Appendix B: Case studies

Case study I – Complex networks

Transportation, traffic, communication and energy networks form the backbone of our modern society. To deal with the uncertainty, variation, unpredictability, size and complexity inherent in these networks, radically new ways of thinking need to be developed. NETWORKS is a 10-year programme, funded by the Dutch Ministry of Education, Culture and Science, hosted by the mathematics departments of four research institutions: CWI, TU/e, UvA, UL. The programme started in the Summer of 2014 and covers a broad range of topics dealing with *stochastic* and *algorithmic* aspects of networks. The aim is to address the pressing challenges posed by large-scale networks, through modelling, understanding, controlling and optimising networks that are complex and highly volatile. The ultimate goal is to build *self-organising* and *intelligent* networks.

Involvement of the MI
Frank den Hollander is PI of NETWORKS. Luca Avena is fully employed by NETWORKS. Rajat Subhra Hazra, Floske Spieksma and Evgeny Verbitsky are affiliated members. A total of 5 PhDs and 3 PDs funded by the program have completed their stay at UL. Presently 7 PhDs and 2 PDs are employed. A few more PhDs and PDs will come in, because NETWORKS has acquired additional funding through two COFUND-programs (for a total of 14 PhDs, respectively, 14 PDs). Through NETWORKS, there has been active collaboration with LION (Leiden Institute of Physics) and LIACS (Leiden Institute of Advanced Computer Science).

Research
The UL node of NETWORKS is involved in three research themes: (1) Spatial Networks, (2) Dynamics of Networks and (3) Dynamics on Networks. Examples of topics in each of these themes are:

(1) Breaking of ensemble equivalence for constrained networks, spectra of random networks, spatial genetic populations with seed-bank.

(2) Exploration of sparse networks through random rooted forests, sparse graph limits and statistical mechanics, dense graph limits and graphons.

(3) Metastability of spin-flip dynamics on random graphs, spontanenous synchronisation in brain networks, reaction-diffusion on sparse random graphs.

Teaching and co-organisation
The UL node has developed courses on complex networks for bachelor students of mathematics, computer science and physics (UL Faculty of Science), and for master students of mathematics (through MasterMath). Lecture notes are available. All PhD candidates and PDs have their own topic of expertise, but there are training programmes that give them a broad view on the mathematical aspects of networks. The scientific training programme provided by NETWORKS comprises the following activities each year: two Training Weeks, three specialised workshops, and two NETWORKS days where all members of NETWORKS meet. Once every three years, NETWORKS organises a major international conference on networks, attracting researchers worldwide. All these activities are open to PhDs and PDs outside NETWORKS as well. The Leiden Complex Networks Network (LCN2) is a seminar series that brings together scientists from different disciplines, based on their common interest in both theoretical models and empirical analyses of networks.

Outreach
The UL node has been involved in various outreach events. For example, for high-school students there is NETWORKS Goes to School and there are Pre-university college projects, while for the general public there is a dedicated webpage called The Network Pages, which is an interactive web portal aimed at a broad audience interested in network science. In addition, there are activities like KNAW evening symposia, Studium Generale UL, Meet the Professor at the Dies of UL, Leiden City of Science 2022.

Future
The UL node is in the process of expanding its research scope and collaboration to the social and economic sciences, and to biomedical research groups at LUMC (Leiden University Medical Centre). The COFUND PhDs are expected to do an internship, which opens up collaboration with the research wing of engineering companies.

Case study II – Personalized cancer care by optimizing chemotherapy and surgery for bone cancer patients

Marta Fiocco and her team develop mathematical methods and prediction models for a wide variety of cancer therapies. This research is executed in interdisciplinary teams involving oncologists, surgeons and radiologists at Leiden University Medical Center (LUMC) and the Prinses Máxima Centre for child oncology. Two recent studies on the treatment of bone cancer illustrate the contributions of Fiocco's group.

Optimizing bone cancer chemotherapy
Osteosarcoma is an aggressive bone cancer, which typically occurs in childhood. The standard treatment involves the surgical (partial) removal of the tumor followed by several cycles of chemotherapy. The effect that different combinations of cytotoxic drugs, drug dosages and time to complete chemotherapy regimens have on the survival outcome is still unknown. Possible reduction in cytotoxic drug dosage and increased time to complete the regiment are desirable since patients often experience severe side effects from the toxic drug regiments. The aim of this research was to develop proper mathematical tools to investigate the effect of the received dose-intensity on survival, by using a large cohort of osteosarcoma patients who were treated with neo-adjuvant chemotherapy in randomized and non-randomized studies from six European osteosarcoma study groups.

