Medicinal chemists are people too

And that's a problem

Epizyme

Epizyme

"Why do people always say it was natural for man to assume that the Sun went round the Earth rather than that the Earth was rotating around the sun?"

Epizyme

"Because it just looks as though the Sun is going around the Earth."

Epizyme

"Well, what would it have looked like if it had looked as though the Earth was rotating around the sun?"

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An answer I favor…

David Foster Wallace
2005 Kenyon College Commencement

"Here is just one example of the total wrongness of something I tend to be automatically sure of: everything in my own immediate experience supports my deep belief that I am the absolute center of the universe; the realest, most vivid and important person in existence…."

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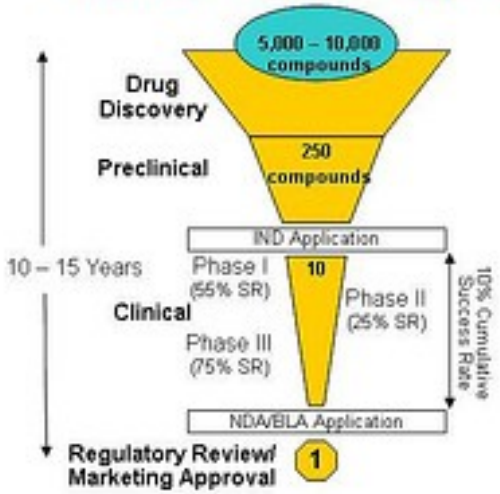
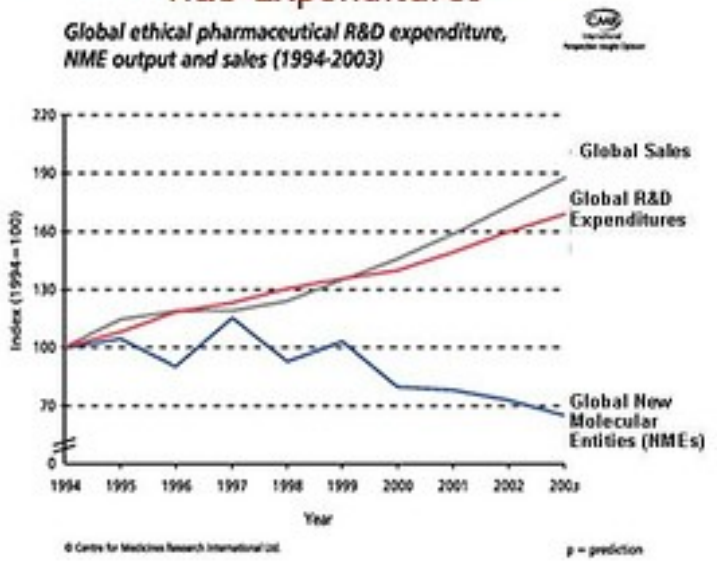
A significant challenge

Big Pharma : Dramatic Decline in R&D Productivity

Attrition Remains Very High



Output Not Keeping Up With R&D Expenditures



Source: PhRMA, CMR, Genentech, Booz Allen Hamilton: *The Global Innovation 1000*, 2006

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Two Critical Questions

- Which biological target / approach?
- What compound do I make next?

Two Critical Questions

- Which biological target / approach?

- What compound do I make next?

Our focus for this talk

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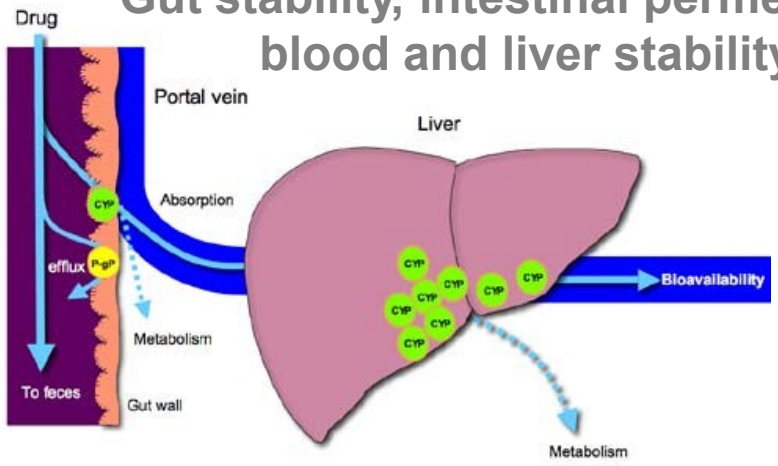
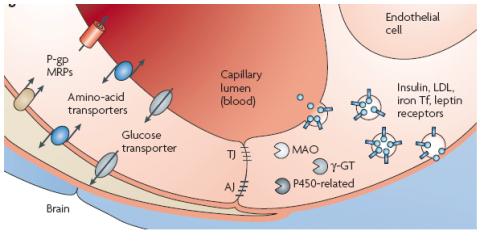
A compound must leap many hurdles…..

