

Technische Wetenschappen “Wiskunde Toegepast”

Project title

Mesoscale simulation paradigms in the Silicon Cell

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Embedding

The project is partly embedded in the “Silicon Cell” program (see also Section 4 “Utilisation” and [30]). The long-term goal of this program is the computation of Life at the cellular level on the basis of the complete genomic, transcriptomic, proteomic, metabolomic, and cell-physiomic information that will become available in the forthcoming years.

Requested support from other sources

None for this project.

Keywords

Whole-cell modelling, simulation of reaction-diffusion in disordered and fractal media, mathematical and numerical analysis, particle-based methods, partial differential equations, adaptive grids.

Duration of the project

Four years, 2 PhD students

1 Summary

A major challenge in the computer simulation of biological systems is the treatment of the vast temporal and spatial scales. Nowadays, one can observe biological systems in great detail, but often at the cost of other important attributes of the system. Without “disturbing” the system it is possible to see - with the naked eye - structures of up to 200 μm such as a large cell. With a light microscope one can distinguish the compartments of a human cell, and with an electron microscope one can even see very small details such as proteins, but observations on the reactions between proteins are beyond current experimental capabilities. Moreover, laboratory (“wet”) experiments are extremely expensive and time-consuming due to the size and the fragility of the living cell. To steer “wet” experiments into a promising direction computational models - a silicon cell - are therefore adamant.

1.1 Research

In the proposed project we want to develop and compare computational models of parts of the living cell that can calculate in detail system properties from experimentally obtained molecular and physical-chemical data. Such a model is as close as possible to the biological experiments and therefore can be used not only for understanding the principles of function but also to steer further biological experiments. We focus on two subjects: (i) simulation of reaction-diffusion phenomena with non-trivial chain-like reaction mechanisms in three dimensions, and (ii) incorporating real data, as obtained from confocal microscopy, into the model. The latter includes coupling of the reaction-diffusion model at fractal-like interfaces with a model (for example an aggregation model) of a dynamically changing interface. We want to compare two different model approaches in the *mesoscopic* regime: the first using particle-based methods (lattice Boltzmann) and the second using methods based on partial differential equations (PDEs). We will compare the simulated results from both methods with each other and with actual observations on both types of reaction mechanisms.

1.2 Utilisation

The project is embedded in the “Silicon Cell” initiative (cf. [30]) in which our groups and the biological research groups of van Driel (SILS/UvA) and Westerhoff (IMBS/VU) participate. *SiC* aims at doing science in the sense of a “systematic study in which experiment and theory go hand in hand”. The ultimate goal is the computer simulation of a living cell. Such a Silicon Cell can then be utilized as a “cell factory” to produce pharmaceuticals or to develop rational treatments of diseases. This project concerns more modest ambitions: computer models for some important cellular processes. The use of these models will be twofold. On the one hand they will enhance the understanding of the functioning of the cell. But on the other hand they can be used to design and steer biological experiments. Due to the small spatial scale - in the order

of nanometers - at which these biological processes take place and due to the fragility of a living cell these experiments are extremely time-consuming and expensive. A reduction of search-directions will therefore save both money and labour.

Samenvatting

Een belangrijke uitdaging in de computersimulatie van biologische systemen is de behandeling van de grote tijd- en ruimteschalen. Tegenwoordig kunnen biologische systemen zeer gedetailleerd geobserveerd worden, maar vaak ten koste van andere belangrijke kenmerken van het systeem. Zonder het systeem te “verstoren” zijn - met het blote oog - structuren te onderscheiden tot $200 \mu m$ zoals een grote cel. Met een lichtmicroscop kunnen de compartimenten van een menselijke cel onderscheiden worden en met een elektronenmicroscop zijn zelfs zeer kleine details zoals eiwitten te zien, maar waarnemingen aan de reacties tussen eiwitten liggen nu nog buiten de experimentele mogelijkheden. Bovendien zijn laboratorium - of “natte” - experimenten buitengewoon kostbaar en tijdrovend wegens de grootte en de kwetsbaarheid van de levende cel. Om “natte” experimenten in een veelbelovende richting te sturen zijn daarom computermodellen - een silicon cel - essentieel.

