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Polyelectrolytes: Research, Development, and Applications

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Abstract: A brief overview is provided of the principal research and development activities of the Laboratory of Polyelectrolytes and BioMacromolecules at the Swiss Federal Institute of Technology. These include, in particular, the synthesis of tailor-made polyelectrolytes, the development of novel materials based on polyelectrolytes as well as basic research in the field of process technologies for synthesis and structure formation. The applications focus on the environment, biotechnology and medicine.

Keywords: Bioartificial pancreas · Heterophase polymerization · Microencapsulation · Polyelectrolyte complexes · Solid/liquid separation

What are Polyelectrolytes?

Polyelectrolytes (PEL) are a particular class of macromolecular compounds possessing the properties of both polymers and simple electrolytes. Nevertheless, the resulting behavior is not merely a superposition of macromolecular and electrolytic properties. In comparison with uncharged polymers, the polyelectrolyte chains carry a large number of ionic or ionizable groups. Therefore, long-range Coulombic interactions are additional influences to be considered in the chain conformation of charged polymers. These electrostatic effects contribute to many macromolecular characteristics such as intrinsic viscosity, chain dimensions, and transport parameters. In contrast to low molecular electrolytes, polyelectrolyte charges are fixed along the polymer chain and cannot be diluted. Consequently, the strongly localized electrical field influences the electrochemical solution behavior.

A classification of PEL can be based on various perspectives such as the origin, chemical composition, molecular architecture, or electrochemistry. Natural PEL include proteins, nucleic acids, and polysaccharides. Examples of synthetic compounds are poly(acrylic acid), poly(styrene

sulfonic acid) as well as their salts and poly[2-(methacryloyloxy) alkyltrialkylammonium] salts, or poly(diallyldimethylammonium chloride). The number of ionic groups is small in comparison to the structural variety of the polymer chain. The most important functional groups include carboxy, sulfate, sulfonate, phosphate, amino, imino, ammonium, sulfonium, and phosphonium moieties.

PEL are essential to many technical applications and play an important role in biological processes. Solution-based interactions are relevant to several technical processes and PEL are broadly employed in solid/liquid separations such as flocculation, coagulation, flotation, dewatering, or retention. The electrostatic properties render it possible for them to function as surface modifiers and as anti-static agents or stabilizers in many cosmetics, hair care products, and detergents. However, PEL are not merely used in auxiliary roles. Considerable interest is now directed toward their applications as new materials resulting from structure forming processes in solution and at interfaces having novel and unusual properties.

Laboratory of Polyelectrolytes and BioMacromolecules

The Laboratory of Polyelectrolytes and BioMacromolecules (LPBM), created in September 1996, focuses on the synthesis and structure of hydrophilic

polymers. The core competencies in characterization, in particular analytical ultracentrifugation, light scattering and liquid chromatography, provide highly precise, customized, and occasionally, unique means to optimize the synthesis of complex polymers. This includes random copolymers with long chain branches, block copolymeric dispersants for precipitation polymerization, hybrid natural-synthetic grafts based on polysaccharides and olefinic monomers as well as polyelectrolyte complexes and gels.

Research at the LPBM on the structure of PEL permits the understanding of fundamental phenomena related to their application in two 'systems' where water dominates the thermodynamics: the environment and the human body. Hence, the projects are targeted at applications involving the remediation of aqueous resources as well as the preparation of semipermeable microcapsules for cell encapsulation and the treatment of hormone deficient diseases, principally type I diabetes. While seeming far ahead, the core skills in macromolecular characterization, synthesis and engineering permit the team to interact with biologists, microtechnologists, physicists and enzymologists in the resolution of problems as diverse as drug delivery, depyrogenation and immobilization. The vast majority of these developments, which have yielded licensed patents, stem from knowledge of the physical chemistry of heterophase synthesis methods, including inverse-emulsion, inverse-micro-

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emulsion and solution/gel polymerizations.

The expertise in process development, and macromolecular and colloidal chemistry, is coupled with the aforementioned characterization method development, to elucidate the structure of polymers in solution, the elementary reaction mechanisms, which control their properties, as well as the thermodynamic nature of polyelectrolyte complexes, membranes and microcapsules. When the latter is coupled with new technologies for cell encapsulation, microcapsules with controlled permeability and mechanical properties can be produced under highly pure conditions, yielding clinical grade biomaterials in large quantities, several of which outperform the top polymers currently on the market.

