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Citation: Manbachi, Amir, et al. "Starting a Medical Technology Venture as a Young Academic Innovator or Student Entrepreneur." Annals of Biomedical Engineering, vol. 46, no. 1, Jan. 2018, pp. 1–13.

As Published: https://doi.org/10.1007/s10439-017-1938-x

Publisher: Springer US

Persistent URL: http://hdl.handle.net/1721.1/115505

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Title Page:

Starting a Medical Technology Venture as a Young Academic Innovator or Student Entrepreneur

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Abstract

Following the footprints of Bill Gates, Steve Jobs and Mark Zuckerberg, there has been a misconception that students are better off quitting their studies to bring to life their ideas, create jobs and monetize their inventions. Having historically transitioned from manpower to mind power, we live in one of the most rapidly changing times in human history. As a result, academic institutions that are supposed to be pioneers and educators of the next generations have started to realize that they need to adapt to a new system, and change their policies to be more flexible towards patent ownership and commercialization. There is an infrastructure being developed towards students starting their own businesses while continuing with their studies. This paper aims to provide an overview of the existing landscape, the exciting rewards as well as risks awaiting a student entrepreneur, the challenges of the present ecosystem, and questions to consider prior to embarking on such a journey. Various entities influencing the start-up environment are considered, specifically for the medical technology sector. These parties include but are not limited to: scientists, clinicians, investors, academic institutions and governments. A special focus will be set on the seemingly unbridgeable gap between founding a company and a scientific career.

Key Terms: Entrepreneurship, bioentrepreneur, student entrepreneurship, medical devices

1. Introduction

During the past decade or so, the number of student entrepreneurs has been increasing drastically[7, 18]. This is particularly the case for the medical technology (MedTech) sector, for which many inventions arise from laboratory benches and academic institutions[8, 14, 27]. One of the most prominent revolutions occurring in our society is a shift of perception towards entrepreneurship. Previously, a common misconception was that becoming a successful entrepreneur necessitated dropping out of one's academic studies. Prominent examples such as Bill Gates, Mark Zuckerberg and Steve Jobs underscored this perception. This has certainly not been the case for the MedTech sector and specifically for bioentrepreneurs. There are many noticeable examples of established academic bioentrepreneurs in this field who can serve as an inspiration to the younger generation of scientists and students. Examples include Faculty of the Johns Hopkins Department of Biomedical Engineering's Center for Bioengineering Innovation and Design (CBID), Faculty of the Stanford Byers Center for BioDesign, Professor Robert Langer [Massachusetts Institute of Technology (MIT), Departments of Chemical and Biological Engineering], Professor George Whitesides (Harvard University, Department of Chemistry), Professor Stuart Foster (Scientist, Sunnybrook Research Institute, Toronto), Professor Paul Santerre (University of Toronto, Dentistry), and many more.

Furthermore, due to fundamental transformations in our global society and economy during the past few years, universities have been changing their policies[10, 22] and education curriculum[2, 37] to allow an easier start for academic spin-offs: enabling business-minded students or faculty to pursue their academic journeys while founding companies in parallel. (See **Fig. 1**.) Aside from the programs mentioned above at Johns

Hopkins University and Stanford University, established programs include the Oshman Engineering Design Kitchen at Rice University, the Center for Entrepreneurial Studies at the University of North Carolina at Chapel Hill (UNC), and the joint Department of Biomedical Engineering at UNC and North Carolina State University, which includes a Senior Design Symposium. Many younger programs have followed, such as the Harvard Innovation Lab (i-lab), and Master in Design Engineering at the School of Engineering and Applied Sciences at Harvard University; the Yale Center for Engineering Innovation & Design, and Yale Entrepreneurial Institute; the MIT Design Lab, graduate “Venture Classes” at the MIT Media Lab, and an undergraduate Minor in Entrepreneurship and Innovation at MIT.

With this new awareness and the support of academic institutions, a new era of entrepreneurship has started[25]. Unlike earlier, founders do not necessarily have to become dedicated to business for the rest of their lives. Instead, students can get inspiration from the model already proven for academic scientists to start companies based on their own research projects, and choose whether they would like to hire someone to run the daily operations of the companies for them.

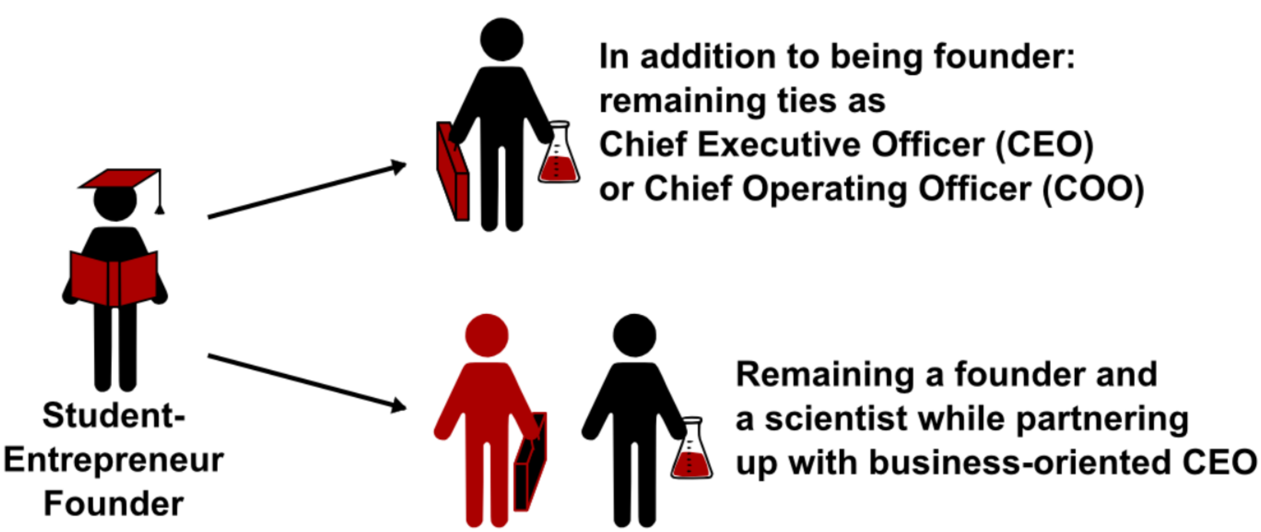

Fig. 1. Depiction of the choices facing a business-minded student scientist. Student bioentrepreneurs in the MedTech field can now easily start their own business based on their own research projects. They can subsequently have the choice of whether to become the Chief Executive Officer (CEO) and run the daily operations of the company, or to hire a CEO and remain involved only in the capacity of founder and advisor.

