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Review Article

Mechanistic Modelling of Chromatographic Processes: Its Trends, Development, Challenges and Applications

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ABSTRACT

In biopharmaceutical manufacturing chromatography technique has been the backbone of purification process. As bioprocessing has advanced, a growing trend has emerged toward gaining a thorough understanding of the fundamental principles underlying the pertinent unit operations, which for some operations includes the use of mechanistic modelling in a manner similar to how it is used in the chemical industry. Due to the complexity of the impurity kinds and contents originating from high titer cell culture harvest, developing and optimizing chromatography processes is a time-consuming task. Mechanistic modelling is one such approach that aids in depth understanding of the process step, underlying physicochemical processes. A model that is well calibrated and has an acceptable predictability can be of great help in process optimization as well as characterization. Mechanistic models for process optimization have continued to bloom for almost 10 decades now, yet only a very little of it has been understood. Though the simpler and essential features of the models have received a thorough investigation, the complex parameters and specialization of the simpler models into biopharmaceutical processing requires greater clarifications. The purpose of this review is to encompass the modelling approaches that have been used before and are currently in use, estimation of model parameters, their application and evolution over time.

Keywords: Biopharmaceutical, Characterization, Chromatography, Mechanistic models, Purification.

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INTRODUCTION

Biopharmaceutical industry is a relatively new, yet rapidly blooming industry. The trends and scopes of this industry have steadily expanded through years and biopharmaceutical technology is now recognized as one of the 'crucial strategic technologies' for the 21st century (Zhang *et al*., 2019). The development of so-called biologics or biopharmaceuticals has been a significant impetus for accelerating the growth of the industry in recent years. This covers small complex molecules like enzymes, hormones, protein vaccines and monoclonal antibodies (Baumann *et al*., 2017). As compared to traditional medications, biopharmaceuticals have a high level of specificity and activity. The use of biopharmaceuticals has made it much easier to treat patients who do not respond effectively to conventional synthetic drugs. Therefore, the safety and efficacy of the biopharmaceuticals, combined with the ability to tackle previously untreated diseases has set new expectations from the biopharmaceutical industry (Pirrung *et al*., 2017).

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Biopharmaceuticals are structurally very complex due to the formation of polymeric chains, which also vary greatly in their structure (Nikita *et al*., 2020). Due to this comparatively larger size and complex structure of biopharmaceuticals, especially larger ones like mAbs and hormones, it is often a challenge to manufacture and extract from biological systems. Usually, the target molecule is typically accompanied by large amounts of contaminants, such as media components, product related molecules, host-cell proteins, etc. Hence, to guarantee a safe and efficacious product, all these impurities are clarified from the final drug by the down streaming process. Downstream processing, therefore, can be referred to as the separation and purification of the bio-product from the impurities formed in the fermenter (Gomis-Fons *et al*., 2020). With the increase in product titers accrued over the past decade, the downstream process has attracted attention and its importance has been highlighted. Few recent regulatory directives like the process analytical technology and quality by design has shifted the industry's perspective towards the development and implementation of new downstream strategies (Melissa *et al*., 2012). Despite the fact that non-chromatographic methods pose a stiff competition to reduce costs and increase throughput, chromatographic methods are still dominant and most widely used techniques in the downstream processing (Nfor *et al*. 2012). The requirement of highly purified

therapeutics during product polishing makes it very unlikely for mainstream chromatographic techniques to lose its importance in biopharmaceutical industry. Apart from chromatography, filtration techniques have also evolved into another strong pillar to support the downstream processing. The versatility and separation power of filtering units account for its ubiquitous use in downstream processing (Nfor *et al*., 2010).

Increase in production of a diverse range of products increase the necessity of implementing new, systemic, reliable and effective techniques for process development. The combinations of unit operations and modes of operations create a requirement for optimized process development tools that will eventually help in exploring and understanding the advancements in the experimental designing (Baumann *et al*., 2017). Thus, the straightforward routines followed in downstream process development are transited to personalized customization of the development processes, like high-throughput screening and in recent years, design-of-experiment methodologies have gained popularity.

As described by Nfor *et al*., (2010) downstream process development strategies are broadly classified into three categories, which are expert-based, experimental-based and model-based approaches refer to Figure 1 (Nfor *et al*., 2012). All these approaches, if utilized in full potential individually or in combinations, have been highly effective in optimization and development. However, the use of modern technologies like mechanistic modelling tools with additional statistical and *in silico* methods are recently favored. Even though heuristic or experimental methods can be employed to comprehend the process, *in silico* models and simulations significantly reduce the number of experiments that must be carried out but still captures the experimental content (Moses *et al*., 2023). In this review, the main aim is to discuss about such *in silico* mechanistic models and their contribution in downstream process development. Through years mechanistic modelling tools have evolved to a great extent.

