
The Flory-Huggins Theory of Polymer Solutions

**Purdue University
Biomedical Engineering**

Professors Kinam Park & Luis Solorio

Thermodynamics of Ideal Solutions

$$\Delta G_m = G_{\text{Mixture}_{A\&B}} - (G_A + G_B)$$

$$G = H - TS$$

$$\Delta G_m = \Delta H_m - T\Delta S_m$$

Ideal Solution: Mixture of molecules that are identical in

1. size
2. energy of like and unlike molecular interactions are equal

Results in athermal mixing, or $\Delta H_m = 0$

$$\Delta G_m = -T\Delta S_m$$

Solutions are homogenous mixtures of two or more components on the molecular scale

$G \leq 0$ for spontaneous events,

Gibbs free energy is related to enthalpy and entropy

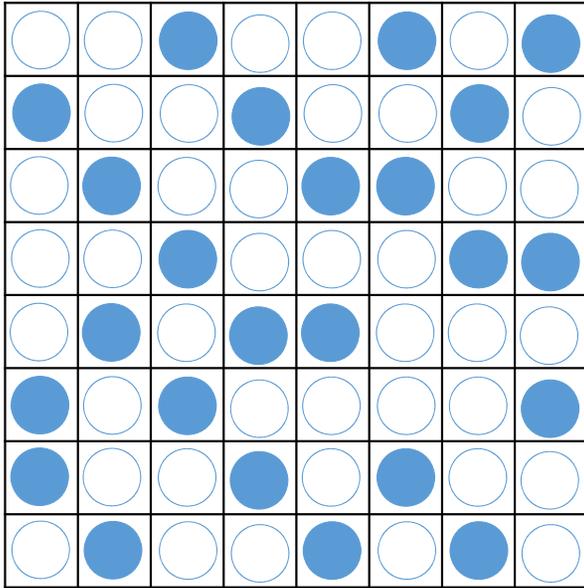
Driven towards creating the greatest chaotic dispersal

Gasses don't spontaneously contract

How does athermal mixing affect rotation, vibrational, and translation of molecules in the system?

Boltzmann's Equation

$$S = k \ln \Omega$$



○ Solvent ● Solute
□ Lattice

$$S_m^{comb} = k \ln \left(\frac{\Omega_{ideal_mix}}{\Omega_{solvent} \Omega_{solute}} \right)$$

$$S_m^{comb} = k \left[\ln \Omega_{ideal_mix} - (\ln \Omega_{solvent} + \ln \Omega_{solute}) \right]$$

$$\Omega_{solvent} = \Omega_{solute} = 1$$

$$S_m^{comb} = k \ln \Omega_{ideal_mix}$$

From statistical mechanics

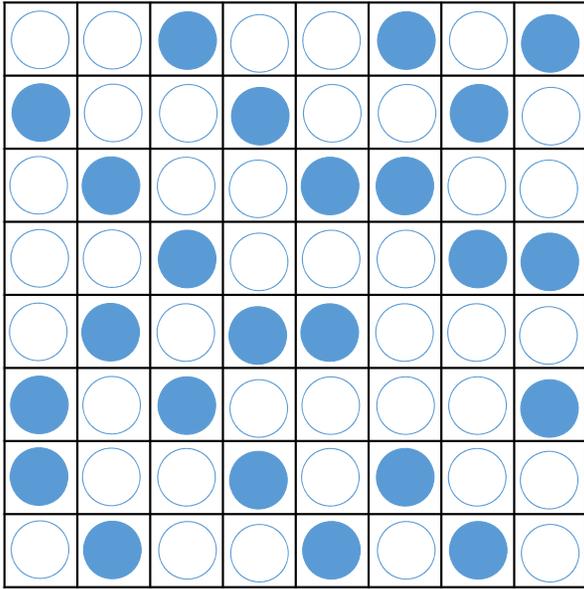
S=entropy

Ω =number of distinguishable equal energy states

k=Boltzmann constant

Identical pure substances have only 1 spatial arrangement

Ideal Liquids



$$Lattice_size = N_1 + N_2$$

$$N_1 = Solvent$$

$$N_2 = Solute$$

$$\Omega_{ideal_mix} = \frac{(N_1 + N_2)!}{N_1! N_2!}$$

Sterling's approximation: $\ln N! = N \ln N - N$ (for significantly large N)

$$S_m^{comb} = k \ln \left(\frac{(N_1 + N_2)!}{N_1! N_2!} \right) = -k \ln \left(\frac{N_1! N_2!}{(N_1 + N_2)!} \right)$$

$$S_m^{comb} = -k \left\{ N_1 \ln \left[\frac{N_1}{(N_1 + N_2)} \right] + N_2 \ln \left[\frac{N_2}{(N_1 + N_2)} \right] \right\}$$

$$N_A = (N_1 + N_2) \text{ and } n_i = N_i$$

$$S_m^{comb} = -k [n_1 \ln X_1 + n_2 \ln X_2]$$

$$k = \frac{R}{N_A}$$

$$S_m^{comb} = -R [n_1 \ln X_1 + n_2 \ln X_2]$$

$$\Delta G_m = -TdS = RT [n_1 \ln X_1 + n_2 \ln X_2]$$

Ideal Gasses

$$G = H - TS$$

$$dG = dH - SdT - TdS - dSdT$$

$$H = U + PV$$

$$dH = dU + PdV + VdP + dVdP$$

$$dG = dU + PdV + VdP - SdT - TdS$$

$$dU = TdS - PdV$$

$$dG = TdS - TdS - PdV + PdV + VdP - SdT$$

$$dG = VdP - SdT$$

At Constant Temperature

$$dG = VdP$$

$$\int dG = \int V dP$$

$$V = \frac{nRT}{P}$$

$$\int dG = nRT \int_{P_1}^{P_2} \frac{1}{P} dP$$

$$\Delta G = nRT \ln \left| \frac{P_2}{P_1} \right|$$

$$\Delta G_{molar} = RT \ln \left| \frac{P_2}{P_1} \right|$$

Raoult's Law

$$\Delta G_m = -TdS = RT [n_1 \ln X_1 + n_2 \ln X_2]$$

Look at a single component system:

$$\Delta G = RTn \ln X$$

$$\mu = \left(\frac{\partial G}{\partial n} \right)_{P,T} = \frac{G}{n} = G_{molar}$$

$$\Delta G_{molar} = \Delta \mu = RT \ln X$$

$$\mu_i = \mu_i^0 + RT \ln X_i$$

$$\Delta G_{molar} = RT \ln \left| \frac{P_2}{P_1} \right|$$

Raoult's Law

$$X_i = \frac{P_i}{P^0}$$

Raoult's law is used to define an ideal solution

It is used to identify how solutes affect factors such as changes in boiling temperature, freezing temperature, or to calculate the osmotic pressure

It can also be used to determine how the solute is affecting the vapor pressure of the solvent above the solution

Could these equations be used to accurately describe a polymer system?

