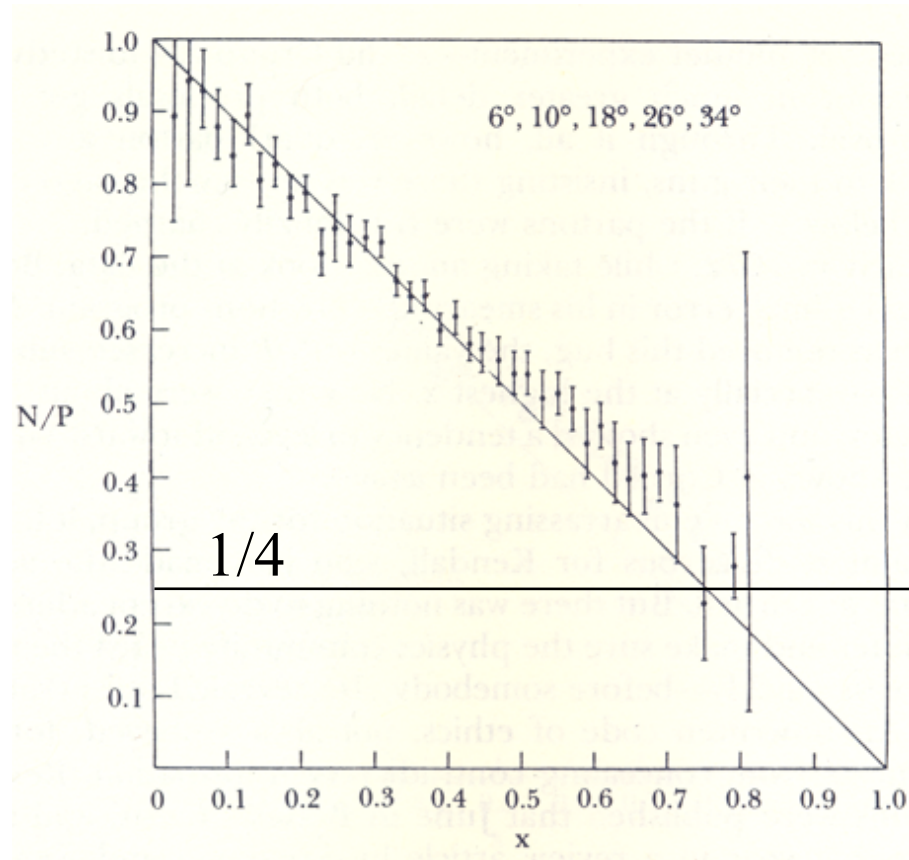
Escaping the Parameter Trap: Prospective Science



Galileo Galilei
1564 - 1642

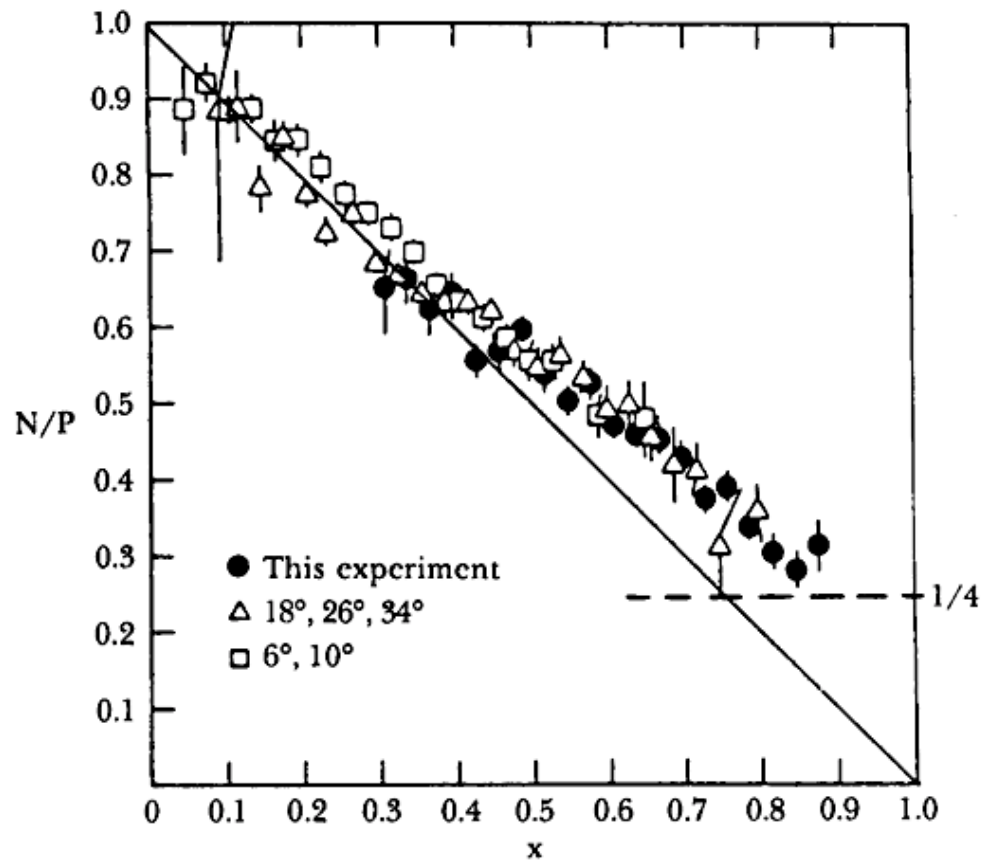
1. Resolution
2. Demonstration
3. Experiment

My Favorite Graph



Quarks Exist
Quarks Don't

Six Months Later



Deeply Missed



“It doesn't matter how beautiful your theory is, it doesn't matter how smart you are. If it doesn't agree with experiment, it's wrong.”
- Richard Feynman, 1918-1988