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Replacing Animal Testing by Virtual Experiments: A Challenge in Computational Chemistry

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Abstract. Computer modeling is used to study small-molecule interactions with macromolecular receptors with the aim to reduce *in vivo* testing of new chemicals and drugs.

Angelo Vedani received his doctorate in 1981 at the University of Zürich under the supervision of *H.R. Oswald* and *E. Dubler*. He then spent a post-doctoral period with *E.F. Meyer jr.* at Texas A&M and then worked with *J.D. Dunitz* and *M. Dobler* at the ETH Zürich until 1986. From 1986 until 1990, he was an assistant professor at the University of Kansas. Since 1991, he has been director of the Biographics Laboratory in Basel. He is concurrently completing his habilitation in the group of *M. Neuburger-Zehnder*.

The last decade has seen an enormous enhancement in computer power, but the complexity of biochemical events still leaves accurate simulations on a long time scale an unmet challenge. Since the mid 1980s, molecular modeling has been widely used in pharmacological research, partially due to the increasing availability of key protein structures. The impact of molecular modeling on drug development has often been demonstrated, but less obvious is its effectiveness in reducing animal testing. By recognizing inactive or toxic compounds by means of computational screening, undesired substances can be withdrawn from the evaluation pipeline before *in vivo* experiments become necessary.

Our laboratory develops computational approaches to pharmacological and toxicological screening. In the mid 1990s, a pseudoreceptor-modeling concept for predicting the activity of drug molecules was devised [2][3]. More recently, we have developed a 3D-QSAR concept based on

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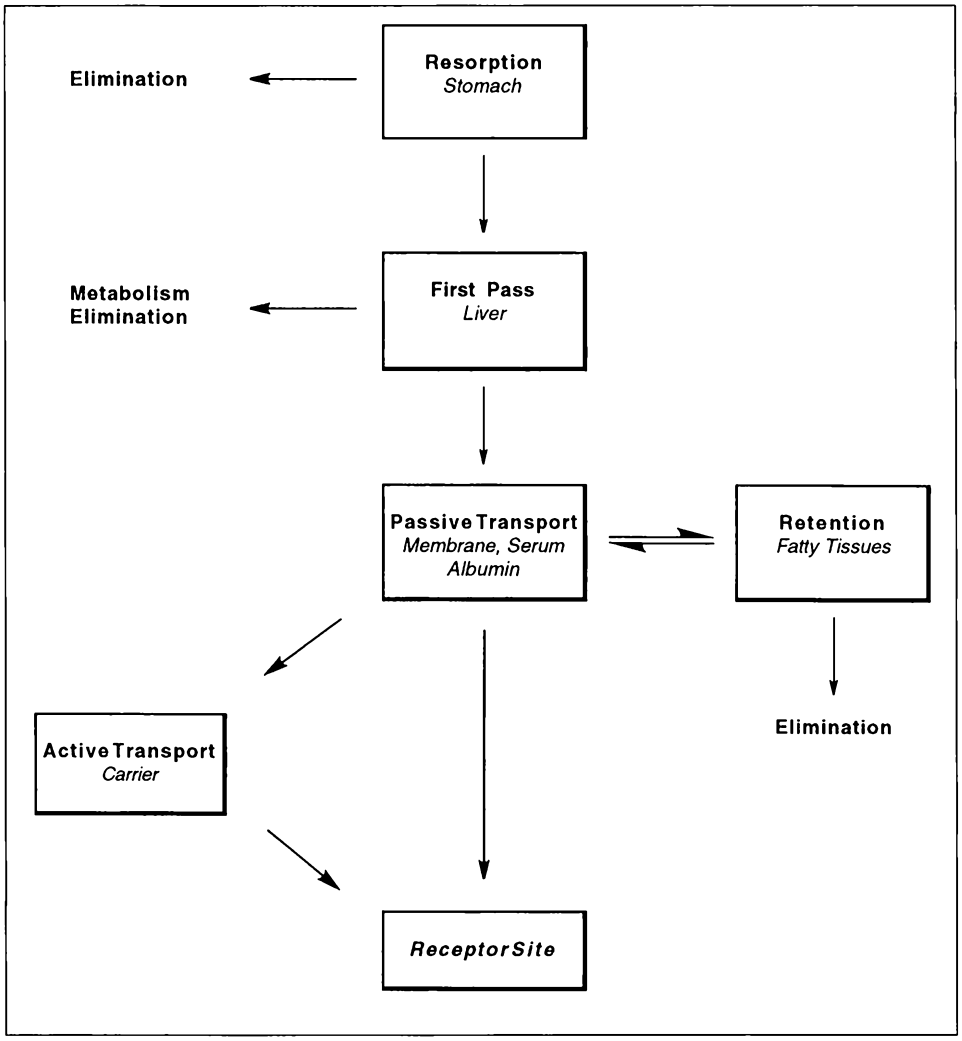
Scheme. *Surrogate Compartments Defining the Bioavailability-Modeling Cascade*



