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# Kick-Fukui: A Fukui Function-guided Method for Molecular Structure Prediction

Oswaldo Yañez,<sup>1,2,3</sup> Rodrigo Báez-Grez,<sup>3</sup> Diego Inostroza,<sup>3,4</sup> Ricardo Pino-Rios,<sup>5</sup> Walter A. Rabanal-León,<sup>6</sup> Julia Contreras-García,<sup>7\*</sup> Carlos Cardenas<sup>8,9\*</sup> and William Tiznado<sup>3\*</sup>

<sup>1</sup> *Center of New Drugs for Hypertension (CENDHY), 8380494 Santiago, Chile.*

<sup>2</sup> *Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences, Universidad de Chile, 8380494 Santiago, Chile.*

<sup>3</sup> *Computational and Theoretical Chemistry Group, Departamento de Ciencias Químicas, Facultad de Ciencias Exactas, Universidad Andres Bello, República 498, 8370035 Santiago, Chile*

<sup>4</sup> *Universidad Andres Bello, Programa de Doctorado en Fisicoquímica Molecular, Facultad de Ciencias Exactas, 8370035 Santiago, Chile.*

<sup>5</sup> *Laboratorio de Química Teórica, Facultad de Química y Biología, Universidad de Santiago de Chile (USACH), 8320000 Santiago, Chile*

<sup>6</sup> *Departamento de Química Analítica e Inorgánica, Facultad de Ciencias Químicas, Universidad de Concepción, Edmundo Larenas 129, Casilla 160-C, 4070371 Concepción, Chile.*

<sup>7</sup> *Sorbonne Universités, UPMC and CNRS, Laboratoire de Chimie Théorique (LCT), 75005 Paris, France.*

<sup>8</sup> *Departamento de Física, Facultad de Ciencias, Universidad de Chile, Casilla 653 Santiago, Chile.*

<sup>9</sup> *Centro para el Desarrollo de la Nanociencias y Nanotecnología, CEDENNA, Avenida Ecuador 3493, 9170124 Santiago, Chile.*

E-mail: J. Contreras-Garcia (Julia.Contreras@lct.jussieu.fr), C. Cardenas (cardena@uchile.cl) and W. Tiznado (wtiznado@unab.cl)

## **Abstract**

Here we introduce a hybrid method, named Kick-Fukui, to explore the potential energy surface (PES) of clusters and molecules using the Coulombic integral between the Fukui functions in a first screening of the best individuals. In the process, small stable molecules, or clusters whose combination has the stoichiometry of the explored species are used as assembly units. First, a small set of candidates has been selected from a large and stochastically generated (Kick) population according to the maximum value of the Coulombic integral between the Fukui functions of both fragments. Subsequently, these few candidates are optimized using a gradient method and DFT calculations.

The program's performance has been evaluated to explore the PES of various systems, including atomic and molecular clusters. In most cases studied, the global minimum (GM) has been identified with a low computational cost. The strategy does not allow to identify the GM of some silicon clusters; however, it predicts local minima very close in energy to the GM that could be used as the initial population of evolutionary algorithms.

## **Introduction**

Phenomenologically, chemical reactivity is related with the susceptibility of molecules to transform (react), and its study is a foundational activity in chemistry. Conceptual density functional theory (CDFT),<sup>1-7</sup> allows to study chemical reactivity using "response functions" of both electron energy and electron density.<sup>6,8,9</sup> In its more than thirty years of history, CDFT has been extensively used to study several reactions, both with an interest in the fundamentals of chemistry (e.g., pericyclic reactions)<sup>10</sup> as well as in potential applications (e.g., in toxicology, biology, catalysis, and material characterization).<sup>11-15</sup> However, these studies focus on interpreting and understanding experimentally characterized reactions. To the best of our understanding, CDFT is still developing to become a

predictive tool to guide molecular design, as was the case with molecular orbital-based models, i.e., Woodward and Hoffman rules for predicting the stereochemistry of pericyclic reactions based on orbital symmetry.<sup>16-18</sup> Recently, Geerlings et al. outlined this shortcoming of CDFT through the question: "Can we move from interpretation to prediction?".<sup>19</sup>

The potential energy surface (PES) is the relationship - mathematical or graphical - between energy and a molecule's geometry. Thus, the PES is a crucial concept in computational chemistry. Through its exploration, it is possible to identify the preferred geometries and the best among these, local minima, and global minima, respectively, for a given group of atoms. Moreover, chemical reactions, which involve a rearrangement of nuclei and electron density, can be rationalized as the lowest energy pathway connecting reactants and products through a maximum point (transition state) on the potential surface.

The PES exploration becomes more complicated as the system under study grows, which motivates the development of modern techniques to facilitate this task.<sup>20,21</sup> The quality and capability of methods proposed to find the global minimum (GM) on the PES of clusters and molecules have increased significantly through the years, including those based on the classical Monte Carlo (MC) annealing,<sup>22-27</sup> genetic algorithm (GA),<sup>28-36</sup> particle swarm,<sup>37-40</sup> basin hopping (BH),<sup>41-45</sup> Kick method,<sup>46-50</sup> among others.<sup>51-53</sup> On the other hand, there is a scarcity of methods that use chemical intuition –e.g., using Lewis electron-dot diagram<sup>54</sup> and valence-shell electron-pair repulsion (VSEPR) theory<sup>55-57</sup>– for predicting lower energy structures of yet unknown systems.

Here we introduce a strategy that invokes the Fukui function (FF), a local CDFT reactivity descriptor,<sup>58</sup> to identify chemically relevant regions on the PES (lower energy structures) automatically and with low computational cost. The FF allows predicting the most favorable orientation for a hypothetical interaction between two reactive species. Typically, these configurations are established qualitatively by the researcher by contrasting the most reactive regions of the two reactive species. Here, however, it will be done automatically.

