The nonlinear nature of biology

Marthe Måløy

July 22, 2018

Abstract

In this thesis I explore the stability and the breakdown of stability of biological systems. The main examples are the blood system and invasion of cancer. However, the models presented in the thesis apply to several other examples.

Biological systems are characterised by both competition and cooperation. Cooperation is based on an unsolvable dilemma: Even though mutual cooperation leads to higher payoff than mutual defection, a defector has higher payoff than a co-operator when they meet. It is not possible to represent this dilemma with a linear and deterministic model. Hence, the dilemma of cooperation must have a nonlinear and/or stochastic representation.

More general, by using a linearised model to describe a biological system, one might lose dimensions inherent in the complexity of the system. In this thesis I illustrate that a nonlinear description of a biological system is potentially more accurate and might provide new information.

The thesis is made up of three papers. Paper 3 presents the most general model which considers a relative stable population that is invaded by an alternative strategy. That is, a new type of individual is in general not advantageous when it appears in stable population. The newcomers can grow in number due to stochasticity. However, they can only become advantageous if they manage to change the environment in such a way that they increase their fitness. The model presented in paper 3 is an extension of the Moran process that captures this dynamics.

Paper 2 proposes a model that links self-organisation with symmetric and asymmetric cell division. The model assumes that cell divisions are completely random events, and that the daughter cells resulting from asymmetric and symmetric divisions are, in general equal, and still, the tissue has the flexibility to self-renew, produce mature cells and regenerate, due to self-organisation.

Paper 1 presents a model that illustrates that if symmetric stem cell division is regulated by differentiated cells, then the fitness of the stem cells can be affected by modifying the death rate of the mature cells. This result is interesting because stem cells are less sensitive than mature cells to medical therapy, and our results imply that stem cells can be manipulated indirectly by medical treatments that target the mature cells.

Acknowledgements

First I would like to thank my supervisors, Per Jakobsen and Bjørn Brandsdal, who have given me the freedom to pursuit my ideas and at the same time being available for questions and feedback. In particular, the conversations with my main supervisor, Per Jakobsen, regarding nonlinear phenomena and how models in physics can be applied to biology, have been vitally important in the process of developing the models presented in this thesis.

I would also like to thanks Rafael Lahoz-Beltrá, Juan Carlos Nuño and Antonio Bru. I learned a lot about biology and the amazing culture of Spain during my stay in Madrid in 2010.

I owe a great thanks to my supervisor for my master thesis, Boris Kruglilov, who were the first to point out to me that there is no clear distinction between deterministic and random behavior, and to the teachers of *Examen facultatum* for interesting lectures and conversations that enabled me to see my work in a in a broader context. What I learned from Boris and the philosophy teachers is the backbone of this thesis.

I must also express my gratitude to my co-author and brilliant mathematician, Frode Måløy. This thesis would not be possible without you – such a cliche, but so true. You have helped me with everything: programming, figures, proofreading. The list goes on. I would lost in the code without you.

I would also like to thanks Kristian Meisingset and the rest of editorial of *Minerva* for giving me the opportunity to write to a broader audience, for their feedback on how I can improve my writing, and for their attempts to teach me the comma rules. Many of the ideas presented in my latest scientific paper springs from the *Minerva* texts.

I have learned a lot about how to improve the efficiency of algorithms from conversations with Arthur Schuchter. But most of all, you are a really great person who have meant a lot to my family and me. When this is all over, I hope we can celebrate together on *Kvalhornet*.

I would like to express gratitude to my family for doing fun stuff with my children when their mother is being really boring. Thanks for Christmas dinners, New Year parties, fishing trips and road trips. Especially thanks to Ingrid Måløy, Torgeir Johansen, Ragnhild Rørvik and Odd Høyem.

And finally, the most amazing people in the world, Liv and Trym, and the best parent ever, Frode. I am so lucky to have you in my life. I look forwards to spend more time with you.

List of publications

The three papers that make up the thesis:

Paper 1 Marte Rørvik Høyem, Frode Måløy, Per Jakobsen and Bjørn Brandsdal Stem cell regulation: Implications when differentiated cells regulate symmetric stem cell division. *Journal of Theoretical Biology* 380, 203–219 (2015).

Paper 2 Marthe Måløy, Frode Måløy, Per Jakobsen and Bjørn Brandsdal. Dynamic self-organisation of haematopoiesis and (a)symmetric cell division. *Journal of Theoretical Biology* 414, 147–164 (2017).

Paper 3 Marthe Måløy, Frode Måløy, Rafael Lahoz-Beltrá, Juan Carlos Nuño and Antonio Bru. Extended Moran process that captures the struggle for fitness

Other contributions that serve as background material of the thesis

- Marte Rørvik Høyem. Differential Invariants of the 2D Conformal Lie Algebra Action. *Acta Applicandae Mathematicae - An International Survey Journal on Applying Mathematics and Mathematical Applications* 109, 61–73 (2010).
- Marthe Måløy. Samarbeid for selvbevisste. Minerva 25.08.2016 *https://www.minervanett.no samarbeid-for-selvbevisste/.*
- Marthe Måløy. Immunterapi må tilbys til alle. Minerva 20.09.2016 *https://www.minervanett.no/immunterapi-ma-tilbys/.*
- Marthe Måløy. Hvordan vet kroppen vår når vi trenger mye blod, og når vi trenger lite? Forskning.no 12.04.2017 *https://forskning.no/menneskekroppen-blod/2017/04/hvordan-vet-kroppen-var-nar-vi-trenger-mye-blod-selvregulering.*
- Marthe Måløy. CRISPR kan revolusjonere behandlingen av kreft og genetiske sykdommer. Minerva 17.08.2017. *https://www.minervanett.no/crispr-revolusjonere-behandlingen-kreft-genetiske-sykdommer/.*
- Marthe Måløy. Helse-Norge bør ta i bruk nye og dyre medisiner. Minerva 04.11.2017 *https://www.minervanett.no/helse-norge-bor-ta-bruk-nye-dyre-medisiner/.*
- Marthe Måløy. Frp blør legge innvandrings—og integreringsministeren på bordet. Minerva 15.12.2017 *https://www.minervanett.no/frp-bor-legge-innvandrings-integreringsministeren-pa-bordet/.*

Contents

Part I

Introduction

The fundamental and defining principles of evolutionary theory are replication, selection and mutation [1]. Based on these three principles, it is possible to describe a biological system with mathematical equations. However, since living organisms reproduce, die and change strategy based on feedback from their environment, it is very hard to derive a mathematical model that is both general and gives an accurate description of a specific biological system.

An important question, both in this thesis as well as in mathematical modelling in general, is what level of complexity should be included in a model. For instance, flipping a coin could be represented by an extremely complex model that includes Newton's laws, the laws of thermodynamics and so on. However, a simple stochastic model, with equal probability of head and tail, is in general better.

For similar reasons, a very simplistic and stochastic model might be the best representation of blood formation, in general. That is, *haematopoiesis* is the generation of blood, and at the root of this process is a small group of slowly replicating cells, called the *haematopoietic stem cells* [2], [3], which have the capability to maintain themselves through *self-renewal* and produce mature blood cells through *differentiation*. Under normal conditions, the number of haematopoietic stem cells is approximately constant, and Lenaerts et al. [4] show that the haematopoietic stem cells dynamics can be described by the Moran process, which represents the simplest possible model of stochastic evolutionary dynamics in a finite population. However, the production of mature blood cells increases after blood loss, and research results by Gokoffski et al. [5] indicate that the number of haematopoietic stem cells increases when the number of mature blood cells decreases. A deterministic model of haematopoietic stem cell dynamics with only one regulation mechanisme, such as the model presented in paper 1, can give a better description of these specific data than the Moran process. Nevertheless, as I make a case for in Section 2, because the regulation of haematopoiesis is an extremely complex process, a model that treats stem cell behaviour as purely random events fits general data better than a deterministic model with a single regulation mechanism.

In a nutshell, if a process is "very complex", it is in general better to use a simple stochastic model, than a complex deterministic model. However, as discussed more thoroughly in Section 6, machine learning and neural networks challenge the concept of "very complex". That is, neural networks will almost certainly have a transformative impact on modelling high-dimensional complex systems in the years to come. Neural networks have challenged traditional mathematical models and outperformed competing methods without providing clear evidence why they are doing so [6].

1 Nonlinearity can generate stochasticity

A human child has 23 chromosomes from each parent and these chromosomes contain basic genetic rules. However, a child is more than half of each parent, and this illustrates why linear representation of genetic information is problematic because linear equations cannot produce something new. On the contrary, nonlinear rules can actually produce something new and unexpected. That is, even a very simple nonlinear relation can generate complex patterns that no mathematical tools can penetrate. A good example is the logistic map

$$Y_{T+1} = 4Y_T(1 - Y_T), \tag{1}$$

which is described in more details below.

In a nutshell, a linear mathematical equation is easy to understand and simple to solve, whereas a nonlinear mathematical equation might be hard or even impossible to understand and solve, and it can generate new knowledge. Since living organisms reproduce, die, and change strategy based on feedback from their environment, their behaviour is seldom captured by linear equations. Even some of the simplest biological systems require nonlinear representations. This is illustrated below, where it is shown how the behaviour of a system of replicating individuals changes dramatically when the description changes from linear to nonlinear, when time is represented by time steps instead of a continuous variable, and when the feedback from the environment is delated.

