Hansen Solubility Parameters: Introduction and Applications

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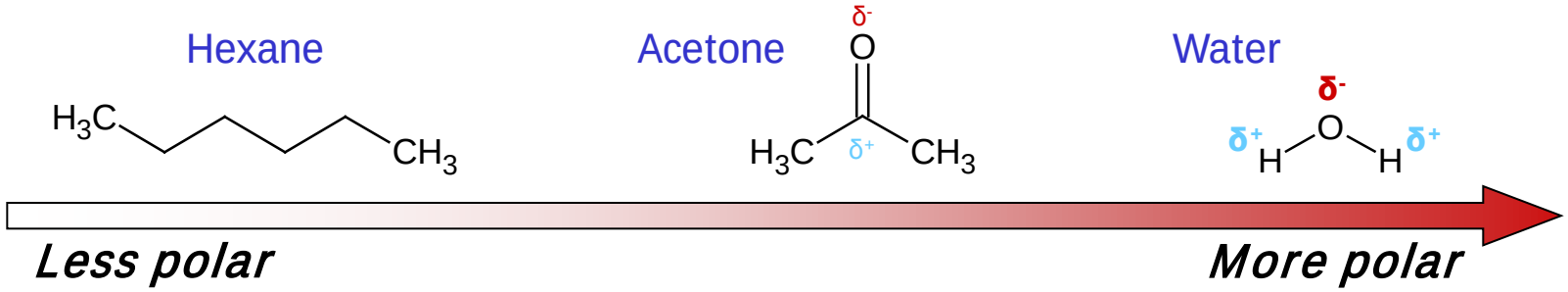
Solubility

- How do we understand solubility?
  - "Like dissolves like"
  - Polar vs. non-polar solvents
    - Typically refers to the degree of charge separation in the solvent molecule
    - The greater the strength and / or separation of charges, the more polar the solvent



Quantifying Behavior

- If we want to be quantitative, there are several approaches; two examples:
  - Kauri-butanol (Kb) value (ASTM D1133)
    - Indicates maximum amount of compound that can be added to solution of kauri resin (resin from the kauri tree of New Zealand) in butanol without causing cloudiness
  - Octanol-water partition coefficient (K_{OW} or log P) (ASTM E1147)
    - High values indicate compound prefers octanol phase (less polar)
    - Low values indicate compound prefers water phase (more polar)

Quantifying Behavior

- Can also make a thermodynamic argument – for example, based on the removal of a single molecule from a material
  - Must overcome all intermolecular interactions ("stickiness") between molecule and its neighbors to do this
  - This occurs during vaporization, and also during dissolution
  - Prof. Joel Henry Hildebrand (UC Berkeley Chemistry) proposed this treatment
  - Hildebrand solubility parameter defined as the square root of the aforementioned quantity (the cohesive energy density)

Hildebrand Solubility Parameter

Hildebrand solubility parameter [typical units are $(cal/cm^3)^{1/2}$ or $MPa^{1/2}$]

Heat of vaporization of compound (energy/mol)

Thermal energy available at a given temperature (energy/mol)

$$\delta = \sqrt{CED} = \sqrt{\frac{\Delta H_v - RT}{V_m}}$$

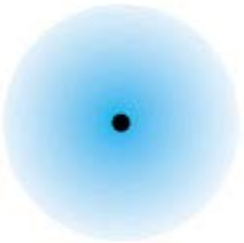
Cohesive energy density of compound ("molecular stickiness", energy/volume)

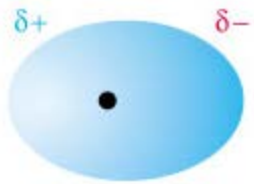
Molar volume of compound (volume/mole)

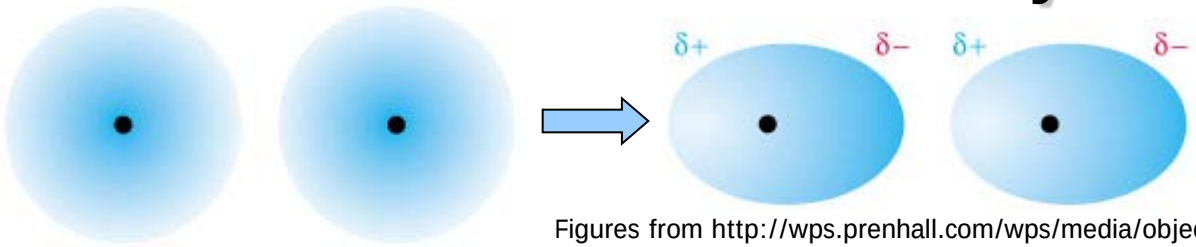
Hardest thing to find is the heat of vaporization of a compound (think about plastics!)

