

Max-Planck-Institut  
für Mathematik  
in den Naturwissenschaften  
Leipzig

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Preprint no.: 36

2014





# A Statistical Theory of co-solvent-induced coil-globule transitions in dilute polymer solution

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We present a statistical model of a dilute polymer solution in good solvent in the presence of low-molecular weight co-solvent. We investigate the conformational changes of the polymer induced by a change of the co-solvent concentration and the type of interaction between the co-solvent and the polymer. We describe the polymer in solution by the Edwards model, where the partition function of the polymer chain with a fixed radius of gyration is described in a field-theoretical manner. The polymer-co-solvent and the co-solvent-co-solvent interactions are treated in the framework of the mean-field approximation.

For convenience we separate the system volume on two parts: the volume occupied by the polymer chain expressed through its gyration volume and the bulk solution. Considering the equilibrium between the two subvolumes we obtain the total Helmholtz free energy of the solution as a function of radius of gyration and the cosolvent concentration within gyration volume.

After minimization of the total Helmholtz free energy with respect to its arguments we obtain a system of coupled equations with respect to the radius of gyration of the polymer chain and the co-solvent concentration within the gyration volume. Varying the interaction strength between polymer and co-solvent we show that the polymer collapse occurs in two limiting cases - either when the interaction between polymer and co-solvent is repulsive or when the interaction is attractive. The reported effects could be relevant for different disciplines where conformational transitions of macromolecules in the presence of a co-solvent are of interest, in particular in biology, chemistry and material science.

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## I. INTRODUCTION

The coil-globule transition in dilute polymer solutions is one of the most fascinating phenomena in physical chemistry of polymers. The mechanism of conformational transition of a chain molecule upon a change of environment has found many applications in recent technological advances ranging from encapsulation of drug molecules in a polymer coil and targeted delivery<sup>1-3</sup> to smart materials changing their properties in response to the environment<sup>4,8</sup>. Numerous applications are based on a conformational transition of a polymer sensing the presense of specific molecules at low concentrations<sup>7</sup>, inducing a phase change aggregation of suspensions of colloids coated with pH or temperature responsive polymers<sup>5</sup>, gels comprising thermoresponsive polymer networks<sup>5,6</sup> to name only a few. In organisms proteins fold into a compact state attaining a well defined biological function by exposing functional groups to their environment. Viral DNA collapses to a condensed state to fit in the confined space of a viral capsid<sup>10</sup>. First steps in DNA separation for subsequent analysis involve condensation of DNA using osmolytes or denaturants<sup>11,12</sup>. Especially water soluble polymers are used to exert a lateral pressure on the DNA to induce a collapse<sup>9</sup>. In the present article an alternative mechanism is outlined that could also lead to a collapse when the low molecular weight co-solvent has entered the coil of a chain molecule compressing the coil from within.

The ubiquitous presence of chain molecules and the principal possibility to control the conformational transition by an external stimulus has therefore attracted much attention from experimental point of view in chemistry, biology and material science.

Theoretical efforts on the other hand formulating a coil-globule transition theory contributed much to a qualitative understanding of this phenomenon.

Today many theoretical contributions exist dedicated to the coil-globule transition ranging from simplified self-consistent field treatment of the solvent to theories based on the field-theoretic formalism<sup>13-20,22-26</sup>. It has been shown that, as the solvent becomes poorer, the polymer coil shrinks leading eventually to a collapse of the polymer coil. Predominantly the theoretical models describe the solvent only implicitly, i.e. its influence on macromolecule taken into account through effective monomer-monomer interaction. However, nowadays, due to the importance of conformation control of macromolecules in solution by low-molecular weight co-solvents (for example, adding of osmolytes or denaturants in protein aqueous solutions<sup>28-33</sup>) explicit account of the co-solvent in the model seems to be

indispensible.

However, up to now only a few attempts considering the co-solvent explicitly have been reported. Notably in the work of Tanaka, et al.<sup>27</sup> the conformational phase transition of an isolated polymer chain capable of forming physical bonds with solvent molecules treated the solvent explicitly. On the basis of a Flory type mean-field theory, a formula for the temperature dependence of the expansion factor of the chain has been derived. The physical-bond formation between polymer and solvent molecules causes a reentrant conformational change between coiled and globular state of the polymer chain when temperature is varied.

In the work<sup>33</sup> the collapse and swelling behavior of a homopolymer has been studied using implicit-solvent, explicit co-solvent Langevin dynamics computer simulations. Varying the interaction strength the results of two theoretical models have been compared with the simulation findings. The first model was based on an effective one-component description where the co-solutes have been averaged out - the second model treated the fully two-component system in a Flory-de Gennes type of approach. A conclusion has been reached that the simulation results were in accord with the predictions of the second model.

However, to our best knowledge, there does not seem to exist an approach starting from first principals of statistical mechanics describing the influence of the co-solvent on conformational behaviour of the polymer chain - specifically the concentration dependence of the radius of gyration of the polymer chain taking into account the type of co-solvent interactions with the polymer. In the present work such a statistical model of a flexible polymer chain in good solvent in the presence of a low-molecular co-solvent is developed. The influence of co-solvent concentration and quality of its interaction with monomers on the collapse and swelling behavior of polymer chain is investigated.

The paper organized as follows. In Sec. II, we present our theoretical model and in Sec. III the numerical results are given. In Sec. IV, we discuss the obtained results and summarize our findings.

## II. THEORY

We consider the case of a polymer chain immersed in a good solvent. We will describe the polymer in the framework of the Edwards model (flexible polymer chain with excluded volume)<sup>38</sup>. The polymer chain molecule and the low-molecular weight co-solvent at a

specified concentration are immersed in a solvent described by a continuous, structureless medium. We assume further that the volume of the system consists of two parts: the gyration volume containing predominantly monomers of the polymer chain and a bulk solution (see, fig. 1). Thus, we consider the co-solvent concentration at equilibrium in the two sub-volumes varying the strength of interaction of the polymer-co-solvent. In order to find the solution of the posed problem the minimum of total Helmholtz free energy of the system as function of the radius of gyration and the number of co-solvent molecules within gyration volume is sought.