Bottlenecks in downstream processing

The biopharmaceutical manufacturers frequently complain about the bottlenecks faced by the downstream processing in terms of either matching productivity rate with Upstream Processing (USP) or efficient recovery of the huge amount of product. Recently, the advancements like strain construction, strain screening, etc., in USP has led to an overall increase in the product titers at a commercial scale (Baur *et al*., 2016). To cope up with the increasing product titers from USP, there also has been development in the downstream processing, but it was comparatively much slower. Upstream can increase the product titers depending on biological limits which require very less or no cost hike (Baur *et al*., 2018). The huge feed volume thus produced from upstream faces instruments in downstream that are designed for much lower amount of product feed. As a result, the capacity limits of such equipment's used are surpassed, leading to increase in time, heightened product consumption, less output and decreased efficiency (Benner *et al*., 2019). Therefore, this issue increases the overall manufacturing cost, which has slowly shifted from Upstream Processing (USP) to Downstream Processing (DSP), with respect to high product titers. Furthermore, any change in type and concentration of either product or impurities also contribute to the cost hike of downstream processing (Borg *et al*., 2014). Hence, designing and introducing new technologies to aid the downstream processing is considered as the only reliable solution to the downstream bottlenecks. These process development techniques must be fast, robust, highly innovative to maximize product capacity, decrease the time taken and be cost-effective.

Mechanistic models

Mechanistic models necessitate a basic comprehension of the underlying mechanism that drives the separation process and produces different process outcomes. Mechanistic models must take into account the physicochemical characteristics of the various interacting species in order to present the end result, unlike empirical models (Baumann *et al*., 2017). A good mechanistic model should not only be able to tackle the actual problems but also account for all the process requirements. Therefore, it should be as detailed as necessary, but the simplicity of the model should also be maintained (Brestrich *et al*., 2016). Throughout the years many researchers have made attempts to comprehensively summarize the different modelling approaches as well as provided many analytical solutions based on it (Briskot *et al*., 2019; Brooks *et al*., 1992). The models try to take into account various effects like mass transfer, pore diffusion, convection, dispersion, surface diffusion and adsorption kinetics. Out of all these factors the ones that are mostly focused are the mass transfer effects and the adsorption kinetics. There are a few assumptions that must be made during the modeling process, though and the resulting simplification must be considered (Michel *et al*., 2005). These assumptions include:

- Homogeneously packed adsorption bed with uniformly sized spherical particles having constant diameter,
- Negligible radial distribution,
- The process is isothermal and isobaric,
- Axial dispersion coefficient is constant,
- Constant fluid density and viscosity,
- The liquid phase inside the pores is stationary and remains unaffected by the movement of mobile phase i.e., convection inside the particles is absent,
- All the solutes are presumed to permeate the entire particle pore space i.e., the size-exclusion effects are not accounted,

- Inert eluent.

Mass Transport Models

Various mass transport models can be found in the literature that has been used over the years to model the chromatographic processes. Broadly these can be categorized into three major classes namely Equilibrium Theory, Plate Theory and Rate Models, with the General Rate Model being then most comprehensive and accepted amongst all the models (Ruthven DM, 1984). The most basic model amongst the three is the ideal equilibrium model which follows the equilibrium theory. Wicke (1939) was the first person to introduce the ideal equilibrium model and later it was derived in its present form by De Vault (1943) (Wicke, 2019; De Vault *et al*., 1943). The mass transfer effect is completely ignored in this theory, which liberally assumes a local equilibrium between the mobile and stationary phases. Axial dispersion, mass transfer resistance, external film mass transfer and intra-particle diffusion are all examples of mass transfer effects (Lee *et al*.,1989). In mathematical terms, this model sets the coefficients responsible for mass transfer to zero while the axial dispersion coefficient remains constant. For its ability to promote quick mass transfer rates in both analytical and preparative scale chromatography, equilibrium theory has received a lot of praise. Because of its effective ability to investigate the dynamics of chromatographic columns for single, binary and multicomponent systems, it is mostly used in the modeling of Simulated Moving Beds (SMV) (Mazzotti *et al*., 2006). Another model under equilibrium theory is the Equilibrium Dispersive Model, first developed by Van Deemter and colleagues (1956). It is essentially an extension of the ideal equilibrium model. This model was enhanced by lumping together the mass transfer resistances and axial dispersion-induced peak broadening effects into an apparent dispersion coefficient. (van Deemter *et al*., 1956).