Chemical Stability

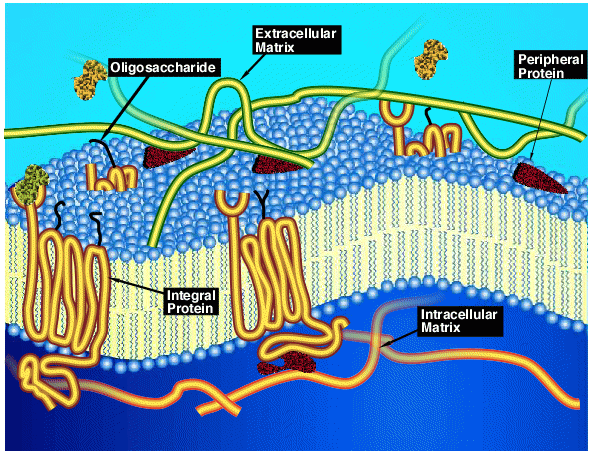
Gut stability, intestinal permeability, blood and liver stability



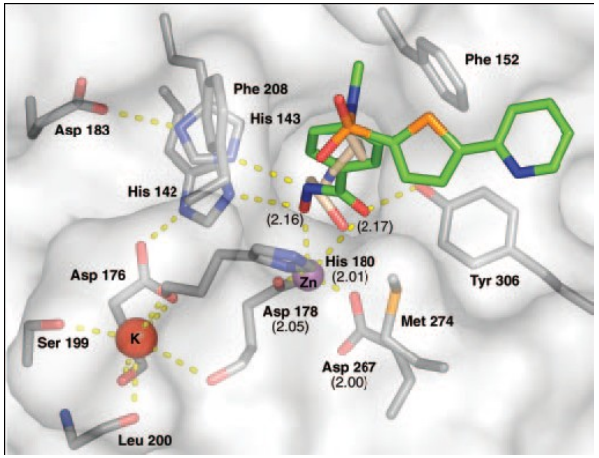
Blood brain barrier



Cell membrane permeability



Interactions with the bio target



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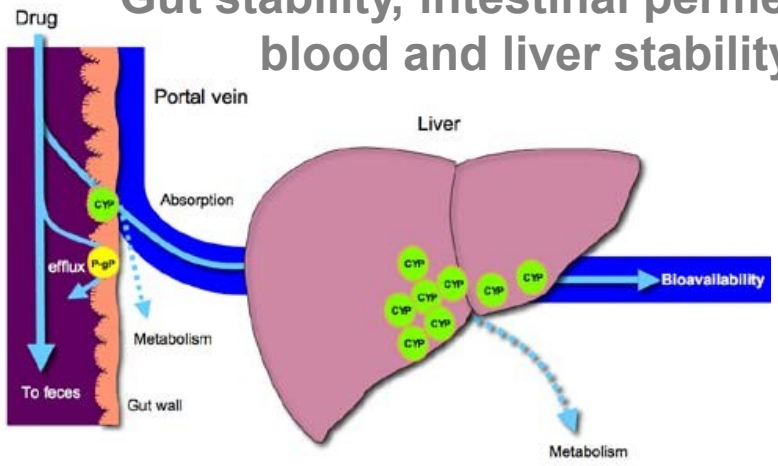
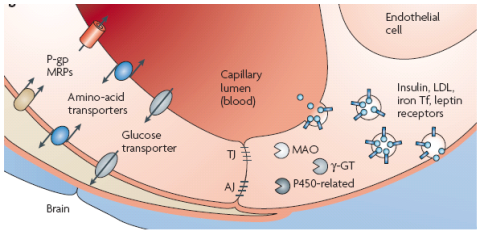
A compound must leap many hurdles…..

