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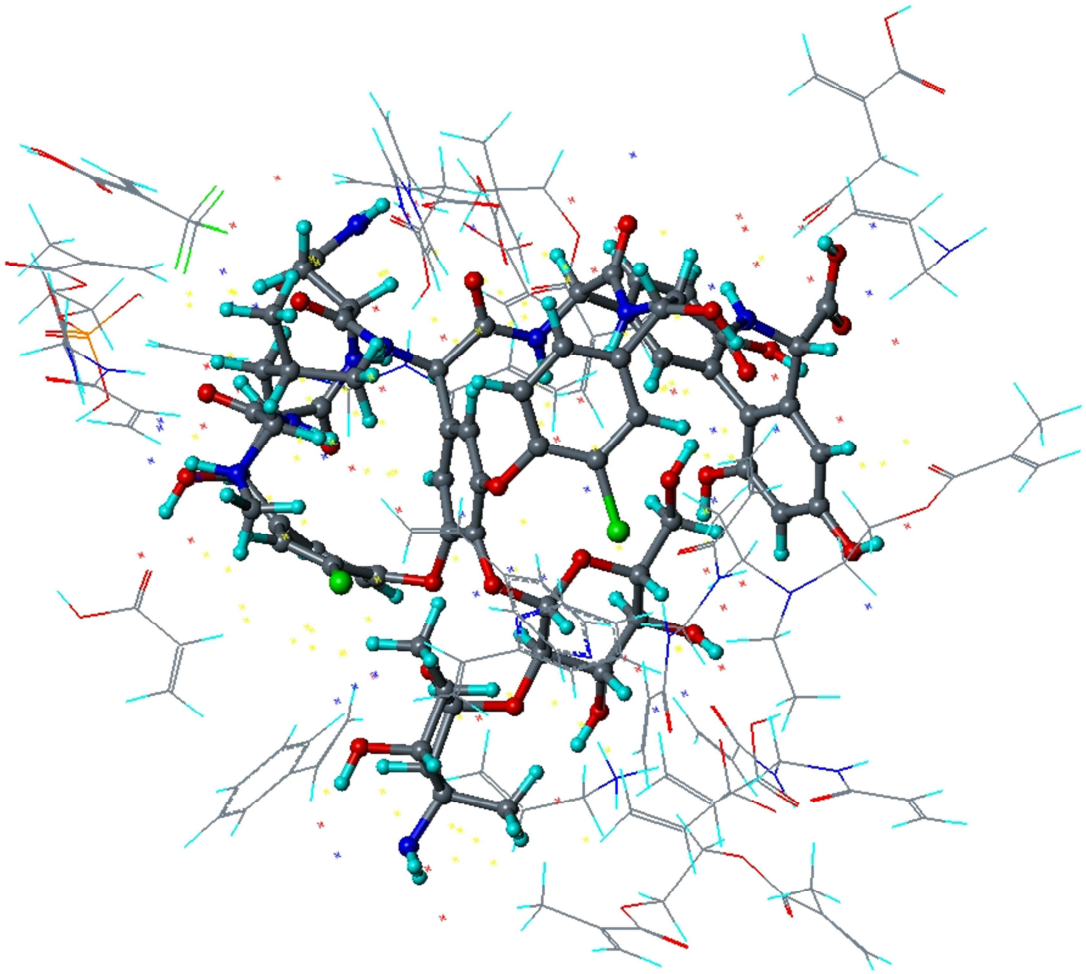

Highlights

- A review of computational modelling in the design of molecularly imprinted polymers
- Target analytes and method of analysis for the vast majority of recent articles
- Explanations are given of all the popular and emerging techniques used in design
- Highlighted examples of sophisticated analysis of imprinted polymer systems

Computational Approaches in the Design of Synthetic Receptors – A Review

Todd Cowen*, Kal Karim, Sergey Piletsky

Leicester Biotechnology Group, Department of Chemistry, University of Leicester, LE1 7RH, UK

Abstract

The rational design of molecularly imprinted polymers (MIPs) has been a major contributor to their reputation as "plastic antibodies" – high affinity robust synthetic receptors which can be optimally designed, and produced for a much reduced cost than their biological equivalents. Computational design has become a routine procedure in the production of MIPs, and has led to major advances in functional monomer screening, selection of cross-linker and solvent, optimisation of monomer(s)-template ratio and selectivity analysis. In this review the various computational methods will be discussed with reference to all the published relevant literature since the end of 2013, with each article described by the target molecule, the computational approach applied (whether molecular mechanics/molecular dynamics, semi-empirical quantum mechanics, *ab initio* quantum mechanics (Hartree-Fock, Møller–Plesset, etc.) or DFT) and the purpose for which they were used. Detailed analysis is given to novel techniques including analysis of polymer binding sites, the use of novel

* Corresponding author.
Leicester Biotechnology Group, Department of Chemistry, University of Leicester, LE1 7RH, UK
Email address: tc203@le.ac.uk (T. Cowen); phone: +44 (0)116 252 2100 (departmental).

screening programs and simulations of MIP polymerisation reaction. The further advances in molecular modelling and computational design of synthetic receptors in particular will have serious impact on the future of nanotechnology and biotechnology, permitting the further translation of MIPs into the realms of analytics and medical technology.

Keywords: molecularly imprinted polymer, chemical sensor, assay, polymer simulation, density functional theory, molecular dynamics

Contents

Acronyms and explanations

ΔE	Difference in potential energy; in the context of this paper this refers to the equation $\Delta E = E_C - (E_T + \Sigma E_M)$, a common method of determining the relative affinity for a particular complex (see section 3.1). Potential energy may be given in Hartree with QM methods, though Gibbs free energy is now more common.
Ab initio	"From the beginning"; techniques which start from fundamental principles of quantum mechanics. Typically refers to Hartree-Fock and related levels of theory in which individual atomic orbitals are calculated and built into molecular orbitals.
AIM	Atoms in molecules theory, or the quantum theory of atoms in molecules (QTAIM); structure can be determined from the electron density of the molecule or molecules.
B3LYP	Becke 3-parameter Lee-Yang-Parr; commonly used hybrid functional combining Becke's three-parameter exchange functional with Lee, Yang and Parr's nonlocal correlation functional [1]. These functions relate to more accurate representations of the spin interactions of electrons.
Basis set	A set of functions used to create a representation of the molecular electron distribution. Those used in the papers reviewed are all split valence or 'Pople' basis sets (see section 3.1).
Cross-linker	Monomers used to give greater rigidity to a MIP. Screening of cross-linkers is relatively unusual compared to that of functional monomers.
DFT	Density functional theory. DFT treats molecular orbitals as continuous bands and treats electron density as fundamental property from which calculations can be performed, as opposed to HF which must account for all particles.
Force field	A set of parameters used to describe and refine the energy of an arrangement of atoms in molecular mechanics and molecular dynamics.
Functional monomer	Monomers used to maximise the electrostatic interactions between the target molecule and the MIP binding site. Screening of functional monomers is a typical use of