The Plate theory is the next theory proposed under mass transport models. One of the earliest attempts to explain chromatography using mathematics was the plate theory, which was initially presented by Martin and Synge (1941) (Martin *et al*., 1941). Similar to distillation, the theory characterizes the chromatographic column as a group of fictitious, well mixed stages or plates. A system's axial dispersion and other mass transfer resistances can be directly determined by the number of stages it has (Lee *et al*., 2015). Since, its introduction, the initial plate model has been updated and extended for several decades and the works have been well documented in many books and articles. One of the notable extensions of the theory is the 'van Deemter equation' used to predict the effective plate height also known as the height equivalent to a theoretical plate (van Deemter *et al*., 1956). Since it is one of the best methods for assessing column performance and packing quality-both of which are crucial for process optimization and scale up-Height Equivalent To A Theoretical Plate (HETP) is fundamentally important in linear chromatography (Dewaele *et al*., 1989). The "continuous flow plate" model was the most widely used plate model. It makes the assumption that, for all plates that reach equilibrium instantly, the column is made up of a certain number of theoretical plates that are equivalent and have the same volume ratio between the stationary and mobile phases (Ishihara *et al*., 2005). This model has an advantage over the equilibrium model in that it offers the same level of precision as the rate model when applied to the optimization of linear ion-exchange chromatography systems (Velayudhan *et al*., 1993). The model's inability to simulate multicomponent chromatographic systems, however, originates from the fact that different components' equilibrium stages cannot be taken for granted. The Craig model (1987), a modified plate model that employs distribution factors to ascertain the equilibrium for every component in every step, was consequently put forth (Eble *et al*., 1987). In this case, the solute distribution between the mobile and stationary phases is treated as a continuum in contrast to the plate model which considers the column as a series of plates of finite length. The Craig plate model describes counter the separation exactly as it happens in the current distribution machine.

The most advanced of the three models are the rate models, which take into consideration all mass transfers and kinetic processes, including adsorption-desorption kinetics between the mobile and stationary phases, intra-particle diffusion and external film mass transfer (Ruthven *et al*., 1984). Amongst all the rate models, General Rate Model (GRM) is the most eclectic and complex model in chromatography. In addition to film diffusion and axial dispersion, all the other mass transport phenomena and their impact is considered in this model (Schmidt-Traub *et al*., 2012). The General Rate Model (GRM) which is most widely used was proposed by Gu *et al*., (1990) which complements the general mass balance by the description of diffusion inside the particle pores, which is also the reason for it to going by the name of pore diffusion model and the equation is given by (Gu *et al*., 1990)

$$\partial ci/\partial t = Dax,\ i(\partial 2ci/\partial 2x) - uint(\partial ci/\partial x) - (1-\epsilon)/\epsilon(\ \epsilon p\ (\partial ci\ /\partial t) + (1-\epsilon p)\ (\partial qi/\partial t))$$

The many kinetic and mass transport parameters that are included for various processes allow the General Rate Model (GRM) to be decomposed into a number of smaller models due to its greater sophistication than other rate models (Gu *et al*., 1990). These models are popularly known as the lumped rate models and have been discussed in detail in various textbooks and a few have been discussed here (Guiochon *et al*., 2006; Schmidt-Traub *et al*., 2012). Apart from axial dispersion, they have a second parameter that describes rate restrictions. This second parameter differentiates the models into those that have rate limiting mass transfer or kinetic terms (Michel *et al*., 2005). The Thomas Model is a more straightforward model that takes connective transport and adsorption rate kinetics into account while ignoring axial dispersion and mass transfer dynamics, which include all effects of internal and external diffusion both