Chemical Stability

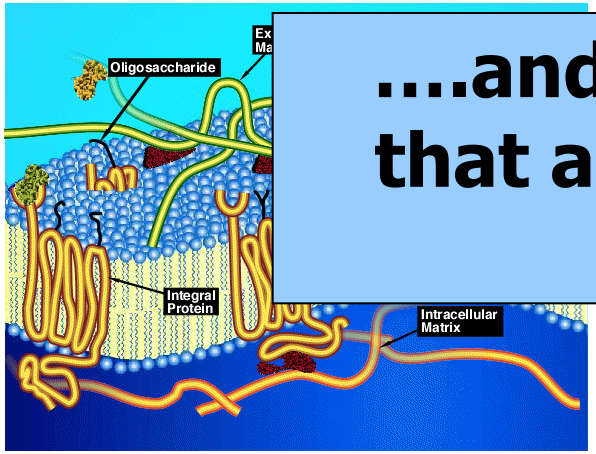
Gut stability, intestinal permeability, blood and liver stability



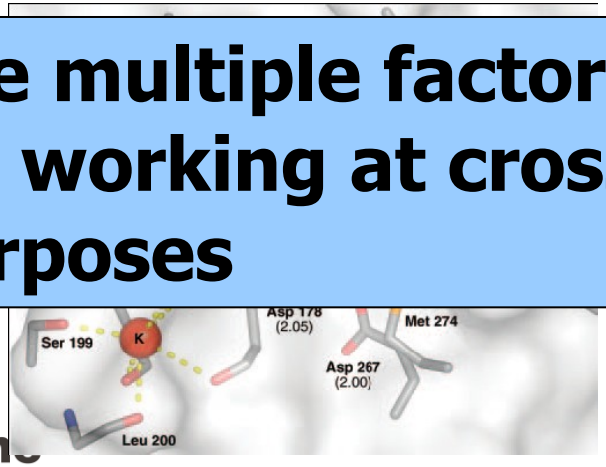
Blood brain barrier



Cell membrane permeability



Interactions with the bio target



….and balance multiple factors that are often working at cross purposes

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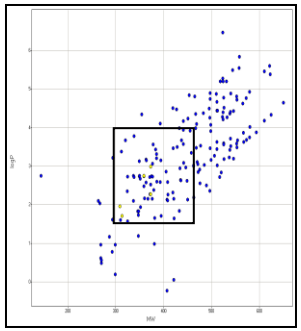
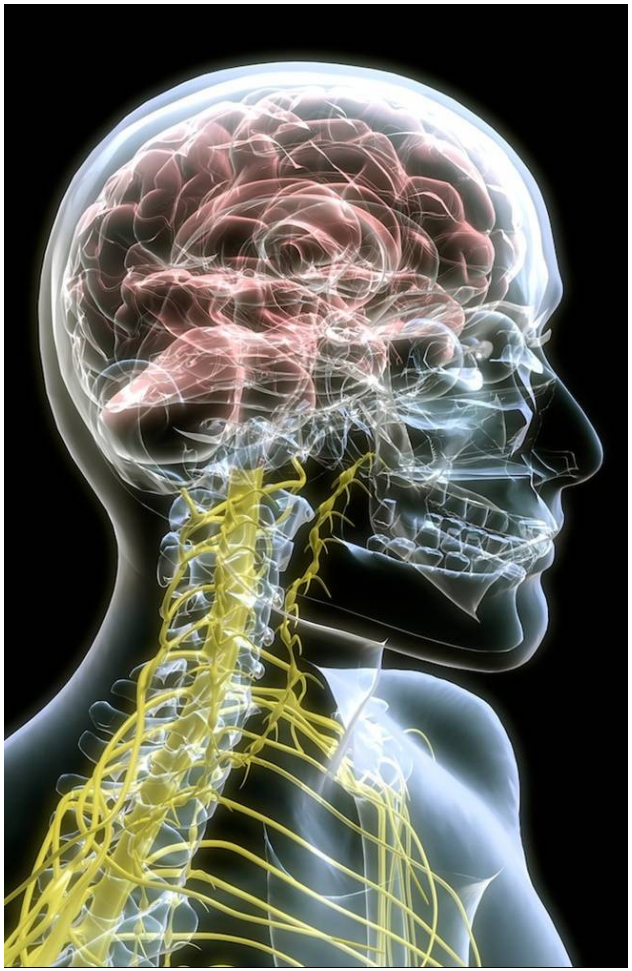
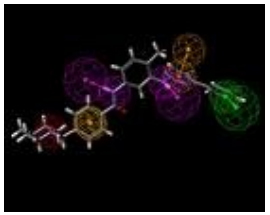
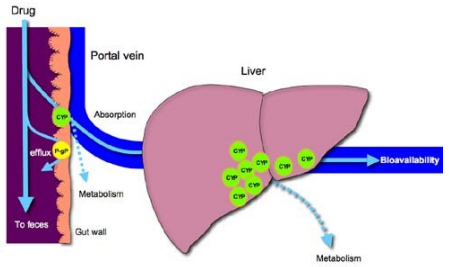
There are many considerations that go into deciding what compound to make next.









