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Computational insight into the chemical space of plant growth regulators

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ABSTRACT

An enormous technological progress has resulted in an explosive growth in the amount of biological and chemical data that is typically multivariate and tangled in structure. Therefore, several computational approaches have mainly focused on dimensionality reduction and convenient representation of high-dimensional datasets to elucidate the relationships between the observed activity (or effect) and calculated parameters commonly expressed in terms of molecular descriptors. We have collected the experimental data available in patent and scientific publications as well as specific databases for various agrochemicals. The resulting dataset was then thoroughly analyzed using Kohonen-based self-organizing technique. The overall aim of the presented study is to investigate whether the developed *in silico* model can be applied to predict the agrochemical activity of small molecule compounds and, at the same time, to offer further insights into the distinctive features of different agrochemical categories. The preliminary external validation with several plant growth regulators demonstrated a relatively high prediction power (67%) of the constructed model. This study is, actually, the first example of a large-scale modeling in the field of agrochemistry.

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1. Introduction

PGRs (plant growth regulators) is a class of compounds that includes natural plant hormones (phytohormones) and their synthetic analogs (Basra, 2000). They represent organic molecules that regulate the growth of cultivated plants and are active in different concentrations (Teale et al., 2006). A distinct phytohormone can affect a number of crucial processes occurring in plants thereby promoting their growth and progression. Whereas, a particular process can be controlled by different plant hormones. Commonly, the mechanism of action of these molecules is determined by exogenous application (Gray, 2004). To date, eight classes of natural plant hormones have been described (Fig. 1): auxins, cytokinins, jasmonic acid, abscisic acid, ethylene, gibberellins, brassinosteroids (Nambara and Marion-Poll, 2005) and strigolactones (Dun et al., 2009).

The other extensive class of compounds used in agriculture is pesticides, which comprise three groups considered below. Insecticides and fungicides defend plants from needless insects and fungi, respectively. Herbicides share about 40–60% of all pesticides and, in many cases, are toxic towards weeds improving crop yield. According to Weed Science Society of America, there are 29 classes of herbicides with different mechanisms of action (Fig. 2).

Many papers comprehensively discuss the application and properties of various pesticides (Dayan et al., 2012; Gandy et al., 2015; Santner et al., 2009; Ulrich et al., 2012). Such chemicals are valuable tool for agricultural biotechnology to circumvent the need for genetic engineering that results in cost reduction. However, due to the potential negative environmental impact and the decrease in effectiveness after prolonged application (Adesemoye et al., 2009; Khan et al., 2008), an urgent demand is continuously observed on safer and more effective alternatives.

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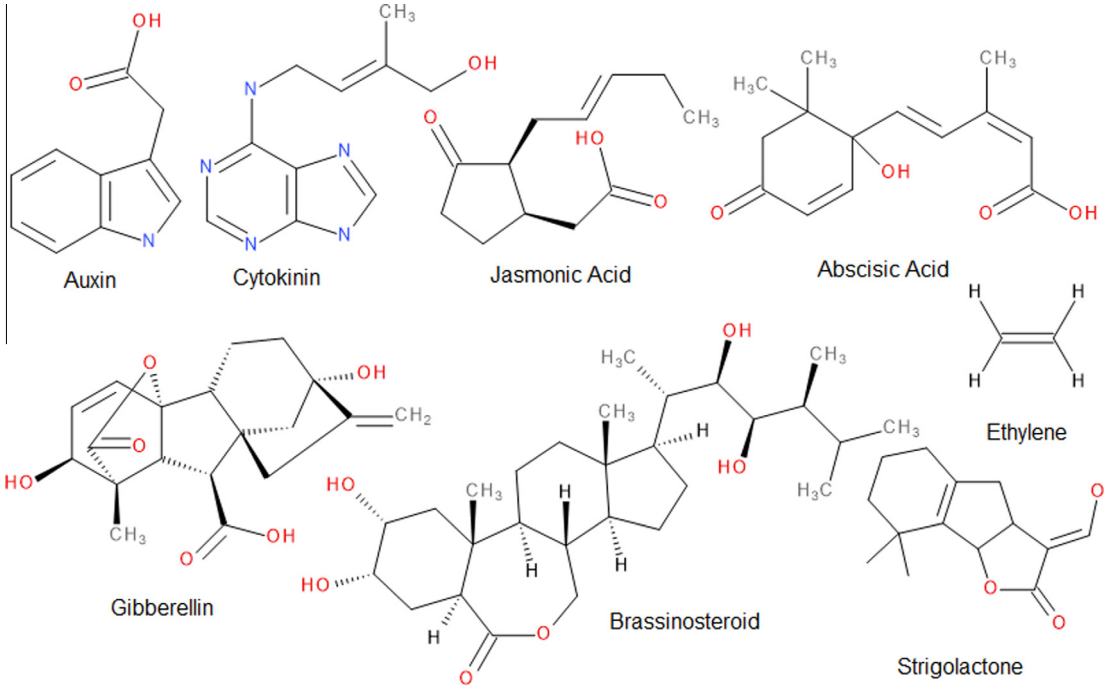

Fig. 1. Representative examples of phytohormones.