What contributes to molecular "stickiness"?

- **Dispersion Forces**
  - All atoms are surrounding by electron "clouds"
  - The electron cloud is, <u>on average</u>, evenly distributed around the atom
  - At a given instant, however, the electron distribution may be lopsided
  - This temporary polarization results in attractive interactions with nearby atoms



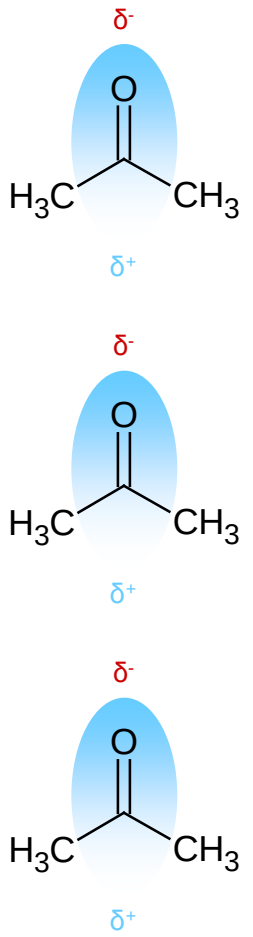




Figures from http://wps.prenhall.com/wps/media/objects/946/968975/ch10_02.htm

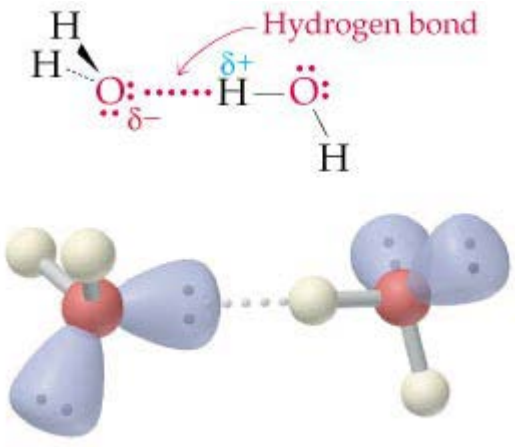
What contributes to molecular "stickiness"?

- **Polar interactions**
  - Some atoms have a greater affinity for electrons than others (more electronegative)
  - Bonds between atoms of differing electronegativities are polarized as a result
  - Dipoles thus formed attract one another
  - Same idea as with dispersion forces, but dipoles are permanent, not temporary



What contributes to molecular "stickiness"?

- **Hydrogen bonding**
  - Hydrogen has just one electron, so when electron density is pulled away from hydrogen (i.e. by an electronegative atom), the nucleus is exposed
  - This results in exceptionally strong polar interactions with other atoms possessing extra lone pairs of electrons
  - As with previous cases, the interaction is electrostatic in nature (opposites attract)



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Shortcomings of a single parameter approach

- The Hildebrand solubility parameter can be useful, but it does not account for the origins of molecular "stickiness" (or their consequences)
  - This means it is possible for various combinations of intermolecular interactions to give rise to the same Hildebrand solubility parameter
  - EXAMPLE: nitroethane and 1-butanol have the same Hildebrand solubility parameter (~23 $MPa^{1/2}$); neither will dissolve epoxy resin alone, but a blend of the two <u>will</u>
- Hildebrand recognized this, and tried to address it by further classifying compounds according to hydrogen bonding ability (weak, moderate, strong), but this approach has limited utility

Accounting for interactions: Hansen Solubility Parameters

- Hansen solubility parameters address this issue by specifying separate quantities for each of the three aforementioned intermolecular forces:
  - δ_d – Dispersion parameter
  - δ_p – Polar parameter
  - δ_h – Hydrogen-bonding parameter
- Can still define total solubility parameter ($\delta_{total}^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$), but can separate cohesive energy density by interaction type

Thinking about Hansen Solubility Parameters (HSPs)

- HSPs mean we can represent each compound as a point in 3D "solubility space"
- Distance between HSP points in solubility space is defined as follows:

$$R_a^2 = 4\left(\delta_{d1} - \delta_{d2}\right)^2 + \left(\delta_{p1} - \delta_{p2}\right)^2 + \left(\delta_{h1} - \delta_{h2}\right)^2$$

- With some work, it is also possible to define an interaction radius (R_0) and a reduced energy difference (RED = R_a/R_0)
  - RED > 1 → Incompatible, RED < 1 → Compatible

Thinking about Hansen Solubility Parameters (HSPs)