	computational methods in MIP design.
GAFF	General Amber force field; a molecular mechanics force field available primarily in the Amber programs.
HF	Hartree-Fock; an *ab initio* technique based on the self-consistent field method of repeating calculations with improving values for orbital energies and their coefficients until self-consistent.
LeapFrog	A program available within the Sybyl software used to automatically screen a library of functional monomers.
MD	Molecular dynamics; a method of simulating the change of a system through time based on MM, allowing the consideration of thermodynamic and related physical effects.
MIP	Molecularly imprinted polymer; a typically organic polymer synthesised with a template molecule resulting in a selective 'imprint' binding site.
MM	Molecular mechanics; empirically based atomistic models used to predict the energies of different molecules, allowing structural predictions, interaction energies, etc.
PCM	Polarisable continuum model; the application of a dielectric constant (or similar) across the observed system to replicate solvent effects.
QM	Quantum mechanics; electronic structure based techniques used to predict molecular energies, allowing structural predictions, interaction energies, etc.
RDF	Radial distribution function; used within MD simulations, RDF gives the relative length of time that a particular distance (the density) was observed between one atom and another atom or group of atoms.
Semi-empirical	QM techniques which use *ab initio* methods to replicate valence electronic structure and empirical parameters for the core electrons. This has benefits in computational expense but has recently fallen out of favour.
Template/ Target	The template is the molecule used to the form the MIP imprint, the target is that for which the MIP is being prepared. This is usually but not necessarily the same compound.

1. Introduction

Molecularly Imprinted Polymers (MIPs) have developed a strong reputation in the analytic fields, and are increasingly recognised for their potential in less traditional areas of biotechnology. Whilst used conservatively as a separation/purification material, MIPs have been recognised in recent times as superior replacements for biological macromolecules in a variety of research areas and practical applications [2-4]. Advances in the synthesis of molecularly imprinted nanoparticles [5-7], combined with advantages over their natural counterparts in terms of cost and stability [8, 9] and possible utility in antimicrobial, antiviral and anticancer therapy [10-12] has secured these nanomaterials the moniker of "plastic antibodies" [13-15]. Figure 1 shows the general method of MIP synthesis.

[Figure 1]

The adoption of computational methods in MIP design has permitted the efficient preparation of high affinity polymers by a rational design protocol. Monomer selection by template interaction analysis allows the selection of high affinity MIPs with control over their binding strength. While the use of simple molecular modelling to visualise template-monomer interactions was a practice observed at the time [16], adoption of computational methods explicitly for the purpose of MIP design first appeared in the late 1990s [17, 18]. The molecular modelling based approaches to rational design however were only widely acknowledged as having strong general utility with the 2001 publication by Piletsky *et al*. who described the use of monomer modelling software in monomer screening [19]. This paper demonstrated that good predictions could be generated without recourse to expensive empirical methods such as combinatorial screening, which, although highly efficient compared to traditional methods [20], would still require an unreasonable amount of time and resources to replicate the data obtained from computational modelling. While the number of researchers focused primarily on the theoretical element of MIP design remains relatively

low, computational approaches to MIP design have become well established in the 15 years since this publication, and some of the methods applied in this modelling are quite ingenious. Greater understanding of monomer-template complexation and the impact of polymerisation on the structure of the binding site could provide the means to facilitate the production of advanced dynamic and reactive materials, responsive to their environment and target binding in as yet unthought-of ways.

The focus of this review is an examination of recent applications of computational methods in MIP design, updating similar works published on the same topic previously [21, 22]. Here however we are obliged to modify the relative weighting of topics and to introduction of new subject matter, primarily concerning quantum mechanical modelling, an inevitable consequence of the technological development and increasing number of groups working in the area. The emphasis remains on theoretical modelling as an alternative to empirical screening and as a technique for extracting information which may be difficult, expensive or time consuming to obtain via traditional methods.

2. Methods and targets in the rational design of MIPs

To the best of our knowledge Table 1 below contains a reference to vast majority of available articles employing computational methods to the design of imprinted polymers that were written since 2013, when the last major review was published [21]. The major categorical divisions are by the application of the technique employed, with the majority of research falling into functional monomer screening, detailed observation of molecular (typically electronic) structure and monomer-template interactions. The categories are then subdivided into the methods used, being either molecular mechanics/molecular dynamics (MM/MD), or one of three broad quantum mechanics based techniques: semi-empirical, *ab initio* and DFT.

Table 1: Compilation of the use of computational approaches in MIP design, with references given according to the target selected, the computational technique applied in the modelling, and the manner in which the models were used.

Application	Method	Targets
Functional monomer screening (* using screening/docking program)	*MM/MD*	*Curcumin [23], *fenthion [24], *methidathion [25], *propofol [26], *amlodipine [27], *endotoxins [28], *cocaine [29], thymopentin [30-33], diuron [34], *metoprolol [35], *paracetamol (modified) [36], iprodione [37], 5-(3,5-Dichloro-2-hydroxybenzylamino)-2-hydroxybenzoic acid [38], naproxen [39], biotin [40], hexazinone [41], 1-(2,4-Difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone [42].
	Semi-empirical	Metaproterenol [43], diuron [34], ciprofloxacin [44], baicalein [45], Sulfamethizole [46], 4-(2-Aminoethyl)aniline [47], hexazinone [41], theophylline [48], cotinine [49].
	Ab initio	Baicalein [50], phenothiazine [51], phenol [52], acephate [53], phenazopyridine [54], fusaric acid [55], uracil [56], 5-fluorouracil [56], metformin [57], tanshinone IIA [58], pantoprazole [59].
	DFT	(S)-Warfarin [60], hydrochlorothiazide [61], Atrazine [62], sulfanilamide [63], carbofuran [64], fenitrothion [65], 2,3,7,8-Tetrachlorodibenzo-p-dioxin [66], butylphthalide [67], mesalamine [68], enrofloxacin [69], 1,4-dihydroxyanthraquinone [70], ractopamine [71], acephate [53], Sulfamethizole [46], dopamine [72], Δ^9-tetrahydrocannabinol [73], 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol [73], tramadol [74], 5-(3,5-

