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Practical Prediction of Heteropolymer Composition and Drift

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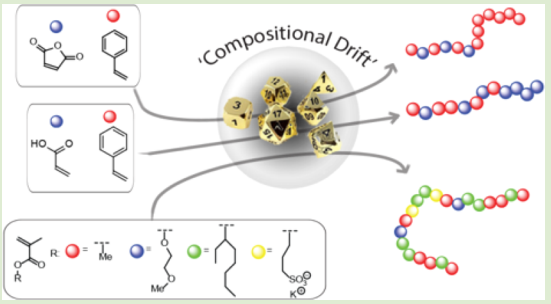
Supporting Information

ABSTRACT: Composition drift in batch polymerizations is a well-known phenomenon and can lead to composition gradients in polymers synthesized using controlled polymerization methodologies. With known reactivity ratios of monomers, the drift, and thus resultant gradient copolymer, can be designed by adjusting reagent ratios and targeted conversions. Although such prediction is straightforward, it is seldom done, likely due to the perceived difficulty and unfamiliarity for nonspecialists. We seek to remedy this by providing the communities using copolymers with an easy-to-use program called Compositional Drift which is based on the Mayo−Lewis model and the penultimate model of monomer addition, using Monte Carlo methodology. This tool can also be applied to predict composition in nondrifting polymerizations. Herein we supply this tool to the community, showcasing two recent examples of use to guide experimental design and understanding of heteropolymers (RHP).



Polymer scientists have long looked at proteins with envy. The unparalleled control of monomer distribution and dispersity in proteins invokes awe and is still well beyond the reach of current polymer chemistry. That gap, however, is narrowing, and the possibilities and limits of monomer sequence distribution control in radical polymerization is a rapidly expanding field of interest.[1−6] The theoretical understanding toward monomer distribution in gradient-block copolymers is well developed, though experimentally it is rarely utilized. One barrier is the complexity of design and analysis involved.[7,8] While comprehensive software packages for predicting polymerizations have been developed, most prominently Predici by M. Wülkow, they are rarely used to plan for exploratory experimental work or in the phase of a system's design due to their perceived complexity.[9−11] There are exceptions,[12,13] but they are notable. With the sole aims to facilitate the development of random heteropolymers (RHP) and lower design barriers for communities outside of polymer chemistry, we supply a straightforward tool for predicting copolymer composition, instantaneous copolymer composition, and compositional drift, inspired by the work of Harrisson et al.[7]

The reported program, called "Compositional Drift", uses a Monte Carlo method to give a quick and user-friendly overview of copolymer composition in controlled radical polymerizations (CRP). The program offers a simplified understanding of how change in monomer composition in batch polymerizations is reflected in the polymer. The parameters needed are the number of unique monomers, their relative molar ratios, the number-average degree of polymerization (DP) at 100% conversion, and the reactivity ratios of all monomers with each other. The program was developed while performing reversible addition−fragmentation chain-transfer (RAFT) polymerizations, though it is equally applicable to Atom Transfer Radical Polymerization (ATRP) or Nitroxide-mediated polymerization (NMP).

It is important to note, however, that reactivity ratios are affected by solvent and reaction temperature.[14,15] For CRP of polymers with small DP at low conversions, the assumptions of the Mayo−Lewis model are invalidated due to deviating reactivities of short chain radicals, kinetics of the initiation step, and the activation/deactivation equilibria. Thus, the apparent reactivity ratios, as measured for low DP polymers in CRP, may differ from those of free radical polymerizations.[16] Moreover, the reactivity ratios need to be determined for a given set of reaction conditions, i.e. temperature and solvent, for the program to yield the most accurate representation of the polymerization. Likewise, it is important to know which model of monomer addition is applicable.