1.1 Population growth

When a population is in an isolated environment, only replication can change the population size. Suppose that the function $x(t)$ describes the size of an isolated population at time t, and that the derivative of $x(t)$ with respect to t, $\frac{\mathrm{d}x}{\mathrm{d}t}$, exists. Let b and d denote the birth rate and the death rate, respectively. Since all changes in $x(t)$ are caused by birth or death, we have that

$$\frac{\mathrm{d}x}{\mathrm{d}t} = bx(t) - dx(t) = rx(t), \tag{2}$$

where $r = b - d$. If r is a constant, then the differential equation given above is linear and have solutions on the form

$$x(t) = x(0)\exp(rt), \tag{3}$$

where $x(0)$ is the population size at time $t = 0$. Moreover, if r is positive, then $x(t)$ describes a growing population in an isolated environment where there is no competition for resources. Nevertheless, a population cannot expand infinitely. Eventually, resources become limited, and then competition occurs. Ecologists have introduced a variety of modifications to the linear differential equation given in (2) to take account of saturation effects. The main idea in all of them is to reduce the growth as $x(t)$ becomes large. One approach is the differential equation

$$\frac{\mathrm{d}x}{\mathrm{d}t} = rx(t)\left(1 - \frac{x(t)}{C}\right), \tag{4}$$

where the constant C is the carrying capacity of the population. As discussed in the beginning of the introduction, most nonlinear problems are very hard, and sometimes even impossible, to solve. However, the differential equation in (4) is one of relatively few nonlinear problems that have neat solutions, namely

$$x(t) = \frac{Cx(0)\exp(rt)}{C + x(0)(\exp(rt) - 1)}, \tag{5}$$

where $x(0)$ is the population size at time $t = 0$.

Some populations nurture their offspring before these reach reproductive age, and in this case it might be better to include different generations. The following nonlinear recurrence relation captures this competition dynamics:

$$X_{T+1} = RX_T\left(1 - \frac{X_T}{C}\right), \tag{6}$$

where T is a non-negative integer denoting time steps, X_T is the population size at time step T, and R is a positive constant less than or equal to 4. Like for the continuous differential equation given in (4), C is the carrying capacity. But in contrast to the continuous case, if the population described by the discrete representation reaches the the carrying capacity, the population will get extinct the next time step. The reason why the behaviour of the discrete description of the population is very different from the continuous description, is that the feedback from the environment is implemented differently in the two cases.

By substituting the function $Y_T = X_T/C$ into the recurrence relation given in (6), we obtain the logistic map

$$Y_T + 1 = RY_T(1 - Y_T).$$

The logistic map does not have any neat formula for the solution in terms of T. However, for $R < 4$ it is possible to predict the outcome of the logistic map by using advanced mathematical analysis [7]. On the contrary, for $R = 4$ we obtain the logistic map given in Equation (1). It has been proved that the statistical mechanics of this system has exactly the same statistical properties as a random system. Actually, according to Ian Stewart [7]: "Random means that no obvious structure exists, but that on average we can say various things, such as how often the values occur in a given range. Random has carried the connotation of *indeterministic*, that is, a system is deterministic if it follows exactly some regular law, random if not". Nevertheless, the logistic map given in (1) shows there is no clear distinction between deterministic and random behaviour, because this map is a deterministic system which behaves randomly.

2 Randomness and self-organisation

The logistic map given in Equation (1) is an example of a deterministic equation which behaves randomly. And in point of fact, for deterministic, nonlinear, dynamical systems, strange attractors, chaos and random behaviour are the rule rather than the exception, and as the number of variables increase, the phenomena become more peculiar [8].

The DNA of cells in a multicellular organism contains deterministic rules. However, complex and nonlinear interactions between cells can create patterns that not only seem totally random, but that actually are random. Furthermore, it is possible that the organisms make use of the randomness, because randomly organised systems can exhibit *self-organisation* which is a spontaneous order that arises from local interactions between parts of an initially disordered system. This possibility is explored in the next subsection.

2.1 Haematopoiesis and self-organisation

Even though the haematopoietic system in a healthy adult is stable and robust, the behaviour of each blood cell seems chaotic and random. This indicates that haematopoiesis is a self-organised process.

A healthy adult contains about five litres blood, which corresponds to about 37×10^{15} blood cells. Each day, the body produces around 10^{15} blood cells. Thus, most of the cells in the haematopoietic system is replaced each month [9].

At the root of the blood forming process are the haematopoietic stem cells, which are located within the bone marrow and segregated among different bones throughout the body. The haematopoietic stem cells differentiate into progenitor cells, which differentiate into red blood cells, white blood cells or platelets, through sequential division. Since the number of haematopoietic stem cells is much smaller than the number of more differentiated blood cells,

the haematopoietic stem cells must be tightly regulated and protected. The haematopoietic bone marrow niches may be crucial in both aspects [10], [11]. Since a niche cannot be reconstructed experimentally, it is difficult to study haematopoietic stem cells in vitro, because stem cell survival, self-renewal and differentiation are regulated by signals from the niche. Hence, relatively little is known about the exact behaviour of haematopoietic stem cells. For example, when a haematopoietic stem cell divides, exactly what determines whether a daughter cell becomes a stem cell or starts to differentiate, is still unclear. This is related to the symmetry of the stem cell division, which is discussed in the next subsection.

2.2 Symmetric and asymmetric stem cell division

An important concept related to stem cell self-renewal and differentiation, is the symmetry of the stem cell division. That is, an asymmetric stem cell division results in one daughter cell that has stem cell identity, and another daughter cell that starts to differentiate, whereas a symmetric stem cell division generates two daughter cells that are destined to the same fate [12], [13]. There are two types of symmetric stem cell division, namely *symmetric self-renewal*, which results in two stem cells, and *symmetric differentiation*, where both daughter cells start to differentiate. Under normal conditions, the number of cells in a given tissue is approximately constant, and the stem cells differentiate and self-renew at relatively constant rates to replace mature cells and to keep the stem cell number at a certain normal level [14], [15]. By dividing asymmetrically, the stem cells manage to both self-renew and produce differentiated cells in a single division. However, a disadvantage of asymmetric stem cell division is that it leaves stem cells unable to expand in number. It is, in general, believed that the stem cells can regenerate [12], [13]. For instance, haematopoietic stem cells can expand rapidly in response to injury to the bone marrow, such as stem cell transplantation [16]. Hence, asymmetric self-renewal cannot be the complete story, since it leaves stem cells unable to expand in number. The number of stem cells increases by one after symmetric self-renewal. Since the haematopoietic bone marrow can regenerate after injury, it is likely that the rate of symmetric self-renewal depends on the number of haematopoietic stem cells. On the contrary, the number of stem cells decreases by one after a symmetric commitment. Thus, the two types of symmetric divisions must occur at the same rate under normal conditions.

As discussed more thoroughly in paper 2, several experiments on Safari cats by Abkowitz et al. indicate that haematopoietic stem cells divide mostly asymmetrically under normal conditions, whereas when the haematopoietic bone marrow niche regenerates after injury, the haematopoietic stem cells start to divide symmetrically [16], [17], [18]. But does this mean that a stem cell somehow "knows" that it must divide asymmetrically under normal conditions and self-renew symmetrically when stem cells need to be replaced? This would also mean that the daughter cells inherit this "knowledge". However, as discussed in paper 2, the assumption that each cell "knows" how to behave in different situations is too rigorous and potentially misleading. Thus, it is more likely that each stem cell behaves completely random. Nevertheless, the stem cells divide mostly asymmetrically under normal conditions and symmetrically under regeneration, due to dynamic regulation and self-organisation in the haematopoietic bone marrow niche.

As discussed more thoroughly in paper 2, several experiments on *Drosophila* germline stem cells indicate that the stem cell niche can contain up to a certain number of cells, and that the niche is approximately full under normal conditions. When a stem cell divides, one of the daughters inherits the mother's place in the niche and retains stem cell identity. The fate of the second daughter depends on whether there is a vacant place in the niche or not. In the first case, the second daughter daughter remains in the niche and retains stem cell identity. If the niche is full, the second daughter is placed outside the niche, and loses its stem cell identity. Thus,

research on *Drosophila* germline stem cells indicates that the stem cells do not "know" whether they must divide asymmetrically or symmetrically. That is, the stem cells divide randomly, and the availability of the niche, and perhaps some other factors, determines whether the division is asymmetric or symmetric. This implies that an undifferentiated cell must be in the niche to function as a stem cell: Once a cell is placed outside the niche, it is no longer a stem cell.

3 Moran process and the invasion of mutants

As discussed in the previous subsection, under normal conditions, the rate of symmetric self-renewal must equal the rate at which the stem cells leave the niche, and in this case, the haematopoietic stem cell dynamics can be described by the Moran process, which assumes that the population size is constant and that at each time step, a random cell is selected to self-renew symmetrically and a random cell is selected to leave the growth environment. Dingli et al. present a version of the Moran process which includes all types of stem cell division [19]. However, for simplicity, we only consider symmetric stem cell division here.

Genetic changes called *mutations* can occur in any cell that divides [20]. Even though most mutations are harmless to the body, progressive accumulation of mutations can lead to cancer [21].

Results from theoretical work indicate that the tissue architecture of the haematopoietic system, where only a small number of stem cells have the ability to self-renew, has evolved to minimise the risk of malignant transformations [19]– [22]. That is, if a mutation occurs in a mature blood cell, it is likely to be washed out of the system before it becomes a cancer phenotype, because these cells do not self-renew. On the other hand, a mutation in a haematopoietic stem cell can generate a different type of stem cell, denoted *mutant stem cell*. This leads to an evolutionary process with competition between the mutant stem cells and the normal stem cells [1]. Lenaerts et al. [4] show that this competition dynamics might be captured by the Moran process. That is, the Moran process assumes that initially, all the stem cells are normal. When a normal stem cell self-renews, a mutation that creates a mutant stem cell occurs with probability u. The normal stem cell self-renews at rate 1 whereas the mutant stem cells self-renew at rate r. All stem cells are selected to leave the niche at the same rate. Hence, the mutant type is advantageous if $r > 1$, neutral if $r = 1$ and disadvantageous if $r < 1$. At each time step, the number of mutant stem cells can either increase by one, remain constant or decrease by one. The probability for these three events are

$$P(i+1|i) = \frac{u(N-i)+ri}{N-i+ir}\frac{N-i}{N}, \tag{7}$$

$$P(i-1|i) = \frac{(1-u)(N-i)}{N-i+ir}\frac{i}{N}, \tag{8}$$

$$P(i|i) = 1 - P(i+1|i) - P(i-1|i), \tag{9}$$

respectively, where N is the number of stem cells in the niche and i is the number of mutants. If u is sufficiently small, the mutant type typically has time to take over the whole niche or get extinct before another mutant is created from the normal type. By using the approximation $u \approx 0$, Wodarz and Komarova [23] show that the probability that i mutant stem cells eventually invade the whole niche is

$$\rho_i = \frac{r^{N-i}\left(1-r^i\right)}{1-r^N} \tag{10}$$

if $r \neq 1$ and

$$\rho_i = \frac{i}{N} \tag{11}$$

if it is a neutral Moran process, i.e. $r = 1$.

