



UNIVERSITAT AUTÒNOMA DE BARCELONA
FACULTAT DE CIÈNCIES
DEPARTAMENT D'INFORMÀTICA

**HIGH-SPEED POLYMERASE CHAIN REACTION IN
CMOS-COMPATIBLE CHIPS**

Ivan Erill Sagalés



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CMOS-COMPATIBLE CHIPS**

Memòria presentada per
Ivan Erill Sagalés
per optar al grau de
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Els directors de la tesi:

Jordi Aguiló Llobet

Jordi Barbé Garcia

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ABSTRACT

In the last decade of the twentieth century, the fields of μ -TAS and, more specifically, DNA-chips have acquired increasing importance in the microsystems arena. The main reason for this surge of interest lies in the advantages these new devices seek to bring forth: faster, cheaper and completely automated analyses, and also in the outbreak of novel analytical techniques (e.g. hybridization chips). In the particular case of DNA-chips, functional prototypes have been demonstrated for PCR, LCR, gel electrophoresis, di-electrophoresis, hybridization and various combinations of these techniques, whilst hybridization chips (mainly arrayer chips) have become a successful market application. But, even though a considerable amount of work has been carried out in these few years, much research is still required to address fundamental problems of DNA-chips.

In this doctoral work, a common-ground technological setup for the production of multifunction DNA-chips (i.e. PCR plus electrophoresis systems) has been laid down, placing strong emphasis in its compatibility with standard CMOS processes in order to produce proto-industrial prototypes. As a demonstrator of this technological setup, PCR-chips have been designed, manufactured and tested, and the chip PCR reaction has been optimized with respect to surface materials, insertion and extraction methods, biochemical mix composition, heater/sensor setups (Peltier/thermocouple vs. thin-film driven systems) and reaction kinetics.

RESUMEN

En la última década del siglo XX, el campo de los microsistemas para análisis total (μ -TAS) y, más concretamente, el de los DNA-chips ha adquirido una importancia preponderante en el ámbito de los microsistemas. En gran parte, el creciente interés por estos dispositivos se debe a las substanciales mejoras que prometen: análisis más rápidos, baratos y automatizados, pero también es debido a la posibilidad de implementar técnicas analíticas antes impensables (e.g. chips de hibridación). En el caso particular de los DNA-chips, se han desarrollado prototipos funcionales para PCR, LCR, electroforesis en gel, di-electroforesis, hibridación y varias combinaciones de estas técnicas, al tiempo que los chips de hibridación masiva (mayoritariamente basados en arrayers) han llegado a convertirse en un éxito comercial. Aun así, y aunque se ha llevado a cabo mucho trabajo en estos años, es necesaria todavía mucha investigación para afrontar algunos de los principales retos de los DNA-chips.

En el transcurso de esta tesis doctoral, se ha llevado a cabo el desarrollo un proceso tecnológico común para la fabricación de DNA-chips multifunción (i.e. sistemas versátiles basados en PCR y electroforesis), poniendo un especial énfasis en la compatibilidad con los procesos CMOS estándar, a fin de conseguir desarrollar prototipos proto-industriales. Como demostrador de esta puesta a punto tecnológica, se han diseñado, fabricado y testado chips de PCR, y la PCR en chips ha sido optimizada con respecto a materiales de fabricación, metodologías de inserción/extracción, composición bioquímica de la mix de PCR, diferentes configuraciones de calentadores/sensores (Peltier/termopares vs. resistencias integradas) y la cinética de la reacción.

To mom, dad and Nadina.

If you take a bale of hay and tie it to the tail of a mule, and then strike a match and set the bale of hay on fire; and if you then compare the energy expended shortly thereafter by the mule with the energy expended by yourself in the striking of the match, then you will begin to understand the concept of amplification. William Shockley.