Polymerizations are simulated by the Monte Carlo method. The Mayo−Lewis model statistically describes how a copolymerization progresses in terms of relative consumption of monomers as described in eq 1[17]

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1](r_1[M_1] + [M_2])}{[M_2]([M_1] + r_2[M_2])}, \qquad r_x = \frac{k_{xx}}{k_{xy}} \tag{1}$$

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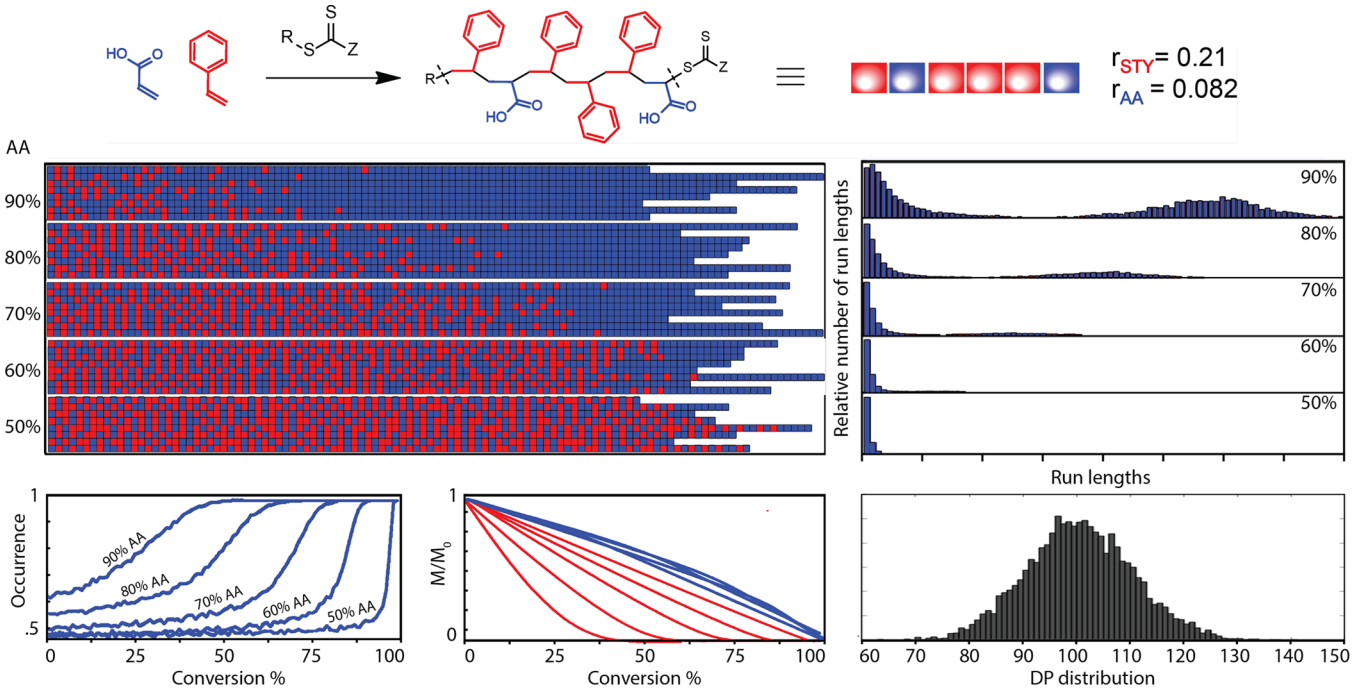

Figure 1. Program output for 50%−90% acrylic acid (AA), 50%−10% styrene (Sty) at [M]:[CTA] = 100, conversion = 100%. Reactivity ratios: r_{Sty} = 0.21, r_{AA} = 0.082. Top left: rows of simulated polymers, with each horizontal line representing one polymer and each row representing one simulation. Top right: distributions of monomer run lengths. Bottom left: probability of AA being incorporated as a function of conversion. Bottom center: Individual monomer consumption relative to the initial conditions. Change in monomer feed composition is reduced as the initial conditions approximate the azeotrope (46.3% AA, 54.7% Sty). Bottom right: Normalized DP distribution.

with $[M_x]$ being the concentration of monomer x, and r_x being the reactivity ratio, where k_{xy} is the rate constant for the addition of monomer y to a radical with terminal monomer x. The equation describes the relative instantaneous rates of incorporation of monomers in free radical polymerizations. However, this copolymer equation has also been used together with CRP to predict and synthesize statistical gradient copolymers, as all chain growth is ideally initiated at the same time in CRP of copolymers.[7,18,19] Once all of the required parameters are defined in the program, the method is executed in three steps as described below.