Approximately half of LPBM focuses on the preparation of novel PEL *via* chemical or process modifications whereas the other half is oriented toward biotechnological applications, principally the bioartificial pancreas (immunoisolated islets of Langerhans) and the production of high value added fine chemicals *via* enzyme immobilized biocatalysts. Details on the specific projects will be elaborated upon herein. Appropriate recent key publications, which provide more information, are summarized at the end of this article.

Novel Polyelectrolytes for Environmental Applications [1-3]

The maintenance and clarification of mankind's aqueous resources has rendered water, at one time an abundant resource, a commodity whose price is accelerating, with the demand for reuse increasing, particularly in developing regions. High molar mass (10^6 – 10^7 g/mol) anionic and cationic macromolecules are employed as soluble filters for aqueous solid-liquid separations, including the clarification of municipal, industrial and, in certain instances, potable water. They find application in systems where physical filtration would present too large a pressure drop, and hence excessive energy consumption. Therefore, LPBM's objective has been the synthesis of new water soluble polymers, either through novel chemical routes or *via* process modifications. As an example of the former, a hybrid chitosan-graft-trimethylaminoethyl-methacrylate copolymer is shown in Fig. 1 to outperform traditional linear flocculants, including those which are presently commercially available (patent pending).

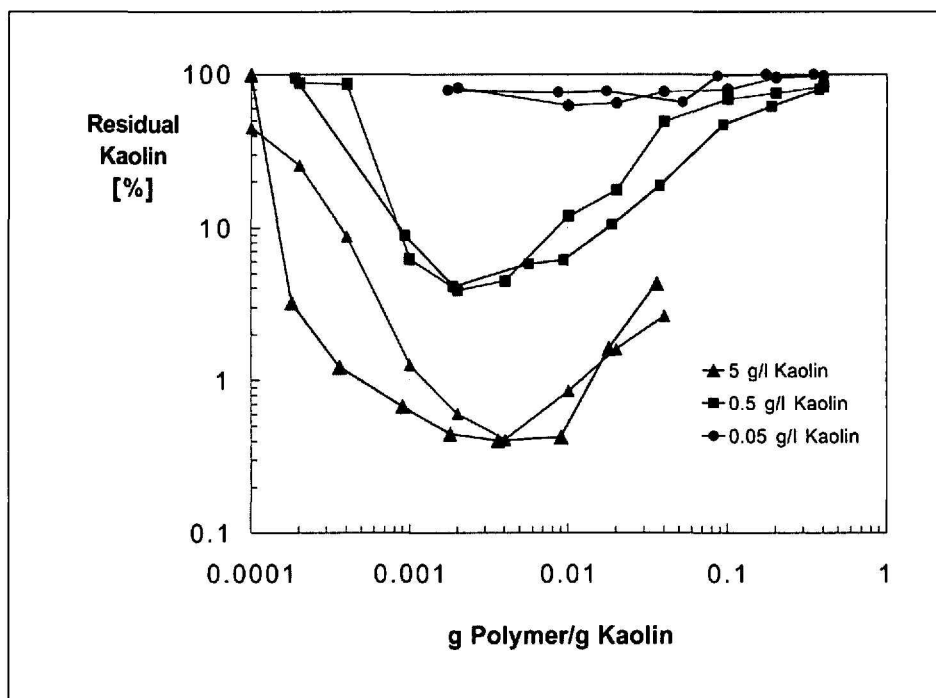


Fig. 1. Comparison of chitosan-graft copolymers with linear poly(acrylamide-co-trimethylaminoethylmethacrylate) in the clarification of a model kaolin suspension. At a lower dosage, a faster filtration time is observed. The polymer also has a larger window of application, rendering it suitable to small water treatment facilities for which no flocculants are presently designed.

An alternative approach is based on improvements to the inverse-emulsion polymerization process. Briefly, this involves the dispersion of an aqueous monomer solution in a sterically stabilized, generally parafinic, organic phase. The kinetically stable emulsion typically has a rather broad composition distribution. However, by preparing novel block copolymeric surfactants, and with appropriate stabilizer blending, conditions can be created wherein an artificial azeotrope is produced. This generates more homogeneous flocculants, as summarized in the Table. Therefore, by considering, designing and manipulating the chemical role of surfactants, in addition to their physical stabilization, higher performance polymers can be created. AlpineFloc™ which is marketed by AQUA+TECH Specialties

S.A. (Orbe, Vaud), provides improved water clarification at 20–40% lower dosages than other commercial materials. As the Table indicates, the application of the analytical ultracentrifugation has permitted a product-based patent to be derived from process modifications.