		Dichloro-2-hydroxybenzylamino)-2-hydroxybenzoic acid [38], 6-thioguanine [75], metformin [57], melamine [76-78], spermidine [79], epinephrine [80], quinoline [81], triamterene [82].
Advanced structural analysis / ratio optimisation	*MM/MD*	Curcumin [23], amlodipine [27], phosmet [83], estrone [83], metolcarb [83], enrofloxacin [83], tetracycline [84], tyramine [85], octopamine [86], paracetamol (modified) [36], butylated hydroxyanisole [87], bupivacaine [88-90], norfloxacin [91], dibenzothiophene [92], 4-nitrophenol [93], bisphenol A [94], phenylalanine [95], 5-(3,5-Dichloro-2-hydroxybenzylamino)-2-hydroxybenzoic acid [38], naproxen [39], copper(II) [96], caffeine [97], theophylline [97], 1-(2,4-Difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone [42], bupivacaine [89, 90], (S)-propranolol [98], 1,2,3-trichlorobenzene [99].
	Semi-empirical	Metaproterenol [43], phosmet [83], estrone [83], metolcarb [83], enrofloxacin [83], tetracycline [84], ciprofloxacin [44], sulfamethizole [46], uracil [56], 5-fluorouracil [56], aspartame [100], theophylline [48], erythromycin [101], sulfadiazine [102].
	Ab initio	Tetracycline [84], phenol [52], acephate [53], metformin [57], tanshinone IIA [58], cotinine [49], sulfadiazine [102].
	DFT	Metaproterenol [43], uric acid [103], (S)-warfarin [60], tyramine [85], fenitrothion [65], minoxidil [104], Famciclovir [105], melamine [76-78], cichoric acid

		[106], 2,3,7,8-Tetrachlorodibenzo-p-dioxin [66], deltamethrin [107], enrofloxacin [69] barbital [108], ractopamine [71], 5-fluorouracil [109], acephate [53], sulfamethizole [46], carnosine [110], butylated hydroxyanisole [87], dopamine [72], Δ^9-tetrahydrocannabinol [73], 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol [73], 6-thioguanine [111], flumequine [112], benzothiophene sulfone [113, 114], dibenzothiophene sulfone [113, 114], 4,6-methyldibenzothiophene sulfone [113, 114], erythromycin [115], tramadol [74], α-amanitin [116], propranolol [117], salbutamol [118, 119], cocaine [120], palmitic, oleic and elaidic acids [121], nicotine [122], 5-(3,5-Dichloro-2-hydroxybenzylamino)-2-hydroxybenzoic acid [38], naproxen [39], copper(II) [96], atrazine [123], quercetin [124], metformin [57], pyrene [125], caffeine [126], spermidine [79], gallic acid [127], ciprofloxacin [128], quinoline [81], sulfadiazine [102], neopterin [129].
Analysis of interactions in dynamic system	*Molecular Dynamics*	Naproxen [39], (S)-propranolol [98], bupivacaine [88-90], norfloxacin [91], dibenzothiophene [92], 4-nitrophenol [93], bisphenol A [94], cholesterol [130], 1,2,3-trichlorobenzene [99].
Comparative binding site interaction energy/polymer simulation	*Various*	Tyramine [85], octopamine [86], 6-thioguanine [111], cholesterol [130], caffeine [97], theophylline [97], 1-(2,4-Difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone [42].

3. Quantum mechanics based approaches in MIP design

3.1. The general QM approach to MIP design

The application of quantum mechanical modelling methods to MIP design has grown from a novelty to routine since the end of the last decade, when the use of QM based methods was comparatively rare [22]. Noticeable too in the somewhat small pool of researchers using these techniques before 2010 is the dominance of semi-empirical methods, a tendency that has not continued to the present. Density functional theory (DFT), and specifically the hybrid functional B3LYP are currently the most popular model applied in synthetic receptor design, which combine the benefits in accuracy associated with quantum mechanical calculations with a more efficient method of describing the electronic structure than is found in the ab initio methods (see below).

QM methods are typically employed for the precise analysis of monomer template interactions to determine the appropriate polymerisation mixture for the affinity of high affinity MIPs. The equation: $\Delta E = E_C - (E_T + \Sigma E_M)$ is generally used in QM based design, and frequently in other techniques. ΔE is the association energy associated with the interaction observed, and is taken from E_C, the potential energy associated with the monomer-template complex, E_T, the energy of the template, and E_M, the energy of the monomer or monomers (thus, ΣE_M) involved in the complex. Each of these values provides little useful information in isolation, but comparison of the different values for ΔE gives an indication of the relative stability of different components in the system. Deviations from this exact method may involve analysis of an oligomer or polymer matrix and the interaction between this structure and one or several target analytes, but the principle of measuring the calculable relative energy difference, and therefore the energy of association, remains the same.

[Figure 2]

Amongst the most detailed examples of this approach is the theoretical work of Khan *et al*. in their design of a 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, Figure 2) imprinted polymer [66]. In this research, the template TCDD, a library of 35 functional monomers, three different cross-linker molecules and three commonly encountered template analogues were energetically minimised using a B3LYP/6-31+G(d,p) method. Using the equation above, the functional monomers were screened against the template to determine a small number of likely candidates, which were then analysed with a polarisable continuum model (PCM), which simulates the effects of a particular solvent of the system components by the application of a dielectric constant on the surrounding environment. This process allowed the researchers to select an appropriate monomer-solvent combination for successful complex formation. Cross-linkers were then also analysed for their affinity for the template, selecting that with the lowest ΔE value, therefore further increasing the relative affinity of the functional monomer selected. Analysis of the selected monomers with the template analogues under the effects of the polarised continuum gave an indication of the MIPs likely selectivity for the chosen target over possible contaminants.

The energy minimisation performed in the binding analysis above was performed using the B3LYP (Becke three-parameter Lee-Yang-Parr) hybrid functional, which is the most common method found in the theoretical MIP design; though some researchers working in MIP design have found that it compares less favourably with crystal data than other hybrid functionals [77, 119]. Hybrid functionals combine Density Functional Theory (DFT) with Hartree-Fock (HF) and other QM techniques to overcome some of the limitations associated with each of these used in isolation. Briefly, Hartree-Fock and related pure *ab initio* techniques begin with the Schrödinger equation, or some modification thereof, and determine desired properties from first principles. This method requires initial estimation of the

coefficients of the atomic wave functions which describe the contribution of each to the molecular orbital, and allowing calculation of a preliminary orbital energy. The energy is then fed back into the algorithm to give more accurate values for the coefficients and so on, until the results are self-consistent. This process is computationally expensive and has led to a number of attempts at simplification, including the sufficient but now rarely used semi-empirical methods. These approaches typically only perform the processes described previously on the valence shells, with the 'core' electrons being described using empirically determined factors. This gives advantages in terms of computer time and power requirements, but can also allow the model to give approximations accounting for relativistic effects observed in electrons near the nuclei and electron correlation (the distribution of each electron within an orbital), which traditional *ab initio* techniques neglect.

