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## Interactive evolutionary algorithms and data mining for drug design

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## Curriculum Vitae

Eric-Wubbo Lameijer werd geboren op 11 augustus 1976 in Hilversum. In diezelfde stad volgde hij een gymnasiumopleiding aan het Alberdingk Thijm College, welke hij in 1994 voltooide. In hetzelfde jaar won hij de Nationale Chemie Olympiade en werd als lid van het Nederlandse team uitgezonden naar de Internationale Chemie Olympiade in Oslo, waar hij een bronzen medaille behaalde. Daarna ging hij scheikunde studeren aan de Vrije Universiteit in Amsterdam. Zijn hoofdstage, het ontwerp van een substraatmodel voor het geneesmiddel-metaboliserende enzym cytochroom P450 2D6, deed hij in de groep van Nico Vermeulen onder begeleiding van Jennifer Venhorst. Daarnaast volgde hij stages in de chemische informatica en in de computationele organische chemie. In het jaar 2000 studeerde hij *cum laude* af in de farmacochemie, en ontving hij ook de Taeke Bultsma Award voor zijn afstudeerscriptie over antisense geneesmiddelen. Van 2001 tot 2005 deed hij promotieonderzoek aan de Universiteit Leiden, waar hij in het kader van het bioscience-initiatief onderzoek deed naar de toepassingsmogelijkheden van evolutionaire algoritmen en datamining voor het ontwerp van nieuwe geneesmiddelen. Dit onderzoek heeft onder andere geleid tot een vermelding in het blad *Chemistry World* onder de titel 'To boldly go where no chemist has gone before', en het computerprogramma 'Molecule Evuator', dat tegenwoordig commercieel verkrijgbaar is. Sinds 2005 heeft Eric-Wubbo onder andere gewerkt als programmeur en als freelance wetenschapsjournalist.

## Curriculum Vitae (English)

Eric-Wubbo Lameijer was born on August 11<sup>th</sup>, 1976 in the city of Hilversum. He also received his highschool education there, at the Alberdingk Thijm College, obtaining his diploma in 1994. In the same year, Eric-Wubbo won the Dutch National Chemistry Olympiad and was sent with three other highschool students to represent the Netherlands at the International Chemistry Olympiad in Oslo, where he won a bronze medal. Subsequently, he studied chemistry at the Free University in Amsterdam. The project of his major was creating a substrate model for the cytochrome P450 2D6 enzyme. This research was performed in the group of professor Nico Vermeulen, under supervision of Jennifer Venhorst. He also had internships in the areas of chemical informatics and theoretical organic chemistry. He graduated with honors (*cum laude*) in

2000, and in the same year received the Taeke Bultsma award for his master's thesis on antisense drugs. From 2001 to 2005 Eric-Wubbo performed his PhD studies at Leiden University under the supervision of Ad IJzerman, Joost Kok and Thomas Bäck, on applying evolutionary algorithms and data mining to drug design. This research has led to several publications, one of which inspired the magazine *Chemistry World* to publish an article entitled “to boldly go where no chemist has gone before”. It has also produced a software package for drug design, the Molecule Evaluator, which has since been commercialized. Since 2005 Eric-Wubbo has worked as a programmer and as a freelance science journalist.

## List of publications

Lameijer, E.W.; Bäck, T.; Kok, J.N.; IJzerman, A.P. Evolutionary algorithms in drug design. *Natural Computing*, **2005**, 4, 177-243.

Lameijer, E.W.; IJzerman, A.P.; Kok, J.N. The molecule evaluator: an interactive evolutionary algorithm for designing drug molecules. *GECCO 2005*, 1969-1976.

Lameijer, E.W.; IJzerman, A.P.; Kok, J.N. Using data mining to improve mutation in a tool for molecular evolution. *Congress on Evolutionary Computation 2005*, 314-321.