We assume further that the concentration of the co-solvent beyond the gyration volume is rather small so that the assumption of an ideal gas holds. Our aim is to study the dependence of polymer chain conformations as a function of the co-solvent concentration and the type of interaction between co-solvent and monomers.

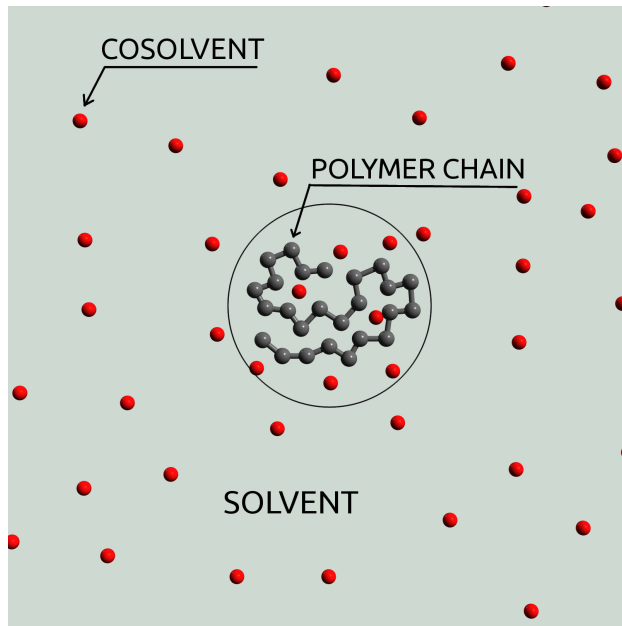


Figure 1. *Pictorial representation of the model. The system consists of a polymer chain in a good solvent which is represented by a continuous, structureless medium and a low-molecular weight co-solvent at a specified concentration. The total volume of the system consists of two parts: the gyration volume containing predominantly monomers of the polymer chain and a bulk solution.*

The partition function of the polymer-co-solvent system takes the form (for details, see Appendix)

$$Z(R_g, N_1) = Z_c(R_g, N_1)Z_p(R_g), \quad (1)$$

where

$$Z_c(R_g, N_1) = \frac{(V_g - N_1 v_c)^{N_1} (V - V_g)^{N_c - N_1}}{(N_c - N_1)! N_1!} e^{-\frac{w_{pc} N_1 N}{V_g}} \quad (2)$$

is a partition function of low-molecular weight co-solvent in solution;  $N_1$  is a number of co-solvent molecules which are within the gyration volume  $V_g = \frac{4\pi R_g^3}{3}$  ( $R_g$  is the radius of gyration);  $N$  is a degree of polymerization - e.g. length of the polymer chain;  $w_{pc}$  is a parameter of volume interaction polymer-co-solvent corresponding to the second virial coefficient;  $N_c$  is a total number of co-solvent molecules and  $v_c$  is the excluded volume of co-solvent molecules. The second term in the product (1)

$$Z_p(R_g) = \int d\Gamma(R_g) e^{-\frac{w_p}{2} \int_0^N \int_0^N ds_1 ds_2 \delta(\vec{r}(s_1) - \vec{r}(s_2))} \quad (3)$$

is a partition function of the polymer chain with fixed radius of gyration; the symbol  $\int d\Gamma(R_g)(\cdot)$  denotes an integration over microstates of the polymer chain at a fixed radius of gyration;  $w_p$  is a parameter of volume monomer-monomer interaction which corresponds to the second virial coefficient too.

Using the standard Hubbard-Stratonovich transformation<sup>38</sup>, we rewrite  $Z_p(R_g)$  as follows

$$Z_p(R_g) = \int \frac{\mathcal{D}\varphi}{C} e^{-\frac{1}{2w_p} \int d\vec{x} \varphi^2(\vec{x})} \int d\Gamma(R_g) e^{i(\hat{\rho}\varphi)} = Z_{id}(R_g) \int \frac{\mathcal{D}\varphi}{C} e^{-\frac{1}{2w_p} \int d\vec{x} \varphi^2(\vec{x})} \langle e^{i(\hat{\rho}\varphi)} \rangle_{R_g}, \quad (4)$$

where  $Z_{id}(R_g)$  is the partition function of the ideal gaussian polymer chain at a fixed radius of gyration; the symbol  $\langle (\cdot) \rangle_{R_g} = \frac{1}{Z_{id}(R_g)} \int d\Gamma(R_g)(\cdot)$  denotes the average over microstates of the ideal polymer chain at a fixed radius of gyration;  $\hat{\rho}(\vec{x}) = \int_0^N ds \delta(\vec{x} - \vec{r}(s))$  is the local density of monomers. Moreover, we introduce a following short-hand notation  $(\hat{\rho}\varphi) = \int d\vec{x} \hat{\rho}(\vec{x}) \varphi(\vec{x})$ . Evaluating the functional integral (4) in the case when  $N \gg 1$  the following relations hold

$$\hat{\rho}(\vec{x}) = \langle \hat{\rho}(\vec{x}) \rangle_{R_g} + \delta\hat{\rho}(\vec{x}), \quad (5)$$

$$\langle \hat{\rho}(\vec{x}) \rangle_{R_g} \simeq \begin{cases} \frac{N}{V_g}, & |\vec{x}| \leq R_g \\ 0, & |\vec{x}| > R_g; \end{cases}$$

$$\varphi(\vec{x}) = \phi(\vec{x}) + \psi(\vec{x}), \quad (6)$$

$$\phi(\vec{x}) = \begin{cases} \phi_0, & |\vec{x}| \leq R_g \\ 0, & |\vec{x}| > R_g. \end{cases}$$