DFT has steadily risen as an alternative to the previously described methods across theoretical and computational chemistry, most obviously in its extensive use in MIP design. DFT differs from other *ab initio* methods in its combination of atomic orbitals into electronic bands, unlike HF which forms atomic orbitals, and must therefore attempt to include terms which account for the parameters for all particle interactions. Band theory regards extended areas of molecular orbitals as a continuum, allowing the same electronic structure to be represented in a much simpler fashion, regarding the electron density (on which the functionals act) as a fundamental property and ignoring the details of individual atoms' properties.

Issues arising from the simplicity of DFT regarding electron correlation and Pauli repulsion led to many progressions in the model, but the combination of DFT with other methods as hybrid functionals has come to prominence in a number of fields, and B3LYP (Becke 3-parameter Lee-Yang-Parr) dominates the hybrid functionals in both popularity and effectiveness over broad areas of modelling research.

In the above study a 6-31+G(d,p) basis set was used with B3LYP in the energy minimisation of a large number of molecules and molecular complexes. This is a form of STO-nG (split-valence) basis sets which uses a number of Gaussian functions (nG) to better approximate the exponential decay and electron density maxima cusp of the more accurate for, but more difficult to manipulate, Slater-type orbital (STO). The split valence basis sets come from the desire to better represent molecular binding, and thus focuses on the valence orbitals. The description of the inner shell electrons is given by a linear combination of six Gaussian functions (thus 'G'), the smaller valence orbitals by three, and the larger valence orbitals by a single Gaussian function, with the hyphen representing the splitting of the valence shell. The polarisation term, (d,p), account for the change in electron distribution in proximity to other atoms. Often in QM MIP design, '(d)' polarisation functions (sometimes denoted with a single asterisk) will be included, which account for the effect of d-orbital functionality on p-orbital electrons. In this research p-orbital functionality (often shown '**') has also been added to the hydrogen atoms and any d-orbital electrons which may be present. Finally, the '+' indicates that diffuse functions have been included in the basis set, for better representation of the p-orbitals at distance; '++' may been seen when diffuse functions for the s-orbitals are also included in the calculation.

[Figure 3]

The group designing a TCDD imprinted polymer also conducted some less common QM based analytic techniques that are likely to rise in popularity. Amongst the most useful of these include the determination of the HOMO-LUMO gap, which may be useful in predicting the relative stability of monomer-template complexes [66, 131]. The HOMO and LUMO of TCDD and methacrylic acid, as used by Khan *et al.* are shown in Figure 3. This frontier orbital analysis could become more common in QM design of MIPs as it can be used to calculate the interaction energy whilst also provides information on electron structure, which

may be of use in considering further improvements to the system analysed. Similarly, molecular electrostatic potential (MEP) maps, intermolecular bond angle and distance analysis, and theoretical IR spectroscopy, were all considered useful in the example mention, and may also become more prevalent generally in the future.

3.2. QM method selection

Possible barriers to the widespread use of QM in developing MIP theory largely grow from its inherent complexity. The computational expense required for calculations of systems larger than a few molecules is still prohibitively high. None of the cited research using QM based studies includes the use of explicit solvent molecules in modelling interactions for this reason, instead applying the PCM. However, when the purpose of the research is analysis of the intermolecular interactions of a system, it is at best an oversimplification. The choice of QM method might also cause difficulties without relatively extensive preliminary experimental research, as for accurate results different techniques display varying qualities of representation [132, 133]. The importance of appropriate quantum mechanical method selection has been noted by several researchers in the field, such as that of Gao *et al.* in their modelling of the interactions of a target molecule with a small piece of functionalised surface to gauge the appropriate ratio for polymerisation [128]. This group found that B3LYP hybrid functions were not the most reliable when compared to crystal data, and instead opted for the LC-WPBE functional with a 6-31G(d,p) basis set. The dependence of modelling results on any particular functional was further shown in a very thorough study in the optimisation of an MAA functionalised enrofloxacin imprinted polymer [134]. In this work a number of different hybrid functionals were tested (including LC-WPBE) using the same basis set as that in the Gao study against crystal data, and it was found that B3LYP yields the most accurate results [128]. This group calculated the optimal ratio of template to monomer in the

typical manner by forming the complex and measuring the difference in energy associated with formation, but unusually also applied atoms in molecules (AIM) theory. AIM theory states that molecular structure can be determined from the molecule's electron density, similar to elements of the Hohenberg-Kohn theorem, which heavily informed the development of DFT [135]. Within AIM theory is the concept of bond critical points (BCPs), the position of minimal electron density in a bond, associated with a value which gives an indication of bond strength. In the case of the enrofloxacin study this was useful for determining the strength of the hydrogen bonds in the simulated cavity. AIM theory and BCPs have been used in other examples of MIP design [136], but this approach is currently not common.

3.3. QM based polymer simulation

Under the general assumption that the template-monomer complex survives the polymerisation process, the monomer screening method which includes several functional monomers with a template can be viewed as the analysis of simple models of MIP binding cavities. An example of this can be found in the work of Huynh *et al.*, where large monomers selected for their affinity for nicotine were 'frozen' in place, allowing the binding site of the complex to be analysed for its selectivity using structural analogues of the target [122]. In an attempt to expand this approach, Sobiech *et al*. added cross-linker molecules to the existing (and already analysed) complexes, and found that the minimised structures of the cross-linker containing systems followed a much closer correlation with the empirical data that the results from using the monomer alone [42, 86]. The researchers then proceeded to modify each of the reactive alkene functionality in the monomers by effective saturation, further approximating the polymer binding cavity, and performed comparative analysis with their chosen template (1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone) and a number of

analogues. A similar approach was taken in the design of a tyramine imprinted polymer, where the theoretical and experimental data were founds to be in close agreement [85]. The results of these experiments should be informative to researchers designing analytic instruments based on imprinted polymer technology for pharmaceutical monitoring, as the greater level of detail in the model gained by the introduction of cross-linkers can give very different predictions, which will be reflected in the quality of the sensor produced.