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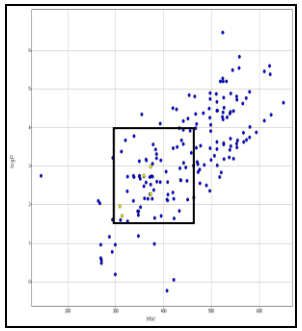
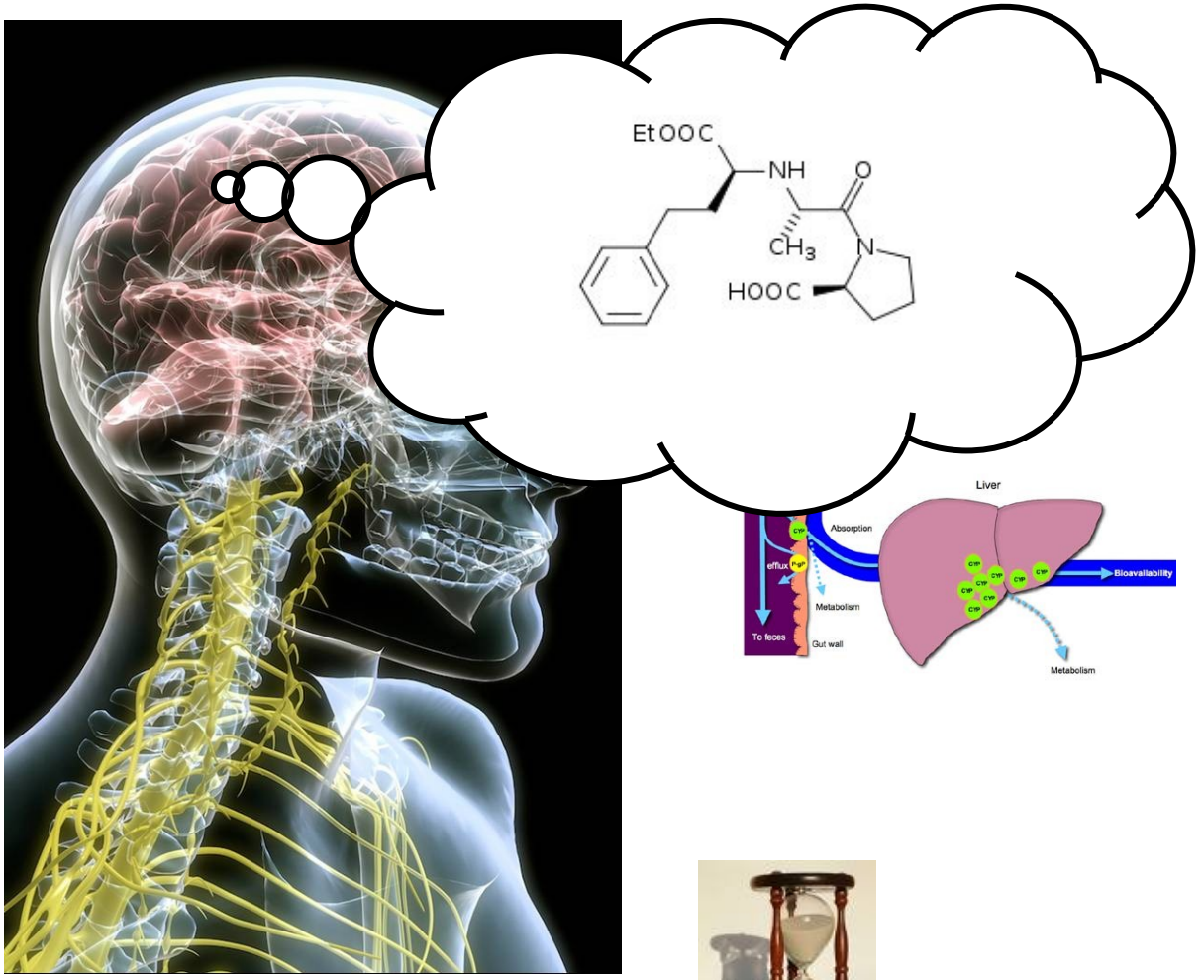
Do we really understand how these factors influence the choices we make?