Onderzoek

In het voorgestelde project willen we computermodellen van delen van de levende cel ontwikkelen en vergelijken, die in detail systeemeigenschappen kunnen berekenen uit experimenteel verkregen moleculaire en fysisch-chemische data. Zo'n model lijkt zo veel als mogelijk op de biologische experimenten en kan daarom niet alleen gebruikt worden om de functieprincipes te begrijpen, maar ook om richting te geven aan biologische vervolgentexperimenten. We richten ons op twee onderwerpen: (i) het simuleren in drie dimensies van reactie-diffusie verschijnselen met niet-triviale ketting-reactie mechanismen en (ii) het opnemen in het model van echte data zoals verkregen met confocale microscopie. Het laatste houdt in dat het reactie-diffusie model op fractaal-achtige grensvlakken gekoppeld moet worden met een model (bv. een aggregatiemodel) van een dynamisch veranderend grensvlak. We willen twee verschillende *mesoscopische* modelaanpakken vergelijken: de eerste gebaseerd op deeltjesmethoden (rooster Boltzmann) en de tweede gebruikmakend van methoden die op partiële differentiaalvergelijkingen gebaseerd zijn. We zullen de met beide methoden gesimuleerde resultaten met elkaar vergelijken en met echte waarnemingen aan beide soorten reactiemechanismen.

Utilisatie

Het project is ingebed in het “Silicon Cell” initiatief (zie [30]) waarin onze groepen en de biologische onderzoeksgroepen van van Driel (SILS/UvA) en Wester-

hoff (IMBS/VU) participeren. *SiC* richt zich op het bedrijven van wetenschap in de zin van een “systematische studie waarin experiment en theorie hand in hand gaan”. Het ultieme doel is de computersimulatie van een levende cel. Zo’n silicon cel kan dan gebruikt worden als een “cel fabriek” om farmaceutica te produceren of om rationele behandelingen van ziekten te ontwikkelen. Dit project heeft bescheidener ambities: computermodellen voor een aantal belangrijke processen in de cel. Deze modellen zullen op tweeërlei wijze gebruikt worden. Enerzijds zullen ze het begrip van het functioneren van de cel vergroten. En anderzijds kunnen ze gebruikt worden om biologische experimenten te ontwerpen en te sturen. Wegens de kleine ruimteschaal - in de orde van nanometers - waarop deze biologische processen plaatsvinden en wegens de kwetsbaarheid van een levende cel zijn deze experimenten buitengewoon tijdrovend en kostbaar. Het terugbrengen van het aantal zoek-richtingen zal daarom zowel geld als werk uitsparen.

2 Composition of the research team

Personnel	Task	Financed by	Fte/yr
Dr. J.A. Kaandorp	supervision PhD 1	IvI/UvA	0.2
Drs J.G. Blom	supervision PhD 2	CWI	0.2
PhD student 1 (AIO)	research	Wiskunde Toegepast	1.0
PhD student 2 (OIO)	research	Wiskunde Toegepast	1.0
Prof.dr. P.M.A. Sloot	promotor PhD 1	IvI/UvA	pm
Prof.dr. J.G. Verwer	promotor PhD 2	CWI/KdV/UvA	pm
Prof.dr. R. van Driel	biological advice	SILS/UvA	pm
Prof.dr. H.V. Westerhof	biological advice	IMBS/VU	pm
Dr.ir. J.E. Frank	algorithmic advice	CWI	pm
Dr. M.A. Peletier	analysis advice	CWI	pm

3 Scientific description

Reaction-diffusion phenomena on complex-shaped surfaces represent an important class of problems relevant to a wide range of applications in the natural sciences. Usually these reaction-diffusion problems can be accessed experimentally only to a limited extent. In many cases simulation models are the only available option to study these phenomena. For instance, simulation models for reactivity on interfaces with a complex geometry have been developed for studying reactivity on disordered porous catalysts in chemical reactors [1], ground water pollution [2] and complex fluids [23]. A major problem in the development of these simulation models is that reactions occur on irregular surfaces with a complex geometry, which may grow and where the whole process is in a non-equilibrium state.

Using particle-based models, existing studies are traditionally limited to two-dimensional problems [1] and simulation boxes with relatively low dimensions

due to computational restrictions. Furthermore, many reaction-diffusion phenomena on irregularly shaped surfaces are characterized by complicated reaction processes, while existing studies are limited to simple reactions as for example the formation of Liesegang patterns [11].