Paul J. Flory, Ph.D. The Nobel Prize in Chemistry 1974

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1974/flory-autobio.html

Born on 19 June, 1910, in Sterling, Illinois.

B.S. Manchester College in Indiana, 1931.

Ph.D. Physical Chemistry, Ohio State University, 1934.

“I joined the Central Research Department of the DuPont Company. There it was my good fortune to be assigned to the small group headed by **Dr. Wallace H. Carothers**, inventor of nylon and neoprene, and a scientist of extraordinary breadth and originality. It was through the association with him that I first became interested in exploration of the fundamentals of polymerization and polymeric substances. His conviction that polymers are valid objects of scientific inquiry proved contagious. The time was propitious, for the hypothesis that polymers are in fact covalently linked macromolecules had been established by the works of Staudinger and of Carothers only a few years earlier.”

“A year after the untimely death of Carothers, in 1937, I joined the Basic Science Research Laboratory of the University of Cincinnati for a period of two years. With the outbreak of World War II and the urgency of research and development on synthetic rubber, supply of which was imperiled, I returned to industry, first at the Esso (now Exxon) Laboratories of the Standard Oil Development Company (1940-43) and later at the Research Laboratory of the Goodyear Tire and Rubber Company (1943-48). Provision of opportunities for continuation of basic research by these two industrial laboratories to the limit that the severe pressures of the times would allow, and **their liberal policies on publication**, permitted continuation of the beginnings of a scientific career which might otherwise have been stifled by the exigencies of those difficult years.”



Paul J. Flory, Ph.D. The Nobel Prize in Chemistry 1974



“In the Spring of 1948 it was my privilege to hold the George Fisher Baker Non-Resident Lectureship in Chemistry at Cornell University. The invitation on behalf of the Department of Chemistry had been tendered by the late **Professor Peter J.W. Debye**, then Chairman of that Department.

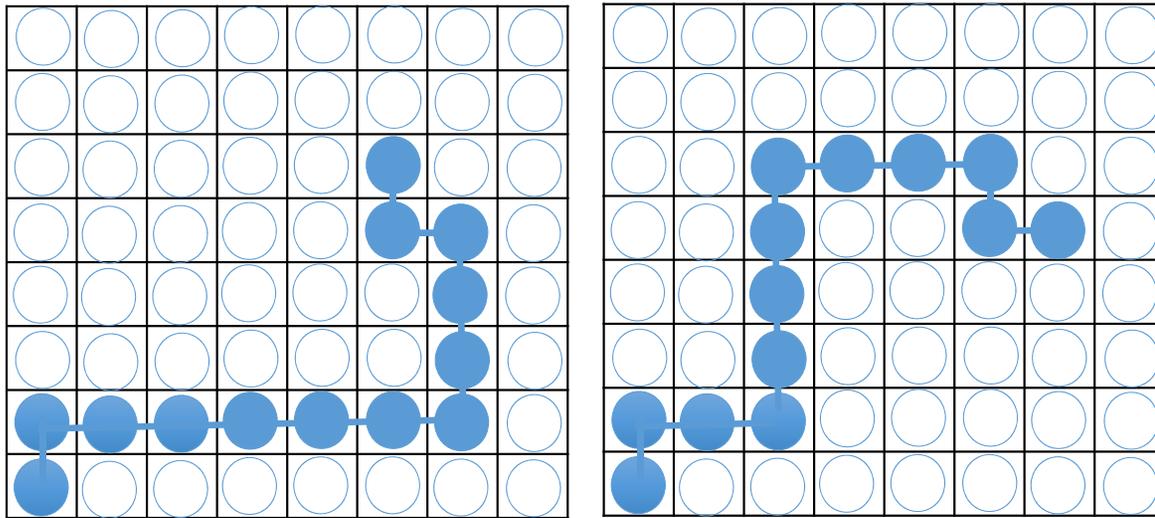
The experience of this lectureship and the stimulating associations with the Cornell faculty led me to accept, without hesitation, their offer of a professorship commencing in the Autumn of 1948. There followed a most productive and satisfying period of research and teaching "Principles of Polymer Chemistry," published by the Cornell University Press in 1953, was an outgrowth of the Baker Lectures”

“It was during the Baker Lectureship that I perceived a way to treat the effect of **excluded volume on the configuration of polymer chains**. I had long suspected that the effect would be non-asymptotic with the length of the chain; that is, that the perturbation of the configuration by the exclusion of one segment of the chain from the space occupied by another would increase without limit as the chain is lengthened. The treatment of the effect by resort to a relatively simple "smoothed density" model confirmed this expectation and provided an expression relating the perturbation of the configuration to the chain length and the effective volume of a chain segment. It became apparent that the physical properties of dilute solutions of macromolecules could not be properly treated and comprehended without taking account of the **perturbation of the macromolecule by these intramolecular interactions**.

Out of these developments came the formulation of the hydrodynamic constant called **theta**, and the recognition of **the Theta point at which excluded volume interactions are neutralized**. Criteria for experimental identification of the Theta point are easily applied. **Ideal behavior of polymers, natural and synthetic, under Theta conditions** has subsequently received abundant confirmation in many laboratories. These findings are most gratifying. More importantly, they provide the essential basis for rational interpretation of physical measurements on dilute polymer solutions, and hence for the quantitative characterization of macromolecules.

Polymer Solution. Flory-Huggins Mean Field Theory

$$S = k \ln \Omega$$



- Solvent
- Solute
- Lattice

Spatial arrangement of polymers is increased due to the different chain segment conformations

$$\Omega_{Polymer} > 1$$

$$\Omega_{ideal_mixture} > 1$$

$$\Omega_{Solvent} = 1$$

$$\Delta S_m^{comb} = k \ln \left(\frac{\Omega_{ideal_mixture}}{\Omega_{Polymer} \Omega_{Solvent}} \right)$$

$$\Delta S_m^{comb} = k \ln \left(\frac{\Omega_{ideal_mixture}}{\Omega_{Polymer}} \right)$$

$$N_0 = N_1 + x N_2$$

N_0 : number of lattice positions

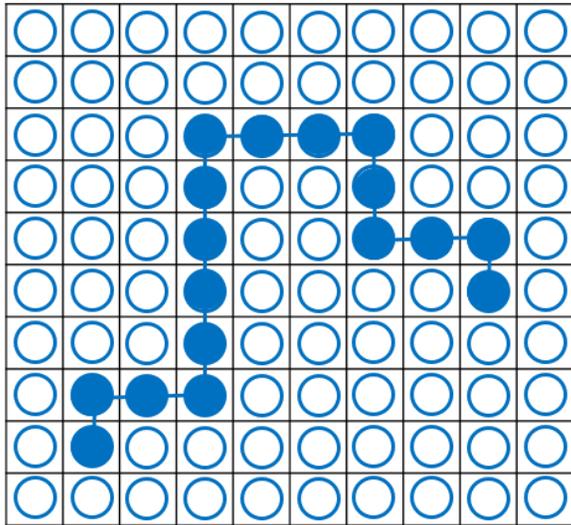
N_1 : number of solvent molecules

N_2 : number of polymer molecules

x : ratio of molecular volumes of solvent and polymer (~number of mers)

Polymer Solution. Flory-Huggins Mean Field Theory

Mean field approximation: Effect of the other individuals on any single individual is approximated by a single average effect



○ Solvent ● Repeating unit
□ Lattice z neighboring lattice sites

$$\Omega_{ideal_mixture} = \frac{1}{N_2!} \prod_{i=1}^{N_2} v_i$$

Continuous product of v ,
 v =possible conformations of the polymer in the lattice

$1/N_2!$ accounts for identical indistinguishable conformations (over counting)

Each polymer molecule occupies x lattices, and i polymer molecules have already been placed in the lattice.