i. Determination of number of chains: The program determines the number of chains to be generated from the size of the monomer pool and the number-average DP, i.e. the molar ratio between the monomers and the controlling agent, be it the RAFT agent, ATRP initiator, or NMP initiator.

$$\text{Number of Chains} = \frac{\text{Monomer Pool}}{\text{Number Average DP}}$$

These chains are represented as empty lists to be populated with monomers.

ii. First monomer: The first monomer for each chain is determined by eq 1, such that the probability of a given monomer being first is equal to its composition fraction at the initial conditions. The first monomer can also be chosen to be exclusively one monomer. Experimentally, this is relevant when the initiating species have a higher reactivity toward a particular monomer, which can be the case,[20] though this will only impart a small impact on the overall composition for polymers with high DP.[16] As monomers are added to the propagating polymer chains, they are subtracted from the monomer pool. After the initial monomers are chosen, the program proceeds to the next step.

iii. Growth and termination: The program adds single monomers to random polymer chains until the chosen conversion of the monomer pool is reached. The monomers added are subtracted from the monomer pool. The monomer to be added is determined by the terminal monomer of the chain, the composition of the monomer pool, and the reactivity ratios for the given monomers, using a Monte Carlo method in the following manner

$$P(x|y) = \frac{k_{yx}[M_x]}{\sum_z k_{yz}[M_z]} \tag{2}$$

where x is a monomer being appended to the growing chain, y is the terminal monomer on the chain, $[M_x]$ is the monomer fraction of monomer x, k_{xy} is the relevant rate constant derived from the given set of reactivity ratios, and z is all of the unique monomers used. For example, if $[M_x]$ = 0.2, $[M_y]$ = 0.8, and r_y = 0.082, the probability of x adding to the chain ending with y:

$$P(x|y) = \frac{\frac{1}{0.082}(0.2)}{\frac{1}{0.082}(0.2) + 0.8} = 0.75$$

The method remains the same regardless of the number of unique monomers in the polymerization. By setting the homopropagation rate to be 1 for each monomer in the weighted random selector, the relative rate constants needed to calculate the weighted probability of monomer addition are found. This is only valid in terms of describing the probability of which monomer is added to the chain.

$$r_{xy} = \frac{k_{xx}}{k_{xy}}, \quad k_{xy} = \frac{1}{r_{xy}}, \quad r_{xz} = \frac{k_{xx}}{k_{xz}}, \quad k_{xz} = \frac{1}{r_{xz}} \tag{3}$$

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The instantaneous copolymerization equation used to determine the starting monomer has only been implemented in the program for up to 3 monomers at this point.

The user can manually choose a specific monomer to be initiated, or have it determined from the weighted distribution in the monomer feed. Both options can introduce a minor inaccuracy in the composition that diminishes with increasing DP. For RHPs with all reactivity ratios close to 1, there is likely little bias in the initiated monomer, and thus the weighted distribution provides the best approximation for the actual composition. If the reactivity ratios are far from 1, the monomer with highest reactivity toward the initiating radical should be chosen.

For terpolymers, the program yields identical cumulative composition plots to those published by Scott and Penlidis.[21] This study also found that ternary reactivity ratios can differ from those determined from binary systems. Consequently, using these in the program will yield a higher quality simulation and should be done if available.

The program can also accommodate the penultimate addition model, using reactivity ratios measured while taking the effect of penultimate monomers into account. The method for determining monomer addition remains the same in this case but with the relative rate constants changed accordingly.

Any deviations from these models are not accounted for. Since the program randomly adds monomers to polymers, a distribution of polymer lengths arises, with the theoretically most narrow dispersity index possible for living polymerization. The simulation data is plotted directly in the program according to the user's needs; graphs, images, and a raw data text file can be exported for further analysis.