Expertise in heterophase polymerizations (*e.g.* inverse-suspension and dispersion) has led to spin-off projects including the immobilization of enzymes for the production of fine chemicals. The laboratory also has a tertiary activity on ecomaterials, attempting to modify waste natural products to obtain high value added surfactants. The development of indicators which combine environmental, technical and economic attributes is summarized in a 'Return on Environment' publication.

Table. Parameters from AUC experiments for copolymers of 60:40% acrylamide: acryloyloxyethyltrimethylammonium chloride

Copolymer	Crosslinker ppm	Association/Aggregation in 0.05M NaCl %	Sedimentation Coefficient of the Soluble Portion Svedberg	Association/Crosslinker Ratio
1	0	0	6.17	–
2 ^a	4	< 10	20.2	< 2.5
3 ^a	8	< 10	9.36	< 0.8
4 ^a	16	30–40	14.3	1.9–2.5
5	4	10–20	3.73	2.5–5
6	8	45–55	6.13	5.6–6.9

^aLPBM's new technology

Polyelectrolyte Complexes for Medical and Biotech Applications [4–8]

Membranes created by electrostatic interaction of oppositely charged PEL molecules have increasingly attracted scientific and commercial attention. Such materials may be employed in a variety of geometries including as components of flat devices or as self-containing hollow fibers, microcapsules, or microcapsules.

The development of a bioartificial pancreas is in progress and intends to provide a therapy for diabetes type I treatment without recourse to immunosuppressive drugs. It is based on the transplantation of islets of Langerhans covered by a semipermeable PEL complex membrane. Key parameters for successfully applicable microcapsules are the mechanical and chemical stability, a defined membrane cutoff, biocompatibility as well as a technology for their reproducible production under sterile conditions. Therefore, the expertise of LPBM includes patented capsule chemistries, which allow to decouple the adjustment of mechanical properties and membrane permeability. Fig. 2 shows, as an example, encapsulated islets. Small and large animal experiments with internationally leading medical centers (University Hospital of Geneva, Switzerland; University of Alberta, Edmonton, Canada) are in progress.

To fulfill regulatory requirements a principal procedure for the removal of the polyanionic endotoxin from likewise polyanionic membrane components, below the FDA threshold, has been developed, which is now in the phase of optimization and scale-up. Advanced sterile microencapsulation technologies are also being developed.

Basic Research Supports Materials Development [9–11]

The ultimate properties of PEL complex membranes depend on the molecular characteristics of the PEL, the electrochemical environment, and the design of the experimental conditions. Knowledge regarding the kinetics and mechanism of the membrane formation allows the goal-directed optimization of the membrane properties. A new method has been developed to follow the membrane formation process, and its kinetics, online. This has been accomplished by applying a specific technique of analytical ultracentrifugation, the synthetic boundary experiment. The method offers new possibilities for the study of complex formation at a defined interface, under a broad range of experimental conditions, including in physiological buffers which are essential for biomedical uses. Moreover, a membrane of defined thickness and structure, and having an area of approximately 300 mm², can be recovered for additional off-line investigations. Fig. 3 gives an example for the time dependent detection of the membrane formation.

Despite the fact that the solution behavior of PEL has been intensely investigated globally over the past 50 years, it is far from being fully understood. However, for the preparation of tailor-made

PEL and the optimization of characterization methods as well as PEL applications, it is necessary to understand how the molecular and electrochemical parameters influence the behavior and function of PEL. Basic studies in highly diluted solutions provide information about the polyion-counterion interaction. The model presented in Fig. 4 considers the influence of both macromolecular and medium parameters on the polyion-counterion interaction. The appropriate parameters are the contour length, as a measure of the dimension of the PEL chain, and the Debye length, as a measure for the ionic strength influence. The activity coefficient represents the polyion-counterion interaction.