Note, that the coordinates are taken with the origin at the center of mass of the polymer. The function  $\psi(\vec{x})$  satisfies a following condition

$$\int_{V_g} d\vec{x} \psi(\vec{x}) = 0. \quad (7)$$

Using equalities (5-7), one can express for the partition function of the polymer in the following form

$$Z_p(R_g) = Z_{MF}(R_g) Z_{fl}(R_g), \quad (8)$$

where

$$Z_{MF}(R_g) = Z_{id}(R_g) \int_{-\infty}^{\infty} \frac{d\phi_0}{C_0} e^{-\frac{V_g \phi_0^2}{2w_p} + iN\phi_0} = Z_{id}(R_g) e^{-\frac{N^2 w_p}{2V_g}} \quad (9)$$

is the partition function in the framework of the mean-field approximation with  $C_0 = \int_{-\infty}^{+\infty} d\phi_0 e^{-\frac{V_g \phi_0^2}{2w_p}} = \sqrt{\frac{2\pi w_p}{V_g}}$  as a normalization constant;

$$Z_{fl}(R_g) = \int \frac{\mathcal{D}\psi}{C_1} e^{-\frac{1}{2w_p} \int d\vec{x} \psi^2(\vec{x})} \langle e^{i(\delta\hat{\rho}\psi)} \rangle_{R_g} \quad (10)$$

is the partition function describing the fluctuation corrections to mean-field approximation;  $C_1 = \int \mathcal{D}\psi e^{-\frac{1}{2w_p} \int d\vec{x} \psi^2(\vec{x})}$  is a normalization constant in a gaussian measure for the functional integral (10). In the framework of a gaussian approximation<sup>38</sup> the fluctuation partition function can be written as

$$Z_{fl}(R_g) = \int \frac{\mathcal{D}\psi}{C_1} e^{-\frac{1}{2w_p} \int d\vec{x} \psi^2(\vec{x})} \exp \left[ -\frac{1}{2} \int d\vec{x} \int d\vec{y} \langle \delta\hat{\rho}(\vec{x}) \delta\hat{\rho}(\vec{y}) \rangle_{R_g} \psi(\vec{x}) \psi(\vec{y}) \right]. \quad (11)$$

For  $N \gg 1$  the correlator of local density fluctuations becomes translationally invariant, i.e.

$$\langle \delta\hat{\rho}(\vec{x}) \delta\hat{\rho}(\vec{y}) \rangle_{R_g} \simeq \frac{N}{V_g} S(\vec{x} - \vec{y}). \quad (12)$$

The structure factor  $S(\vec{x} - \vec{y})$  is nonzero when ends of radius vectors  $\vec{x}, \vec{y}$  lie within the gyration volume, so that

$$\begin{aligned} Z_{fl}(R_g) &= \int \frac{\mathcal{D}\psi}{C_1} e^{-\frac{1}{2w_p} \int d\vec{x} \psi^2(\vec{x})} \exp \left[ -\frac{1}{2} \int_{V_g} d\vec{x} \int_{V_g} d\vec{y} \langle \delta\hat{\rho}(\vec{x}) \delta\hat{\rho}(\vec{x}) \rangle_{R_g} \psi(\vec{x}) \psi(\vec{y}) \right] = \\ &\simeq \exp \left[ -\frac{V_g}{2} \int \frac{d\vec{k}}{(2\pi)^3} \ln \left( 1 + w_p \frac{N}{V_g} S(\vec{k}) \right) \right]. \end{aligned} \quad (13)$$

In the last expression in the exponent it is necessary to exclude due to convergence reasons a term related to the self-interaction energy of the polymer chain  $\frac{Nw_p}{2} \int \frac{d\vec{k}}{(2\pi)^3} S(\vec{k})^{39}$ . Using the well known interpolation formula for the structure factor  $S(\vec{k})^{37}$

$$S(\vec{k}) = \frac{1}{1 + \frac{k^2 R_g^2}{2}} \simeq \frac{2}{k^2 R_g^2}, \quad (14)$$

excluding the self-interaction energy we arrive at an expression for the fluctuation partition function within the gaussian approximation (random phase approximation)

$$Z_{fl} = \exp \left[ \frac{V_g \kappa^3}{12\pi} \right], \quad (15)$$

where  $\kappa^2 = \frac{2w_p N}{V_g R_g^2}$ . Therefore, we have a following expression for the polymer free energy

$$\beta F_p(R_g) = -\ln Z_p(R_g) = \beta F_{id}(R_g) + \frac{N^2 w_p}{2V_g} - \frac{V_g \kappa^3}{12\pi}, \quad (16)$$

where  $\beta F_{id}(R_g) = -\ln Z_{id}(R_g)$  is the Helmholtz free energy of the ideal polymer chain,  $\beta = \frac{1}{k_B T}$ . Based on the results of Fixman<sup>36</sup> we construct an interpolation formula for the free energy of the ideal polymer chain:

$$\beta F_{id}(R_g) = \frac{9}{4} \left( \alpha^2 + \frac{1}{\alpha^2} \right) - \frac{3}{2} \ln \alpha^2, \quad (17)$$

where  $\alpha = \frac{R_g}{R_{0g}}$  denotes the expansion parameter,  $R_{0g}^2 = \frac{Nb^2}{6}$  is a mean-square radius of gyration of the ideal polymer chain and  $b$  is the Kuhn length of the segment. Rewriting the polymer free energy in terms of the expansion parameter  $\alpha$  we obtain

$$\beta F_p(\alpha) = \frac{9}{4} \left( \alpha^2 + \frac{1}{\alpha^2} \right) - \frac{3}{2} \ln \alpha^2 + \frac{9\sqrt{6}w_p\sqrt{N}}{4\pi b^3 \alpha^3} - \left( \frac{3}{\pi} \right)^{3/2} \frac{6^{1/4}}{N^{3/4}} \left( \frac{w_p}{\alpha^3 b^3} \right)^{3/2}. \quad (18)$$

The expression for the co-solvent Helmholtz free energy takes the form

$$\begin{aligned} \beta F_c(R_g, N_1) = & \frac{w_{pc} N N_1}{V_g} - N_1 \ln(V_g - N_1 v_c) - (N_c - N_1) \ln(V - V_g) + \\ & + N_1 (\ln N_1 - 1) + (N_c - N_1) (\ln(N_c - N_1) - 1). \end{aligned} \quad (19)$$