We will now describe the methodological ingredients of this proposal. Using DFT perturbation theory, an expression can be obtained for the interaction energy between a donor (D) and an acceptor (A) of electrons species. Where, one of its components corresponds to the Coulomb interaction between the corresponding Fukui functions:<sup>59</sup>

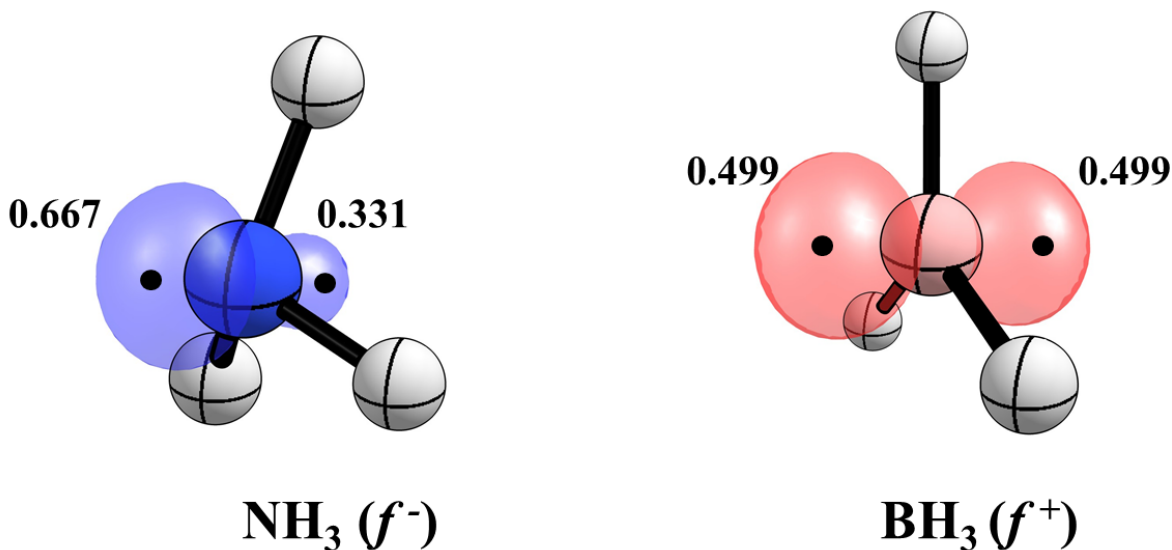
$$J_{fD,A} = \iint \frac{f_D^-(\vec{r})f_A^+(\vec{r}')}{|\vec{r} - \vec{r}'|} d\vec{r}d\vec{r}' \quad (1)$$

In this way,  $J_{fD,A}$  will be maximum, with a higher contribution to the interaction energy, when the most donating regions (D) match those most susceptible to accept (A) electrons. Therefore, we have chosen  $J_{fD,A}$  as a suitable descriptor of the interaction energy to guide us to position in those regions of the PES where there is a bigger chance of converging to the lowest local minima and ideally to the global minimum. However, the evaluation of the integral in equation (1) is computationally demanding, which goes against our motivation to propose a simple and computationally inexpensive method. Note that some of the current authors used this approach in the past in a qualitative way to explore silicon cluster structures.<sup>60,61</sup> Additionally, Grillo et al. recently used an analog equation to explore the PES of enzymatic reactions.<sup>62</sup> To accelerate the algorithm, we have resorted to condensed values of the FF, which allow Eq. 1 to be reduced to a discrete sum:

$$J_{fD,A} \approx \sum_{k'=1}^{m'} \sum_{k=1}^m \frac{f_{D,k}^- f_{A,k'}^+}{r_{kk'}} \quad (2)$$

Where  $f_k^-$  is the condensed value of  $f_r^-$  in a volume k (similarly,  $f_{k'}^+$  is obtained). Commonly, FF is condensed using atomic charge analysis centered on atoms.<sup>63-65</sup> Some of us, however, have proposed to condense FF in its basins, as we can see in Figure 1. In this way, the condensed values are not restricted to the nuclei positions, thus recovering the information of the regioselectivity. In Eq. 2,  $k$

and  $k'$  correspond to the attractors' position, i.e., the maximum values within each basin (see Figure 1) and  $r_{kk'}$  is the distance between these attractors.



**Figure 1.** FF isosurfaces (0.018 *au*), condensed values, and FF basins attractors in black dots.

Different random conformations between the two reactive species are generated to navigate different regions on the PES. Subsequently, the descriptor  $J_f$  (Eq. 2) is used to identify the best conformations, subsequently optimized using a gradient method and DFT computations. To assess the methodology, we search for the lowest energy structures of a broad range of chemical species, including molecular,<sup>66-68</sup> atomic,<sup>61,69,70</sup> and ligand-stabilized Zintl-type clusters.<sup>71</sup> Satisfactorily we have identified the global minimum (GM) reported in the literature in all the cases studied with few exceptions.<sup>61,66-72</sup> These results encourage us to envisage this proposal as a first step, in an alternative direction, towards using CDFT as a source of predictive tools to help in molecular design. In addition, recent studies are revitalizing the use of DFTC descriptors to guide PES exploration. For instance, the minimum electrophilicity principle (MEP) and maximum hardness principle (MHP) were proposed as complementary tools to explain chemical reactions.<sup>73</sup> Besides, it was studied how local reactivity descriptors, such as the Fukui function and the local spin density distribution, shape the

potential energy surface (PES) associated with chemical reactions.<sup>74</sup> A correction to the 6-311G(d) basis set compute global reactivity descriptors with quality of larger basis sets (Aug-cc-pVQZ and Aug-cc-pV5Z) was also proposed.<sup>75</sup> Moreover, the feasibility of calculating the FF with semiempirical methods to access the study of biological systems was shown.<sup>76</sup>

Finally, it is essential to note that the Kick-Fukui is a hybrid method. It considers one term of the interaction energy equation, which contains local reactivity information, between two interacting species as the energy interaction descriptor (the entire equation is reported in SI, Eq. S1). The other counterparts of this algorithm are the Kick process and local optimizations using a gradient method and DFT calculations. Therefore, this should provide flexibility to evaluate systems with various interactions, electrostatic, covalent, or intermediate in between.