$N_0 - x_i$: The number of vacant positions:

f_i : The fraction occupied by i molecules

$(1 - f_i)$: The fraction of remaining vacant positions

$z(1 - f_i)$: The number of ways arranging the next segment

$(z-1)(1 - f_i)$: The number of ways arranging the third (and all the remaining) segment

$(Z-1)(1-f_i)$: The number of ways arranging the $(i+1)th$ polymer molecule

$$v_{i+1} = \underbrace{(N_0 - xi)}_{1st\ segment} \underbrace{Z(1 - f_i)}_{2nd\ segment} \underbrace{(z - 1)(1 - f_i)}_{3rd\ segment} \underbrace{(Z - 1)(1 - f_i)}_{4th\ segment} \dots\dots$$

$$(1 - f_i) \approx \frac{N_0 - xi}{N_0}$$

$$z(z - 1)^{x-2} \approx (z-1)^{x-1}$$

Polymer Solution. Flory-Huggins Mean Field Theory

V_{i+1} : The number of configurations of just one polymer molecule in the lattice

$$V_{i+1} = (N_0 - xi)^x \left(\frac{Z-1}{N_0} \right)^{x-1} \quad V_{i+1} = \frac{(N_0 - xi)!}{[N_0 - x(i+1)]!} \left(\frac{Z-1}{N_0} \right)^{x-1}$$

The Stirling approximation

Ω : The number of ways to place the N_2 indistinguishable polymer molecules

$$\Omega = \frac{1}{N_2!} \left(\prod_{i=1}^{N_2} V_i \right) = \frac{1}{N_2!} \left(\prod_{i=0}^{N_2-1} V_{i+1} \right)$$

$$\Omega = \frac{N_0!}{N_2!(N_0 - xN_2)!} \left(\frac{Z-1}{N_0} \right)^{N_2(x-1)} = \frac{N_0!}{N_1!N_2!} \left(\frac{Z-1}{N_0} \right)^{N_2(x-1)}$$

There are many fewer configurations possible for the polymer solutions compared to small-molecule solutions.

$$\Omega_{ideal_mixture} = \left[(z-1)^{(x-1)N_{Polymer}} \left[\left(\frac{x}{e^{x-1}} \right)^{N_{Polymer}} \left[\left(\frac{N}{N_{Solvent}} \right)^{N_{solvent}} \left(\frac{N}{xN_{Polymer}} \right)^{N_{Polymer}} \right] \right] \right]$$

Total conformations of the polymer molecules with complete freedom in the lattice

Conformations when polymer molecules are competing for cells in a pure amorphous polymer

The number of conformations of the polymer in a solvent

$\Omega_{polymer}$ is provided by the first two factors

Polymer Solution. Flory-Huggins Mean Field Theory

The configurational entropy represents the entropy of mixing of the perfectly ordered pure solid polymer, for which $S = 0$, with pure solvent.

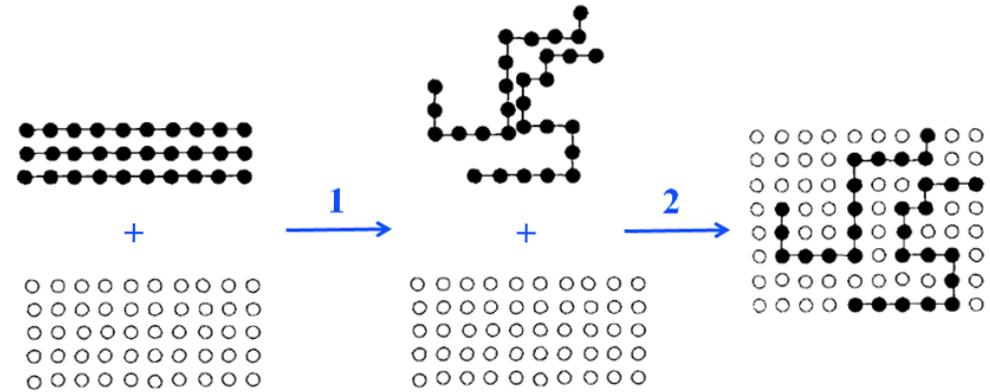
$$S_c = -k \left[N_1 \ln \frac{N_1}{N_1 + xN_2} + N_2 \ln \frac{N_2}{N_1 + xN_2} - N_2(x-1) \ln \frac{Z-1}{e} \right]$$

$$S_c = \Delta S_{dis} + \Delta S_{mix}$$

Disordering & dissolution of a polymer

1. Formation of an amorphous polymer (disorientation)

$$\rightarrow \Delta S_{dis}$$



2. Dissolution of the amorphous polymer in the solvent $\rightarrow \Delta S_{mix}$

$$\Delta S_{dis} = \lim_{N_1 \rightarrow 0} S_c = k \left[N_2 \ln x + N_2(x-1) \ln \frac{Z-1}{e} \right] \quad \Delta S_{mix} = -k \left[N_1 \ln x \frac{N_1}{N_1 + xN_2} + N_2 \ln \frac{xN_2}{N_1 + xN_2} \right]$$

Polymer Solution. Flory-Huggins Mean Field Theory

Assume $x = \bar{V}_2/\bar{V}_1$

$$\Delta S_{mix} = -R(n_1 \ln \phi_1 + n_2 \ln \phi_2)$$

Polymer molecules

$$\Delta S_{mix} = -R[n_1 \ln X_1 + n_2 \ln X_2]$$

Small molecules

n : number of moles

ϕ : volume fraction

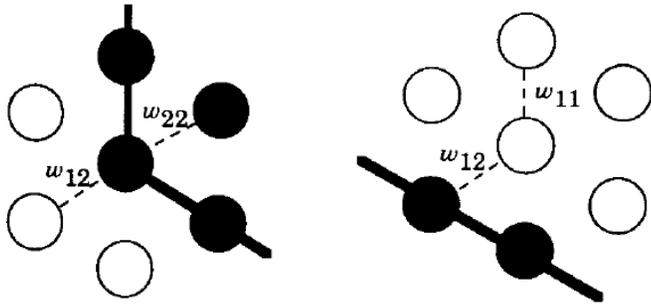
G=H-TS

This provides the entropy and is sufficient for the cases when no enthalpy occurs

