Chemical Biology

Chemical *versus* Biological Space

&

Chemical Genomics

Nowadays,

A growing interest in using chemicals as probes/detectors in basic and clinical research

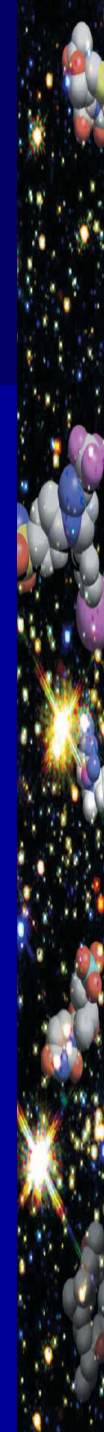
Chemical Genetics

Chemical Genetics: the study of biological processes using small molecule intervention (rather than genetic intervention)

Genetics — Mutation modulating function of biological components →

Chemical Genetics — Small Molecule modulating function of biological components →

Study of Biological processes



Chemical Genetics and Chemical Genomics

Chemical Genomics is the extension of Chemical Genetics to a Genome-Wide Scale

Chemical Genomics

The goal of Chemical Genomics is to map the "biological activity space" in the "chemical space" using small molecules

Forward and Reverse Chemical Genomics

Reverse
(target based screen)

Target (e.g. protein)

↓ Small Molecules Interacting with target

Phenotype

Commonly used

Forward
(phenotype based screen)

Phenotype

↓ Small Molecules Causing Phenotype

Target (e.g. protein)

More recent

Forward Chemical Genetics

From a phenotype to the target

Cells

Small molecules (Libraries)

Assay and "hit" identification

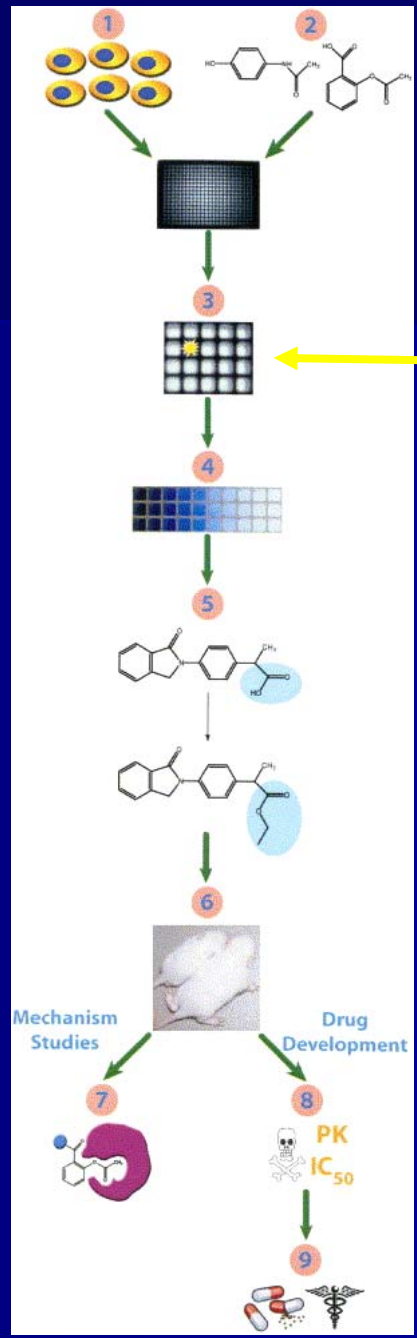
Wanted Phenotype

Confirmation- dilution series

Optimization by testing analogs

Confirmation of desired phenotype in model organisms

Identification of target small molecule



Optimizing for a drug (e.g. toxicity tests and clinical testing

The Field of Chemical Genomics

- Systematic exploration of the interactions between small molecules and biological systems

- Discovery and elucidation of novel targets and mechanisms of action

Chemical Genomics

- Examines known, biologically active small molecules but requires novel collections of small molecules with large diversity

- Rich collections of small molecules will increase the chance of discovering biologically active molecules for basic and applied (e.g. drugs) research

