INTEGRATED CIRCUIT DESIGN BASED ON CHARGE-MODULATED FIELD EFFECT TRANSISTOR FOR DEOXYRIBONUCLEIC ACID BIOSENSING

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Specially dedicated to my family and friends

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ABSTRACT

The aim of this thesis is to design an on-chip Complementary Metal Oxide Semiconductor (CMOS) potentiometric biosensor circuit based on Charge-Modulated Field-Effect Transistor (CMFET) for label-free deoxyribonucleic acid (DNA) detection. Due to increasing demand for point-of-care testing to aid in medical diagnostics, the research and development of inexpensive and small handheld biosensor device is growing rapidly every year. The potentiometric biosensors show great potential towards low cost and future miniaturization, but are thermally unstable due to the properties of the semiconductor structure and sensing films. Long-term stability in a solution and reduced signal-to-noise ratio can be obtained by using a cascode source-drain follower as the detection circuit. However, the cascode topology is not suitable for low supply voltage environment. Therefore, this work proposes a low voltage circuit design for an efficient and low power potentiometric DNA detection circuit. CMFET is used as a sensing device since it offers simplicity by eliminating the use of an external reference electrode and is compatible with the standard CMOS process. The detection circuit consists of a self-cascode source-drain follower and a two-stage differential amplifier. Self-cascode approach is used to improve the accuracy and input voltage range of the source-drain follower. The proposed detection circuit is designed and simulated using 0.18 μm Silterra CMOS fabrication process with 1.8 V supply. The input voltage range of the improved source-drain follower ranges from 0.104 V to 1.28 V within ± 5 mV of accuracy and the frequency range is 15.21 kHz. The power consumption of the improved source-drain follower is as low as 1.8 nW. The two-stage differential amplifier achieves a voltage gain of 76.19 dB and a frequency range of 2.45 kHz. The proposed potentiometric detection circuit gives a total gain of 79.81 dB with a frequency range of 1.528 kHz. The total power consumption is 0.19 mW and the optimized size of the layout area is 5405 μm^2.

ABSTRAK

Kajian ini bertujuan untuk merekabentuk litar biosensor potentiometrik yang menggunakan piawaian semasa semikonduktor oksida logam pelengkap (CMOS) dan berasaskan transistor kesan medan cas termodulat (CMFET) untuk pengesanan bebas label asid deoksiribonukleik (DNA). Oleh kerana peningkatan permintaan terhadap ujian *point-of-care* untuk sokongan diagnostik perubatan, penyelidikan dan pembangunan biosensor yang murah dan mudah-alih berkembang pantas setiap tahun. Sensor potentiometrik menunjukkan potensi yang tinggi untuk kos rendah dan pengecilan pada masa hadapan, tetapi adalah tidak stabil terhadap haba disebabkan oleh sifat-sifat struktur semikonduktor dan lapisan penderiaannya. Kestabilan jangka panjang dalam larutan dan mengurangkan nisbah isyarat-hingar boleh diperoleh dengan menggunakan litar pengikut punca-salir kaskod dalam litar pengesan. Tetapi, topologi kaskod tidak sesuai untuk bekalan voltan rendah. Satu reka bentuk litar voltan rendah untuk litar pengesan DNA pontentiometrik berkuasa rendah serta cekap telah dicadangkan dalam kajian ini. CMFET digunakan sebagai pengesan kerana ia lebih ringkas dengan menghapuskan penggunaan elektrod rujukan dan serasi dengan proses pembuatan CMOS. Litar pengesan terdiri daripada pengikut punca-salir kaskod dan dua-peringkat penguat pembezaan. Kaedah kaskod kendiri digunakan bagi meningkatkan ketepatan serta julat voltan input pengikut punca-salir. Litar pengesan yang dicadangkan telah direkabentuk dan disimulasi dengan menggunakan proses teknologi 0.18 μm Silterra CMOS dengan bekalan voltan 1.8 V. Julat voltan input litar pengikut punca-salir yang telah ditambahbaik ialah di antara 0.104 V dan 1.28 V dalam lingkungan ketepatan ± 5 mV, dan julat frekuensi ialah 15.21 kHz. Dua-peringkat penguat pembezaan mencapai gandaan voltan sebanyak 76.19 dB dan julat frekuensi sebanyak 2.45 kHz. Litar pengesan DNA potentiometrik yang dibangunkan mempunyai jumlah gandaan voltan sebanyak 79.81 dB dengan julat frekuensi 1.528 kHz. Jumlah penggunaan kuasa ialah 0.19 mW dan keluasan pelan litar optimum adalah 5405 μm^2.