Lameijer, E.W.; Kok, J.N.; Bäck, T.; IJzerman, A.P. The Molecule Evaluator. An Interactive Evolutionary Algorithm for the Design of Drug-Like Molecules. *J. Chem. Inf. Model.*, **2006**, 46(2), 545-552.

Lameijer, E.W.; Kok, J.N.; Bäck, T.; IJzerman, A.P. Mining a Chemical Database for Fragment Co-occurrence: Discovery of “Chemical Clichés”. *J. Chem. Inf. Model.*, **2006**, 46 (2), 553–562.

Lameijer, E.W.; Tromp, R.A.; Spanjersberg, R.F.; Brussee, J.; IJzerman, A.P. Designing Active Template Molecules by Combining Computational De Novo Design and Human Chemist's Expertise. *J. Med. Chem.*, **2007**, 50 (8), 1925–1932.

Ye, K.; Lameijer, E.W.; Beukers, M.W.; IJzerman, A.P. A two-entropies analysis to identify functional positions in the transmembrane region of class A G protein-coupled receptors. *Proteins*, **2006**, 63(4), 1018-1030.

The research described in this thesis has also been the subject of an article in “Chemistry World”,

Evans, J. To boldly go where no chemist has gone before. *Chemistry World*, **2006**, February 8th.

## Epilogue

There exists a stereotype of a lone scientist toiling in a laboratory, making great discoveries that will amaze the world because of his or her great mind seeing the Truth. However, pursuing a PhD makes one aware how wrong that image is, especially on the 'lone' part. While it may be possible to make great discoveries with nothing but your own observations and the knowledge of your predecessors to aid you, my research at least would never have been possible without ample intellectual, material and emotional support by many different people.

First of all, this thesis would never have come into being without the encouragement and support of my three supervisors, Ad IJzerman, Joost Kok, and Thomas Bäck. Next to obtaining the funds that made it possible for me to pursue my PhD without needing a second job to cover my expenses, they guided me in exploring their fields of interest, from medicinal chemistry (Ad IJzerman) to data mining (Joost Kok) and evolutionary algorithms (Thomas Bäck). Furthermore, they were always willing to listen to me whenever I was stuck at something, and mentored me through the process of getting my first papers in publishable form.

Further support and stimulation during my Leiden period was provided by the contacts and discussions with my colleagues both inside and outside the division of Medicinal Chemistry. Most of all I enjoyed the discussions within the 'computer group' with Jeroen Kazius, whose ominous clothes have never concealed his big heart, Kai Ye, who combines a serene spirit with a quick and innovative mind, and last but not least algorithm whizz, architecture buff and good friend Siegfried Nijssen. I fondly remember the talks with these three on subjects ranging from computer science to natural science, from surviving professors to supervising students, and from life as a PhD-student to Life as a whole.

But not only 'computer people' were important for my research. Crucial for developing the Molecule Evuator were the discussions with and critiques by the medicinal chemists, Johannes (Hans) Brussee, Reynier Tromp, Aniko Göblyös, Jaco van Veldhoven, Lisa Chang and Ron Spanjersberg, who were willing to help me transform the idea of an interactive evolutionary algorithm to something that chemists could use. Neither will I forget the great atmosphere in the medicinal chemistry group contributed by the biology league/band/posse, Margot, Miriam, Ann, Elisabeth, Rianne, Henk, and their students innumerable. My special thanks in the social category go to Thea Mulder and Laura Heitman for co-organizing laboratory events, and to the memory of Jacobien von Frijtag Drabbe Künzel, organizer, cook and person *par*

*excellence*, who, despite our very different interests and personalities, always made me feel a welcome and worthwhile person.