The Chemical Space

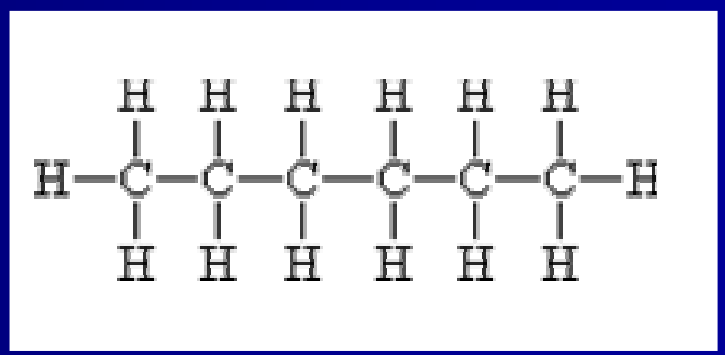
- Analogous to the cosmological universe in its size/extent

- Chemical compounds populating space instead of stars

- Estimated number of small carbon-based compounds (up to 500 Da) is more than 10^{60}

The Chemical Space

Theoretical chemists have calculated that there are more possible molecules based on hexane (10^{29}) than there are stars in the visible universe



The Chemical Space

- Chemists made a minor amount of visits into this (chemical) space

- Largest chemical databases currently contain up to 25 million different molecules

The Chemical Space

Chemicals can be mapped in the chemical space by multiple "descriptors" that describe their structure, activities and properties

Examples of descriptors are: molecular mass, lipophilicity, geometric properties and many more…

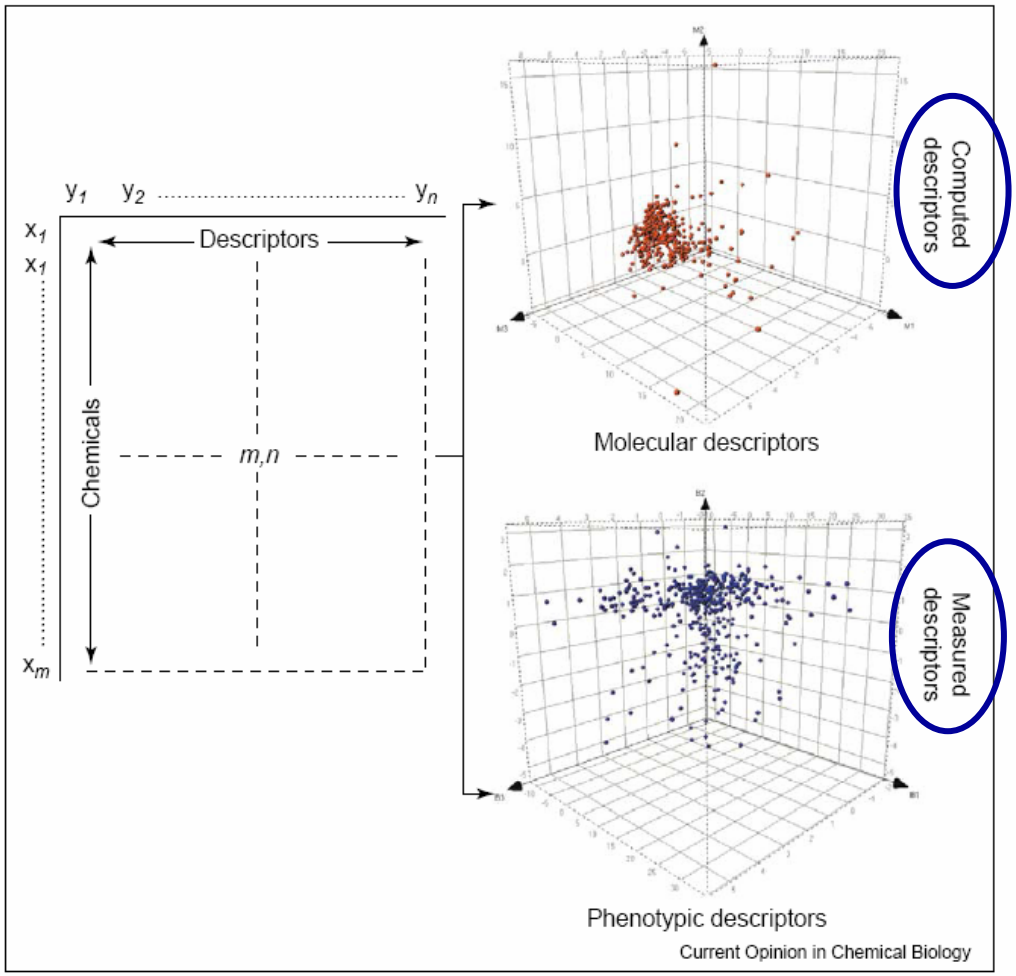
The Chemical Space

- Two fundamentally different classes of descriptors used to map chemicals in the chemical space