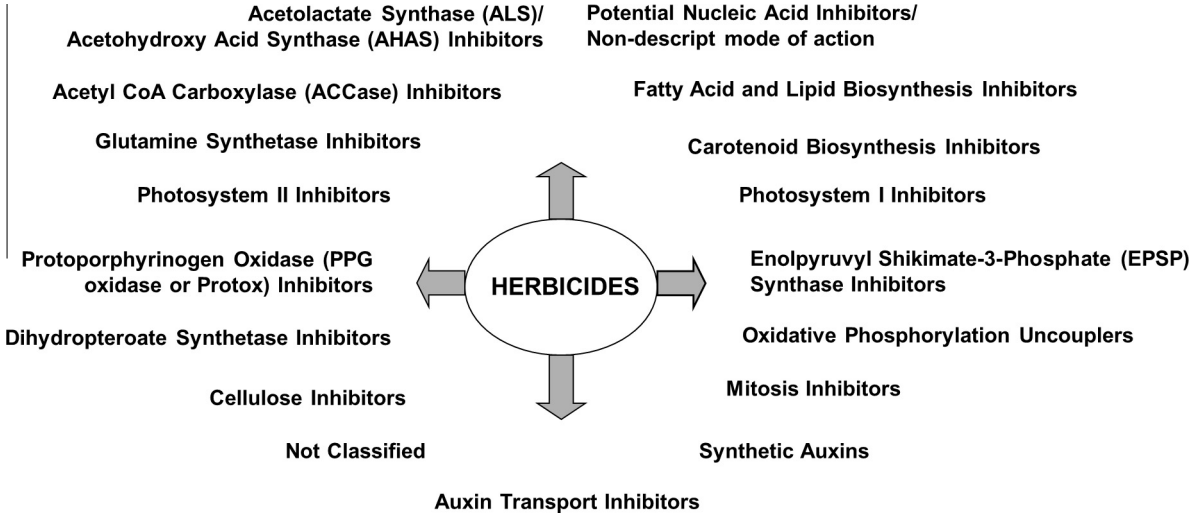

Fig. 2. The mechanisms of action for herbicides (examples).

Phenotypic screening of chemical libraries, including a high-throughput scale, has become an indispensable tool to identify novel active compounds in agrochemistry by analogy with medicinal chemistry issues (Mutka and Bart, 2015). The workflow is associated with a significant increase in costs with the number of substances examined; generally, screening is highly time-consuming, especially in the case of PGRs. In turns, *Arabidopsis thaliana* can be regarded as a convenient model system, particularly because of one of the smallest genome among plants that is easy to handle. In order to monitor growth regulation, the majority of studies investigate either plant cell cultures or whole seedlings, where molecules influence target processes. These processes include cell wall biosynthesis (Brabham and Debolt, 2012), cytoskeleton functions (Peng et al., 2013), hormone biosynthesis (Meesters et al., 2014) and signaling (Brabham and Debolt, 2012; Pieterse et al., 2009), gravitropism (Mähönen et al., 2014), pathogenesis, purine biosynthesis and intracellular transport (Blackwell and Zhao, 2003; Norambuena et al., 2009; Robert et al., 2009; Rubilar-Hernández et al., 2014). Regulation of the target pathways results in phenotypic changes usually observed during *in vivo* trial. Thus, there is the need in effective methods for rational compound selection that could minimize the relative costs keeping the hit-rate at the desired level.

To identify the most attractive candidates for biological screening, it is reasonable to explore the related chemical space, especially the areas populated by different agrochemicals. The overall chemical space conception is widely used in different segments of modern drug development and chemoinformatics. In general, the chemical space is the entire collection of all small molecules reported to date (Dobson, 2004), and MD (Molecular Descriptor) is a numerical value that encodes an intrinsic feature of a structure, e.g. lipophilicity, H-bonding capacity, 2D/3D-topology, solvation energy, and charge distribution. Commonly, these properties are calculated using specific software tools. In other words, these parameters can be presented as input vectors within *n*-dimensional chemical space. MD is

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