- In some cases, HSP values are intuitive
  - Hydrocarbons are dominated by δ_d
  - Water is dominated by δ_h
  - Similar compounds will have similar HSPs (for example, *n*-butanol will be similar to *n*-propanol)
- HSPs can be correlated with other properties
  - Strong correlation between refractive index and δ_d
  - Strong correlation between dipole moment and δ_p
  - Strong correlation between surface energy and a mix of parameters plus molar volume
- Not perfect
  - Molecular size and shape are not captured
  - Some interaction types are ignored (ion-dipole for example)
- Nevertheless, “good enough” to give reasonable predictions

Defining HSPs: Group Contributions

- Break molecule into functional groups
- Add up the δ_d, δ_p, and δ_h contributions from each group to generate estimate
- Van Krevelen, Hoy, Beerbower
  - Based on a restricted range of functional groups
  - Different starting values so different end results
- Stefanis-Panayiotou – more modern
- All require manual group assignment

Hansen Solubility Parameters in Practice (HSPiP)

- Software package developed by Hansen, Abbott and Yamamoto
- Able to provide HSPs for arbitrary molecules
  - Has a large look-up table for materials whose HSPs are known
  - Utilizes “Yamamoto Molecular Breaking” (Y-MB) model for other compounds
    - Carefully chosen / optimized set of functional groups
    - Sanity checking vs. other data sources (refractive index, dipole moment, surface tension, heat of vaporization)
    - Tested against “over-fitting”
  - Best estimate of HSPs available at the moment
  - HSPiP also automates aforementioned manual methods

Hansen Solubility Parameters in Practice (HSPiP)

- As HSPs are related to heat of vaporization, HSPiP can:
  - Estimate boiling point
  - Estimate vapor pressure
  - Estimate Antoine coefficients
- Melting point predictions are made independently using an external model based on an extensive validated melting point database

The Classic HSP Measurement Technique

- The key to HSP's practical success
- Widely applicable
  - Crystalline solids
  - Polymers
  - Nanoparticles
  - DNA
- Take 20 test tubes, find if the stuff is "happy" in 20 different, representative, known solvents
  - Set of solvents should neither be "all bad" or "all good"
  - Best to cover a decent range of HSP values with solvents
- Plot the solubility sphere in 3D HSP solubility space
  - Can define center of sphere (i.e. HSPs for "stuff")
  - Can define radius of sphere (i.e. interaction radius R_0)

High Throughput Options

- Assembling even 20 solvents can be a big barrier to HSP measurement
- Small labs /companies/universities may not want to do this
- Big companies have robots
  - All large HSPiP users have automated HSP determination systems
    - Some better than others
    - Some automate solubility measurements
      - Agfa-Gaevert, Belgium offering this as a service
      - Also VLCI in the Netherlands

High Throughput Example: VLCI

- Chemspeed FORMAX unit enables automated high-throughput testing

Grid Technique

- Use 4 pairs of solvents
- Create a “grid” spanning the relevant solubility space
- Developed at U. Erlangen for organic photovoltaics
- Much easier with robotics
- Great for targeted measurements

Contents lists available at SciVerse ScienceDirect

Solar Energy Materials & Solar Cells

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Determination of the P3HT:PCBM solubility parameters via a binary solvent gradient method: Impact of solubility on the photovoltaic performance