- Computed: defined by calculations and algorithms

- Observed: observation of the effect of the chemical on for example genes, proteins

Creating Maps of Chemical Space



PCA models of a chemical space for 480 small molecules

24 computed molecular descriptors

60 measured phenotypic descriptors derived from a cell-based assay

The Biologically Relevant Chemical Space

- Biological systems use a tiny portion of the possible amount of compounds possible in the same range of molecular masses

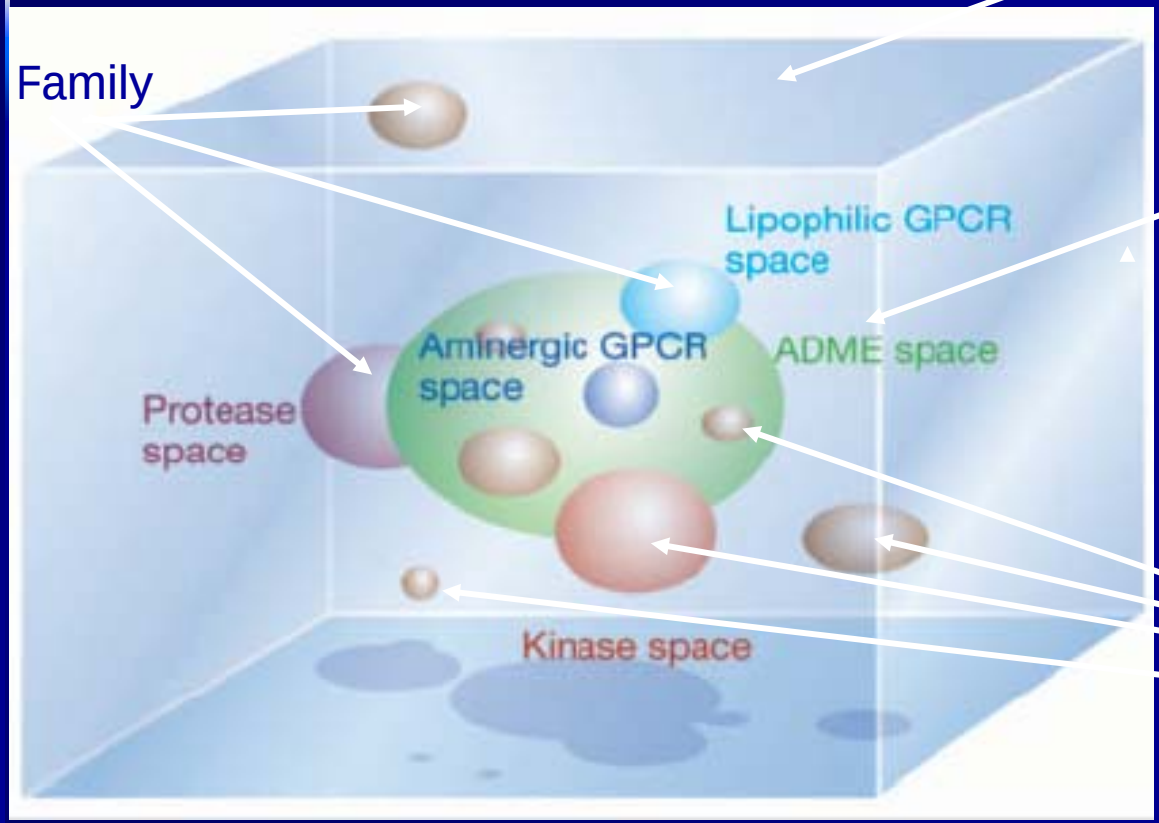
- Living systems contain from hundreds to thousands of compounds

The Biologically Relevant Chemical Space

Thus, in terms of numbers, "biologically relevant chemical space" is only a tiny fraction of the "chemical space"

The limits of the biologically relevant chemical space is defined by the interaction between the small molecules and the biological molecules such as DNA, RNA and proteins

The Biologically Relevant Chemical Space



Compounds that bind to certain "target classes" (proteins from the same family such as G-protein-coupled receptors, cluster together in specific regions of the chemical space

The Biologically Relevant Chemical Space & Evolution

- So many complex processes in a cell could be carried out with a limited number of molecules!!

- A limited range of chemical reactions exploited during the evolution of living systems,

WHY?