The reason why the mutant type can invade the whole niche, starting from a single mutant stem cell, is that the stem cells self-renew symmetrically. Note that if the stem cells only divided asymmetrically and no new mutation in a normal stem cell occurred, the number of mutants would remain constant. However, most type of cancers require more than one mutation, and it is illustrated in the paper by Shahriyari and Komarova [24] that symmetrically dividing cells can delay a second mutant production compared to an equivalent system with only asymmetrically dividing stem cells. More precisely, if stem cells only divide asymmetrically, then a mutation acquired in a stem cell will remain in the system indefinitely, and it is only a matter of time before the second mutation occurs. On the contrary, a mutant stem cell generated in a symmetric division has a less certain fate – half of the lineages will differentiate out after the very first division and only 1/K of all lineages will expand to size K. Thus, that the uncertainty of the fate of single mutant stem cells can be the reason for the statistically longer time it takes for the symmetrically dividing stem cell model to produce a double-hit mutant.

Unlike most types of cancers, the first phase of *chronic myeloid leukaemia* is caused by a single mutation in a haematopoietic stem cell that creates a *leukemic stem cell*. Since the mutation rate from normal cells to leukemic cells is nonzero, it follows from the Moran process that any person will eventually develop chronic myeloid leukaemia, given that he or she has a sufficiently long life. This might seem to contradict the phrase *the survival of the fittest*, that originated from Darwinian evolutionary theory as a way of describing the mechanism of natural selection. However, as discussed more thoroughly in the next sections, the cooperation among cells in a multicellular organism is based on an unsolvable dilemma, and, hence, it will sooner or later dissolve. So maybe we should rather say: *the survival of the one that keeps it together until after successful reproduction.* That is, the one thing that protects us from most types of cancer, is death.

4 The rise and fall of unconditional co-operators: the prisoner's dilemma and evolutionary stable games

There are approximately 5×10^{30} bacteria on Earth, and their biomass exceeds that of all plants and animals. Bacteria are present in most habitats: soil, water, radioactive waste, acidic hot springs, the deep portions of Earth's crust as well as in symbiotic and parasitic relationships with plants and animals. Furthermore, bacteria were among the first life forms and will most likely exist longer than multicellular organisms. It might seem like a mystery that multicellular organisms evolved from bacteria about 1.5 billion years ago, given that bacteria in so many ways are fitter than multicellular organisms.

The first life forms adopted the most basic strategy, which is to outcompete other individuals by dividing as fast as possible, when life started to evolve about four billion years ago [1]. Nevertheless, proliferation requires resources such as nutrient molecules and space, and different individuals can have access to different resources. Thus, cooperation can be beneficial in these situations [25], [26]. A simplified example of cooperation among single-celled organisms is that one cell has access to enough nutrient molecules for two cell divisions but no space, whereas another cell has access to enough space for two cell divisions but no nutrient molecules. Hence, if both cells share their resources, i.e. mutual cooperation, they will both reproduce. On the

contrary, if both cells do not share their resources, i.e. mutual defection, none of the cells reproduce. However, if only one cell shares its resources and the other does not share, then the co-operator does not reproduce and loses its resources whereas the defector reproduces twice. This simple example illuminates the dilemma of cooperation: even though mutual cooperation leads to higher payoff than mutual defection, a defector has higher payoff than a co-operator when they meet. Indeed, this example is a version of the well-known game called the prisoner's dilemma [1]. Moreover, it illustrates why unconditional cooperation is an unstable strategy: Consider a group of co-operators. If a mutation causes a cell to change strategy to defection, this cell increases its payoff. On the contrary, a strategy is a *Nash equilibrium* if no player, which in our example are cells, can deviate from this strategy and increase its payoff [27]. Defection is a Nash equilibrium both in our example with cells and in prisoner's dilemma in general, because if a defector mutates into a co-operator, it increases its payoff.

A Nash equilibrium is also an evolutionarily stable strategy if selection opposes the invasion of an alternative strategy [25]. That is, if a sufficiently large population adopts an evolutionarily stable strategy, it cannot be invaded by a alternative strategy that is initially rare. For prisoner's dilemma, defection is an evolutionarily stable strategy. Hence, co-operators cannot invade a large population of defectors. However, as illustrated by the Moran process, a relatively small group of defectors can be invaded by co-operators. Moreover, if the co-operators develop regulation mechanisms that control the cooperation, for instance by modifying the microenvironment such that the defectors lose their advantages, then the group can survive in the long term. Indeed, the evolution of multicellular organism was driven by increasingly advanced regulation mechanisms among cooperating cells [1].

5 Evolution of multicellular organisms: From randomness to strict regulation and back

The healthy life and development of an advanced multicellular organism, for instance a human being, depend upon the cooperation between millions of cells. Nevertheless, as discussed in Section 4, unconditional cooperation, such as the cooperation given in the prisoner's dilemma, is an unstable strategy. Hence, cooperation among cells in an advanced multicellular organism must be regulated by by a complex network of cellular checkpoints and signals.

Multicellular organisms consists of more than one cell. Similar to single-celled organisms that belong to a colony, the cells in a multicellular organism must cooperate. Be that as it may, even the simplest multicellular organisms have cells that depend on each other to survive, whereas the single-celled organisms that live in colonies, can survive on their own.

Multicellular organisms evolved from colonies of single-celled organisms. As discussed in the previous section, cooperating cells are vulnerable to mutants that change strategy to defection since these cells can invade the colony by exploiting the cooperation.

In paper 3, an extension of the Moran process with non-constant fitness is presented. This model captures the competition between co-operators and defectors, but also how the co-operators can change their environment such that the fitness of the defectors is reduced.

Advanced multicellular organisms, such as human beings, are maintained by very complex regulation networks. And, as illustrated in Section 1, as interactions get more complex and nonlinear, they can generate chaos and random behaviour. Indeed, as discussed in Section 2, it is possible that advanced multicellular organisms have evolved to make use of the randomness that is generated by the complexity of the multiple signals.

5.1 Multicellularity and cancer

The cooperation among cells in a multi-cellular organism is regulated by advanced control mechanisms that promote stability for a relatively long time. Nevertheless, multicellular organisms and all other forms of cooperation will eventually break down because natural selection favours defection.

Since children need care of for several years, humans must have a long life to reproduce successfully. As discussed in Section 3, mutations can occur in any cell that divides [20], and even though most mutations do not harm the body, progressive accumulation of mutations can lead to cancer. That is, mutations in the genetic code can make a cell ignore signals from other cells. For example, a mutant cell can divide when it is not needed and fail to undergo apoptosis. In general, mutant cells that stop cooperating are attacked by the defence system of the body, for instance killer T-cells. Thus, as discussed more thoroughly in paper 3, mutant cells are in most cases disadvantageous when they first appear in the body. However, if the mutant type manages to change the microenvironment such that at least some variants of the mutant cells become advantageous, the mutant type is likely to spread and cause cancer, which is the breakdown of cellular cooperation. That is, cancer is really a calculated risk of multicellularity: Cooperation is not a stable state, and hence, it will eventually break down. Control mechanisms increase the probability that the cooperation lasts long enough to lead to successful reproduction. However, there is no guarantee that mutations create defective cells that escape the control network and destroy the body.

Some cancer cells are programmed to adopt the strategy of primitive single-celled organisms: divide as fast as possible and outcompete all other cells. Healthy human cells cannot survive on their own. On the other hand, cancer cells might behave more like single-celled organisms and in some cases they can survive on their own. An example is the HeLa cell line, which are the cancer cells of Henrietta Lacks who died of cervical cancer in 1951. The HeLa cell is still used for scientific pursuits [28].

As discussed more thoroughly in Section 11, even though treatment for cancer and other genetic diseases are getting better every year, many types of cancer are so complex that we might never fully understand them. Nevertheless, machine learning and deep neural networks challenge the concept of "very complex", and will almost certainly have a transformative impact on modelling high-dimensional complex systems, such as cancer, in the years to come.

6 Machine learning

Machine learning enables computer systems to learn through progressively improving performance on a specific task. That is, the computer system is not explicitly programmed, but uses statistical techniques on big data. Deep neural networks are a type of machine learning that is inspired by biological neural networks. Deep neural networks have become the dominant mining tool for big data applications in the last decade, and it is expected that this type of machine learning will make their mark in the general area of high-dimensional, complex dynamical systems [6].