a genetic algorithm, allowing for induced fit, H-bond flip-flop, and solvent effects [4]. In this concept (*quasi-atomistic receptor modeling*), the properties of individual parts of the receptor surrogate are reduced to points mapped onto a three-dimensional envelope surrounding the ligand molecules. Using this approach, we have semiquantitatively predicted the toxicity of a series of dibenzodioxins, dibenzofurans, and biphenyls – thereby demonstrating the capability of this approach to replace stressful toxicity tests on animals [5].

Another application of toxicity modeling at our laboratory aims at the identification of an antidote for ochratoxin A (OcA), a compound which causes nephrotoxic, genotoxic, teratogenic, carcinogenic and immunosuppressive effects and which has also been linked to *Balkan Endemic Nephropathy*. The toxicity of OcA is thought to be primarily due to its inhibition of phenylalanine-tRNA synthetase (PheRS). Simulating the molecular-dynamical behavior of PheRS–OcA in aqueous solution, we have identified three quite different binding modes, all of which suggest an affinity only in the millimolar range [6]. This would seem to be in conflict with older toxicological findings but is in agreement with more recent *in vitro* studies. *In vivo*, OcA binds preferentially to serum albumin, a plasma protein, with a corresponding effect on its toxicokinetics. Antagonizing this effect would lead to an enhanced elimination rate, thereby reducing all adverse effects of ochratoxin A. Based on the three-dimensional structure of human serum albumin [7], we have simulated its interaction with ochratoxin A. The long-term goal of our study is the computational identification of a synthetic antagonist with an affinity between that of the endogenous ligands and OcA.

Our currently most challenging project aims at computationally determining the bioavailability of a class of compounds. This parameter is crucial for potential drug molecules as a high intrinsic affinity towards the target receptor is a mandatory but not a sufficient condition for clinical success. A sufficiently high bioavailability – the parameter that determines the actual concentration of a natural or synthetic drug at the receptor site – is often difficult to achieve: premature elimination from the body, storage at remote sites, and biotransformation all reduce the concentration of a compound at the 'therapeutic site'. We plan to address this task by defining a cascade of receptor-surface models (I: resorption, II: first pass, III: passive transport, IV: retention, V: active transport) linked by a set of kinetic equations.

More complex events, such as metabolic transformation and elimination, cannot be directly modeled but will be described by additional terms to the kinetic equations instead. The individual compartments I–V will be represented by quasi-atomistic receptor models, featuring different hydrophilic and hydrophobic properties, different three-dimensional shapes, and different levels of solvent accessibility. If applicable in preclinical research, this approach could lead to a substantial reduction in animal testing as bioavailability can presently only be determined *in vivo*.

Computer-based simulations ('virtual experiments') may not be capable of replacing complex biological experiments in the near future. But their impact on chemical engineering and biomedical research is substantial, thereby contributing to the analysis, understanding, and design of real experiments, helping to save energy and resources, and reducing animal testing. Advantages of virtual over real experiments include the capability to simulate hypothetical substances, to analyze experiments step by step, and to screen large structural databases in short time at low cost. Virtual experiments along with current computing power also suggest that the 'practice is better than theory' philosophy might be due for reconsideration. Why else would we want supercomputer power on our laps ?

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[1] The *Biographics Laboratory 3R*, a private non-profit research enterprise aimed at developing computational tools for reducing and replacing animal experiments in biomedical research, was founded in 1990. The institution is controlled by the state of Basel and is supervised by a scientific advisory board.

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