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Heat Transfer Simulation of Various Material for Polymerase Chain Reaction Thermal Cycler

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ABSTRACT

Medical diagnosis is the initial stage in identifying a person's condition, disease or injury from its signs and symptoms. The diagnostic method is carried out quantitatively by using a diagnostic kit which measures data such as blood pressure, heart rate frequency and blood cell concentration. These diagnostic kits are available in their respective capabilities and their activities require medical facilities and logistical readiness to function. Furthermore, Indonesia's geographical condition which consists of many islands and mountains causes uneven distribution of health facilities and laboratories in each region. Therefore, resulting in problems such as inadequate access and availability of these diagnostic kit in each region. Presently, one of the most widely used diagnostic methods is the Polymerase Chain Reaction (PCR) which allows the amplification of specific fragments from complex DNA. In PCR, only a small amount of DNA is needed to produce enough replication copies which were further analyzed by microscopic examination. This process begins with thermal cycling, which is the reactant's exposure to the heating cycle and repetitive repairs to produce reactions to different temperatures. This study aims to examine the material used for thermal cyclers which is an essential aspect of the heat transfer

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needed by the PCR process. In this study, heat transfer from several materials were simulated and analyzed by COMSOL Multiphysics 5.3 Software. The following results were obtained from the simulation: the saturation time for heating aluminum, copper and nickel were 29,37 and 51 seconds, respectively. Meanwhile, the cooling time was 26, 35 and 55 seconds, respectively. In addition, the saturation time for heating and cooling silver and Polydimethylsiloxane (PDMS) were 26 and 1480 seconds, respectively.

Keywords: *COMSOL Multiphysics 5.3; Material; Heat Transfer Simulation; Polymerase Chain Reaction; Portable Thermal Cycler*

Introduction

Medical diagnosis is the initial stage in identifying a person's condition, disease or injury from its signs and symptoms. Furthermore, the diagnostic method is carried out quantitatively by using a diagnostic kit which measures data such as blood pressure, heart rate frequency and blood cell concentration. These diagnostic kits are available in various capabilities, ranging from blood pressure measuring devices to devices that require laboratory treatment such as blood cell checking devices. All of these diagnostic activities require the readiness of facilities and medical logistics to function.

Presently, one of the most widely used diagnostic methods is the Polymerase Chain Reaction (PCR) which allows the amplification of specific DNA fragments from complex DNA. In PCR, only a small amount of DNA is needed to produce enough replication copies which were further analyzed by microscopic examination [1]. It requires a thermal cycle or repeated temperature changes between two or three separate temperatures to amplify the specific nucleic acid target sequence [2]. Thermal cyclers with metal heating blocks powered by Peltier elements are widely used commercially by researchers in this field [3].

Furthermore, in making a thermal cycler machine, the material used as a container for heat transfer is of great importance because the use of PCR thermal cycler device material affects the time needed in the reaction process [4]. Some PCR thermal cycler devices are used commercially and have been patented using several materials such as Aluminum [5] – [8], Copper [9, 10], Nickel [8, 9, 11] and Silver [6, 12].

In general, the size of a commercial PCR machine is quite large and heavy therefore, it only allows PCR reactions to be carried out in a fully equipped laboratory [13]. However, the geographical condition of Indonesia, which consists of many islands and mountains, has resulted in an uneven distribution of health facilities and laboratories in each region. There are 2820 hospitals spread across Indonesia which are unevenly distributed, with 1345 hospitals in region 1 (DKI Jakarta, West Java, Central Java, DI Yogyakarta, East Java, and Banten). This is inversely proportional to the number of hospitals in region 5 (NTT, Maluku, North Maluku, Papua, and West Papua), where the number of hospitals is 159 for the entire region [14]. This results in problems such as inadequate access and availability of health facilities for underdeveloped areas.

Modeling and simulation is one of the methods used in testing the effectiveness of a material as a conductor in the PCR reaction. In this study, several materials and thermal cycler designs will be simulated if used as heat transfer containers to carry out the PCR reaction.