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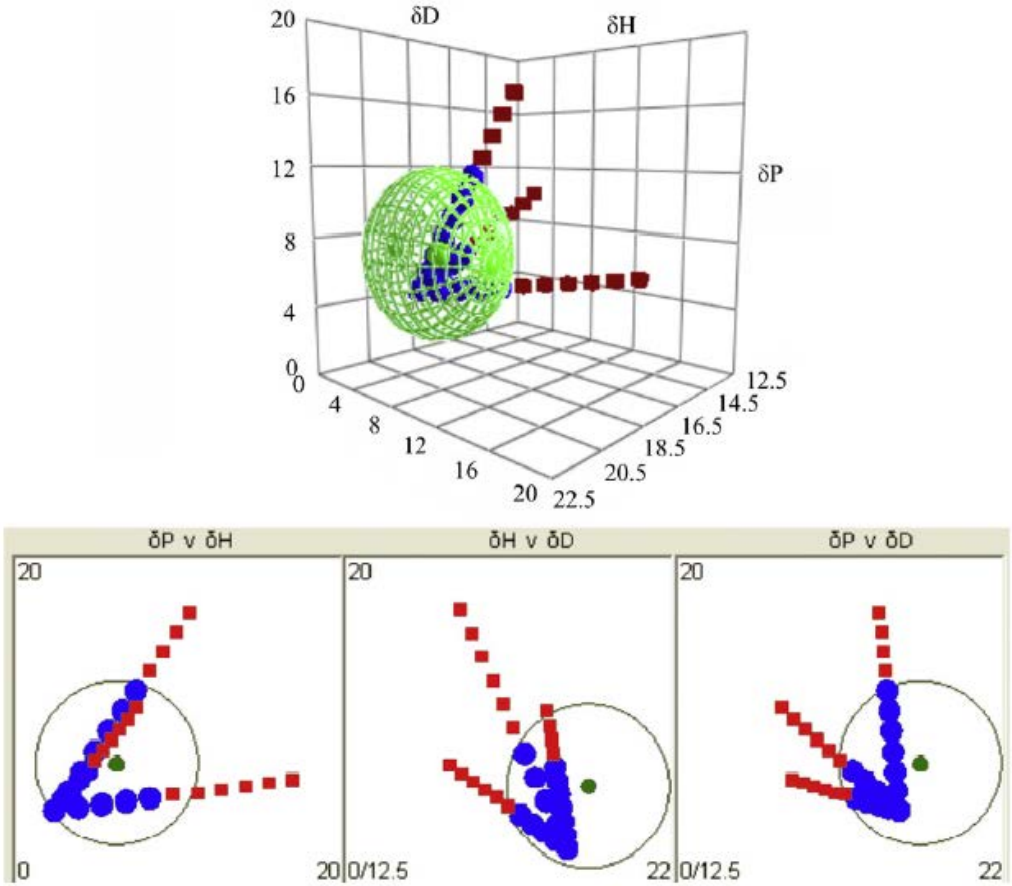
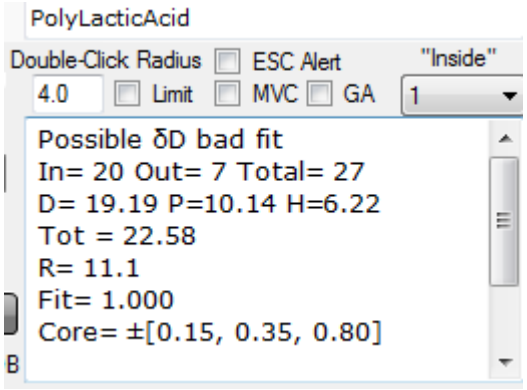


Fig. 4. HSP diagrams of PCBM: a) different solvents method and b) binary solvent gradient method with solubility limit 5 mg mL^{-1}.

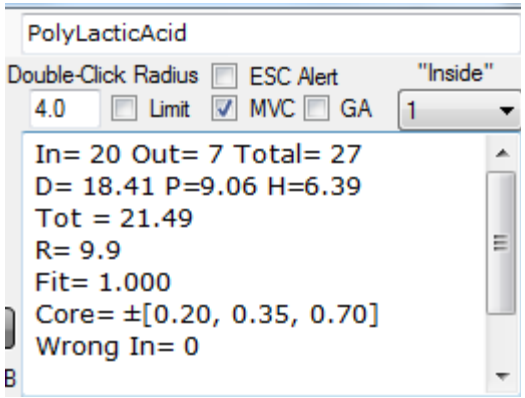
Notes on Polymer Solubility

- An important asymmetry
  - A polymer can be rather insoluble in a solvent
  - The same solvent can be quite soluble in the polymer
- This relates to the entropy of mixing
  - Much more to be gained (entropically) dissolving small molecules than polymers
  - Likewise, semi-crystalline polymers resist dissolution all the more (greater “stickiness” between molecules in crystalline domains)
    - For example, polyethylene and polypropylene dissolve in hydrocarbons (as predicted by HSP values) – but only at elevated temperatures

HSPiP Refinements: Molar Volume Correction (MVC)