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LIST OF ABBREVIATION

A	-	Adenine
AC	-	Alternating Current
ADC	-	Analog-to-Digital
ADE	-	Analog Design Environment
C	-	Cytosine
CMFET	-	Charge-Modulated Field-Effect Transistor
CMOS	-	Complementary Metal-Oxide Semiconductor
CMRR	-	Common-Mode Rejection Ratio
CvMOS	-	Chemoreceptive Neuron MOS Transistor
DC	-	Direct Current
DNA	-	Deoxyribonucleic Acid
DPBS	-	Dulbecco's Phosphate-Buffered Saline
DRC	-	Design Rule Check
dsDNA	-	Double-Stranded Deoxyribonucleic Acid
EDA	-	Electronic Design Automation
EEPROM	-	Electrically Erasable Programmable Read Only Memory
EPROM	-	Erasable Programmable Read Only Memory
FET	-	Field-Effect Transistor
FF	-	Fast-Fast
FGMOS	-	Floating Gate Metal-Oxide Field-Effect Transistor
FS	-	Fast-Slow
G	-	Guanine
GBW	-	Gain Bandwidth Product

I/O	-	Input/Output
IC	-	Integrated Circuit
ICMR	-	Input Common-Mode Range
ISFET	-	Ion-Selective Field-Effect Transistor
JFET	-	Junction Field-Effect Transistor
LVS	-	Layout Versus Schematic
MIM	-	Metal-Insulator-Metal
MOSFET	-	Metal-Oxide Field-Effect Transistor
NMOS	-	N-type MOS Transistor
PC	-	Personal Computer
PCR	-	Polymerase Chain Reaction
PEX	-	Parasitic Extraction
PM	-	Phase Margin
PMOS	-	P-type MOS Transistor
POC	-	Point-Of-Care
PSRR	-	Power Supply Rejection Ratio
QCM	-	Quartz Crystal Balance
RE	-	Reference Electrode
RF	-	Radio Frequency
RNA	-	Ribonucleic Acid
SF	-	Slow-Fast
SPICE	-	Simulation Program with Integrated Circuit Emphasis
SPR	-	Surface Plasma Resonance
SR	-	Slew Rate
SS	-	Slow-Slow
SSC	-	Saline-Sodium Citrate
ssDNA	-	Single-Stranded Deoxyribonucleic Acid
T	-	Thymine
TIA	-	Transimpedance Amplifier

TT	-	Typical-Typical
UGFET	-	Umbrella-Shaped Floating Gate Field-Effect Transistor
USD	-	United States Dollar
VGA	-	Variable Gain Amplifier

LIST OF SYMBOLS

A	-	Area of the electrode surface
β	-	Transconductance coefficient
A_V	-	Voltage gain
A_{V1}	-	First stage DC gain of differential amplifier
A_{V2}	-	Second stage DC gain of differential amplifier
A_i	-	Current gain
$I_{D(SAT)}$	-	Saturation current
I_D	-	Drain current
K^{-1}	-	Debye length
K_BT	-	Boltzmann energy
K_i	-	Component of the incident light wave vector that parallel to the prism
K_p	-	Surface plasma wave vector
$M_\emptyset$	-	Phase margin
Q_{DNA2}	-	Charge of the complementary target ssDNA
V_{DD}	-	Supply voltage
$V_{DS(SAT)}$	-	Saturation voltage
V_{DS}	-	Drain to source voltage
V_{GS}	-	Gate to source voltage
V_{THF1}	-	Effective threshold voltage due to the charge of immobilized ssDNA probe on the sensing site
V_{THF2}	-	Effective threshold voltage due to the charge of complementary target ssDNA.
V_{bias}	-	Bias voltage