The distribution of monomers appearing in sequence along the polymer chain can be plotted as a histogram. This plot is particularly relevant in systems with a high degree of cross propagation, such as styrene-maleic anhydride copolymers.[22,23] The extent of alternating propagation can be ascertained through this plot. The plots available directly in the program are shown in Figure 1 and are the following:

Monomer occurrence: This displays the probability of finding a given monomer alongside the chain, distanced from the initiating terminal group. It is calculated as the average monomer consumption over an increment in monomer additions, equal to the number of polymer chains.

M/M0: This plots the consumption of individual monomers as a function of the global monomer conversion. It can be used to assess the validity of the model through subsequent experimental measurements of individual monomer conversions.

Run length: This plots the average run length, i.e., block length, of monomers, depicted as a histogram. This is useful for ascertaining the extent of alternating behavior and the overall distribution of monomers along polymer chains.

Polymer composition: This plots the overall polymer composition as a function of the conversion. In addition to this plot, the composition of the polymer at the chosen conversion is also given. The program adds one monomer per activation/deactivation cycle, which is the ideal case. As the program uses a simplified method and does not take initiation or termination kinetics nor the activation/deactivation equilibrium into account, it can only provide a simplified overview of individual chain composition and true chain compositions can vary.

The validity of our program in terms of monomer consumption was tested with parameters used for styrene and acrylic acid, at different monomer ratios, with the results being identical to the composition trajectories reported by Harrisson et al.[7] Neat polymerizations of styrene and acrylic acid can spontaneously form gradient copolymers, when the initial monomer composition deviates from that of an azeotropic copolymerization. Under the conditions shown, the monomers are incorporated in accordance to the reactivity ratios of $r_{Sty} = 0.21$ and $r_{AA} = 0.082$. By choosing the reactant ratios judiciously, one-pot gradient copolymers can be formed with little effort. The reactions were tailored such that the polymers produced exhibited morphology akin to block copolymers, as measured by AFM on annealed thin films, and showed pH dependent amphiphilic behavior.[7] In this case, the program is useful to determine the proper reaction conditions to yield polymers of desired gradient and DP and to elucidate the monomer distributions in RHPs, enabling better understanding of their structure-function relationships and use in *in silico* studies.

Below we describe two studies in which 'Compositional Drift' was used to highlight how the program can guide both experimental design and subsequent analysis in functional assays. The program has gone through several iterations before its current version. In the examples below, we used an earlier version that iterated through all chains in the propagation step, adding one monomer to each polymer. Consequently, these simulations do not yield dispersity of polymer lengths.

I. Gradients copolymers of styrene-co-maleic acid: We recently employed the program to understand the polymer architecture favorable in the formation of styrene-maleic acid lipid particles (SMALPS).[24] The program was used to guide the experimental design and subsequent analysis (Figure 2). We used the penultimate model of monomer addition, with reactivity ratios determined from free-radical polymerizations.[25] The polymers synthesized did not differ significantly in composition to what was predicted by the program, though this is not always the case.[16] 'Compositional Drift' allowed us to visualize possible gradients at different monomer to RAFT ratios and at different conversions. Styrene and maleic anhydride exhibit an extreme degree of cross-propagation. The gradient in polymer composition was controlled by using excess styrene and terminating the polymerization at different conversions. Interestingly, the experiments validated the program through a highly visual cue. The RAFT agent used was cyanopropyl dithiobenzoate, which exhibits a change in color depending on the terminal monomer. The reaction mixture turns from orange to red upon maleic anhydride depletion, suggesting that polymers with terminal maleic anhydride give the orange color. This effect was even more striking in aqueous solutions of the hydrolyzed polymers. These observations corroborate the considerations on this copolymerization by Klumperman.[23]

II. Monomer distribution in nongradient random heteropolymers: The program has also been used to estimate the distribution of monomers in nonalternating polymerizations (Figure 3). Our recent work shows how a RHP, in this case made from 4 monomers, can enable the use of enzymes in foreign environments, such as organic solvents and retain activity when electrospun into fiber mats.[26] 'Compositional Drift' allows for an estimate of the distribution of monomers in the chain. While experimentally verifying this distribution in a multimonomer system is not possible at this time, the