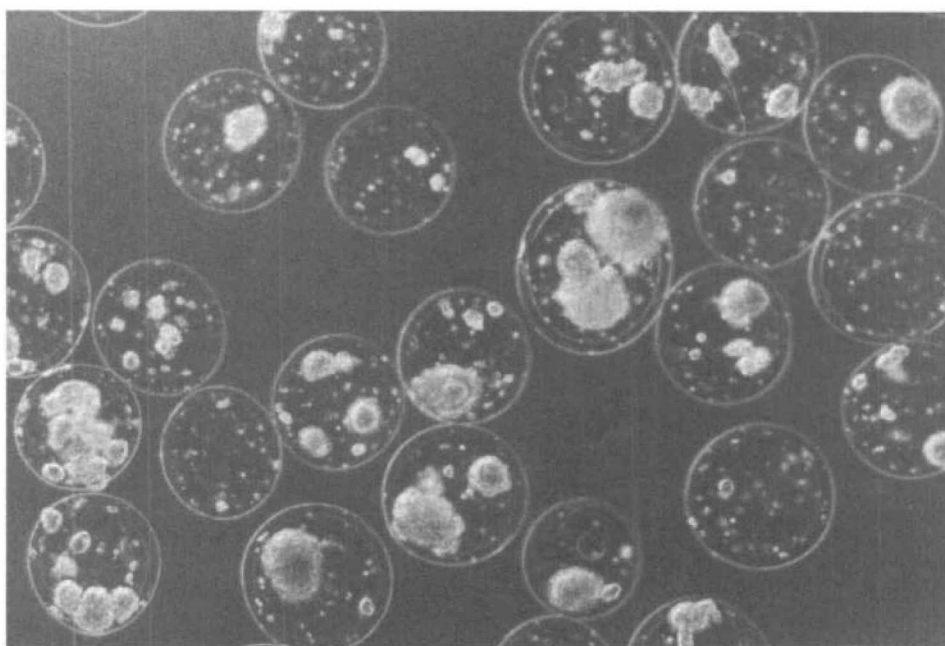


Fig. 2. Encapsulated balb/c mouse islets. Capsule size 400 $\mu\text{m} \pm 10\%$, membrane thickness 30 $\mu\text{m} \pm 10\%$.

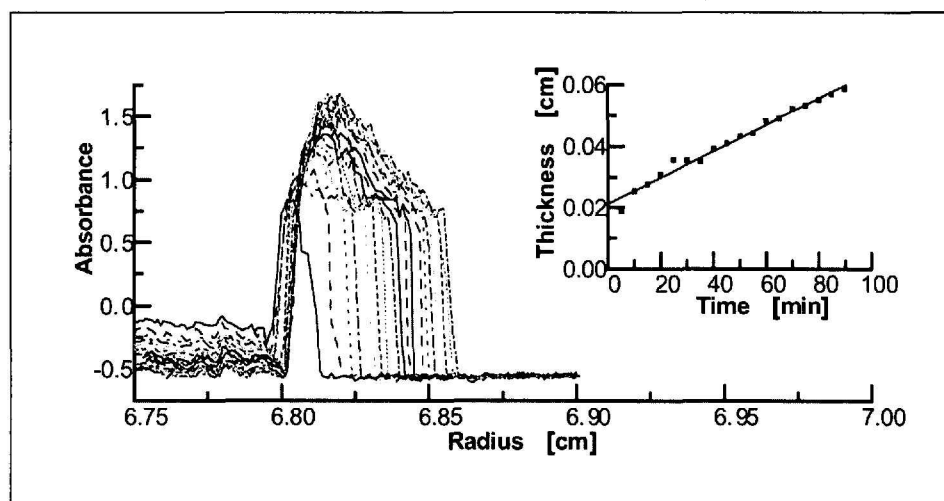


Fig. 3. Study of membrane formation in an analytical ultracentrifuge, along with complementary kinetic data on the rate of membrane growth. Alginate was used as a polyanion with chitosan as a polycation.