Although names of a few world-renowned scientists have been mentioned above as inspiring role models, in this review, our focus will remain solely on student entrepreneurs in the MedTech sector, that is, in the biomedical engineering instrumentation track. We will discuss some of the rewarding aspects as well as challenges associated with their journeys, and we will name a few examples as case studies. Here, we will not refer to the pharmaceutical sector, due to major differences in the entrepreneurial considerations of such a journey.

1.1. A trend in society for transition from a top-down to bottom-up approach:

As mentioned previously, one of the reasons behind the rise of a new era of entrepreneurship can be attributed to a general shift in economic structure during recent years. The difficulties associated with job creation from a top-down approach (industry and governments expected to create jobs) have led to much underemployment. This situation has subsequently affected younger generations worldwide[6, 13]. As a result, a bottom-up approach to job creation has proved beneficial, whereby any individual in society with novel ideas and an entrepreneurial character is allowed to start an initiative to pursue his/her dream, create jobs for others and make a fortune for himself/herself as well as society[30]. This process provides small businesses and early-stage start-ups with the capacity to act as innovative motors of society to create jobs[23]. In 2013, over 50% of the United States (US) working population was employed by small businesses[32]. Moreover, since 1995, 65% of net new jobs have been created by small businesses[32].

The statistics mentioned above may sound counter-intuitive. This is because for a long time, technological innovation was limited to large businesses, perhaps due to the high costs of research and development required for commercializing a product within the MedTech field. Improved accessibility to smart information technology devices, wider distribution of prototyping expertise and fundamental changes in the policies of academic institutions have allowed collaborations and partnerships, which are instrumental for smaller business ventures gaining center stage for such an impact. These factors are some of the elements discussed in this article, when discussing various components involved in starting a bioentrepreneurship journey.

1.2. Various stages of bioentrepreneurship:

Within the lifetime of every biotechnology / MedTech company, there are certain milestones and various strategies essential for the company's success. Founding a company and managing its growth until ultimately taking one of many strategies for an exit can be a long journey. Before even founding a startup, several prerequisites have to be fulfilled to allow a chance of success.

Idea: Firstly, the founder or founders need to have an innovative idea. This idea should not only address a specific problem, but also it should have the potential to either enter a market, or even preferably, generate a market. Especially in the MedTech field, such an idea should be well accepted by customers and end-users. This is particularly the case when considering clinically innovative devices designed for use by clinicians and surgeons, as patient safety is at stake.

Validation / Prototyping: In order to prevent rejection by end-users, it is typically recommended to seek feedback early on during the bioentrepreneurial journey. To do so, when transitioning an idea into a product, various prototype designs and manufacturing steps should be explored. This process of incremental development can set the stage for more detailed feedback from experts and end-users at each phase of progress. This process is iterative, hence improvements on the prototype are evaluated with experts, and feedback obtained can be implemented in the next round of prototyping. (See **Fig. 2**.)

Based on the “lean start-up” theory, first proposed by Eric Ries[33], customer validation can shorten the product development cycle. Entrepreneurs should always be open to pivoting from their original idea to incorporate new feedback and / or explore new markets. To this end, student entrepreneurs should learn to get out of the building and communicate their ideas with the real world. In contrast with Master of Business Administration (MBA) programs that encourage students to build a large network of people, scientists tend to exist in a more contained culture. However, understanding the customer segment cannot be achieved without getting into the real world and talking to potential end-users and customers.

Especially in MedTech, for which user acceptance is vital for the idea's and the company's survival, the above-described feedback also serves to improve specific aspects concerning application or integration in the medical workflow[3, 31]. Additionally, feedback at an early stage can help in determining the marketability. Various forms of seeking feedback include, but are not limited to, personal interviews and surveys of key opinion leaders in the field, as well as attendance at exhibitions and scientific conferences. However, there may be concerns about theft of intellectual property (IP). In order to protect IP, bioentrepreneurs may sometimes be discouraged from scientific publications or discussions with potential industrial partners. However, if such public disclosures are done with the right timing and with proper legal protection (e.g. discussions under non-disclosure agreements, presentations subsequent to patent applications, etc.), they can have great benefits for the quality of the product, as well as the reputation of the company.