Using PDE-based models, which have been successfully applied in other types of reaction-diffusion problems [22], reaction-diffusion on irregular surfaces is difficult to capture. But, if adaptive grids are used, it has been proven that systems of time-dependent PDEs on irregular domains can be successfully solved even if the solution develops steep gradients (see e.g., [7, 8, 26, 21, 24, 29]).

3.1 Case studies and simulation paradigms

We will examine the potential use of both mesoscopic computational approaches and verify model assumptions in actual case studies from cell biology that are very challenging from a mathematical and computational point of view. The models will be partly based on existing knowledge and partly on new algorithms.

3.1.1 Case studies

In the first case study we address the influence of the intracellular environment on the functioning of the biochemical reaction networks in the cell. An issue here is that the cytosol of the cell cannot be simply considered to be a homogeneous space. In reality this space is densely packed with a complex mixture of proteins, nucleic acids and small molecules and is more a spaghetti-like medium (see Fig. 1). Local increase of protein concentrations near the membrane may lead to an increase in the intensity of the signalling transduction chain (see, e.g. [3, 15, 16]).

We will investigate different scenarios of biochemical reaction networks including transmembrane transport and spatial effects on the reactivity and we will compare our results to the actual observations carried out on cytoplasmic signalling proteins (see also Section 4 “Utilisation”).

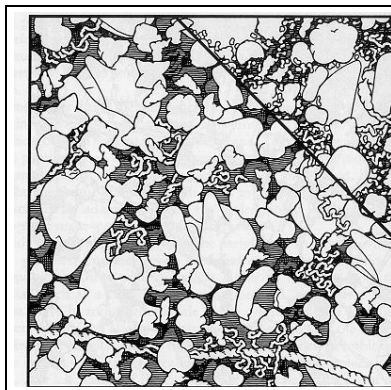


Figure 1: Artist impression of the cytoplasm of *E. coli*. (1,000,000 x). Picture taken from [17].

In the second case study we will develop a model of reactivity at the surface of chromatin aggregates during the transcription process. RNA synthesis and processing take place at the border of condensed chromatin which is the morphological site of transcription [13]. By visualisation of the transcription sites [27, 12] it was found that transcriptionally active chromatin is markedly compartmentalized. One of the major open questions in cell biology is what role spatial configurations of chromatin play in the regulation of gene expression. One additional issue we expect to be important but which is hardly mentioned

in the literature, is that those spatial configurations themselves may be caused by the transcription processes.

In this case study we want to couple the three-dimensional model of reaction-diffusion with a particle-based model of chromatin aggregates which act as the reaction substrate. We are planning to capture the production of gene products, using a cellular automaton model for reaction-diffusion. The chromatin domains itself will be represented by an aggregation model based on cellular automata. We will investigate spatial effects of simulated chromatin substrate on the reaction rates and compare this with actual observations. Data sets for the second case study, 3D and 4D (including the dynamic behaviour of chromatin) confocal microscopy data originating from actual experiments, will be used to investigate the influence of the actual spatial configurations of chromatin on reaction rates. For this purpose we are planning to use the actual configuration, stemming from the 3D data set, in our reaction-diffusion simulation.

3.1.2 Particle-based approach

An appropriate model for reaction-diffusion, characterized by a non-linear behaviour in the reaction process in combination with the complexity of a growth mechanism or irregularly shaped interface, is a mesoscopic particle-based approach using local microscopic rules. In this approach it is feasible to represent spontaneous precipitation (or nucleation) of a chemical substance, when a local saturation point is reached or to capture interfaces with a complex shape. It is also possible to model growth processes, as for instance aggregation processes, in a particle-based method for modelling diffusion and flow [19, 18] or reaction-diffusion [10]. With these methods complex geometries can be modelled in a relatively straightforward manner and it is possible to study the spontaneous emergence of growth patterns in these models.