Fiocco and postdoc Carlo Lancia developed an innovative method to measure the mismatch between target and achieved dose intensity of chemotherapy. Chemotherapy data are complex because their longitudinal nature encompasses many clinical details like composition and organization of multi-drug regimens, or dynamical therapy adjustments to the patient's toxicity history. The novelty of the method is its focus on these clinical dynamical processes of therapy adjustment and the causal effect on the outcome. This novel method was used to address the association between received dose intensity and survival of osteosarcoma patients from a randomized chemotherapy trial. An important conclusion of the research project was the benefit of approaching treatment intensification at a more individualized level, in particular the possibility of reducing chemotherapy doses. The research revealed the benefits of analyzing longitudinal data by showing why such a level of detail is needed for both treatment and adverse event data.

Optimizing bone cancer surgery
The standard treatment for patients with high-grade sarcoma of the extremities involves surgical resection of the tumor followed by radiotherapy. A difficult decision in this treatment concerns the size of the tumor margins, balancing between removing all of the tumor necessary for cure while preserving as much as possible of the extremities to optimize quality of life afterwards. Again, risk prediction models are not only scarce, but also have little validity. The aim of this research was to build a prognostic model for high-grade sarcoma patients, to predict survival outcomes from diagnosis and surgery and to develop an online prediction model to guide clinicians in the medical decision process.

Marta Fiocco and PhD candidate Anja Juana Rüten-Budde developed a dynamic prognostic model for high-grade sarcoma tumor of the extremities to predict survival outcomes at the time of diagnosis and during treatment. The model combines patients, treatment-specific and time-dependent variables such as local recurrence and distant metastasis. The model provides accurate survival predictions throughout follow-up, which serve as an important guide for clinicians in deciding on the size of the resected tumor margins.

Relevance for cancer patients: personalized medicine
The first project contributes to the development of personalized precision medicine by addressing the relationship between dose intensity and survival of individual patients. The novel method developed by Fiocco and Lancia has impact on the drafting of future trials, because it revealed that longitudinal treatment data could be used to link survival outcome with drug metabolism. The second project has generated an important model to predict the survival of individual patients. As part of the study, Fiocco and Rüten-Budde developed an app for clinicians to monitor disease progression during follow-up, available through the PERSARC (Personalized Sarcoma Care). Rüten-Budde received the C.J. Kok Prize 2020 for the best PhD thesis of the Science Faculty of Leiden University for this research.

There is increasing interest to extend results of this nature to many other types of cancer. The concept of dynamic prediction that was used in both research projects provides predictions of overall survival at different times during follow-up, which will certainly be of tremendous support for clinicians and patients to make proper decisions in cancer treatment. These research lines are hence being continued by PhD candidates Maria Benedito Quelhas (cure models) and Marta Spreafico (time varying covariates for survival models), with further involvement from Hein Putter and Mirko Signorelli at the MI and collaborators from the University of Amsterdam (Eni Musta) and Milano politecnico (Francesca Ieva).

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- C. Lancia, J. K. Anninga, C. Spitoni, M. R. Sydes, J. Whelan, P. C. W. Hogendoorn, H. Gelderblom and M. Fiocco, *Method to measure the mismatch between target and achieved received dose intensity of chemotherapy in cancer trials: a retrospective analysis of the MRC BO06 trial in osteosarcoma.* BMJ Open (2019).
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- J. Rueten-Budde, C. Liu, A. Ranft, U. Dirksen, H. Gelderblom and M. Fiocco, *Dynamic prediction of overall survival: a retrospective analysis on 979 patients with Ewing sarcoma from the German registry*. BMJ open 10(10) (2020).

Grants

- Meta-analysis of individual patient data to investigate dose-intensity relation with survival outcome for osteosarcoma patients. Funding KIKA (Stichting Kinderen Kankervrij).
- Personalized Sarcoma Care: predicting outcome and improving the balance between prognosis and quality of life for sarcoma patients. Funding KWF (Kankerbestrijding Nederland).

Case study III – Rational Points

Pythagoras' Theorem states that the sides $a < b < c$ of a right-angled triangle satisfy $\mathrm{a}^2 + \mathrm{b}^2 = \mathrm{c}^2$. Before Pythagoras, in old Babylonia and India, it was already known that this equation has infinitely many solutions in *integral* numbers, such as $(a, b, c) = (3,4,5)$ or $(5,12,13)$; such triples were used in the precise construction of altars.

It follows from Pythagoras' Theorem that the unit circle in the xy-plane is given by the equation $x^2 + y^2 = 1$; the triples above correspond to the points $\left(\frac{3}{5}, \frac{4}{5}\right)$ and $\left(\frac{5}{13}, \frac{12}{13}\right)$ on this circle, with rational numbers as coordinates. The infinitely many solutions mentioned above correspond with infinitely many of such *rational points* on the circle.

More generally, *Diophantine equations* are polynomial equations to which we are looking for rational solutions. By viewing these rational solutions as rational points on the *varieties* described by the equations, we open the door for a plethora of tools from algebraic geometry, a field that has become indispensable in the study of Diophantine equations.