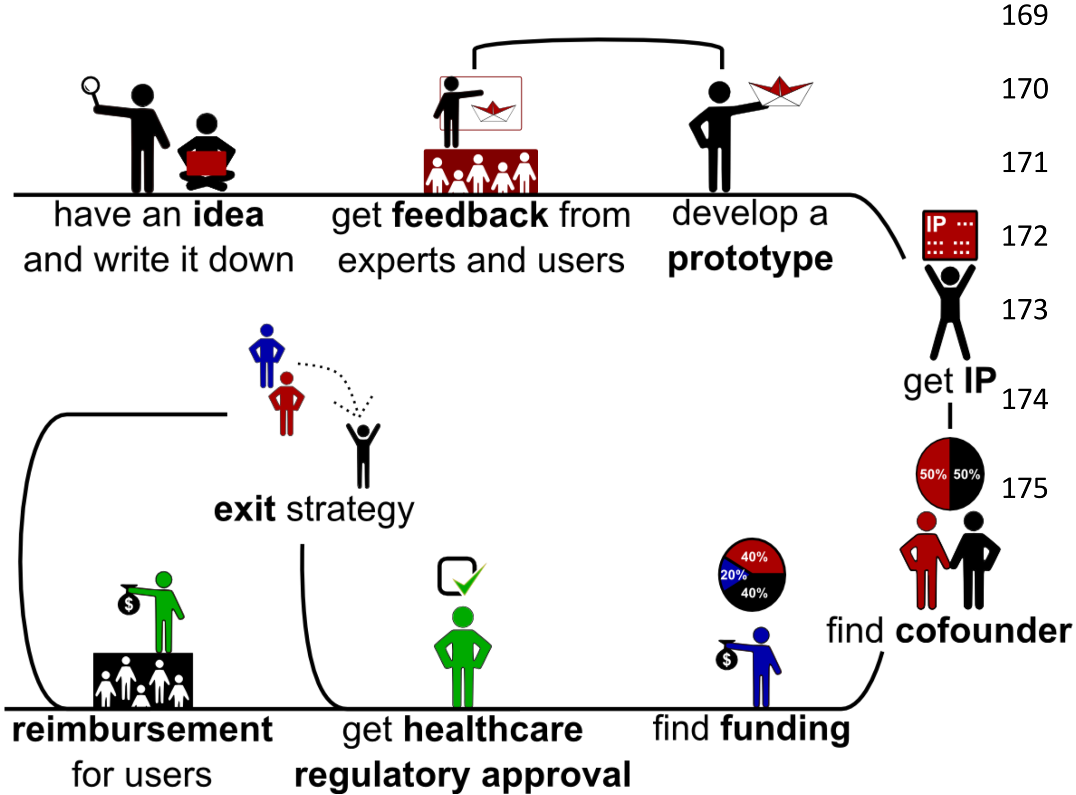

Fig. 2. Various stages of bioentrepreneurship. The diagram presents one possible approach going from an idea to prototyping, regulatory approval and monetization.

<u>IP:</u> Having encouraged obtaining feedback and scientific publications, it is important to note the following: In order to prevent the aforementioned theft of ideas, IP must be secured. Apart from protecting ideas by patenting, IP is a strong requirement for the acquisition of funding[39]. There are different forms of IP, and the strategy for how and where to obtain IP protection differ from country to country[17]. This topic will also be a core subject of the review, as filing for IP protection is both an inspiration for young innovators wanting to found a company, as well as a potential challenge.

<u>Funding:</u> "*An entrepreneur without funding is a musician without an instrument*." This quotation by Robert A. Rice, Jr. underscores the imminent necessity of every entrepreneur and company to find sufficient funding. For young bioentrepreneurs without the means to fund projects personally, finding funding sources is vital to keeping a company alive[21]. Funding can come from a variety of sources, ranging from government grants to private investors[15]. However, each funding opportunity comes with its own challenges. This topic will be discussed in great depth in the remaining sections of the article.

Regulatory approval: Of particular importance in the entrepreneurship of MedTech is the healthcare regulatory approval process. The process involves filing an approval application to the respective national regulatory administration [e.g. Food and Drug Administration (FDA) in the US, European Medicines Agency (EMA) in Europe and HealthCanada for the Canadian market]. It is a mandate to perform thorough preclinical tests, followed by clinical trials, in which the safety and efficacy of the medical device or application can be proven. Only if these studies are successful, can an application be filed and healthcare regulatory approval be given. This process can typically take several years, depending on the required thoroughness associated with a particular regulatory approval category[34]. In the next paragraph, some of these classes of healthcare regulatory approval are listed. (See **Fig. 3**.) High risk technologies (class III) include active and non-active implantable devices, such as pacemakers, stents or artificial joints, as well as devices with new indications or unique technologies that have not been previously taken to market. Technologies that are similar to devices that are already commonly used, but are possible improvements, are classified as having intermediate risk [class IIA (lower risk) or IIB (higher risk)].

Finally, all less risky devices that are commonplace to society, such as band-aids, are rated as low risk (class I). Each class has different steps for gaining approval, and approval must be granted before one can sell a product.

Of the most difficult steps in an inexperienced entrepreneur's path towards success is interactions with the FDA. Included in this process is one of the most overlooked parts of a correct submission: the appropriate utilization of testing standards for characterizing the safety and efficacy of a device. The FDA has numerours guidelines describing the appropriate testing that should be performed, though they do not describe the exact methodology or data capture that may be necessary. Furthermore, tests such as biocompatibility characterization are expensive and are more effectively performed by a contract research organization than an inexperienced entrepreneur. This is because performing the wrong studies can quickly drain funding. A student with minimal understanding of the proper path should seek the advice of a regulatory consultant to help navigate the complex series of tasks involved in a proper device submission.

Fig. 3. Healthcare regulatory approval is essential for MedTech innovations around the world. Each device can fall within one of the classes depicted above. Adapted from[20].

Reimbursement for end-users: Another issue that strongly affects the marketability of a product and should hence be considered early on is reimbursement for end-users[16]. In most cases, clinicians are the ones to use the product, but neither them nor the patients can afford a costly treatment. As a consequence, insurance is an important factor for companies in the MedTech sector. If an insurance company agrees to support the use of a medical device, the success rate and marketability of the product can significantly increase, since the device becomes affordable for a much larger group of people[16, 29]. In this manner, not only is the product accessible to a larger group of individuals, but also insurance serves as a reference for the reliability of the product.

In the US, reimbursement is largely defined by how a new company interacts with the Centers for Medicare and Medicaid Services (CMS): New companies should attempt to be reimbursed by CMS, not only because of the sizable population that they cover, but also due to the fact that many private insurance companies await CMS' decision on novel technologies before adopting them into their own coverage plans. To this end, it is the goal of a new technology to receive a Current Procedural Technology (CPT) code, where CMS decide that the novel technology is "reasonable and necessary" and lay out exactly how reimbursement payment will work.

Exit strategy: Ultimately, every entrepreneur needs to decide on an exit strategy. An exit does not necessarily end the lifetime of the company. Choosing the right timing, as well as the right way to exit, is vital for both the product as well as the personal development of the entrepreneur.

One of the most common exit strategies for bioentreprenur scientists is to be acquired by major companies in the field, which usually is a fruit of creating relationships and partnerships prior to the exit point. As mentioned above, timing is extremely important and can be a big game changer for a start-up's exit strategy. Achieving major milestones such as FDA clearance, collecting clinical data and capturing a small portion of the market can be definitive time points in the fate of a start-up that impact the valuation of the company.

In the following section, we will discuss the landscape of the MedTech market. This analysis will be used as a starting point to present both the inspirations for student bioentrepreneurs to found a company, as well as the risks and challenges associated with such a venture. Finally, we discuss important open questions and give a conclusion about the *status quo* of student entrepreneurship, especially in the context of medical devices and biotechnology.

2. MedTech market landscape

In order to bring the healthcare industry into perspective with respect to the other comparably sized markets, **Fig. 4** may be helpful. As shown in **Fig. 4(a)**, the size of the financing round for the healthcare industry has increased from $1M in 2012 to $1.6M in 2013 and $2M in 2014. Interestingly, this jump is greater than that in the internet and mobile / telecom industries[26]. **Fig. 4(b)** illustrates the geographical distribution of the above-mentioned angel financing rounds within the US. Furthermore, as shown in **Fig. 4(c)**, 24.8% and 18.9% of funding by angel investors in 2012 and 2014 were devoted to the healthcare industry[4].