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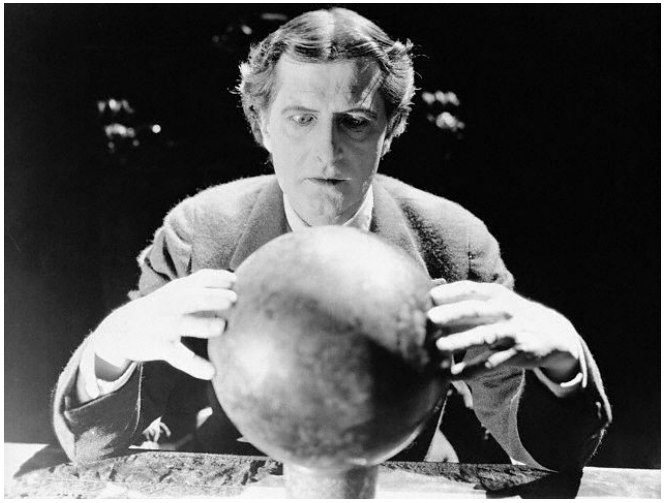
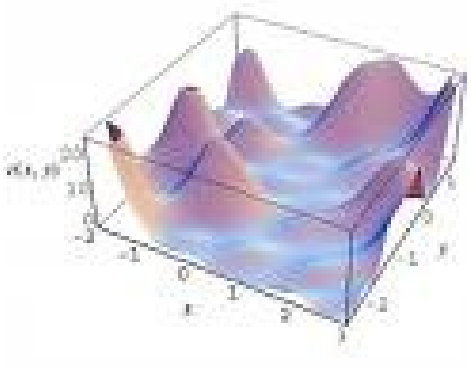
What is medicinal chemistry?

- Predicting the future



- A multi-parametric optimization problem



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Humans are bad at making predictions

- Once we form a mistaken belief about something - we tend to cling to it
  - Discount disconfirming evidence
  - Focus on evidence that supports our preexisting beliefs

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Overconfident in our predictions and slow to change in the face of new evidence

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How confident are you in making predictions?

- Pick a range of values which you are 90% confident contains the correct value
  - What was Martin Luther King Jr.'s age at death?
  - What is the length of the Nile River in miles?
  - How many countries belong to OPEC?
  - How many books are there in the Old Testament?
  - What is the diameter of the moon in miles?

How confident are you in making predictions?

- What was Martin Luther King Jr.'s age at death? 39
- What is the length of the Nile River in miles? 4,187 miles
- How many countries belong to OPEC? 13 countries
- How many books are there in the Old Testament? 39 books
- What is the diameter of the moon in miles? 2,160 miles

In a study of 1,000 people on 10 questions:

- 99% were overconfident in their estimates.
- Only 1% got 9 or 10 correct.

How do people approach multi-parametric optimization?

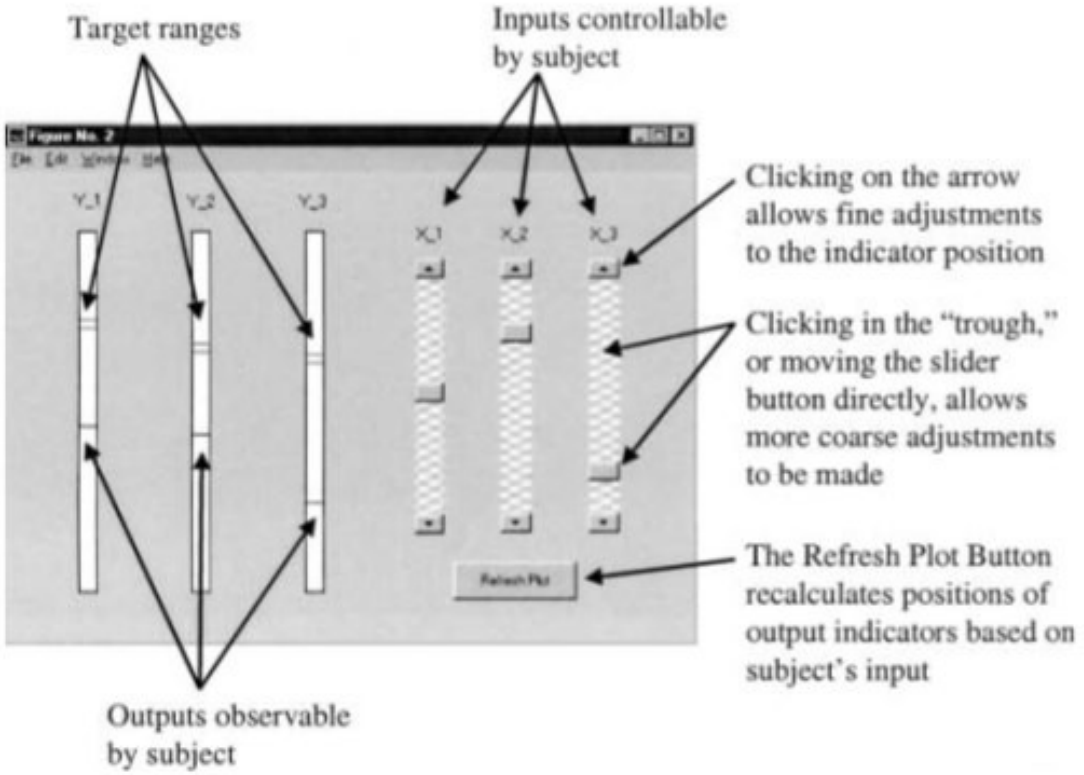

Fig. 1. The GUI for the design task surrogate

Cognition and Complexity: An experiment on the effect of coupling in parameter design