Li *et al*. took this approach further by forming a simple binding site for 5-fluorouracil by first optimising the geometry of N-isopropylacrylamide functional monomers and joining them into a ring with N,N′-methylene bisacrylamide cross-linker molecules (Figure 4) [109]. The resulting anti-cancer drug specific oligomer was then analysed and contrasted with the lone template, giving indications of the strength of the interactions in the real system. This modelling is symbolic of the current tendency that drifts away from monomer screening as a primary focus in the design of synthetic receptors. Structural analysis without monomer screening is increasingly popular, and apparently frees researchers to perform sophisticated and creative research in the quest for better understanding of their systems. Some more unusual applications of DFT to MIP design and analysis include the simulated adsorption of the antibiotic flumequine onto a gold surface [112], research that stands alone in analysing the affinity of their target for a non-polymeric material, and the design of multi-template MIPs [137] for the adsorption of several different compounds from a variable medium. This trend will presumably continue, as researchers find QM based techniques suitable for detailed structural analysis and polymeric binding site interactions, while understanding of the properties of components in solution and rapid monomer screening can most efficiently be performed with alternative techniques.

[Figure 4]

4. Molecular mechanics based approaches in MIP design

4.1 MM, MD, and their applicability to MIP design

Molecular mechanics (MM) and molecular dynamics (MD) are the generally preferred methods for modelling multi-component systems and assessing large numbers of molecular interactions. Twenty or more functional monomers can be easily screened via observations of electrostatic interaction energies and optimal geometries with relatively little computational expense [40], and MD techniques can be used to observe these interactions through time, studying the motion of individual molecules or the system as a whole.

MM is based on generalising the empirically observed properties of molecules, in the simplest case those of bond lengths, bond angles, dihedral angles and non-bonding interactions, each of which are taken and combined as a particular energy value; the summation of the energies associated with the bond lengths may be given by E_l for example, and the combined energy of all dihedral interactions as E_θ. The total energy of the system can then be calculated by taking the summation of these different values, and a common action in molecular mechanics modelling is minimisation, in which the energy of the system is reduced as far as permitted by relaxing the energy associated with each individual energy value; the energy of one bond length for example may be reduced by allowing the bond to lengthen or shorten to an empirically, or sometimes QM, determined optimal length.

[Figure 5]

Different functions are used to describe the different interatomic interactions within and between programs. For example, the energy associated with bond stretching and angle bending can be described by harmonic functions, where positive or negative displacement from an optimal length by a given value results in the same increase in energy [138, 139],

allowing the total energy of, the bond or angle stretching to be calculated by some variation on $E_x = \Sigma\, k(x–x_0)^2$, where k is a constant, x is the value of the length, angle, etc. and x_0 is the optimal value for x. Under most circumstances the harmonic oscillator model for bond and angle stretching is sufficiently accurate, but for some applications a more realistic description is required, for example the use of a Morse potential for the bond [140], in which the energy increases more rapidly with bond shortening and less with lengthening. The harmonic oscillator and Morse Potential models are shown in Figure 5. The combination of the different functions and constants used in describing the energy of a system make up the force field, of which there are many, and which are generally built for use on a particular subject.

Molecular dynamics is in simplest terms the application of time to molecular mechanics; a system observed acts upon the particular energetic gradients of its chemical environment (as in a minimisation) and the classical laws of motion, with the specifics of these actions governed by a set temperature and pressure. Experiments are usually performed either under the canonical ensemble, NVT (constant number of particles, volume and temperature) or, less commonly, the isothermal-isobaric ensemble, NPT (constant number of particles, pressure and temperature), and can readily be used to simulate time length of femtoseconds to nanoseconds or longer depending on the requirement, allowing analysis of the time-evolved structure of the system as it tends towards its energy minimum.

4.2. Screening programs in MM based design

MM force fields are relatively simple equations drawing on finite tables of atom and bond types, and can therefore be used for rapid calculations on a typical computer. This allows monomer-template interactions to be qualified by energy minimisation at a much greater rate than is possible with QM software, or the development of more sophisticated programs

automatically drawing monomers from a library of predetermined compounds, positioning them about a template and measuring the interaction energy associated with this arrangement, ultimately providing a prediction of the most appropriate monomer with which to synthesise a particular MIP.

An example of the use of a screening program in the selection of appropriate functional monomers can be found in the recent work of Mistry *et al*., in their design of a paracetamol imprinted nanoMIP exhibiting cooperative binding behaviour [36]. In this research the structure of the template was modified *in silico* to better resemble the structure which would be attached to the glass bead for solid phase synthesis of the MIPs, before being energetically minimised with applied Tripos force field and Gasteiger-Hückel charges. The template structure was then subjected to an automated process of presentation to 25 commonly used functional monomers via application of the Tripos LeapFrog program available in the SYBYL modelling package. The monomers are then given an individual binding score and ranked according to the relative strength of the interaction. The ranking is in part based on the method described earlier (see Section 3.1), in which the ΔE values of the monomers are directly compared to determine the relative strength of interaction and complex stability. The LeapFrog ranking process however includes an additional site-point score for each monomer in addition to the ΔE value, which is assigned according to the appropriateness of the interaction according to an automatic assignment of functionalities of interest on the template/target and the monomer as either hydrogen bond donors or acceptors. The ideal positions for monomer donor/receptor atoms are then plotted about the compound being screened as 'site-points', and the positioning of these site-points relative to each other and to the interacting monomer are monitored. These site points can be seen in Figure 6, where they are shown as small blue, red and yellow crosses representing the charge of their associated atom or region. In this way the monomers ranked highly by LeapFrog not only allow for a

highly stable complex, but also account for potential monomer–template interactions related to monomers which are at the time of observation not present. While use of this program has been limited to a small number of research groups in the past due to the high licensing cost of commercial software, the ease with which this process can be employed has led to an increase in popularity in recent years [28, 29].

[Figure 6]

The use of LeapFrog has been important in the history of synthetic receptor design, being responsible for success in predictive design of MIPs which first brought strong interest in molecular modelling as a method of monomer screening [19]. This technique is still regularly used [23-25], and has led to the development of the new materials known as 'custom design adsorbents', micron sizes polymer particles with surface functionalities tailored to a particular target, making them useful in extraction procedures [141]. Beyond this use of MM screening software there are also examples of docking programs being employed, which are designed for analysing the interactions between large biomolecules and their ligands. Zhang *et al.* used CDOCKER, a program using a CHARMM force field, to design a receptor for amlodipine using a library of six functional monomers [27]. The template was used in place of the biomolecule and the monomers treated as ligands, giving a ranked list of the affinity found in each monomer-template complex. Ratio optimisation was then performed using MM minimisation and comparison of the resultant ΔE values. This was then followed by a molecular dynamics experiment, which was conducted for purposes of hydrogen bond analysis rather than design, though this precise approach has been thoroughly used to great effect in determining appropriate prepolymerisation mixtures for the effective production of imprinted polymers.

