P R
B X

When power electronics makes PCR test possible and accurate!

On 11th of February 2020, the International Committee on Taxonomy of Viruses adopted the official name 'severe acute respiratory syndrome coronavirus 2' for the coronavirus that causes COVID-19 otherwise known as SARS-CoV-2. During the past two years or so, in one way or another the world population has been affected by this virus, and the polymerase chain reaction (PCR) test has entered into our daily lives. At this point we could quite easily question what a power supply has to do with PCR, but behind the scenes the power supply industry and the latest digital power technologies have contributed greatly to make the PCR process efficient and accurate. Before we disclose how, let's go back in time to the origin of everything.

Reading inside the double helix!
We all learned at school about the human hereditary material known as deoxyribonucleic acid, or DNA, carrying all the genetic information and instructions needed for organisms to develop, grow, survive, and reproduce. Originally discovered in 1866 by Gregor Mendel, known as the 'Father of Genetics', it was to be many years later that scientists discovered how to break the DNA's secret code and how it could be best used for the good of humanity.

With high regard for the numbers of scientists making discoveries, a major cornerstone was reached in 1953 when James Dewey Watson and Francis Harry Compton Crick published on DNA's double helix structure that twists to form the typical ladder-like structure we have all seen in many representative forms (Figure 01). Their work was rewarded in 1962 with the Nobel Prize in Medicine, which they shared with Maurice Hugh Frederick Wilkins for their discoveries concerning the molecular structure of nucleic acids and its significance in information transfer in living material.