The expected results were obtained by applying simulation and modeling the conduction heat transfer equation in order to obtain the heat transfer profile during the PCR reaction as well as the saturation time of each material and the heat transfer process.

Methods

In this study, Modeling discussed the uses and stages of work carried out using COMSOL Multiphysics 5.3. In the PCR reaction chamber, the heat comes from the heating element of the Al2O3 ceramic Peltier which experiences conduction passing through the material (PCR reaction chamber material). The geometry of the first model was done using a PCR tube, which became a container for placing samples for PCR reactions.

Determining models limitation and modeling

The modeling stages were carried out by the COMSOL Multiphysics 5.3 application using the HP 14-an002ax computer specifications with an AMD Quad-Core A8-7410 APU processor with Radeon™ R5 Graphics (2.2 GHz, up to 2.5 GHz, 2 MB cache) with 4 GB DDR3L memory -1600 SDRAM (1 x 4 GB) and AMD Radeon™ R5 M430 Graphics (2 GB DDR3 Video Memory) graphics card.
Conduction heat transfer equation:

$$\rho C_p \frac{\partial T}{\partial t} + \rho C_p u.\nabla T + \nabla.q = Q + Q_{ted} \quad (1)$$

where, $q = -k\nabla T$
Convection heat transfer equation:

$$\rho C_p \frac{\partial T}{\partial t} + \rho C_p u.\nabla T + \nabla.q = Q + Q_p + Q_v \quad (2)$$

where, $q = -kA\frac{dT}{dx}$

ρ is the density of the fluid in units (kg/m^3), C_p is the Heat Capacity in units (J.kg/K) and k is the Heat Conductivity in unit (W/m.K). Furthermore, Q is the heat source that comes from the heating carried out by the Peltier element in units (W/m^3). Meanwhile, Q_{ted} is thermoelastic damping which is the result of the irreversible heat flow across a temperature gradient produced by inhomogeneous compression and expansion of the resonating structure with units (W/m^3). In addition, Q_p is the pressure works in units (W/m^3).

There are also model limitations set as follows,

Thermal Insulation,

$$-n \cdot q = 0 \tag{3}$$

Temperature,

$$T = T_0 \tag{4}$$

Heat Source,

$$Q = Q_0 \tag{5}$$

Geometrical design

The heat transfer event that occurs in the PCR reaction using a PCR tube is conduction through the chamber material. The heat moves to the PCR tube and the convectional heat is transferred to the PCR reagent solution. The size of the Peltier element used for heating was 80 mm x 40 mm x 4 mm figured in Figure 1.

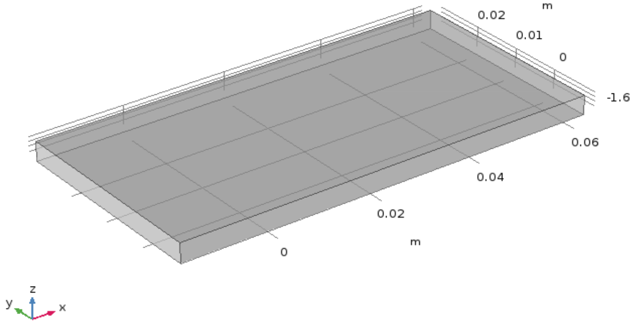


Figure 1: Geometry of Peltier element.

A geometry with the shape of a block was made for the PCR chamber having a size of 81 mm x 40 mm x 15 mm [15]. The chamber had an upper outer diameter of 10.7 mm, an inner diameter of 6.7 mm, a height of 10.5 mm and a radius of 1.5 mm. The distance between the chambers was designed to be 10 mm and 22 mm. This geometric shape was used as a material in the simulation stage until the PCR reaction stage figured in Figure 2.