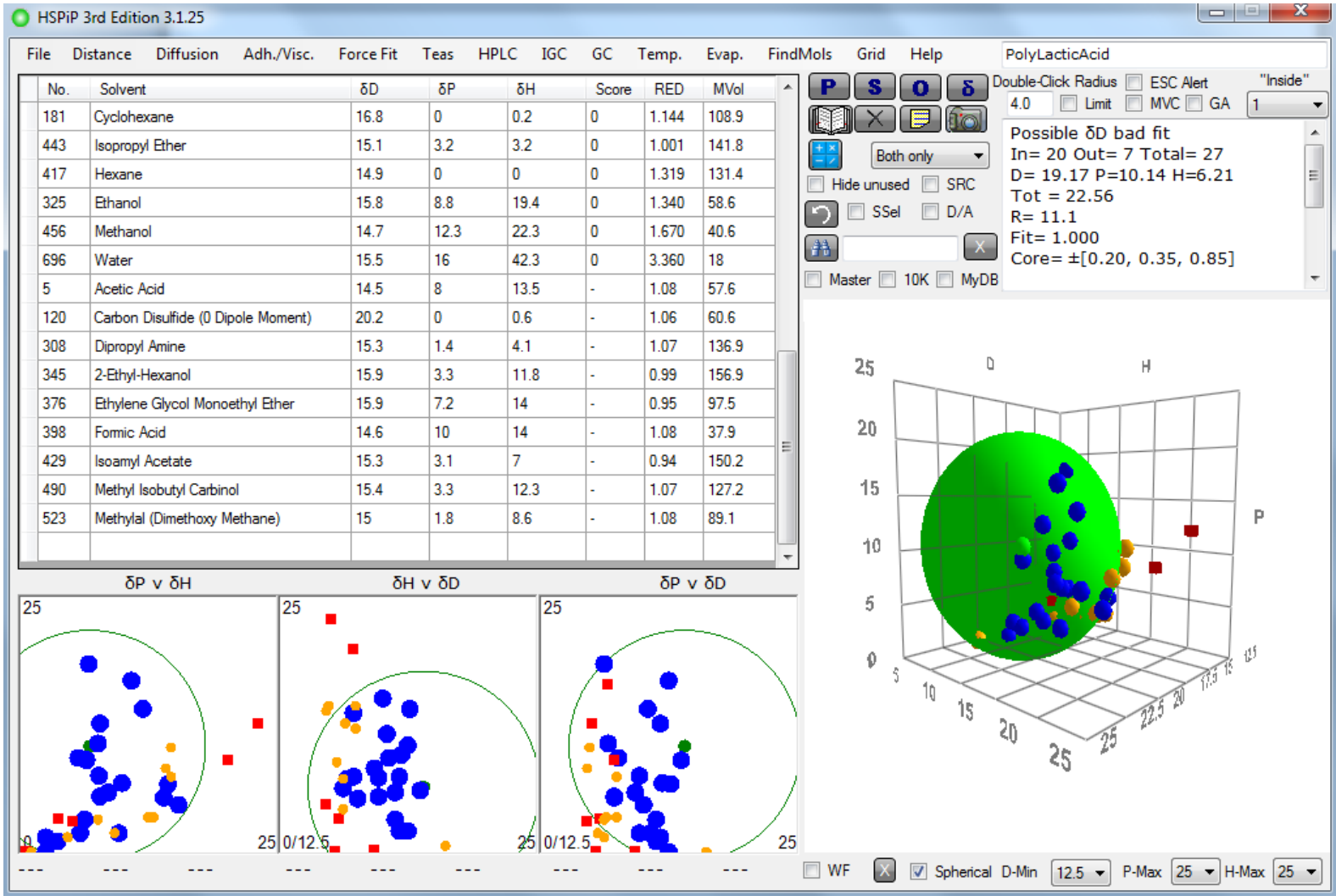
Classic fit – size of solvent not included



MVC fit – small solvents "penalized", large solvents "accommodated"

HSPiP Refinements: Solvent Range Check (SRC)

- **Identifies solvents at the edge of the apparent solubility sphere**
- **These improve fits the most with the least effort**