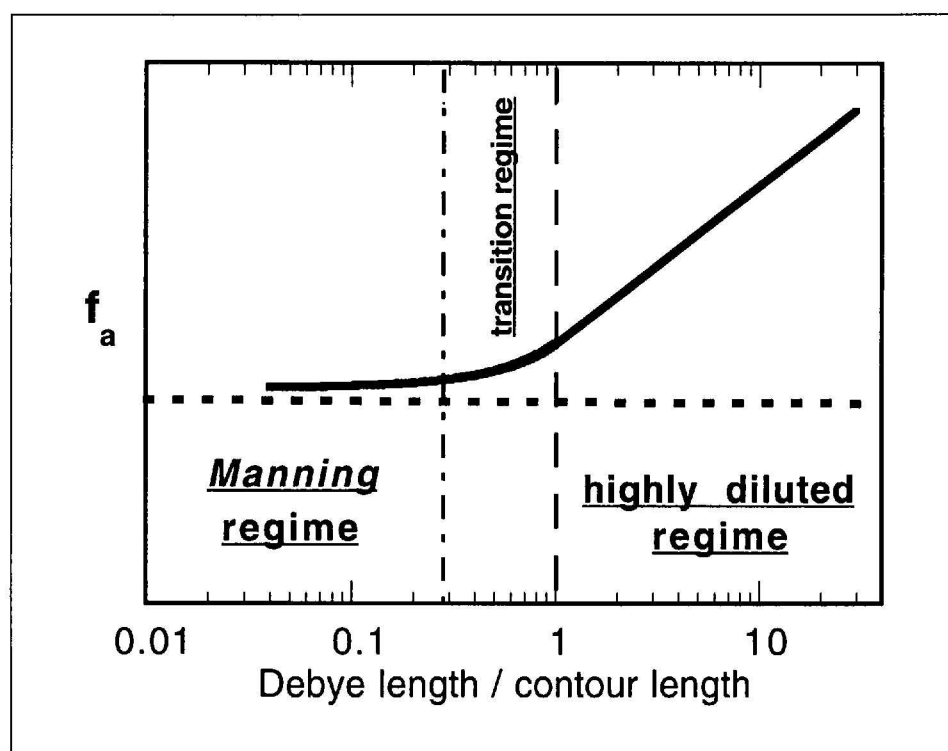


Fig. 4. The counterion activity coefficient, f_a , as a function of the ratio of the Debye length to the contour length: (· · ·) = $(4\pi)^{-1/2}$, (- · -) = 1, (—) Model curve based on poly(sodiumstyrene sulfonate) and poly(vinylbenzyltrialkylammonium) chloride data. (· · ·) Existing theories, which do not consider this influence.

Characterization as an Indispensable Tool for Product Optimization [12][13]

Fig. 5 plots the variance in the estimation of the Rayleigh factor, a parameter required for the estimation of molar mass via light scattering, as a function of the concentration of the polymer solution and the angle of the scattered light. A clear non-linearity is observed. By developing a single-concentration method, which estimates molecular properties only at the concentration, and angles,

where the variance is lowest, the precision in the estimation of the radius of gyration and weight averaged molar mass can be improved twofold (to $\pm 4\%$) concomitant with a reduction in measurement time. The 'One Concentration Method' has been applied to homo- and co-polymers in aqueous and organic solvents.

Fig. 6 illustrates the deconvolution of the bivariate distribution for a random poly(styrene-co-methylmethacrylate). The method is based on the balancing of the entropic and enthalpic separation

mechanisms using a binary eluent as the mobile phase which combines adsorption- and desorption-promoting fluids. A 'limiting' condition can be created where a homopolymer elutes at the limit of its adsorption onto the stationary phase. Under such conditions, there is no separation by molar mass for homopolymers. Hence, the first dimension of the liquid chromatograph separates by composition with the second by size without a coupling of the mechanisms.

Concluding Remarks [14–18]

LPBM takes an interest in the social-political implications involved in alternative medical therapies, with a specific interest in cell transplantation and the hotly contested debate over the benefits of human *versus* animal (xenotransplantation) tissue. This, and the subjectivity involved in indicators used in decision making, has been discussed in a series of reviews and commentaries.