Moreover, it magically turns out that the *geometry* of these varieties governs their *arithmetic*, which is what we call the behaviour of the rational points. For example, in the one-dimensional case of curves, such as the circle, we can associate to each curve a geometric invariant, called its *genus*; a celebrated theorem by Faltings (1983) states that if the genus is at least 2, then there are only finitely many rational points on the curve. The modern study of rational points goes beyond this in at least the following two directions.

(A) To describe as precisely as possible the set of rational points on one concrete variety; for curves of genus at least 2 this entails finding all finitely many rational points and proving there are no others. (Faltings' Theorem gives no information on the number of them.)
(B) To investigate the amazing extent to which the geometry of a variety affects its set of rational points in *higher* dimensions.

Fermat's Last Theorem consists of infinitely many examples of (A): for each natural number $n > 2$, there are no rational points on the curve given by $x^n + y^n = 1$ besides the trivial points with x or y equal to zero. Wiles' proof of this theorem, based on *modular forms* and *elliptic curves*, shocked the world in 1993/1994. The following year, Boston University hosted a large 10-day conference dedicated to this proof. No fewer than five of the authors of the popular associated book are currently affiliated with our Mathematical Institute: **Edixhoven**, **Lenstra**, **Schoof** (guest appointment), **De Smit**, **Stevenhagen**.

The presence of these world leaders in Number Theory and Algebraic Geometry has made Leiden the perfect breeding ground for the field in between, also known as *arithmetic geometry*, which studies rational points. Indeed, it is fair to say that Leiden is currently one of the world's most active hubs in the study of rational points.

One of the current hot topics in (A) is *Quadratic Chabauty*, the most advanced tool for proving one has found all rational points on a curve of genus at least 2. **Vonk** is an expert on Quadratic Chabauty, having co-authored the famous paper [Annals of Math., 2019] in which they prove that the so-called *Cursed Curve* contains exactly 7 rational points. This paper has been the main object of various research seminars around the world, and has even featured in XKCD. Edixhoven shocked the field by realising a *geometric version* of Quadratic Chabauty [J. Inst. Math. Jussieu, 2021] and was invited to present this at the famous Arizona Winter School. Vonk and Edixhoven make Leiden the world's leading center on Quadratic Chabauty.

The work of **Derickx** (guest appointment) on determining rational points on so-called *modular curves* over number fields also fits perfectly in (A).

Bright and **Van Luijk**'s work fits mainly in (B). Bright is an expert on *Brauer-Manin obstructions* in particular on *K3 surfaces*. This is an advanced tool to prove that some varieties have no rational points at all, and combines deep knowledge from both Algebraic Number Theory and Algebraic Geometry. Bright and Van Luijk are working on a book on the subject, together with Testa (Warwick). Van Luijk is known for his work on rational points on *elliptic surfaces*, as well as an analog of the *Manin conjectures* for K3 surfaces, predicting the asymptotic growth of the number of rational points of bounded *height* (i.e., maximum of the occurring numerators and denominators), as the height goes to infinity. **Bruin**'s work on counting elliptic curves of bounded height comes down to counting rational points on certain so-called *stacks*, and also fits perfectly in this framework.

Heights happen to also be the expertise of **De Jong** and **Holmes**, whose other expertise on *Arakelov theory* and *Néron models* are of tremendous importance to the study of rational points as well. Both have written seminal papers on these topics. Bruin, Edixhoven and **Streng**'s expertise on modular forms, modular curves and elliptic curves are invaluable for the study of rational points.

Last but not least, **Evertse** is an expert on *Diophantine Approximation*, which has close ties with both (A) and (B). Techniques from Diophantine approximation have been successfully applied first to obtain general methods to determine the solutions of Diophantine equations from a large class, and second to obtain good estimates for their number of solutions. Together with Gyory (Debrecen), Evertse has written two books on this matter, and a third book is nearly finished.

All these **14** people are world experts on their specialisations. At the time of writing this document, they have grant applications running with NWO for a combined worth of more than 5 million euros, including a joint NWO-XL proposal with Groningen and Utrecht. We expect Leiden to continue to be a world leading hub in the field of rational points for a long time to come.