Since we are focusing on student bioentrepreneurs in this article, it is critical to gain a better understanding of the breakdown associated with the entrepreneurship landscape with respect to the age range and education level of the founders. As shown in **Table 1**, the number of start-ups founded by college graduates has increased from 23.7% to 33% from 1996 to 2014[11]. However, as shown in **Table 2**, the age for starting a business has increased. Specifically, the percentage for entrepreneurs in the age range of 20-44 years has dropped, while the proportion of entrepreneurs within the age range of 45-64 years has increased. While surprising at first glance, these trends make sense.

This is because those who have achieved a higher degree of education tend to start their careers later on in their lives. Furthermore, it is indicated that 34% and 40% of start-up founders fall within the age ranges of 20-29 and 30-39 years, respectively[11]. Assuming that the start-ups founded by college graduates are based on an inventive and pioneering technology, these data are promising and indicative of a growing trend for inventive initiatives.

Such variations in the landscape are influenced by policies such as the 2010 Affordable Care Act, which is providing more incentive for small companies to join the healthcare industry. Incubators and accelerators as well as angel investment groups have become much more common across many cities in North America, which has promoted start-ups and helped them flourish. These entities provide services for start-ups such as business strategy, management training, office space and more. With this support, starting a company becomes less overwhelming, and seems like a more viable way to create jobs for many young entrepreneurs. However, in general, still most start-ups fail. This demands the birth of more field-specific incubators in order to avoid some of the top reasons for failure.

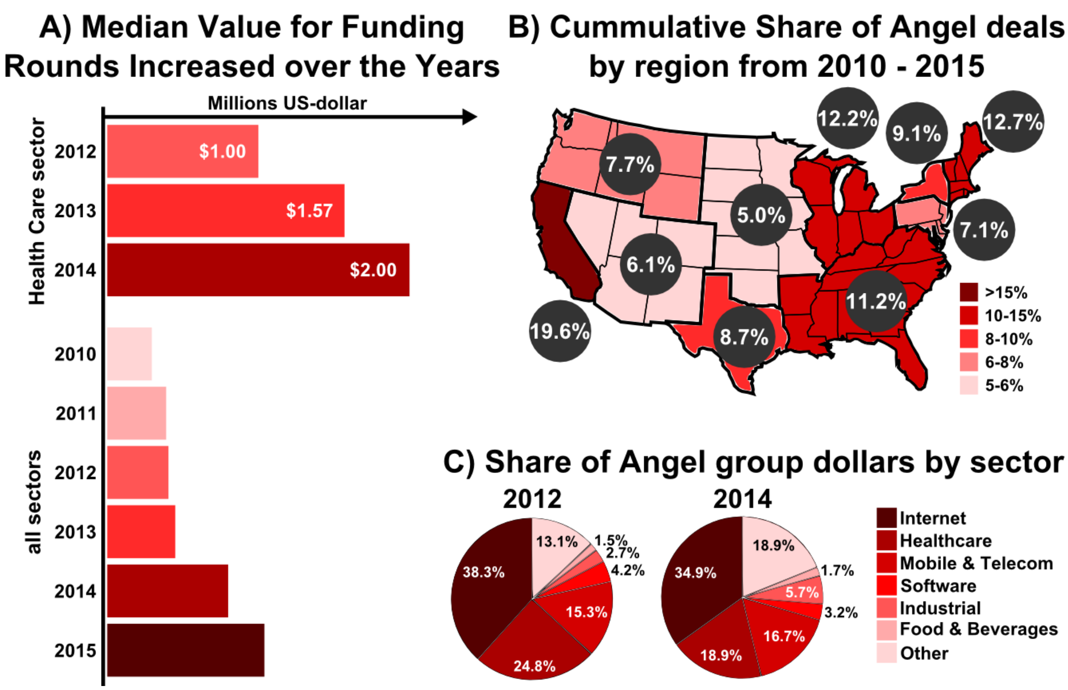

Fig. 4. (a) The size of financing round for the healthcare industry increased from $1M in 2012 to $1.6M in 2013 and $2M in 2014. (b) Geographical distribution of the above-mentioned angel financing rounds within the US[26]. (c) 24.8% and 18.9% of funding by angel investors in 2012 and 2014 were devoted to the healthcare industry[4].

Education	1996	2014
Less than High School	17.2%	15.1%
High School Graduate	32.3%	29.5%
Some College	26.8%	22.5%
College Graduate	23.7%	33.0%
Other	1.0%	2.7%

Table 1. Education level of entrepreneurs for years 1996 and 2014[11].

Age (years)	1996	2014
Ages 20-34	34.3%	24.7%
Ages 35-44	27.4%	22.9%
Ages 45-54	23.5%	26.6%
Ages 55-64	14.8%	25.6%

Table 2. Age range of entrepreneurs for years 1996 and 2014[11].

3. Case studies

Previously, we have mentioned that the next generation of students can get inspiration from some of the established and well-known professors and scientists who have already established a track record of co-founding various startups. In this section, we aim to list a few in order to prove that making an impact and commercialization are things that scientists have done and students can certainly do.

As mentioned earlier, a prominent example is of a well-established professor who may serve as a source of inspiration to students is Robert Langer from MIT. He holds over 1,150 patents worldwide. Professor Langer's patents have been licensed or sublicensed to over 300 pharmaceutical, chemical, biotechnology and medical device companies[36]. As a role model to his peers and trainees, it is no wonder that he is emulated by many of his students. One of these successful inventions is the GLIADEL® wafer, a biodegradable polymer loaded with a chemotherapeutic agent used for the treatment of recurrent gliomas. This work is a perfect example of academic entrepreneurship involving Professor Langer (Departments of Chemical and Biological Engineering), Professor Henry Brem (neurosurgeon at Johns Hopkins University) and W. Mark Saltzman, student at the time and now a Professor at Yale University's Department of Biomedical Engineering.