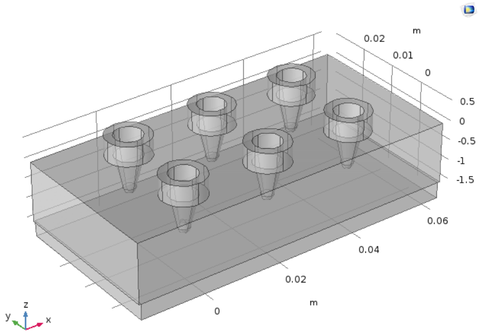


Figure 2: Geometry of PCR block.

The next step was to add the geometry of the PCR tube and the PCR reagent solution to the geometry of the Peltier element. The PCR tube was shaped like a chamber made with a height of 2 mm above the surface of the PCR chamber hole. This geometry was used to simulate heating in the PCR tube and the PCR reaction reagent solution figured in Figure 3.

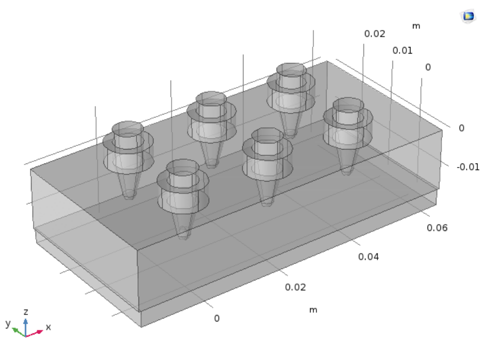


Figure 3: Geometry of PCR block, with PCR tube and reagents.

In this study, the time set for simulation was 60 seconds. Heat enters through the bottom of the Peltier element and moves towards the y-axis. The following is a heat transfer profile that occurs every 10 seconds for each material being simulated—the lowest and highest temperatures were set at 32.64°C and 105.06°C, respectively. The material properties for simulation used from COMSOL Application are shown in the Table 1.

Table 1: Material properties from COMSOL Multiphysics 5.3

Material	Thermal Conductivity (W/m.K)	Heat Capacity (J.kg/K)	Density (kg/m^3)
Aluminum	238	900	2700
Copper	400	385	8960
Nickel	90,7	445	8900
Silver	429	235	10500
PDMS	0.16	1460	970

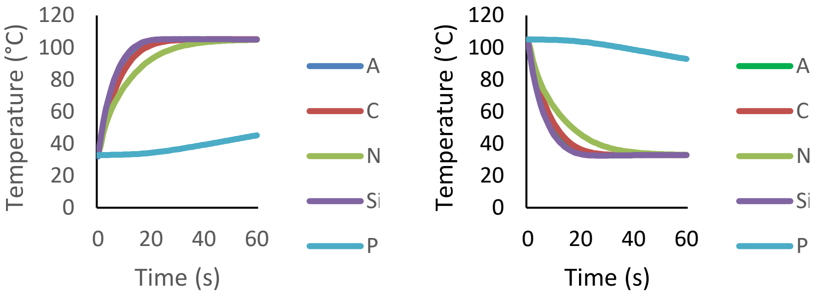
As of July 2020, the prices of materials based on the IMF were 1621.25, 6328.37, 12179.61 and 1968.60 dollars per metric ton for aluminum, copper, nickel and silver, respectively. Furthermore, based on Alibaba.com as of July 2020, the price of PDMS was 2.75 dollars per kilogram.

Results and Discussion

Simulation results for various material

From Figure 4 below, it was observed that the saturation time for heating aluminum, copper and nickel were 29, 26 and 37 seconds, respectively. Meanwhile, the saturation time for cooling was 35, 51 and 53 seconds, respectively. In addition, the heating and cooling time for silver was 26 seconds.

In Figure 5 the heating and cooling values for the PDMS material were set to 60 seconds however, the material had not reached its saturation time at that simulation. The new PDMS material may reach its saturation time at 1480 seconds or around 24 minutes.



(a) (b)

Figure 4: Temperature curve for each material for 60 seconds (a) heating (b) cooling.