4.3. Molecular Dynamics based approaches to design

The analysis of dynamic systems allows a more realistic understanding of the actual pre-polymerisation composition and can aid in finding a global energy minimum, and therefore may be regarded as producing more accurate data than any other available technique. While QM methods provide better representations of individual molecules, exclusion of explicit solvent molecules (or other components of monomer mixtures) reduces their validity in representing the system. MD simulations also allow analysis of the effects of different monomers ratios, which can be dramatic. The work of Golker *et al.* in this area is exemplary, with prepolymerisation system of thousands of molecules observed over many nanoseconds, with chemometric analysis and quantified hydrogen bond quality rankings providing excellent predictive capacity [88-90].

Kong *et al*. similarly studied dynamic prepolymerisation mixtures to determine the optimum ratio of template norfloxacin to monomer MAA and cross-linker EGDMA [91]. The radial distribution functions (RDFs) of MAA atoms were calculated to determine the probability of finding particular template atoms adjacent to the reference atom through the dynamic simulation. RDF analysis involves the measurement of distances between a given observed atom and a number of other specified atoms over a given period of time. The resultant plot for each interaction therefore gives the duration of a distance as a function of that distance, from which significant electrostatic interactions can be determined by the presence of peaks at short distances from the observed atom. An example is given in Figure 7. Higher maxima and smaller distances therefore show stronger interactions, allowing the selection of high affinity functional monomers (by simulation of different systems with different monomers or by inclusion of numerous monomers in one large experiment). The potential for other solution components (cross-linker, solvent, other template molecules) to inhibit complexation, ratio optimisation by repetition with modified systems, and other potentially useful information also can be analysed. The researchers studying norfloxacin

examined three different ratios of template to functional monomer and cross-linker; 1:4:20 (MIP1), 1:8:40 (MIP2), and 1:12:60 (MIP3). In these experiments MIP2 demonstrated a dramatic association between template norfloxacin's carbonyl groups and the acidic proton of the MAA. This interaction is not observed in MIP1 or MIP3, a result which would be difficult to predict without the aid of MD modelling. Empirical analysis demonstrated that these results were accurate, with the polymer produced using the intermediate ratio (MIP2) showing the highest adsorption properties. Further studies showed that this high adsorption capacity was essentially unchanged with reuse, making the method applied suitable for producing sensors for norfloxacin. Related research was also performed using the same techniques in evaluating the effects of cross-linker on MIP performance, and in the development of molecularly imprinted quantum dots for detecting environmental toxins [92-94].

[Figure 7]

RDF and related MD techniques were employed by Cleland *et al*. to predict the imprinting factor of a synthetic receptor by measuring the relative frequency of monomer-template interactions [99]. Using a combination of Amber99 and GAFF force fields, the interactions between the different components of methanolic solutions of trichlorobenzene and different functional monomers were observed using RDF and effective fragment potential (EFP), a similar technique used to observed π-π stacking interactions. The researchers found that the relative duration for which component interactions could be observed, correlated with the empirical imprinting factor (IF, the affinity of a template for a MIP relative to a not imprinted polymer of the same composition) in synthesized MIPs with the equivalent functional monomer component. The analysis showed that the lower IF value for one system was likely caused by the interactions between the cross-linker and the

functional monomer disrupting the formation of the template-functional monomer complex, highlighting the importance of considering all possible interactions in component screening.

4.4. MM and MD based imprinted polymer simulation

As discussed, the major advantage of MM and MD over QM is the ability to easily model relatively large systems. In the past this has allowed researchers to build large oligomeric structures to aid in design and analysis, as in the work of Monti *et al*. who used these techniques to construct 50 unit oligomers composed of high affinity monomers to observe the interactions with their target molecule [142]. More recent examples of modelling polymers in MIP analysis atomistically are somewhat rare and vary considerably in their approach. Luo *et al* created a cubic mesh of poly(methacrylic acid) to model the interaction involved in a cholesterol imprinted polymer using MD and RDF, observing the effects of altering various factors in the model [130, 143]. Via a completely different approach, Huynh *et al* simulated the polymerisation process in the design of a 6-thioguanine specific synthetic receptor, using monomers which combined a large thiophene based segments for radical polymerisation attached to a cytosyl functionality for binding to the target [111]. Molecular dynamics simulations were performed using eight template molecules with the equivalent number of monomers and cross-linkers, and accompanied by the addition of bonds between thiophene moieties when they came within 0.3 nm of each other. The analysis suggested that the complex and resultant polymer network were stable despite the large monomer units, and this was supported by fluorescence titration. The sensor produced was found to have a detection limit of 8 μM for the target 6-thioguanine, and a sensitivity to this compound several times greater than that for all the observed target metabolites.

[Figure 8]

Among the most interesting articles relating to modelling of imprinted polymers published in recent years was that of Schauperl and Lewis in 2015, in which a polymer was grown around a template via an evolutionary process [97]. The researchers employed the program ZEBEDDE (zeolites by evolutionary *de novo* design) to randomly select monomers (functional and cross-linking, in a selected proportion) which are then bonded to the growing oligomer in a head-to-tail arrangement, with the growth being allowed only if the interactions between the template and the polymer are favourable [144]. Nicotine and theophylline were used as template molecules with MAA and EGDMA monomers in this simulation, and the polymer was allowed to grow until the density of the box reached 0.65 g cm^{-3}, a value likely similar to the surface of an MAA/EGDMA polymer. The resulting structures (shown in Figure 8) were then minimised, with or without prior dynamics simulation, and the adsorption of the targets were analysed, giving good correlation with empirical data. This research demonstrates the closest approximation to a polymerisation process relevant to atomistic modelling of MIPs thus far produced.

5. Conclusion

The rational design of high affinity molecularly imprinted polymer nanoparticles has led to some of the major developments in the field, and secured their reputation as effective synthetic receptors. In this review several popular computational approaches have been briefly summarised and explained, with additional comment on their usefulness in MIP modelling. This represents the results of compiling every known relevant article published since the last major publication on the topic, and organising them according to target, application and technique. From this some observations have been noted, including the popularity of DFT based methods and the tendency to use these techniques routinely. It is clear that these techniques have become both a common part of the design procedure and that

they are often used solely as a tool to achieve an end which would be expensive or exhausting otherwise. There is also however a sizable community of researchers interested in developing understanding of the fundamental principles underlying the science of imprinting. Computational design, both ambitious and routine, has advanced MIP technology since its adoption in late 90s, and this trend will doubtless continue as the technology moves towards its own ambitious position as routine in all its own potential applications.