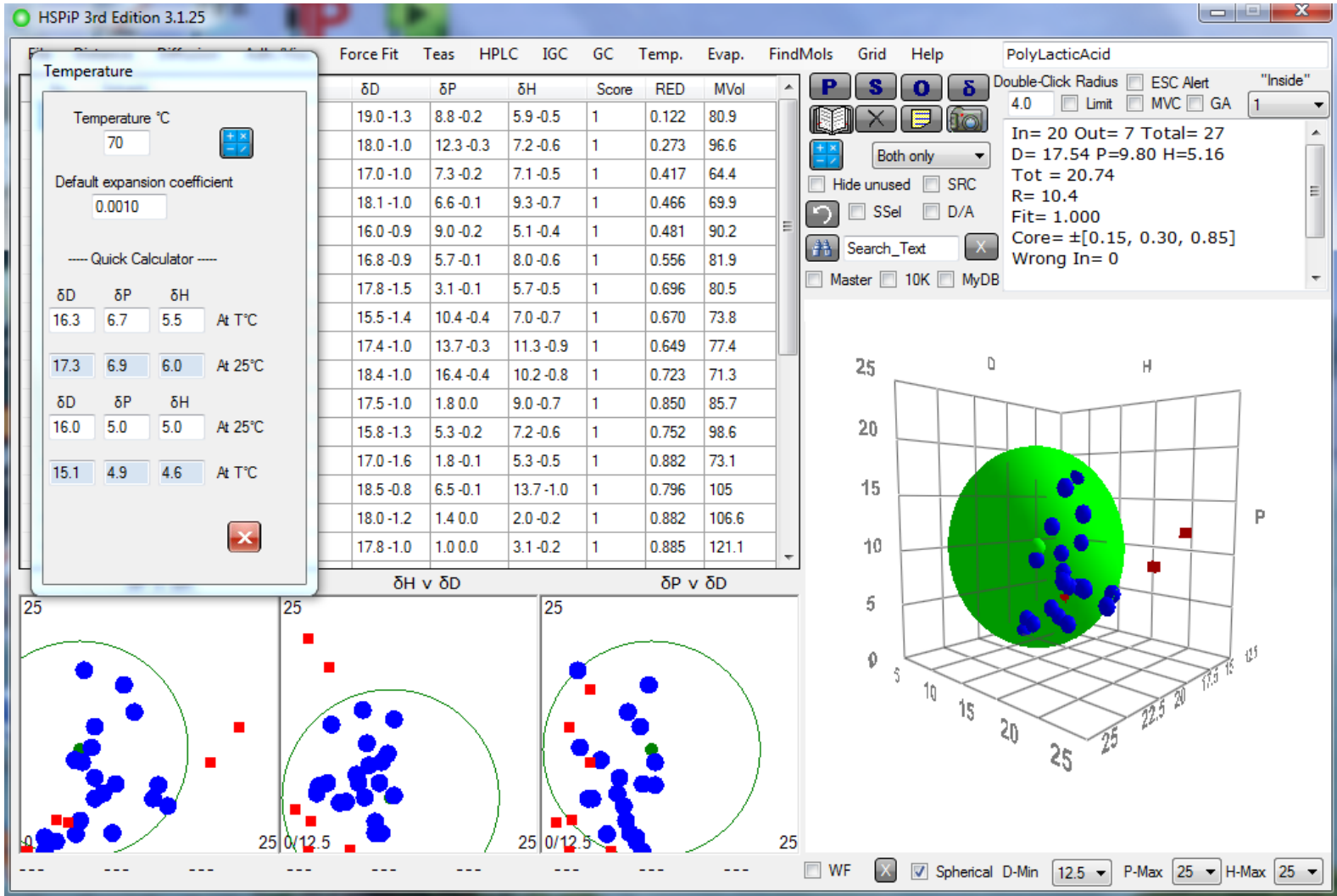


HSPiP Refinements: Hydrogen Bond Donors and Acceptors

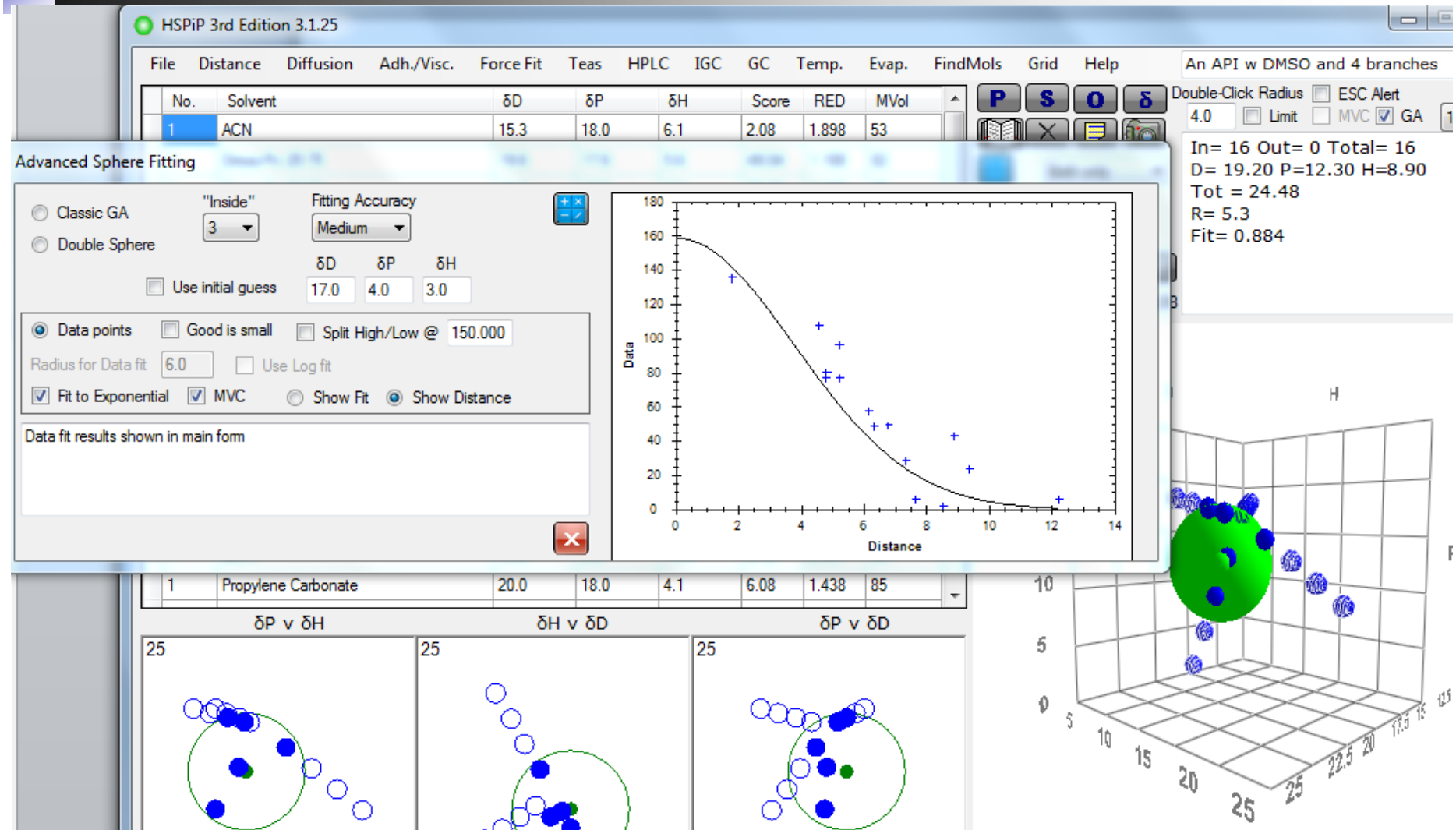
- Divide δ_h into hydrogen bond donor and acceptor components
- Allows for specific interactions that might increase solubility, such as C=O acting as acceptor and –OH as donor
- Careful analysis shows it's important
  - So far not a great success for normal fits
  - Continuing development work