Minimizing  $\beta F_c(R_g, N_1)$  with respect to  $N_1$ , i.e. equating to zero the derivative  $\frac{\partial(\beta F_c(R_g, N_1))}{\partial N_1}$  and expressing  $N_1$  we obtain (to the first order in  $\frac{V_g}{V}$ )

$$N_1 \simeq \frac{N_c (V_g - N_1 v_c)}{V} \exp \left[ -\frac{\rho_1 v_c}{1 - \rho_1 v_c} - \frac{w_{pc} N}{V_g} \right]. \quad (20)$$

Introducing the notations  $\rho_1 = \frac{N_1}{V_g}$  and  $\rho = \frac{N_c}{V}$  we finally obtain the equation for the density of the co-solvent within the gyration volume  $\rho_1$

$$\frac{\rho_1}{1 - \rho_1 v_c} = \rho \exp \left[ -\frac{\rho_1 v_c}{1 - \rho_1 v_c} - \frac{w_{pc} N}{V_g} \right], \quad (21)$$

which valid for  $V \gg V_g$ .

It should be noted that the value of the expansion parameter, which corresponds to a minimum of the total Helmholtz free energy. Thus, using the equations (18-21), and calculating a derivative of the total free energy with respect to  $\alpha$  and equating it to zero, we obtain

$$\begin{aligned} \alpha^5 - \frac{2}{3}\alpha^3 - \alpha &= \frac{3\sqrt{6}}{2\pi} \tilde{w}_p \sqrt{N} - \left( \frac{3}{\pi} \right)^{3/2} 6^{1/4} \frac{\tilde{w}_p^{3/2}}{N^{3/4} \alpha^{3/2}} - \\ &- \frac{2\pi\sqrt{6}}{81} N^{3/2} \alpha^6 \left( \tilde{\rho} - \frac{\tilde{\rho}_1}{1 - \tilde{\rho}_1 \tilde{v}_c} \right) + \frac{2}{3} N \tilde{w}_{pc} \tilde{\rho}_1 \alpha^3, \end{aligned} \quad (22)$$

where  $\tilde{w}_p = w_p b^{-3}$ ,  $\tilde{w}_{pc} = w_{pc} b^{-3}$ ,  $\tilde{\rho} = \rho b^3$ ,  $\tilde{v}_c = \frac{v_c}{b^3}$ ;  $\tilde{\rho}_1 = \rho_1 b^3$  satisfies the equation

$$\frac{\tilde{\rho}_1}{1 - \tilde{\rho}_1 \tilde{v}_c} = \tilde{\rho} \exp \left[ -\frac{\tilde{\rho}_1 \tilde{v}_c}{1 - \tilde{\rho}_1 \tilde{v}_c} - \frac{9\sqrt{6}\tilde{w}_{pc}}{2\pi\sqrt{N}\alpha^3} \right]. \quad (23)$$

The first term in a right hand side of equation (22) relates to the monomer-monomer volume interaction. At  $\tilde{\rho} \rightarrow 0$  we have a swelling regime  $\alpha \sim \tilde{w}_p^{1/5} N^{1/10}$  that is described by the classical Flory theory<sup>40</sup>. The second term is a fluctuation correction to the mean-field approximation. This term gives very small correction to the mean-field approximation for long polymer chains. The third term relates to a pressure difference between the co-solvent molecules within gyration volume and in the bulk solution. The last term is related to the polymer-co-solvent interaction.

Now, we consider the situation when  $\frac{\tilde{w}_{pc}}{2\pi\sqrt{N}\alpha^3} \gg 1$ , i.e. when interaction co-solvent-polymer is strongly repulsive. In this case  $\tilde{\rho}_1 \ll \rho$  and the equation (22) simplifies to

$$\alpha^5 - \frac{2}{3}\alpha^3 - \alpha = \frac{3\sqrt{6}}{2\pi} \tilde{w}_p \sqrt{N} - \left( \frac{3}{\pi} \right)^{3/2} 6^{1/4} \frac{\tilde{w}_p^{3/2}}{N^{3/4} \alpha^{3/2}} - \frac{2\pi\sqrt{6}}{81} \tilde{\rho} N^{3/2} \alpha^6. \quad (24)$$

If the third term on the right hand side of equation (24) dominates then neglecting all except the first and third terms we obtain the following relations for expansion parameter and radius of gyration

$$\alpha \simeq \left( \frac{243}{4\pi^2} \right)^{1/6} \left( \frac{\tilde{w}_p}{\tilde{\rho}} \right)^{1/6} N^{-1/6}, \quad \frac{R_g}{b} \simeq \frac{\sqrt{6}}{6} \left( \frac{243}{4\pi^2} \right)^{1/6} \left( \frac{\tilde{w}_p}{\tilde{\rho}} \right)^{1/6} N^{1/3}, \quad (25)$$

which corresponds to a globular conformation. This regime occurs when the following conditions

$$\frac{\tilde{w}_p}{N} \ll \tilde{\rho} \ll 1. \quad (26)$$

are fulfilled.

We turn now to the opposite limiting case when  $\tilde{w}_{pc} < 0$  and  $\frac{|\tilde{w}_{pc}|}{2\pi\sqrt{N}\alpha^3} \gg 1$ , i.e. when interaction co-solvent-polymer is strongly attractive. In this case  $\tilde{\rho}_1 \gg \rho$ . Therefore the difference of co-solvent pressures between interior of the gyration volume and the bulk can lead to an additional swelling the polymer coil. The excluded volume of co-solvent molecules has the same affect. However, the strong attraction between co-solvent and monomers leads to a shrinking of the polymer coil. Due to the competition between these trends the coil-globule transition can occur. Two collaps regimes can take place. In the first case, when  $\tilde{w}_p \rightarrow 0$  (near the  $\theta$ -temperature), one can neglect in equation (22) all terms except last two terms in the right hand side. The expansion parameter  $\alpha$  and radius of gyration are therefore

$$\alpha \simeq \left( \frac{9\sqrt{6}|\tilde{w}_{pc}|}{2\pi} \right)^{1/3} (1 - \tilde{\rho}_1 \tilde{v}_c)^{1/3} N^{-1/6}, \quad \frac{R_g}{b} \simeq \left( \frac{3|\tilde{w}_{pc}|}{4\pi} \right)^{1/3} (1 - \tilde{\rho}_1 \tilde{v}_c)^{1/3} N^{1/3}. \quad (27)$$

In this regime the size of the globule is determined by a competition between the co-solvent-polymer attraction and the co-solvent excluded volume effect.