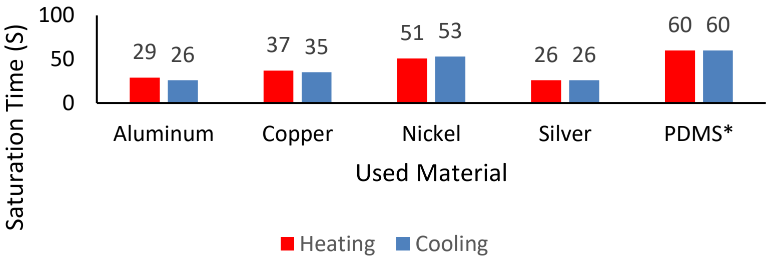


Figure 5: Saturation time for each material.

Considering that each type of material was tested in the same geometry, the factors affecting the time difference based on Equation (1) were density, thermal conductivity and thermal capacity values. The thermal conductivity value in Equation (1) also appeared in Equation (2) namely Fourier's law, where q is the heat transfer rate influenced by k which is the thermal conductivity and ∇T is the temperature gradient.

In Equation (1), the multiplication value of thermal density and capacity is also known as thermal mass. This is an energy requirement needed to increase the temperature at a specific volume [17]. Therefore, these two valueshave an effect on the heat transfer that will occur in the PCR thermal cycler [18].

Thermal conductivity is one of the crucial factors in the conduction of material. Therefore, a good thermal conductivity value determines the quality of a good conductor material [19]. It was observed that silver had the highest thermal conductivity value of 429 W/mK. Meanwhile, copper, aluminum, nickel and PDMS had thermal conductivity values of 400, 238, 90.7 and 0.16 W/mK, respectively. Based on thermal conductivity alone, the order for selecting the best materials for producing a portable thermal cycler design is silver, copper, aluminum, nickel and PDMS.

However, study carried out by [16] used thermal mass as the basis for selecting a material to be developed as a portable thermal cycler design. Therefore, in addition paying attention to the conductivity value, it is necessary to pay attention to the value of the thermal mass of each material used. The higher the thermal mass value of a material, the higher the heat required for the material to raise the temperature. Therefore, much longer time would be required. Thermal mass is obtained by multiplying the density value of the material by its heat capacity. For materials with high thermal conductivity, aluminum had the smallest value of 2430000 J/K m^3, silver, copper and nickel had values of 2467500, 344960 and 3960 500 J/K m^3, respectively. Meanwhile, the PDMS material had a thermal mass of 1416200 J/K m^3.

In the saturation time graph, it was observed that the combination of thermal capacity and thermal mass significantly affects the saturation time of each material. For example, although silver and copper have close thermal capacity values with differences in thermal mass values, the saturation times differ quite significantly. In addition, although aluminum has a low calorific capacity value compared to silver and copper, with a smaller heat mass the transfer of heat is faster than in copper but differs slightly when compared to silver. Aluminum benefits from its low density even though it has a high heating capacity and an average high thermal conductivity. Conversely, silver and copper have high thermal conductivity and low heat capacity. However, the density of the two materials is high enough that there is a little difference between these materials and aluminum.

For nickel and PDMS, with a conductivity value that is not too high, the results obtained were not very satisfying however, the nickel material still managed to reach its saturation time in 60 seconds. Meanwhile, the PDMS material was unable to reach its saturation time in 60 seconds at such a thickness condition. Therefore, the next study will focus on aluminum, copper and silver.

Furthermore, from the economic perspective, the market price of aluminum is low compared to copper and silver. This was reinforced by the statement of the company producing PCR, Eppendorf which stated that aluminum is widely used as a base material for commercial PCR thermal cycler blocks. In addition, they stated the use of other stuff as a coating on aluminum or as an alloy. However, there are also commercial PCR thermal cycler manufacturers that use pure silver as the primary material because of its effectiveness [20].

Aluminum is the best material that may be used as a portable design for thermal cycler PCR as a result of its low price and performance which is slightly different from silver. This material is also used by several methods of low-cost microfabrication [21].