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Figure Captions

Figure 1: molecularly imprinted polymer synthesis; a) the template (grey) forms a complex with high affinity functional monomers, b) The polymer is synthesised around the template, c) elution of the template leaves a selective binding site in the polymer.

Figure 2: the structure and electron densities of the template TCDD, functional monomer methacrylic acid, and template-monomer complex. Khan *et al.*, 2015.

Figure 3: the lowest unoccupied molecular orbitals (LUMO) and highest occupied molecular orbitals (HOMO) of the TCDD template and methacrylic acid monomer. Khan *et al.*, 2015.

Figure 4: a 5-fluorouracil specific oligomeric ring composed of N-isopropylacrylamide functional monomers and N,N′-methylene bisacrylamide cross-linkers. Li *et al.*, 2016.

Figure 5: two commonly used models for bond stretching energy in molecular mechanics. The harmonic oscillator model is often used in more general purpose force fields, while the Morse potential may be used for more detailed studies of a specific structure.

Figure 6: screening of a vancomycin using LeapFrog with a library of common functional monomers. The site-points can be seen as small crosses surrounding the structure, and act as a guide for the placing and scoring of the monomers being screened.

Figure 7: the RDFs of interactions between the ketone of template norfloxacin and the acid proton of methacrylic acid. MIP2 here represents the intermediate ratio between monomers and template. Kong *et al.*, 2016.

Figure 8: Polymer synthesis simulation using ZEBEDDE. The templates (blue) are placed in the box and monomers are added to the chain via an evolutionary growth mechanism. Schauperl and Lewis, 2015.

Figures

Figure 1

Figure 2

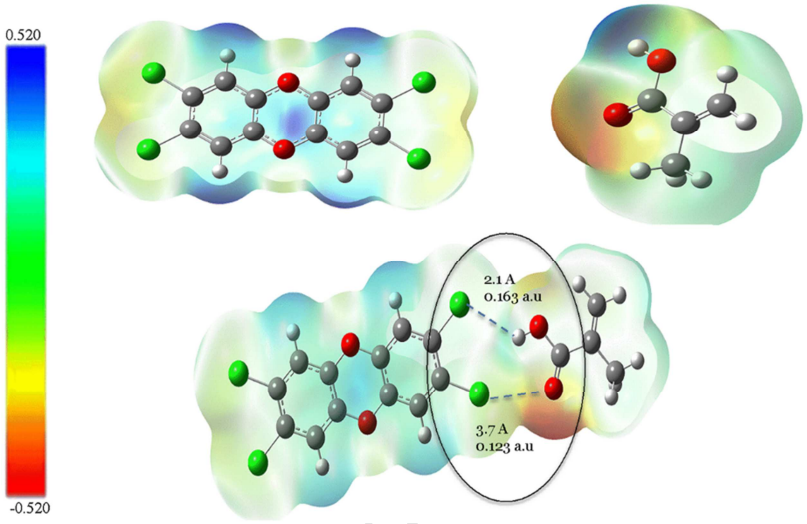
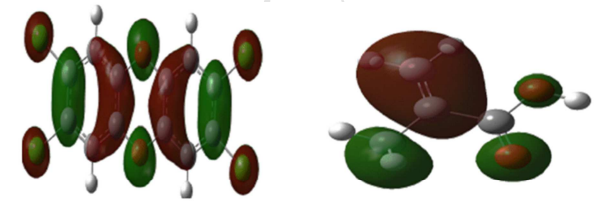
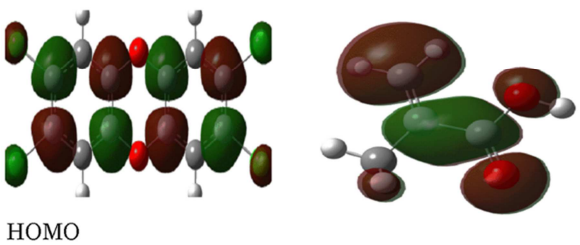