inside and outside the resin particle. This model, which was developed from the general rate model, is also referred to as the kinetic model or the response model (Cavazzini *et al*., 2002). An improved version of the Thomas model, the Reaction Dispersion Model takes into account axial dispersion in addition to connective transport and adsorption rate kinetics. However, the mass transfer dynamics are also neglected in Reaction Dispersive Model. Another model under this category is the Transport Dispersive Model (TDM) that assumes fast rate kinetics but slow mass transfer kinetics (Golshan-Shirazi *et al*., 1992). The TDM is essentially the General Rate Model (GRM) with the implicit assumption of a homogeneous concentration inside the particle. A linear driving-force approximation is created by combining all mass transfer resistance. Lastly, there is the Transport Model Figure 2, which takes convective adsorption equilibrium and mass transfer resistances into account but ignores axial dispersion (Golshan-Shirazi S *et al*., 1992). The equilibrium dispersive model is the most straightforward of all the models covered above and it allows for the most realistic column simulations (Close *et al*., 2014). Even though this model is straightforward, its applicability is restricted since it fails to take into consideration the constraints on interparticle transmission. However, the equilibrium dispersive model is outperformed by the reaction dispersive model and the Transport Dispersive Model (TDM) in relation to its rigor. These models have the advantage of requiring less time and effort to solve model equations while maintaining some depiction of mass-transfer restrictions in the resin bed (Winderl *et al*., 2016; Hahn *et al*., 2016). Lumping can lead to considerable mistakes in the representation of intraparticle concentrations, even yet these models are still used to predict elution peak patterns (Traylor *et al*., 2011). However, the estimation of at least a subset of the model parameters based on independent trials that are consistent with the simplified models is one area where shorter descriptions might be useful.

Adsorption isotherm

A description of the adsorption process on the inner adsorbent surface is also required for a better description of the chromatography processes, even if the majority of the models captured the fluid dynamics of the chromatographic column with regard to the interstitial phase and pore volume. As a result, an adsorption isotherm was included to better explain the adsorption activities taking place on the inner adsorbent surface. The most widely used adsorption isotherms, in which the rate of adsorption is thought to be exactly proportional to the product of the activities of the involved components, are often derived using the law of mass action. Furthermore, one of the biggest sources of heterogeneity in chromatographic models is the description of the adsorption behavior for a model that is used for adsorption and desorption kinetics or equilibrium isotherm (Kumar *et al*., 2020). Mollerup has provided a thorough overview of the existing thermodynamic framework of protein chromatography adsorption isotherms (Mollerup *et al*., 2008).

Therapeutic protein molecules are structurally complex and are involved in a variety of solute-stationary phase interactions. The adsorption and desorption rate may be either fast or slow based on the complexity of the interactions the equilibrium isotherm connects the solute concentrations of the stationary phase with the mobile phase inside the porous particle for extremely quick adsorption kinetics. However, for slower adsorption kinetics, a kinetic equation relates the solute concentration inside the porous particle in the mobile phase and the stationary phase (Shekhawat *et al*., 2019). Over the years, different kinetic models have evolved for liquid chromatography (Kopaciewicz *et al*., 1983; Raje *et al*., 1997). The Langmuir model, stoichiometric displacement model, steric mass action model, non-ideal surface solution models, extended Langmuir and exponentially modified isotherm are few of the eminent members of the kinetic model family. The most popular and straightforward kinetic binding model for protein adsorption is the Langmuir model (Kumar *et al*., 2015). Each solute molecule attaches to a single binding site while ignoring the nearby sites, according to the Langmuir model's drawback of treating binding sites as independent and equivalent (Raje *et al*., 1998). But in practice, protein adsorption on a heterogeneous stationary phase surface is much more complex due to multi-pointed or multivariate interaction-a feature that the Langmuir model entirely ignores (Jennissen *et al*., 1978). Not only are the interactions multivariate and multi-pointed but also their interaction is influenced by type of salt and its concentration used; another property that is not accounted by Langmuir model (Shekhawat *et al*., 2017). The influence of steric shielding of the stationary phase and the non-linear behavior of the chromatographic system must be included in the model since the multi-pointed protein-protein interaction shields several adsorption sites. As a result, Brook and Cramer developed the Steric Mass Action (SMA) model, which took into consideration the steric hindrance effects on pre-adsorbed solute (Brooks CA *et al*.,1992). Regnier *et al*.'s (1983) stoichiometric displacement model and Velayudhan and his team's molecular steric shieling model were combined to create the model (Kopaciewicz *et al*., 1983; Drager *et al*., 1986). The model was able to describe non-linear adsorption at higher loading concentrations for the ion exchange chromatographic process in addition to taking into account the steric hindrance. Among the few presumptions made for this model are the multi-point nature of protein binding, the constant model parameters that are unaffected by the concentration of salt in the mobile phase and the few conformational changes that occur in the protein molecule during adsorption (Shekhawat *et al*., 2017). The stoichiometric displacement model is one of the several kinetic models for liquid chromatography that researchers have proposed (Raje *et al*., 1997; Kumar *et al*., 2015).