Heat transfer to reagents

From the Figure 6, it was observed that the saturation time for heating the chamber material, PCR tube and PCR solution were 29, 30 and 32 seconds, respectively. Meanwhile for cooling, the saturation time was 26, 30 and 35 seconds, respectively.

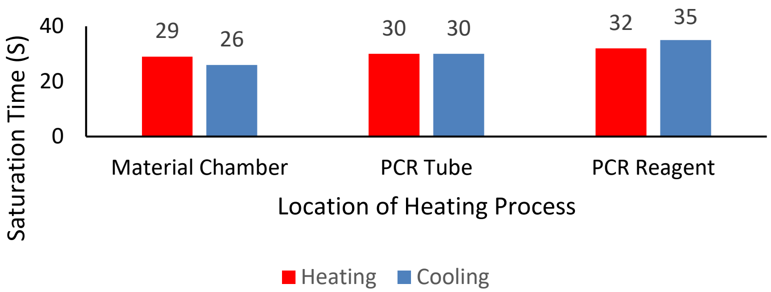


Figure 6: Saturation time for each heat transfer process.

The phenomenon that occurs is the transfer of heat to PCR tubes made of polypropylene [22]. The difference observed in saturation time was 1 second for heating and 4 seconds for cooling. This is the time required for conduction from aluminum to the PCR tube. The heat moves from the PCR tube to the PCR reagent and takes 2 seconds to warm up and 5 seconds to cool down. Therefore, with a total time of 32 seconds for heating and 35 seconds for cooling, the time required for heat to move from the metal to the reagent is 3 seconds for heating and 9 seconds for cooling. This is because a thermal cycler with static heater has more constant heat flux and gives good temperature uniformity [23].

Conclusions

From this study, the following conclusions were drawn. The heat transfer rate on a thermal cycler PCR machine may be influenced by the thermal conductivity and thermal mass values of the material used. The saturation time obtained in this design for heating was 29, 37 and 51 seconds for aluminum, copper and nickel, respectively. Meanwhile, the saturation time obtained for cooling were 26, 35 and 53 seconds for aluminum, copper and nickel, respectively. In addition, the saturation time for heating and cooling were 26 seconds and 1480 seconds for silver and PDMS, respectively. In this design, the saturation time obtained to heat and cool the reagent when using aluminum was 32 seconds and 35 seconds, respectively after the heat had passed through the thermal block and the PCR tube

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References

[1] L. Garibyan and N. J. T. J. Avashia, "Research techniques made simple: polymerase chain reaction (PCR)," *J. Investigative Dermatology*, vol. 133, no. 3, pp. 1 – 8, 2013.

[2] H. Nagai, Y. Murakami, K. Yokoyama, and E. Tamiya, "High-throughput PCR in silicon based microchamber array," *Biosensor Bioelectronic*, vol. 133, no. 9, pp. 1015 – 1019, 2001.

[3] S. Yamaguchi, T. Suzuki, K. Inoue, and Y. Azumi, "DC-driven thermoelectric peltier device for precise DNA amplification," *Japanese J. Applied Physics*, vol. 54, no. 5, pp. 057001, 2015.

[4] S. Jeong, J. Lim, M. Y. Kim, J. Yeom, H. Cho, H. Lee, and J. H. Lee, "Portable low-power thermal cycler with dual thin-film Pt heaters for a polymeric PCR chip" *Biomedical microdevices*, vol. *2, no.* (1), pp. 14, 2018.

[5] T. Reid, R. Taylor, and L. Brown, *U.S. Patent No. 7,459,302*, Washington, DC: U.S. Patent and Trademark Office, 2 December 2008.

[6] M. J. Mortillaro, and D. A. Cohen, *U.S. Patent No. 9,604,219*, Washington, DC: U.S. Patent and Trademark Office. 28 March 2017.

[7] W. J. Benett, J. T. Andreski, J. M. Dzenitis, A. J. Makarewicz, D. R. Hadley, and S. S. Pannu, *U.S. Patent No. 8,778,663*, Washington, DC: U.S. Patent and Trademark Office, 15 July 2014.