Another successful example of a student entrepreneur in Professor Langer's group is Samir Mitragotri. In their *Nature* publication in year 2000, entitled "*Transdermal monitoring of glucose and other analytes using ultrasound*"[12], the authors demonstrated painless and convenient methods to measure blood analytes, particularly glucose, without the need for injections. This research subsequently led to the founding of *Sontra Medical Inc.*, which was later acquired by *Echo Therapeutics*. In addition to founding several other companies, Dr. Mitragotri continued his academic career path and is now a professor at Harvard University, which makes his journey a perfect example of bioentrepreneurship by young academics.

Another case study from Professor Langer's group is Armon Sharei's doctoral studies and their translation into a company. Dr. Sharei performed his PhD from 2008 to 2013 under the supervision of Professor Langer and Professor Klavs Jensen at MIT. During this time, he worked on the intracellular delivery of macromolecules, nanomaterials and other compounds. He achieved this by a technique called cell squeezing, which utilized physical stress for direct cytosolic delivery of molecules in the proximity of the cell. As this technique was key to many therapeutic and biotechnological applications such as targeted cancer therapies, genetic engineering and a more effective administration of various medications, Dr. Sharei, Professor Langer and Professor Jensen decided to make the *CellSqueeze*® platform openly available by founding *SQZ Biotech*®. Both of these case studies highlight how Professor Langer has successfully helped commercialize his research, without the necessity to dedicate his occupation to the daily operations of the start-up companies.

Unlike the examples above, there are others who have taken the opposite route (i.e. starting a business from their studies and becoming the pilot of the commercialization of their inventions). These individuals believe that no one is as passionate as the inventor about the successful commercialization of their nascent technology. One successful example of these types of individuals is Cameron Piron. In 1992, Sunnybrook Research Institute (SRI) senior scientist, Dr. Donald Plewes, and his then-graduate student Cameron Piron began developing magnetic resonance imaging (MRI) technology for improved detection and biopsy of breast cancer. Twelve years later, they had a system that was prompting other researchers and clinicians to ask how they could use it. In 2010, *Hologic Inc*. aquired *Sentinelle Medical Inc.*, the spin-off company from Dr. Piron's graduate work, for $85M[24].

Another great example of this type of entrepreneurial academics is Dr. Beau Standish, CEO of *7D Surgical Inc*. Dr. Standish left a full time Professor position in the Department of Electrical and Computer Engineering at Ryerson University to become the CEO of *7D Surgical*, a company he founded with Dr. Victor Yang, that aimed to redefine the surgeon's navigation experience by providing a detailed 3-dimensional view of what lay beyond the surgical incision.

The final example of student-driven entrepreneurship we would like to mention is *Interface Biologics Inc*. (IBI). Their primary areas of focus are anti-thrombogenic additives that reduce thrombosis and programmable combination drug delivery devices.

The company was founded in 2001 based on the work of Dr. Paul Santerre at the University of Toronto. At that time, Jeannette Ho was a graduate student in his laboratory, and helped Professor Santerre found his company. After 15 years, she is still involved with the company in the capacity of Vice President of Operations, and is currently leading one of their main projects on additives in blood dialysis membranes.

Finally, we would like to name two start-ups primarily started and driven by students of the abovementioned academic programs for entrepreneurship. *Sonavex, Inc*. is a student spin-off from Johns Hopkins University's CBID program that has recently raised $3M in Series A financing. In addition, *iRhythm Technologies, Inc.* is the seventh company launched from the Stanford BioDesign program. This company, with its *ZioPatch* technology, is now the biggest company initiated from a BioDesign Innovation Fellowship project to date, impacting 400,000 patients by 2016.

4. Rewards of student entrepreneurship

As a student entrepreneur considers embarking on such a journey, there will be many exciting rewards awaiting him/her, which will provide the incentive to overcome the many challenges on the way to success. Below, we aim to list some of these motivations:

- **Hitting two birds with one stone:** Many graduate students tend to make discoveries during their studies. Some think about why and how things end up the way they do. However, there are others who tend to create things from scratch, build new gadgets and say, "why not?!", "let's make this", "let's try this approach." These folks tend to invent. The rewarding aspect of commercializing inventions is that one can hit two birds with one stone: develop a technology, which can be patented and sold, and publish it in a scientific journal, allowing the individual to obtain a degree based on the performance of the prototype. One of the greatest achievements of student entrepreneurs is that although they may work on one project, they may be able to experience the best of both worlds. It is definitely rewarding to be considered as an achieved entrepreneur, patent holder and inventor, and continue one's scientific journey, which typically involves scientific publications, committee meetings and thesis defenses.

- **Having a bigger impact:** In recent years, due to the improvements made to the world's connectivity, facilitated by the advancement of media and online services, the world's healthcare problems have become more tangible and addressable. Problems such as infectious diseases require rapid, easy and inexpensive solutions or prevention techniques. For many students who are interested in applied sciences, the impact that they can make is no longer limited to sharing ideas in peer-reviewed journals, as they can also take the initiative and create innovative tools and real products that can contribute to resolving worldwide medical issues.
- **Stepping stone for one's career**: Regardless of whether a start-up ends up successful or not, as a student entrepreneur, one gains experience and a new network, which by themselves open up many doors. Among the network one may gain, competitors, collaborators and funding agencies can become one's next employer. Starting a company can be considered a real-life MBA experience!
- **Job creation:** One of the main motivations for many entrepreneurs is the job creation aspect. It is a win-win scenario, whereby one gets to see a venture grow,

while helping others grow professionally up the career ladder. Small businesses and start-ups provide a large pool of jobs, especially for younger generations who are looking for exciting new job opportunities.

- **Contribution to the economy:** As a student entrepreneur, one will be able to contribute to society through both job creation and potential monetization of one's invention. In the case of monetization of inventions, either in the form of selling the product or acquisition of patents, the money spent funding the company will ultimately be brought back into society. This benefit is in addition to the contribution of job creation to society.

- **Success stories for academic institutions:** There is no doubt that patents and successful spin-offs are an important merit for universities and teaching hospitals. As a result, successful student entrepreneurs make the university well renowned to both future students and other companies. This means that innovation and commercialization of inventions bring prestige and licensing revenue, not only for the entrepreneur, but also the host institution[35].

5. Challenges of student entrepreneurship

- **Scarcity of funding:** Much like in an academic setting, the most important challenge facing any entrepreneur is funding. Money to any venture is like blood to the body. One may not realize the value and key role of funding until it runs out, and when that happens, the death of the enterprise is inevitable. One reason for start-up failures is the lack of ability to gain the trust of funding agencies and investors to support the project in the long-term. The "valley of death" scenario typically happens exactly when the project still needs funding to be further developed. (See **Fig. 5**.) However, because of the early stage nature of the technology, there is limited capability in terms of raising capital.