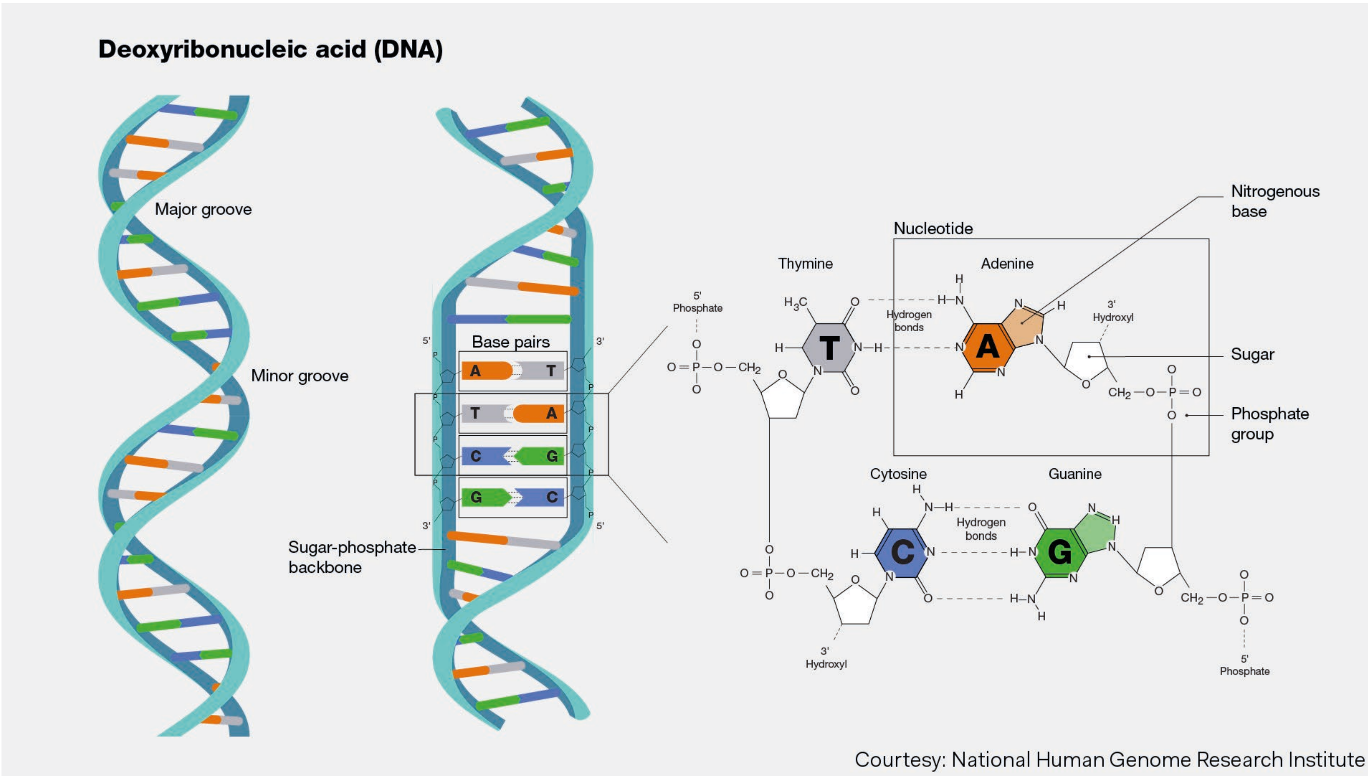

Figure 01: DNA double helix structure (Courtesy National Human Genome Research Institute)

DNA composition is like individual letters of the alphabet. When they are combined with one another in a specific order they form to make words, sentences, and stories. Reading the book and understanding its contents required intensive research and it was only in March 2022 that scientists finally mapped the first complete human genome, composed of more than 3 billion of base-pairs. It is hard to visualize what it represents, but translated into something more tangible it would be the equivalent of a book with one million pages – a lot of bed time reading.

The completion of the human genome has been made possible by a great number of technological innovations e.g., Oxford Nanopore's DNA sequencing method which can sequence up to 1 million DNA letters at once but with some mistakes, and the PacBio HiFi DNA sequencing method, which can read 20,000 letters with 99.9% accuracy. Great achievements, but both would not have been possible without pioneering inventors' discoveries.

Understanding DNA has been a very important research area and a developing toolbox to decode, it is the dream of every biochemist and it is worth mentioning Kary Banks Mullis who in 1983 invented the PCR that has contributed to boost the research and speed of in depth DNA understanding (Figure 02).

The DNA copy-machine is born!

Urban legend or reality? it is said that in 1983 while driving from the Bay area to his cabin in Mendocino, like a bolt of lightning out of the California sky Dr. Kary Banks Mullis imagined a way to pinpoint a particular stretch of DNA and synthesize an enormous amount of copies. At that time Mullis worked for the company Cetus and focused on turning his vision into a process.

Figure 02: Dr. Kary Banks Mullis

After many ups and downs, in 1987 Mullis submitted a paper to the review Nature : "Methods in Enzymology" which was the trigger of the PCR evolution. In 1993 he received a Nobel Prize in chemistry for his invention of the polymerase chain reaction (PCR). The process, which Mullis conceptualized in 1983, is hailed as one of the monumental scientific techniques of the twentieth century.

What is PCR and how does it work?
The polymerase chain reaction (abbreviated PCR) is a laboratory technique for rapidly producing (amplifying) millions to billions of copies of a specific segment of DNA, which can then be studied in greater detail. PCR involves using short synthetic DNA fragments called primers to select a segment of the genome to be amplified, and then multiple rounds of DNA synthesis to amplify that segment (Figure 03). This is done by using a specific process that requires the samples to be placed in tubes and exposed to a very precise thermo-cycling, and this is where the power supply meets the DNA!

This process includes several steps but three are the most critical (Denaturation, Annealing, Extension) and repeated a number of times to make copies of the DNA segments (Figure 04). Without entering into too much detail we can summarize the three critical steps below:

Step One - Denaturation
The preparation contained in the tube is heated to at least 94°C. The heat breaks the hydrogen bonds of the original DNA sample and separates the DNA into single strands.