V_{in}	-	Input voltage
V_{out}	-	Output voltage
f_{SP}	-	Frequency at which the second pole occurs
f_{UGW}	-	Unity gain bandwidth
g_m	-	Transconductance
r_{in}	-	Input resistance
r_o	-	Output resistance
ε_0	-	Vacuum permittivity
ε_1	-	Dielectric permittivity constant of the gold film
ε_2	-	Dielectric exit medium
ε_r	-	Relative permittivity of the solution
θ_i	-	Incident light angle
C_{CF}	-	Capacitance of the control capacitor
C_{FB}	-	Capacitance between floating gate and silicon substrate
C_{OX}	-	Net gate capacitance per unit area formed by the gate and the channel
C_{SF}	-	Capacitance results from the spacer
E	-	Measured electrode potential
E^0	-	Standard electrode potential
E_{REF}	-	Constant potential of the reference electrode
f_0	-	Natural resonance frequency of the crystal
I_{in}	-	Input current
I_{out}	-	Output current
L	-	Length of the channel
n	-	Number of moles of electrons transferred in the balanced Eq.
q	-	Electron charge
Q_B	-	The depletion charge in the silicon
Q_C	-	Reaction quotient. The mathematical product of the concentrations of the products of the reaction divided by the mathematical product of the concentrations of the reactants.

Q_{F0}	-	Electric charge trapped inside the floating gate
Q_i	-	The charge induced on polysilicon surface by the surface charge
Q_{OX}	-	The accumulated charge in the oxide
Q_S	-	Bound surface charge
Q_{SS}	-	The accumulated charge in the oxide-silicon interface
V_{CG}	-	Control gate voltage
V_{FG}	-	Floating gate voltage
V_{TH}	-	Threshold voltage
V_{THF}	-	Effective threshold voltage
W	-	Width of the channel
Δf	-	Resonant frequency change
Δm	-	Changes in mass of the crystal
μ	-	Carrier mobility
μ_q	-	Shear modulus of the quartz
ρ_q	-	Density of the quartz
ϕ_f	-	Substrate Fermi potential
χ^{sol}	-	Surface dipole potential of the solvent
Ψ	-	Chemical input parameter that varies with the solution pH
ϕ_M	-	Work function of gate metal
ϕ_{Si}	-	Work function of silicon
I	-	Ionic strength of the solution
n	-	Refractive index of the prism
q	-	Elementary charge
z	-	Valency of the ions in the solution
λ	-	Channel length modulation

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CHAPTER 1

INTRODUCTION

1.1 Introduction

Point-of-care (POC) testing brings the test conveniently and immediately to the patient. Due to increasing demand for POC testing, the research and development of an inexpensive, rapid and small handheld biosensor device is growing rapidly every year. With the available Complementary Metal-Oxide Semiconductor (CMOS) technology, it allows the realization of a complete system that integrates the sensing unit and transducer element in the same device. In particular, realization of an integrated deoxyribonucleic acid (DNA) biosensor is the main interest of scientists due to the completion of human genome project and advances in genetic sequencing of pathogenic species [1]. Label-based DNA detection method such as optical DNA microarray is now a mature technology with applications in health care and biological researches. However, the technology is still far from POC applications and even from its implementation in home-diagnosis due to the expensive and bulky equipment. In contrary, label-free electrochemical DNA detection method can provide significant advantages including high sensitivity, small size, low cost, fast, and compatibility with standard CMOS fabrication for future integration.

The general architecture of the sensor system is shown in Figure 1.1. The sensor is a device that gives a signal for the detection or measurement of a physical, chemical, or biological property to which it responds. The sensor system can be categorized into three main types based on the type of the sensor signal or the type of the transducer: mechanical, optical and electrochemical. The sensor gives an output

signal, which is then converted by a transducer to an understandable signal. The weak signal later will be amplified by the amplification and processing unit. The amplified signal will be converted to digital form before appearing at the output. Some of the important characteristics of the sensor systems are as follows:

i. **Sensitivity** - The input parameter change that is required to produce standardized output change. Higher is always better especially for small molecules.

ii. **Selectivity** - The essence of the sensor systems. It is defined as the ratio of the sensor's response to the analytes of interest to its response to other analytes not of interest. Selectivity is infinity in an ideal sensor system.

iii. **Response Time** - Defined as the time the sensor system takes to react to a change in the input.

iv. **Repeatability** - Presents the stability of the sensor systems. It indicates the noise and error level of the sensor systems.

v. **Size and Cost** - Smaller size provides portability and lower cost is easy to be widely spread. This can be easily realized with the available CMOS technology.