Neural networks are inspired by the work of Hubel and Wiesel on the primary visual cortex of cats [29], which they won the Nobel prize for. Their experiments demonstrated that neuronal networks were organised in hierarchical layers of cells that process visual stimulus. The first mathematical model of a neural network was presented in 1980 by Fukushima et. al [30], but up until the last decade, the neural networks have not been widely used. The recent success of deep neural networks has two major reasons [6], namely:

1. The continued growth of computional power.

2. Exceptionally large labelled data sets which take advantage of the power of multi-layers (deep) architecture.

Despite the success of deep neural networks, several basic questions remain wide open, for instance:

1. How many layers are necessary for a given data set?
2. How many nodes at each layer are needed?
3. How big must my data set be to properly train the network?
4. What guarantees exist that the mathematical architecture can produce a good predictor of the data?
5. What is the uncertainty and/or statistical confidence in deep neural network output?
6. Can I actually predict data well outside my training data?
7. Can I guarantee that I am not overfitting my data with such a large network.

The next decade will most likely witness significant progress in addressing these issues.

Part II
Results

In this part, the three papers which make up the thesis, are presented and discussed.

Paper 3, which was published in 2018, presents a model that capture the dynamics that occurs when a relatively stable population is invaded by an alternative strategy. Since this model is the most general, it is discussed first. Paper 2 was published in 2017 and presents a model of haematopoiesis that links self-organisation with symmetric and asymmetric cell division. This model can reproduce several experimental results. In paper 1 from 2015 we use a mathematical model to show that if symmetric cell division is regulated by differentiated cells, then changes in the population dynamics of the differentiated cells can lead to changes in the population dynamics of the stem cells.

7 Paper 3: Extended Moran process that captures the struggle for fitness

Natural selection can cause evolution if there is enough variation in a population. When a mutant is generated in a stable population, the ability to create new variants is important for the mutant type if it is going to have any chance to invade the population. However, as discussed in Section 4, no individual has anything to gain from changing only its strategy in an evolutionary stable population [27], and this indicates that the mutant type must also change its environment to become advantageous.

That is, when a mutant is generated in a relatively stable population, it is most likely not advantageous. However, the number of mutants can grow due to stochasticity, and indeed, the mutants can invade a relatively small population, as illustrated by the Moran process presented in Section 3. Nevertheless, the mutants become advantageous only if they change their environment such that their fitness increases. This dynamics was present in the evolution of cooperation among bacteria and multicellularity [26], [31], [32], the invasion of cancer [33] and evolution of ideas that contradict social norms [34], [35]. In paper 3, we propose an extension of the Moran process with non-constant fitness that captures this dynamics. To be ore specific, individuals of the population can change the environment in such a way that the fitness landscape of the population is modified. That is, the model presented in paper 3 captures the struggle for fitness as well as the competition between different types of individuals.

Interestingly, the model can capture the invasion of defection as well as invasion of co-operators. That is, unconditional co-operators are expected to be exploited until they are extinct if they appear in a large group of defectors. The best possible scenario for this type of co-operators is that they manage to change their environment such that another type of co-operators that only cooperate under certain conditions, becomes advantageous. Similarly, when defectors appear in a regulated cooperation, the first generation of defectors typically dies while changing the environment such that coming generations become more advantageous.

7.1 Invasion of co-operators

As discussed in Section 4, it might seem like a mystery that multicellular organisms evolved from bacteria since natural selection favours defection over cooperation. The model presented in paper 3 illustrates that a small group of co-operators can invade a large population of defectors if they manage to change the environment such that defection becomes a disadvantageous strategy. That

is, the model presented in paper 3 assumes that initially the population dynamics is captured by a neutral Moran process, described in Subsection 3, and that all the individuals in the population are single-celled organisms that defect. A mutation can create a single-celled organism that co-operate. In this model, cooperation is captured by so-called detain entities that are activated by the co-operators. If a detain entity and a co-operator located at the same site, then the co-operator can be selected to die to give room for reproduction. On the other hand, the defectors ignore the detain entities, but reproduce if there is room for new daughter cells. Thus, the defectors are initially fitter than the co-operators. However, due to stochasticity, the co-operators can avoid extinction, and what is more, the model has an additional parameter called the *temperature*. In this example, the temperature represents regulation mechanisms. That is, initially, when there are only defectors in the population, the temperature is zero. However, the co-operators raise the temperature, and when the temperature reaches a certain limit, Υ, the regulation mechanisms start to kill the single-celled organisms that defect, and hence, defection becomes a disadvantageous strategy in the population.

7.2 Invasion of defectors and the Warburg effect

The model presented in paper 3 can also capture the dynamics of cancer invasion in solid tissues. As discussed more thoroughly in Subsection 5, mutant cells are in general not advantageous when they first appear in a human body because these cells are attacked by the defence system of the body. In this example, the detain entities represent the immune response. However, it is assumed that the immune cells are activated only if the mutant cells are harming healthy tissue. Moreover, the body can limit the blood flow to the microenvironment where the mutant cells are located. Consequently, the mutant cells break down the end product of glycolysis anaerobically, and this causes an acidic microenvironment. Hence, the temperature represents the acid level in the model, and it is assumed that the death rate of the healthy cells and the mutant cells that are not acid-resistant, increase when the acid level reaches the limit Υ.

To be more concrete, when the first mutant cell is generated, the acid level is zero. The mutant cells raise the acid level, but as long as the healthy tissue is not harmed, the competition dynamics between the healthy cells and the mutants cells is captured by the neutral Moran process. However, when the acid level reaches Υ, the healthy tissue is damaged, and consequently, the immune cells are activated. If none of the mutant cells are acid resistant, then the mutant type becomes disadvantageous, whereas if the mutant cells have generated a type of cells that are acid-resistant, then these cells are advantageous as long as there are less than N immune cells in the microenvironment. Hence, there is a race between the resistant mutants and the immune cells to reach population size N. If the immune cells respond quickly and reach population size N before the healthy cells in the microenvironment are extinct, the acid-resistant mutants are neutralised. In this case, the mutant cells are vulnerable to new immune attacks. On the other hand, the invasion of the resistant mutants represents the onset of a much more aggressive form of cancer, and in point of fact, in many cases, cancer cells exhibit glucose fermentation even when there is enough oxygen present. This is called the Warburg effect [33].

7.3 Further work

The model presented in paper 3 could be extended by including the interplay between evolution and learning, which is an important issue in evolutionary computation [36]. This plays a significant role in application areas that were used as examples in paper 3, such as biological modelling, multi-agent systems, economics and politics. All of these studies involve systems of interacting autonomous individuals in a population, and this raises several questions, like “Is

there any equilibrium?" and "How can cooperative behaviours evolve?". It is possible to apply methods from machine learning to seek an answer to these questions.

In the version of the prisoner's dilemma given in Subsection 4, single-celled organisms, that either cooperate or defect, compete in a finite population. Each cell has a fixed strategy, and after a normal cell division, both daughter cells inherit the strategy of the mother cell. However, when a cell divides, a mutation that changes the strategy of the daughter cells, can occur. Thus, if the population is relatively small, the co-operators can invade the population due to stochasticity. Nevertheless, if the population is sufficiently large, it will, eventually, be dominated by defectors, since defection is an evolutionarily stable strategy.

In contrast, a mix between cooperation and defection is often observed in several examples of prisoner's dilemma, for instance in human society [37]. One explanation is that in human life, a player often expects to meet the same opponent in the future, and he might remember a previous defection and take revenge [36]. On the other hand, if all the opponents know that a player always cooperate, they are likely to exploit him and defect. In a nutshell, the players use previous knowledge to decide whether to cooperate or defect.

In [36], the authors investigate the challenge of developing intelligent machine learning applications to address the problems of adaptation that arise in multi-agent systems, like expected long tem profit optimization. Moreover, the authors propose a learning algorithm for the emphiterated prisoner's dilemma problem and show that it performs strictly better than the tit-for-tat algorithm and many other adaptive and non-adaptive strategies. It would be interesting to study how these examples apply to the model presented in paper 3.

8 Paper 2: Dynamic self-organisation of haematopoiesis and (a)symmetric cell division

As discussed in Section 2, the blood system consists of approximately 37 trillion cells, and most of the differentiated blood cells are replaced each month. Hence, it is likely that haematopoiesis is regulated by self-organisation.

The model presented in paper 2 has a flexible and dynamically regulated self-organisation based on cell–cell and cell–environment interactions and extracellular regulations. What is more, the model links symmetric and asymmetric cell division with self-organisation, and as far as we know, our model is the first to make this connection.

The classical definition of a stem cell is an undifferentiated cell capable of self-renewal, production of a large number of differentiated cells, regenerating tissue after injury and a flexibility in the use of these options. This definition is fundamentally based on a functional perspective. As discussed by Loeffler and Roeder [38], the flexibility criterion attracted little attention when the definition of stem cells was first introduced. Yet considerable experimental results indicate that flexibility is a fundamental property of the stem cells [39], [40], [41]. For example, Zhang et al. [39] managed to bias the degree of lineage commitment by several maneuvers that altered the growth environment of the haematopoietic system.

Furthermore, many experiments show that haematopoietic stem cells can be manipulated such that they act as stem cells for another tissue such as neuronal and myogenic [40]. These experiments indicate that the growth environment is an important factor when tissue specification of stem cells are redirected.

The bone marrow niche contains both localised signalling cells and an extracellular matrix that support stem cell behaviour and control the fate of the undifferentiated cells [10], [11]. However, since it is not possible to reconstruct a bone marrow niche experimentally, the exact behaviour of haematopoietic stem cells is unknown. On the other hand, research on *Drosophila*

germline stem cells provides a clearcut example of how the niche maintains stem cell behaviour. That is, experiments on *Drosophila* germline stem cells support the following conjectures:

1. The stem cell niche promotes stem cell maintenance.
2. The stem cells self-renew at random.
3. When a stem cell self-renews, one of the daughter cells inherits the mother's place in the stem cell niche and retains stem cell identity, whereas the fate of the second daughter depends on the availability of space in the stem cell compartment – it either slips into a random vacant place in the stem cell compartment and remains a stem cell (symmetric self-renewal), or the second daughter leaves the stem cell compartment and loses its stem cell identity (asymmetric self-renewal).
4. Under normal conditions, the stem cell compartment is approximately full, and the stem cells typically self-renew asymmetrically.
5. When the stem cell compartment is not full, the rate of symmetric self-renewal generally increases, which leads to an expansion in the number of stem cells. The cells swift back to asymmetric self-renewal as the stem cell compartment reaches normal conditions.