### Methodological issues

In the CDFT, one of the main ingredients to analyze reactivity is the FF, defined as the response of the chemical potential to a variation of the external potential at a fixed electron number:<sup>1,6</sup>

$$f(\vec{r}) = \left( \frac{\partial \mu}{\partial v(\vec{r})} \right)_N \quad (3)$$

Since the chemical potential is a first derivative of the energy with respect to the electron number, the FF is a second derivative and, according to Maxwell relationships, it can be expressed as follows:

$$f(\vec{r}) = \left( \frac{\partial \rho(\vec{r})}{\partial N} \right)_{v(\vec{r})} \quad (4)$$

where  $\rho(\vec{r})$  is the electron density. This last derivative has a discontinuity of the Fukui function at an integer number of electrons and, therefore, it should be calculated from the left or right side of N as follows:

$$f^+(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}) \quad (5)$$

and

$$f^{-}(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \quad (6)$$

The FFs, calculated by Eqs. 5 and 6, are the key regioselectivity indicators for chemical species prone to accepting and donating electrons in chemical reactions, respectively. A simple molecular orbital model (in which electron correlation and orbital relaxation is neglected) is commonly used to obtain simple FF's expressions:

$$f^{+}(\vec{r}) = |\phi_{LUMO}(\vec{r})|^2 \quad (7)$$

$$f^{-}(\vec{r}) = |\phi_{HOMO}(\vec{r})|^2 \quad (8)$$

Eqs. 7 and 8 correspond to the square of module of the highest occupied molecular orbital (HOMO) and the square of the lowest unoccupied molecular orbital (LUMO), respectively. Note that this approximation is used in this work. Additionally, in those cases where the frontier orbitals are degenerate or quasi-degenerated, an average over the set of degenerate orbitals is used.<sup>77,78</sup>

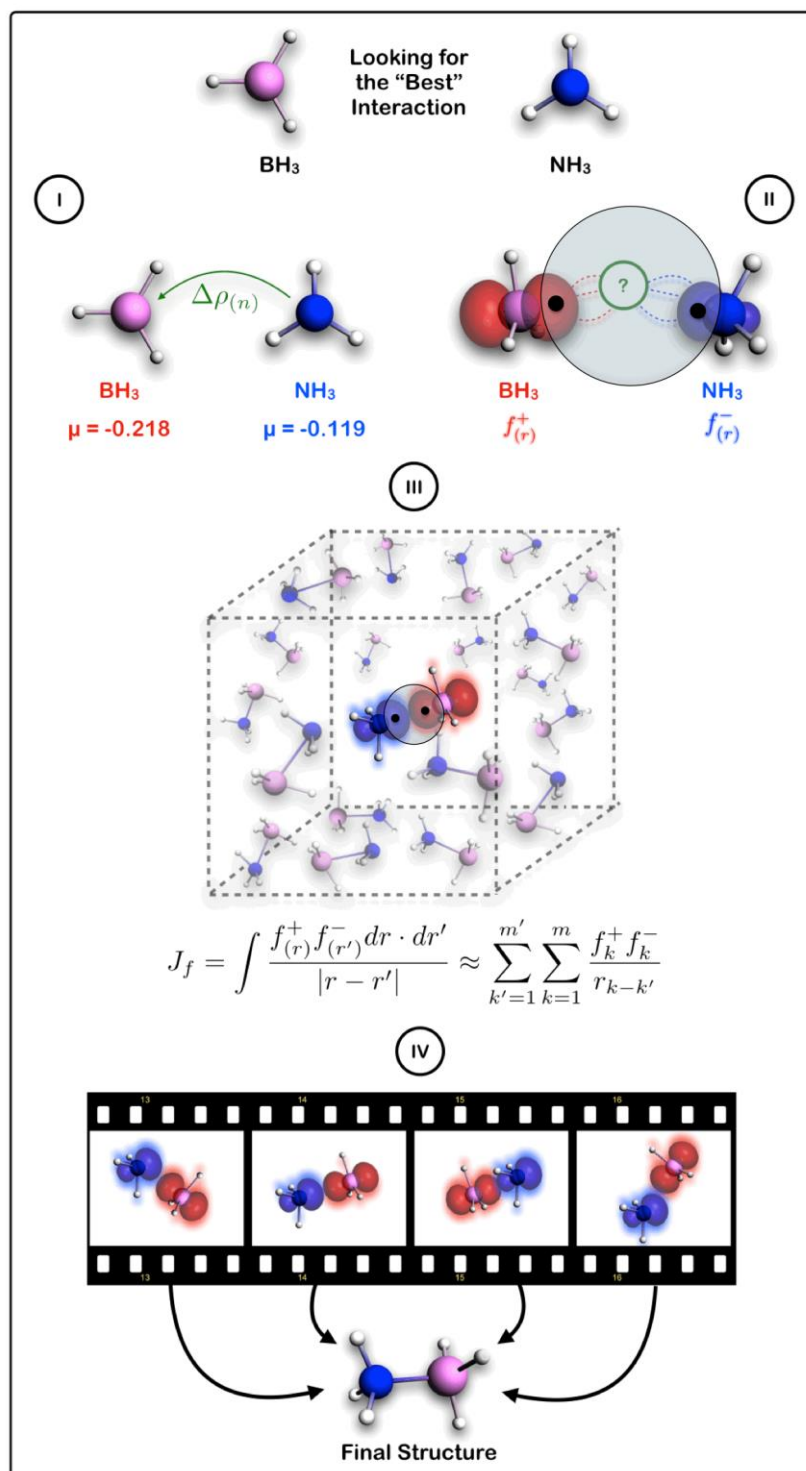
In our proposal, in contrast with the classical condensation schemes (i.e., by means of atomic charges), the molecular space is partitioned into FF basins, which in turn are characterized by attractors at position  $k$ , according to the topological analysis of the gradient field of the FF.<sup>79-81</sup> Not only does this scheme avoid some ambiguities related with others (such as basis set dependence), but it also provides regions of chemical interest that are not necessarily nuclear positions, enriching regioselectivity information. Then,  $f_k^{\pm}$  values are obtained by integrating  $f^{\pm}(\vec{r})$  into the basins,  $\Omega_k$ ,

$$f_k^{\pm} = \int_{\Omega_k} f^{\pm}(\vec{r}) d\vec{r} \quad (9)$$

Scheme 1 shows the different steps that make up the method proposed here, using an acid and a base of Lewis,  $\text{BH}_3$ , and  $\text{NH}_3$  as benchmark molecules. In step I, the electrophilic (nucleophilic) species are identified, according to their most (least) negative value of the chemical potential ( $\mu$ ). Then, in