However that is an unrealistic assumption with polymers

Polymer Solution. Flory-Huggins Mean Field Theory

Mixing Enthalpy: Interaction energy between solvent molecules and solute segments



$$\frac{1}{2}[1,1] + \frac{1}{2}[2,2] \rightarrow [1,2]$$

$$\Delta w_{1,2} = w_{1,2} - \frac{1}{2}(w_{11} + w_{22})$$

$$\Delta H_{mix} = RT\chi_1 n_1 \phi_2$$

The energy change (in units of RT) that occurs when a mole of solvent molecules is removed from the pure solvent (where $\phi_2 = 0$) and is immersed in an infinite amount of pure polymer (where $\phi_1 = 0$).

$$\frac{\Delta H_{mix}}{N} = RT\chi_{12}v_1v_2$$

$\Delta H_{mix} < 0$: Exothermal

$\Delta H_{mix} = 0$: Athermal

$\Delta H_{mix} > 0$: Endothermal

$\chi_{12} = z\Delta w_{12}/RT$: Interaction parameter

Polymer Solution. Flory-Huggins Mean Field Theory

$$\Delta G_{mix} = RT \left[\chi_1 n_1 \phi_2 + n_1 \ln \phi_1 + n_2 \ln \phi_2 \right]$$

ϕ_1 and ϕ_2 are always lower than 1.
Thus, $\ln \phi_1$ and $\ln \phi_2$ have always negative value.

$$\Delta G_{mix} < 0 \quad \text{Polymer dissolves in solvent}$$

$$\chi_1 n_1 \phi_2 > n_1 \ln \phi_1 + n_2 \ln \phi_2 \quad \text{Polymer does not dissolve in solvent}$$

For complete miscibility over all concentrations, χ_1 for the solute-solvent pair at the temperature (T) of interest must be less than 0.5.

- If $\chi > 0.5$, then $\Delta G_{mix} > 0$ and phase separation occurs
- If $\chi < 0.5$, then $\Delta G_{mix} < 0$ over the whole composition range.
- The temperature at which $\chi = 0.5$ is the θ temperature.

$$\mu_1 - \mu_1^o = \left(\frac{\partial \Delta G_{mix}}{\partial n_1} \right)_{p_1, T_1, n_2}$$

μ_1^o : Pure solvent activity
 μ_1 : Solvent activity in solution

$$\mu_1 - \mu_1^o = RT \left[\ln(1 - \phi_2) + \left(1 - \frac{1}{x} \right) \phi_2 + \chi_1 \phi_2^2 \right]$$

Polymer Solution. Flory-Huggins Mean Field Theory

$$\Delta G_{mix} = RT[\chi_1 n_1 \phi_2 + n_1 \ln \phi_1 + n_2 \ln \phi_2]$$

ϕ_1 and ϕ_2 are always lower than 1.
Thus, $\ln \phi_1$ and $\ln \phi_2$ have always negative value.

Flory-Huggins equation makes it possible to account for the thermodynamic properties of polymer solutions

Accounts for the large deviations from Raoult's Law

It is great for predicting general trends, but theory still deviates from the experimental data

Deviation occurs as a result of the necessary assumptions needed to create a solution

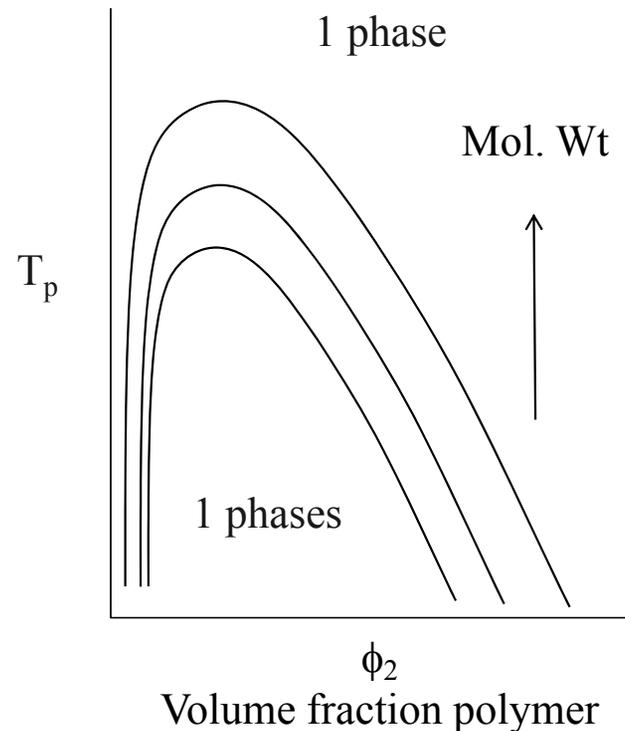
- Does not account for volume change during mixing
- Does not exclude self-intersections of the chain
- Mean field approximations are more accurate for high polymer concentration

Regardless, it was a huge step forward in understanding how polymers behave

Application: Polymer Solubility

- Polymer with higher molecular weight precipitates more readily than the polymer with lower molecular weight.
- Add non-solvent until solution becomes turbid
- Heat, cool slowly and separate precipitate
- Finite drop in temperature always renders finite range of molecular weight insoluble
- Some high molecular weight polymer will also remain soluble!
- Solubility of polymers generally decreases with increasing molecular weight.

T_p : Precipitation temperature at which detectable turbidity can be first observed.



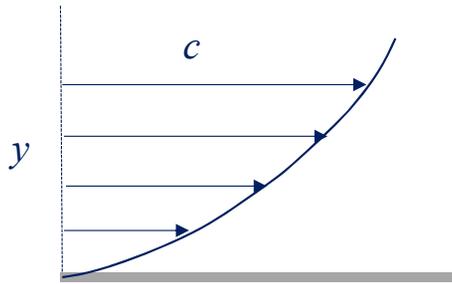
The θ Conditions Described in Movies



Viscosity of Polymer Solutions

Dynamic Viscosity (Absolute or Shear Viscosity)

Dynamic viscosity is a measure of the resistance of a fluid to gradual deformation by shear stress. The resistance is a result of friction caused by sliding layers of fluid.



Newton's Law of Friction

$$\tau = \eta \dot{\gamma}$$

τ : Shear stress in fluid in Pascal (N/m²)

η : Dynamic viscosity of fluid (N·s/m²)

$\dot{\gamma}$: Shear rate (s⁻¹) = $\Delta c / \Delta y$

Δc : Unit velocity (m/s)

Δy : Unit distance between layers (m)

$$\eta = \frac{\tau}{\dot{\gamma}} = \left(\frac{N}{m^2} \right) / \left(\frac{m}{s} \right) / m = \frac{Ns}{m^2}$$

$$1 \frac{Ns}{m^2} = 1 \left(\frac{Kg \cdot m}{s^2} \right) \left(\frac{s}{m^2} \right) = 1 Pa \cdot s = 10 P = 10 \frac{g}{cm \cdot s}$$

1 Pa·s (Pascal second) P: Poise

1 Pa·s: Two plates are separated by 1 m with a fluid in between, and one plate is moving parallel to the other plate with a shear stress of 1 pascal to move 1 m/s. If 2 m/s, then the viscosity is ½ Pa·s.