Step Two – Annealing
The temperature is lowered to approximately 5°C below the melting temperature of the primers, between 50 to 60°C, allowing the DNA primers and the DNA polymerase enzyme to bind to the individual strands of DNA that were separated by the heat. At this point, the nucleotides (A, T, C, G) from the added mixture solution will pair with the individual separated strands of DNA that resulted from the heating process.

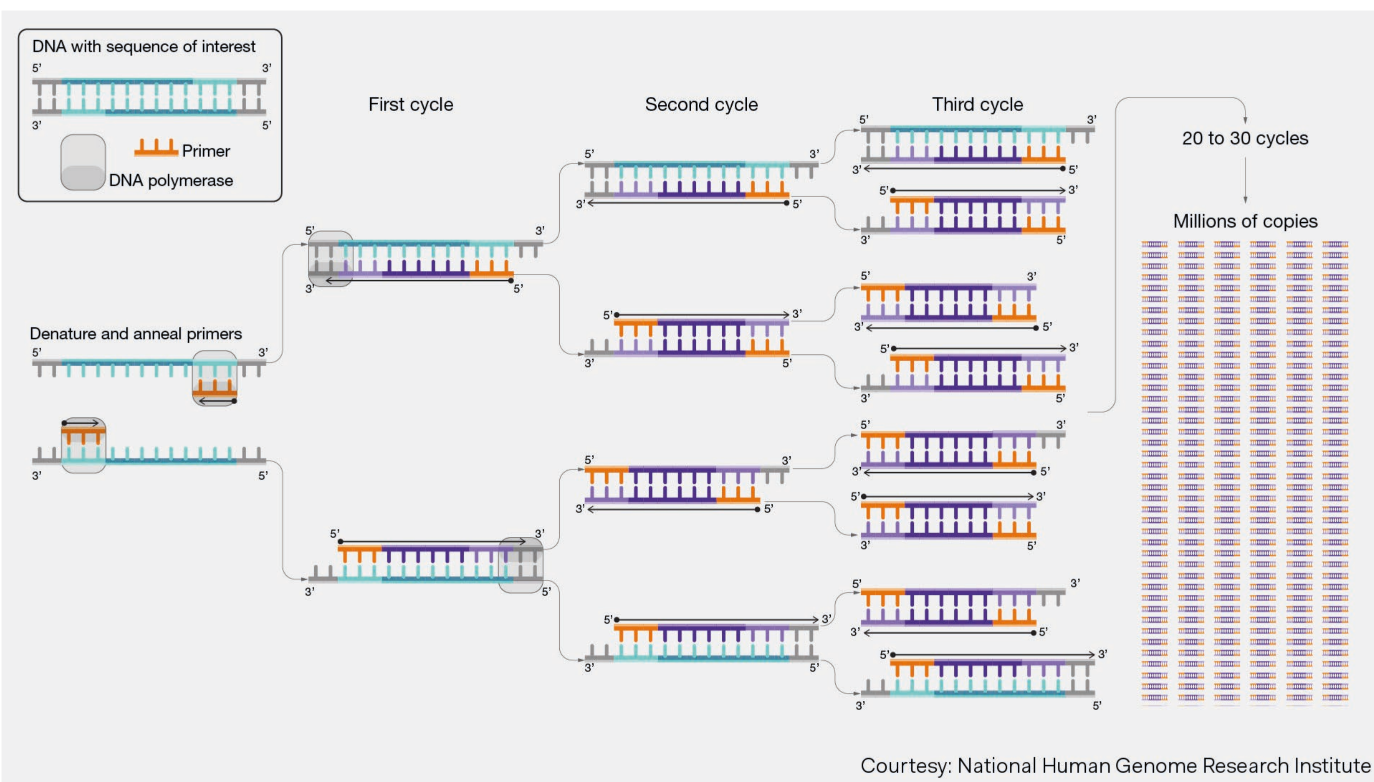

Figure 03 : PRC Process and Cycles (Courtesy National Human Genome Research Institute)