HSPiP Refinements: Accounting for Temperature

- **Thermal expansion reduces cohesive energy density**
- **HSP values decrease as a result**
- **Accounted for by indicating CTE**



HSPiP Refinements: Fitting Solubility Data



Special Topics: HSPs and Surfactants

- They don't mix
- You *can* estimate or measure the HSP of a surfactant molecule – it's just an ordinary molecule
- Solubility parameter models in general (not just HSPs) assume that the same parameters apply everywhere ("mean field")
  - Cannot deal with situations where interactions are with specific parts of a molecule, molecules orient, etc.
  - This can be a problem when dealing with nanoparticles as well, i.e. if they possess multiple types of surfaces (modified or not, ends vs. sides, edges vs. faces, etc.)

Special Topics: Stain Removal

- No issues when using HSP to guide solvent selection for stain removal
  - Important to keep in mind however that diffusion in is faster than diffusion out
  - That's why our plastic microwave dishes become stained over time
- With surfactants, other models needed
  - Ex. Hydophilic-Lipophilic Difference - Net Average Curvature (HLD-NAC) model

Specific Topics: Solvent Blends

- A perfect HSP match with a perfect solvent (from the standpoint of cost, safety, vapor pressure, odor, regulatory approvals, etc.) is very rare (few new solvents)
- Can create blends to address this issue
- An X:Y mix of two solvents leads to an X:Y average of their HSPs (where X and Y are in vol%)
- You can even create a perfect solvent from a mix of two non-solvents
  - This was the proof of the power of HSP 40 years ago
  - Impossible to do with Hildebrand
- HSPiP can propose both binary and ternary blends, estimate and optimize evaporation rates

Special Topics: Example of Rational Green Substitution

- FAME (Fatty Acid Methyl Esters) are not particularly good solvents, but are "green" [16.4, 2.6, 4.5]
- Glycerol carbonate comes from bio-glycerol, CO_2 (in principle) and is bio-degradable – but is much too polar to be highly useful [17.9, 25.5, 17.4]
- A 60:40 mix is an impressive match for a great (but unusable) solvent like dimethyl acetamide (DMAc)