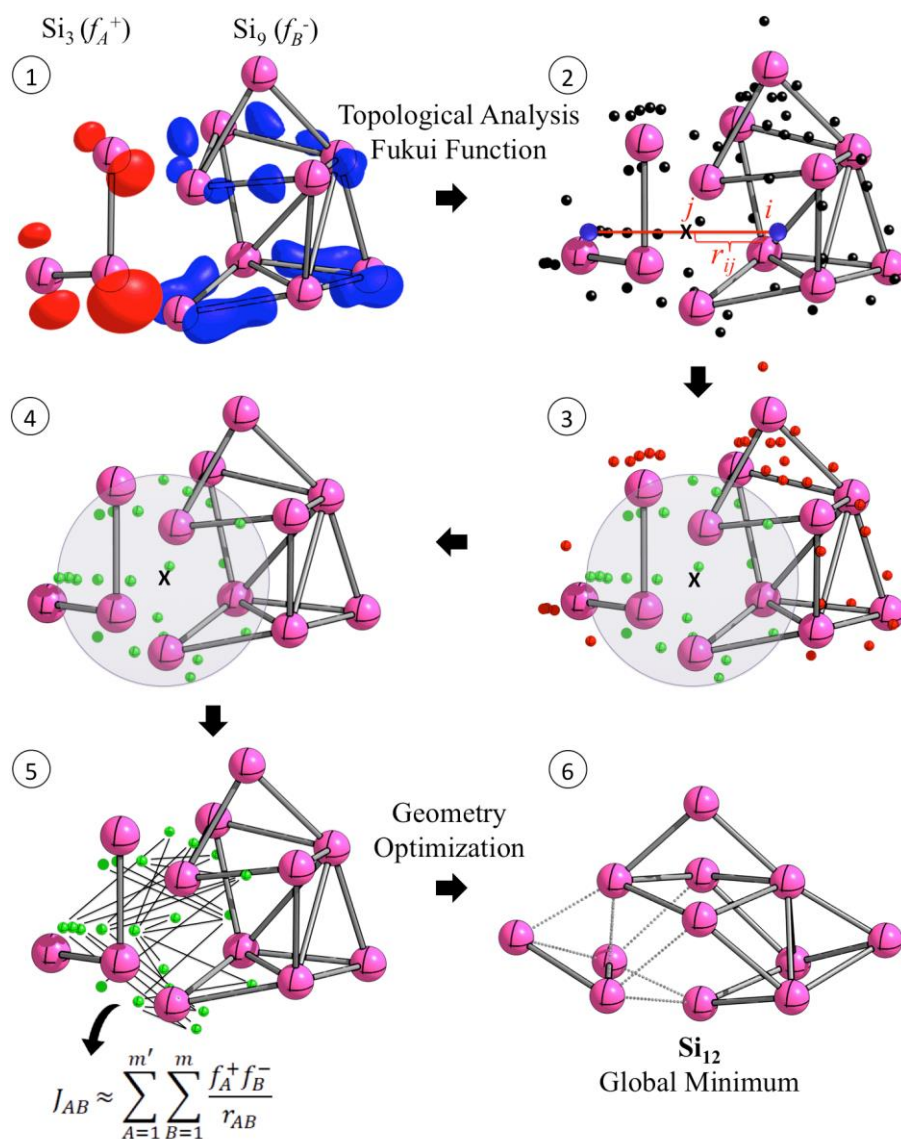
step II, the corresponding FF's are calculated ( $f^+$  or  $f^-$ ) according to Eqs. 7 and 8, and their basins, attractors and condensed values are obtained from topological analysis (Eq. 9). The condensed values are assigned to each attractor, which are defined by their spatial coordinates, as are the atomic nuclei. In this way, when the assembly unit is moved (in step III) the attractors also move maintaining their connectivity. In step III, the different conformations are randomly generated. This is done by defining a cubic space whose side is equal to the sum of the sizes of the assembly units. Then, the assembly units are placed in the center of the box (according to their mass center) and are randomly rotated. Subsequently, they are displaced along random trajectories towards the walls of the box (our implementation of the Kick method<sup>82,83</sup>). Then, the connectivity of the resulting structures is analyzed, discarding those with overlapping covalent radii between neighboring atoms of the two reactive species. The Kick procedure and connectivity analysis process is repeated until a desired number of conformations are obtained. Finally, in step IV, the best assemblies, according to their maximum  $J_f$  value, are optimized using a gradient method and DFT calculations. This final step is the most expensive computationally, so it is convenient for the fewest possible candidates to be optimized and that the initial conformations are as close as possible to the optimized structure.  $J_f$  will have an intrinsic limitation in this last point. Some assemblies can suffer substantial geometrical and electronic changes through the optimization process.



**Scheme 1.-** Schematic representation of the PES exploration procedure.

**Identifying effective reagent basins.** One of the problems in simplifying Eq. 1 as Eq. 2 is that we lose relevant information about the overlapping of the interacting FFs (effective reactive regions). To

recover this, we propose a simple approach to select reactive attractors as illustrated in Scheme 2 (building of  $\text{Si}_{12}$  from fragments  $\text{Si}_3$  and  $\text{Si}_9$ ). First, the centers of mass of the attractors (in this assumption mass of each attractor is its condensed value) are connected by a line of distance " $d$ " (2). Next, a sphere of radius  $0.5d$  is projected, centered in the middle of the connecting line (3). Thus, attractors within the sphere are considered interacting ones, and the others are discarded for  $J_f$ 's calculation (4 and 5).



**Scheme 2.** Selection of the reactive basins for  $f_A^+$  and  $f_B^-$  interactions. The fragments correspond to the  $\text{Si}_3$  and  $\text{Si}_9$  clusters to form  $\text{Si}_{12}$ .