The viscosity of water = 1 cP (= 0.01 g/cm·sec = 1 mPa·sec = 0.001 Pa·sec = 0.001 N·s/m²).

Viscosity of Polymer Solutions

Viscosity of a polymer solution can be measured by various methods. Viscosity of a polymer solution is a function of temperature, solvent, polymer concentration, and polymer molecular weight. When a polymer molecular weight is determined

Viscosity of a polymer solution provides insightful information on the configuration of the polymer molecules in solution. At high polymer concentrations, polymer molecules tend to entangle each other, and this affects the measurement of viscosity. Thus, it is necessary to estimate the effect of solvent viscosity and polymer concentration on the overall viscosity. Since the viscosity measurement procedures do not remove the effects of polymer-solvent interactions, the viscosity average molecular weight (\overline{M}_v) depends on some extent on the solvent used

In a dilute solution, the disturbance of the flow pattern of the suspending medium by one particle does not overlap with that caused by another. Solvent trapped inside a polymer molecule has lower viscosity than the bulk solution. Thus, the polymer coil behaves as an impenetrable sphere.

Viscosity of Polymer Solutions

Viscosity of spheres and random coil molecules.

$$\eta = \eta_o \left(1 + \frac{5}{2} \phi \right) = \eta_o \left(1 + \frac{5 N_A c V_h}{2 M} \right)$$

where N_A is the Avogadro's number, c is the polymer concentration (g/ml), M is the polymer molecular weight, and V_h is the volume of a solvated molecule.

Relative viscosity (η_{rel}):

$$\eta_{rel} = \frac{\eta}{\eta_o} = 1 + \frac{5}{2} \phi$$

Specific viscosity (η_{sp}):

$$\eta_{sp} = \frac{\Delta\eta}{\eta_o} = \frac{\eta - \eta_o}{\eta_o} = \eta_{rel} - 1 = \frac{5}{2} \phi$$

The specific viscosity accounts for the effect of solvent viscosity. The specific viscosity (η_{sp}) is a suitable indicator for the changes in shape.

Spherical polymer has low resistance to flow, and so, small η_{sp} .

Stretched, rod-like shape has higher resistance to flow, leading to high η_{sp} .

Viscosity of Polymer Solutions

Reduced viscosity (η_{red}):
$$\eta_{red} = \frac{\eta_{sp}}{c} = \left(\frac{1}{c}\right) \frac{\eta - \eta_o}{\eta_o}$$

The concentration effect is adjusted and it is valid only for dilute solution.

Intrinsic viscosity ($[\eta]$)
$$[\eta] = \frac{\Delta\eta}{c\eta_o} \Big|_{c \rightarrow 0} = \lim_{c \rightarrow 0} \frac{\eta_{sp}}{c} = \frac{5}{2} \frac{N_A V_h}{M} = \frac{5}{2} \frac{N_A}{M} \frac{4\pi \langle R_g^2 \rangle^{\frac{3}{2}}}{3} = \frac{\Phi \langle R_g^2 \rangle^{\frac{3}{2}}}{M} = KM^\alpha$$

The contribution of the individual macromolecules to the viscosity increase will be independent and additive only when the polymer molecules are infinitely far from each other. N_A and M are constants, so V_h can be calculated from the viscosity measurement.

Huggins Equation:
$$\eta_{red} = \frac{\eta_{sp}}{c} = [\eta] + k_H [\eta]^2 c$$

The reduced viscosity is related to $[\eta]$ by a power series of the form.

The constant k_H is termed the Huggins constant and has values ranging from 0.3 in good solvents to 0.5 in poor solvents. It contains information about hydrodynamic and thermodynamic interactions between coils in solution.

Solubility Parameters

Poly(lactide-co-glycolide) (PLGA)

Solubility Parameters

Solubility parameters are frequently used to predict compatibility between polymers and solvents. The dissolution rate and extent of polymer dissolution in a solvent depend on the thermodynamic compatibility of the polymer with solvent and the T_g of the polymer, the nature of solvent (solubility parameters), temperature, chemical composition and molecular structure of the polymer, and crystalline form of solid polymorphism. The solubility of a given polymer in different solvents largely depends on its chemical structure. Polymers dissolve in solvents whose solubility parameters are similar to their own, and in general, structural similarity favors solubility, known as the ‘like dissolves like’ principle.

Dissolution of a polymer in a solvent requires the energy (E_{vap}) to break all intermolecular physical links in a unit volume, which is known as the cohesive energy density (CED):

$$CED = \frac{E_{vap}}{V_m} = \frac{\Delta H_{vap} - RT}{V_m}$$

where ΔH_{vap} is the enthalpy of vaporization, RT is the thermal energy, and V_m is the molar volume of the polymer. Thus, CED is the energy of vaporization in calories (or Joules) per cubic centimeter. CED reflects the degree of van der Waals forces that hold the molecules together.

The Hildebrand Solubility Parameter (Total Solubility Parameter), δ_t

The Hildebrand solubility parameter (or total solubility parameter), δ_t , is defined as:

$$\delta_t = \left(\frac{E_{vap}}{V_m}\right)^{1/2} = \left(\frac{\Delta H_{vap} - RT}{V_m}\right)^{1/2}$$

ΔH_{vap} of polymers cannot be measured directly, and thus, indirect methods are used to calculate the solubility parameters of polymers. The enthalpy of mixing a polymer with a solvent per unit volume, $\Delta H_{mix}/V_{mix}$, is given by:

$$\frac{\Delta H_{mix}}{V_{mix}} = (\delta_{t,1} - \delta_{t,2})^2 \phi_1 \phi_2$$

where V_{mix} is the volume of mixing, and ϕ_1 and ϕ_2 are the volume fractions of solvent and polymer, respectively. As a general rule, $(\delta_{t,1} - \delta_{t,2})^2$, the difference in solubility parameters of a solvent and a polymer, must be small for dissolution to occur over the entire volume fraction range. In fact, it is related to the Flory-Huggins parameter χ by the following relation:

$$\chi = \frac{V_{mix}}{RT} (\delta_{t,1} - \delta_{t,2})^2$$

The Hildebrand solubility parameter does not account for any specific interaction, especially hydrogen bonding. Thus, if polar contributions are significant to the total *CED* of a solvent, the Hildebrand solubility parameter may not be able to explain the lack of interaction between the solvent and the polymer.

The Hansen's Partial solubility parameters

Since slight differences in polar contributions cause significant differences in solubility behavior, different types of polar contributions were identified to more accurately reflect the solubility behavior of solvents. The Hildebrand solubility parameter can include the hydrogen bonding based on the assumption that solubility is highest if the two materials have similar polarities. In this approach, solvents are divided into three categories of hydrogen bonding, such as poor (or weak), moderate, and strong hydrogen bonding capabilities.