The model presented in paper 2 assumes that Conjecture 1—6 also hold for the haematopoietic system. More specifically, the model assumes that all haematopoietic cell divisions occur randomly and that a haematopoietic stem cell is an undifferentiated cell located in a niche. That is, if a stem cell leaves the niche, it loses its stem cell identity. What is more, the daughter cells resulting from a stem cell division are phenotypically identical regardless of whether the division was asymmetric or symmetric. Due to self-organisation, the daughter cells remain in the niche and obtain stem cell identity or are placed outside the niche and commit to differentiation, depending on the need for self-renewal and differentiation. This is implemented by subdividing the niche into sites which represent signals and the environment as well as physical space.

8.1 Results from experiments on Safari cats can be explained by a self-organised model

As discussed above, relatively little is known about the exact behavior of the haematopoietic stem cells. On the contrary, haematopoietic progenitors have been studied both in vivo and in vitro. Loosely speaking, progenitors are cells on the first stage of the differentiation process.

Abkowitz et al. designed a set of experiments, using female Safari cats, to predict the contribution of haematopoietic stem cells to progenitor cells [17], [16], [42]. The Safari cat is a hybrid of the Geoffroy's cat (a South American wildcat) and a domestic cat (which is of Eurasian origin). These two species have evolved independently for twelve million years, and have distinct phenotypes of the X chromosome-linked enzyme glucose-6-phosphate dehydrogenase (G6PD). Female Safari cats have some cells that contain Geoffroy-type G6PD (G G6PD) and other cells that contain domestic-type G6PD (d G6PD). The G6PD phenotype is retained after replication and differentiation, and is functionally neutral. Therefore, it provides a binary marker of each cell and its offspring. In particular, this means that a progenitor cell that expresses G G6PD is the daughter of a stem cell that expresses G G6PD, and likewise, a progenitor cell that is d G6PD-positive is the daughter of a stem cell that is d G6PD-positive. Abkowitz et al. tracked the contributions of haematopoietic stem cells to the progenitor cells by observing the G6PD phenotype of haematopoietic progenitor cells.

Abkowitz et al. found that the percentage of progenitor cells expressing d G6PD remained relatively constant in normal female Safari cats. On the contrary, they observed that the percentage

of progenitor cells expressing d G6PD variated while the cells in the bone marrow regenerated, and, what is more, they found that the pattern of clonal contribution to haematopoiesis in each cat was unique. For instance, some of the cats that both had cells expressing d G6PD and cells expressing D G6PD when the regeneration started, had only cells expressing either d G6PD or D G6PD when the production of bone marrow cells stabilised after regeneration. Thus, one of the phenotypes had got extinct during the regeneration. On the contrary, in other cats, the percentage of cells expressing d G6PD and D G6PD remained on average relatively constant. Moreover, in some cats, significant variation in the percentage extended for years after the number of cells reached normal population levels, whereas in other cats, the percentage remained approximately constant.

Since the percentage of cells expressing d G6PD remained relatively constant when normal female Safari cats were observed, the experiments by Abkowitz et al. indicate that haematopoietic cells divide asymmetrically under normal conditions, because this type of division cannot change the number of stem cells expressing d G6PD. On the other hand, the number of stem cells expressing d GPD can increase or decrease by one after a symmetric stem cell division. Hence, since wide fluctuations in the percentage of cells expressing d G6PD were observed when the bone marrow regenerated, the experiments by Abkowitz et al. indicate that the rate of symmetric stem cell division increases during regeneration of the stem cell niche.

Other mathematical models of the haematopoietic system that include symmetric and asymmetric stem cell division, have been proposed, and they can reproduce several of the results obtained by Abkowitz et al. For instance, Wodarz and Komarova [23] propose a model where the haematopoietic stem cells divide asymmetrically under normal conditions and to symmetric division during regeneration. On the contrary, in the model presented by Abkowitz et al. [18], the haematopoietic stem cells only divide symmetrically. That is, under normal conditions, the haematopoietic stem cells undergo symmetric self-renewal and symmetric commitment at the same, constant rate, and under regeneration, the rate of the former type of division increases. Even though these models capture important aspects related to stem cell behaviour, it is a drawback that stem cell self-renewal and differentiation do not depend on local growth conditions because this implies that a stem cell somehow "knows" that it must self-renew symmetrically when stem cells need to be replaced. However, as discussed in Section 2, this assumption is potentially misleading and too rigorous. On the contrary, since the model presented in paper 2 links self-organisation with symmetric and asymmetric cell division, the rate of symmetric and asymmetric stem cell division is regulated by the needs of the haematopoietic system.

8.2 Differentiated cells

The model presented in paper 2 also includes the differentiated cells. It is assumed that these cells go through N stages of differentiation and that the cells that are at stage i in the differentiation process, are located in the i-th compartment. These compartments represent the sum of signals in the environment of the cells and not just physical locations. Moreover, it is assumed that the commited cells can only differentiate symmetrically. That is, if a cell in the i-th compartment divide, then both daughter cells migrate to the $i+1$-th compartment. Under normal conditions, there are approximately $2^i M$ cells in the i-th compartment, where M is the number of cells is stem cell niche when it is full, and the cells commit symmetrically to differentiation at the same, constant rate. However, the model assumes that there is a feedback from compartment i to compartment $i-1$, such that the system regenerates if there are less cells than under normal conditions.

8.3 Further work

The model presented in paper 2 is very simple with two parameters only, M and K, which are the number of sites in the stem cell niche and the number of compartments of differentiated cells, respectively.

In an extended version of the model, the committed haematopoietic cells should be divided into the erythroid lineage, the lymphoid lineage and the myeloid lineage. The first lineage is composed of red blood cells, the second of immune cells and the third includes granulocytes, megakaryocytes and macrophages [9]

It is still not clear exactly how differentiation of haematopoietic cells is regulated. In 1957, Waddington presented an epigenetic landscape that describes the differentiation of cells as the trajectories of balls rolling at random into branching valleys, where each branch represents a developmental state [43]. Based on Waddington's model, Furusawa and Kaneko propose a dynamical system model of cells with intracellular protein expression dynamics and interactions with each other [44]. The model predicts that cells with irregular, or chaotic, oscillations in gene expression dynamics have the potential to differentiate into other cell types. During development, such complex oscillations are lost successively, leading to loss of pluripotency. Their results are consistent with the view that pluripotency is a statistical property defined at the cellular population level, correlating with intra-sample heterogeneity, and driven by the degree of signalling promiscuity in cells.

To extend the model to include different lineages of the committed haematopoietic cells, it could be an advantage to use methods from big data analysis, such as machine learning, because these methods offer new ways to study the genome, transcriptome, proteome, and epigenome at the single-cell level. An increasing number of single-cell sequencing data makes it possible to carry out statistical inferences of pluripotency regulating genetic networks. In the work by Lin et. al, the authors develop a framework based on machine learning which explicitly account for the promoter architectures and gene state-switching dynamics. Their framework is useful for disentangling the various contributions that gene switching, external signaling, and network topology make to the global heterogeneity and dynamics of transcription factor populations. Their findings indicate that the pluripotent state of the network might be a steady state which is robust to global variations of gene-switching rates.

Differentiation modifies molecular properties of stem and progenitor cells, which leads to changing shape and movement characteristics. Buggenthin et al. present a method based on machine learning that predicts lineage choice in differentiating haematopoietic progenitors. Their method can detect lineage choice up to three generations before conventional molecular markers are observable. Thus, their approach manages to identify cells with differentially expressed lineage-specifying genes without molecular labelling.

9 Paper 1: Stem cell regulation: Implications when differentiated cells regulate symmetric stem cell division

Similar to the model discussed in the previous section, the model presented in paper 1 is used to study how stem cell division is regulated by other cells. However, the main focus of this paper is that changes in the population dynamics of the differentiated cells can lead to changes in the population dynamics of the stem cells if symmetric stem cell division is regulated by differentiated cells, and this means that the relative fitness of the stem cells can be affected by modifying the death rate of the differentiated cells. This result is interesting because stem cells are in general less sensitive to medical therapy than differentiated cells, and our result implies that stem cells

can be manipulated indirectly by medical treatments that target the differentiated cells.

9.1 Symmetric stem cell division and cancer

As discussed more thoroughly in Subsection 2.2 and Section 8, the number of stem cells increases by one after a symmetric self-renewal, whereas after a symmetric differentiation, the number of stem cells decreases by one.

It is assumed that under normal condition the number of stem cells is approximately constant, and that these cells self-renew and differentiate at relatively constant rates to keep the number of stem cells at normal level and replace mature cells [45] Moreover, it has been shown that the haematopoietic stem cells can expand rapidly in response to stem cell transplantation and other injuries to the bone marrow. This indicates that the rate of symmetric self-renewal depends on the number of stem cells in the niche, since this is the only type of division that increases the number of stem cells.

As discussed more thoroughly in Section 2, the production of mature blood cells increases after blood loss. A symmetric differentiation produces two daughter cells that commit to differentiations, whereas an asymmetric stem cell division produces only one. However, since asymmetric stem cell division leaves the stem cell number unchanged, the stem cell niche is protected against fluctuations if only the differentiated regulate asymmetric stem cell division. Indeed, Wodarz propose a model where the rate of symmetric self-renewal depends only on the number of stem cells in the niche, whereas the differentiated cells regulate the rate of asymmetric stem cell division when there are only healthy cells in the system [46]. This means that the population dynamics of the stem cell niche is not influenced by the differentiated cells. However, as I make a case for in Section 8, it is likely that tissues, such as the haematopoietic system, is regulated by self-organisation and that all three types of stem cell divisions depend on both the number of stem cells and the number of differentiated cells. In particular, it is also possible that the rate of symmetric self-renewal increases when the number of differentiated cells is less than under normal conditions, which means that the number of stem cells increases and that more differentiated cells are produced than under normal conditions. Research by Gokoffski et al. (2011) on mice indicates that when there are less differentiated cells than under normal conditions, then the stem cell populations expand [5]. Indeed, this is the case for the model presented by Lander et. al [47]. Similarly, the model presented in paper 1 assumes that symmetric self-renewal is regulated by differentiated cells.