**Geometry optimization and Similarity check algorithm.** After geometric optimizations, several starting structures can converge to the same minimum, which is why our proposal involves a similarity analysis. This is performed by evaluating Eq. 10,<sup>84</sup> which is a modification of Grigoryan and Springborg's proposal:<sup>85-87</sup>

$$d^s(\alpha, \beta) = \left[ \frac{2}{N(N-1)} \sum_{n=1}^{\frac{N(N-1)}{2}} \left( \frac{d_n^\alpha}{D_{ave}^\alpha} - \frac{d_n^\beta}{D_{ave}^\beta} \right)^2 \right]^{1/2} \quad (10)$$

Where  $d^s(\alpha, \beta)$  is a non-dimensional quantity, N is the number of the atoms in the system,  $d_n^\alpha$  ( $d_n^\beta$ ) and  $D_{ave}^\alpha$  ( $D_{ave}^\beta$ ) are the ordered interatomic distances (shortest to longest) and the average bond length between the atoms of the two systems under comparison ( $\alpha$  and  $\beta$ ), respectively. Our group has shown that this similarity algorithm is very useful in exploring the PES of clusters and molecules.<sup>35,82,88</sup>

### Computational Details

The chemical potential ( $\mu$ ) and the Fukui function  $f^\pm(\vec{r})$  of the assembly units were calculated at PBE0<sup>89</sup>/Def2-TZVP<sup>90</sup> level, the wave functions were computed with Gaussian 09 program<sup>91</sup> and the topological analysis of the FF was performed with the Multiwfn 3.3.6 software.<sup>92</sup> To facilitate these calculations the TAFF pipeline,<sup>77</sup> previously developed by our group, is used. TAFF automates the calculations of the topological analysis of the FF, which consists of using the wave function from the \*.fchk files (Gaussian 09 program<sup>91</sup>). Then, the topological analysis is performed on the density of the frontier orbitals (Multiwfn 3.3.6 software<sup>92</sup>). TAFF provides a summary file with the atomic coordinates, the coordinates of the attractors that characterize each basin, and their respective condensed values.

Subsequently, the Kick process<sup>49</sup> was performed, and the best configurations (structures) were chosen according to their maximum  $J_f$  values (Eq.2). Then, these selected structures were optimized at PBE0/SDDALL<sup>93,94</sup> level and subsequently reoptimized at PBE0/Def2-TZVP<sup>90</sup> level (with Gaussian 09 program<sup>91</sup>). Vibrational frequency calculations were done at the same level to confirm that the reported structures are true minima on the PES.

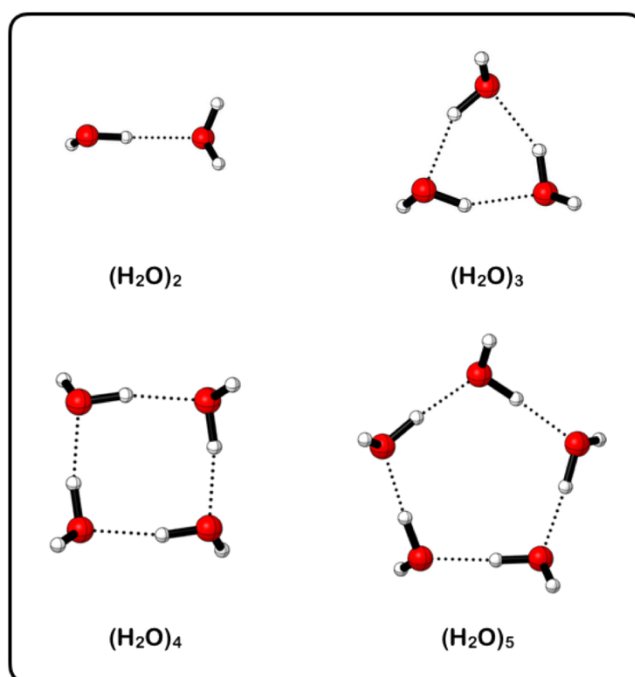
## Results and Discussion

To evaluate the performance of our proposal, we have evaluated several systems whose minimum energy structures are well identified in the literature.<sup>61,66-72</sup> We used the Kick process to generate 1000 initial conformations. The 10 structures with the maximum value of  $J_f$  were selected and optimized. The most stable structure (at PBE0/Def2-TZVP level) has been selected to compare with the global minimum (GM) reported in the literature.

The assembly units used correspond to the lowest energy (GM) structures taken from the literature. However, this is not restrictive; the use of local minima as assembly units can enrich the exploration of the PES.<sup>61,95</sup> The systems studied can be classified into two groups: 1) those where the initial (reactive) fragments maintain their (structural) identity in the products and 2) systems where the shapes of the initial fragments change significantly within the products. It is expected that the method will perform better in the former since the FF prediction should be more effective in identifying the important regions on the PESs, due to the significant rearrangement of the nuclei and the electron density in the second group.

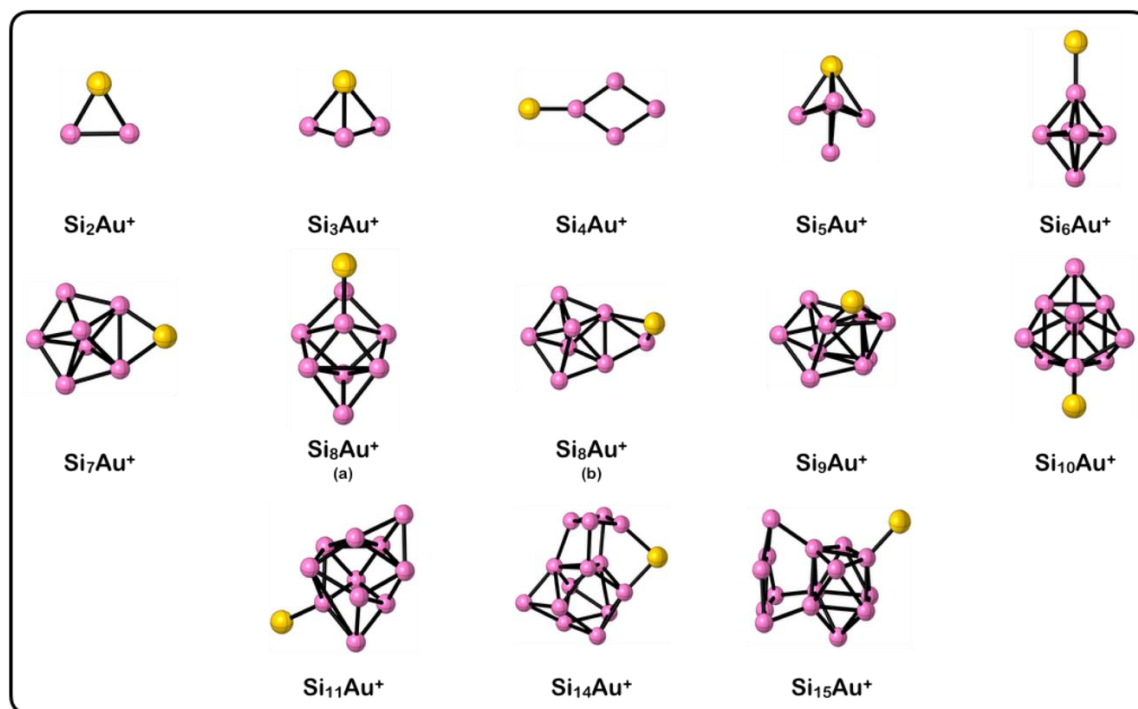
**Group 1.** In this group, we have studied  $(\text{H}_2\text{O})_n$  molecular clusters ( $n=2-5$ ). For the PES exploration we consider the interaction between  $(\text{H}_2\text{O})_{n-1}$  and  $\text{H}_2\text{O}$  units. It should be noted that the study was performed from the smallest cluster  $[(\text{H}_2\text{O})_2]$  to the largest one, allowing us to obtain the fragments