Cycle	Step	Temp (°C)	Duration	Cycles
Pre-denaturation	Denature DNA	95	5 minutes	1x
Thermal Cycling	Denature	95	1 minute	30 – 40x
	Anneal primers	55	1 minute	
	Extend	72	2 minutes	
Final extension	Extend	72	10 minutes	1x
Hold	Hold	4		1x

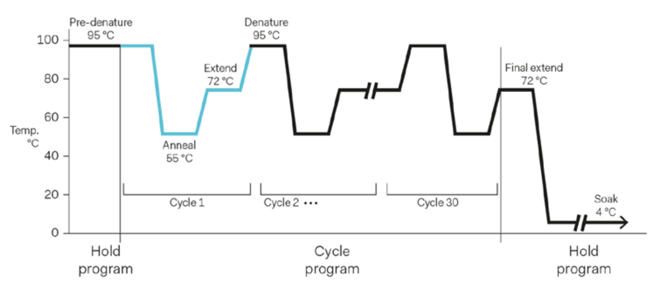

Figure 04 : PCR Cycles and Durations (PRBX)

Step Three - Extension
The temperature is then increased up to 72°C to start the extension process. Then, once segments are joined together they form a new complementary strand of DNA. A new duplicate double-stranded DNA molecule has been formed from each of the single strands of the original sample molecule. When the sequence is completed the temperature is then increased to start a new cycle.

Steps one to three are then repeated about 30 to 40 times which automatically repeats the heating and cooling cycles of the process, resulting in the DNA sequence being doubled each time the heating/cooling cycle is conducted. At the end of the process millions of copies of the original sample are obtained.

Step Four – Final extension and storage
A final step of extension is required to allow all the PCR products to be correctly synthesized, usually at 72°C for 10 min. Finally, the temperature should be reduced to 4°C to store the PCR product until analysis.

Depending on the final target, time or level of accuracy required, variations of this process are often used e.g., Quantitative real-time PCR (qPCR), Reverse transcription-PCR (RT-PCR), Reverse transcription-quantitative PCR (RT-qPCR), Digital PCR (dPRC) and digital droplet PCR (ddPCR), Microfluid PCR.

Power supplies for efficient PCR
There are many medical applications requiring thermal control e.g., neonatal incubators, blood warming for Hemolysis, laboratory incubation chambers and so on. Most of those applications require accurate thermal regulation and most of the medical power supplies with output voltage control are suitable for such applications. In the case of the PCR equipment (Figure 05) and the specificity of the thermal cycling with high accuracy and repetitive sequences, they require a specific power solution, and often adopt a modular approach with the power train and control built in the PCR thermal-control loop.

Figure 05 : Typical laboratory PCR equipment (PRBX/ Natatravel/ Shutterstock)

As shown in figure 04 the thermal cycles are fairly short, requiring the heating element to adjust its temperature between +95°C high, +50°C low, +72°C plateau and back to +95°C after four minutes. This cycle is repeated 30 to 40 times, with a very high accuracy level.

There are different methods to generate and control the temperature in thermocyclers but many are using Peltier effect elements. If the main application of the Peltier effect is cooling, the Peltier effect can also be used for heating or control of temperature. It could also be associated to another heating element and then using a controlled hysteresis, cool down the thermal chamber.

PCR thermocycler manufacturers have developed very complex algorithms to adjust and control the level of temperature with high accuracy. With the introduction of digital power and control and energy management it has become easier to interface the thermocycler CPU to the switching stage and to control voltage and current via a digital interface e.g., PMBus, to power the heating/cooling elements (Figure 06).