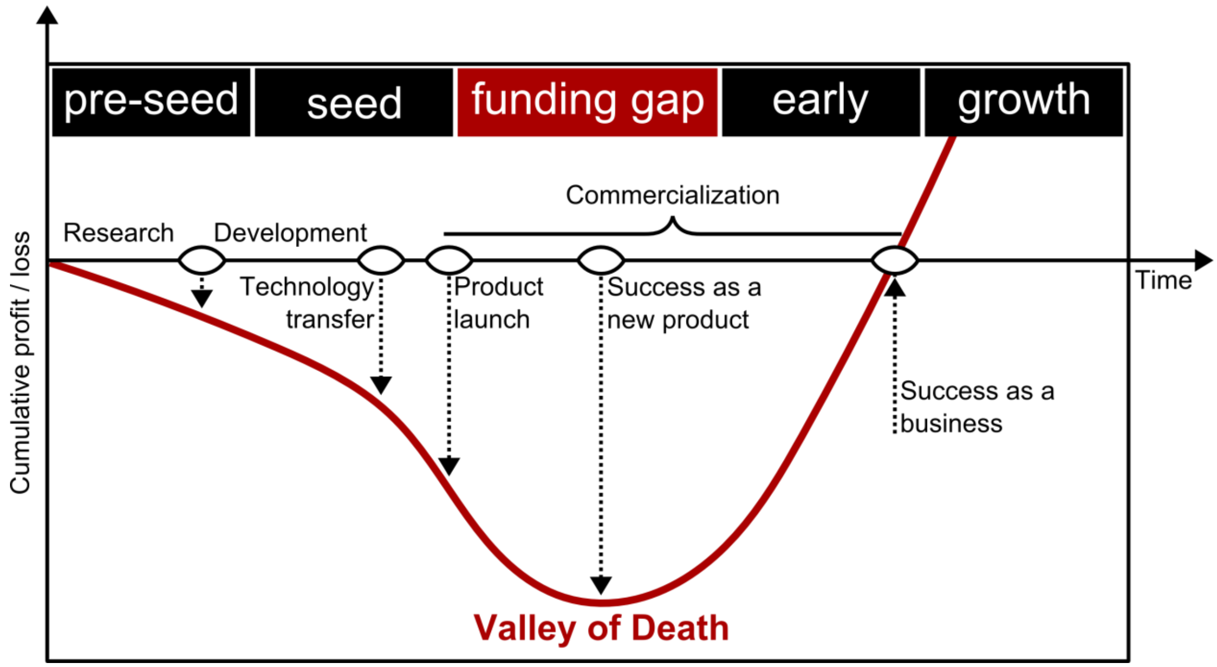

Fig. 5. Funding phases for a typical start-up. Adapted from[38].

- **The high cost of funding:** In fundraising, one needs to provide incentives to the investors, including company shares. When in desperate need of capital, one may actually need to provide more shares for the same capital. As a result, it is important to conduct a cost-benefit analysis and assess the expenses paid by the start-up for a certain amount of cash. Such an expense could appear in the form of company shares, or the amount of return on investment (ROI) interest, or even be as simple as giving up control over your "baby technology." Depending on how urgently and badly the company needs cash, there is more or less dilution associated with venture capital (VC) investment. That said, it is generally encouraged to seek governmental grants, angel investors and crowd-funding whenever possible, as opposed or banks or VC sources. In the case of MedTech where many years of development and millions of dollars of investment are required prior to sales revenue, this fact poses some very serious potential issues. As a result, specifically in the world of MedTech, one needs to consistently ask the following two questions: (1) What is the right type of funding? (2) What are some of the requirements and drawbacks associated with a certain type of funding?

- **Long and costly journey:** As mentioned above, founding and nurturing a company is a long and costly journey. It is estimated that on average, 5-10 years and $5-10M are required prior to sales revenue for a class II product[34]. Because of these costs, as one decides to start such a journey, he / she should be aware of the level of commitment involved, both financially as well as the time invested.

- **The risk:** Aside from the considerable amount of time and money needed for investment into a single product idea, there is always a chance that it may fail! In fact, commercialization of a technology is an extremely high-risk, high-reward route. (See **Fig. 6**.) What if the technology fails? What if a better alternative is introduced? Can you sell your product? Is your business model meaningful? Is your market large enough? Is the customer acceptance rate reasonable? Who are your competitors, and does your product have enough competitive advantage over the current standard of care? Does your technology provide a platform for other applications? If your first product fails, will your company fail as well? **Fig. 6(a)** aims to elucidate some of the top reasons for invention-based start-up failures. This is followed by the rate of failure per year since inception [**Fig. 6(b**)], as well as the ratio of the number of initial raw ideas capable of monetization to successfully commercialized ideas [**Fig. 6(c**)].