to be used in the search for the next cluster. As reported in Figure 2, in all the cases analyzed, we have identified the GM in agreement with previous results reported in the literature.<sup>66-68</sup>



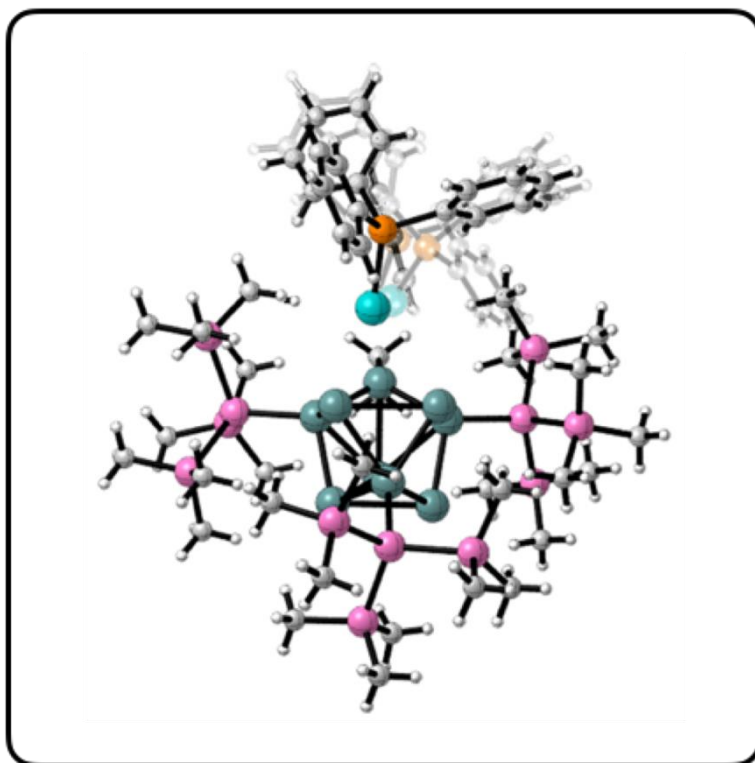
**Figure 2.** GM structures obtained by the *Kick-Fukui* algorithm for the water clusters, (H<sub>2</sub>O)<sub>n</sub> (n=2-5).

In the group 1, we have also searched the GM structures of Si<sub>n</sub>Au<sup>+</sup> systems. For the PES exploration we consider the Si<sub>n</sub> GM structures as the nucleophilic and the Au<sup>+</sup> cation as the electrophilic fragment. As shown in Figure 3, we were able to identify the GM structures<sup>69</sup> in all cases.



**Figure 3.** GM structures obtained by the *Kick-Fukui* algorithm for the  $\text{Si}_n\text{Au}^+$  ( $n=2-11,14,15$ ) clusters.

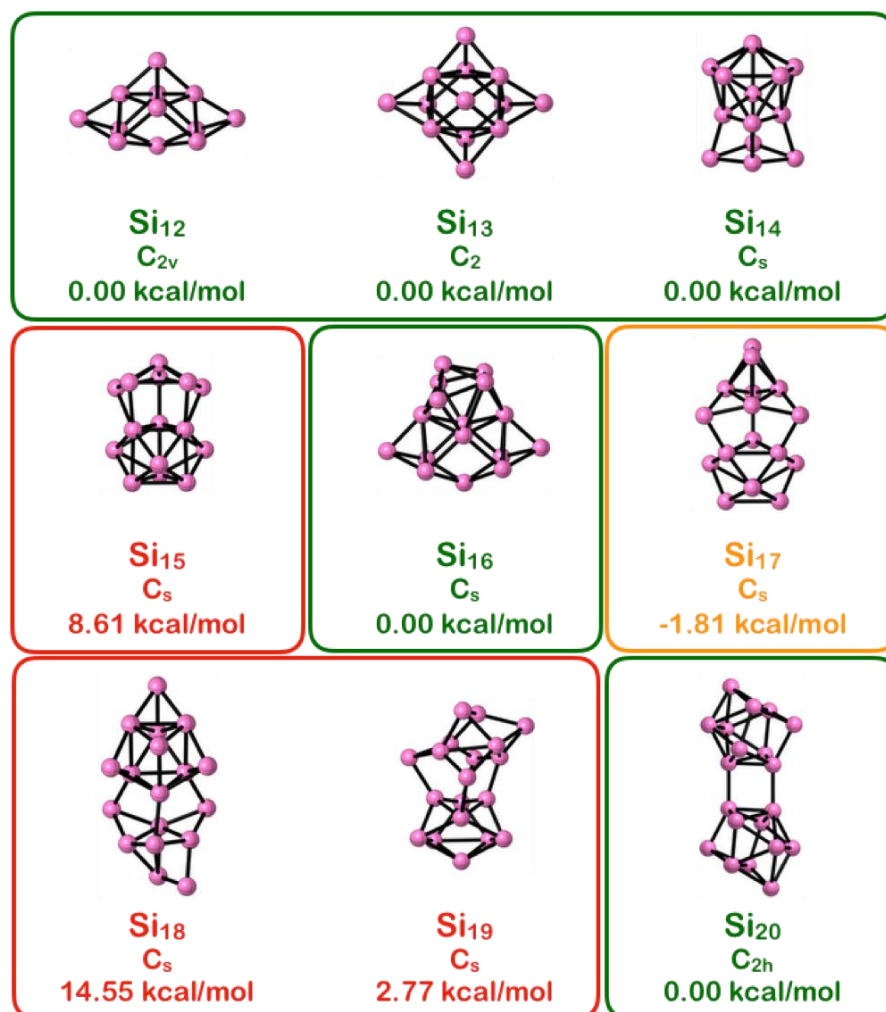
Finally, we have explored the PES of the tetrasubstituted neutral cluster  $[\text{Ge}_9\{\text{Si}(\text{SiMe}_3)_3\}_3\{\text{SnPh}_3\}]$  synthesized experimentally from the reaction between the trisubstituted  $[\text{Ge}_9\{\text{Si}(\text{SiMe}_3)_3\}_3]^-$  species with the triphenyltin chloride,  $\text{Ph}_3\text{SnCl}$ .<sup>71</sup> In our exploration we have used as reagents the species  $[\text{Ge}_9\{\text{Si}(\text{SiMe}_3)_3\}_3]^-$  (nucleophile) and  $\text{Ph}_3\text{Sn}^+$  (electrophile). As shown in Figure 4, the GM is correctly identified. Additionally, several of the predicted structures chosen by  $J_f$  (translucent images in the Figure) converge to the GM after the optimization process.