Case Study IV: Mathematical Biology in Leiden

Background
Mathematics is central to many of the natural sciences, including physics and chemistry. However, despite the enormous complexity of biological systems, paradoxically biology has long remained the least mathematically-oriented among the natural sciences. Mathematicians and physicists have long filled up this lack of mathematical theory in biology. Applied mathematicians have developed biological theory independently through ad-hoc collaborations, and soft matter physicists have developed quantitative mathematical and experimental approaches for a range of problems in the life sciences. Over the last 15 years these approaches have led to breakthroughs in the understanding of problems ranging from genetic regulation and evolution, to biological development and mechanobiology, and hence to an increased understanding and mutual appreciation of the fields. Indeed mathematical biology has come to bloom as a field: 2018 was declared the 'Year of Mathematical Biology'. It included a four-month program at the Institut Mittag-Leffler near Stockholm, Sweden organized jointly by the European Mathematical Society (EMS) and the European Society for Mathematical and Theoretical Biology (ESMTB). In his role as president of ESMTB, Prof. dr. R.M.H. Merks of the Mathematical Institute acted as lead contact for this research program.

Research approach
At the mathematical institute the rising attention and appreciation for mathematical biology has fueled ties between the Mathematical Institute and the Institute of Biology Leiden. Mathematicians Sander Hille and Bert Peletier (retired) together with biologists Bert van Duijn and Remko Offringa run the Plant BioDynamics Laboratory (PBDL). A key example of the work of the PBDL is the mathematical modeling and quantification of polar transport of phytohormone auxin through the stem of the seed plant *Arabidopsis* [1].

Following a part-time appointment at the MI since 2014, in 2018 Roeland Merks has moved to Leiden full-time as professor of mathematical biology through a joint appointment at the IBL and the MI. Merks works on a variety of biological problems, including cardiovascular development (including tumor angiogenesis) and mechanobiology, plant development, dynamics of the gut microbiota, and metabolism. He combines an independent interdisciplinary mathematical-experimental research line on angiogenesis, funded by an NWO VICI and on the evolution of multicellularity, funded through the NWA-funded Origins Center, alongside collaborative work with experimental biologists and mathematicians that is funded externally (ENW-GROOT, FrieslandCampina) as well as several projects funded through internal funding schemes.

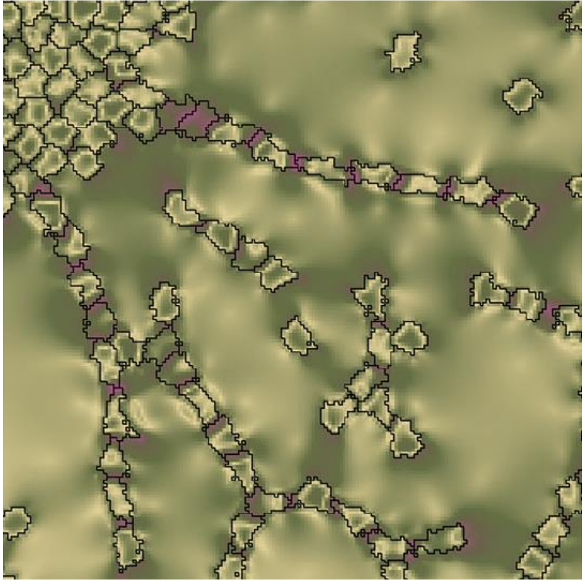

Figure 1 Pulled in line – detail of art work produced using the model in Ref. [2] and published in *The Art of Theoretical Biology* (2020) Matthäus, Matthäus, Harris and Hillen (Eds.). Springer.

Highlights over the reporting period include explanatory models of the effect of substrate stiffness and cell contractility on cell shape [2, 3, 4], performed by PhD students Koen Schakenraad [3] and Lisanne Rens [2,4]. For her series of multiscale numerical models explaining the dependence of cell shape on substrate mechanics, Rens received the prestigious H.D. Landahl Award for Mathematical Biophysics of the Society for Mathematical Biology at the Annual Meeting in Salt Lake City, UT, USA.

These models combine the stochastic cellular Potts model with ordinary-differential equations of subcellular structures called focal adhesions and a finite-element model of the deformation of the substrate. Further examples include mathematical models of the origins of multicellularity organisms [5] a novel model of zebrafish metabolism and its genetic regulation [6] (still listed among the most-read papers of the journal). Collaborative projects include three-dimensional analysis of cell motility during the embryonic development of the heart [7] and modeling of the effect of cell shape of differentiation of neurons [8].

The collaboration between IBL and the MI is part of the growing attention to life sciences within the MI. Highlights include the work of Arjen Doelman, discussed elsewhere in this report, and the work by Vivi Rottschäfer and Liesbeth de Lange (LACDR) on drug delivery in the brain [9]. Further collaborations are maintained with LION and LACDR by Merks. Investments in the fundamentals of mathematical biology include the recent hire of Frits Veerman, working on dynamical differential geometric models of morphogenesis through mechanochemical feedback models and ongoing collaborations between Merks and Hermen Jan Hupkes on analytical models of auxin transport waves and computational models of cell and extracellular matrix interactions. The

MI also contributes towards education in mathematical biology at the BSc and MSc level within the Faculty of Science (UL) and nationally and internationally through the MasterMath program and summer schools.

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