Hirschi and Frey, Research in Engineering Design, 2002, 123-131

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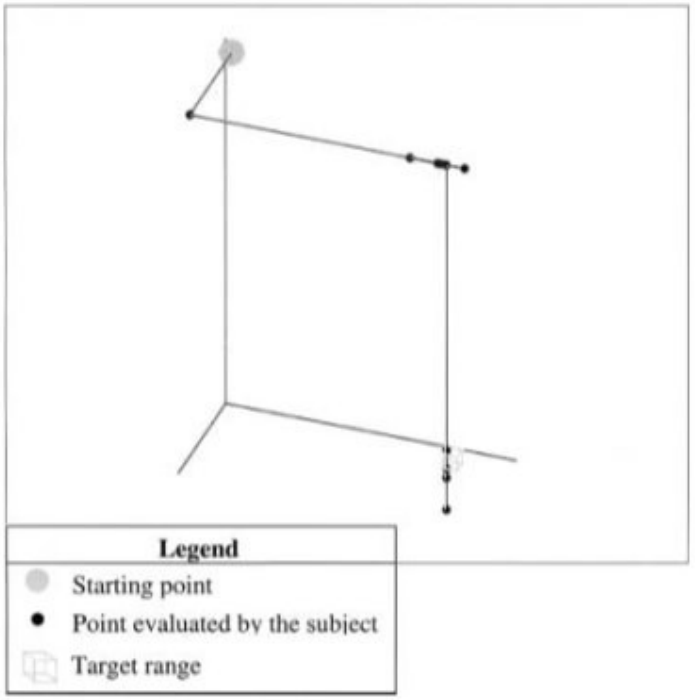
Uncoupled versus Coupled



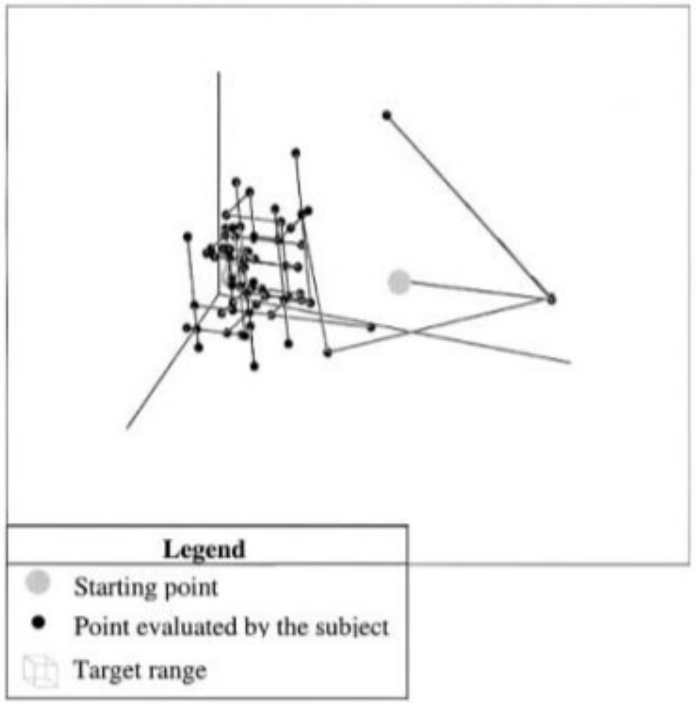


Fig. 2. A typical solution strategy employed by a subject solving an uncoupled system