Hansen also developed solubility parameters based on three specific interactions: dispersive (non-polar), polar cohesive (dipole-dipole), and hydrogen bonding interactions. Thus, it is called **Hansen's three-component solubility parameters** (or **partial solubility parameters**) in comparison with Hildebrand's total solubility parameter. In this approach, the cohesive energy (E) has dispersive (d), polar (p), and hydrogen bonding (h) components.

$$\delta_t = \left(\frac{E}{V_m}\right)^{1/2} = \left(\frac{E_d + E_p + E_h}{V_m}\right)^{1/2} \quad \text{Thus,} \quad \delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$$

For selecting good solvents for PLGA, each solvent needs to be examined by individual contributions, i.e., δ_d , δ_p , and δ_h separately, instead of the total solubility parameter δ_t . If a solvent has high polar contribution, the solvent molecules may be attracted to each other than to PLGA. Thus, to avoid any inconsistencies in the 'like dissolves like' principle, all 4 solubility parameters (δ_d , δ_p , δ_h , and δ_t) need be measured for each PLGA.

Solubility Parameters of Solvents

Solubility parameters of solvents can be determined from experimentally measuring ΔH_{vap} , and the values of most solvents are available in the literature. The ΔH_{vap} value of a solvent measured at one temperature can be converted to the values at any other temperature using the following empirical equation:

$$\frac{\Delta H_{vap,T_2}}{\Delta H_{vap,T_1}} = \left(\frac{T_c - T_2}{T_c - T_1} \right)^{0.38}$$

where T_c is the critical temperature, i.e., the theta (θ) temperature, at which a polymer of infinite size mixes with the solvent completely.

The solubility parameters of the solvent blends can be calculated by averaging the solubility parameter values of the individual solvents by their volume fractions (ϕ_i):

$$\bar{\delta} = \sum_i \phi_i \delta_i$$

This equation is useful when different solvents need to be mixed to generate a solvent with particular solubility parameters, and/or solvents in need are not readily available or too toxic to use. It may sound strange but the mixture of two bad solvents can result in a good solvent, assuming that the two mix well.

Solubility Parameters of Polymers

The solubility parameters of polymers are difficult to obtain, because there is no measurable value of ΔH_{vap} or boiling point for polymers. Thus, indirect methods are used to obtain the values. The classical method of determining Hansen solubility parameters of a polymer involves testing of polymer solubility in different solvents with known partial solubility parameters (Hansen's three solubility parameters).

The partial solubility parameters of solvents that interact with the given solvent (i.e., either dissolves the polymer or the polymer swells in the solvent) are plotted in 3 planes of the $2\delta_d$, δ_p and δ_h axes to form circles of radius R , which is **the radius of interaction sphere**. The coordinates of the center of the spheres represent Hansen solubility parameters of polymers. This classical method has a shortcoming that good solvents may not be included in the interaction sphere or poor solvents may be included in the sphere. This shortcoming was overcome by calculating the maximum separation distance and using it as the diameter of the interaction sphere to find the coordinates of its middle as the Hansen parameters. The limitation of this method is that the position of the middle is not well defined, if there exist several equal maximum separation distances. In addition, this method treats good and limiting solvents of a polymer with equal weight, i.e., there is no mechanism of distinguishing the good from the limiting solvents. Limiting solvents are those that have limited interactions, e.g., the polymer may not dissolve but can swell in them.

Solubility Parameters of Polymers

The more accurate radius of interaction sphere can be obtained by assigning different weights to good and limiting solvents of a polymer. The weights of the solvents can be easily determined by the intrinsic viscosities $[\eta]$ which can be readily measured by a triple-detector GPC.

The measured $[\eta]$ is normalized to unity as follows.

$$\delta_t = \frac{\sum \delta_{t,i}[\eta]_i}{\sum [\eta]_i} \quad \delta_d = \frac{\sum \delta_{d,i}[\eta]_i}{\sum [\eta]_i} \quad \delta_p = \frac{\sum \delta_{p,i}[\eta]_i}{\sum [\eta]_i} \quad \delta_h = \frac{\sum \delta_{h,i}[\eta]_i}{\sum [\eta]_i}$$

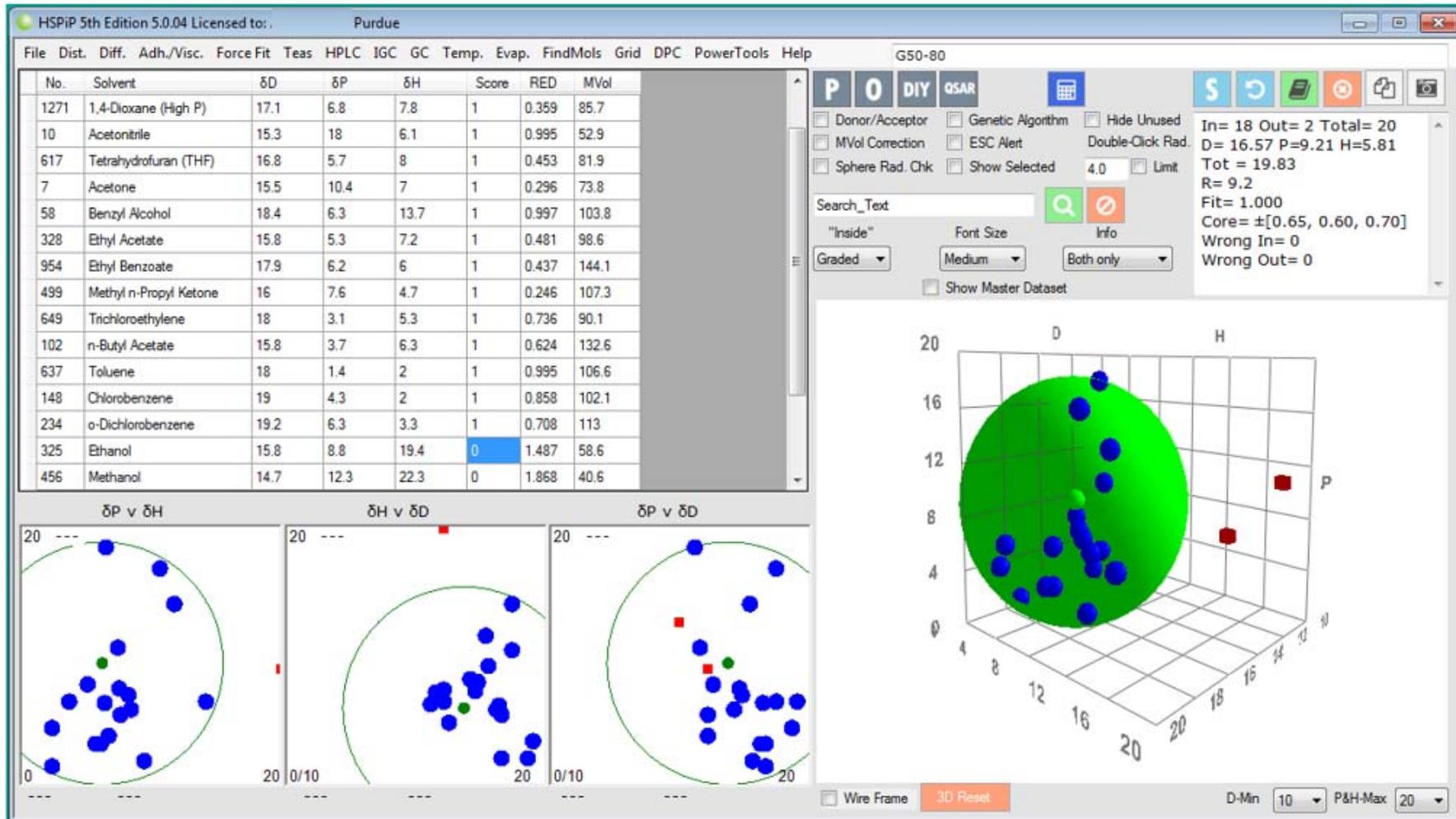
where the subscript i indicates individual solvents. Solvents that do not dissolve the polymer are given an intrinsic viscosity of zero. The good solvents result in higher $[\eta]$, while the limiting solvents results in much lower $[\eta]$. The accuracy of the experimentally measured $\delta_{d,i}$, $\delta_{p,i}$ and $\delta_{h,i}$ increases as more solvents are tested.