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FOREWORD

To some extent, writing is always influenced by what the writer might be reading at the moment of his writing. And it happens to be the case that, among other books, I've been reading Richard P. Feynman's "*The pleasure of finding things out*" during the painstaking process of writing (I hope the reading proves easier) this thesis. In this wonderful collection of short essays and interviews, Feynman tells the reader about his life and its anecdotes, his doubts and his convictions and, most importantly, about his concept of science. And, indeed, Professor Feynman thought and did many things throughout his life. He did celebrate with champagne the bombardment of Hiroshima, he did work out the complicated mathematical methods of quantum electrodynamics, and he was to give his first oral presentation to an audience containing, among other, Pauli, Einstein and von Neumann. He would also tamper with safe-locks at the top-secret Los Alamos facility, with the same easygoing nature with which he would pinpoint a faulty valve design in a blueprint for the nuclear production plant of Oak Ridge without understanding any of the symbols drawn on it. He was a born critic too and, in his idiosyncratic manner, he would demolish pseudoscience with the same emphasis and ease he would criticize the NASA Space Shuttle program after the Challenger disaster. Indeed, were he alive today, I'm pretty sure he would hammer down all the nanotech mongers that herald him as their ultimate messiah.

All in all, and saving the distance, there are many thoughts and doings I share with and positively envy of Feynman's life. Nobel and Einstein prize awards, for one, are things I'll most likely never get, nor do I desire, although I could make use of Feynman's irreverent retort to the reporter who informed him of the Nobel prize award, in the middle of the night: "You could have told me that in the morning!" Nevertheless, there are also many things I do not envy Feynman for. I would not like upon my shoulders the responsibility, which he carried so well, for the development of nuclear fission bombs, nor do I envy his long childhood strolls in the woods with his father, which he recalls too well, full of wonder, discovering science. To be honest, maybe I envy those strolls a bit, the bucolic essence in them. In fact, mom and dad did not take me into such long forest promenades; it was another place, another time: modern times. But they did succeed in imbuing my sister and me with a passion for science and doubt that, together with the gift of life, I hold as their greatest endowment, my greatest

tenet. For this, and to my sister for kindly -most of the time- sharing it with me, I would like to thank them all again, and yet again.

But returning to Feynman and his influence on this small piece of scientific (I hope he would call it so) work, I can but quote him: "*there is one feature I notice that is generally missing in Cargo Cult Science**... *It's a kind of scientific integrity, a principle of scientific thought that corresponds to a kind of utter honesty- a kind of leaning over backwards. For example, if you're doing an experiment, you should report everything that you think might make it invalid- not only what you think is right about it... In summary, the idea is to try to give all the information to help others judge the value of your contribution...*" Thus, even thinking mine won't be such a great contribution to science at all, that is precisely what I have tried to do here. And, if in the process of doing so I have made reading a bit rougher or extended myself too much, I can only give reviewers and readers alike Professor Feynman's and mine's most sincere apologies and, maybe, suggest leaving the toughest parts for the preliminary steps of a welcome and well-earned siesta.

* Feynman's name for pseudoscience, in reference to Solomon Islands natives' practice of constructing fake wooden airports to attract good-delivering planes like those they had seen landing during the II World War, as reported by John Frum in 1949 [Harris1989].

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Even though, at times, this one came close to it, a doctoral thesis is not, or should never be, a one-man quest. Many are the people who have lent a hand in this work, either professionally or personally, and to whom I feel very much indebted. Even at the risk of extending the already substantial length of this treatise, I'll try to name them all since, without them, this work could have never reached completion. If, along the way, I miss someone who should be mentioned here, I can but offer my deepest apologies.

My first acknowledgment must be towards my family and close friends, who have endured my varying moods and absences during these years with much patience and, almost, without reproaches. I feel also much indebted to Dr. Jordi Aguiló of the CNM-IMB Biomedical Applications Group¹ and Dr. Jordi Barbé of the UAB Molecular Microbiology and Bacterial Genetics Group², for assuming the direction of this work, and to Dr. Elena Valderrama of the UAB Computer Sciences Department³, for initiating the research line that ultimately led to it.

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² Molecular Microbiology and Bacterial Genetics Group, Department of Genetics and Microbiology, Faculty of Sciences, Universitat Autònoma de Barcelona (UAB)

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³ Microelectronics Unit, Computer Sciences Department, Technical and Superior School of Engineering, Universitat Autònoma de Barcelona (UAB)

⁴ Fundació IRSICaixa, HIV Day-care Hospital. Hospital Universitari Trias i Pujol.

⁵ BioPAT - Biopathology Laboratory, Hospital de Barcelona