SDM, which is founded on the concept of conversation of energy, was initially presented to describe reverse phase liquid chromatography. Since then, it has also been applied to various other chromatographic processes, especially ion-exchange chromatography. Protein adsorption is predicated solely on the ion exchange mechanism, whereas the stationary and mobile phases are presumed to be thermodynamically optimal. However, this model is applicable only in case of lower protein loading. In contrast to ion-exchange systems with greater loadings, the low loading capacity eliminates the likelihood of undesired protein-protein, protein-solvent, or solvent-solvent interactions. The undesirable interactions that take place in higher loading ion exchange systems complicate the process of separation of biomolecules especially in the case of closely related impurities (Shekhawat *et al*., 2019; Shekhawat *et al*., 2017). This prompted Li and Pinto (1994) to present the NISS model, a thermodynamically consistent model in which activity coefficients were used to characterize the non-idealities (Li *et al*., 1994).

Estimation of Model Parameters

The features of the transport or isotherm model employed are frequently chosen based on how easy it is to estimate the corresponding parameters. As discussed earlier, the Generate Rate Model (GRM) is the most comprehensive of all the models that includes all of the transport terms (Schmidt-Traub *et al*., 2012). Inclusion of all the transport terms requires huge computational force to simulate the peak shapes. However, the advent in computational facilities has made this limitation of lesser significance. The bigger area to focus is probably, the confounding of effects between transport and isotherm parameters or between different transport contributions that can lead to correlated parameter values. This demands the formulation of independent measurements for estimation of at least a subset of the parameters to avoid correlations due to confounding, notwithstanding the fact that time and materials can itself be a major restraint for process development. It is advisable to either minimize the experimental effects or account for the same if they are not directly related to column model, given the fact that only column measurements are used to estimate the parameter values. (Gu T *et al*., 1990) In case of the Generate Rate Model (GRM), it comprises of parameters that can describe transport processes at column and individual bead levels. Amongst the different parameters few can be determined very easily or might not cause any noticeable deviation in the results, but others are principal to model accuracy (Golshan-Shirazi *et al*., 1992). One such parameter is the axial dispersion of the column that can be easily determined from experiments in non-binding conditions or run at different flow rates. The method of moments or height-of-theoretical-plate methods (Carta *et al*., 2010).[55] Similarly, the external mass transfer co-efficient can be estimated from published correlations but again it is not a major transport effect for concentration of proteins that are generally used for preparative chromatography. The dominant limitation remains to be the intraparticle effect which resumes to create doubts regarding the physical reality of the model. For most of the Generate Rate Models (GRMs) available in the literature the contributions for pore and surface/homogeneous diffusion are lumped together into a single pore diffusion contribution (Kumar *et al*., 2015). However, this is not the case in reality, as for Generate Rate Models (GRMs) there is separate contribution for pore and surface/homogeneous diffusion. In practice either the Van Deemter equation under non-binding conditions is used to determine the pore diffusivity or it is usually calculated from diffusion, porosity and tortuosity correlations (van Deemter *et al*., 1956). What is noteworthy here is that both of the above discussed approaches completely neglect the possibility of surface diffusion contributing to intraparticle transfer. On the same line,

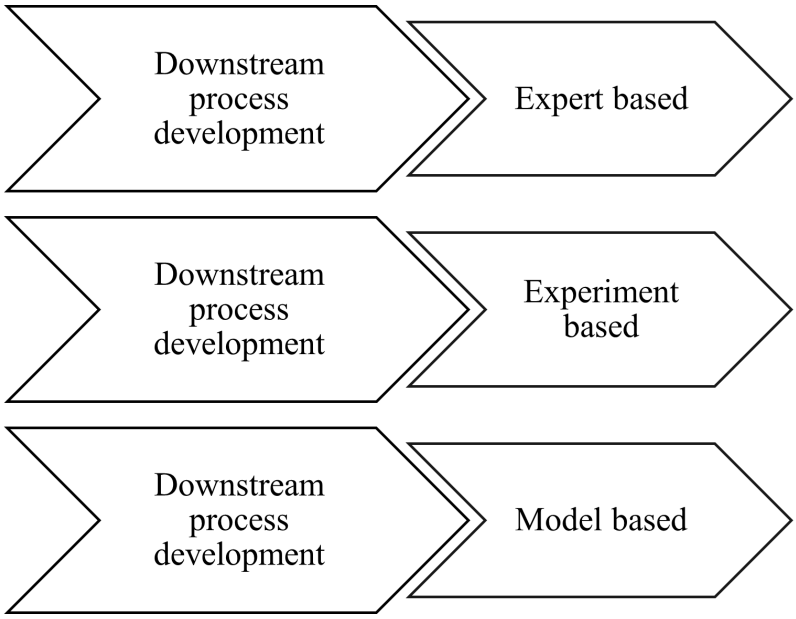

Figure 1: Downstream process development strategies (Nfor BK *et al*., 2010).