The Biologically Relevant Chemical Space & Evolution

- Essential chemistry for life (atoms and other elements/groups):

- 99% of the atoms within a biological system are C, H, O or N

- Side chains of proteins (methyl group, isopropyl, thiol and others), approximately 20 of them

- Metal ions and co-factors incorporated into folded structures

The Biologically Relevant Chemical Space & Evolution

Solubility in water is a key issue:

- Many of the small organic molecules used by biological systems are derivatives of carboxylic acids and organic amines (charged, hydrophilic at physiological pH)

- Amino acid side chains are in part very hydrophobic and others are hydrophilic and this allows folding (at low energy cost)

The Biologically Relevant Chemical Space & Evolution

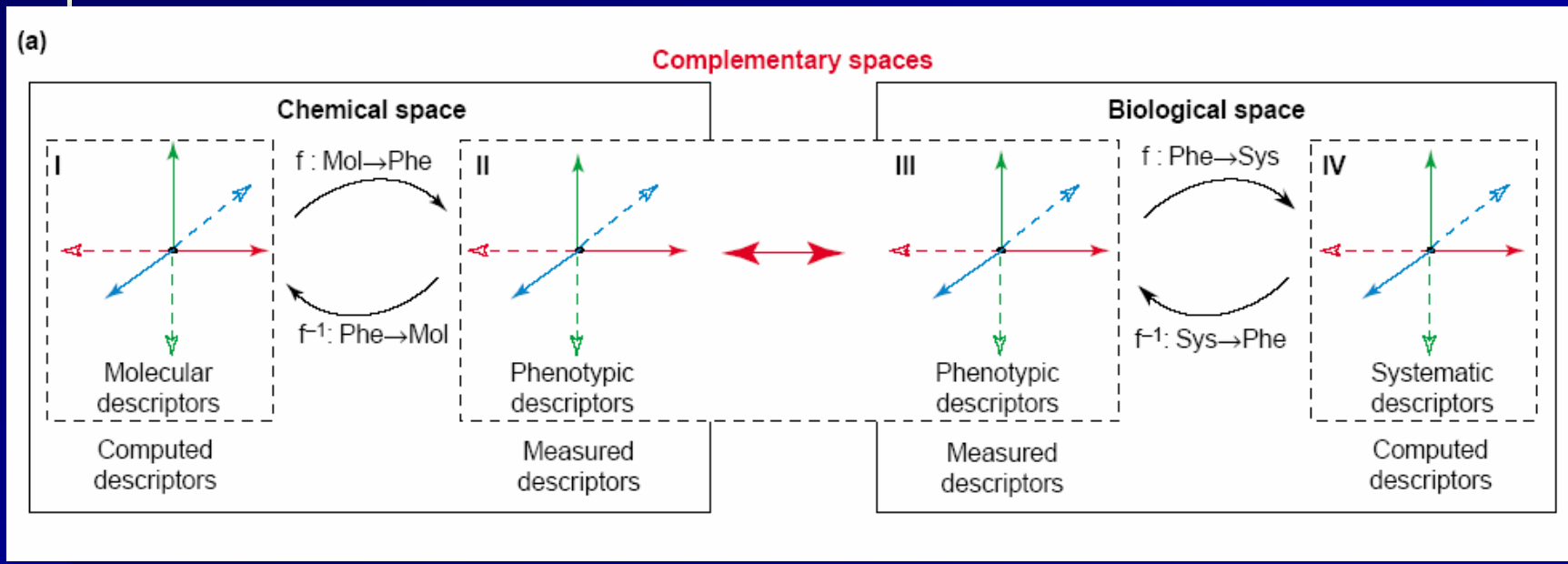
Another key issue is the production of ATP:

- ATP is the energy store in biology and the building block for DNA and RNA

- Many small molecules in living organisms are derivatives of phosphoric acid, the precursor for ATP formation

- Phsophoric acid derivatives, phospholipids are key components of biological membranes

The Biological Space



- Biological systems are classified instead of chemicals

- The biological space is mapped by using the small molecules as descriptors

The Biological Space

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- The biological space is mapped by using the small molecules as descriptors

- The analysis of multi-dimensional data (with dimensiobility reduction and pattern finding methods) provides a computational framework for mapping multidimensional chemical and biological descriptor spaces

Next Week

Navigating the Chemical Space for Biology and Medicine

Tools and Examples