[8] J. L. Danssaert,, R. J. Shopes,, and D. D. Shoemaker, *U.S. Patent No. 5,525,300*, Washington, DC: U.S. Patent and Trademark Office, 11 June 1996.

[9] T. C. Gubatayao, K. Handique, K. Ganesan, and D. M. Drummond, *U.S. Patent No. 9,765,389*, Washington, DC: U.S. Patent and Trademark Office. 19 September 2017.

[10] H. Koeda, *U.S. Patent No. 9,144,800*, Washington, DC: U.S. Patent and Trademark Office, 29 September 2015.

[11] R. M. F. Jones, & E. T. McDevitt, *U.S. Patent No. 9,869,003*, Washington, DC: U.S. Patent and Trademark Office, 16 January 2018.

[12] J. Courtney, *U.S. Patent No. 10,307,762*. Washington, DC: U.S. Patent and Trademark Office, 4 June 2019.

[13] S. A. B. Hermsen, B. R. Roszek, A. W. van Drongelen, and R. E. Geertsma, "Lab-on-a-chip devices for clinical diagnostics: Measuring into a new dimension", 2014.

[14] O. O'Donnell, E. Van Doorslaer, R. P. Rannan-Eliya, A. Somanathan,, S. R. Adhikari, D. Harbianto, and G. M. Leung, "The incidence of public spending on healthcare: comparative evidence from Asia", *The World Bank Economic Review*, vol. *21, no.* (1), pp. 93-123, 2007.

[15] K. S. Chong, K. B. Gan, and S. M. Then, "Development of a portable low-cost real-time PCR system", In *2017 International Conference on Robotics, Automation and Sciences (ICORAS)* (pp. 1-5). IEEE, 2017.

[16] S. Jeong, J. Lim, M. Y. Kim, J. Yeom, H. Cho, H. Lee, and J. H. Lee, "Portable low-power thermal cycler with dual thin-film Pt heaters for a polymeric PCR chip", *Biomedical microdevices*, vol. *20, no.* (1), pp. 14, 2018.

[17] G. Wong, I. Wong, K. Chan, Y. Hsieh, and S. Wong, "A rapid and low-cost PCR thermal cycler for low resource settings" *PLoS one*, vol. *10,* no. (7), pp. 0131701, 2015.

[18] Q. Zou, Y. Miao, Y. Chen, U. Sridhar, C. S. Chong, T. Chai, and C. Heng, "Micro-assembled multi-chamber thermal cycler for low-cost reaction chip thermal multiplexing", *Sensors and Actuators A: Physical*, vol. *102, no.* (1-2), pp. 114-121, 2002.

[19] K. S. Chong,, and K. B. Gan, "Portable polymerase chain reaction (PCR): thermal ramping rate performance evaluation". In *2016 IEEE EMBS Conference on Biomedical Engineering and Sciences (IECBES)* (pp. 447-449). IEEE, 2016.

[20] J. G. Atwood, A. Fawcett, K. S. Ferrara, P. M. Hetherington, R. W. Noreiks, D. E. Olsen, and C. M. Wittmer, *U.S. Patent No. 7,537,377*. Washington, DC: U.S. Patent and Trademark Office, 26 May 2009.

[21] J. Charmet, R. Rodrigues, E. Yildirim, P. K. Challa, B. Roberts, R. Dallmann, & Y. Whulanza, Low-Cost Microfabrication Tool Box. *Micromachines*, vol. 11, no. (2), pp. 135, 2020.

[22] X. Huang, L. Hou, X. Xu, H. Chen, H. Ji, and S. Zhu, "One-PCR-tube approach for in situ DNA isolation and detection", *Analyst*, vol. *136, no.* (20), pp. 4254-4259, 2011.

[23] V. S. Duryodhan, S. G. Singh, & A. Agrawal. (2020). The Concept of Making On-Chip Thermal Cycler for RT-PCR Using Conjugate Heat Transfer in Diverging Microchannel. *Transactions of the Indian National Academy of Engineering*, 1.