**Figure 4.** Candidate structures generated by the *Kick-Fukui* algorithm (translucent structures) and the GM structure identified after optimization.

**Group 2.** In this group, we have explored the PES of small silicon clusters,  $\text{Si}_n$  ( $n=12-20$ ), from various possible combinations (see Table S1 and Table S2 in the ESI). As shown in Figure 5, we fail to identify the GM in  $\text{Si}_{15}$ ,  $\text{Si}_{18}$ , and  $\text{Si}_{19}$  clusters. The lowest energy structures identified are at 8.6, 14.6, and 2.8  $\text{kcal.mol}^{-1}$  above the GM, respectively. Nonetheless, it is worth highlighting that we have identified a better putative GM for  $\text{Si}_{17}$ , our candidate is 1.8  $\text{kcal.mol}^{-1}$  more stable than the one reported in the literature.<sup>70</sup> In general, although some GMs are not identified in these series, good local minima are identified, which could be good starting populations to evolve with other methods, such as genetic algorithms.<sup>61</sup> The Cartesian coordinates of the identified lowest energy structures are shown in Table S3.



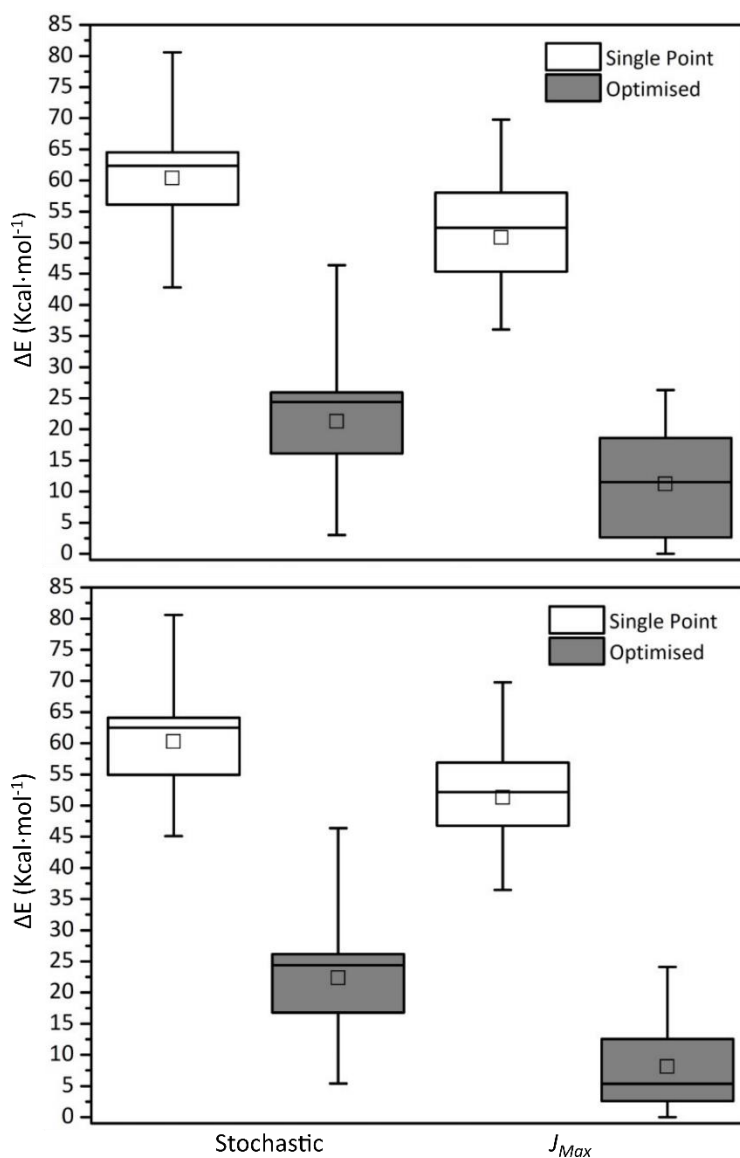


**Figure 5.** Final structures obtained from the *Kick-Fukui* algorithm for the Si<sub>n</sub> (n=12-20) cluster. The structures reported are GM (green), lowest isomers but not GM (red) and better putative GM than those reported in the literature (yellow).