Outside our group, I was honored to work with the “Chris team” from Amsterdam, comprising of the constantly busy but ever supportive young scientists Chris Oostenbrink and Chris de Graaf. Chapter 6 is the result of this collaboration. I also thank the companies Grünenthal and Organon/Schering Plough and their medicinal and computational chemists for their willingness to take the time and effort to give feedback on the first versions of the Molecule Evoluator. Within Leiden University I am grateful for the help of Jelle Goeman, a young mathematician with the rare and precious gift of being able to explain statistics clearly to non-statisticians. Jelle was a great aid in getting chapter 3 of this thesis published. Also within Leiden University I am grateful for the coaching by and conversations with ‘P&O’-man Kick Moors, who encouraged me to continue even when the going was rough, and helped me with perhaps the most tricky part of science for an “exact” scientist: managing the emotional aspects of research. Finally, as my ‘farthest collaborator’ I thank Wanjin Tang, my listening ear in distant Sweden and later in the even more distant Texas, who sometimes made me see a situation differently with her Chinese wisdoms, or made me smile with her photographs of humorously prepared food. I am grateful for our LDF (long distance friendship) during these last six years.

I also thank six special persons for helping in the construction of the Molecule Evoluator, for teaching me to teach, and for providing me with perhaps the most stimulating and inspiring part of my work in Leiden: my students. Computer scientists Tijmen and Kim challenged me to extend my communication style to non-chemists, which was valuable training. But especially I thank my chemical and biopharmaceutical students, whom I had the pleasure and privilege of supervising for a longer time: Eelke van der Horst, who would never let so-called ‘midnight’ stop his efforts to solving a programming problem (and has later single-handedly dragged the Molecule Evoluator into the age of Windows), Jurre Kamphorst, who tackled (and still tackles) research with the same discipline and professionalism as he applied to his rowing, Daan Acohen, who sometimes seemed to prefer molecule revolution to molecule evolution yet nevertheless made an essential contribution to the Molecule Evoluator and chapter 6 by designing and implementing fragment-based evolution, and finally Guoxiang Liu, my student from farthest away, for whom computer science in Leiden may have been a very strange and stressful environment, but whose perseverance and willingness to tackle research problems far out of his comfort zone I

greatly admire. I enjoyed my contacts with them, and I hope that they will become successful and happy in whatever field they choose.

One can however not give to others what one has not been given first. While the faults in this thesis are of course wholly my responsibility, for its qualities it is greatly indebted to the people who guided my growth as a scientist. Next to my three Leiden supervisors, these are the teachers and mentors I had before, who edged me towards formulating more sharply and thinking more critically. Most prominent among these were Jennifer Venhorst, Rosa Bulo, Andreas Ehlers and Jan Commandeur. I am grateful for their guidance. Yet one person among my educators stands out: my high school teacher, Olaf Budde. Whereas my other mentors taught me *how* to do science, “Mr Budde” (also informally known as the 'jazz man') did something even deeper and more important: teaching me *why* to do science. He was the living embodiment that chemistry is not merely 'interesting', but that it can be creative, fun and wonderful. He was a true teacher of the joy of chemistry, and has always inspired me on my path.

Lastly, I thank my family for their unwavering support. I thank my sister Nanette and her partner Ron for their frequent hospitality, excellent cooking and being there for me when I walked through my personal valleys of PhD-doubt. I also thank them for the initial designs for the cover of this thesis. I thank my mother for always giving me a home in Hilversum whenever I was ill or needed relaxation from work, and for the almost unlimited amounts of postcards she has sent me to cheer me up and encourage me with my projects, next to taking care that I would exercise properly by walking in healthy woods, and would not lack the essential nutrients provided by chocolate and Limburg flans. Finally, I thank my father, who from my earliest youth helped ignite a love for science and learning in me. When I was little, he read the biographies of famous chemists to me at bedtime. He pointed me towards my first chemistry book, and has provided me with many volumes of old but fascinating chemistry literature even before my official first chemistry lesson in high school. Throughout the years, he shared his love of knowledge, science, and pharmacology with me, and he was my mentor for my first presentations. But above all he was to me an example of integrity and compassion, living the principle that knowledge can be interesting and useful, but that a person cannot be complete without compassion and willingness to help others, and the courage to do what he or she knows is right. It is the greatest regret of my PhD-period that I could not finish my thesis in time for him to witness it, but I know that he would be proud of me.