In the particle-based approach the cytosol will be modelled as a porous medium, using a simplified approximation, comparable with techniques used for example in modelling the porosity of fibre networks [20]. We will model the cytosol as a mixture of suspended aggregates. The carrying fluid will be modelled using the lattice Boltzmann method, in which populations of particles advect and diffuse in a cubic lattice. The mean populations of particles move simultaneously from one lattice node to neighbouring lattice nodes. The evolution of the lattice is described by the following dynamical rule:

$$n_i(r + c_i, t + 1) = n_i(r, t) + \Delta_i(r, t)$$

where $n_i(r, t)$ is the continuous particle distribution function, which describes the number of particles at a node at position r , at time t and with direction c_i and $\Delta_i(r, t)$ is the collision operator describing the changes in n_i due to collisions

at the nodes. The moments of the particle distribution function $n_i(r, t)$:

$$\begin{aligned}\rho &= \sum_i n_i \\ j &= \sum_i n_i c_i = \rho u \\ \Pi &= \sum_i n_i c_i c_i\end{aligned}$$

correspond to the hydrodynamic fields mass density ρ , momentum density j (u is the flow velocity at node r), and momentum flux Π . In a Chapman-Enskog expansion of the dynamical rule and the conservation laws, macroscopical equations can be derived, which approximate the hydrodynamical equations [10]. With this lattice Boltzmann method advection and diffusion can be modelled; by defining various types of tracer particles in the system, it is possible to model reactivity [9], [10]. Within this system sources and sinks (sites of absorption of a tracer) can be specified around arbitrarily shaped geometries. The method uses local interactions between the populations. For this reason the method is fully scalable and suitable for large-scale computing.

3.1.3 PDE-based approach

In the PDE-based model we start from the macroscopic point of view and implicitly adopt the continuum hypothesis, i.e., we assume that the behaviour of the reactants concerned can be modelled by considering a continuous representation (a concentration). This is a reasonable assumption for a metabolic pathway like the PTS system, an essential element in the glucose metabolism of bacteriae, but in other processes the number of reacting molecules might not be large enough.

The time variation of each of the reacting species inside the cytosol is modelled by equations of the form

$$\frac{\partial A}{\partial t} - \nabla \cdot (D_A \nabla A) = R_A \quad \text{for } (x, t) \in \Omega \times (0, \infty),$$

where A is the volume concentration of any one of the species. The reaction rates R_A can be obtained from the stoichiometry matrix and the corresponding rate coefficients of the biochemical network. The coefficients D_A are the corresponding diffusion rates. In this model paradigm non-reactive entities are only part of the system through the diffusion coefficients.

The species which are confined to the cell membrane, are modelled by surface concentrations defined on the boundary of the domain, $\partial\Omega$. They are also assumed to undergo diffusion, as well as reaction:

$$\frac{\partial B}{\partial t} - \nabla \cdot (D_B \nabla B) = R_B, \quad \text{for } (x, t) \in \partial\Omega \times (0, \infty),$$

For the mass balance of the interior species the reaction at the boundary represents a source/sink term. The corresponding boundary condition is obtained by equating the source/sink with the local flux at the boundary.

If these PDE-systems are to be solved on a domain with (time-dependent) irregular boundaries or interfaces, traditional finite-difference or finite-element methods using fixed grids and fixed-order methods are highly inefficient. They often fail to find solutions or, worse, find solutions with spurious behaviour.

Adaptive methods, however, automatically refine, coarsen, and relocate grids; hence, these are capable of resolving the local non-uniformities and they are among the most efficient and robust computational techniques available for solving systems of partial differential equations. One can either choose for a cascade of grids or for a non-uniform grid, possibly moving in time. After discretisation of the spatial operators on these grid(s) a system of ordinary differential equations (ODEs) results that has to be integrated in time. These ODE systems are in general very stiff and therefore need some form of implicit time integration. In previous projects we have developed codes based on a moving-finite-element technique [29] and on the cascade approach [24, 4, 5]. Although the latter has proved to be very effective in comparable case studies (see, e.g., [7, 8, 26, 25]) the code can no longer be considered state-of-the-art.

In this project we will develop an adaptive finite-element method on a non-uniform grid (see, e.g., [14]). In adaptive algorithms a posteriori estimates of discretisation errors are used to both guide grid and method enrichment and to provide an effective way to judge solution accuracy. Error estimates can be replaced by enrichment indicators, like solution gradients, which may be efficient, but possibly at the cost of robustness. The basic enrichment strategies of grid refinement/coarsening (h-refinement), grid motion (r-refinement), and method order variation (p-refinement) may be used singly or in combination. The combination of h- and p-refinement is efficient and capable of achieving exponential rates of convergence.