As evidenced by the results shown above, our methodology effectively identifies the GM of the species studied. Nevertheless, some questions arise that we will discuss below: How much does the FF help explore the PES? In addition to the GM, are other relevant minima identified by this

procedure? To answer these questions, we have chosen to analyze in detail the search of the  $\text{Si}_{12}$  system. Because, as already mentioned,  $\text{Si}_n$  clusters are particularly challenging given the drastic structural changes of the initial fragments when optimizing the product. In our approach, what is novel is the use of FF to pre-select candidates from many candidates (an initial population of 1000 individuals). That is, a strategy to identify relevant positions on the PES. However, the structure generation method (Kick) already has certain restrictions that allow us to have good candidates from the beginning, like the size of the box and the connectivity analysis between neighboring atoms when joining fragments. Thus, the challenge of FF is to help in identify conformations that, when optimized, converge to the best minima and ideally to the global minimum.

Furthermore, the fitness criterion is the energy. Therefore, it is expected that conformations with lower energy will converge to the best minima. The latter is the justification for using  $J_f$  as a descriptor of this energy. A simple way to assess the help provided by FF is shown in the boxplots in Figure 6, where a random selection of individuals is compared with a selection guided by the  $J_f$  value. For this analysis, we consider the interaction between  $\text{Si}_9$  and  $\text{Si}_3$  building units. In agreement with our hypothesis, the population chosen with the FF is of lower energy than the one randomly chosen. Therefore, it converges to better minima, including the GM. This improved selection is shown more clearly when we reduce the population from 40 to 20 individuals. Also, the structures selected according to their  $J_f$  value converge to the lowest energy isomers when optimized, as shown the boxplot distribution in Figure 6.



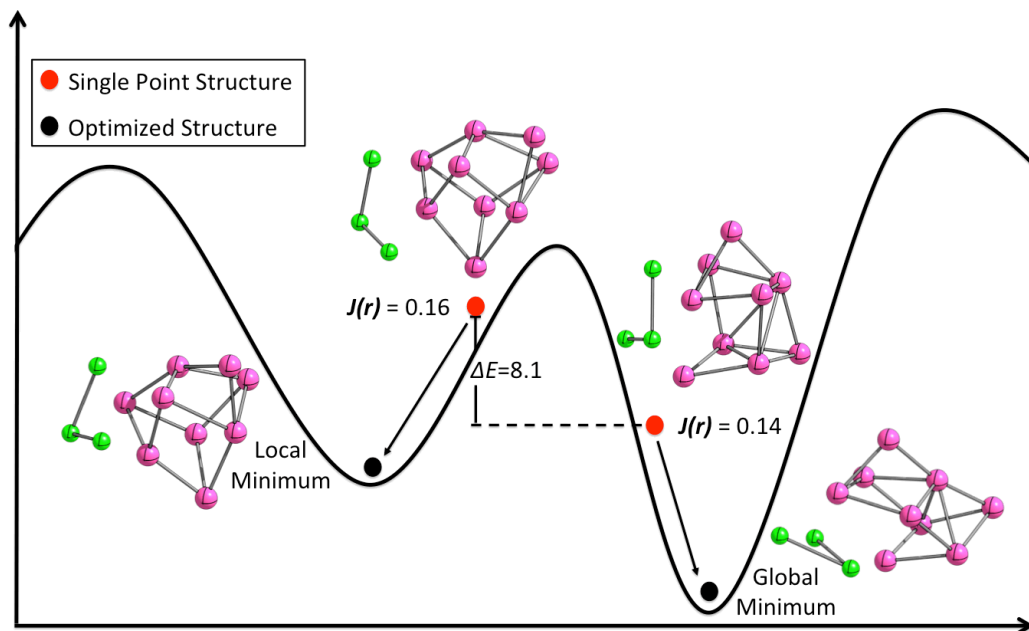
**Figure 6.** Boxplots showing the energy distribution of  $\text{Si}_{12}$  candidates. Comparison between *Stochastic* and  $J_{Max}$  guided selection of individuals. An initial population of 1000 individuals were generated by the Kick procedure using the  $\text{Si}_9$  and  $\text{Si}_3$  fragments. A selection of 40 (above) and 20 (below) individuals was considered for this comparison. Box plots white and grey correspond to single point energy and geometry optimized energy of the selected individuals.

## Conclusions and Perspectives

Herein, a hybrid method is introduced to explore the potential energy surface (PES) of atomic and molecular clusters that combines a stochastic process with the Coulombic integral between the Fukui functions of the fragments to make an initial optimal candidates' selection. The method's performance has been assessed in search of different clusters; in almost all of them, the GM and other relevant minima are identified. Only in the case of in silico clusters, some GMs are not identified; however, good minima are identified that could be used as the initial population of evolutionary strategies.

This work opens a new direction for better and faster PES exploration. Nevertheless, several perspectives exist to improve the algorithm. It is important to be aware of changes during the optimization process. This is sketched in Figure 7, for two initial conformations of  $\text{Si}_3$  and  $\text{Si}_9$  to produce  $\text{Si}_{12}$  cluster. We see that the conformation with the lower value of  $J_f$  can converge to a better minimum after the optimization process. These results agree with what the boxplots show (Figure 6), where there is a more extensive spread between the preliminary structures concerning the optimized structures.

In addition,  $J_f$  is only one component of the interaction energy derived by perturbation theory;<sup>59</sup> there are other parameters that could be considered. These other terms could improve the relationship between this descriptor and the interaction energy of the fragments. This work is under development.



**Figure 7.-** A schematic diagram illustrating the relation between  $J_f$  value and energy on one-dimensional potential energy surface. Illustrated example for the  $\text{Si}_{12}$  cluster, showing the local minimum (left) and global minimum (right), with an energy difference of  $8.1 \text{ kcal}\cdot\text{mol}^{-1}$ .

### Data and Software Availability

The TAFF (Topological Analysis of the Fukui Function) pipeline was used to perform the Fukui function's topological analysis and, it is available in <https://github.com/HumanOsv/TAFF>. The initial population was built using the SnippetKick code, which is our Kick method implementation, and it is available in <https://github.com/HumanOsv/SnippetKick>.

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## **Associated Content**

Supporting information available:

Equation S1. The total interaction energy between an electron donor and electron acceptor species from detailed density functional perturbation theory analysis.

Table S1. The chemical potential and cartesian coordinates of the small silicon clusters (used as building blocks).

Table S2. All evaluated combinations of different size building blocks (in the PES exploration).

Table S3. Structures and cartesian coordinates of the minimum energy structures for  $\text{Si}_n$  ( $n=12-20$ ) clusters.

References of the supporting information.

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