A mutant haematopoietic differentiated cell is likely to be washed out of the system before it becomes a cancer cell because haematopoietic differentiated cells do not in general self-renew. On the other hand, if a mutation occur in a haematopoietic stem cell, an evolutionary process with competition between the normal stem cells and the mutant stem cells might take place [1]. A critical aspect is whether the mutation affects how the mutant stem cells divide. That is, the population size of the mutants remains constant if they only divide asymmetrically. Since symmetric differentiation decreases the population size, the mutant stem cells have decreased fitness if the rate of this type of division increases. And finally, an increased rate of symmetric self-renewal increases the fitness of the mutant stem cells, because this type of division increases the population size.

9.2 Treatment of chronic myeloid with the tyrosine kinase inhibitors

Treatment of chronic myeloid with the *tyrosine kinase inhibitors* such as imatinib, represents a successful application of molecularly targeted anti-cancer therapy [48] (Druker et al., 1996, 2001; Kantarjian et al., 2002). These inhibitors reduce the fitness of Philadelphia-positive differentiated

cells. Nevertheless, the effect on Philadelphia-positive stem cells remain incompletely understood. For many patients, discontinuation of tyrosine kinase inhibitors results in a relapse of the disease within a few months [49]. Several explanations have been proposed to explain this phenomenon. For instance, tyrosine kinase inhibitors might not have any effect on the Philadelphia-positive stem cells [50], or the Philadelphia-positive stem cells can be susceptible to therapy when they are in an active state, but they are not be susceptible when they are in quiescent state [51]. Be that as it may, a small study involving 12 patients has shown that in some individuals the disease has remained undetected for two years after discontinuation of tyrosine kinase inhibitors. This raises the possibility that tyrosine kinase inhibitors have cured chronic myeloid leukaemia in these patients [52]. Furthermore, all studies indicate that the effect of tyrosine kinase inhibitors increases when treatment starts early. The model presented in paper 1 can explain these results: Tyrosine kinase inhibitors have most likely no direct effect on the Philadelphia-positive stem cells. Nevertheless, since differentiation regulates the proliferation of the stem cells, the tyrosine kinase inhibitors can change the population dynamics of the stem cells. More precisely, the following results observed in studies of chronic myeloid leukaemia patients treated with tyrosine kinase inhibitors, can be reproduced by the model:

1. The effect of tyrosine kinase inhibitors increases when treatment starts early in disease progression.

2. In some cases the treatment slows down the disease progression without erasing the Philadelphia-positive stem cells, which drive the disease.

3. In other cases the treatment reverses the disease progression and seems to erase the Philadelphia-positive stem cells stem cells.

If a model which assumes that stem cell activity is not regulated by the differentiated cells, is used, result 1–3 seem contradictory [50]. However, our model implies that these results can be explained by a negative feedback from the differentiated cells that regulate symmetric stem cell division [53].

9.3 Further work

The model presented in paper 1 is a simplification of the one presented in paper 2. Hence, the extensions discussed in Subsection 8.3 apply to both models.

Part III
Discussion

In 1953, James Watson and Francis Crick discovered that the DNA molecule exists in the form of a three-dimensional helix, and this brought new energy to the *paradigm of genetic determinism* [53], which claims that any characteristic of a living organism is directly proportional to the genes expressed in the DNA. This implies that the genetic rules that determine the behaviour of an organism, can be represented by linear equations, and hence, complex organisms, such as human beings, should have a much higher number of genes than a less complex organism, such plants.

Another significant milestone in molecular biology was the publication of the complete sequence of the human genome in 2003 [54]. The complete human genome is composed of over three billion bases and contains approximately 20,000 genes that code for proteins. This is much lower than earlier estimates of 80,000 to 140,000 and astonished the scientific community when revealed through human genome sequencing. Equally surprising was the finding that genomes of much simpler organisms contained a higher number of protein-coding genes than humans. For example, the mustard plant, *Arabidopsis thaliana*, which used as a model for studying plant genetics, has a genome size of 125 bases but a higher number of protein-coding genes than humans [55]. It is now clear that the size of a genome does not correspond with the number of protein-coding genes, and these do not determine the complexity of an organism.

As I make a case for in Subsection 2, the haematopoietic system is not regulated deterministically, but by self-organisation. That is, the body can regenerate blood cells to compensate for a loss of more than 15 percent of the circulating blood cells, and after a bone marrow transplantation, the haematopoietic stem cells, which are located in the bone marrow, can regenerate. Moreover, each day the body produces around a billion new blood cells. And since the human body contains about 37 billion blood cells, this means that most of the circulating blood cells are replaced each month [9].

Nevertheless, some biological traits are actually determined by a single gene. In contrast to the haematopoietic system, the fingers only grow out once. The Sonic Hedgehog gene is essential for normal limb development [56]. When a foetus, lying in the womb, develops fingers, the Sonic Hedgehog gene sends out a signal to shape the pattern of digits. Normally, five fingers are made. However, if a mutation occurs in the Sonic Hedgehog gene that turns down the effect of this gene, then fewer fingers are made, whereas if the mutation increases the effect of the Sonic Hedgehog gene, then each hand gets an extra finger.

Even though there are some examples where biological traits are determined by a given set of genes, the publication of the complete sequence of the human genome illuminates that that the paradigm of genetic determinism does not in general hold true, since complex organisms such as humans have a lower number of protein-coding genes than much simpler organisms such as the mustard plant, *Arabidopsis thaliana*. As illustrated in Subsection 1.1, nonlinear, high-dimensional and complex interaction between genes and regulation mechanisms can create new phenomena that cannot be explained by simply analysing the genetic code. Thus, the high complexity of humans compared to *Arabidopsis thaliana* might be explained by a higher complexity in the interaction between genes and regulation mechanisms.

Despite the fact that the paradigm of genetic determinism does not in general hold true, a new and generally accepted paradigm has not yet been established. There is almost no general information about nonlinear systems, except that they very often are chaotic and it is quite often impossible to find an exact solution. Nonlinear systems are often sensitive to starting conditions. For example, if you were given a list of numbers generated by the logistic map given in Equation (1) with starting condition $Y_0 = A$, you could not use this list to predict the outcome generated

by the logistic map with another starting condition, say $Y_0 = B \neq A$. Moreover, nonlinear systems quite often respond dramatically to changes in the feedback from the environment. For example, the differential equation in (4) is one of relatively few nonlinear problems that has a neat solution. Nevertheless, if the feedback from the environment is delayed, then the system can start to behave chaotically, as described by the logistic map given in (1). This illustrates that there is no set of mathematical tools that can be used on any nonlinear system. Thus, each nonlinear system must in general be analysed individually, and this requires more than basic mathematical knowledge. Moreover, small changes in a nonlinear system can lead to new behaviour.

10 New methods to analyse complex interactions

Genome editing, such as CRISPR/Cas9, machine learning and big data offer new ways to tackle the problems described above. Machine learning is explored in the previous two parts, whereas big data and CRISPR/Cas9 are briefly discussed in the following subsections.

10.1 Big data and the impact of the Human Genome Project

"The Human Genome Project led to a paradigm shift in the way science is conducted and data is shared," according to researcher in biotechnology, Rehma Chandaria [57]. The *Bermuda Principles* are rules for publication of DNA sequence data, and were proposed in 1996 by a group of international scientists who came together on Bermuda to discuss how sequence data from the Human Genome Project should be released. Challenging traditional practice in the sciences, which is to make experimental data available only after publication, the Bermuda Principles ensures that the data is immediately shared. The original Bermuda Principles were:

1. Automatic release of sequence assemblies larger than 1 kb (preferably within 24 hours).
2. Immediate publication of finished annotated sequences.
3. Aim to make the entire sequence freely available in the public domain for both research and development in order to maximise benefits to society.

The Bermuda Principles demonstrated how a global community of scientists could collectively produce and use data far more efficiently than a small group of scientists could.

The price of the Human Genome Project was 3 billion US dollars and it lasted for 13 years [55]. Today it is possible to sequence a human genome within days and it costs less than 1000 dollars. This big data requires that researchers from different specialities co-operate to process, analyse, store and utilise the vast quantities of data.

10.2 CRISPR/Cas9

CRISPR/Cas9 is one of the most effective gene-editing tools the word have seen, and originates from the immune system of bacteria [58]. With CRISPR/Cas9 the genome can be edited almost as easily as the text in a book [59]. CRISPR is an abbreviation of *Clustered regularly interspaced short palindromic repeats*, and is a family of DNA sequences in archaea and bacteria [60]. The sequences contain snippets of DNA from viruses that have attacked the prokaryote. Cas9, which is short for CRISPR-associated protein 9, is an RNA-guided DNA endonuclease enzyme associated with CRISPR. Cas9 uses the snippets to detect and destroy viruses with similar DNA [61], [62].

A study published on the 2th of August 2017, describe how a group of American and South Korean scientists for the first time successfully edited genes in human embryos to repair a common

and serious disease-causing mutation, producing apparently healthy embryos [63]. These results potentially open the door to preventing 10.000 disorders that are passed down the generations.