Special Topics: HSPs and Biological Systems

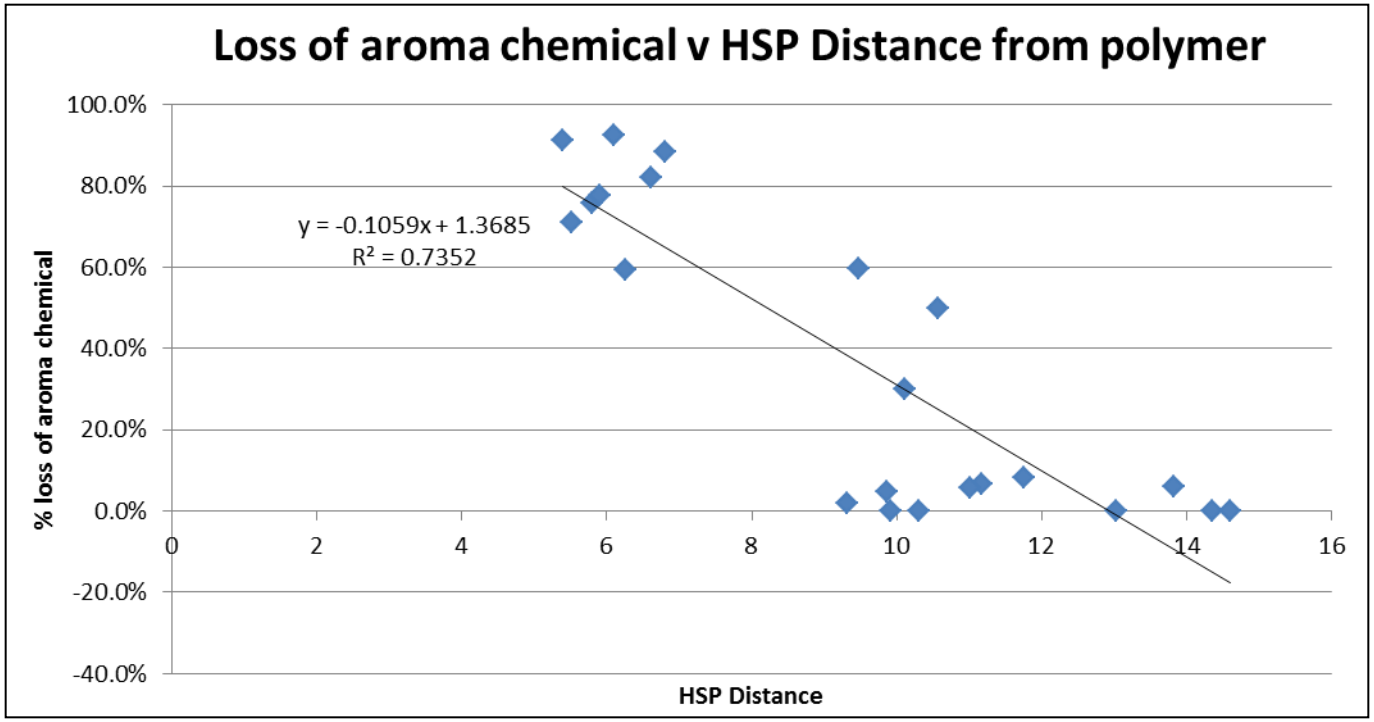
- Proteins, DNA bases exist in high HSP space (DNA bases → [19, 8, 8])
  - Chemicals that interact with and / or disrupt these biomacromolecules should have similar HSPs
    - Useful for identifying potentially cytotoxic and / or therapeutic agents
- Skin permeation is predicted in a much more nuanced manner than log K_{OW} method
  - DMSO is a good HSP match for skin; doesn't destroy it, permeates through it
  - Terpenes indicated as permeation enhancers, but this depends on what they're mixed with; 50:50 ethanol / terpenes gives HSP match with skin as well
  - Alternatively, stay away from [17,8,8] if you want to avoid skin permeation

Special Topics: Glove Selection

- If there's interest in choosing the right gloves for a chemical, make sure there's a big HSP mismatch between chemical and glove
  - Rather obvious, but confirmed by large studies
  - A rational way to choose gloves for handling cytotoxic chemicals
  - Also good for handling any new chemicals with unknown properties more generally

Special Topics: Aromas/Fragrances

- Many aroma and fragrance HSPs are known
- Unknowns are often simple molecules, enabling accurate HSP predictions
- Flavor scalping, migration etc. explained using partition coefficients (from HSPs) and diffusion theory (depends on molecular size, shape)



Conclusions

- HSPs represent a useful middle ground when treating solubility
  - Not just empirical correlations (thermodynamic basis)
  - Detailed enough to approximate reality much of the time
  - General enough to apply to a range of materials
    - Highly polar / charged species represent one exception
    - Amphiphilic species (i.e. where different interactions are localized to different parts of the molecule) represent a second exception
  - Determined relatively easily (depending on definition)
- Once HSPs are known, there are many, many applications
  - Finding a solvent for a new polymer or chemical
  - Replacing a bad solvent with greener options
  - Looking to cause or prevent skin permeation
  - Identifying appropriate personal protective equipment (PPE)
  - Controlling flavor scalping, migration, etc.

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THANK YOU FOR YOUR ATTENTION!