In the second regime, when  $\tilde{w}_p \gg 1$  all terms except first and last on the right hand side of the equation (22) can be neglected. This leads to the following result

$$\alpha \simeq \left( \frac{9\sqrt{6}}{4\pi} \right)^{1/3} \left( \frac{\tilde{w}_p}{|\tilde{w}_{pc}|\tilde{\rho}_1} \right)^{1/3} N^{-1/6}, \quad \frac{R_g}{b} \simeq \left( \frac{3}{8\pi} \right)^{1/3} \left( \frac{\tilde{w}_p}{|\tilde{w}_{pc}|\tilde{\rho}_1} \right)^{1/3} N^{1/3}. \quad (28)$$

In this case size of the globule is determined by a competition between co-solvent-polymer attraction and monomer-monomer repulsion. We would like to stress that in the globular regimes the co-solvent concentration  $\tilde{\rho}_1$  within gyration volume does not depend on the expansion parameter.

### III. NUMERICAL RESULTS

Turning to the numerical analysis of the system of equations (22-23) we will fix the excluded volume parameter of co-solvent  $\tilde{v}_c = 1$ .

We first discuss the case when the interaction polymer-co-solvent is a purely repulsive. Fig. 2 (a) shows the expansion parameter  $\alpha$  as a function of the co-solvent concentration  $\tilde{\rho}$  at different values of  $\tilde{w}_{pc}$  and at  $N = 10^4$ . At increasing co-solvent concentration the expansion parameter monotonically decreases and is asymptotically close to limit given by (25) corresponding to a globular conformation. Increasing the interaction parameter  $\tilde{w}_{pc}$  the coil-globule transition becomes sharper. Fig. 2 (b) shows the co-solvent concentration in the gyration volume as a function of co-solvent concentration in the bulk for two values of polymer-co-solvent interaction parameters. In the region of coil-globule transition the co-solvent concentration within the gyration volume shows a sufficiently pronounced maximum. Such behaviour can be interpreted as follows. At small values of  $\tilde{\rho}$  the gyration volume offers enough space for the co-solvent to intrude leading to a swelling of the polymer coil. In contrast, increasing  $\tilde{\rho}$  the size of polymer coil decreases leading to a more confined space increasing therefore the repulsion between co-solvent and monomers and as a consequence the co-solvent is expelled from polymer coil. Thus, when the co-solvent concentration in the bulk drops below a certain value the co-solvent concentration within the gyration volume tends to zero.

It is instructive to evaluate the dependency of the maximum of co-solvent concentration within gyration volume  $\tilde{\rho}_1$  on parameters of interaction  $\tilde{w}_p$  and  $\tilde{w}_{pc}$ . We rewrite  $\tilde{\rho}_1$  as function of  $\tilde{\rho}$  and optimize it with respect to  $\tilde{\rho}$ . Since in the considered regime  $\tilde{\rho}_1 \ll \tilde{\rho}$  the expansion parameter  $\alpha$  can be evaluated via (25) such that we can write

$$\tilde{\rho}_1 \simeq \tilde{\rho} \exp \left[ -\frac{\sqrt{2}\tilde{w}_{pc}}{\tilde{w}_p^{1/2}} \tilde{\rho}^{1/2} \right]. \quad (29)$$

The optimization of a function (29) with respect to  $\tilde{\rho}$  yields

$$\tilde{\rho}^* \simeq \frac{2\tilde{w}_p}{\tilde{w}_{pc}^2}, \quad \tilde{\rho}_1^* \simeq \frac{2}{e^2} \frac{\tilde{w}_p}{\tilde{w}_{pc}^2}. \quad (30)$$

Thus the maximal co-solvent concentration  $\tilde{\rho}_1^*$  in the gyration volume is determined only by two parameters - the volume interaction  $\tilde{w}_p$  and  $\tilde{w}_{pc}$  and is approximately  $e^2 \approx 7.389$  times less than co-solvent concentration in the bulk solution.

For the case when the polymer-co-solvent interaction is attractive ( $\tilde{w}_{pc} < 0$ ) an abrupt collapse of the polymer chain takes place. Fig. 3 (a) shows the expansion parameter  $\alpha$  as a function co-solvent concentration for different values of  $\tilde{w}_{pc}$ . At values of bulk co-solvent concentration at which the collapse occurs there is also a jump of co-solvent concentration

in the gyration volume to very dense packing (fig. 3 (b)). In contrast to the previous case, in this regime the polymer collapse happens as a first - order phase transition at which the jump of the co-solvent concentration takes place. As mentioned above, this phase transition is due to the competition between polymer - co-solvent attraction, which tends to shrink the polymer chain, and a steric factor of the co-solvent molecules, which tends to expand it.

It is interesting to consider the dependence of the expansion parameter  $\alpha$  on the polymer-co-solvent interaction  $\tilde{w}_{pc}$  parameter. As shown in fig. 4 this dependence is sufficiently nonmonotonic. The collapse of polymer chain takes place in this case in the range of negative values of  $\tilde{w}_{pc}$ . At increasing  $\tilde{w}_{pc}$  the expansion parameter towards zero a maximum occurs. Further increasing (towards positive values)  $\tilde{w}_{pc}$  the expansion parameter again monotonically decreases and smoothly approach the globule regime. Such behaviour is in agreement with results of computer simulations obtained in<sup>33</sup>.