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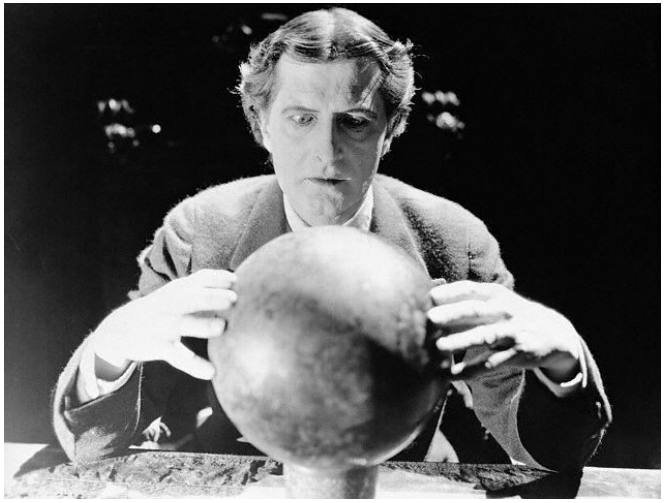
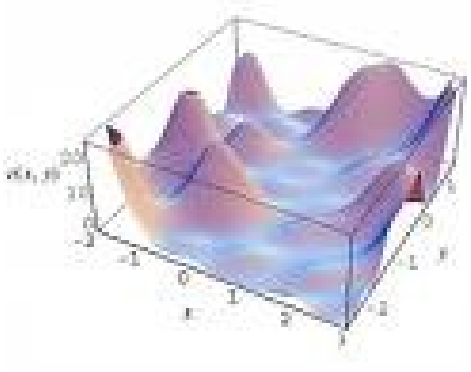
Where can we go for help?

- Predicting the future



- A multi-parametric optimization problem



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Algorithms vs experts

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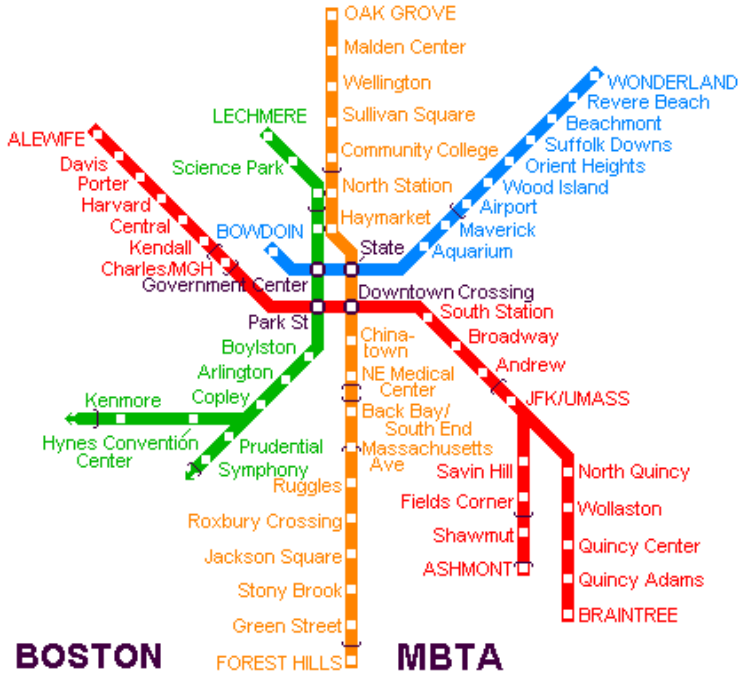
Global and series-specific models

Global model: low resolution predictions across a wide swath of compounds

Series-specific model: more accurate predictions within a narrower series of analogs



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What is needed for better in silico global models?

Data, data, data!

High quality, collected in the same manner, available to everyone

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NIH Molecular Libraries Screening Centers – A source of large, quality datasets?

- >300,000 Compound File
- Sites experienced in developing and running high throughput assays
- A source of consistently obtained, high quality data for global model building purposes?

NCGC
NIH Chemical Genomics Center

BIMR
BURNHAM INSTITUTE
for MEDICAL RESEARCH
From Research, the Power to Cure

THE JOHNS HOPKINS UNIVERSITY BALTIMORE 1876

THE UNIVERSITY of NEW MEXICO

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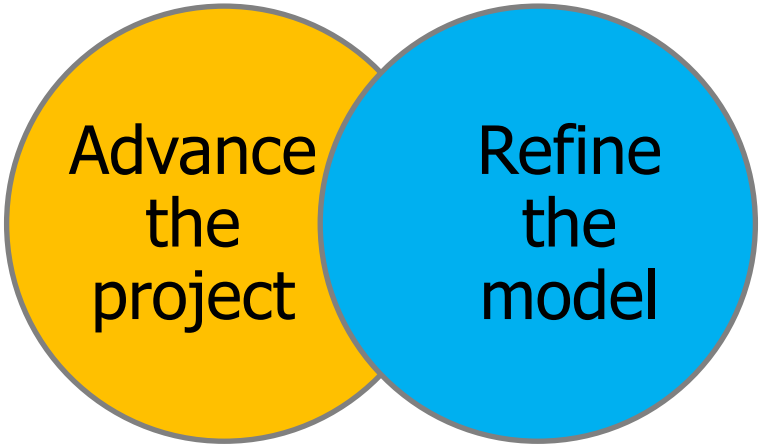
Building series specific models using the fewest compounds possible

One idea: Design compounds with model building in mind



How do you know which situation you are in?