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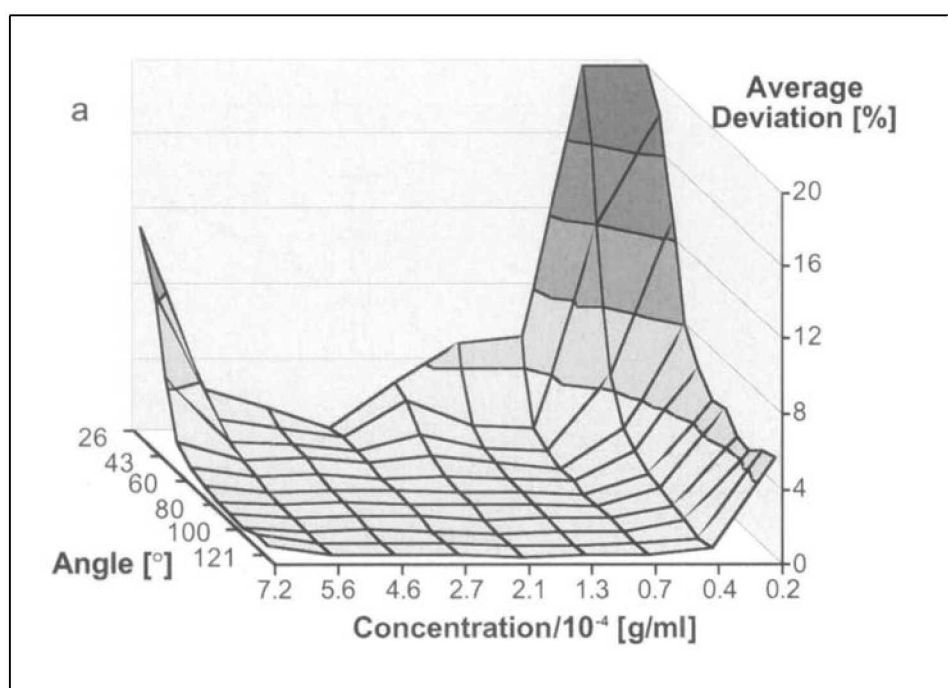


Fig. 5. Variance in the Rayleigh factor, a key parameter in molar mass estimation by light scattering, as a function of the angle of scattered light and the solution concentration. A method based on measuring the intensity at a single concentration doubles the precision in the molar mass and radius of gyration determination (to $\pm 3.7\%$).

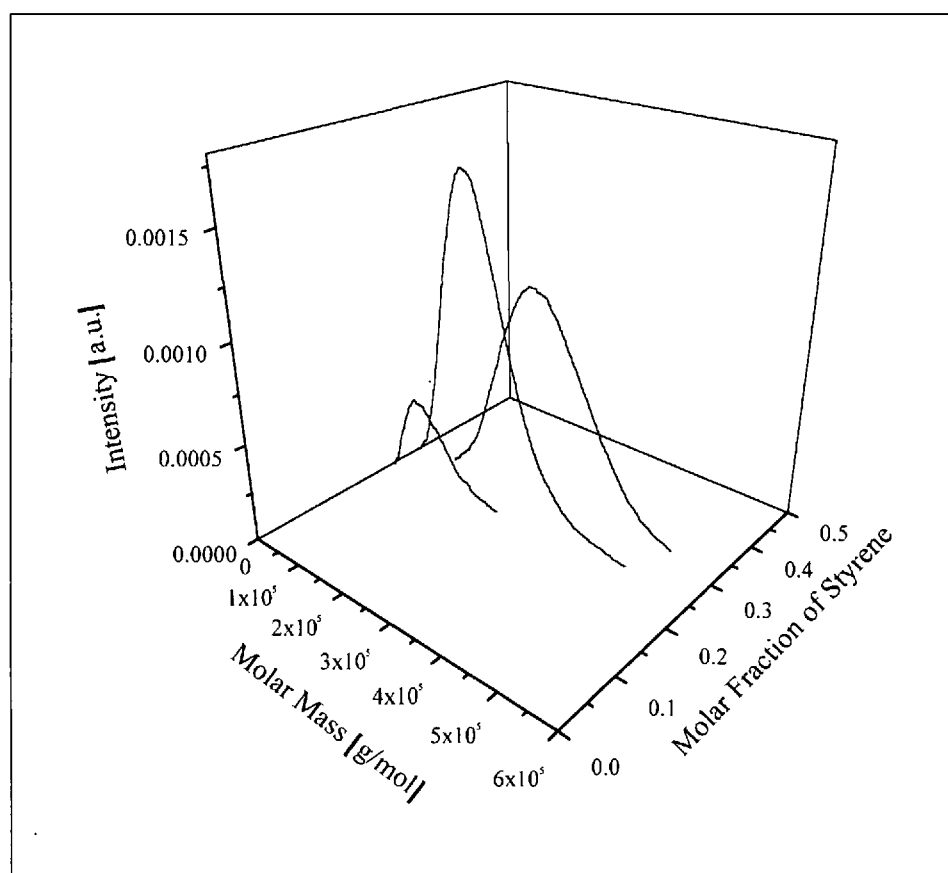


Fig. 6. Demonstration of the separation of poly(styrene-co-methylmethacrylate) into fractions homogeneous in copolymer composition, each with a molar mass distribution. To the authors' knowledge this represents the first demonstration of the analytical resolution of the bivariate distribution for a random copolymer.

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