#### IV. SUMMARY

We have outlined a first principles theory of conformational changes of a polymer chain depending on the co-solvent concentration and the type of interactions between co-solvent and the polymer. The explicit account of the co-solvent leads to the fundamentally new effects, namely polymer chain collapse occurs in two limiting cases. The first case, when the co-solvent-polymer interaction is a strongly repulsive and, in the opposite case, when this interaction is strongly attractive. In the first case, the coil-globule transition is smooth accompanied by a maximum concentration of the co-solvent molecules within the gyration volume. Interestingly, the location of the maximum is determined only by the virial coefficients of the monomer-monomer and monomer-co-solvent. In the second case when polymer-co-solvent interaction is attractive the collapse occurs as a first-order phase transition, i.e. discontinuous change of the radius of gyration and the co-solvent density within the gyration volume. We call these phenomena “co-solvent-induced coil-globule transitions”.

The described phenomena may be relevant for applications, where the mixed-solvent polymer solutions are used. In particular where the solvent conditions are used to induce a change in polymer conformation the described mechanism might offer an additional routine to exert control on the polymer conformational transition. In addition we have provided an estimate of the co-solvent concentration within the polymer coil, which might prove

useful in drug delivery technologies where the amount of the captured co-solvent need to be controled.

The present theory, however has natural limitations. Firstly, it can not describe a dilute polyelectrolyte solutions, where many-body effects due to long-range electrostatic interactions play crucial role. Such a first-principals theory, which can describe the collapse of the charged polymer chain in dilute polyelectrolyte solution, has been recently developed in the work<sup>42</sup>. Moreover, our theory does not take into account a possibility the formation of chemical bonds between polymer and co-solvent molecules. Apart from the above limitations our theory does not account for specific interactions, such as hydrogen bonds formation. We note that work in this direction has been recently published<sup>43</sup>, where the problem of the helix-coil transition in explicit solvent has been addressed analytically. Employing a spin-based models the influence of the hydrogen bonds formation on the helix-coil transition has been investigated. It would be interesting to investigate how the chemical bond formation and specific interactions influence on the coil-globule transition in dilute polymer solutions. We believe, that these problems can be a subject worthwhile for forthcoming publications.

## V. APPENDIX

To address a derivation of expression (1) for the partition function of the solution we start from the canonical partition function of the solution which can be written as follows

$$Z(R_g) = \int d\Gamma_p(R_g) \int d\Gamma_c \exp[-\beta H_p - \beta H_c - \beta H_{pc}], \quad (31)$$

where the symbol  $\int d\Gamma(R_g)(.)$  denotes the integration over microstates of polymer chain performed at a fixed radius of gyration; the symbol  $\int d\Gamma_c(.) = \frac{1}{N_c!} \int d\vec{r}_1.. \int d\vec{r}_{N_c}(.)$  denotes the integration over cosolvent molecules coordinates;

$$\beta H_p = \frac{w_p}{2} \int_0^N ds_1 \int_0^N ds_2 \delta(\vec{r}(s_1) - \vec{r}(s_2)) = \frac{w_p}{2} \int d\vec{x} \hat{\rho}_p^2(\vec{x}) \quad (32)$$

is the Hamiltonian of the monomer-monomer interaction;  $w_p$  is a second virial coefficient for the monomer-monomer interaction and  $\hat{\rho}_p(\vec{x}) = \int_0^N ds \delta(\vec{x} - \vec{r}(s))$  is the monomer local density;

$$\beta H_{pc} = w_{pc} \int_0^N ds \sum_{j=1}^{N_c} \delta(\vec{r}(s) - \vec{r}_j) = w_{pc} \int d\vec{x} \hat{\rho}_p(\vec{x}) \hat{\rho}_c(\vec{x}) \quad (33)$$

is the Hamiltonian of the polymer-co-solvent interaction;  $w_{pc}$  is the second virial coefficient for the polymer-cosolvent interaction and  $\hat{\rho}_c(\vec{x}) = \sum_{i=1}^{N_c} \delta(\vec{x} - \vec{r}_i)$  is the local density of co-solvent molecules;

$$\beta H_c = \frac{1}{2} \sum_{j \neq i} V_{hc}(\vec{r}_i - \vec{r}_j) \quad (34)$$

is the Hamiltonian of interaction co-solvent-co-solvent;

$$V_{hc}(\vec{r}) = \begin{cases} \infty, & |\vec{r}| \leq d_c \\ 0, & |\vec{r}| > d_c; \end{cases}$$

is the hard-core potential ( $d_c$  is a co-solvent molecule diameter). Thus we describe the co-solvent-co-solvent interaction purely as an excluded volume interaction.

Making the following identity transformation

$$Z(R_g) = \int d\Gamma_p(R_g) e^{-\beta H_p} \int d\Gamma_c e^{-\beta H_c - \beta H_{pc}} = Z_p(R_g) \int d\Gamma_c e^{-\beta H_c} \langle e^{-\beta H_{pc}} \rangle_p, \quad (35)$$

where

$$Z_p(R_g) = \int d\Gamma(R_g) e^{-\frac{w_p}{2} \int_0^N \int_0^N ds_1 ds_2 \delta(\vec{r}(s_1) - \vec{r}(s_2))} \quad (36)$$

is the polymer partition function; the symbol  $\langle (..) \rangle_p = \frac{1}{Z_p(R_g)} \int d\Gamma(R_g) (..)$  denotes averaging over polymer microstates with a fixed radius of gyration. Truncating the cumulant expansion<sup>41</sup> at first order we obtain

$$\langle e^{-\beta H_{pc}} \rangle_p \approx e^{-\beta \langle H_{pc} \rangle_p}. \quad (37)$$