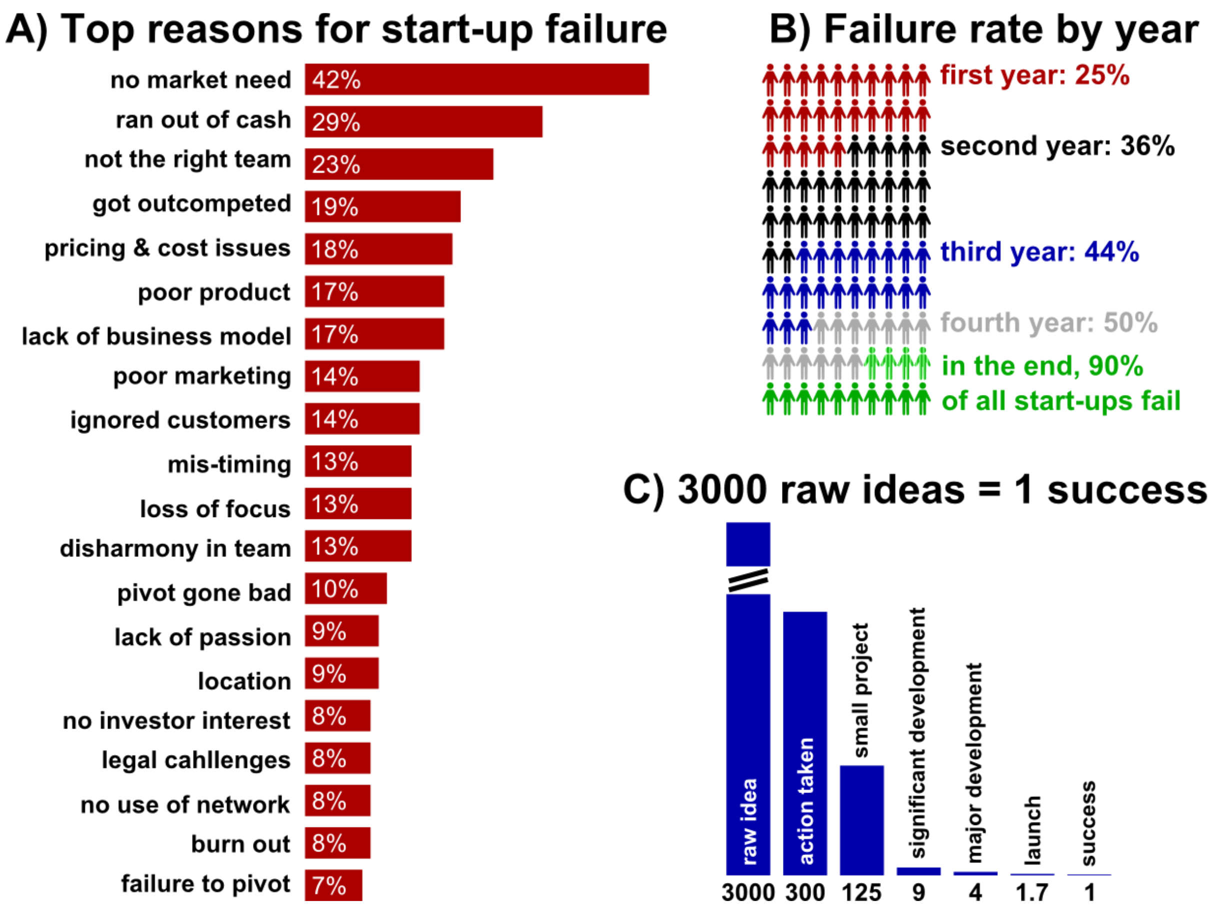

Fig. 6. Challenges of invention-based entrepreneurship: (a) Breakdown of the top reasons for start-up failure. (b) Failure rate by year since inception. (c) The ratio of the number of initial ideas to the number of cases of successful monetization. Figures adapted from[4, 28, 38].

- **Navigating amidst various parties with divergent interests:** As an entrepreneur, one of the most vital skillsets is to create win-win scenarios on a routine basis. This is because as a start-up owner, one does not possess much capital or prestigious affiliations to attract know-how from either industry or academia. As a result, an entrepreneur has to remain sensitive to what motivates various parties involved. These parties happen to possess highly differing interests. Below, some of these parties are listed:

- **Scientific advisors:** It is important to realize what motivates a scientific advisor: some may see the success of their trainees in publishing, whereas some may be more open to partnering up with their students to monetize inventions. Regardless, as co-inventors of the patents, professors will have a key role in whether / how to proceed with commercialization of the technology. This factor is especially important in the case that a mentor is not interested in founding a company, and rather is focused on academic merit.
- **Host institutions:** Academic institutions, universities and teaching hospitals are not in the business of launching enterprises, investing capital in their external spin-offs or dedicating staff to help with the daily operations of these entities. That said, they are indeed interested in the monetization of the patents for which they have paid legal fees[19]. Due their interest in monetization, they typically prefer the acquisition of the patent as early as possible, so that they would need to pay less for the patent costs, and receive some money before the costs would get out of control. As a student entrepreneur running a small start-up, unfortunately, one typically is not capable of providing such amounts of cash. As a result, the

academic institution may not be cooperative in transferring the ownership of the IP to the company (because one simply cannot afford the patent fees)[9]. At the same time, one may not be able to conduct fundraising and ask for investments if one is not the owner and the decision maker with respect to the IP, which is the most important piece of any start-up company[1]. Unfortunately, this "chicken-egg" cycle is an extremely common point of failure for many university spin-offs.

- **Incubators:** These entities can provide exciting resources, workshops and inexpensive or free space to small business enterprises. However, one of the challenges associated with dealing with these entities is that they typically lack the domain knowledge and field-specific network necessary for the success of a MedTech product. This is less so of an issue in the software and app industry. Fortunately, there is a recent trend towards having incubators specific to bioentrepreneurship and MedTech innovations. As examples, see JLabs and Onestart.

- **Funding agencies and investors:** These entities are great resources to tap into in order to finish prototyping and to bring a product to the market. However, there are requirements associated with each funding opportunity, which may affect the way one envisions the development and / or sales of the product. In addition, as discussed previously, any private equity provided by investors and VCs dilutes the founders' shares in the company, resulting in less control over the directions towards commercialization of the invention.

- **Founding team:** One needs to team up with teammates whose level of initial passion, long-term dedication and ultimate vision are shared at a similar basis. Otherwise, disagreement over exit strategies, potential partnerships and ownerships can easily lead to legal conflicts, whereas an optimal team is probably one of the most important qualities for a successful turnout.

It should be noted that managing parties with differing interests is one of the most sensitive topics requiring ethical considerations, the lack of which can easily lead to the failure of the entire initiative. While this topic can form the subject matter of an entire article, due to the importance of the issue and the potential effect on students' career paths, we will briefly describe it here. On one hand, faculty members may exclude or minimize the shares of trainees who may have co-developed the invention; while extreme, this situation is not unheard of. It is crucial to form a committee encompassing those with expertise in academia, business, and ethics, and those representing student bodies, faculty, and the technology transfer office to ensure fair and standard practices. On the other hand, faculty members may want graduating students to remain committed for at least a reasonable amount of time to see the project through. Here, ownership of the company may be structured to incentivize their commitment for a pre-specified number of years, for example by vesting shares or having a buyback policy.