For the time integration several options are still open: operator splitting, (linearly) implicit solvers with approximate matrix factorisation, etc. This is a subject of ongoing research at the CWI group (see e.g., [28, 6]) and will also be an important research subject in the current project.

3.2 Comparison and evaluation of models and simulation paradigms

Comparison of the particle- and PDE-based methods We are planning to compare the results of both approaches with analytic solutions and computed reference solutions. Furthermore we want to investigate the effectiveness of both approaches by simulating reaction diffusion systems in various geometries with a controlled degree of complexity.

At the algorithmic level we will study the convergence (finer grid / more particles), the stability, the complexity, and the accuracy of both methods. At the implementation level we want to compare the efficiency, parallelisation and scalability, the “ease of use” and the generality of both approaches.

Comparison of the particle- and PDE-based methods with real data

We also want to compare the results of both approaches with real data and experiments available in the literature and from the end-user groups. We will investigate which model describes best reactions in cytoplasm and membrane and which model is the most flexible when applied to complex-shaped boundaries and interfaces, possibly dynamically changing in time.

3.3 Scientific importance

Both particle-based models and PDE-discretisation models are widely used methods to describe reaction-diffusion phenomena. But, as far as we know, there has not been a systematic comparison of the two approaches for specific case studies. We expect that within this project a number of methods will be developed which can be applied in a broad range of disciplines where research is being done on the physics of disordered and fractal media. Furthermore, the results of the two case studies may advance the field of research on cell biology by providing some insights into a number of long standing questions from cell biology, in which reactivity on surfaces with a complex geometry is involved. We believe that, after the deciphering of complete genomic sequences, the development of new computational methods suitable for modelling the processes within cells is urgent. In this development, methods from mathematics and physics for studying disordered and fractal media play a fundamental role.

3.4 Requested personnel and instrumentation

2 PhD positions are requested. One to develop the particle-based model, the other to develop the PDE-based model.

The models will be developed initially on the locally available computer facilities, which is for the particle-group a distributed computing environment (the Beowulf cluster) and for the PDE-group either a PC/workstation or the 32-processor SGI Origin 2000 at CWI. At a later stage large scale computing experiments will require the use of supercomputers. Independent funding will be sought via NCF for computation time if the need arises.

3.5 Work programme

Year 1, PhD 1: Development of a particle-based model for diffusion and reactivity for relatively complicated reaction schemes. In this phase we are planning to use a reaction interface with a simple Euclidean geometry.

Year 1 and 2, PhD 2: Development of an adaptive grid method for reaction-diffusion PDE systems which allow for irregular, dynamically changing, interfaces.

Year 2, PhD 1: Development of a model for diffusion and reactivity coupled with an interface with a complex geometry, using aggregation models. First comparison between actual observations on chromatin aggregates and simulated results.

Year 3, PhD 1,2: Testing both models for diffusion and reactivity coupled with an interface stemming from CLSM data and a comparison between simulated and actual results.

Year 3 and 4, PhD 1,2: Comparison of results from the particle-based model, from the PDE-based model and from actual observations on signal transduction on membranes.

Year 4, PhD 1,2: Writing PhD thesis.

3.6 Embedding in research groups

The proposal concerns joint research between CWI and IvI/UvA in the field of computational life sciences. The two PhD projects will be carried out in close collaboration, one within CWI's research cluster MAS (Modeling, Analysis and Simulation), the other within the section Computational Science of the University of Amsterdam. For biological input and model validation we will cooperate with the "end-users", the research groups of van Driel and Westerhoff. The group of van Driel (SILS) studies, among others, the dynamic organisation of the nucleus in relation to its function. The group of Westerhoff (IMBS) focuses on quantitative studies on molecular cell physiology in micro-organisms.

For the particle-based part, the proposed project fits well within several ongoing research projects in the Computational Science group of the University of Amsterdam. Research on lattice gas automata, the lattice Boltzmann model and other particle-based modelling methods as computational models for dynamical complex systems belongs to one of the major research themes within this group. Furthermore the group is involved in research on bioinformatics within the Amsterdam Genomics Centre (AmGC, a collaboration between research groups from the Faculty of Science of the University of Amsterdam and the Amsterdam Medical Centre). The research group at CWI has extensive expertise in the analysis and computation of (time-dependent) partial differential equations, including the development of adaptive and moving grid methods, discretisation of spatial operators and time integration of the stiff systems that occur in (chemical) reactions. The project fits in the research theme "PDEs from the life sciences" of the MAS department of CWI.