The work presented in this thesis focuses on the electrochemical biosensor system for DNA detection.

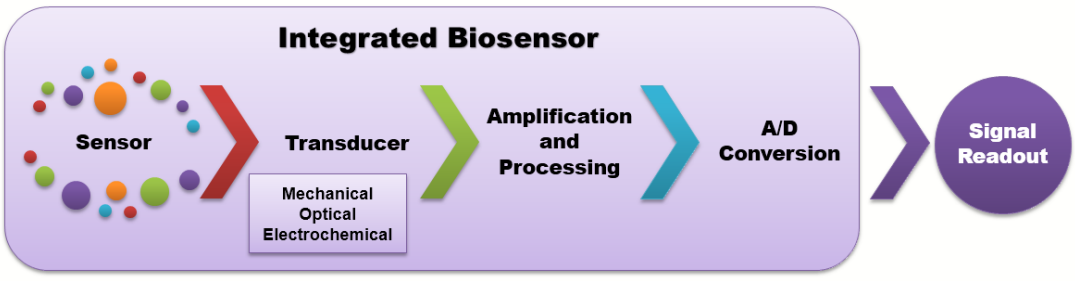

Figure 1.1 Architecture of the typical sensor system.

1.1.1 Deoxyribonucleic Acid

Deoxyribonucleic acid (DNA) is the chemical responsible for preserving, copying and transmitting information within cells and from generation to generation. DNA as the basis of life can be transcribed to ribonucleic acid (RNA), which further translated to the protein structure. For instance, human's DNAs contain genetic information that determines personal attributes such as height, eyes colour and so on. Nucleotides are single building blocks of DNA. It is made up of a phosphate group and deoxyribose as the sugar, and a nitrogen base. The only difference between the nucleotides is the nitrogen bases. There are four different nitrogen bases: adenine (A), guanine (G), cytosine (C) and thymine (T). In fact, DNA is made up of two single strands that are complementary to each other. The nitrogen base pairs, adenine and thymine will only bond with each other while guanine and cytosine will only bond with each other. This hydrogen bonding causes them to form the double-helix structure as shown in Figure 1.2 [2]. For instance, one strand contains a sequence such as CTAGG and the other strand will contain the complementary sequence, GATCC. The double-helix structure of DNA is discovered by Watson and Crick in 1953 [3]. The double-helix structure can be separated into two single strands by increasing the temperature (approximate 95 ^{o}C) or mechanical force.

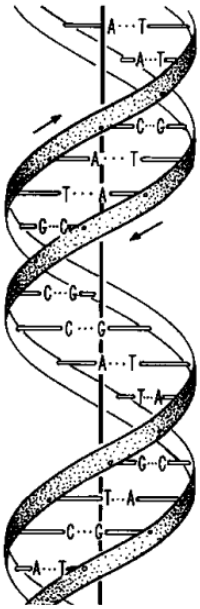

Figure 1.2 Diagram of the DNA double helix.

DNA hybridization is a binding event between two complementary single-stranded DNA (ssDNA) that leads to the formation of a double-stranded DNA (dsDNA). The DNA hybridization is discovered by E.M. Southern in 1975 [4]. His contribution to the development of DNA biosensor is significant since most of the DNA detection techniques today based on the concept of DNA hybridization. The commonly used DNA detection method is shown in Figure 1.3 [5]. First, ssDNA with known sequence (probe) is immobilized on the sensor area using surface chemistry approach. Then, ssDNA with unknown sequence (target) will be injected into the solution and hybridized if its sequence is complementary to the probe. If it is non-complementary, hybridization will not occur. In washing step, the unbind target is washed away and left over dsDNA which is the result of complementary hybridization. Various kinds of methods can be used to detect DNA hybridization, such as optical, electrochemical, and mechanical based.