However, the main use of CRISPR/Cas9 is less spectacular. CRISPR/Cas9 is mostly used as a laboratory tool and is for instance used to study the expression of genes. Even though the complete sequence of the human genome was published 15 years ago, relatively little is known about how the genes are turned on and off and which traits they influence. Scientists can gain valuable knowledge by using CRISPR/Cas9 to switch on and off genes in a laboratory, for example they can study which genes must be turned off in a haematopoietic stem cell for it to become an immune cell.

Nevertheless, it is not possible to get the complete picture of how genes are regulated inside the body by just studying cells in a laboratory. For instance, it is still unclear why immune therapy can cure some cervical cancer patients but has no effect on others. To make hypotheses about why a medicine does not cure some patients, the researchers can make use of big data sets from patients by applying methods from machine learning. With solid hypotheses, the use of CRISPR/Cas9 becomes more efficient.

11 New medicines, new dilemmas

In Norway, lung cancer patients did not get the cost of immune therapy covered by the state until the end of 2016, whereas in Denmark the same patient group has been offered this treatment at public hospitals since September 2015 [64]. Similarly, patients with cervical cancer get immune therapy at public hospitals in Denmark, but not in Norway. In both cases, the state argued that the prize was too high because immune therapy does not cure all patients.

However, the price of each drug is only high in the beginning. When the effect of the medicine is more thoroughly documented and more patients can use it, the prize decreases. Large data sets from patients is of great value for scientific purposes, and there is no obvious reasons why Norway should contribute less to this research than other countries such as Denmark.

It is not only cancer treatment that creates new dilemmas. ®Spinraza is the first medicine that has any effect on *Spinal Muscular Atrophy (SMA)*, which is a rare neuromuscular disorder defined by progressive muscle wasting and loss of motor neurons. Approximately ten children are born with SMA each year in Norway. About 95 percent of the children with the most severe form of SMA die before they are two years old, whereas others can have a normal lifespan with a varying degree of disability. No previous drugs has any proven effect on SMA. Thus, Spinraza represents a big breakthrough. Moreover, the drug does not only slow down the progression of the disease – the patients improve motoric function and strengthen the muscles.

In 2017, Biogen, the company that developed Spinraza, let ten Norwegian children with SMA test the drug for free [65]. One of these children was a 11-month-old baby girl called Olivia. Olivia has the most severe form of SMA, and after starting the Spinraza treatment, she manages to sit, eat, hold a toy and turn around. This was impossible for Olivia before the treatment started. When the free trial ended, the government continued to pay for the Spinraza treatment for the ten children that had tried the drug for free. However, the government did not offer the remaining 40 children with SMA Spinraza treatment because the prize on the drug was too high. One of these children is Thea, a two year old girl, and like Olivia, Thea has the most severe form of SMA. Whereas other toddlers develop control of muscles, which enable walking, running, jumping and climbing, Thea managed to do less each day. Her parents lived in fear that she would die while the government negotiated with Biogen, until February 2017, when it was announced that the government would pay for Spinraza-treatment for all children with SMA. But the government does not cover this treatment for persons over 18 years of age. The reason

is that the effect of Spinraza on adults is not documented properly.

However, to evaluate the effect of Spinraza on adults, data from adult patients who actually use the drug is essential, and it seems reasonable that a rich country such as Norway should be one of the first to contribute to this research, whereas poorer countries might have no choice but to wait until the prize decreases and more is known about which patients the drug has any effect on.

One might argue that Biogen should give a discount on Spinraza-treatment for adult patients because the company can increase their final reckoning by gaining more information about the effect of the drug. However, this might increase the prize of the treatment for children.

At the end of the day, Biogen depends on the willingness of the owners to invest in the company. It is very expensive to develop new medicines. The company Bristol-Myers Squibb, which developed the immune therapy ®Opdivo, used 40 billion Norwegian Krones on research and development only in 2014. It is even more risky and potentially costly to try to develop a drug against disorders which no other drugs has any effect on, which was the case with SMA. Thus, it is a reasonable assumption that the owners of Biogen were willing to invest in the research that lead to the development of Spinraza, because there was a big payoff if they succeeded. And indeed, after the launch of Spinraza in 2016, the revenue of Biogen increased by four percent within a year. In the period from July to September 2017, the income from Spinraza is estimated to 2.1 billion Norwegian crones. And what is more, the Government Pension Fund of Norway owns one percentage of the company.

The fact that the Government Pension Fund of Norway is an owner of Biogen, does not mean that the Norwegian government should accept any price offer. However, to me it seems unethical if Norway waits until the prices drop to buy the drug, and at the same time earn money because other countries buy the drug when the price is high.

Moreover, the trust in the Norwegian government decreases when Norwegian patients die while the government is negotiating prices with the drug company, whereas the same patient group is offered the treatment at public hospitals in other countries.

Maybe the use of new medicines is an investment, both in research and in the welfare state.

References

[1] Martin A. Nowak and Karl Sigmund. Evolutionary dynamics of biological games. *Science*, 303(5659):793–799, 2004.

[2] C M Baum, I L Weissman, A S Tsukamoto, A M Buckle, and B Peault. Isolation of a candidate human hematopoietic stem-cell population. *Proceedings of the National Academy of Sciences*, 89(7):2804–2808, 1992.

[3] Sean J. Morrison and Irving L. Weissman. The long-term repopulating subset of hematopoietic stem cells is deterministic and isolatable by phenotype. *Immunity*, 1(8):661 – 673, 1994.

[4] Tom Lenaerts, Jorge M. Pacheco, Arne Traulsen, and David Dingli. Tyrosine kinase inhibitor therapy can cure chronic myeloid leukemia without hitting leukemic stem cells. *Haematologica*, 2009.

[5] Kimberly K. Gokoffski, Hsiao-Huei Wu, Crestina L. Beites, Joon Kim, Euiseok J. Kim, Martin M. Matzuk, Jane E. Johnson, Arthur D. Lander, and Anne L. Calof. Activin and gdf11 collaborate in feedback control of neuroepithelial stem cell proliferation and fate. *Development*, 2011.

[6] J. Nathan Kutz. Deep learning in fluid dynamics. *Journal of Fluid Mechanics*, 814:1–4, 2017.

[7] I. Stewart. *Concepts of Modern Mathematics*. Dover Books on Mathematics. Dover Publications, 2012.

[8] M.W. Hirsch, S. Smale, and R.L. Devaney. *Differential Equations, Dynamical Systems, and an Introduction to Chaos*. Academic Press. Academic Press, 2013.

[9] C. Cooper and C.S. Cooper. *Blood: A Very Short Introduction*. Very Short Introductions Series. Oxford University Press, 2016.

[10] Tong Yin and Linheng Li. The stem cell niches in bone. *The Journal of Clinical Investigation*, 116(5):1195–1201, 5 2006.

[11] Chun-Chun Cheng, Yen-Hua Lee, Shau-Ping Lin, Wei-Chun HuangFu, and I-Hsuan Liu. Cell-autonomous heparanase modulates self-renewal and migration in bone marrow-derived mesenchymal stem cells. *Journal of Biomedical Science*, 21(1):21, Mar 2014.

[12] Sean J. Morrison and Judith Kimble. Asymmetric and symmetric stem-cell divisions in development and cancer. *Nature*, 441(15):1068–1074, 2006.

[13] Yukiko M Yamashita, D Leanne Jones, and Margaret T Fuller. Orientation of asymmetric stem cell division by the apc tumor suppressor and centrosome. *Science (New York, N.Y.)*, 301(5639):1547–50, Sep 2003.

[14] H E Wichmann, M Loeffler, and S Schmitz. A concept of hemopoietic regulation and its biomathematical realization. *Blood cells*, 14(2-3):411–29, 1988.

[15] K. Shortman and S.H. Naik. Steady-state and inflammatory dendritic-cell development. *Nature Reviews Immunology*, 7(1):19–30, 2006.

[16] J L Abkowitz, M L Linenberger, M A Newton, G H Shelton, R L Ott, and P Guttorp. Evidence for the maintenance of hematopoiesis in a large animal by the sequential activation of stem-cell clones. *Proceedings of the National Academy of Sciences of the United States of America*, 87(22):9062–6, Nov 1990.

[17] J L Abkowitz, R M Ott, R D Holly, and J W Adamson. Clonal evolution following chemotherapy-induced stem cell depletion in cats heterozygous for glucose-6-phosphate dehydrogenase. *Blood*, 71(6):1687–92, Jun 1988.

[18] J L Abkowitz, S N Catlin, and P Guttorp. Evidence that hematopoiesis may be a stochastic process in vivo. *Nature medicine*, 2(2):190–7, Feb 1996.

[19] David Dingli, Arne Traulsen, Franziska Michor, and Fransizka Michor. (a)symmetric stem cell replication and cancer. *PLoS computational biology*, 3(3):e53, Mar 2007.

[20] David J Araten, David W Golde, Rong H Zhang, Howard T Thaler, Lucia Gargiulo, Rosario Notaro, and Lucio Luzzatto. A quantitative measurement of the human somatic mutation rate. *Cancer research*, 65(18):8111–7, Sep 2005.

[21] B. Vogelstein and K.W. Kinzler. Cancer genes and the pathways they control. *Nature medicine*, 10(8):789–799, 2004.

[22] N. L. Komarova and P. Cheng. Epithelial tissue architecture protects against cancer. *Mathematical biosciences*, 200(1):90–117, Mar 2006.

[23] D. Wodarz and N. L. Komarova. *Computational Biology Of Cancer: Lecture Notes And Mathematical Modeling*. World Scientific Publishing Company, 2005.

[24] L. Shahriyari and N.L. Komarova. Symmetric vs. asymmetric stem cell divisions: an adaptation against cancer? *PloS one*, 8(10):e76195, 2013.

[25] J.M. Smith. The theory of games and the evolution of animal conflicts. *Journal of theoretical biology*, 47(1):209–221, 1974.