Once the coordinates of δ_d , δ_p and δ_h are plotted as the center, the separating distances from the center to points corresponding to good and limiting solvents are plotted to calculate R_i values. The largest value of R_i is considered the radius of interaction sphere, R .

$$R_i = 4(\delta_{d,i} - \delta_d)^2 + (\delta_{p,i} - \delta_p)^2 + (\delta_{h,i} - \delta_h)^2$$

This improved method based on weighted intrinsic viscosities of a polymer in various solvents results in the interaction sphere including all good and limiting solvents.

Solubility Parameters of PLGA



Solubility Parameters of PLGA

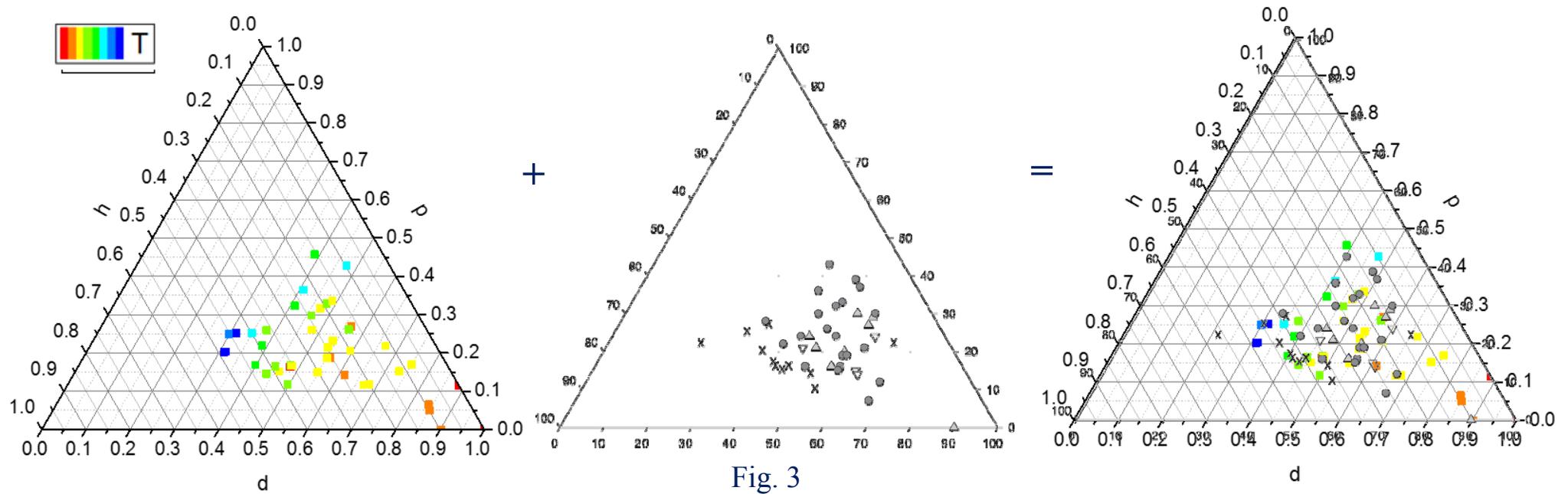


Fig. 3. Comparison of Hansen's solubility parameters for various solvents: contributions of dispersion forces (f_d), polar interactions (f_p), and hydrogen bonding (f_h). (●) Good solvent; (▲) intermediately good solvent; (▼) intermediately poor solvent; and (x) poor solvent. (Yeo et al., *J. Controlled Rel.* 93: 161-173, 2003)

Dried PLGA (L:G=50:50, $[\eta] = 0.58$ dl/g) (125 mg) was added to glass vials containing 5 ml of the test organic solvent. The vials were agitated overnight at room temperature. Solubility of PLGA was judged by visual examination. Solvents were classified into four groups: good solvents that formed clear polymer solutions; intermediately good solvents that formed turbid polymer solutions upon heating; intermediately poor solvents that were marginally able to swell the polymer; and poor solvents in which the polymer remained intact.

The Group Contribution Methods

The solubility parameters of polymers can be measured by the weighted intrinsic viscosity ($[\eta]$) method, but measurement of $[\eta]$ has not been practical until recently when GPC-TDS became available. Thus, the solubility parameter of polymers has been calculated using the group contribution methods, which consider the energy (E) as an additive property for low molecular weight materials.

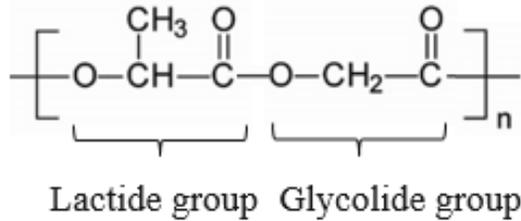
$$\delta_t = \left(\frac{E}{V_m}\right)^{1/2} = \left(\frac{\Delta H_{vap} - RT}{V_m}\right)^{1/2} = \left(\frac{\sum \Delta h_i}{V_m} - \frac{RT}{V_m}\right)^{1/2}$$

where Δh_i is the contribution of i th group to the molar heat of vaporization. The solubility parameter can also be calculated using Small's molar attraction constants (F).

$$\delta_t = \frac{\sum F}{V_m} = \frac{\sum F}{\frac{M}{\rho}} \quad \text{where } \rho \text{ is the density.}$$

From the general structure of PLGA, the F value of each group found in the literature can be used to calculate the Hildebrand solubility parameter of PLGA.