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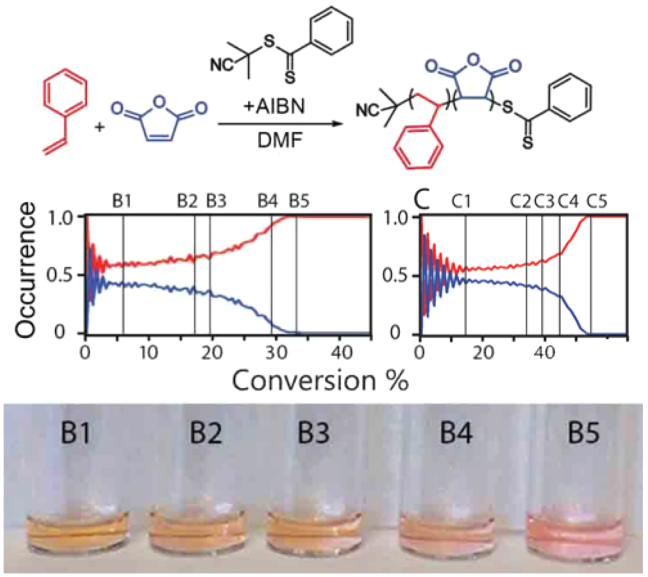

Figure 2. Compositional trajectories for the Sty (Red) and MAnh (Blue) copolymerization B: [Sty]:[MAnh] of 9:1 and a total [M]:[CTA] of 200, C: [Sty]:[MAnh] of 8:2 and a total [M]:[CTA] of 100. Reactivity ratios: r_{SS} = 0.0176, r_{MS} = 0.0455 in DMF. Individual polymers were stopped at the conversions noted by the vertical line. The B series produced gentle gradient compositions, whereas the C series produced a sharp gradient. 'Compositional Drift' enabled the experimental design and predicted polymer composition as well as residual monomer postpolymerization. The picture shows aqueous solutions of the hydrolyzed copolymer, showing the characteristic orange color of the dithiobenzoate next to the carboxylate in B1−B4, and the subsequent color shift to pink in B5, with styrene adjacent to the dithiobenzoate.

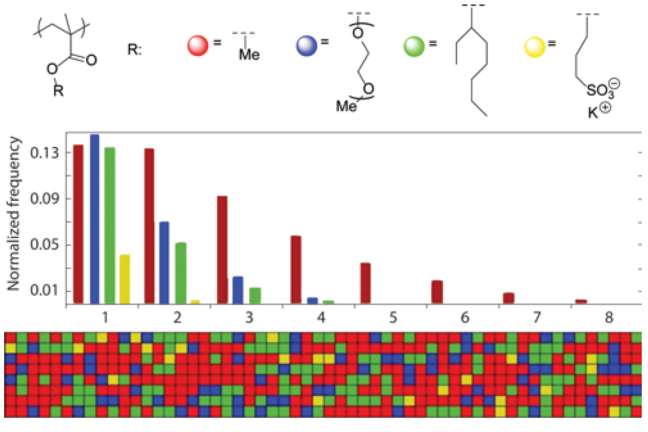

Figure 3. Monomer distribution of a RHP composed of 4 different monomers with reactivity ratios close to 1. The polymer has an overall composition of 50% methyl methacrylate, 25% oligo(ethylene glycol) methyl ether methacrylate (Mn = 500 g/mol), 20% 2-ethylhexyl methacrylate, and 5% 3-sulfopropyl methacrylate. Histograms show distribution of monomer run lengths. Rows are individual polymer compositions, with each row representing a single polymer.

calculated distribution can be used to support the analysis. We imagine this will find further utility for *in silico* studies of noncovalent polymer complexes.

The program has proved a useful tool in both designing and understanding polymerizations. With a thorough understanding of the limitations of this method and the polymerization in question, meaningful information can be ascertained. We share this tool believing others will find it useful as well.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.8b00813.

Compositional Drift ReadMe and usage tutorial (PDF)

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Notes

The authors declare no competing financial interest.

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