4 Utilisation

An important part of the motivation of the project stems from the significance the calculated problems have in the study and understanding of biological cells. The knowledge at the genetic level, at the biochemistry level and at the molecular mechanistic level is expanding rapidly. These developments make it possible to strive for a fundamental and quantitative understanding of the cell. If the cell can be approached in a rational and integrated way, it can be utilized as a "cell factory" to produce chemicals or pharmaceutical components. In biomedical research, once the molecular basis of diseases is known, a rational treatment can be developed, which can even be personalized based on the patient's gene

information. At the moment, however, these are still dreams of the future, even now that for a growing number of living organisms a complete genomic sequence is available. An often used metaphor for the genome is that of a parts list for Life, only no-one knows how to build the engine.

Our groups are involved in the “Silicon Cell” initiative (cf. [30]), which is a collaboration between research groups from different disciplines (mathematics, computer science, physics and biology). The proposed project will be conducted within this framework. The other partners in the Silicon Cell Consortium are the Institute for Molecular Biological Sciences (IMBS, coordinator Prof. Dr. H.V. Westerhoff), Vrije Universiteit Amsterdam and the Swammerdam Institute for Life Sciences (SILS, Prof. Dr. R. van Driel), University of Amsterdam. The long-term goal of the Consortium is “the computation of Life at the cellular level on the basis of the complete genomic, transcriptomic, proteomic, metabolomic, and cell-physiomic information that will become available in the forthcoming years”. It is to be expected that completing this ambition will take decades. Model cells are *E. coli* (prokaryote) and *S. Cerevisiae* (baker’s yeast, eukaryote). These are the best-characterized simple organisms in terms of DNA sequence and regulation. Moreover, for these two cells extensive experimental knowledge and facilities are available at SILS and IMBS.

In contrast to many international initiatives aiming at whole-cell simulation which are mainly based on bio-informatics, *SiC* aims at doing science in the sense of a “systematic study in which experiment and theory go hand in hand”. Rather than a qualitative understanding of the principles of cell function, *SiC* will calculate the implications for cell functioning based on real experimental data and mathematical models. In previous work [3, 15, 16] we developed an *in silicon* replica of the glucose-PTS pathway in *E. coli*. The components of this pathway act at different locations in the cell. Rough estimates suggested that the induced concentration gradients might have a significant control over the flux - the uptake of glucose by the cell - which could be experimentally verifiable. Simulations with the *in silicon* replica showed that in a cell of bacterial size the influence of the spatial locality of the components is not significant. For larger cells (human, plant) however, the uptake of “food” would be significantly limited, which could be an explanation why the highly effective bacterial PTS-system for the uptake of glucose is not present in mammalian cells.

This project focusses on the study of spatial aspects of the cell, such as the dynamic organisation of the nucleus - and more specific the chromatin - in relation to its function - gene expression -. Development of computational methods with which reactivity on complex-shaped structures can be studied in cells are of crucial importance. The methodology and simulation methods will be applicable to a wide range of applications in the natural sciences, like ground water pollution, the study of reactivity on disordered porous catalysts in chemical reactors, and complex fluids.

Biological experiments will be the base of the computational models - they will be validated by experimentally obtained data -, and the developed models themselves will be the base of biological research as they will be used for

understanding the principles of cell function. Moreover, the use of realistic computer models is a sound base to steer and design further biological experiments, thereby saving both money and human capital.

4.1 Users

The project will be carried out in close cooperation with molecular biologists from SILS (Swammerdam Institute for Life Sciences), University of Amsterdam and IMBW (Institute for Molecular Biological Sciences), Vrije Universiteit Amsterdam.

Contacts are:

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Both van Driel and Westerhoff have promised to participate in the project (see also letter of support).

5 Requested Budget

Budget: Salary costs for 2 PhD students for 4 years + 30k€ nonstaff costs (equipment costs - workstations + software - 10k€; travel expenses - conference visits + visitors from abroad - 20k€).

6 Literature

Referenties

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