Need to have some mechanism to determine if a compound helps with model building or adds little value

Is high uncertainty in the prediction a way to identify compounds useful for model building?

- Using Stardrop – run virtual compounds covering compound space the project would like to explore through model(s)
- Look at uncertainty associated with the predicted values
- Synthesize and test selected compounds with high uncertainty – that is, those structurally diverse from the training set
- Use those data to feed back into model

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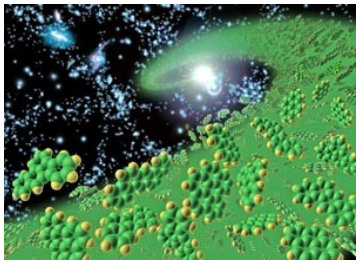
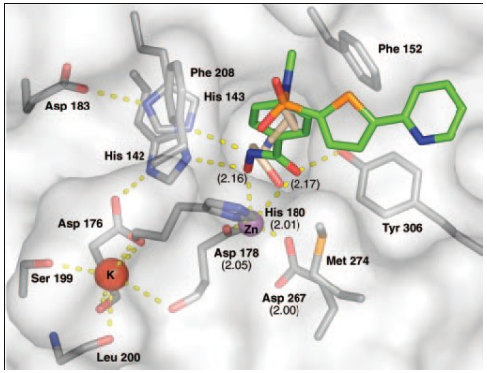
Building series specific models

Virtual library of analogs of interest generated by combining med chem/ comp chem/syn chem perspectives

Run virtual library through global in silico model or nascent series specific model built in StarDrop

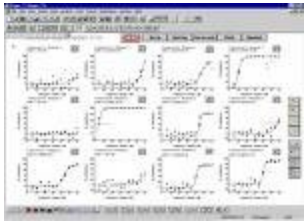
Lead





Select compounds for synthesis and testing based on level of uncertainty in the predictions

Prioritized compounds synthesized and experimental data collected



Data used to build series specific models

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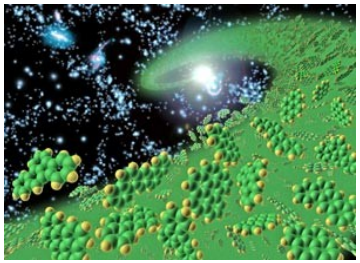
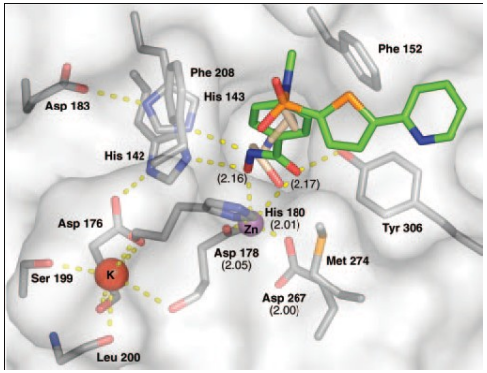
Pulling it all together

Lead

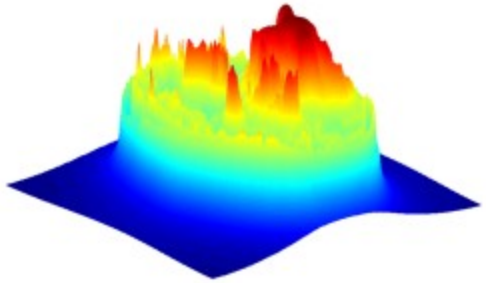
Very large virtual library generated by combining med chem/ comp chem/syn chem perspectives



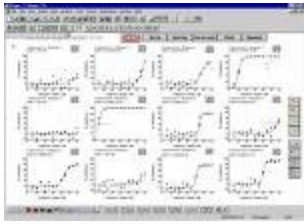
Run virtual library through comp models of: Activity, Selectivity, BBB, Solubility, ADME, Tox



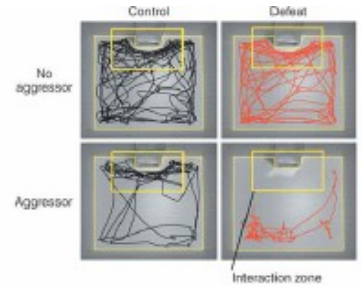
Results of models put through optimization algorithms seeking best balance of parameters



Prioritized compounds synthesized and experimental data collected



Data used to refine models



Compounds meeting criteria for advancement are put into more advanced models

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"Science is a way of trying not to fool yourself.
The first principle is that you must not fool yourself,
and you are the easiest person to fool."

Richard Feynman
Physicist
Caltech commencement address, 1974

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