Thus we obtain

$$\beta \langle H_{pc} \rangle_p = w_{pc} \int d\vec{x} \hat{\rho}_c(\vec{x}) \langle \rho_p(\vec{x}) \rangle_p \simeq \frac{N w_{pc}}{V_g} \int_{V_g} d\vec{x} \hat{\rho}_c(\vec{x}), \quad (38)$$

where the approximation

$$\langle \hat{\rho}(\vec{x}) \rangle_{R_g} \simeq \begin{cases} \frac{N}{V_g}, & |\vec{x}| \leq R_g \\ 0, & |\vec{x}| > R_g. \end{cases}$$

has been introduced. Therefore, we obtain the following expression for the partition function of the solution

$$Z(R_g) = Z_p(R_g) Z_c(R_g), \quad (39)$$



where  $Z_c(R_g)$  has a form

$$Z_c(R_g) = \int d\Gamma_c e^{-\beta H_c - \frac{w_{pc}N}{V_g} \int_{V_g} d\vec{x} \hat{\rho}_c(\vec{x})} = \frac{1}{N_c!} \int d\vec{r}_{1..} \int d\vec{r}_{N_c} e^{-\beta H_c - \frac{w_{pc}N}{V_g} \int_{V_g} d\vec{x} \hat{\rho}_c(\vec{x})}. \quad (40)$$

Rewriting the last expression in the form

$$Z_c(R_g) = \frac{1}{N_c!} \sum_{n=0}^{N_c} \frac{N_c!}{(N_c - n)!n!} e^{-\frac{w_{pc}Nn}{V_g}} Z_c(R_g, n), \quad (41)$$

where

$$Z_c(R_g, n) = \int_{V_g} d\vec{x}_{1..} \int_{V_g} d\vec{x}_n \int_{V-V_g} d\vec{y}_{1..} \int_{V-V_g} d\vec{y}_{N_c-n} e^{-\beta H_c} \approx (V_g - nv_c)^n (V - V_g)^{N_c-n} \quad (42)$$

is the co-solvent partition function with fixed number  $n$  of co-solvent molecules in the gyration volume and  $v_c = \frac{\pi d_c^3}{6}$  is an excluded volume of co-solvent molecules and applying the mean-field approximation we finally arrive at

$$Z_c(R_g) = \sum_{n=0}^{N_c} \frac{(V_g - nv_c)^n (V - V_g)^{N_c-n}}{(N_c - n)!n!} e^{-\frac{w_{pc}Nn}{V_g}}. \quad (43)$$

The above equation is based on the same mean-field approximation as the Van-der-Waals theory. In the thermodynamic limit ( $N_c \rightarrow \infty$ ) in the sum (43) only the highest order term giving the main contribution is relevant. This term corresponds to the number  $n = N_1$  which can be obtained from the extremum condition

$$\frac{\partial}{\partial n} \ln \left( \frac{(V_g - nv_c)^n (V - V_g)^{N_c-n}}{(N_c - n)!n!} e^{-\frac{w_{pc}Nn}{V_g}} \right) = 0. \quad (44)$$

Therefore we arrive at the expression which already has been used in the main text

$$Z_c(R_g) \simeq Z_c(R_g, N_1) = \frac{(V_g - N_1 v_c)^{N_1} (V - V_g)^{N_c - N_1}}{(N_c - N_1)!N_1!} e^{-\frac{w_{pc}NN_1}{V_g}}. \quad (45)$$

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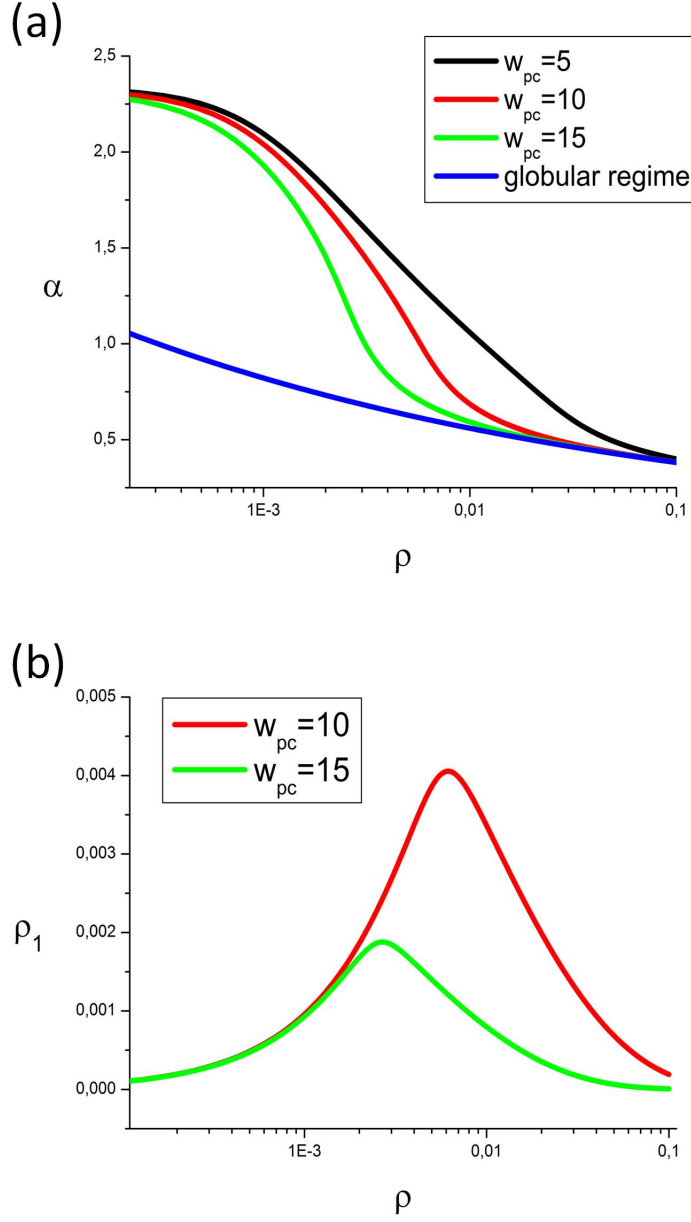


Figure 2. Repulsive polymer-co-solvent interaction ( e.g.  $\tilde{w}_{pc} > 0$  ). (a) The expansion parameter  $\alpha$  as a function of co-solvent concentration  $\tilde{\rho}_1$  in the gyration volume. (b) on the cosolvent bulk concentration  $\tilde{\rho}$  at different positive parameter of interaction polymer-cosolvent  $\tilde{w}_{pc}$ . It is seen that at increasing of cosolvent concentration the expansion parameter is monotonically decrease and asymptotically close to limit (25) corresponding to globular conformation. It is easy to seen that at increasing of parameter  $\tilde{w}_{pc}$  the coil-globule transition becomes sharper. In the region of coil-globule transition the co-solvent concentration within the gyration volume shows a sufficiently pronounced maximum. We use  $\tilde{w}_p = 0.1$ ,  $N = 10^4$ .