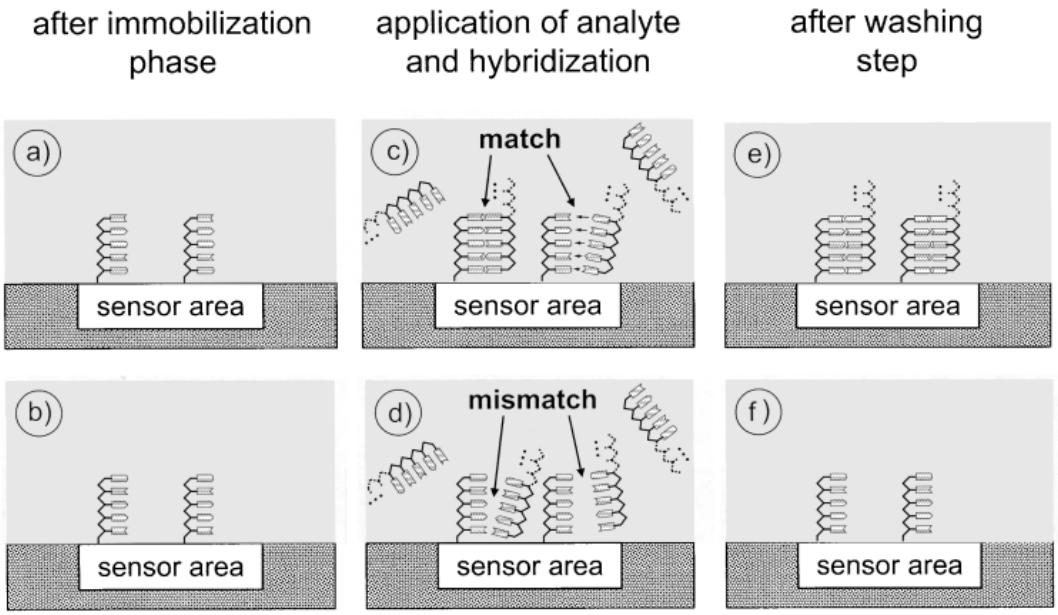

Figure 1.3 Hybridization of DNA. (a) and (b) Immobilization of ssDNA (probe) on the sensor area. (c) Hybridization occurs between complementary ssDNAs. (d) Hybridization will not occur between non-complementary ssDNAs. (e) Sensor area is left with dsDNAs (complementary hybridization). (f) Sensor area is left with ssDNAs (non-complementary hybridization).

1.1.2 Applications of DNA Testing

The discovery of DNA testing has brought many technological accomplishments in different kinds of aspects. For example, clinical diagnostics field including gene-based diseases detection, cancer diagnosis, and viral or infectious bacteria identification. Besides that, the authorities such as police department can use the DNA testing to identify a victim or criminal in forensic investigations. Furthermore, human origin can also be discovered with the help of DNA testing.

With the rapid development of the DNA microarray, large volume of genetic data can be obtained with a single experiment. The paying cost for having ancestry-related genetic testing becomes lower every year. For example, 23andMe company offers a package with the price of 99 USD for an ancestry-related genetic report [6]. The affordable price will encourage more people to take the DNA testing for early detection of fatal diseases and health monitoring.

1.2 Problem Statement

The development of a potentiometric DNA biosensor has been started since P. Bergveld introduced the ion-selective field-effect transistor (ISFET) in early 1970s [7]. There are more than 600 ISFET-related papers published from 1970 to 2002 [8]. Other than ISFET device, there are several novel potentiometric biosensors have been reported such as charge-modulated field-effect transistor (CMFET) and umbrella-shaped floating gate field-effect transistor (UGFET) [9][10]. The huge popularity of potentiometric device is due to its simplicity in measurement, which operates in a label-free manner and significantly saves analysis cost. Furthermore, it is fully compatible with the standard CMOS fabrication technology and allows flexibility to be integrated with other circuits thus contributes towards a small and low power biosensor for the realization of a portable handheld POC device. However, potentiometric biosensors are reported to be thermally unstable due to the properties of semiconductor structure and sensing films [11][12].

To overcome these drawbacks, one of the detection circuit that frequently used in potentiometric biosensor is a source-drain follower [8][13]. This circuit is operated under fixed gate-source voltage and gate-drain voltage. Thus, long-term stability in a solution and reduced signal-to-noise ratio can be obtained. However, conventional source-drain followers are constructed by op-amps and not suitable to be used as the detection circuit for an on-chip biosensor due to the high power consumption and large occupied area.