the event of surface diffusion potentially occurring has been a contentious topic since; pore and surface diffusion often yield comparable uptake profiles (Weaver *et al*., 1996). The confocal microscopy observations of individual particles uptake profile provided evidence for the occurrence of surface diffusion events (Yang *et al*., 2008). Surface diffusion is frequently disregarded for column models, despite the evidence to the contrary. This is especially true for high-load breakthrough curves and elution simulations in situations when protein binding is minimal. When there is extremely strong binding, it makes more sense to ignore surface diffusion because the coupling of pore diffusion with a nearly rectangular isotherm results in uptake behavior that is compatible with the shrinking core model. Then the transient concentration profiles inside a resin bead recorded using confocal imaging can subsequently be used to estimate the pore diffusivity during uptake conditions (Traylor *et al*., 2011). Nonetheless, a thorough grasp of surface diffusivity and its calculation is crucial, as the precise estimation of pore diffusion and surface diffusion remains a significant challenge in column modeling. The situation is comparatively simpler and easier in case of lumped models like the reaction dispersive model or transport dispersive model as the number of parameters involved are nominally less.

The task of estimation of model parameters in case of isotherms can be particularly challenging as there are very less prior information regarding the isotherm model that can be best suited to serve as a standard. So, the most widely used method for isotherm parameter estimation is estimating it directly from the measured batch isotherm data (Nfor *et al*., 2012).

The measurements are truly independent of the transport behavior if the system is well-equilibrated. The operational utilization of this real equilibrium in a column model remains an urgent concern because in some systems it can take up to a day, longer than any column experiment. Real column experiments can yield accurate measurements for model parameter estimation; however, the disadvantage is that a significant number of materials would be needed. Model simulations can alternatively be fitted with fewer column tests; however, this would necessitate deconvolution of the transport effects. For Ion Exchange Chromatography (IEX) and MMC, Yamamoto's linear gradient elution method is used to evaluate the dependence of the linear region of the isotherm on the modifier concentration (Lee *et al*., 2015). The normalized gradient is shown against the modifier concentration at the peak maximum and the parameter is determined using a short pulse load with elution at numerous gradient slopes. This has a drawback as well because the procedure only takes into account the isotherm's linear region; the remaining isotherms to be determined separately. Inverse techniques, on the other hand, reduce the error between simulated chromatograms and experimental column data in order to determine the best-fit parameters. These estimations are included into widely used packages for chromatography modeling and simulation, such as ChromX and Chromatography Analysis and Design Tool Kit (CADET).

Applications of Mechanistic Modelling

Ion Exchange Chromatography

As is well known, ion exchange is the most widely used technique for creating and purifying biopharmaceuticals. It has also drawn the most interest when it comes to chromatography process modeling. If we take an example of process development for mAb, the anion exchange chromatography is mostly used for the removal of host cell proteins and DNA, whereas the function of cation exchange chromatography is to eliminate contaminants associated with the product (Stone *et al*., 2018). Precise modelling of all the components involved in the process is not significantly or consistently achieved. However, having said so, there has been considerable efforts by the researchers to ease up the process

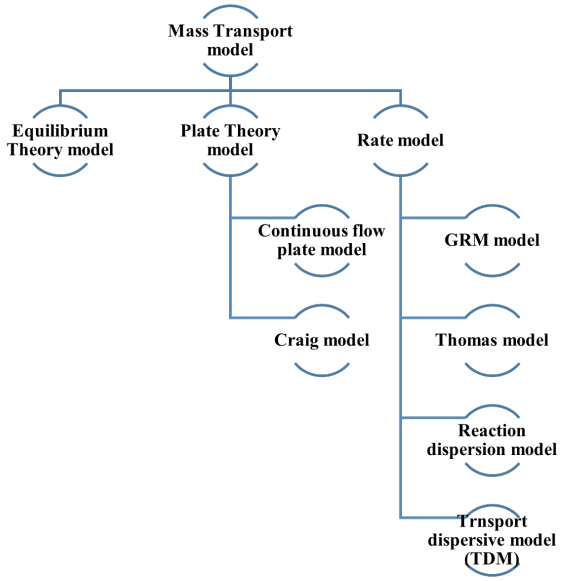

Figure 2: Mass transfer model (Golshan-Shirazi S, Guiochon G, 1992).