The Group Contribution Methods



Group	CH ₃	CH ₂	CH	C=O	O
F	214	133	28	310	70

$$F: (\text{cal}\cdot\text{cm}^3)^{1/2} \text{ cm}^3/\text{mol at } 25 \text{ }^\circ\text{C}$$

The Units of the solubility parameters: $1 (\text{MPa})^{1/2} = 1 \left(\frac{\text{J}}{\text{cm}^3}\right)^{1/2} = 0.4888 \left(\frac{\text{cal}}{\text{cm}^3}\right)^{1/2}$

Although the solubility parameters of polymers can be estimated using the group contribution methods, the estimated values are likely to be different from the experimentally measured values. This is because the group contribution methods only consider the chemical structure without considering the molecular weight of the polymer, and a polymer as a whole may have different interactions with solvents unlike small groups do. Even though the polymer has the same structure regardless of the molecular weight, the reality is that the same polymer often has different solubility in a given solvent depending on the molecular weight. Thus, it is important to obtain the partial solubility parameters based on experimental values, such as weighted intrinsic viscosity values.

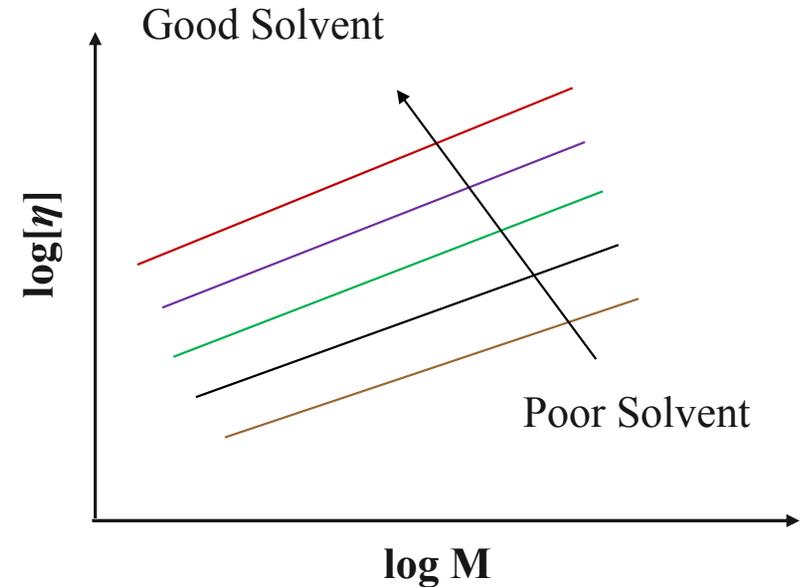
The Mark-Houwink Plot

The dependence of intrinsic viscosity $[\eta]$ of a polymer on its molecular weight M is given by the Mark-Houwink(-Sakurada) equation:

$$[\eta] = KM^\alpha \quad \text{or} \quad \log[\eta] = \log K + \alpha \log M$$

where K and α are two parameters that depend on the solvent, polymer, and temperature.

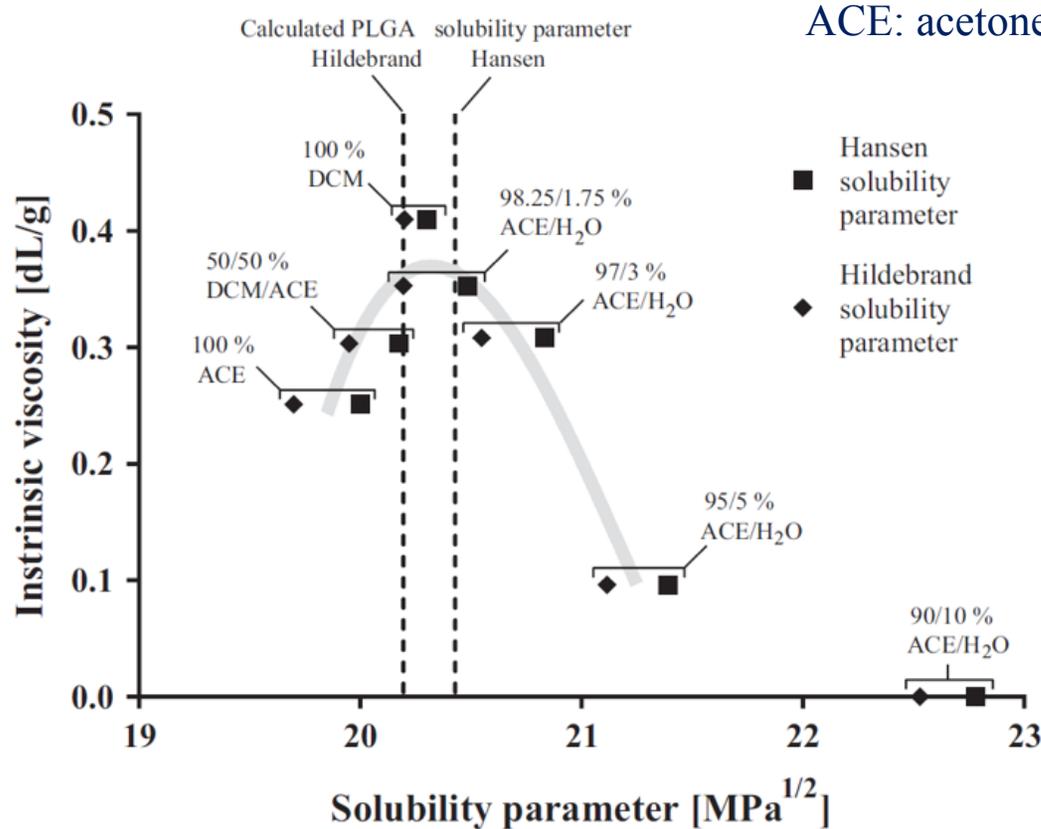
It is common to plot the Mark-Houwink equation in a log-log graph to calculate the K and α values from the intercept and the slope. The slope is related to the shape of the polymer molecules and the polymer-solvent interactions. $\alpha = 0.5$ for a polymer under θ conditions (i.e., an unperturbed random coil). $\alpha = 0.8$ for a polymer in a good solvent, while $\alpha = 2$ for rod-like polymers. The slope α is related to the solubility parameters of the polymer and the solvent.



Mark-Houwink plots of a polymer in different solvents.

The molecular weight (M) remains the same but the V_h of the polymer changes in different solvents. The intrinsic viscosity $[\eta]$ increases as the V_h increases in good solvents. Thus, the solvent quality for each PLGA can be characterized by using the K and α values.

The Intrinsic Viscosity and Solubility Parameters



Intrinsic viscosities and solubility parameters of PLGA (L:G=50:50) in various solvents.

Solvents in which the polymer is insoluble were given an intrinsic viscosity of zero. The calculated Hildebrand and Hansen solubility parameters of PLGA are indicated by broken lines. The shaded line indicates best cubic fit ($R \leq 0.95$). The 90/10% ACE/H₂O blend was excluded from the fit.

C.G. Madsen, A. Skov, S. Baldursdottir, T. Rades, L. Jorgensen, N.J. Medicott.

Simple measurements for prediction of drug release from polymer matrices – Solubility parameters and intrinsic viscosity.

Eur. J. Pharm. Biopharm. , 92 (2015) 1-7.