[26] Guillaume Lambert, Saurabh Vyawahare, and Robert H Austin. Bacteria and game theory: the rise and fall of cooperation in spatially heterogeneous environments. *Interface focus*, 4(4):20140029, Aug 2014.

[27] John Nash. Non-cooperative games. *Annals of mathematics*, pages 286–295, 1951.

[28] Raheleh Rahbari, Tom Sheahan, Vasileios Modes, Pam Collier, Catriona Macfarlane, and Richard M Badge. A novel l1 retrotransposon marker for hela cell line identification. *BioTechniques*, 46(4):277–84, Apr 2009.

[29] David H Hubel and Torsten N Wiesel. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *The Journal of physiology*, 160(1):106, 1962.

[30] K Fukushima. Neocognitron: a self organizing neural network model for a mechanism of pattern recognition unaffected by shift in position. *Biological cybernetics*, 36(4):193–202, 1980.

[31] P E Turner and L Chao. Prisoner's dilemma in an rna virus. *Nature*, 398(6726):441–3, Apr 1999.

[32] M A Nowak and K Sigmund. Phage-lift for game theory. *Nature*, 398(6726):367–8, Apr 1999.

[33] Marco Archetti. Evolutionary dynamics of the warburg effect: glycolysis as a collective action problem among cancer cells. *Journal of theoretical biology*, 341:1–8, Jan 2014.

[34] Karl Marx and Friedrich Engels. *Manifesto of the communist party*. CH Kerr and Company, 1906.

[35] Marthe Måløy. Frp bør legge innvandrings- og integreringsministeren på bordet. *Minerva*, December 2017.

[36] Anurag Agrawal and Deepak Jaiswal. When machine learning meets ai and game theory. 2012.

[37] Steven Pinker, Martin A Nowak, and James J Lee. The logic of indirect speech. *Proceedings of the National Academy of Sciences*, 105(3):833–838, 2008.

[38] Markus Loeffler and Ingo Roeder. Tissue stem cells: definition, plasticity, heterogeneity, self-organization and models–a conceptual approach. *Cells, tissues, organs*, 171(1):8–26, 2002.

[39] P Zhang, G Behre, J Pan, A Iwama, N Wara-Aswapati, H S Radomska, P E Auron, D G Tenen, and Z Sun. Negative cross-talk between hematopoietic regulators: Gata proteins repress pu.1. *Proceedings of the National Academy of Sciences of the United States of America*, 96(15):8705–10, Jul 1999.

[40] Timothy R Brazelton, Fabio MV Rossi, Gilmor I Keshet, and Helen M Blau. From marrow to brain: expression of neuronal phenotypes in adult mice. *Science*, 290(5497):1775–1779, 2000.

[41] M Z Ratajczak, M Kucia, R Reca, M Majka, A Janowska-Wieczorek, and J Ratajczak. Stem cell plasticity revisited: Cxcr4-positive cells expressing mrna for early muscle, liver and neural cells 'hide out' in the bone marrow. *Leukemia*, 18(1):29–40, Jan 2004.

[42] J L Abkowitz, M L Linenberger, M Persik, M A Newton, and P Guttorp. Behavior of feline hematopoietic stem cells years after busulfan exposure. *Blood*, 82(7):2096–103, Oct 1993.

[43] C.H. Waddington. *The Strategy of the Genes*. Routledge, 1957.

[44] Chikara Furusawa and Kunihiko Kaneko. Chaotic expression dynamics implies pluripotency: when theory and experiment meet. *Biology direct*, 4:17, 2009.

[45] Ken Shortman and Shalin H Naik. Steady-state and inflammatory dendritic-cell development. *Nature reviews. Immunology*, 7(1):19–30, Jan 2007.

[46] Dominik Wodarz. Stem cell regulation and the development of blast crisis in chronic myeloid leukemia: Implications for the outcome of imatinib treatment and discontinuation. *Medical Hypotheses*, 70(1):128 – 136, 2008.

[47] Arthur D Lander, Kimberly K Gokoffski, Frederic YM Wan, Qing Nie, and Anne L Calof. Cell lineages and the logic of proliferative control. *PLoS biology*, 7(1):e1000015, 2009.

[48] B J Druker, S Tamura, E Buchdunger, S Ohno, G M Segal, S Fanning, J Zimmermann, and N B Lydon. Effects of a selective inhibitor of the abl tyrosine kinase on the growth of bcr-abl positive cells. *Nature medicine*, 2(5):561–6, May 1996.

[49] Jorge Cortes, Susan O'Brien, and Hagop Kantarjian. Discontinuation of imatinib therapy after achieving a molecular response. *Blood*, 104(7):2204–5, Oct 2004.

[50] Franziska Michor, Timothy P Hughes, Yoh Iwasa, Susan Branford, Neil P Shah, Charles L Sawyers, and Martin A Nowak. Dynamics of chronic myeloid leukaemia. *Nature*, 435(7046):1267–70, Jun 2005.

[51] Ingo Roeder, Matthias Horn, Ingmar Glauche, Andreas Hochhaus, Martin C Mueller, and Markus Loeffler. Dynamic modeling of imatinib-treated chronic myeloid leukemia: functional insights and clinical implications. *Nature medicine*, 12(10):1181–4, Oct 2006.

[52] Philippe Rousselot, Francoise Huguet, Delphine Rea, Laurence Legros, Jean Michel Cayuela, Odile Maarek, Odile Blanchet, Gerald Marit, Eliane Gluckman, Josy Reiffers, Martine Gardembas, and François-Xavier Mahon. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. *Blood*, 109(1):58–60, 2007.

[53] Richard C Strohman. The coming kuhnian revolution in biology. *Nature biotechnology*, 15(3):194–200, 1997.

[54] L Goodman. The human genome project aims for 2003. *Genome research*, 8(10):997–9, Oct 1998.

[55] Leroy Hood and Lee Rowen. The human genome project: big science transforms biology and medicine. *Genome medicine*, 5(9):79, 2013.

[56] P C Edwards, S Ruggiero, J Fantasia, R Burakoff, S M Moorji, E Paric, P Razzano, D A Grande, and J M Mason. Sonic hedgehog gene-enhanced tissue engineering for bone regeneration. *Gene therapy*, 12(1):75–86, Jan 2005.

[57] Julie Gould. Big data: The impact of the human genome project. *NatureJobs Blog*, October 2015.

[58] Lauren R Polstein and Charles A Gersbach. A light-inducible crispr-cas9 system for control of endogenous gene activation. *Nature chemical biology*, 11(3):198–200, 2015.

[59] Marthe Måløy. Crispr kan revolusjonere behandlingen av kreft og genetiske sykdommer. *Minerva*, August 2017.

[60] Isabel Lokody. Genetic therapies: Correcting genetic defects with crispr-cas9. *Nature Reviews Genetics*, 2013.

[61] Seung Woo Cho, Sojung Kim, Jong Min Kim, and Jin-Soo Kim. Targeted genome engineering in human cells with the cas9 rna-guided endonuclease. *Nature biotechnology*, 2013.

[62] Prashant Mali, Kevin M Esvelt, and George M Church. Cas9 as a versatile tool for engineering biology. *Nature methods*, 10(10):957–963, 2013.

[63] Hong Ma, Nuria Marti-Gutierrez, Sang-Wook Park, Jun Wu, Yeonmi Lee, Keiichiro Suzuki, Amy Koski, Dongmei Ji, Tomonari Hayama, Riffat Ahmed, Hayley Darby, Crystal Van Dyken, Ying Li, Eunju Kang, A.-Reum Park, Daesik Kim, Sang-Tae Kim, Jianhui Gong, Ying Gu, Xun Xu, David Battaglia, Sacha A. Krieg, David M. Lee, Diana H. Wu, Don P. Wolf, Stephen B. Heitner, Juan Carlos Izpisua Belmonte, Paula Amato, Jin-Soo Kim, Sanjiv Kaul, and Shoukhrat Mitalipov. Correction of a pathogenic gene mutation in human embryos. *Nature*, 548(7):413–419, 2017.

[64] Marthe Måløy. Immunterapi må tilbys til alle. *Minerva*, September 2016.

[65] Marthe Måløy. Helse-norge bør ta i bruk nye og dyre medisiner. *Minerva*, November 2017.

Liste over publikasjoner i ph.d.-avhandling

Vitenskapelige publikasjoner

Marthe Måløy, Frode Måløy, Rafael Lahoz-Beltra, Juan Carlos Nuno og Antonio Bru (2018) An extended Moran process that captures the struggle for fitness. Under review

Arbeidsfordeling: Rafael Lahoz-Beltra, Juan Carlos Nuno, Antonio Bru og Marthe Måløy: Utvikling av modell.

Marthe Måløy: Skrive artikkel, programmering av modell, korrespondanse med journal.

Frode Måløy: Korrektur lesning, programmering av modell

Marthe Måløy, Frode Måløy, Per Jakobsen, Bjørn Olav Brandsdal (2017) Dynamic self-organisation of haematopoiesis and (a)symmetric cell division. *Journal of Theoretical Biology*.

Marthe Måløy: Utvikling av modell, skrive artikkel, programmering av modell, korrespondanse med journal.

Frode Måløy: Korrektur lesning, programmering av modell

Per Jakobsen: Samtaler om modellering og forklaringsnivå.

Marte Rørvik Høyem, Frode Måløy, Per Jakobsen, Bjørn Olav Brandsdal (2015) Stem cell regulation: Implications when differentiated cells regulate symmetric stem cell division. *Journal of Theoretical Biology.*

Marthe Måløy: Utvikling av modell, skrive artikkel, programmering av modell, korrespondanse med journal.

Frode Måløy: Korrektur lesning, programmering av modell

Per Jakobsen: Samtaler om modellering og forklaringsnivå.

Marthe Måløy

Per Jakobsen