Figure 3



LUMO



HOMO

Figure 4

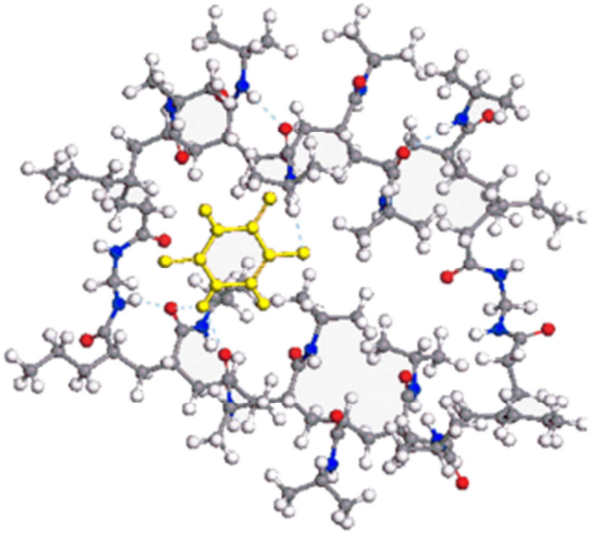


Figure 5

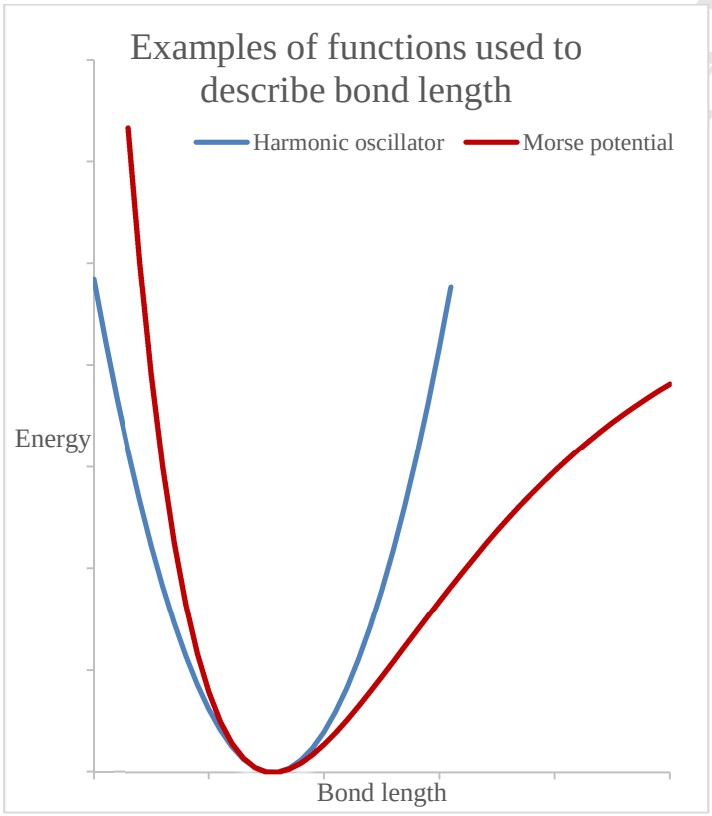


Figure 6

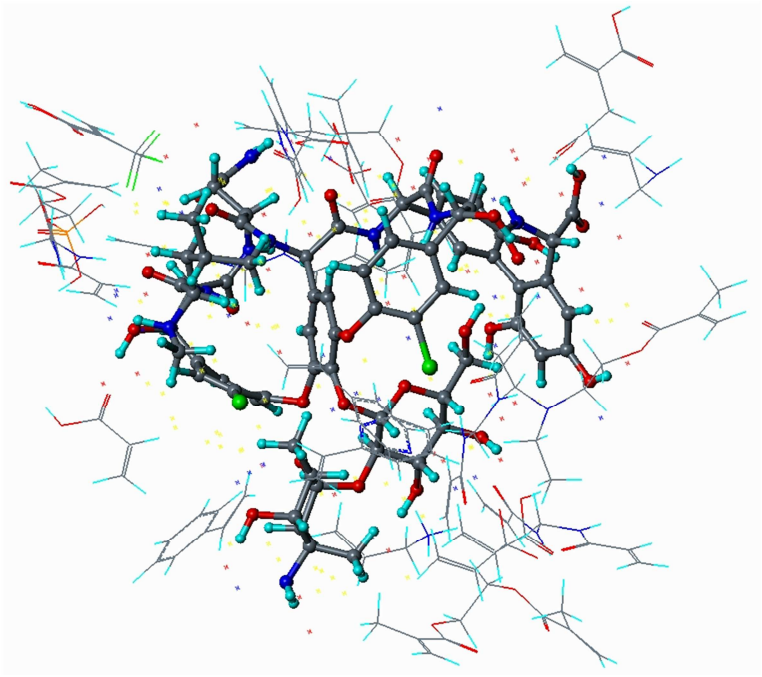


Figure 7

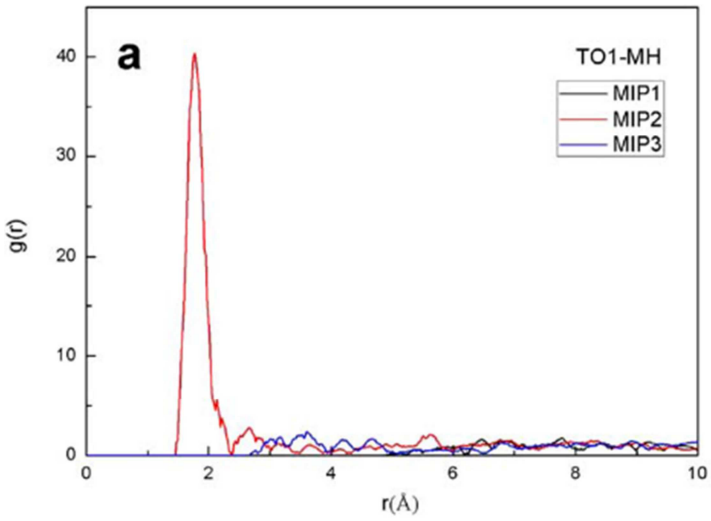
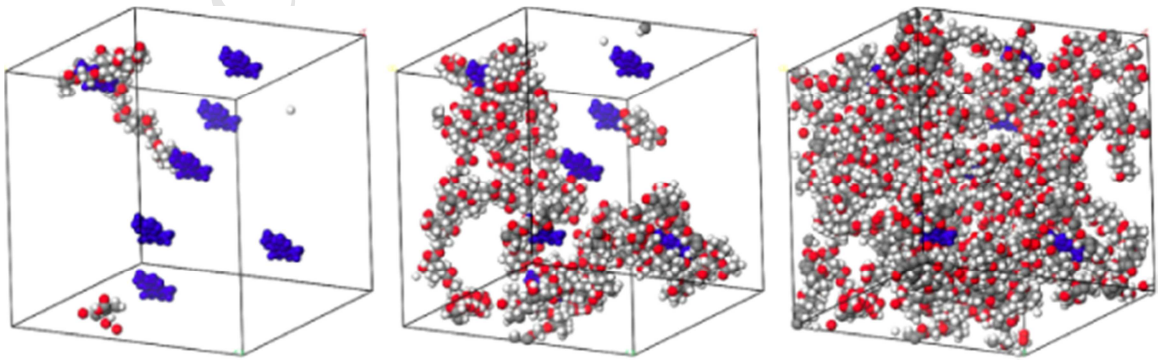


Figure 8



Todd Cowen Biography

Todd Cowen is a postgraduate researcher in the Leicester Biotechnology Group at the University of Leicester. His doctoral studies are primarily on the application of computational and theoretical chemistry to the design and development of molecularly imprinted polymers, with emphasis on monomer-template interactions and the polymerisation process. Cowen completed his master's degree performing research into the extraction and purification of biologically derived antiprotozoal agents using custom design adsorbents and has published research in the development of MIP sensors for monitoring anaesthetics in clinical procedures.

Kal Karim Biography

Kal Karim is a senior lecturer in organic and computational chemistry at the University of Leicester. Dr Karim's research in the computational design of molecularly imprinted polymers has led him to become one of the main academic contributors to the field, with his generic modelling protocols being implemented in numerous laboratories worldwide. His major scientific achievements beyond this are in the design and development of MIP sensors and purification materials specific for drug targets, environmental pollutants and food toxins. Dr Karim's current research interests focus on predictive design of nanoparticles for diagnostics and therapeutic applications.

Sergey Piletsky Biography

Sergey Piletsky is professor of bioanalytical chemistry at the University of Leicester and head of the Leicester Biotechnology Group. He was previously professor in bioorganic and polymer chemistry at Cranfield University, where he received his DSc and was the recipient of several awards, including the Royal Society Wolfson Research Merit Award. Professor Piletsky's research interests include biomimetic polymers, the computational design of MIPs, bioanalytical chemistry and the development of MIP nanoparticles for diagnostic and therapeutic applications. Professor Piletsky has co-authored over 290 peer-reviewed papers and patent applications, has chaired several international and national conferences and has an H-index of 51.