using various mechanistic models. Efforts have been made to understand the purification of biopharmaceuticals and its scale up process that involved the use of mass transfer models, general rate model, lumped rate models and many more. Speaking of applications, antibody aggregation is a huge bottle-neck that is encountered during downstream purification. Vogg *et al*., (2020) created model-based design spaces for counter-current batch procedures for the elimination of antibody aggregates using a lumped rate kinetic model (Vogg *et al*., 2020). A molecular model has been created by Poplewska and colleagues (2021) to explain how Monoclonal Antibodies (mAbs) unfold during ion exchange chromatography (Poplewska *et al*., 2021). Multiple peak elution, aggregation formation and recovery reduction-all of which are signs of structural changes in antibodies after adsorption-were accurately described by the model. Mechanistic modelling has also found its use in understanding the elution behavior of antibodies in process optimization. To better understand the impact of ligand density fluctuations in anion exchange chromatography, Reyes *et al*., (2021) used mechanistic modeling. Protein adsorption on ion-exchange resin was described using a Stoichiometric Displacement model (SD) and protein elution profiles in various salt gradient elution scenarios were simulated using a lumped rate kinetic model. BSA and a monoclonal antibody was used to check the model reliability, where it was found that the linear salt gradient experiments showed good correlation with the stoichiometric displacement model (Sanchez-Reyes G *et al*., 2021). It is known that during downstream purification, the charged variant composition of a product is controlled mainly via peak fractionating and pooling of elution fractions using Cation Exchange Chromatography (CEX). This can be a time-consuming operation with low resolution, which substantially lowers the amount of output produced. In order to overcome this difficulty, Khanal and team (2019) developed a mechanistic model using the general rate model, where they were able to enrich the process yield above 90% (Khanal *et al*., 2019). In addition, process changes, column age, or processing errors in chromatographic protein purification might cause product and contaminants to elute differently than predicted, resulting in lower pool purity or yield. A deviating chromatogram is caused by the variable elution behavior of all or some of the implicated species. The reasons of deviations, on the other hand, are difficult to determine by visual inspection, making it more difficult to remedy an issue in the next cycle or batch. Brestrich *et al*., (2016) developed a technique for root cause analysis in protein chromatography to solve this issue that made use of transport dispersive model in association with stoichiometric displacement isotherm for IEX (Brestrich *et al*., 2016). Saxena and her associates used the comprehensive general rate model to create a mechanistic model for the continuous processing of biopharmaceuticals. In order to determine the maximum flow rate for Cation Exchange Chromatography (CEX) for maximum separation of charge variant, the Reinforcement Learning (RL) technique was applied for the first time. All the simulations and equation solving was done using. In addition to these, developability criteria are occasionally taken into consideration to facilitate the production of a possible therapeutic candidate when multiple antibody candidates have comparable biological activity. While current developability evaluation methodologies put emphasis on drug product stability, there is a scarcity of data on how antibody candidates with minor structural variations behave throughout downstream processing (Saxena *et al*., 2021). Saleh *et al*., (2021) used a transport dispersive model to simulate the effects of monoclonal antibody amino acid substitution on cation exchange chromatography in order to comprehend its adsorption process (Saleh *et al*., 2021). Their experiments' outcomes improved our knowledge of lead compound optimization in downstream processing for antibody drug development.

Affinity chromatography

Affinity chromatography is widely used in labs, but Protein A chromatography is the industry standard for large-scale manufacture because it enables the highly selective capture of mAbs and mAb-like biotherapeutics (Hober *et al*., 2007). Since affinity separations have exceptional selectivity and are typically used for capture rather than polishing, modeling has been viewed as unnecessary. But as attempts are made to enhance protein loading, especially in multicolumn designs that enable high throughput, this is starting to change. The Langmuir binding model is physically adequate for the biomolecular recognition phenomenon exhibited by protein A chromatography and it is not a surprise that most of the affinity models designed by mechanistic modelling has either used the Langmuir model or variants of the same keeping in mind the simplicity of its implementation. For instance, Pabst *et al*., (2018) accurately predicted the Dynamic Binding Capacity (DBC) by fitting batch isotherm data for 12 distinct affinity resins using the Langmuir isotherm without any modifications (Pabst *et al*., 2018). A modified Langmuir isotherm has also been used for modelling the general route of elution by changing pH, accounting the effects of pH changes on the equilibrium binding co-efficient.[12] In addition, Steinebach *et al*., created a model for the continuous capture of the production process of monoclonal antibodies. The process of affinity chromatography was described using a lumped mass-transfer model and a heterogeneous binding model. The model's ability to forecast process performance in terms of yield, productivity and capacity utilization was determined (Steinebach *et al*., 2016). A lumped rate kinetic model has also been used as the backbone, for improvement of protein A resin lifetime and its optimization, where the model equations were solved using MATLAB. Fons and co-workers took the support of mechanistic modelling in order to optimize the process for periodic counter-current chromatography of a mAb where a general rate model was used to determine the breakthrough curve of protein-A capture step (Gomis-Fons *et al*., 2020). In addition,