Nakazato et al. proposed a CMOS cascode source-drain follower for on-chip detection that provides simple circuit implementation with lower power consumption [14]. The cascode topology can improve the accuracy (difference between the output voltage and input voltage) and input voltage range of the source-drain follower by reducing the channel length modulation effect. However, the cascode technique is not suitable for low voltage environment lower than 2 V supply due to the reduced voltage headroom available [15]. Thus, the main objective of this work is to develop a fully CMOS integrated potentiometric biosensor circuit for low power supply operation (< 2V). In addition, an improved sensitivity is also required in order to detect DNA in a small volume of samples. Table 1.1 shows the comparison between this work and other works.

Table 1.1: Comparison between this work and other works.

	Barbaro et al., 2012 [16]	**Nakazato, 2009** [17]	**This Work**
Potentiometric Sensor	CMFET	ISFET (Require an external reference electrode)	CMFET
Detection Circuit	CMFET/MOSFET Differential Pair (Need programmable current generators)	Cascode Source-Drain Follower (Cannot perform well under low voltage)	Self-Cascode Source-Drain Follower
Measurement Method	Threshold Voltage	Gate Voltage	Gate Voltage
Supply Voltage [V]	3.3	2.5	1.8
IC Technology	0.35 μm	0.35 μm	0.18 μm

1.3 Research Objectives

The main objective of this study is to develop an efficient potentiometric biosensor for potentiometric sensing of DNA hybridization. Three specific objectives are considered in this study:

i. To design a low voltage and high sensitivity CMOS detection circuit and physical layout for potentiometric sensing of DNA.

ii. To analyze the electrical performance of the proposed potentiometric biosensor circuit.

1.4 Scope of Work

The scopes of the study are as below:

i. CMFET device is used as the potentiometric sensor in the detection circuit.

ii. Low voltage technique is used to improve the accuracy and input voltage range of the source-drain follower.

iii. Differential amplifier is used in conjunction with source-drain follower to enhance the sensitivity of the biosensor circuit.

iv. Silterra 0.18 μm (CL180G) standard technology with 1.8 V supply is used in the design process.

v. Cadence EDA Tools is used as the simulation software in the design process.

vi. Circuit performance analysis is carried out by comparing both pre-layout and post-layout simulations.

vii. This work is limited to circuit design consideration and no experimental work will be carried on.

1.5 Significance of the Study

The continuous development in the DNA biosensor is important as it provides such many benefits to the mankind. Today, the main problem of available DNA biosensor is the portability and sensitivity of the device. Most of the analysis using state-of-the-art DNA biosensors have to be done in the laboratory due to the size and complexity of the device. With the latest CMOS technology, biosensors can be integrated together with the readout and signal-processing circuits. Moreover, shrinking in the supply voltage of CMOS technology allows biosensors to be battery-operated and mobile. On the other hand, DNA biosensor requires high sensitivity especially for detecting short-stranded DNA which is less than 10-mer. Besides that, highly sensitive DNA biosensor only needs a small volume of DNA sample to produce a readable output change.

This work proposed a fully integrated and high sensitivity CMOS DNA biosensor. It can operate in label-free and low voltage environments that are vital for the development of an ultra-small portable biosensor to meet current market demand. The achieved low power and small area consumption shows high possibility towards future array integration for massively parallel analysis of DNA detection, which is highly desirable in POC testing applications.

1.6 Organization of the Thesis

The rest of this thesis is organized as follows. Chapter 2 describes the literature review of DNA biosensors, for both label and label-free based. Currently available potentiometric sensors and detection circuits are discussed and their operational principles are explained briefly. Also, low voltage techniques are introduced.

Chapter 3 illustrates the design of the proposed CMFET based potentiometric biosensor circuit using Silterra 0.18 μm CMOS process technology. The research methodology and IC design flow are explained briefly and the circuit simulation tools

used in this work are listed. The issues in analog layout are discussed and the physical layout of the designed circuit is presented.

In Chapter 4, the pre-layout and post-layout simulation results of the proposed potentiometric biosensor circuit are presented. Lastly, in Chapter 5, a conclusion of the research work is given. The possible directions of the future research are also described.

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