6. Other considerations for this journey

- **Chief executive officer vs. founder:** Starting a company is different from managing the daily operations of the company. On one hand, there are many entrepreneurial characters, such as Mark Zuckerberg, Bill Gates and Steve Jobs, who have started a company and continued with the daily operations of their enterprises until successful monetization. On the other hand, there are scientific role models, such as Professors Robert Langer (MIT) and Paul Santerre (University of Toronto), who have remained dedicated to their academic positions. As one starts forming a company, one needs to consider whether he / she is interested in starting an establishment, delegating business tasks, giving away shares and letting others run with the commercialization, or whether he / she is purely dedicated to the success of this enterprise no matter the length, cost and risk of the journey. This is probably one of the most vital questions one needs to ask early on.
- **Partnership vs. dilution:** As one launches an organization from scratch, there are many things to do, and achieving the objectives in a timely manner is by no means feasible for one person. Consequently, the founder has a choice: he / she can try to own everything and do everything by himself / herself, which typically comes at the cost of extremely slow pace and lack of a proper network. Alternatively, the founder can leverage energy, time and other resources (e.g. network, capital, etc.) of others at the cost of giving away company equity, which is certainly not the most desirable option for most founders. An analogy for this decision-making scenario is to *have all of nothing* vs. *a piece of something.*

- **Outsourcing vs. in-house prototyping:** This is another choice facing most start-ups, specifically in the area of MedTech. Those businesses with enough capital can always outsource the fabrication and development of their devices. Typically, outsourcing results in much faster pace for development, in addition to access to another organization's resources, and sometimes, technical support after prototyping. However, this is an extremely expensive option for companies with limited amounts of cash, especially those at early stages surviving on governmental funding opportunities.
- **Prototyping vs. scalability:** One should realize that there is a major difference between prototyping in a laboratory vs. the complexity of scaling a product to commercial volumes. FDA regulations involve strict quality assurance guidelines that must be followed in a manufacturing facility. Such regulations include Good Manufacturing Practices (GMP), and are designed to maintain the safety of a device while it is being built. Meeting these standards is complicated, and the final product design will be far different than the initial prototype.
- **Patent strategy:** Given the ever-increasing costs of patent fees, it is imperative to select the right IP strategy. Typically, this decision-making involves determining when to file for patent applications, as well as which countries to enter into.
    - **Timing:** An ideal timing allows the start-up to be able to conduct adequate fundraising so as to be able to pay the patent fees. However, filing for patent applications should also be done early enough to allow the inventors to disclose the invention and seek funding. An early application

may leave the enterprise without enough funding to pay for the legal fees, whereas a late application may position the inventors at a risk of public disclosure and of course, encourages increased technical competition.

- **Target markets:** In addition to the timing, particularly in the case of international patent applications, it is critical to decide wisely in terms of which countries to enter into. Obviously, the more countries to be covered, the higher the costs of the legal fees. It is important to note that in some countries (e.g. China), the enforcement of IP laws may not be easy and so many consider the associated fees as not necessary. Furthermore, IP protection in Japan seems to be more difficult than in some other countries. Most early stage North American start-ups choose to file in the US, Canada and perhaps Europe.

- **Company incorporation strategy:** The same concept described above regarding optimal timing of filing for patent applications holds true for when to legally incorporate the company's existence. Incorporating a company too early results in using commercialization funding to conduct early stage research, while late incorporation of the company can lead to other consequences, such as permitting competitors to legally register the name / website domain of one's company or technology. One also needs to note whether the incorporation of the company needs to be a federal incorporation, as opposed to a provincial / state registration. This requires thorough study of the possible level of expansion foreseen based on the potential impact of the technology. By means of example, some inventions can improve the status of healthcare in some countries, but not in other jurisdictions or countries.

- **Co-founder(s):** As discussed previously, when teaming up with other co-founders, one needs to consider their level of initial passion, long-term dedication and ultimate vision. Moreover, one also needs to consider other factors, such as availability to commit time, energy and how established they are in their personal and professional lives. On one hand, while energetic and ambitious founders are essential in the success of a start-up, their career and family choices may influence them to move on from one city and career stage to another. On the other hand, established founders will have more experience and network to add to the team.

- **Exit strategy:** This is one of the subjects that investors always inquire about during the due diligence and assessment of a company. The reason is that investors would like to know when / how the company is going to make money. In the MedTech sector, whereby regulatory approvals and patent protections add to the complexity of an already long, costly and risky journey, many scientists, student entrepreneurs and academic institutions would prefer to sell the ownership of the IP and / or the associated spin-off company. This option allows the buyer to save on the amount of time and money spent on the research and development of a risky idea. It also permits the academic institution to make a profit from its investment (costs of the patent incurred). Finally, university professors and student entrepreneurs favor this option, since they can easily continue their academic journey while making sure their invention continues reaching the market, and helping patients receive better care. Nonetheless, acquisition is an exit strategy that requires many factors, including luck, to happen. However, at the moment, it remains one of the most desirable alternatives to scientist inventors and student entrepreneurs. Because of the possibility of such acquisitions, students no longer need to quit their studies in order to ensure the success of their commercialization efforts. That said, still to date, the chances of acquisition remain low, calling for some policy changes and considerations in the structure of the entrepreneurial ecosystem, including the various parties listed in this article.

7. Conclusion

In this article, we have looked into how recent transformations in society, followed by changing attitudes of academic institutions, have allowed for a younger generation of student entrepreneurs to start a business based on their inventions, while being able to complete their studies and even further pursue their academic ambitions, without compromising the successful commercialization of their inventions. Particular emphasis has been placed on bioentrepreneurship and enterprises geared towards the MedTech ecosystem. Various aspects of student entrepreneurship are listed and discussed. Of particular interest are the rewarding aspects and challenges associated with such a journey, as well as some of the issues one needs to consider prior to embarking on this journey. A few case studies have been presented and analyzed in order to study diverse approaches chosen by corporations to survive in the long run, after being founded by a student or academic bioentrepreneur.

Conflicts of Interest:

The authors report no conflicts of interest. AM and KTT are affiliated with a Canadian start-up called *Spinesonics Medical Inc*. (this company is not mentioned in this manuscript). NT and ML are entrepreneurial neurosurgeons affiliated with start-ups, but their companies are not mentioned in this manuscript. HB was a visionary in a product called Gliadel™, which is named in the manuscript as an example of successful academic entrepreneurship (no commercial endorsement). All individuals named in the case studies have agreed to their names being published in this article.

Acknowledgements:

The authors would like to thank Professors Alireza Khademhosseini (Harvard-MIT Division of Health Sciences and Technology), Robert Langer (MIT) and President Ronald J. Daniels (Johns Hopkins University) for helpful discussions.

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