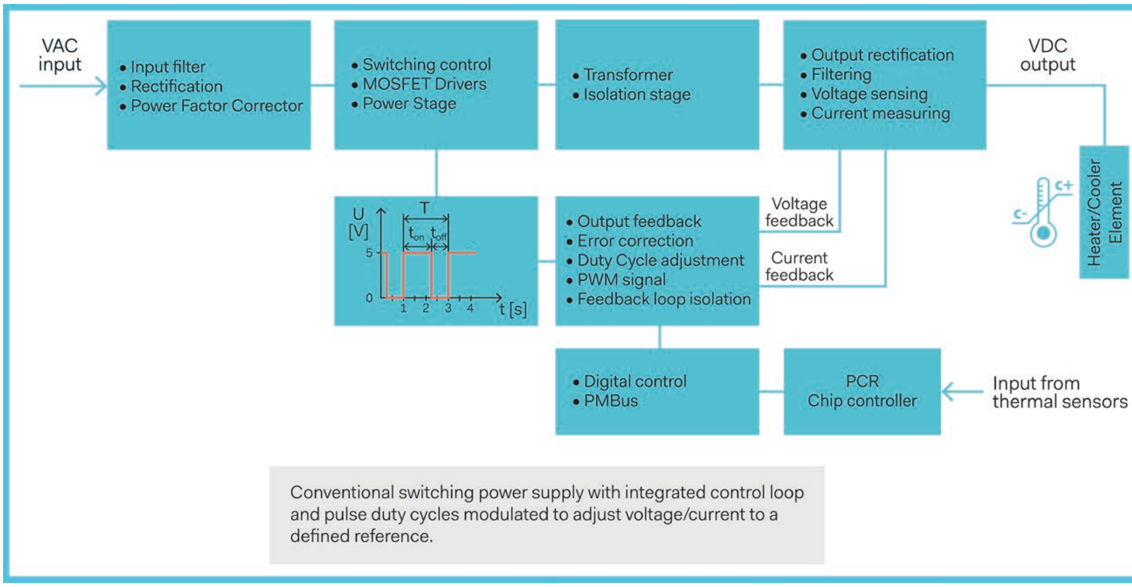

Figure 06 : Conventional power supply with digital control and monitoring via digital input e.g., PMBus (PRBX)

In some case the PWM signal is generated by the thermocycler controller and injected into the power supply switching stage to tightly control the parameters without additional steps (Figure 07). Because the power stage is highly integrated into the thermal control loop, it often becomes a part of it and power designers have to work in close cooperation with the programmers to offer the most optimized response time to a specific demand, which is very interesting and indeed quite different from the more conventional ways of working when designing power solutions.