a PBPK (Physiologically Based Pharmacokinetic) model was developed for understanding the pH-dependent target binding behavior of antibodies to FcRn (Yang *et al*., 2008). The application of mechanistic modelling has also extended to understanding of fouling of Pro A chromatography resin (Pathak *et al*., 2016).

Hydrophobic interaction chromatography

Hydrophobic interaction chromatography frequently plays important role in purification of intermediates and downstream processing purification steps. In the mAb purification process, this particularly means removing product-related impurities such protein clumps and fragments from the monomer (McCue *et al*., 2008). Relatively, simpler models like the Langmuir model is generally used for HIC. For most of the cases the standard Langmuir model can just serve the purpose, but quadratic forms of the same model have also been used with its subsequent validation for linear gradient as well as displacement separations (Nagrath D *et al*., 2011; Jakobsson *et al*., 2005). Shekhawat and team (2017) developed a mechanistic model for HIC based purification of mAbs. The model is based on the general rate model and the exponentially modified Langmuir adsorption model (Andris *et al*., 2020). One major issue with the chromatographic purification of therapeutic proteins is batch-to-batch fluctuation in the feed's contaminant levels and product concentration. By foreseeing the effects of such variations, mechanistic models can facilitate the application of Process Analytical Technology (PAT), increasing the robustness of the resulting process and controls (Shekhawat *et al*., 2019). Shekhawat and Rathore (2017) used the same mechanistic model as used in their previous work where HIC has been represented as a PAT tool for facilitating the removal of aggregates for mAbs (Shekhawat *et al*., 2017). Apart from these, a lumped rate transport dispersive model for preparative HIC chromatography was developed by Andris and Hubbuch (2020) for the separation of cysteine engineered mAbs (Andris *et al*., 2020). In addition, Wang *et al*., (2016) reported a mechanistic model for HIC where an isotherm model was derived by considering an equilibrium on the protein-ligand hydrophobic surface. As model systems, glucose oxidase, Bovine Serum Albumin (BSA) and lysozyme on CaptoTM Phenyl were employed. for demonstrating the model accuracy. ChromX was used for model calibration and simulation in this case (Wang *et al*., 2016).

CONCLUSION

The last ten years have seen a substantial rise in computational capacity, allowing researchers to use and solve complicated models for modelling liquid chromatography. The chromatographic modelling that is mostly prevalent now differs only slightly than the ones emerged in the mid of the twentieth century. The industry's need for model-based support and the growing availability of computational partial differential equation solvers designed especially for these issues are what are primarily fueling the tremendous interest that such modeling is garnering for biopharmaceutical applications. The expanding body of research in this area is directing both model design and model interpretation, despite the fact that there is still much to learn about modeling isotherms and transport. Researchers have used these mechanistic models successfully over the past ten years for process characterization, control and optimization, most notably for model assisted robust pooling techniques. Process development, automation and control of biopharmaceutical chromatographic processes have a great deal of potential to reach the same level of underlying quantitative understanding as is already common for many unit operations in the traditional chemical process industries, especially as this body of research is complemented by molecular understanding and rapidly growing databases of empirical data.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

USP: Upstream Processing; **DSP:** Downstream Processing; **SMV:** Simvastatin; **HETP:** Height Equivalent to a Theoretical Plate; **GRM:** General rate model; **TDM:** Transport Dispersive Model; **SMA:** Steric Mass Action; **IEX:** Ion EXchange chromatography; **CADET:** Chromatography Analysis and Design Tool kit; **CEX:** Cation EXchange chromatography; **SD:** Stoichiometric Displacement model; **RL:** Reinforcement Learning; **DBC:** Dynamic binding; capacity; **PBPK:** Physiologically based pharmacokinetic; **PAT:** Process Analytical Technology; **BSA:** Bovine serum albumin.

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