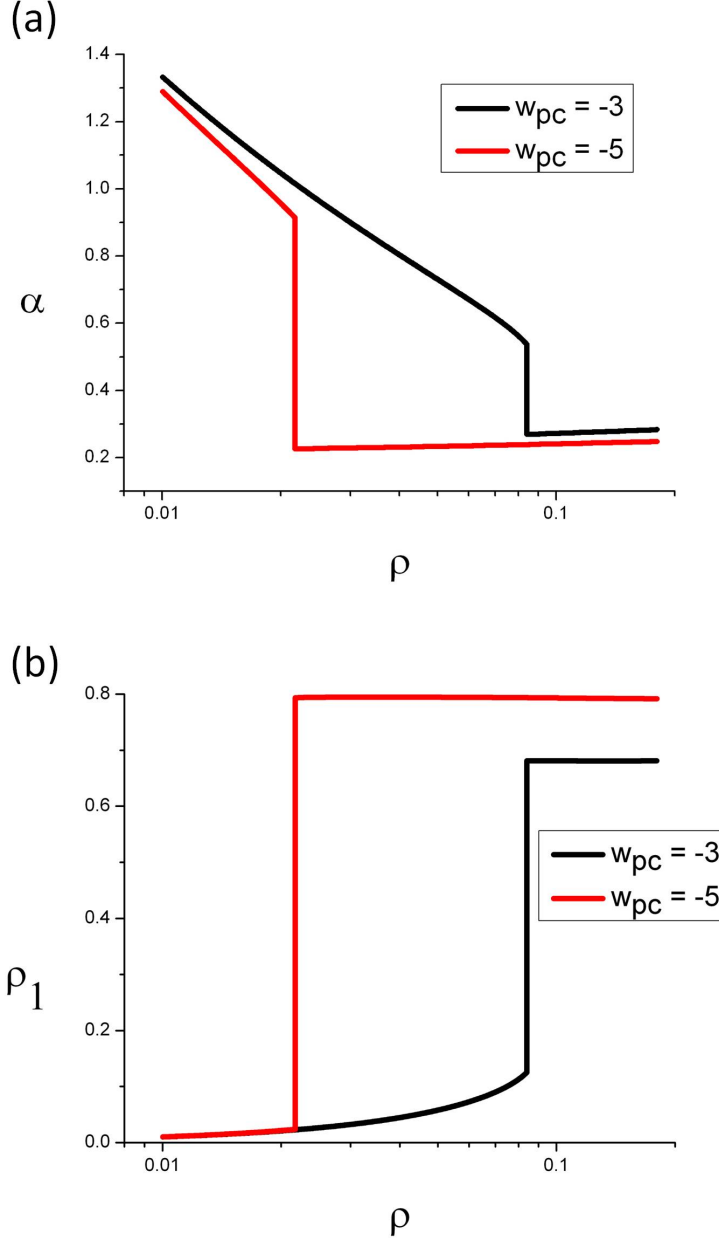


Figure 3. *Attractive polymer-co-solvent interaction ( e.g.  $\tilde{w}_{pc} < 0$  ). (a) The expansion parameter  $\alpha$  as a function of the co-solvent bulk concentration  $\tilde{\rho}$ . (b) The co-solvent concentration in the gyration volume  $\tilde{\rho}_1$  as a function of co-solvent concentration in the bulk shown for polymer-co-solvent interaction parameter  $\tilde{w}_{pc} = -3; -5$ . The bulk co-solvent concentration at which the chain collapse occurs coincides with the jump in the co-solvent concentration within the gyration volume. In this regime the polymer collapse happens as a first - order phase transition. Values are shown for  $\tilde{w}_p = 1$ ,  $N = 10^4$ .*

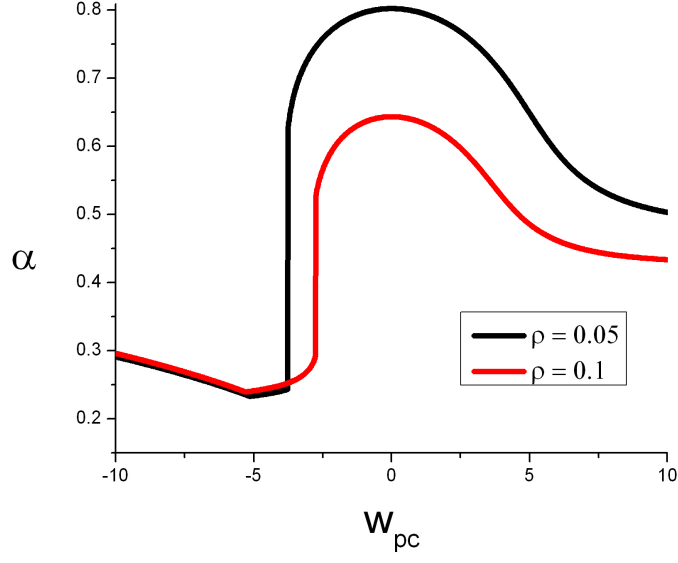


Figure 4. The expansion parameter  $\alpha$  as a function of polymer-co-solvent interaction parameter  $\tilde{w}_{pc}$  at different co-solvent bulk concentrations  $\tilde{\rho}$ . At negative values of  $\tilde{w}_{pc}$  the collapse of polymer chain takes place. Increasing  $\tilde{w}_{pc}$  towards zero a maximum occurs. Further increasing (towards positive values)  $\tilde{w}_{pc}$  the expansion parameter again monotonically decreases and smoothly approach the globule regime. Shown here for  $\tilde{w}_p = 1$ ,  $N = 10^4$ .