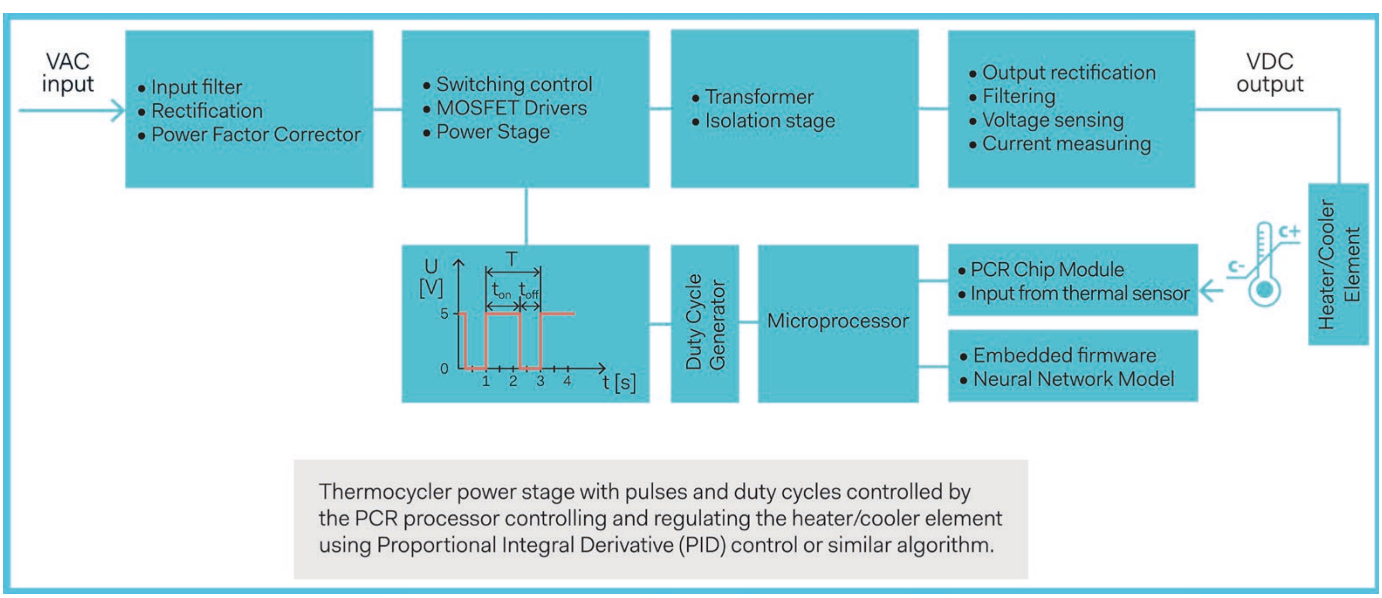

Figure 07 : Power supply controlled by and external PWM signal part of the PCR control loop (PRBX)

In conclusion:
From its discovery by Dr. Kary Banks Mullis in 1983 to the mass application to detect the presence of SARS-CoV-2 virus in billions of samples, PCR technology has played a very important role in medical research and public health. This has also been a very interesting area for power electronics engineers to design power solutions (Figure 08) in tight cooperation with the medical industry to develop very specific power supplies with a high level of programming and system integration.

Who said the power supply industry is boring?

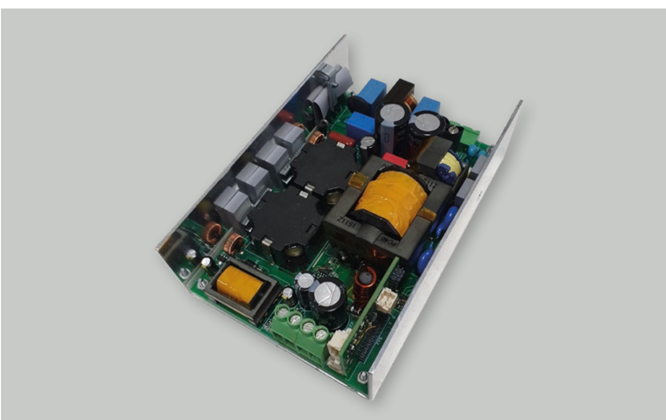

Figure 08 : POWERBOX power supply for thermocycler application (PRBX)

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About Powerbox
Founded in 1974, with headquarters in Sweden and operations in 15 countries across four continents, Powerbox serves customers all around the globe. The company focuses on four major markets - industrial, medical, transportation/railway and defense - for which it designs and markets premium quality power conversion systems for demanding applications. Powerbox's mission is to use its expertise to increase customers' competitiveness by meeting all of their power needs. Every aspect of the company's business is focused on that goal, from the design of advanced components that go into products, through to high levels of customer service. Powerbox is recognized for technical innovations that reduce energy consumption and its ability to manage full product lifecycles while minimizing environmental impact. Powerbox a Cosel Group Company.

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About the author
Chief Marketing and Communications Officer for Powerbox, Patrick Le Fèvre is an experienced, senior marketer and degree-qualified engineer with a 40-year track record of success in power electronics. He has pioneered the marketing of new technologies such as digital power and technical initiatives to reduce energy consumption. Le Fèvre has written and presented numerous white papers and articles at the world's leading international power electronics conferences. These have been published over 450 times in media throughout the world. He is also involved in several environmental forums, sharing his expertise and knowledge of clean energy.

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